

ANA 2016 Program

Movement Disorder

S101. Dissociated Cognitive Impairments Associated with Midbrain and Hippocampal Microstructural Atrophy in Parkinson's Disease: A 7-Tesla MRI Study

Kathleen L. Poston, Michael Zeineh, Matthew A.I. Ua Cruadhlaoich, Jeffrey Bernstein, Sudarshan Ranganathan, Laura Santoso, Michelle Fenesy, Seoni Llanes, Gayle Deutsch, Brian Rutt and Geoffrey Kerchner. Stanford, CA and Stanford, CA

Cerebrovascular Disease

S102. Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis: CREST-2 Update

Thomas G. Brott, Brajesh K. Lal, George Howard, Gary Roubin, Robert D. Brown, Jr, Kevin M. Barrett, Seemant Chaturvedi, Marc I. Chimowitz, Bart M. Demaerschalk, Virginia J. Howard, John Huston III, Ronald M. Lazar, Wesley S. Moore, Claudia Scala Moy, Tanya N. Turan, Jenifer H. Voeks and James F. Meschia. Jacksonville, FL

S103. Burden and Outcomes of Acute Ischemic Stroke in Patients with Major Depression

Zeeshan Mansuri, Achint Patel, Zabeen Mahuwalla, Uvesh Mansuri, Ruchir Goswami, Tapan Mehta, Sagar Patel, Kinsuk Chauhan, Sarah Noble, Girish Nadkarni and Sanjeeva Reddy Onteddu. Philadelphia, PA; New York, NY; Dallas, TX; Storrs, CT and Fayetteville, AR

Epilepsy

S104. Adjunctive Everolimus Therapy for the Treatment of Refractory Seizures Associated with Tuberous Sclerosis Complex: Results from a Randomized, Placebo-Controlled, Phase 3 Trial

Jacqueline A. French, John A. Lawson, Zuhai Yapici, Tilman Polster, Rima Nabbout, Paolo Curatolo, Petrus J. de Vries, Noah Berkowitz, Maurizio Voi, Diana Pelov, Severine Peyrard and David N. Franz. New York; Randwick, Australia; Istanbul, Turkey; Bielefeld, Germany; Paris, France; Rome, Italy; Cape Town, South Africa; East Hanover, NJ; Rueil-Malmaison, France and Cincinnati, OH

Movement Disorder

S105. Deep Brain Stimulation in Early Stage Parkinson's Disease: Long-Term Motor Benefit Through 5 Years

Mallory L. Hacker, Maxim Turchan, Lauren E. Heusinkveld, Amanda D. Currie, Sarah Millan, William Fisher, Madelyn Bollig, Thomas L. Davis, Peter E. Konrad, Fenna T. Phibbs, Peter Hedera and David Charles. Nashville, TN

S106. Increased Dendritic Excitability and Calcium-Dependent PKC Activation: A Novel Mechanism Underlying Purkinje Neuron Dendritic Degeneration in Cerebellar Ataxias

Ravi Chopra, Aaron G. Wasserman, David D. Bushart, James M. Dell'Orco and Vikram G. Shakkottai. Ann Arbor, MI

S107. Rare Recurrent *NRXN1* Deletions and *CNTN6* Duplications Increase Risk for Tourette Syndrome

Jeremiah M. Scharf, Alden Y. Huang, Dongmei Yu, Lea K. Davis, Jae-Hoon Sul, Vasily Ramensky, Ivette Zelaya, Fotis Tsetos, Peristera Paschou, Carol A. Mathews, Giovanni Coppola and The Tourette Syndrome Association International Consortium for Genetics and the GTS GWAS Replication Initiative. Boston, MA; Los Angeles, CA; Nashville, TN; Alexandroupoli, Greece and Gainesville, FL

S108. Spatio-Temporal Analysis and Modeling of Gait in Parkinson's Disease

Christine E. Ashton, Catherine Tocci, Veronique G. Vanderhorst and Ludy C. Shih. Boston, MA

Multiple Sclerosis

S109. Vitamin D Genetic Risk Score Is Strongly Associated with Vitamin D Levels and Relapse Rate in Pediatric MS Patients

Jennifer Graves, Lisa Barcellos, Lauren Krupp, Anita Belman, Michaela George, Xiarong Shao, Hong Quach and Emmanuelle Waubant. San Francisco; Berkeley; New York and Stonybrook, NY

Cerebrovascular Disease

S110. Hospitalization Risk Following Acute Stroke: The Atherosclerosis Risk in Communities (ARIC) Study

Andrea L.C. Schneider, Rebecca F. Gottesman, Sara B. Jones, Josef Coresh, Anna Kucharska-Newton, Wayne Rosamond and Silvia Koton. Baltimore, MD; Chapel Hill, NC and Tel Aviv, Israel

S111. Burden and Outcomes of Acute Hemorrhagic Stroke in Patients with Psychosis

Zeeshan Mansuri, Achint Patel, Girish Nadkarni, Zabeen Mahuwalla, Tapan Mehta, Uvesh Mansuri, Ashutosh Lodhi, Ruchir Goswami, Sarah Noble, Sagar Patel and Sanjeeva Reddy Onteddu. Philadelphia, PA and Fayetteville, AR

Epilepsy

S112. Widespread Migration and Integration of Neurons in the Early Postnatal Human Frontal Cortex

Mercedes F. Paredes, David James, Sara Gil-Perotin, Hosung Kim, Jennifer Cotter, Duan Xu, Jose-Manuel Garcia-Verdugo, Eric Huang and Arturo Alvarez-Buylla. SF, CA and Valencia, Spain

S113. Dynamic Participation Patterns of Superficial Cortex During Absence Seizures

Jochen F. Meyer, Atul Maheshwari, Jeffrey L. Noebels and Stelios M. Smirnakis. Houston, TX and Boston, MA

Movement Disorder

S114. To Study Falls in Parkinson Disease

Abraham Lieberman, **Aman Deep** and Saulena Shafer. Phoenix, AZ

S115. White Matter Abnormalities in Distinct Phenotypes and Putative Genotype of Spasmodic Dysphonia
Serena Bianchi, Giovanni Battistella and Kristina Simonyan. New York

S116. A Translational Approach to Analyze Spatial and Temporal Gait Parameters: Normal and Parkinsonian Gait Signatures in Mice and Human

Lauren Broom, Audrey Worley, Lara Wagenaar, Brian Ellison, Aron Buchman, Jeffrey Hausdorff and Veronique G. VanderHorst. Boston, MA; Tel Aviv, Israel and Chicago

S117. Distinct Synuclein Seeds in Parkinson Disease and Multiple System Atrophy

Tritia R. Yamasaki, Brandon B. Holmes, Jennifer L. Furman, Dhruva D. Dhavale, Nigel J. Cairns, Paul T. Kotzbauer and Marc I. Diamond. Lexington, KY; St Louis, MO and Dallas, TX

Multiple Sclerosis

S118. Coordinated B Cell Compartmentalization with Antigen Presentation in a Murine Autoimmune Model of Multiple Sclerosis

Chelsea R. Parker Harp, Angela S. Arachambault and Gregory F. Wu. St. Louis, MO

S119. Macromolecular Proton Fraction (MPF) Mapping Strongly Correlates with Histologically Assessed White and Gray Matter Demyelination in the Murine Cuprizone Model

Marina Yu Khodanovich, Irina V. Sorokina, Valentina Yu Glazacheva, Elena P. Krutenkova, Aliya S. Nakesbekova, Alexander G. Romashchenko, Andrey E. Akulov, Tatyana G. Tolstikova and Vasily L. Yarnykh. Tomsk, Russian Federation; Novosibirsk, Russian Federation and Seattle, WA

S120. In Vivo Imaging of Cortical Demyelination and Remyelination in a Mouse Model of Multiple Sclerosis

Jennifer L. Orthmann-Murphy, Ethan G. Hughes, Peter Calabresi and Dwight Bergles. Baltimore, MD

Cerebrovascular Disease

S121. Differences Between Lacunar Infarcts and Deep Intracerebral Hemorrhage: A Nested Case-Control Study from the Framingham Heart Study

Vasileios-Arsenios Lioutas, Alexa Beiser, Jayandra Himali, Hugo Aparicio, Jose Rafael Romero, Charles DeCarli and Sudha Seshadri. Boston, MA; Boston and Davis, CA

S122. Large Vessel Occlusion Predicted by Stroke Screening Scales

Norma K. Castillo, Melissa Angulo, Maureen Hillmann and Fernando D. Testai. Chicago, IL

S123. Normalization of BUN/Creatinine Ratio in Acute Ischemic Stroke Patients Is Associated with Less Infarct Expansion

Mona N. Babouth, Alexis N. Simpkins, Puneet Ghotra, Argye E. Hillis, Rebecca F. Gottesman and Richard Leigh. Baltimore, MD and Bethesda, MD

Epilepsy

S124. HLA-B*40:02 and HLA-DRB1*04:03 as Genetic Markers for Oxcarbazepine Induced Maculopapular Eruption

Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Korea

S125. Cyclicity and Clustering of Spontaneous Recurrent Seizures in Mouse Pilocarpine Model of Temporal Lobe Epilepsy

Hye Rim Shin, Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun and Jung-Ah Lim. Seoul, Republic of Korea

S126. Is Laser Ablation of Mesial Temporal Structures the New Surgical Treatment of Intractable Temporal Lobe Epilepsy?

Andres M. Kanner, Ramses Ribot, Enrique Serrano, Naymee Velez-Ruiz, Merredith Lowe, Raquel Lopez, Gustavo Rey, Walter Jermacowicz and Jonathan Jagid. Miami, FL

S127. Distinct Modes of Seizure-Like Hyperexcitability as Revealed in *Drosophila* Sodium Channel Mutants

Atulya Iyengar, Atsushi Ueda, Junko Kasuya, Scott Gratz, Kate O'Connor-Giles, Toshi Kitamoto and Chun-Fang Wu. Iowa City, IA and Madison, WI

Movement Disorder

S128. Disrupting Abducens Nerve Development Causes Duane Retraction Syndrome

Jong G. Park, Max A. Tischfield, Alicia A. Nugent, Long Cheng, Silvio Alessandro Di Gioia, Wai-Man Chan, Gail Maconachie, Thomas M. Bosley, Gail Summers, David G. Hunter, Caroline D. Robson, Irene Gottlob and Elizabeth C. Engle. Boston, MA; Durham, NC; Chevy Chase, MD; Cambridge, MA; Leicester, United Kingdom; Baltimore, MD and Minneapolis, MN

S129. Framingham Risk Scores Predict a 2 Year Worsening in Motor Impairment in Parkinson Disease

Vikas Kotagal, Nicolaas I. Bohnen, Martijn L.T.M. Müller, Roger L. Albin and Kirk A. Frey. Ann Arbor, MI

S130. Use of Selective Serotonin Reuptake Inhibitors Does Not Improve Survival in Multiple System Atrophy

Elizabeth A. Coon, J. Eric Ahlskog, Michael H. Silber, Robert D. Fealey, Eduardo E. Benarroch, Paola Sandroni, Jay N. Mandrekar, Phillip A. Low and Wolfgang Singer. Rochester, MN

S131. Preclinical Investigations of Sex-Specific Risk for Mild Cognitive Impairment in Parkinson's Disease: Androgen Effects on the Subthalamic Nucleus

Paula Askalsky, Dana Lengel, Rachel Kery, William F. Collins and Mary F. Kritzer. Stony Brook, NY

S132. Apical Dendrite Degeneration, a New Cellular Pathology in Amyotrophic Lateral Sclerosis

Baris Genc, Javier H. Jara, Peter Pytel, Raymond P. Roos, Marsel M. Mesulam, Changiz Geula, Eileen H. Bigio and Hande Ozdinler. Chicago, IL

S133. If We Build It, Will They Come? Motivating Factors and Barriers for Participation in the DBS in Early PD Pivotal Trial

Lauren Heusinkveld, Mallory Hacker, Maxim Turchan, Christina Tamargo, William Fisher, Lauren McLaughlin, Adria Martig and David Charles. Nashville, TN and New York, NY

S134. Effects of Optimal Drug Therapy versus Deep Brain Stimulation on Employment in Early Stage Parkinson's Disease

Christina L. Tamargo, Mallory L. Hacker, Taylor Hudson, Maxim Turchan, Sarah H. Millan and David Charles. Nashville, TN

S135. Mass Spectroscopic Evidence for the Amine Inhibition of DOPAL Triggered Alpha-Synuclein Aggregation: New Neuroprotective Treatment Strategy for Parkinson Disease

Vijaya B. Kumar, Fong-Fu Hsu, Vijaya M. Lakshmi, Kathleen N. Gillespie and William J. Burke. Saint Louis, MO

S136. A Novel Spasticity Diagnostic Algorithm - A Case Study of the Kappa Paradox

Maxim Turchan, Taylor S. Hudson, Chandler Gill, Mallory L. Hacker, Amanda D. Currie, Anna L. Molinari, Thomas Davis, Fenna Phibbs, Christopher Tolleson, Candace Grisham, Daniel Byrne and David Charles. Nashville, TN and Chicago, IL

S137. Statins and Risk of Parkinson's Disease: Insight Gained from a Large, National Claims Database

Guodong Liu, Nicholas W. Sterling, Lan Kong, Mechelle M. Lewis, Richard B. Mailman, Honglei Chen, Douglas L. Leslie and Xuemei Huang. Hershey, PA and Research Triangle Park, NC

S138. Cognitive Impairment in Parkinson's Disease: Association Between Patient-Reported and Clinically Measured Outcomes in the Parkinson's Disease Biomarker Program

Kelly A. Mills, Jiangxia Wang, Angela Zhang, Emma Powers, Zoltan Mari, Catherine C. Bakker, Vanessa Johnson, Gregory M. Pontone, Alexander Pantelyat, Ted M. Dawson and Liana S. Rosenthal. Baltimore

S139. Medullary Neuronal Loss and Alpha-Synuclein Burden in Multiple System Atrophy

Elizabeth A. Coon, Ann M. Schmeichel, Joseph E. Parisi, Phillip A. Low and Eduardo E. Benarroch. Rochester, MN

S140. The α -Synuclein Concentration in Plasma of Patients with Parkinson's Disease and Its Relation with Clinical Features as Well as with Mutation of Glucocerebrosidase

Michalina M. Litwinowicz, Andrzej Plewka, Danuta Plewka, Agnieszka Gorzkowska, Andrzej Szczudlik, Michał Szubiga, Michał Morek, Edyta Bogunia and Monika Rudzińska-Bar. Kraków, Poland and Katowice, Poland

S141. Alterations in 14-3-3 Protein Phosphorylation as a Biomarker for Neurodegeneration

Michael McFerrin, Xiaofei Chi, Leslie McClure, Gary Cutter and Talene A. Yacoubian. Birmingham, AL and Philadelphia, PA

S142. Repeat Associated Non-AUG Initiated Translation from GC Rich Repeats in Neurodegenerative Disease

Peter K. Todd. Ann Arbor, MI

Multiple Sclerosis

S143. Molecular-Based Diagnosis of Multiple Sclerosis and Its Progressive Stage

Peter Kosa, Christopher Barbour, Mika Komori, Makoto Tanigawa, Tianxia Wu, Kory Johnson, Ronald Herbst, Yue Wang, Keith Tan, Mark Greenwood and Bibiana Bielekova. Bethesda; Bozeman; Gaithersburg and Cambridge, United Kingdom

S144. Development of a Sensitive Outcome for Economic Drug Screening for Progressive Multiple Sclerosis

Peter Kosa, Danish Ghazali, Makoto Tanigawa, Irene Cortese, William Kelly, Blake Snyder, Joan Ohayon, Kaylan Fenton, Tanya Lecky, Tianxia Wu, Christopher Barbour, Mark Greenwood, Govind Nair and Bibiana Bielekova. Bethesda and Bozeman

S145. Genetic Risk Factors May Have Larger Effect Sizes in Pediatric- Compared to Adult-Onset MS

Emmanuelle Waubant, Milena Gianfrancesco, Xiorong Shao, B. Rhead, Jennifer Graves, Tanuja Chitnis, Amy Waldman, Tim Lotze, Teri Schreiner, Anita Belman, Ben Greenberg, Bianca Weinstock-Guttman, Greg Aaen, Jan-Mendel Tillema, Jayne Ness, Yolanda Harris, Jennifer Rubin, Meghan Candee, Lauren Krupp, Mark Gorman, Leslie Benson, Moses Rodriguez, Soe Mar, I. Kahn, John Rose, Shelly Roalstad, Charlie Casper, L. Shen, Hong Quach, C. Metayer, Cathy Schaefer, Annette Langer-Gould and Lisa Barcellos. San Francisco; Berkeley; Boston; Philadelphia; Houston; Denver; NYC; Dallas; Buffalo; Loma Linda; Rochester; Birmingham; Chicago; Salt Lake City; Saint Louis; Washington DC; Oakland and Santa Monica

S146. Convergent Effects of a Functional C3 Polymorphism on Cognitive Impairment, Brain Atrophy and Demyelination in Multiple Sclerosis

Tina Roostaei, Shokufeh Sadaghiani, Rabil Mashhadi, Masih Falahatian, Esmail Mohammadi, Aria Nazeri, Rozita Doosti, Abdorreza Naser Moghadasi, Mahsa Owji, Amir Pejman Hashemi Taberi, Ali Shakouri Rad, Amirreza Azimi, Arash

Nazeri and Mohammad Ali Sabraian. Tehran, Islamic Republic of Iran and Toronto, ON, Canada

S147. Relation between Fatigue Severity Scale (FSS) and Pupillary Indices in Patients with Multiple Sclerosis (MS)

Ye Hu, Hong Jiang, Byron L. Lam, Silvia Delgado, Jianhua Wang and Kottil W. Rammohan. Miami, FL

S148. Increased Contact with Clinical Trial Participants May Improve Confirmed Multiple Sclerosis Relapse Detection

Kelsey Zorn, Augustus G. Calabresi, Sandra D. Cassard, Katherine C. Smith and **Ellen M. Mowry**. Baltimore, MD

S149. Effects of Intermittent Fasting in an Animal Model of Multiple Sclerosis

Francesca Cignarella, Claudia Cantoni, Laura Ghezzi, Yan-jiao Zhou, Anne Cross and Laura Piccio. Saint Louis, MO and Farmington, CT

S150. Ovarian Age Is Associated with Gray Matter Volumes and Disability in Women with MS Independent of Chronological Age and Disease Duration

Jennifer S. Graves, Roland G. Henry, Bruce Cree, Marcelle Cedars, Ruth Greenblatt, Emanuelle Waubant, Geralyn Messerlian, Peter Bacchetti, Alyssa Zhu, UCSF EPIC, Steven L. Hauser and Jorge Oksenberg. San Francisco, CA; San Francisco and Providence

S151. Co-Production of GM-CSF, IL-22, or IL-17F Identifies a Pathogenic High IL-17A-Producing T Cell Subset from MS Patients That Is Steroid Resistant

Mark A. Jensen, Pretty Abraham, Anthony T. Reder and Barry G.W. Arnason. Rochester, MN and Chicago, IL

Neurocritical Care

S152. Endovascular Therapy for Acute Stroke in the Mount Sinai Health System: The Role of Neurointensivist-Led System-Wide Triage

Stephan A. Mayer, Justin Mascitelli, Neha Dangayach, Natalie Wilson, Hazem Shoirah, Johanna T. Fifi, Srinivasan Paramasivam, Reade Deleacy, Errol Gordon, Joshua Bederson, J. Mocco and Stan Tuhim. New York, NY

S153. Predicting Survival after Acute Civilian Penetrating Brain Injuries: The SPIN Score

Susanne Muehlschlegel, Didem Ayturk, Aditi Ahlawat, Saef Izzy, Thomas M. Scalea, Deborah M. Stein, Timothy Emboff and Kevin N. Sheth. Worcester, MA; Boston, MA; Baltimore, MD and New Haven, CT

Neuro-Oncology

S154. Impact of NEOD001 on Neuropathy and Organ Biomarkers in Patients with Light Chain Amyloidosis and Persistent Organ Dysfunction: Results from the Expansion Phase of a Phase 1/2 Study

Michaela Liedtke, Raymond L. Comenzo, Heather Landau, Vaishali Santhorawala, Brendan M. Weiss, Jeffrey Zonder,

Jackie Walling, Gene G. Kinney, Martin Koller, Dale B. Schenk, Spencer D. Guthrie, Enchi Liu and Morie A. Gertz. Stanford, CA; Boston, MA; New York, NY; Philadelphia, PA; Detroit, MI; Hillsborough, CA; South San Francisco, CA and Rochester, MN

S155. Clinical Features and Prognostic Factors of 476 Patients with Spinal Astrocytoma: An Integrated Analysis from Multi-Institutional Data and the Literature

Harrison X. Bai, Yingjie Zou, Ranjith Babu, Alessandro Landi, Xiangyan Huang, Maria Martinez-Lage, Jianhua Zhou, Paul Zhang, John Woo and Li Yang. Philadelphia, PA; Changsha, Hunan, China; Durham, NC and Rome, Italy

S156. MR Imaging Features Predict Survival and Molecular Profile in Diffuse Lower Grade Gliomas

Hao Zhou, Harrison X. Bai, Chang Su, Haiyun Tang, Martin Vallieres, Xiangyan Huang, Ena Agbodza, Tochukwu Awachie, Xiangqi Tang, Yongguang Tao, Jianhua Zhou, Maria Martinez-Lage, Bo Xiao, Liming Tan, Paul Zhang and Li Yang. Changsha, Hunan, China; Philadelphia, PA; Pennsylvania, PA and Montreal, QC, Canada

Behavioral Neurology

S157. Cerebellar tDCS to Augment Chronic Aphasia Treatment

Rajani Sebastian, Amy Wright, Cameron Davis, Sadhvi Saxena, Kyrana Tsapkini, Donna C. Tippet, Pablo Celnik and Argye E. Hillis. Baltimore, MD

S158. Differentiating between Subtypes of Primary Progressive Aphasia and Mild Cognitive Impairment on a Modified Version of the Frontal Behavioral Inventory

Donna C. Tippet, Cornelia Demsky, Rajani Sebastian, Amy Wright, Cameron Davis and Argye E. Hillis. Baltimore, MD

S159. Emotion Network Breakdown Relates to Baseline Autonomic Dysfunction in Behavioral Variant Frontotemporal Dementia

Virginia E. Sturm, Jesse Brown, Alice Y. Hua, Sandy J. Lwi, Howard J. Rosen, Bruce L. Miller, Robert W. Levenson and William W. Seeley. San Francisco and Berkeley

S160. Altered MicroRNA Expression in a Mouse Model of Autism Spectrum Disorder

Jun-Sang Sunwoo, Jangsup Moon, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea

S161. Bismuth Neurotoxicity: A Rare Cause of Rapidly Progressive Dementia

Farwa Ali. Rochester, MN

S162. Relevance of Inhibitory Control and Neurocognitive Function to Tactical Self-Regulation in the Context of Driving

Nazan Aksan, Sarah Hacker, Marini Robert and Farmer Amanda. Iowa City, IA

Cerebrovascular Disease

S163. Early Changes in ADC Volumes Are Associated with Absolute Neutrophil Count During Ischemic Stroke
Alexis N. Simpkins, Puneet Ghotra and Richard Leigh. Bethesda, MD

S164. Tumor Necrosis Factor-alpha Potentiates the Effect of Ischemic Brain Injury in Vascular Cognitive Impairment
Luther Creed Pettigrew, Christopher M. Norris and Richard J. Kryscio. Lexington, KY

S165. Severe Stenosis of Internal Carotid Artery Is Associated with Higher Neutrophil-Lymphocyte Ratio: A Concept of Cerebrovascular Stress
Archie Defillo, M. Fareed K. Suri, Muhammad Shah Miran, Kenneth Shea, Melissa Freese, Michelle Peterson, Leah R. Roering and Jerone Kennedy. St. Cloud, MN

Epilepsy

S166. Localized Hippocampal Knockout of TSC1 Gene in Mice Leads to In Vivo Cognitive Dysfunction and Electrophysiological Changes without Seizures
Paul R. Jarvis, Sean P. Flynn, Jeremy Barry and Gregory L. Holmes. Burlington, VT

S167. Palinaousis
Madeline C. Fields, Lara V. Marcuse, Jenna Yoo and Saadi Ghatan. New York, NY

S168. Generalized Tonic Clonic and Psychogenic Non Epileptic Spells Audio Recordings in the Epilepsy Monitoring Units: Identification and Inter-Rater Agreement
Richa Tripathi, Hardik Doshi, Deepti Zutshi, Aashit Shah and Maysaa Basha. Detroit, MI

S169. Seizure Control Does Not Change Abnormal Functional Connections in Temporal Lobe Epilepsy
Mayra A. Lopez, Shalinee Mylvaganam, Beau M. Ances, Robert E. Hogan and Luigi Maccotta. St. Louis, MO

Movement Disorder

S170. Indirect Comparison of Tolerability of Deutetrabenazine and Tetrabenazine in the FIRST-HD and TETRA-HD Trials
Daniel O. Claassen, Benjamin Carroll, Lisa M. De Boer, Eric Wu, Rajeev Ayyagari, Sanjay Gandhi and David Stamler. Nashville, TN; Frazer, PA; Boston, MA and La Jolla, CA

S171. KTKEGV-Motif Mutations in Alpha-Synuclein Cause Neuronal Death and Defects in Neurite Regrowth After Mechanical Injury
Nagendran Ramalingam, Ulf Dettmer, Dennis J. Selkoe and Oren A. Levy. New York, NY and Boston, MA

Multiple Sclerosis

S172. Claudin-4 is Required for Astrocytic Tight Junction Formation and Protects Against Inflammatory Lesion Size and Severity in the Central Nervous System

Sam Horng, Candice Chapouly, Anthony Therattil, Azeb Tadesse Argaw and Gareth John. New York, NY

S173. Selection of First-Line Therapy in Multiple Sclerosis Using Risk-Benefit Decision Analysis
David Bargiela, Matt T. Bianchi, M. Brandon Westover, Lori B. Chibnik, Brian C. Healy, Philip L. De Jager and Zongqi Xia. Boston, MA and Pittsburgh, PA

S174. Longitudinal Spinal Cord Measurements in Neuroinflammatory Diseases
Shila Azodi, Emily Charlip, Winston Liu, Jeanne Billioux, Ashley Vellucci, Joan Ohayon, Goavind Nair and Steve Jacobson. Bethesda, MD and College Park, MD

S175. Polyprenols Stimulate Neurogenesis and Reduce Demyelination in the Murine Cuprizone Model of Multiple Sclerosis
Marina Yu Khodanovich, Valentina Yu Glazacheva, Edgar S. Pan, Andrey E. Akulov, Elena P. Krutenkova, Vladimir B. Trusov and Vasily L. Yarnykh. Tomsk, Russian Federation; Melbourne, Australia and Seattle

S176. HTLV-1 Viral Antigens Detected in Exosomes Isolated from HAM/TSP Patient CSF by Novel Nanotrap Technology
Monique Anderson, Maria Chiara Monaco, Ashley Vellucci, Ben Lepene, Yuetsu Tanaka, Joan Ohayon, Fatah Kashanchi and Steven Jacobson. Bethesda, MD; Manassas, VA; Nishihara-Cho, Okinawa, Japan and Charlottesville, VA

S177. Quantitative Assessment of Demyelination in the Medulla Oblongata in Multiple Sclerosis Using Macromolecular Proton Fraction Mapping
Vasily L. Yarnykh, James D. Bowen, Beena Gangadharan, Pavle Repovic, Angeli Mayadev, Peiqing Qian and Lily K. Jung Henson. Seattle, WA and Tomsk, Russian Federation

Epilepsy

S178. Prevalence and Character of Severe Epileptic Encephalopathy in Patients Affected by MECP2 Duplication Syndrome
Dana Marafie, Rebecca Schultz, Daniel Glaze, Bernhard Suter and Alica Goldman. Houston, TX

S179. Ultrahigh-Field MR Volumetry of the Endopiriform Nucleus in Temporal Lobe Epilepsy
David Ortiz, Bradley Nix, PPierre-Francois Van de Moortele, Julien Sein, Zhiyi Sha, Kamil Ugurbil and Thomas R. Henry. Minneapolis, MN

Movement Disorder

S180. Gender Differences in Symptom Manifestation and Survival Patterns in Multiple System Atrophy
Renee M. Nelson, Elizabeth A. Coon, David Sletten, Jay N. Mandrekar, Phillip A. Low and Wolfgang Singer. Rochester, MN

S181. Polygenic Risk of Spasmodic Dysphonia Is Associated with Functional Connectivity Alterations in the Sensorimotor Cortex

Giovanni Battistella, Gregory Garbés Putzel, Anna Rumbach, Laurie J. Ozelius, Mert R. Sabuncu and Kristina Simonyan. New York, NY; Brisbane, Australia; Charlestown, MA and Cambridge, MA

S182. Repurposing of Prostate Cancer Chemotherapeutics as a Brain Bioavailable Nurr1 Transactivator for Treatment of Synucleinopathies in Parkinson's Disease

Giulio Pasinetti and Kenjiro Ono. New York and Tokyo, Japan

S183. Development of a Brief Ataxia Rating Scale for Children (BARS-c)

Franziska Hoche, Winthrop P. Harvey, Bruna Olson-Bressane, Mark G. Vangel and Jeremy D. Schmahmann. Boston, MA

S185. An Extragenic Safe Harbor Permits Suicide Gene Expression Serving as a Safety Switch for Cell Therapy of Neurological Disorders

Yasuyoshi Kimura, Yonehiro Kanemura, Tomoko Shofuda, Masafumi Onodera, Masaaki Oda, Masayuki Nakamori, Toru Nakano and Hideki Mochizuki. Osaka, Japan and Tokyo, Japan

S186. Predicting the Optimal Stimulation Frequency for Deep Brain Stimulation Patients

Anahita Khojandi, Oleg Shylo, Brian H. Kopell and **Ritesh A. Ramdhani**. Knoxville, TN and New York

S187. Applying Natural Language Processing (NLP) to Verbatim Patient-Reported Outcomes

Jennifer L. Purks, Michael Harris, Karen E. Anderson and Ira Shoulson. Washington DC

S188. Predictors of Neurobehavioral Outcomes in Bilateral Subthalamic Nucleus Deep Brain Stimulation Surgery

Michelle E. Fullard, Diane S. Huss, Matthew J. Barrett, Carol A. Manning, Scott Sperling, Binit Shah, Jeffrey Elias, Eric Turkheimer and Madaline B. Harrison. Philadelphia, PA and Charlottesville, VA

S189. A Novel Presentation of Post-Surgical Edema Associated with DBS Implantation with Review of the English Literature

Nancy Song and Mary S. Feldman. Lebanon, NH

Neuro-Oncology

S190. Analysis of Glioblastoma Physical Characteristics in Patients Benefiting from Tumor Treating Electric Fields Therapy

Pyay P. San, Joshua Timmons, Edwin Lok, Kenneth D. Swanson and **Eric T. Wong**. Boston, MA and Lowell, MA

S191. Temporal Trends and Outcomes of Acute Ischemic Stroke in Patients with Cancer of Brain and Nervous System

Arpita Hazra, Achint Patel, Harshil Shah, Marwa Elnazeir, Tushar Mishra, Mihir Dave, Srilatha Thadur, Varun Shah, Geoffrey Barger and Abdul Samad Zahid. Detroit

Behavioral Neurology

S192. Monogenic Disorders That Mimic the Phenotype of Rett Syndrome

Siddharth Srivastava, Sonal Desai, Julie Cohen, Kristin Baranano, Ali Fatemi and Sakkubai Naidu. Baltimore, MD

S193. Comparative Efficacy of Single-Agent and Combination Therapy with Midodrine and Pyridostigmine for the Treatment of Orthostatic Hypotension— Interim Analysis

Hye Rim Shin, Jung-Ick Byun and Jangsup Moon. Seoul, Republic of Korea

S194. Baseline Aphasia Severity Determines the Effect of Right Pars Triangularis Theta Burst Stimulation on Naming

Joely A. Mass, Denise Y. Harvey, Rachel Wurzman, Priyanka Shah-Basak, Olufunsho Faseyitan, Daniela L. Sacchetti and Roy H. Hamilton. Philadelphia, PA and Toronto, ON, Canada

Cerebrovascular Disease

S195. White Matter Hyperintensity Patterns Associated with Atrial Fibrillation in Embolic Ischemic Strokes

Yunis Mayasi, Johanna Helenius and Nils Henninger. Worcester, MA

S197. More Time Is Taken to Administer Intravenous Tissue-Plasminogen Activator (tPA) in Ischemic Stroke Patients with Earlier Presentations

Kyle C. Rossi, John W. Liang, Stanley Tuhim and Mandip S. Dhamoon. New York, NY

S198. Intra-Arterial ALD401 Cell Therapy Is Associated with Reduction in Stroke Volume at 90 Days in a Subset of the RECOVER-Stroke Trial

Kunakorn Atchaneyasakul, Sushrut Dharmadhikari, Charif Sidani, Kevin Ramdas, Luis Guada, Ryan Pafford, David Huang, Jim Hinson, Sean Savitz and Dileep Yavagal. Miami, FL; Chapel Hill, NC; Nashville, TN and Houston, TX

S199. Reading and Naming Recovery After Left PCA Stroke

Charliem Long, Rajani Sebastian, Cameron Davis, Amy Wright and Argye Hillis. Baltimore, MD

S200. Trends and Outcomes of Acute Ischemic Stroke in HIV-Positive Population (2002-2012)

Tushar Mishra, Harshil Shah, Zeeshan Mansuri, Mihir Dave, Arpita Hazra, Achint Patel, Sidra Rashid, Vishal Jani, Parth Mishra, Zabeen Mahuwala, Tapan Mehta and Teena Chopra. Detroit, MI and

S201. Proportion of Strokes Missed with the FAST Algorithm

Sushanth R. Aroor, Rajpreet Singh and Larry B. Goldstein. Lexington, KY

S202. Stent Retrievers versus Manual Aspiration for Treatment of Large Vessel Intracranial Occlusions: A Comparison Study

Hisham Salahuddin, **Wali Qayoumi**, Kaitlin Seibert, Amelia Heston, Usman Ashraf, Syed Zaidi and Mouhammad Jumaa. Toledo, OH

Epilepsy

S203. Sabril Vision Study: Retinal Structure and Function in Adult Patients with Refractory Complex Partial Seizures (rCPS) Treated with Vigabatrin

Jouko Isojarvi, Robert C. Sergott, Chris A. Johnson, Kenneth D. Laxer, Robert T. Wechsler, Yekaterina Dribinsky, JoAnn Whittle, Ge Feng and Deborah Lee. Deerfield, IL; Philadelphia, PA; Iowa City, IA; San Francisco, CA and Boise, ID

S204. Sabril Vision Study: Pharmacokinetic and Pharmacodynamic Analysis of the Effect of Vigabatrin on Taurine Plasma Concentrations

Dwain Tolbert, Stine Timmermann, Johan Areberg, Deborah Lee and JoAnn Whittle. Deerfield, IL and Copenhagen, Denmark

S205. Effect of Ketogenic Diets on Leukocyte Counts

Karisa C. Schreck, Roy E. Strowd, Bobbie J. Henry, Jaishri O. Blakeley and Mackenzie C. Cervenka. Baltimore, MD and Winston Salem, NC

S206. Brief Potentially Ictal Rhythmic Discharges (B(I)RDs) in the Non-Critically Ill Adults

Ji Yeoun Yoo, Lara V. Marcuse, Madeline C. Fields, Jillian Rosengard and Maria Traversa. New York, NY

S207. The Economic Impact of Epilepsy in Bhutan

Leah Wibecan, Veronica Bruno, Lhab Tshering, Sonam Deki, Damber K. Nirola, Megan B. Diamond, Chench Dorji, Günther Fink and Farrah J. Mateen. Boston, MA and Thimphu, Bhutan

S208. Phase I Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults

Julia Tsai, Jeffrey T. Guptill, David B. MacLeod, Aatif Husain and Albenia Patroneva. Radnor, PA and Durham, NC

S209. Use of Interpreter and Test Duration During IAP in Non-Native English Speakers

Heidi A. Bender, Jessica S. Spat, Ann DeSollar, Madeline Fields, Lara V. Marcuse, Emily Roman, Evelyn Ramirez-Coombs, Rebecca Bind, Lindsay A. Whitman, William B. Barr, Blanca Vazquez, Orrin Devinsky and Chad E. Carlson. New York, NY and Milwaukee, WI

Movement Disorder

S210. Measurement of Effect of Variable Deep Brain Stimulation Frequencies on Static Postural Control in Parkinson Disease (PD) Patients with Bilateral STN or GPi Stimulators by Employing Force Plate

Saulena Shafer, Abraham Lieberman, Aman Deep and Rohit Dhall. Phoenix, AZ

S211. How Long Is the Wait to See a Specialist in Parkinson's Disease in the United States?

Katherine Holmes, Karl Maki, Justin Martello and Stephen G. Reich. Baltimore, MD

S212. Medial Frontal 4 Hz Activity and Cognitive Symptoms of Parkinson's Disease

Nandakumar Narayanan. Iowa City, IA

S213. Application and Correlates of the Progressive Supranuclear Palsy Quality of Life Scale (PSP-QoL)

Lenora A. Higginbotham, Vanessa Johnson and Alexander Pantelyat. Baltimore, MD

Multiple Sclerosis

S214. Immunopathological Study of Glucose and Lactate Transporters in White and Gray Matter Lesions of Multiple Sclerosis and Neuromyelitis Optica

Katsuhisa Masaki, Satoshi O. Suzuki, Shotaro Hayashida, Mitsuru Watanabe, Takuya Matsushita, Ryo Yamasaki, Makiko Suzuki, Toshihiko Suenaga, Toru Iwaki and Jun-ichi Kira. Fukuoka, Japan; Hamamatsu, Japan and Tenri, Japan

S215. What Are Your Patients Not Telling You? Neurological Patients' Perspectives on the Role of Stigma vs. Coordination of Care Issues in the Sharing of Their Psychiatric Records

Alexis A. Adams-Clark, Alison Riehm, Caroline Franke, Steven Arenberg, Dominique Tosi, Kristen Hollinger, Kay Jamison and Adam Kaplin. Baltimore, MD

S216. Cognitive Impairment in Primary-Progressive Multiple Sclerosis: A Role for Functional Connectivity and Neuronal Variability Changes of Resting-State Activity?

Maria Petracca, Catarina Saiote, Heidi A. Bender, Francesca Arias, Colleen Farrell, Paola Magioncalda, Matteo Martino, Aaron Miller, Georg Northoff, Fred Lublin and Matilde Inglese. New York; Naples, Italy; Genoa, Italy and Ottawa, Canada

S217. DTI-Based Whole Brain Sulcal CSF Volume Is Associated with Cognitive Impairment in Multiple Sclerosis

Flavia Nelson, Zafer Keser, Benson Mwangi, Jerry S. Wolinsky, Ponnada A. Narayana and Khader M. Hasan. Houston, TX

Neurocritical Care

S218. High Compliance with Scheduled Nimodipine Is Associated with Better Outcome in Aneurysmal

Subarachnoid Hemorrhage Patients Co-Treated with Heparin Infusion

Aaron Wessell, Matthew Kole, Neeraj Badjatia, Gunjan Parikh, David Schreibman and J. Marc Simard. Baltimore, MD

S219. Added Value of Imaging Characteristics at 12-36 Hours in Predicting Potentially Lethal Malignant Edema

Charlene J. Ong, Jeffrey A. Gluckstein, Osvaldo Laurido-Soto, Rajat Dhar and Jin-Moo Lee. Boston, MA and St. Louis, MO

S220. Neurological Prognostication and Withdrawal of Life-Sustaining Therapy (WLST) Practices for Post-Cardiac Arrest Patients in a Single Academic Medical Center: A Retrospective Analysis

Mary M. Barden, Teddy S. Youn, Carolina B. Maciel, Sonya E. Zhou and David M. Greer. New Haven, CT

Cerebrovascular Disease

S221. Microvascular Brain Disease and Risk of Stroke: The Atherosclerosis Risk in Communities (ARIC) Study

Silvia Koton, **Andrea L.C. Schneider**, B. Gwen Windham, Thomas H. Mosley, Rebecca F. Gottesman and Josef Coresh. Tel Aviv, Israel; Baltimore and Jackson

S222. Is the Treatment Outcome from Thrombolysis for Acute Ischemic Stroke Different in Women versus Men?

Seung-Jae Lee and **Cheryl Bushnell**. Seoul, Korea and Winston Salem, NC

Movement Disorder

S223. Characterization of Vitamin B12 Supplementation and Clinical Outcomes in a Large Longitudinal Study of Early Parkinson's Disease

Chadwick Christine, Soeun Kim, Yunxi Zhang and Cameron Dietiker. San Francisco and Houston

S224. Analysis of MSA Patient iPSC-Derived Neural Cells with COQ2 Mutation

Fumiko K. Nakamoto, Satoshi Okamoto, Jun Mitsui, Shoji Tsuji and Hideyuki Okano. Tokyo, Japan

S225. The Astrocytic Transporter Slc7a10 (Asc-1) Mediates Glycinergic Inhibition of Spinal Cord Motor Neurons

Jeffrey T. Ebmsen, Yong Liu, Yue Wang, Nikhil Paladugu, Anna E. Johnson, Jeffrey D. Rothstein, Sasha du Lac, Mark P. Mattson and Ahmet Hoke. Baltimore

Neuro-Oncology

S226. The Folate Metabolism Pathway Polymorphism MTHFR C667T Increases the Risk of Methotrexate Myelopathy

Kelsey Juster-Switlyk, A. G. Smith, J. R. Singleton, Summer Brown and **Noah A. Kolb**. Salt Lake City, UT

S227. Postoperative Cognitive Status Testing in Brain Tumor Patients: A Review

Abraham Geller, Brooke Fortin, Hassan Dawood, Heloise Dubois and Timothy Smith. Boston, MA

S228. Distinguishing Pineoblastoma from Medulloblastomas Using Tissue Mass Spectrometry Imaging

David Calligaris, Armen Changelian, Frank Tranchese, Jessica Pierre Francois, Daniel Pomeranz Krummel, Jeffrey Agar, Matthew Schniederjan, Scott Pomeroy, Nathalie Y. Agar and **Soma Sengupta**. Boston; Atlanta and Waltham

Behavioral Neurology

S229. Immunoglobulin Class Switch of Anti-Glycolipid Antibodies in Neuroimmunological Diseases

Makoto Samukawa, Motoi Kuwahara, Miyuki Morikawa, Rino Ueno, Yukihiro Hamada, Kazuo Takada, Yoshiyuki Mitsui and Susumu Kusunoki. Osaka-Sayama, Osaka, Japan

S230. Adult Onset Leukodystrophy and Increased Survival as a Presentation of AARS2 Related Disease

Siddharth Srivastava, Sonal Desai, Andrea Poretti and Sakubai Naidu. Baltimore and Baltimore, MD

S231. A Novel PGRN Mutation Presenting as Progressive Aphasic Dementia and Evolving into Corticobasal Syndrome

Hugo Botha, Erin C. Golden, Mary M. Machulda, David S. Knopman, Rosa Rademakers and Bradley F. Boeve. Rochester, MN and Jacksonville, FL

S232. Dynamic Evolution of Hepatic Encephalopathy Suggestive of a Cerebral Vascular Shunt Phenomenon

Humaid Hasan, Divya B. Mella, Yun A. Coronado and Xiang Fang. Galveston, TX

S233. Burden and Outcomes of Acute Hemorrhagic Stroke in Patients with Major Depression

Zeeshan Mansuri, Achint Patel, Uvesh Mansuri, Ruchir Goswami, Girish Nadkarni, Zabeen Mahuwala, Tapan Mehta, Ashutosh Lodhi, Sanjeeva Reddy Onteddu, Narender Annapureddy and Sarah Noble. Philadelphia, PA

Cerebrovascular Disease

S234. Does Timing of Vessel Imaging for Suspected Large Vessel Occlusions Impact Reperfusion Time in Stroke Transfer Patients?

John W. Liang, Laura Stein, Natalie Wilson, Stanley Tuhim and Mandip S. Dhamoon. New York, NY

S235. Hispanic Patients Have Longer Door-To-Needle Times Independent of Age, Gender and Stroke Severity

Jonathan P. Cauchi, John W. Liang, Irene Boniece and Mandip S. Dhamoon. New York, NY

S236. Let7i Regulates Leukocyte Response in Patients with Acute Ischemic Stroke

Glen Jickling, Bradley P. Ander, Natasha Shroff, Dazhi Liu and Frank R. Sharp. Sacramento, CA

S237. Predictors of In-Hospital Ischemic Stroke During Acute Myocardial Infarction Hospitalizations

Arpita Hazra, Mihir Dave, Harshil Shah, Zeeshan Mansuri, Tushar Mishra, Achint Patel, Sonal Mehta, Abhishek Mishra,

Tamam Mohamad, Zabeen Mahuwala and Tapan Mehta. Detroit

S238. Impact of Weekend Admissions on Mortality and Discharge Disposition in Acute Ischemic Stroke: A Nationwide Perspective

Urvish K. Patel, Siddharth R. Bhesania, Mandip S. Dharmoon, Janki B. Patel, Abhi Pandhi, Liseth Lavado, Tapan Kavi, Sonal Mehta and Vishal B. Jani. New York; Los Angeles; Columbia and East Lansing

Epilepsy

S239. Characterization of High Frequency Oscillations in One Patient with Epilepsy

Alyssa Miller, Kentaroh Takagaki, Minsu Cho, Yong Won Cho and Gholam Motamedi. Washington, DC; Magdeburg, Germany and Taegu, Republic of Korea

S240. Intracranial Oscillatory Activity in Patients Performing an Object-in-Place Scene Memory Task

James J. Young, Peter Rudebeck, Madeline C. Fields, Lara V. Marcuse, Jiyeoun Yoo, Fedor Panov, Saadi Ghatan, Arash Fazl and Mark G. Baxter. New York, NY

S241. The Epilepsy Transition Care Gap in Young Adults with Childhood-Onset Epilepsy

Christine M. Baca, Frances Barry, Barbara G. Vickrey, Rochelle Caplan and Anne T. Berg. Los Angeles, CA; New York, NY and Chicago, IL

S242. Clinical Features of Geriatric Epilepsy: Does Age of Onset Make a Difference?

Golshan Fahimi, Hamid Rajebi and Rebecca O'Dwyer. Syracuse, NY and Derby, CT

Movement Disorder

S243. Investigating the Plastic Effects of Rapid Paired Associative Stimulation in Dystonia

Vesper Fe Marie Ramos, Prachaya Srivanitchapoom, Sanjay Pandey, Rainer Paine, Sabana Kukke, Nivethida Thirugnana-sambandam, Nguyet Dang, Tianxia Wu and Mark Hallett. Bethesda, MD

S244. In Parkinson's Disease Subcortical Connections Tighten as Impulsivity, Mood, and Dementia Worsen: A Network Study of Global and Local Efficiency in PD

Jared G. Hesse, Ihtsham U. Haq and Dale Dagenbach. Winston-Salem, NC

S245. The Role of Shooting Exposure in the Military and the Development of Progressive Supranuclear Palsy

Kristen D. Kelley, Harvey Checkoway and Irene Litvan. La Jolla, CA

S246. Early Onset Parkinson's Disease and Chromosome 22q11 Deletion: Case Report

Kelly A. Mills and Stephen G. Reich. Baltimore

S247. Progression of Dysphagia in Spinocerebellar Ataxia Type 6

Chiharu Isono, Makito Hirano, Hikaru Sakamoto, Shuichi Ueno, Susumu Kusunoki and Yusaku Nakamura. Sakai, Osaka, Japan and Osaka Sayama, Osaka, Japan

S248. Developmental Delay, Spasticity, and Progressive Generalized Dystonia in a Patient with Neurodegeneration with Brain Iron Accumulation Due to Mutations in COASY

Linn E. Katus, Rachel Fox, Allison Gregory, Susan J. Hayflick and Toni S. Pearson. New York, NY and Portland, OR

Multiple Sclerosis

S249. Fingolimod Has Diverse Effects on Gene Expression by Differentiating Human Neuronal Progenitors

Micheline McCarthy, Ricardo Martinez and Rebeca Geffin. Miami, FL

S250. Brain Reserve in Multiple Sclerosis: Larger Maximal Lifetime Brain Growth Is Linked to Later Age of Multiple Sclerosis Diagnosis

James F. Sumowski, Maria A. Rocca, Matilde Inglese, Victoria M. Leavitt, Alessandro Meani, Korhan Buyukturkoglu, Paolo Preziosa, Giancarlo Comi and Massimo Filippi. New York, NY and Milan, Italy

Neurocritical Care

S251. Subclinical Neuronal Injury in Good Grade Subarachnoid Hemorrhage

Halinder S. Mangat, Malik Fakhar, Xiangling Mao, Dikoma E. Shungu and Philip E. Stieg. New York, NY

Behavioral Neurology

S252. First Taste Syndrome

Nirmala Nagothu and Alan R. Hirsch. Willemstad, Netherlands Antilles and Chicago, IL

S253. Abstinence from Drug Dependence After Bilateral Globus Pallidus Hypoxic Ischemic Injury

Khaled Moussawi and Jong W. Lee. Boston, MA

S254. Sleep Spindle Activity in Children with Autism Spectrum Disorder (ASD)

Priyanka Chilakamarri, Cristan Farmer, Audrey Thurm, Susan Swedo, Scott A. Burroughs, Gregory L. Holmes and Ashura W. Buckley. Burlington, VT and Bethesda, MD

S255. Propranolol-Induced Psychosis in a Pediatric Patient

Ammar M. Alobaidy, Alicia Parker, Joseph R. Angelo and Lisa M. Nassif. Houston, TX

S256. Axon Guidance Factors and the Development of Psychosis

James A. Wilcox and David Briones. Tucson, AZ and El Paso, TX

S257. Factors Predicting Spontaneous Long-Term Recovery from Post-Stroke Aphasia

Denise Y. Harvey, Claire Healy, Myrna F. Schwartz and Roy H. Hamilton. Philadelphia, PA and Elkins Park, PA

S258. Effects of Cigarette Smoke and Nicotine on Behavioral, Motor and Memory Function and Nervous System Inflammatory Responses in an Animal Model of HIV-1 Infection

Walter Royal III, Todd Gould, Adem Can and Joseph Bryant. Baltimore, MD

S259. Temporal Trends in Drug Abuse in Young Adults with Acute Ischemic Stroke

Zeeshan Mansuri, Achint Patel, Uvesh Mansuri, Ruchir Goswami, Kinsuk Chauhan, Girish Nadkarni, Zabeen Mahuwala, Tapan Mehta, Narendra Annapureddy, Ashutosh Lodhi, Sanjeeva Reddy Onteddu and Sarah Noble. Philadelphia, PA

Cerebrovascular Disease

S260. Clinicopathologic Correlation in Lateral Medullary Stroke with Transient Ocular Motor Findings Mimicking Peripheral Vestibular Dysfunction

Jorge C. Kattah, Ali S. Saber-Tehrani, Sigrun Roeber, Meena Gujrati, Martin Sarah, David E. Newman-Toker and Anja K.E. Horn. Peoria, IL; Munich, Germany and Baltimore, MD

S261. MRI Biomarkers of Blood-Brain Barrier Disruption in Patients with Cerebrovascular Disease

Richard Leigh, Christian Dias, Marie Luby and Lawrence Latour. Bethesda, MD

S262. Low Serum Vitamin D Levels in Patients Presenting with Acute Stroke, a Case-Control Study

Elabe Bordbar, Abbas Rahimi Jaber, Mehdi Taghipour, Aliasghar Karimi, Alireza Gholamigari, Mojtaba Mahmoodi and Seyedeh Azra Shamsdini. Baltimore, MD; Shiraz, Fars, Islamic Republic of Iran; Baltimore, Fasa, Islamic Republic of Iran and Shiraz, Islamic Republic of Iran

S263. Focal Cortical Thinning in Unilateral Asymptomatic High Grade Carotid Artery Stenosis

Randolph S. Marshall, Iris Asllani, MaryKay A. Pavol, Alexander Farfad and Ronald M. Lazar. New York, NY and Rochester, NY

S264. Dynamic Regulation of DNA Methylation Following Perinatal Hypoxic-Ischemic Brain Injury

Ryan J. Felling, Thomas J. Robinson, Frances Northington and Hongjun Song. Baltimore, MD

S265. Modulation of Hippocampal Neurogenesis in the Global Brain Ischemia Model: Effects of p-tyrosol and Fluoxetine

Marina Yu Khodanovich, Alena A. Kisel, Galina A. Chernyshova, Vera I. Smol'yakova, Renata R. Savchenko, Mark B. Plotnikov and Vasily L. Yarnykh. Tomsk, Russian Federation and Seattle

S266. Trends and Outcomes for In-Hospital Ischemic Stroke in Acute Myocardial Infarction from 2002-2012: An Analysis of Nationwide Inpatient Sample Data

Harshil Shah, Achint Patel, Tushar Mishra, Zeeshan Mansuri, Arpita Hazra, Sagar Patel, Uvesh Mansuri, Tapan Mehta, Zabeen Mahuwala and Abhishek Mishra. Detroit, MI and Little Rock

S267. Infection Prior to Stroke—A Risk Factor or Trigger for Stroke?

Brett M. Kissela, Jane Khoury, Kathleen Alwell, Charles J. Moomaw, Daniel Woo, Matthew L. Flaherty, Simona Ferioli, Felipe De Los Rios La Rosa, Jason Mackey, Pooja Khatri, Sharyl Martini, Opeolu Adeoye and Dawn O. Kleindorfer. Cincinnati, OH; Indianapolis, IN and Houston, TX

Epilepsy

S268. Temporal Coordination of Hippocampal Place Cells Reflects Cognitive Outcome Post Febrile Status Epilepticus

Jeremy M. Barry. Burlington, VT

S269. Status Epilepticus in ITU: Epidemiology and 4 Year Follow Up in 39 Cases

Hina Khan and Violeta Sánchez Sánchez. Canterbury, United Kingdom

S270. Genome-Wide Long Non-Coding RNA Analysis in Mouse Pilocarpine Models of Temporal Lobe Epilepsy

Yoonhyuk Jang, Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea

S272. Cognitive, Behavioral and Social Functioning of a Child with Cardiofaciocutaneous Syndrome and Co-Occurring Leukemia: A Case Study

Jessica S. Spat, Hilary Murphy, Eva Keatley, Sarah Mandelbaum, Victoria Stein, Fawad Viqar, Erin Smity-Hyle, Jessica Suzuki, Amanda Bono, Caroline Martinez and Heidi A. Bender. New York, NY

Movement Disorder

S273. Comparison of Effect of Variable Deep Brain Stimulation (DBS) Frequencies on Gait and Balance in Parkinson Disease (PD) Patients with Either Bilateral GPi or STN Stimulators Employing Wearable Wireless Sensors

Aman Deep, Abraham Liebermna and Saulena Shafer. Phoenix, AZ

S274. Phenomenology and Treatment of Idiopathic Adult-Onset Truncal Dystonia

Debra J. Ehrlich and Steven J. Frucht. New York, NY

S275. Myoclonus in Adult Onset Huntington's Disease

Robert Fekete. Valhalla, NY

S276. Five Year Follow-Up: BMI Increase Is Not Associated with Deep Brain Stimulation in Early Stage Parkinson's Disease

Sarah H. Millan, Mallory L. Hacker, Anna L. Molinari, Maxim Turchan, Amanda D. Currie, Lauren Heusinkveld and David P. Charles. Nashville, TN

S277. Treating Orthostatic Tremor with Levetiracetam after Clonazepam Failure

Erin Feinstein, Winona Tse and Steven Frucht. New York, NY

S278. Analysis of the Minimum Data Set in a Long-Term Care Facility – Correlations with Spasticity Diagnosis

William S. Fisher, Taylor Hudson, Maxim Turchan, Amanda Currie, Chandler Gill, Anna Molinari, Fenna Phibbs, Christopher Tolleson, Mallory Hacker and David Charles. Nashville, TN and Chicago, IL

S279. Comparison of Improvement in Swallowing Functions Between Patients with Parkinson's Disease Treated with Rotigotine and Those with Levodopa

Makito Hirano, Chiharu Isono, Hikaru Sakamoto, Shuichi Ueno, Susumu Kusunoki and Yusaku Nakamura. Sakai, Osaka, Japan and Osaka Sayama, Osaka, Japan

S280. Baseline Characteristics of STEADY-PD III: A Phase 3 Study of Isradipine as a Disease Modifying Agent in Patients with Early Parkinson's Disease

Kevin Biglan, Jillian Lowell, David Oakes, Karen Hodgeman, Rebecca Rockhill, Brittany Greco and Tanya Simuni. Rochester, NY and Chicago, IL

Multiple Sclerosis

S281. Immunomodulatory and Neuroprotective Effects of Fingolimod Treatment in Multiple Sclerosis: Patients Modulation of the RAGE Axis

Zohara Sternberg, Channa Kolb, Kailash Chadha, Raphael Nir, Ryan George, Joseph Johnson and David Hojnacki. Buffalo, NY

S282. Superoxide Dismutase in Blood Plasma of Adrenoleukodystrophy Shows Phenotype Specific Reduction, Additionally Correlating with Cranial MRI Loes Score

Bela R. Turk, Ben Theisen, Mertz Christina, Carol Tiffany, Melissa Rosen, Xiao Hai Shi, Paul Watkins, Richard O. Jones, Joel Marx, Ann Moser and Ali Fatemi. Baltimore, MD

Neuro-Oncology

S283. Motor Axonal Neuropathy During Pembrolizumab Treatment of Metastatic Melanoma

Maria Sepulveda, Eugenia Martinez-Hernandez, Nuria Solà-Valls, Jordi Casanova-Molla and Francesc Graus. Barcelona, Spain

Behavioral Neurology

S284. Temporal Trends in Drug Abuse in Older Adults with Acute Hemorrhagic Stroke

Zeeshan Mansuri, Zabeen Mahuwala, Tapan Mehta, Ashutosh Lodhi, Girish Nadkarni, Uvesh Mansuri, Ruchir Goswami, Sanjeeva Reddy Onteddu, Sagar Patel and Sarah Noble. Philadelphia, PA

Cerebrovascular Disease

S285. Long-Term MRI Evaluation of Nicardipine for Leucoaraosis or White Matter Hyperintensities (WMH)

Senna William and Devathasan Gobinathan. Singapore, Singapore

S286. Geospatial Clustering of Patients Presenting to an Emergency Department with Known or Potential Ischemic Stroke

Daniel A. Dworkis and David A. Peak. Boston, MA

S287. Durability Over Time of Strategies to Reduce Door-to-Needle Times in Thrombolysis of Acute Ischemic Stroke

Aimen Moussaddy, Bing Yu Chen, Mark Keezer, Yan Deschaintre and Alexandre Y. Poppe. Montreal, QC, Canada

S288. Acute Video-Oculography for Vertigo in Emergency Rooms for Rapid Triage

David E. Newman-Toker, Vahid Eslami, Kathleen B. Quinlan, David S. Zee, Daniel R. Gold, John P. Carey, Ari Blitz, Hardin Pantle, Daniel A. Herzka, William V. Padula, Richard E. Rothman, Richard E. Thompson, Zheyu Wang, Joshua Betz, Jorge C. Kattah, John Hafner, Kevin A. Kerber, William J. Meurer, Cindy Guede, Janet Obear, Jacob Reiss, Daniel McGillicuddy, Rachel Dlugash, Jennifer Houser, Maningbe Keita, Karen Lane, Vanessa A. Llewellyn, Ryan Majkowski, Steven W. Mayo, Nichol McBee, Andrew W. Mould and Daniel F. Hanley. Baltimore, MD; Peoria, Chicago, IL; Michigan, MI and Ann Arbor, MI

S289. Segmental Arterial Mediolytic: A Rare Cause of Rapidly Progressive Intracranial Artery Dissections

David A. Lapidés, Mazen S. Abusamaan, Jonathan J. Davick, Aditya M. Sharma, James W. Mandell, Kenneth C. Liu, Javier J. Provencio, Bradford B. Worrall and Andrew M. Southerland. Charlottesville, VA

S290. Cerebral Vasoreactivity and Inflammation in Treated HIV Infection in Urban China

Joy Chan, Yanling Li, Yinghuan Hu, Huanling Wang, Weihai Xu, Farzaneh Sorond, Richard Price, Taisheng Li and Felicia Chow. San Francisco, CA; Beijing, China and Chicago, IL

S291. ABCD2 Score Use in Transient Ischemic Attack

Richa Tripathi, Waqar Hafeez, Deepmala Nandanwar, Maysaa Basha and Lakshmi Shankar. Detroit, MI

S292. Cerebral Infarction Secondary to Air Embolism Following Esophagogastroduodenoscopy

Gary P. Ho, Sarane A. Shepherd and Steven K. Feske. Boston, MA

S293. Door-To-Needle Times for IV TPA in Acute Ischemic Strokes and Stroke Mimics and Related Complications

Khalid Khalid, Sameer Sharma and Hesham Masoud. Syracuse, NY

S294. Temporal Trends and Outcomes of Intracerebral Hemorrhage in Cirrhotic Patients

Mihir Dave, Achint Patel, Arpita Hazra, Tushar Mishra, Zee-shan Mansuri, Parth Mishra, Sagar Patel, Uvesh Mansuri, Tapan Mehta, Zabeen Mahuwala and Vishal Jani. Detroit

S295. Embolic Stroke and DVT in a Patient with May-Thurner Syndrome and Homozygous PAI-Gene Polymorphism

Leila Montaser-Kouhsari, Yaojie Wu, John W. Liang and Kara F. Sheinart. New York, NY

S296. Do Language Barriers Cause a Delay in IV t-PA Treatment in Acute Stroke?

Hugo J. Aparicio, Shefali Dujari, Helena W. Lau, Judith Clark, Thanh N. Nguyen, Viken L. Babikian, Carlos S. Kase and Rafael J. Romero. Boston, MA

S297. Neurosyphilis and Antiphospholipid Antibodies in a Patient with Moyamoya Syndrome

Roman Kassa, Gauhar Chaudhary and Jessica Lee. Lexington, KY

Epilepsy

S298. Comparison of Serial Electroencephalography in Creutzfeld-Jakob Disease and Voltage-Gated Potassium Channel Autoimmune Encephalitides

Brin E. Freund, Mackenzie C. Cervenka, Peter W. Kaplan and John C. Probasco. Baltimore, MD

Movement Disorder

S299. An Updated Flowchart for the Diagnosis of Chorea
Ruth H. Walker. Bronx, NY and New York, NY

S300. Dried Blood Spot Glucocerebrosidase Measurement Is Reliable in Controls When Adjusting for White Blood Cell Count

Roberto A. Ortega, Olaf A. Bodamer, Holly Mergelsberg, Cuiling Wang, Amanda Glickman, Nancy Doan, Deborah Raymond, Jeffrey B. Ratliff, Jonathan Squires, Imali Perera, Anna Vaigast, Brooke Johannes, Susan B. Bressman and Rachel Saunders-Pullman. New York, NY; Boston, MA and Bronx, NY

Multiple Sclerosis

S301. Multiple Sclerosis with Hypothalamic Involvement: A Cold Diagnosis

Jason Ramirez and Geden Franck. Baltimore, MD

S302. Helping MS Patients Find Their Purpose in Life: A Pilot Study of the Effect of Participation in an Online Community

Laura Anzaldi, Alexis Adams-Clark and Adam Kaplin. Baltimore, MD

S303. The Pharmacokinetics of Lipic Acid at Baseline and 48 Weeks in Secondary Progressive Multiple Sclerosis Patients

Frank Bittner, Charles Murchison, Dennis Bourdette and Rebecca Spain. Portland, OR

Cerebrovascular Disease

S304. The Utility of INR to Predict Ischemia in Patients on Warfarin

Cathy Cao, Ashley Martinelli, Brian Spoelhof, Rafael H. Llinas and Elisabeth B. Marsh. Baltimore, MD

S305. Amphetamines Use in Adults with ADHD and Embolic Strokes of Undetermined Source; a Casual or Causal Relationship?

Karen Orjuela, Rochelle Sweiss and Jose Biller. Maywood, IL

S306. TOR1A Mutations Are Not Frequent in a Cohort of Parkinson's Disease Patients

Jeffrey B. Ratliff, Laurie Ozelius, Deborah Raymond, Jose Cabassa, Susan Bressman and Rachel Saunders-Pullman. New York, NY; Charlestown, MA and Brooklyn, NY

Multiple Sclerosis

S308. Internuclear Ophthalmoplegia Is a Potential Clinical Marker for Progression in Multiple Sclerosis

Alexis A. Lizarraga, Yesica A. Campos, Silvia Delgado, Leticia Tornes and Kottil W. Rammohan. Miami, FL

Neurocritical Care

S309. Fulminant West Nile Virus (WNV) Encephalitis in a Double Bilateral Lung Transplant Recipient: Case Report

Luka Vlahovic, Rochelle Sweis, Erin Lowery, Ewa Borys and Jose Biller. Maywood, IL

Neuro-Oncology

S310. Comparison of the Use of Volumetry vs Linear Height Measurements to Detect Changes in the Pituitary Gland Using 3D-T1W Non-Contrast MRI

Ramy Zaza, Reza Hakimelahi and Roy Riascos. Galveston, TX; Boston, MA and Houston, TX

S311. Status Epilepticus Secondary to Abrupt Diffuse Parenchymal Hemorrhage in a Patient with Miliary Cerebral Melanoma

Kathleen E. McKee, Mark R. Etherton and Farzaneh A. Sorond. Boston, MA and Chicago, IL

S312. Lower Extremity Spasms Resulting in Bilateral Femoral Fractures in Stiff Person Syndrome Patient

Nicholas R. Metrus, Sudhakar Tummala, Marta Penas-Prado, Monica Loghin, Merry Chen, Barbara O'Brien and Karin Woodman. Galveston, TX and Houston, TX

Cerebrovascular Disease

S313. Cofilin-1 as a Possible Therapeutic Target to Prevent Cognitive Sequelae in Cerebral Malaria

Simhadri Praveen Kumar and Prakash Babu Phanithi. Hyderabad, Telangana, India

S314. Pseudomastoiditis Secondary to Lateral Cerebral Sinus Thrombosis in the Setting of Norgestimate/Ethinyl Estradiol Oral Contraceptive (OCP) Use

Alok Sachdeva, Brian K. Erly, Shivam O. Mittal, Yasir Saleem and Wei Xiong. Cleveland, OH

S315. Cardiac Autonomic Dysfunction After Lacunar Stroke: Does Side Really Matter?

Pranith Kumar, Supriya Gupta, Raj Kapoor, Raghavan Samudrala and Brij Thukral. New Delhi, Delhi, India

S316. Vertebrobasilar Dolichoectasia- An Incidental Finding of a Rare Cause of Obstructive Hydrocephalus

Ali Shebaryar, Sridhara Yaddanapudi, Aparna M. Prabhu and Jonathan Dissin. Philadelphia, PA

S317. The Dilemma of Anticoagulation in Patients with Left Ventricular Assist Devices and Warfarin-Associated Intracerebral Hemorrhage

Chandler E. Gill, Rochelle Sweis and Jose Biller. Maywood, IL

S318. Hypothyroidism Presenting with Dysarthria and Intermittent Weakness of the Extremities

Alicia S. Parker, Ammar M. Alobaidy, Ekta Kakker, Nadeem Tajuddin, Son V. Nguyen, Vitor H. Pacheco and Liang Lu. Houston, TX

S319. An Interesting Case of Unilateral Central Retinal Vein Occlusion Leading to Cilio Retinal Artery Occlusion

Aiga Rakhbesh, Sanam Anwer and Carmen M. Martinez. Syracuse, NY

S320. Procedures Requiring General Anesthesia in Patients with Unruptured Intracranial Aneurysms

Vijayalekshmi V. Nair, Sameer Sharma, J. Thatcher, T. N. Nguyen and Hesham Masoud. Syracuse, NY and Boston, MA

S321. Use of the Computerized Causative Classification System for Ischemic Stroke in the Population-Based Framingham Study

Hugo J. Aparicio, Jayandra Jung Himali, Alexa S. Beiser, Mohammad Huq, John W. Cole and Sudha Seshadri. Boston, MA; Framingham, MA and Baltimore, MD

S322. The First Sign of Loss of Consciousness

Typ Whinnery and Estrella M. Forster. Oklahoma City, OK and Mustang, OK

S323. Burden and Outcomes of Acute Ischemic Stroke in Patients with Psychosis

Zeeshan Mansuri, Achint Patel, Zabeen Mahuwala, Uvesh Mansuri, Ruchir Goswami, Tapan Mehta, Sagar Patel, Sarah Noble, Ashutosh Lodhi, Girish Nadkarni and Sanjeeva Reddy Onteddu. Philadelphia, PA; New York, NY; Dallas, TX; Storrs, CT; Cleveland, OH and Fayetteville, AR

S324. Midbrain Stroke Mimicking Diabetic Third Nerve Neuropathy

Parvinder Kaur, Jared Noroozi, Adil Iqbal, Marks J. Stephens and Brij Ahluwalia. Valhalla, NY

Epilepsy

S325. Obesity in Adult Patients with Psychogenic Non-Epileptic Seizures

Abuhuzeifa Abubakar and Ilse P. Wambacq. Jackson, MS and Montclair, NJ

S326. New-Onset Epilepsy and Vitamin D Deficiency: A Case-Control Study

Riwaj Bhagat, Samyog Khatiwada and Ritesh Neupane. Bharatpur, Nepal; Biratnagar, Nepal and Chittagong, Bangladesh

S327. Isolated Transient Forced Gaze Deviation as Initial Presentation of Anaplastic Oligodendroglioma

Nicholas R. Metrus, Rahul Shah and Xiang Fang. Galveston, TX

Movement Disorder

S328. Symptomatic Isolated Tongue Tremor of Cortical Origin Due to Stroke

Smathorn Thakolwiboon, Doungporn Ruthirago, Pavis Laengvejkal, Jongyeol Kim and Henrik Wilms. Bangkok, Thailand and Lubbock, TX

Multiple Sclerosis

S329. Medication Use Patterns of Glatiramer Acetate 40 mg/mL in Patients with Multiple Sclerosis

Debra Irwin, Ying Wu, Katherine A. Cappell, Brian M. Davis, Augusto Grinspan and Sanjay K. Gandhi. Chapel Hill, NC; Frazer, PA; Ann Arbor, MI and Weston, FL

S330. Patient-Reported Treatment Satisfaction with Multiple Sclerosis Therapy After Switching from a More Frequent to a Less Frequent Injection Administration

Natalia M. Flores, Gary R. Cutter, Ying Wu, Sanjay Gandhi, Lulu K. Lee, Adriana J. Carra, Antonella Veneziano and Augusto Grinspan. Foster City, CA; Birmingham, AL; Frazer, PA; Buenos Aires, Argentina; Assago, Milan, Italy and Weston, FL

S331. Positive Effect of Natalizumab on Depression, as Assessed by BDI-II Scores in the SENTINEL Trial

Dominique M. Tosi, James Potts, Ryoko Susukida, Denise Campagnolo, Alexis A. Adams-Clark, Richard Rudick, Kristen Hollinger, Gisele von Buren and Adam I. Kaplin. Baltimore, MD and Cambridge, MA

Neurocritical Care

S332. Reemergence of Japanese Encephalitis in South Korea, 2010-2015

Jun-Sang Sunwoo, Jangsup Moon, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea

S333. Confirming Smear-Negative Central Nervous System Tuberculosis in a Comatose Patient: Case Report and Review of Literature

Carolina B. Maciel, Ashish Ranpura, Teddy S. Youn, Emad Nourollah-Zadeh, Jonathan Marebbian, Brinda Emu, Evadne Marcolini, Serena Spudich and David Y. Hwang. New Haven, CT

S334. Improvement in Midline Shift Is Associated with Survival after Decompressive HemiCraniectomy in Large Hemispheric Infarctions

Joanna I. Ramiro, Rajat Dhar, Eliahu Feen and Abhay Kumar. Saint Louis, MO

S335. Gabapentin Use to Decrease the Requirement of Intravenous Infusion Sedatives Among Patients with Acute Brain Injury in the Neurocritical Care Unit: A Case Series

Christa O'Hana V. San Luis and Xin Qi. Jackson, MS

S336. Low Cumulative Dose Propofol Precipitating Propofol Infusion Syndrome in an Intra-Cranial Hemorrhage Patient

Alok Dabi and Nicholas R. Metrus. Galveston, TX

Cerebrovascular Disease

S337. Post-Stroke Cognitive Impairment Predicted by Lesion and Functional Status

Richa Sharma, Wendy Chen, Rafael H. Llinas and Elisabeth B. Marsh. Baltimore, MD

Movement Disorder

S338. Remembering James Parkinson (1755-1824): His Historic Essay on the Shaking Palsy, and His Prodigious Eclectic Career as a "Physician for All Seasons"

David Roby, Alison Roby, Anusha Edara and Gary Horowitz. Philadelphia, PA and University Park, PA

Neuro-Oncology

S339. Leptomenigeal Carcinomatosis: A Rare Complication of Gastric Carcinoma

Aashrai Gudlavalleti, Siddharth Shah, Dalvir Gill, Ryan Asterita, Nibaal Saad and Sheila Lemke. Syracuse, NY

S340. A Rare CNS Infection in an Immunocompetent Adult Masquerading as a Metastatic Brain Tumor

Ali Sheharyar and Aparna M. Prabhu. Philadelphia, PA

S341. Extra-Cranial Metastatic Glioblastoma Presenting with Lhermitte's Phenomenon, Torticollis and Quadriparesis

Michael Ruff and Sean Pittock. Rochester, MN

Cerebrovascular Disease

S342. A Rare Case of Cerebral Venous Sinus Thrombosis Secondary to Danazol Therapy

Gobind P. Singh, Apoorv Prasad, Seyedali Hejazi, Armin Maghsoudlou and Carmen M. Martinez. Syracuse, NY

S343. Cerebral Venous Sinus Thrombosis (CVST) Associated with Methylenetetrahydrofolate Reductase (MTHFR) A1298C Mutation During Early Pregnancy: Case Report and Literature Review

Yongxing Zhou, Abhishek Anand, Faranak Najibi, Shariff Dunlap, Roger Weir and Annapurni Jayam-Trouth. Washington, DC

S344. Postpartum Cerebral Angiopathy Presenting with Intracerebral Hemorrhage-Possibly an Under Diagnosed Condition

Syed W. Abbas and Oleg Y. Chernyshev. Shreveport, LA

S345. Management Dilemmas Among Anticoagulated Patients with Intracranial Bleeding and Mechanical Heart Valves

Jorge Ortiz, Rochelle Sweis and Jose Biller. Maywood, IL

S346. Amphetamine Use Presenting as Bilateral Basal Ganglia Hemorrhage

Alyssa E. Bautista, Ima M. Ebong, Erika Marulanda-Londoño and Sebastian Koch. Miami, FL

S347. Thalamic Venous Infarcts: Etiology, Therapy and Outcome

Elina Zakin, John Liang, Gordon Cantor and Stanley Tuh-rim. New York, NY and Elmhurst, NY

S348. A Peculiar Case of Acute Vertebral Artery Dissection in the Setting of Newly Diagnosed Multiple Myeloma

Seyedali Hejazi, Gobind Singh, Armin Maghsoudlou and Gaganjot Singh. Syracuse, NY

S349. A Rare Presentation of Disseminated Cryptococcal Infection as Acute Stroke

Gobind P. Singh, Yi Mao, Varada Nair and Antonio Culebras. Syracuse, NY

Movement Disorder

S350. Enlarged Perivascular-Like Spaces at 3T as an MRI Sign of Multiple System Atrophy

Abhimanyu Mahajan and Christos Sidiropoulos. Detroit

S351. Identification a Novel De Novo Mutation of PRKCG in a Patient with SCA14 by Targeted Next-Generation Sequencing Technology

Wei Song, Yafang Hu, Xiaojia Liu and Suyue Pan. Guangzhou, China

Multiple Sclerosis

S352. Psychometric Evaluation of the Medication Satisfaction Questionnaire (MSQ) to Assess Satisfaction with Glatiramer Acetate Among Patients with Multiple Sclerosis

Lulu K. Lee, Ying Wu, Gary R. Cutter, Jeremy C. Hobart, Natalia M. Flores, Adriana J. Carra, Augusto Grinspan and Sanjay Gandhi. Foster City, CA; Frazer, PA; Birmingham, AL;

Plymouth, Devon, United Kingdom; Buenos Aires, Argentina and Weston, FL

S353. Understanding Seroconversion and Variability of Indices when Performing Serial JC Virus Testing in Patients with Multiple Sclerosis

John J. Peters and Eric M. Williamson. Philadelphia, PA

Neurocritical Care

S354. Septic Cavernous Sinus Thrombosis Secondary to Chronic Corticosteroid Use in a Cancer Patient

Narges Moghimi and Mary Chen. Galveston, TX and Houston, TX

Cerebrovascular Disease

S355WIP. The Importance of Anticoagulation to Prevent Strokes in Patients with Atrial Myxomas

Neeraj Singh and Kathleen Ward. Albany, NY

S356WIP. Pseudobulbar Affect Associated with Auto-immune Encephalitis

Neeraj Singh and Matthew Murnane. Albany, NY

Multiple Sclerosis

S357WIP. Cerebral Peduncle Angle: Unreliable in Differentiating Progressive Supranuclear Palsy from Other Neurodegenerative Diseases

Philip W. Tipton, Takuya Konno, Daniel F. Broderick, Dennis W. Dickson and Zbigniew K. Wszolek. Jacksonville, FL

S358WIP. Efficacy of IncobotulinumtoxinA in the Treatment of Equinovarus Foot in Adults

David M. Simpson, Djamel Bensmail, Astrid Scheschonka, Birgit Flatau-Baqué, Olivier Simon and Jörg Wissel. New York, NY; Garches, France; Frankfurt, Germany and Berlin, Germany

S359WIP. Jerky Dystonic Shoulder After Posterior Thalamic Infarction: Two Cases Report and Literature Review

Yongxing Zhou, Michael H. Pfeiffer, Amal Elhaj, Mohamed Ali-Eltom, Derrick Fox, Marshall S. Balish, Roger Weir and Annapurni Jayam-Trouth. Washington DC

S360WIP. Associations Between Brain Structure and Executive Function in Patients with Rapid-Onset Dystonia-Parkinsonism

Christopher T. Whitlow, Jared F. Cook, Beverly M. Snively, Kathleen J. Sweadner, Ihtsham U. Haq, Mark Stacy, Laurie J. Ozelius and Allison Brashear. Winston-Salem, NC; Boston, MA and Durham, NC

Neuro-Oncology

S361WIP. High Energy Intake from Dietary Fat Increases Relapse Rate in Early Pediatric Multiple Sclerosis

Saeedeh Azary, Teri Schreiner, Jennifer Graves, Amy Waldman, Anita Belman, Bianca Weinstock Guttma, Gregory Aaen, Jan-Mendelt Tillema, Soe Mar, Janace Hart, Jayne Ness,

Yolanda Harris, Lauren Krupp, Mark Gorman, Leslie Benson, Moses Rodriguez, Tanuja Chitnis, John Rose, Lisa F. Barcellos, Tim Lotze, Shelly Roalstad, Charles Casper and Emmanuelle Waubant. San Francisco, CA; Aurora, CO; Philadelphia, PA; Stony Brook, NY; New York, NY; Loma Linda, CA; Rochester, MN; St. Louis, MO; Birmingham, AL; Boston, MA; Salt Lake City, UT; Berkeley, CA and Houston, TX

S362WIP. Investigating the Role of Fibrinogen in Inflammatory Demyelination Using Combined MRI and Histopathology in the Marmoset Experimental Auto-immune Encephalomyelitis Model

Nathanael J. Lee, Seung-Kwon Ha, Nicholas J. Luciano, Emily Leibovitch, Jennifer Lefevre, Matthew K. Schindler, Pascal Sati, Afonso C. Silva, Katerina Akassoglou, Steven Jacobson and Daniel S. Reich. Bethesda, MD and San Francisco, CA

Behavioral Neurology

CD502. Clinicopathological Features of NCL Occur in Humans with Progranulin Haploinsufficiency

Michael E. Ward, Robert Chen, Hsin-Yi Huang, Connor Ludwig, Maria Telpoukhovskaia, Alice Taubes, Helene Boudin, Sakura Minami, Meredith Reichert, Philipp Albrecht, Jeff Gelfand, Andres Crus-Herranz, Marcel Alavi, Shannon Leslie, William Seeley, Bruce Miller, Eileen Bigio, Marsel Mesulam, Matthew Bogyo, Ian Mackenzie, John Staropoli, Susan Cotman, Eric Huang, Li Gan and Ari Green. Bethesda; San Francisco; Chicago; Palo Alto; Boston and Vancouver, Canada

Cerebrovascular Disease

CD503. Accuracy of Wearable Cameras to Track Social Interactions in Stroke Patients

Amar Dhand, Alexandra E. Dalton, Douglas A. Luke, Brian F. Gage and Jin-Moo Lee. St. Louis, MO and Hanover, NH

CD504. New Diagnosis of Cancer and the Risk of Subsequent Stroke

Babak B. Navi, George Howard, Virginia Howard, Hong Zhao, Suzanne E. Judd, Mitchell S.V. Elkind, Costantino Iadecola, Lisa M. DeAngelis, Hooman Kamel, Peter Okin, Susan G. Lakoski, Elsayed Z. Soliman, Mary Cushman and Paul Muntner. New York; Birmingham; Houston; Winston-Salem and Burlington

CD507. A Time Window of Heightened Plasticity to Training After Ischemic Stroke

Steven R. Zeiler, Kwan Ng, Robert B. Hubbard, Ellen M. Gibson, Tony Zheng, Richard J. O'Brien and John W. Krakauer. Baltimore, MD; Sacramento, CA and Durham, NC, United Kingdom

CD508. Cellular and Molecular Disruption of the Oligo-vascular Unit in Metabolic Syndrome and White Matter Stroke

Guanxi Xiao, Stefanie Nunez and Jason D. Hinman. Los Angeles, CA

CD510. ABCD1 Deficiency Causes White Matter Microvascular Perfusion Abnormalities

Patricia L. Musolino, Arne Lauer, Xiao Da, Mikkel Bo Hansen, Jayashree Kalpathy-Cramer, Kim Mouridsen, Bruce Rosen and Florian S. Eichler. Boston, MA; Charlestown, MA and Aarhus, Denmark

CD511. Differential Sex Response to Aspirin in Decreasing Aneurysm Rupture in Humans and Mice

David Hasan. Iowa City, IA

Epilepsy

CD512. Pathologic Mechanisms Underlying Hypomyelination Following Loss of TSC2 from Oligodendrocytes

Robert P. Carson, Mark D. Grier, Birttany Parker, Keliene Verdier and Kevin C. Ess. Nashville, TN

CD514. Neuronal Chloride Concentration Developmental Decrease Is Independent of Slicing Trauma in Thalamo-Cortical Brain Slices

Joseph Glykys and Kevin J. Staley. Boston, MA

CD515. Widespread Migration of Neurons in the Postnatal Human Frontal Cortex

Mercedes Paredes, David James, Sara Gil-Perontin, Hosung Kim, Jennifer Cotter, Carissa Nguyen, David Rowitch, Duan Xu, Jose Manuel Garcia-Verdugo, Eric Huang and Arturo Alvarez-Buylla. San Francisco, CA; Valencia, Spain and San Francisco, CA

CD516. Multimodal Biomarker Discovery in Childhood Epilepsy

Catherine J. Chu, Dan Song, Emily L. Thorn, Wenting Xie, Sydney S. Cash, Kevin Staley and Steven M. Struffebeam. Boston, MA

CD517. Using In Vivo Two-Photon Calcium Imaging to Probe the Dentate Gate Hypothesis of Epilepsy

Matthew Shtrahman, Thanh Tran, Shannon H. Kee, Bloyd Cooper, Johnston T. Stephen, Goncalves J. Tiago and Fred H. Gage. La Jolla, CA

Movement Disorder

CD519. Precisely Timed Optogenetic Inhibition of Dopaminergic Neurons During Motor Skill Acquisition in Rats

Damien J. Ellens, Matt Gaidica, Amy Hurst and **Daniel K. Leventhal**. Ann Arbor, MI

CD520. Contact Location and Non-Motor Outcomes in Subthalamic Deep Brain Stimulation for Parkinson Disease

Darlene P. Floden, Caio M. Matias, Conor A. Wathen, Grace E. Ozinga and Andre G. Machado. Cleveland, OH and Sao Paulo, Brazil

CD521. Synergistic Effects of Botulinum Toxin and Physical Therapy in Primary Cervical Dystonia

Aparna Wagle Shukla, Shanker Kulkarni, Jon Shuster, Michael Okun and David Vaillancourt. Gainesville

CD522. Connectivity and Behavioral Changes in Patients with Parkinson's Disease and Freezing of Gait

Gonzalo J. Revuelta, Rachael Deardorff, Aaron Embry, Clifford Chan, Shonna Jenkins, Logan Dowdle, Leonardo Bonilha, Daniel Lench, Steve Kautz and Jens Jensen. Charleston, SC and Charleston

CD523. Olfactory Deficits Predicts Abnormal Forebrain White Matter in Early PD: Support for the Braak Hypothesis of Spreading Pathology

Frank M. Skidmore, Glenn Brook, Thomas Anthony, Jon Marstrander, Yuliang Liu, Mitchel Horton, Chad Burdyschaw, Lonnie Crosby, Jungi Yin, Gary Cutter and David Standaert. Birmingham, AL and Oak Ridge, TN

CD524. Medial Frontal 4 Hz Activity and Cognitive Symptoms of Parkinson's Disease

Nandakumar Narayanan. Iowa City, IA

CD525. Neurodegeneration in a Novel PARK9/CLN12 Knockout Mouse

Michael C. Kruer, Helen Magee, Nadia Sahir, Lauren McBeth, Joshua Doorn, Elizabeth Jones, Marianna Madeo, Tyler N. Jepperson, Anna Yarrow, Chun-hung Chan, David A. Pearce and Jon Cooper. Phoenix, AZ; Sioux Falls, SD and London, United Kingdom

Multiple Sclerosis

CD527. Leptomeningeal Enhancement on 7T MRI in Multiple Sclerosis Is Associated with Cortical Gray Matter Atrophy

Daniel M. Harrison, Kevin Wang, Julie Fiol, Walter Royal III, Jun Hua and Izlem Izbudak. Baltimore, MD

CD529. Determining the Natural History of Alexander Disease: A Pilot Study

Amy T. Waldman, Geraldine Liu, Amy Lavery, Albee Messing and Adeline Vanderver. Philadelphia, PA and Madison, WI

Neuro-Oncology

CD532. Investigating Histone H3 Post-Translational Modifications Using Paraffin-Embedded Pediatric Glioma Tissue Samples

Amanda M. Saratsis, Tina Huang, Andrea Piunti, Rintaro Hashizume, Elizabeth Bartom, Tadanori Tomita, C. David James and Ali Shilatifard. Chicago, IL

Neurocritical Care

CD534. NMNAT3 Protects Neurons Against Neuronal Degeneration Following Neonatal Cerebral Hypoxia-Ischemia

Rafael Galindo, Marianne B. Greenberg, Toshiyuki Araki, Yo Sasaki, Nehali Mehta, Jeffrey Milbrandt and David M. Holtzman. St. Louis, MO and Kodaira, Tokyo, Japan

CD535. Sarm1 Knockout Attenuates Traumatic Axonal Injury and Improves Functional Outcome After Traumatic Brain Injury in Mice

Nils Henninger, James Boley, Elif M. Sikoglu, Jiyan An, Constance M. Moore, Jean A. King, Robert Bowser, Marc R. Freeman and Robert H. Brown. Worcester, MA and Phoenix, AZ

Autoimmune Neurology

M101. New Clinical and Immunological Features of Anti-GABAA Receptor Encephalitis

Marianna Spatola, Mar Petit-Pedrol, Myrna Rosenfeld, Francesc Graus and Josep Dalmau. Barcelona, Spain; Lausanne, Switzerland and Philadelphia, PA

M102. Antiglycolipid Antibodies in Neurological Diseases Subsequent to Mycoplasma Pneumoniae Infection

Susumu Kusunoki, Motoi Kuwahara, Makoto Samukawa, Miyuki Morikawa, Rino Ueno and Yukihiko Hamada. Osaka-Sayama, Osaka, Japan

M103. Anti-AQP4 Titer Is Not Predictive of Disease Course in Neuromyelitis Optica Spectrum Disorder

Remi A. Kessler, Maureen A. Mealy and Michael Levy. Baltimore, MD

Dementia and Aging

M104. Effect of Sleep Deprivation and Sodium Oxybate on CSF A β 40 and A β 42 Kinetics

Brendan P. Lucey, Terry J. Hicks, Jennifer S. McLeland, Cristina D. Toedebusch, Jill Boyd, Robert Swarm, Kwasi G. Mawuenyega, Vitaliy Ovod, Tom Kasten, John C. Morris and Randall J. Bateman. St Louis, MO

Health Services Research

M105. Trends and Regional Patterns of Care Associated with Hospice for US Stroke Inpatients, 2002-2011

Benjamin P. George, Adam G. Kelly, Bogachan Sahin, Eric B. Schneider and Robert G. Holloway. Rochester, NY and Boston, MA

Neuromuscular Disease

M106. Alpha-M Integrin (CD11b) Facilitates Pathogenic Leukocyte Trafficking in the Acute Inflammatory Demyelinating Polyradiculoneuropathy Variant of Guillain-Barré Syndrome

Eroboghene Ubogu, Steven Palladino, Rebecca Beacham, Eric Scott Helton and Chaoling Dong. Birmingham, AL

M107. Knockdown of a SMN-Associated Long Non-Coding RNA as a Novel Therapeutic Strategy for SMA

Constantin d'Ydewalle, Noah J. Pyles, Daniel Ramos, Celeste M. Pilato, Frank Rigo, Frank Bennett and Charlotte J. Sumner. Baltimore, MD and Carlsbad, CA

M108. Mechanism of Cytoplasmic Protein Aggregation and Neurodegeneration in Drosophila Models of C9-ALS/FTD

Ke Zhang, Kathleen Cunningham, Jonathan Grima, Jeff D. Rothstein and Thomas E. Lloyd. Baltimore, MD

Autoimmune Neurology

M109. Pathological Mechanisms of Glycine Receptor Antibodies

Sarah J. Crisp, John Rothwell, Angela Vincent and Dimitri M. Kullmann. London, United Kingdom and Oxford, United Kingdom

M110. A Novel Type of Autoimmune Encephalitis Associated with Neurexin-3 α Antibodies

Eugenia Martinez-Hernandez, Nùria Gresa-Arribas, Jesús Planagumà, Mar Petit-Pedrol, Thaïs Armangué, Francesc Graus and Josep Dalmau. Barcelona, Spain; Stockholm, Sweden; Madrid, Spain and Philadelphia, PA

M111. Phase II, Placebo-Controlled, Double-Blinded, Crossover Study of Extended-Release Dalfampridine in Monophasic Transverse Myelitis

Kathleen Zackowski, Kateryna Schwartz, Nicholas Wymes, Hua Huang, Allen Jiang, Daniel Becker, Pablo Celnick, Carlos A. Pardo, Maureen A. Mealy and Michael Levy. Baltimore, MD

M112. Tocilizumab Is Effective in Autoimmune Limbic Encephalitis Refractory to Weekly Rituximab

Jung-Ah Lim, Woo-Jin Lee, Soon-Tae Lee, Jun-Sang Sunwoo, Jung-Ick Byun, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Seon-Jae Ahn, Hye Rim Shin, Yoon Hyuk Jang, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea

M113. Tolerization Therapy Reduces Disease Frequency and Severity in Mouse Model of Neuromyelitis Optica

Melina V. Jones, Anne Semon and Michael Levy. Baltimore, MD

Dementia and Aging

M114. Characterization of Molecular Mechanism(s) Underlying ApoE4-Induced Brain Phospholipid Dysregulation in Alzheimer's Disease

Dongming Cai, Farida El Gaamouch, Li Zhu, Michael Ohlmeier, Gregory Elder, Christopher Cardozo and Vahram Haroutunian. New York, NY and Bronx, NY

Health Services Research

M115. Hospital Tax Status and Carotid Artery Stent Utilization in US Hospitals Performing Carotid Revascularization

Justin V. Chandler, Benjamin P. George, Adam G. Kelly and Robert G. Holloway. Rochester, NY

Neuromuscular Disease

M116. Intrathecal Autologous Adipose-Derived MSC Treatment for ALS: Results of Phase I and Design of Phase II Clinical Trials

Nathan P. Staff, Nicolas N. Madigan, Eric J. Sorenson, Mark E. Jentoft, Jonathan M. Morris, Allan B. Dietz, Dennis A. Gastineau and Anthony J. Windebank. Rochester, MN

M117. Fibronectin Connecting Segment-1 Peptide Modulates Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)-Patient Leukocyte Trafficking at the Blood-Nerve Barrier In Vitro and Chronic Demyelinating Neuritis in a Spontaneous Severe Murine Model of CIDP

Eroboghene Ubogu, Kelsey Greathouse, Steven Palladino, Rebecca Beacham, Chaoling Dong and Eric Scott Helton. Birmingham, AL

M118. NK and NKT Cells Are Increased in the Peripheral Blood of ALS Patients

Benjamin J. Murdock, Carey Backus, Stephen A. Goutman and Eva L. Feldman. Ann Arbor, MI

Autoimmune Neurology

M119. Cellularity: A Novel Neuroimaging Approach to Detecting Inflammation in HIV

Jeremy F. F. Strain, Tricia Burdo, Peng Sun and Beau Ances. Saint Louis, MO and Boston, MA

M120. Anti-LGI1 Encephalitis Is Associated with Unique HLA Class II Subtypes

Tae-Joon Kim, Soon-Tae Lee, Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Jin Sun Jun, Byoungsu Park, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seongnam, Republic of Korea and Seoul, Republic of Korea

M121. A Costly Condition: Assessing the Burden of Autoimmune Encephalitis at a Tertiary Institution from 2006-2015

Jesse Cohen, Javier Sotoca, John C. Probasco and Arun Venkatesan. Baltimore and Barcelona, Spain

Dementia and Aging

M122. Cardiac Vagal Tone Is Altered in Pre-Clinical Alzheimer's Disease

Cláudia Y. Santos, Jason T. Machan, Wen-Chih Wu and Peter J. Snyder. Providence, RI

M123. Electrostimulation Effects in lvPPA and nfvPPA

Kimberly T. Webster, Tushar Chakravarty, Bronte Ficek, Chiadikaobi Onyike, Constantine F. Frangakis, Argye E. Hillis and Kyrana Tsapkini. Baltimore, MD

M124. Novel Role of the Neurospecific SCF^{Fbx2}-E3-Ligase in Mechanisms Associated with the Promotion of Synaptic Plasticity Through Rescue of cAMP-CREB Signaling Pathway in a Model of Alzheimer's Disease

Bing Gong and Giulio M. Pasinetti. New York

M125. Increased microRNA-206 Levels in the Brain of Alzheimer's Disease Can Be Detected from Early Stage via Intranasal Biopsy of Olfactory Epithelium

Jangsup Moon, Soon-Tae Lee, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Korea

M126. Fewer Neurofibrillary Tangles and Slower Conversion to AD in MCI Patients Taking RAS Acting Antihypertensives

Whitney Wharton, Liping Zhao, Kyle Steenland, Marla Gearing and Felicia Goldstein. Atlanta, Ga

M127. Relationship Between Orthographic and Phonological Treatments with Brain Atrophy in PPA

Andreia V. Faria, Aaron Meyer, Rhonda Friedman, Donna Tippet and Argye B. Hillis. Baltimore, MD and Washington, DC

M128. A Genetic Study of a Large Pedigree with Late-Onset Alzheimer's Disease

Thomas S. Wingo, David J. Cutler, James J. Lah and Allan I. Levey. Decatur, GA and Atlanta, GA

M129. Alzheimer Disease Associated Presenilin 2 N141I Mutation Leads to Loss of Gamma-Secretase Function and Enhanced Pro-Inflammatory Behavior in Microglia

Susan Fung, Amanda Case, Carole L. Smith, Pete J. Amos, Bryce Sopher, Gwenn A. Garden and Suman Jayadev. Seattle, WA

Headache and Pain

M130. Ziprasidone as a Potential Abortive Treatment for Status Migrainosus

Eric C. Landsness, Leo H. Wang and Robert C. Bucelli. Saint Louis, MO and Seattle, WA

M131. Peripheral Neuropathic Changes in Pachyonychia Congenita

Baohan Pan, Kelly Byrnes, Mary Schwartz, C. David Hansen, Michael Caterina and Michael Polydefkis. Baltimore, MD and Salt Lake City, UT

M132. A Randomized Controlled Study Evaluating the Impact of Gabapentin, Gastroretentive Gabapentin, and Pregabalin on Daytime Function in Healthy Volunteers

Peter Schmidt, Christine Rocha and Srinivas Rao. Newark, CA

M133. Chemogenic Silencing of Nav 1.8 Nociceptors Reverses Neuropathic Pain and Small Fiber Degeneration in Painful Diabetic Neuropathy (PDN)

Nirupa D. Jayaraj, Bula Bhattacharyya, Ren Dongjun, Abdelhak A. Belmadani, Richard J. Miller and Daniela M. Menichella. Chicago, IL

Health Services Research

M134. Successful Reduction in Falls Among Neurology Outpatients After Initiation of a Fall Screening Program

William G. Buxton, Robin Clarke and Andrew Hackbarth. Los Angeles, CA

Interventional Neurology

M135. Amelioration of Peripheral Neuropathy in HFD-STZ Mice Through Dietary Reversal

Phillipe D. O'Brien, Lucy M. Hinder, John M. Hayes, Carey Backus, Elizabeth S. Bruno and Eva L. Feldman. Ann Arbor, MI

Neuromuscular Disease

M136. Direct Motor Neuron Transplantation Maintains the Regenerative Capacity of Chronically Denervated Peripheral Nerves

Christopher R. Cashman, Ruifa Mi and Ahmet Hoke. Baltimore, MD

M137. Response to IVIG in Patients with CIDP: The INSIGHTS Quality Improvement Project

Todd Levine, Jonathan Katz, Richard Barohn, David Saperstein, Gil Wolfe, Lara Katzin, Tahseen Mozaffar, Mazen Dimachkie, Gary Badger, Leslie Vaughan, **Elissa Ritt** and Michelle Greer. Phoenix, AZ; San Francisco, CA; Kansas City, KS; Buffalo, NY; Tampa, FL; Irvine, CA; Burlington, VT and Temecula, CA

M138. Cellular and Molecular Analysis of Corticospinal Motor Neuron Vulnerability in hTDP-43A315T Mice

Mukesh Gautam, Javier H. Jara, Ki Dong Kim and **Hande Ozdinler**. Chicago, IL

M139. Motor Neuron Disease with HIV infection: Activation of HERV-K and Response to Anti-Retroviral Therapy

Lauren N. Bowen, Richa Tyagi, Wenxue Li, Tariq Alfahad, Bryan Smith, Mary Wright, Elyse J. Singer and Avindra Nath. Bethesda, MD and Los Angeles, CA

M140. Microglial, pTDP43, and Neuronal Pathologies in the Brainstem and Spinal Cord of ALS Patients: Relationship to Site of Symptom Onset and Disease Duration

Matthew Cykowski, Suzanne Powell, Hidehiro Takei, Andreana Rivera, Joan Appel, Ellen Chang and Stanley Appel. Houston, TX

M141. CAT-1004, an Oral Agent Targeting NF- κ B: MoveDMD Trial Results in Duchenne Muscular Dystrophy (DMD)

Erika Finanger, Krista Vandenborne, Richard Finkel, H. Lee Sweeney, Gihan Tennekoon, Sabrina Yum, Maria Mancini, Jeff Danis, Pradeep Bista, Andrew Nichols and **Joanne Donovan**. Portland, OR; Gainesville, FL; Orlando, FL; Philadelphia, PA and Cambridge, MA

Sleep Disorders and Circadian Rhythm

M142. JZP-110, a Dopamine Norepinephrine Reuptake Inhibitor (DNRI), with Robust Wake-Promoting Effects and Low Abuse Potential

Michelle Baladi, Jed Black and Lawrence P. Carter. Palo Alto, CA; Redwood City, CA and Little Rock, AR

M143. Novel Application of Brain-Targeting Polyphenol Compounds in Promoting Resilience Against Sleep Deprivation-Induced Cognitive Dysfunction

Wei Zhao, Simoni Tiano and **Giulio M. Pasinetti**. New York Autoimmune Neurology

M144. Optimizing Immunoglobulin Dosing in Chronic Inflammatory Demyelinating Polyneuropathy

Lesley D'Albini, Lori Paulsen and Jill Nellis. St Louis, MO

M145. Treatment of Progressive Multifocal Leukoencephalopathy with Pembrolizumab, a PD-1 Inhibitor

Irene Cortese, Bryan Smith, Matthew Schindler, Joan Ohayon, Maria Chiara Monaco, Caroline Ryschkewitsch, Yoshimi Akahata, Steve Jacobson, Daniel Reich, Eugene Major and Avindra Nath. Bethesda

Dementia and Aging

M146. Differential Effects of IL-12, IL-23 and Their p40 Subunit on Alzheimer's Disease Pathogenesis, Cognitive Performance, and Brain Atrophy

Dimitrios Kapogiannis, Emmette Hutchison, Erez Eitan, Maja Mustapic, Mark P. Mattson and Edward J. Goetzl. Baltimore, MD

M147. Predicting Brain Amyloidosis Using Peripheral Blood-Based Gene Expression Measures

Kristy S. Hwang, Nicole Chow, Naira Goukasian, Kwangsik Nho, Andrew J. Saykin and Liana G. Apostolova. Rochester, MI; Irvine, CA; Los Angeles, CA and Indianapolis, IN

M148. Blood Pressure Trends in Mid-To-Late Life and Risk of Dementia

Emer R. McGrath, Alexa S. Beiser, Carole Dufouil, Genevieve Chene, Kendra L. Plourde and Sudha Seshadri. Boston, MA; Framingham, MA and Bordeaux, France

M149. Carotid Intima-Media Thickness, Plaque, and Cognition: The Northern Manhattan Study

Michelle R. Caunca, Hannah Gardener, Chuanhui Dong, Palma Gervasi-Franklin, Ying Kuen Cheung, Mitchell S.V. Elkind, Ralph L. Sacco, Tatjana Rundek and Clinton B. Wright. Miami, FL and New York, NY

Headache and Pain

M150. Migraine and Complex Regional Pain Syndrome: A Case-Referent Clinical Study

Yohannes W. Woldeamanuel, Corinne Cooley, Katharine Foley-Saldana and Robert P. Cowan. Stanford, CA

M151. Initial Diagnostic Criteria to Warrant Early Therapeutic Intervention in Complex Regional Pain Syndrome, Type 1, Reflex Sympathetic Dystrophy (CRPS/RSD)

Robert L. Knobler. Fort Washington, PA

Neuromuscular Disease

M152. Age-Dependent Painful Neuropathy in Metabolic Syndrome

Joseph F. Ward, Can Zhang, Jacqueline R. Dauch, Liam Cheng, Rudolph E. Tanzi and **Hsinlin T. Cheng**. Boston, MA and Ann Arbor, MI

M153. Is C9orf72 ALS Different from Sporadic Disease? A Comparative Study in an ALS Clinic Population

Mfon Umoh, Christina Fournier, Yingji Li, Meraida Polak, Latoya Shaw, William Hu, Marla Gearing and Jonathan Glass. Atlanta, GA

M154. Closed Loop Intracortical Brain Computer Interface Control in a Person with ALS Using a Filtered Gaussian Process Decoder

David M. Brandman, Michael C. Burkhart, Daniel J. Milstein, Jad Saab, Thomas Hosman, Anish A. Sarma, Brian Franco, John P. Donoghue, Matthew T. Harrison and Leigh R. Hochberg. Providence, RI; Boston, MA and Halifax, NS, Canada

M155. Canine Degenerative Myelopathy-An Emerging Disease Model for ALS

Raghav Govindarajan and Joan Coates. Columbia

M156. Genetic Deletion of Sarm1 Attenuates Vincristine-Induced Neuropathy in a Mouse Model

Stefanie Geisler, Ryan A. Doan, Amy Strickland, Jeffrey Milbrandt and Aaron DiAntonio. Saint Louis, MO

M157. Longitudinal Natural History of Orofacial Muscle Strength Changes in Amyotrophic Lateral Sclerosis Patients

Benjamin R. Brooks, Elena K. Bravver, Kathryn A. Wright, Mohammed S. Sanjak, William L. Bockenek, Velma L. Langford, Nicole M. Lucas, Tamara L. Sanders, Tiffany Williamson and Melissa Johnson. Charlotte, NC

Autoimmune Neurology

M158. FcγRI (CD64) Fc Receptors Are Expressed on CNS Neurons: A Potential Mechanism for Neuronal Immunoglobulin Uptake and Antibody-Mediated Neuronal Injury]

Suzanne C. Liu, Kenneth E. Hill, Susan A. Clawson, Blair Wood, Stacey L. Clardy, Noel G. Carlson and **John E. Greenlee**. Salt Lake City, UT

Dementia and Aging

M159. Levels of Hemostatic Factors in Middle Age and 20-Year Cognitive Change: The Atherosclerosis Risk in Communities (ARIC) Study

Aozhou Wu, Andreea M. Rawlings, A. Richey Sharrett, Josef Coresh, Aaron R. Folsom, Alvaro Alonso, Alden L. Gross, Andrea L.C. Schneider and Rebecca F. Gottesman. Baltimore, MD and Minneapolis, MN

Education

M160. Network for Excellence in Neuroscience Clinical Trials, NeuroNEXT: Increasing Efficiency in Clinical Trials

Marianne K. Chase, Dixie Ecklund, Michael Bosch, Brenda Thornell, Christopher Coffey and Merit Cudkowicz. Boston, MA and Iowa City, IA

Interventional Neurology

M161. Reasons for Failed Mechanical Thrombectomy: Initial Data from Two Tertiary Care Centers

Kaitlin Seibert, Hisham Salahuddin, Wali Qayoumi, Amelia L. Heston, Mouhammad Jumaa and Syed F. Zaidi. Toledo, OH

Sleep Disorders and Circadian Rhythm

M162. Sleep Disturbances Induced by Gastroesophageal Reflux Disease (GERD) in the US General Population

Maurice M. Ohayon and Cristina Milesi. Palo Alto, CA

M163 Outdoor Artificial Lights at Night Relate to Sleep Quality/Quantity and Circadian Rhythms Disorders

Maurice M. Ohayon and Cristina Milesi. Palo Alto, CA

Autoimmune Neurology

M164. Bowman Birk Protease Inhibitor Suppresses GM-CSF, Th17 Cells and CNS Autoimmune Inflammatory Demyelination

Farinaz Safavi, Zichen Li, Bogoljub Ciric, Javad Rasouli, Limei Wang, Guang-Xian Zhang and Abdolmohamad Rostami. Philadelphia and Towson

M165. Central Canal Enhancement and the Trident Sign in Spinal Cord Sarcoidosis

Nicholas L. Zalewski, Karl N. Krecke, Brian G. Weinshenker, Allen J. Aksamit, Brittani L. Conway, Andrew McKeon and Eoin P. Flanagan. Rochester, MN

M166. Functional Analysis of Cx30 in Experimental Autoimmune Encephalomyelitis

Ryo Yamasaki, Mei Fang, Hiroo Yamaguchi and Jun-ichi Kira. Fukuoka, Japan

M167. Abnormal Brain Metabolism on FDG-PET/CT Is a Common Early Finding in Autoimmune Encephalitis

John C. Probasco, Abhinav Nalluri, Krystyna M. Jones, Mehrbod S. Javadi, Lilja Solnes and Arun Venkatesan. Baltimore, MD

M168. Phase 1b, Open Label Study of Ublituximab in Acute Relapses of Neuromyelitis Optica Spectrum Disorder

Maureen A. Mealy and **Michael Levy**. Baltimore, MD

M169. Improving Detection of Neuronal Membrane or Synaptic Antibodies

Maxwell Greene, Lindsey Bandini, Junxian Zhang, Joyce Gonzalez, Elisabeth Burnor, Anne Crivaro, Malek Kamoun and Eric Lancaster. Philadelphia, PA

M170. Cerebrospinal Fluid Findings in Ebola Survivors with Neurological Sequelae

Bridgette Jeanne Billioux, Bryan Smith, Eric Stavale, Deborah Wentworth, Joseph Dorbor, Helen Tarfeh-Burnette, Elizabeth Higgs, Michael Sneller, Clifford Lane, Mosoka Fallah and Avindra Nath. Bethesda, MD; Ft Detrick, MD; Minneapolis, MN and Monrovia, Liberia

M171. Peripheral Nerve Autoantibodies in Acute and Chronic Autoimmune Neuropathies

Elisabeth A. Brunor, Li Yang, Steven S. Scherer, Michael P. Mei and Eric Lancaster. Philadelphia, PA and Hunan, China

M172. A Neuroinflammatory Precision Medicine Board: Leveraging Metagenomics and Proteomics to Advance Diagnosis of Meningitis and Encephalitis

Hannah A. Sample, Kristen L. McCaleb, Sam J. Pleasure, Charles Y. Chiu, Steve A. Miller, Jeffrey M. Gelfand, Michael D. Geschwind, Michael R. Wilson and Joseph L. DeRisi. San Francisco

Dementia and Aging

M173. Lipopolysaccharide (LPS) – Ischemia – Hypoxia Produces Amyloid-Like Plaques in Rat Brain and LPS Co-Localizes with Amyloid Plaques and Peri-Vascular Amyloid in Human Alzheimer's Disease Brain

Xinhua Zhan, Boryana S. Stamova, Bradley P. Ander, DaZhi Liu, Glen C. Jickling and Frank R. Sharp. Sacramento, CA

M174. Cortical Amyloid-beta and Slow Gait in Older Adults without Dementia: Influence of Cognition and APOE4 Genotype

Neelesh Nadkarni, Subashan Perera, Beth E. Snitz, Julie Price, Chester A. Mathis, Jeff D. Williamson, Steven T. DeKosky, William E. Klunk and Oscar L. Lopez. Pittsburgh, PA; Winston-Salem, NC and Jacksonville, FL

M175. An Interferon-Alpha Binding Protein Reverses Behavioral Impairments in a Mouse Model of HIV Associated Neurocognitive Disorders

William Tyor, Rajesh Koneru, Heather Bimonte-Nelson, Woldeab Haile, Vincent Ciavatta, Jennifer Ward and Leonard Maroun. Atlanta, GA; Tempe, AZ; Boston, MA and Grand Cayman, Cayman Islands

M176. Does tDCS Affect Non-Treated Language and Cognitive Functions in Primary Progressive Aphasia?

Bronte N. Ficek, Tushar Chakravarty, Kimberly Webster, Constantine F. Frangakis, Argye E. Hillis and Kyrana Tsapkini. Baltimore, MD

M177. Proton Pump Inhibitor Use Is Associated with Initial Diagnosis of MCI or AD in the www.Alzcenter.com Neurology Clinic

Heenaben Patel, Malini Nair and Anil K. Nair. Quincy, MA

M178. 90 Year Olds Are Less Likely to Fall If They Were Physically Active Two Decades Earlier: The 90+ Study

Dana E. Greenia, Annlia Paganini-Hill, S. Ahmad Sajjadi, Claudia H. Kawas and Maria M. Corrada. Irvine, CA

M179. The Hippocampal Network Model: A Neuroimaging Approach to Identifying Dementia Biomarkers

Eithan Kotkowski and Peter T. Fox. San Antonio, TX

M180. Preclinical Studies Targeting Toxic Tau Oligomers by Immunotherapy

Diana Castillo-Carranza, Julia Gerson, Urmi Sengupta, Kelly Dineley, Alan Barrett and Rakez Kaye. Galveston, TX

M181. Polygenic Risk Scores in Familial Alzheimer's Disease

Giuseppe Tosto, Thomas D. Bird, David A. Bennett, Bradley F. Boeve, Adam M. Brickman, Carlos Cruchaga, Kelley Faber, Tatiana M. Foroud, Martin Farlow, Alison M. Goate, Neil R. Graff-Radford, Rafael Lantigua, Jennifer Manly, Ruth Ottman, Roger Rosenberg, Daniel J. Schaid, Nicole Schupf, Yaakov Stern, Robert A. Sweet and Richard Mayeux. New York; Seattle; Chicago; Rochester; St Louis; Indianapolis; Jacksonville; Dallas and Pittsburgh

Education

M182. Diagnosing Bias in Physicians: The Influence of Language on Diagnostic Judgment

Megan Richie and Scott A. Josephson. San Francisco, CA

M183. The Neurology Clinic as a Training Model for Multiple Health Care Professions

Elena Shanina, Robert G. Smith, Karen Aranha, Jill Seale and Judith Rowen. Galveston, TX

M184. Observing the Effect of Online Educational Modules on Student Satisfaction with the Flipped Classroom

Chanel Wood, Krishan Chandar and Maureen McEnery. Cleveland, OH

Headache and Pain

M185. Headaches Among HIV+ Persons in Rural Rakai, Uganda

Deanna Saylor, Gertrude Nakigozi, Noeline Nakasujja, Kevin Robertson, Ronald H. Gray, Maria J. Wawer and Ned Sacktor. Baltimore, MD; Rakai, Uganda; Kampala, Uganda and Chapel Hill, NC

M186. Clinical Manifestations of Parvovirus B19 Encephalitis in Immunocompetent Patients

Jin Sun Jun, Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Byongsu Park, Seon-Jae Ahn, Hye Rim Shin, Yoon Hyuk Jang, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu Chu. Seoul, Republic of Korea

Health Services Research

M187. Post-Hospitalization Outcomes of Neurologic Inpatients Before and After Mandatory Follow-Up Appointment Scheduling

Alexandra Kvernland, Steven Bondi, Andre Son, Marissa Lanoff, Natali Baner, Peter Benedict, G. Kyle Harrold, Laura Balcer and Jori Fleisher. New York, NY

M188. Screening of Respiratory Virus PCR Panel in Adults with CNS Infection: Seoul Neuroinfection Registry

Seon-Jae Ahn, Jung-Ah Lim, Jang-Sup Moon, Jun-Sang Sun-Woo, Jung-Ick Byun, Tae-Joon Kim, Jin-Sun Jun, Byong-Su Park, Hye-Rim Shin, Yoon-Hyuk Jang, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang-Kun Lee and Kon Chu. Seoul, Korea

M189. Physician Satisfaction with Teleneurology Service Provided via Tablet Technology

Kelly Harper, Maxim Turchan, Derek Riebau, Amber Humphrey, Heather Meyers, Eli Zimmerman, Mark Baker and David Charles. Nashville, TN

Neuromuscular Disease

M191. Comprehensive Characterization of Muscle Disease in *Col6a2* Null Mice, a Novel Mouse Model of Collagen VI-Related Disorders

Payam Mohassel, Jachinta Rooney, Apurva Sarathy, Yaqun Zou and Carsten G. Bonnemann. Bethesda, MD

M192. Post-Exposure Vaccination of *M.leprae*-Infected Armadillos Does Not Exacerbate Peripheral and Cutaneous Sensory Nerve Involvement

Gigi J. Ebenezer, Richard W. Truman, Maria T. Pena, Kelly Cunningham, Michael Polydefkis and Malcolm S. Duthrie. Baltimore, MD; Baton Rouge, LA and Seattle, WA

M193. Effect of Amyloidosis on Small Sensory Nerve Fibers and Peripheral Nerve Function in Distal Leg of Patients with Transthyretin Familial Amyloid Polyneuropathy

Gigi J. Ebenezer, Ying Liu, Kelly Cunningham, Noel Carter, Blessan Sebastian, Kelly Byrnes and Michael Polydefkis. Baltimore, MD

M194. Inhibitory Synapses Formed by Human Spinal Cord Stem Cells: Reversing Excitotoxicity in ALS

Kevin S. Chen, Lisa M. McGinley, Osama N. Kashlan, Carey Backus, Crystal M. Pacut, Elizabeth S. Bruno, Josh S. Chang, Faye E. Mendelson, Maegan A. Tabbey, Samy R. Kashlan and Eva L. Feldman. Ann Arbor, MI

M195. Predicting Respiratory Insufficiency in Guillain-Barré Syndrome Using Clinical Presentation Characteristics and Electrophysiological Findings

K.H. Vincent Lau, Irene Yang, Amanda Lakraj, Daniel DiCapua and Richard Nowak. New Haven, CT

M196. An Assessment of Treatment Guidelines, Clinical Practices, Demographics, and Progression of Disease Among Individuals with Amyotrophic Lateral Sclerosis in Japan and the United States

Koji Takei, Manabu Hirai, Fumihiro Takahashi, Kikumi Tsuda and Joseph M. Palumbo. Jersey City, NJ and Tokyo, Japan

Autoimmune Neurology

M197. Neuromyelitis Optica and Neoplasia

Leticia Tornos, Nida Usmani, Luis Tornos, Silvia Delgado, Alexis Lizarraga, Kottil Rammohan and William Sheremata. Miami, FL

Interventional Neurology

M198. CT Angiography Delays Groin Puncture in Mechanical Thrombectomy for Large Vessel Occlusion in Stroke

Kunakorn Atchaneeyasakul, Anita Tipirneni, Priyank Khandelwal, Vasu Saini, Richard Ronca, Steven Lord, Luis Guada, Kevin Ramdas and Dileep Yavagal. Miami, FL

M199. The Role of Intestinal Microbiota in the Characterization of Novel Natural Drug Compounds in the Treatment of Major Depressive Disorder

Jun Wang, Jeremiah Faith, Lap Ho, Simoni Tiano and Giulio Pasinetti. New York

M200. Development of a Cerebral Angiography Calibration Model Based off of Relative Arterial Diameters

Maximilian J. Bazil, Christopher P. Kellner, J. D. Mocco and Johanna T. Fifi. New York, NY

Neuromuscular Disease

M201. INSIGHTS: Analysis of IVIG Responsiveness in Patients with Myasthenia Gravis

Todd Levine, Leslie Vaughan, Gary Badger, Gil Wolfe, Lara Katzin, David Saperstein, Tahseen Mozaffar, Richard Bahron, Jonathan Katz, Mazen Dimachkie, Michelle Greer and Elissa Ritt. Phoenix, AZ; Temecula, CA; Burlington, VT; Buffalo, NY; Tampa, FL; Irvine, CA; Kansas City, KS and San Francisco, CA

Sleep Disorders and Circadian Rhythm

M202. Hyperglycemia Is Associated with Autonomic Dysfunction During Sleep in Patients with Obstructive Sleep Apnea (OSA)

Amanda C. Peltier, Kanika Bagai, Rene Harder, Farhad Iqbal, Emily Garland, Beth Malow, David Robertson and Andre Diedrich. Nashville, TN

Autoimmune Neurology

M203. Quantitatively Decreased Visual Cortex Metabolism by FDG-PET/CT: An Early Biomarker of Acute Anti-NMDA Receptor Encephalitis

John C. Probasco, Abinav Nalluri, Krystyna M. Jones, Mehrbod S. Javadi, Lilja Solnes and Arun Venkatesan. Baltimore, MD

M204. Depletion of Abundant Sequences by Hybridization (DASH): Using Cas9 to Remove Unwanted High-Abundance Species to Enhance Microbial Detection via Next-Generation Sequencing (NGS)

Brian D. O'Donovan, Wei Gu, Emily D. Crawford, Michael R. Wilson, Eric D. Chow, Hanna Retallack and Joseph L. DeRisi. San Francisco

M205. Clinical Miller Fisher Syndrome in a Patient Who Received Botulinum Toxin A Injections

Daniel A. Graf, Rabul Shah and Todd Masel. Galveston, TX

Dementia and Aging

M206. CD4: CD8 Ratio Is Associated with Brain Subcortical Volume in Women with HIV Infection

Howard A. Crystal, Susan Holman, Diana Marcela Rojas-Soto, Deborah Gustafson, Yvonne W. Lui and Glenn T. Stebbins. Brooklyn, NY; NY, NY and Chicago, IL

M207. Protective Roles of Intestinal Microbiota in Alzheimer's Disease Through Mechanisms Involving Short Chain Fatty Acids and Phenolic Acids

Lap Ho, Jeremiah Faith, Kenjiro Ono, Simoni Tiano and Giulio M. Pasinetti. New York and Tokyo, Japan

M208. Cerebrovascular Disease Risk Factors, Arteriolar Sclerosis, and Cognitive Decline in the Kentucky Appalachian "Stroke-Belt"

Omar M. Al-Janabi, Ahmed A. Bahrani, Erin L. Abner, Charles D. Smith, Peter T. Nelson, Debra Moser and Gregory A. Jicha. Lexington, KY

M209. Clinical Characterization of Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia

Takuya Konno, Kunihiro Yoshida, Toshiki Mizuno, Toshitaka Kawarai, Masayoshi Tada, Hiroaki Nozaki, Shu-ichi Ikeda, Masatoyo Nishizawa, Osamu Onodera, Zbigniew K. Wszolek and Takeshi Ikeuchi. Jacksonville, FL; Niigata, Japan; Matsumoto, Japan; Kyoto, Japan and Tokushima, Japan

M210. The Relationship Between Mutations in the glucocerebrosidase1 (GBA1) Gene and Cognition in Non-Manifesting GBA1 Carriers

Eileen Moran, Mindy Katz, Laurie Ozelius, Robert Ortega, Alison Schwartz, Richard Lipton, Molly Zimmerman and Rachel Saunders-Pullman. Bronx, NY; Boston, MA and New York, NY

M211. NADPH Dehydrogenase Quinone 1 (NQO1) Demonstrates Increased Expression and Pathologic Aggregation in Glial Cells in Chronic Traumatic Encephalopathy

Chadwick Hales, Ahmad Zeineddin, James Webster, Jon Giuliano, Duc Duong, Nicholas Seyfried, Eric Dammer, Ann McKee, Allan Levey and James Lah. Atlanta, GA and Boston, MA

M212. RNA Destabilization in Amyotrophic Lateral Sclerosis and Frontotemporal Lobar Dementia

Sami Barmada, Hilary Archbold, Elizabeth Tank, Xingli Li, Michelle Paulsen and Mats Ljungmann. Ann Arbor, MI

M213. Neurodegeneration-Like Pathological and Behavioral Changes in a AAV9-Mediated p25 Overexpression Mouse Model

Xiao Zhou, Yafang Hu, Suyue Pan, Jianou Huang, Rongni He, Miaojin Xu and Zhong Ji. Guangzhou, China

M214. Simple Test of Manual Dexterity Can Identify Persons at High Risk for Neurodegenerative Diseases in the Community

Sirwan K.L. Darweesh, Frank J. Wolters, Bruno H. Stricker, Albert Hofman, Peter J. Koudstaal and M. Arfan Ikram. Rotterdam, Netherlands and Boston, Netherlands

Education

M215. Clinician-Defined Case Mix on an Academic Inpatient Neurology Service

Robert C. Bucelli, Arun Varadhachary, Gabriela de Bruin and Amar Dhand. St. Louis, MO

M216. Structured Preparation of Neurology PGY3 Residents for Participation in Medical Education Benefits Them as Teachers and Learners

Maureen W. McEnery, David D. Friel, Charles J. Malemud, Patricia Marshall and Chanel Wood. Cleveland, OH

Headache and Pain

M217. Post Partum Bilateral Abducens Nerve Palsy

Advait Mahulikar, Justin Bedford and Evanthea Bernitsas. Detroit, MI

M218. The Effect of Propofol on the Pain and Frequency of Chronic Headaches

Robert T. Knipe, Matthew Wicklund, David Giampetro, Amy Welch, Joseph Nguyen and Ashlee Pruett. Hershey, PA

M219. Diplopia in Children's Headache Drawings Differentiates Pseudotumor Cerebri from Migraine

Erica B. Lee and Carl E. Stafstrom. Baltimore, MD

Health Services Research

M220. Cultural and Contextual Appropriateness of the NIHSS Naming List Test Among Stroke-Free Urban Blacks

Madeleine Gordillo. New York, NY

Neuromuscular Disease

M221. De Novo PMP2 Mutations in Families with Type 1 Charcot-Marie-Tooth Disease

Steven S. Scherer, Paulis Palaima, Sabrina W. Yum, Michael A. Gonzalez, Feifei Tao, Julia V. Wanschitz, Alleene V. Strickland, Wolfgang N. Löscher, Els De Vriendt, Stefan Koppi, Liviya Medne, Andreas Janecke, Alben Jordanova, Stephan Zuchner and William W. Motley. Philadelphia, PA; Antwerpen, Belgium; Miami, FL; Innsbruck, Austria and Rankweil, Austria

M222. Understanding Molecular Basis of the Interplay Between Vulnerable Upper Motor Neurons and Innate Immunity

Hande Ozdinler. Chicago, IL

M223. Targeting Safe Harbor Genomic Loci with Transcription Activator-Like Effector Nuclease (TALEN) Technologies to Produce Clinical-Grade Autologous Mesenchymal Stem Cell Therapies for Amyotrophic Lateral Sclerosis

Nicolas N. Madigan, Soneela Ramesh, Karl J. Clark, Michael J. Polzin, Mary L. Maas, Douglas J. Padley, Allan B. Dietz,

Stephen P. Ekker, Anthony J. Windebank and Nathan P. Staff.
Rochester, MN

M224. Identification of a Post-Translational Modification with Ribitol-Phosphate and Its Defect in Muscular Dystrophy

Tatsushi Toda, Motoi Kanagawa, Kazuhiro Kobayashi, Michiko Tajiri, Hiroshi Many, Atsushi Kuga, Yoshiki Yamaguchi, Yoshinao Wada and Tamao Endo. Kobe, Japan; Osaka, Japan; Tokyo, Japan and Wako, Japan

M225. Spectrum of Non-Dystrophic Pediatric Muscle Channelopathies

Partha S. Ghosh and Fouad A. Alghamdi. Boston, MA

M226. Diverse Etiologies of Hyperckemia in Children

Fouad A. Alghamdi and Partha S. Ghosh. Boston, MA

M227. Hematopoietic Stem Cell Transplantation for Adolescent/Adult Cerebral and Olivo-Ponto-Cerebellar Adrenoleukodystrophy

Takashi Matsukawa, Tomotaka Yamamoto, Takashi Toya, Akihito Shinohara, Yasuhito Nanya, Sachiko Seo, Keiki Kumano, Motoshi Ichikawa, Yuji Takahashi, Hiroyuki Ishiura, Jun Mitsui, Masaki Tanaka, Mineo Kurokawa and Shoji Tsuji. Bunkyo-ku, Tokyo, Japan

M228. Familial Inclusion Body Myositis Associated with Digenic Inheritance of Mutations in Valosin-Containing Protein and Filamin C

Elizabeth H. Michelle, Christine Castro, Ivona Aksentijevich, Adam Schifffenbauer, Qing Zhou, Elaine F. Remmers, Zuoming Deng, James D. Katz, Ami Mankodi, Daniel Kastner, Andrew Mammen, Conrad C. Weihl, Richard Siegel and Thomas E. Lloyd. Baltimore, MD; Bethesda, MD and St. Louis, MO

M229. Quantification of Proximal Nerve Pathology in Charcot-Marie-Tooth Diseases via Magnetization Transfer MRI

Richard D. Dortch, Lauren Brooks and Jun Li. Nashville, TN

M230. Clinical and Electrodiagnostic Correlations of Paraproteinemic Neuropathies

Annie Daniel and **Agnes Jani-Acsadi**. Farmington, CT

Autoimmune Neurology

M231. Transverse Myelitis in Veterans

Verena C. Samara, Michael Sweeney, Haley Carlson, M. Mateo Paz Soldan, John E. Greenlee, Noel G. Carlson, John W. Rose and Stacey L. Clardy. Salt Lake City, UT

M232. The Burden of Neuromyelitis Optica Spectrum Disorder on Patients' Quality of Life

Maureen A. Mealy, Alexandra Simpson, Dorlan J. Kimbrough and Michael Levy. Baltimore, MD and Boston, MA

M233. The Etiology of Acute Encephalitis in Korean Population

Tae-Joon Kim, Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea and Seongnam, Republic of Korea

M234. Recurrent Asystole in Paraneoplastic anti-N-methyl-D-aspartate Receptor Encephalitis Necessitating Permanent Pacemaker Placement

Prachi Parikh and Jinny Tavee. Cleveland, OH

Dementia and Aging

M235. Cognitive Impairment in Spinal Cord Injury: Impact on Quality of Life and Activity Limitation

Krishnan P.S. Nair, Ceri Houldsworth, Ram P. Hariharan and Daniel Wilson. Sheffield, South Yorkshire, United Kingdom

M236. Hypoxia Inducible Factor 1 α Mediates Neuroprotective Role in Rat Model of Chronic Cerebral Hypoperfusion

Ying Yang, Junjian zhang, Min Deng, Jing Wang and Li Xiong. Wuhan, Hubei, China

M237. Clip Test: Manipulospacial and Language Correlates

Yutaka Tanaka, Martin L. Albert, Dalia Cahana-Amitay, Midori Tanaka and Tomomi Yamada. Ikoma-Gun, Nara, Japan; Boston, MA and Suita, Osaka, Japan

M238. Proximal Middle Cerebral Artery Velocity Is Associated with Mean Diffusivity on Brain MRI in Women with HIV

Howard A. Crystal, Alison E. Baird, Hua Yu, Diana Marcela Rojas-Soto, Susan Holman, Yvonne W. Lui, Deborah Gustafson and Glenn T. Stebbins. Brooklyn, NY; New York, NY and Chicago, IL

M239. White Matter Differences Between Dementia with Lewy Bodies and Parkinson's Disease: A Diffusion Tensor Image Study

Jingping Shi, Dayong Sun, Donglin Zhu and Chaoyong Xiao. Nanjing, Jiangsu, China

M240. Alabama Brief Cognitive Screener Demonstrates a Factor Structure Similar to the MMSE and Shows High Levels of Internal Consistency at Multiple Levels

Marissa C. Natelson Love, Giovanna Pilonieta and David S. Geldmacher. Birmingham, AL

M241. The Robotic Assistant for MCI Patients (RAM-CIP) with Proactive Functions

Konrad Rejdak, Sebastian Szklener, Agnieszka Korchut, Gerlowska Justyna, Urszula Skrobas, Katarzyna Grabowska, Carla Abdelnour, Natalia Tantinyà, Hernández Joan, Joan C. Ribes, Dimitrios Tzovaras and RAMCIP Group. Lublin, Poland; Barcelona, Spain and Thessaloniki, Spain

Education

M242. U.S. China Neurology Exchange Program to Improve Clinical Practice, Research, and Global Relationships

Antonio Moya, Richard Isaacson and Dexter Sun. New York, NY

Headache and Pain

M243. Bilateral Cisternal Abducens Nerve Involvement with Ophthalmoplegic Migraine

Richa Tripathi and Evanthia Bernitsas. Detroit, MI

M244. Trigeminal Neuralgia with TS-HDS Antibodies

Syeda Alqadri and Raghav Govindarajan. Columbia

M245. Acceptability of Placebo in Cluster Headache Clinical Trials: A Patient Survey and Literature Review

Melissa L. Rayhill, Brian E. McGeeney and Elizabeth W. Loder. Buffalo, NY; Boston, MA and Jamaica Plain, MA

Health Services Research

M246. Using Telemedicine to Improve Access to Specialty Care for Underserved Patients with Neurodevelopmental Disorders

Deepa U. Menon, Vini Singh and Lana Warren. Baltimore, MD

M247. Should There Be Public Reporting of Acute Stroke Outcome Data?

Nirav Bhatt, Amer Malik, Negar Asdaghi, Jose Romano, Dileep Yavagal, Seemant Chaturvedi and Ralph Sacco. Miami, FL

M248. Does Headache Neuroimaging Reduce Time to Glioma Diagnosis? A Cohort Study Using a Comprehensive Claims-Based Database

James F. Burke, Kevin A. Kerber, Lesli E. Skolarus and Brian C. Callaghan. Ann Arbor, MI

M249. Validation of a Cognitive Testing Battery Using a Mobile, Tablet-Based Software Package: Defense Automated Neurobehavioral Assessment (DANA)

Kristen R. Hollinger, Alexis Adams-Clark, Dominique Tosi, Steven Woods and Adam I. Kaplin. Baltimore, MD

Interventional Neurology

M250. Hypothyroidism is Associated with Cerebral Aneurysms in Women

Kunakorn Atchaneeyasakul, Anita Tipirneni, Tony Zhang, Priyank Khandelwal, Brian Snelling, Sushrut Dharmadhikari, Sudheer Ambekar, Kevin Ramdas, Luis Guada and Dileep Yavagal. Miami, FL

M251. Effect of Hypothyroidism on Unruptured Cerebral Aneurysm Dimensions and Endovascular Coiling Outcome

Kunakorn Atchaneeyasakul, Anita Tipirneni, Tony Zhang, Priyank Khandelwal, Luis Guada, Kevin Ramdas, Sushrut Dharmadhikari, Sudheer Ambekar, Brian Snelling and Dileep Yavagal. Miami, FL

M252. Safety Outcome of Carotid Artery Stenting in Long Carotid Lesion with Proximal versus Distal Embolic Protection Devices

Vasu Saini, Kunakorn Atchaneeyasakul, Sudheer Ambekar, Kevin Ramdas, Luis Guada and Dileep R. Yavagal. Miami, FL

Neuromuscular Disease

M253. Castleman's Disease Neuropathies

Michelle L. Mauermann, Elie Naddaf, Jay Mandrekar and Angela Dispenzieri. Rochester

M254. Co-Morbid Pain Syndromes in HIV-Associated Peripheral Neuropathy

Jessica Robinson-Papp, Jocelyn Jiao, Eric So, Jebakaran Jebakumar, Mary Catherine George and David M. Simpson. New York, NY

M255. Changes in Clinical Outcome Measures in a Longitudinal Prospective Natural History Study of C9orf72 Mutation Carriers

Mary Kay Floeter, Jennifer Farren, Laura E. Braun, Bryan J. Traynor, Zachary Gala, Devin Bageac, Michael Tierney and Edythe Wiggs. Bethesda, MD

M256. Guillain-Barre Like Syndrome: A Manifestation of Nelarabine Therapy

Bushra Javed, Prachi Kale, Anila Thomas and Brij Singh Ahluwalia. Valhalla, NY

M257. Obesity Attenuates Epidermal Nerve Fibers in the Distal Limb

Gigi J. Ebenezer, Shaun Truelove and Michael Polydefkis. Baltimore, MD

M259. Systematic Approach of the Clinical, Serological and Histological Findings in a Cohort of Inclusion Body Myositis

Rey N. Bello, Tulio Bertorini, Lehong Shen and Olivia Yambem. Memphis, TN

M260. Neurolymphomatosis: A Review of 82 Cases

Jose David Avila and Carolina Vivar. St. Louis, MO and Danville, PA

M261. Tracking Nerve Health Following Implantation of Bilateral Femoral Nerve Cuff Electrodes (NCEs)

Max J. Freeberg, Gilles C. Pinault, Ronald J. Triolo and Rabila Ansari. Cleveland, OH

Sleep Disorders and Circadian Rhythm

M262. Results from a Clinician Survey Rating the Use and Utility of the Swiss Narcolepsy Scale

Markus Schmidt, Christian Sturzenegger, Ulf Kallweit and Ann Kim. Bern, Switzerland; Dublin, OH; Zurich, Switzerland and Palo Alto, CA

M263. Case Report: Beneficial Effect of Treatment of Obstructive Sleep Apnea on Neuropathy Symptoms in a Patient with CMT-Type 1A- A Case Report

Pinar Polat, Huong Pham, Jun Li and Kanika Bagai. Nashville, TN

M264. Comorbidity and Mortality in a Longitudinal Study of Narcoleptics' Family Members

Maurice Ohayon and Cristina Milesi. Palo Alto, CA

Autoimmune Neurology

M265. Recurrent Guillain Barre Syndrome Associated with Herpes-Zoster Attack-A Case Report

Syed W. Abbas and Robert N. Schwendimann. Shreveport, LA

Dementia and Aging

M266. A Case of Alice in Wonderland Syndrome Due to Heidenhain Variant of CJD

Emer R. McGrath, Ayush Batra, Alice D. Lam, Joseph F. Rizzo and Andrew J. Cole. Boston, MA

M267. Whole Exome Sequencing in an Early Onset ADRC Dementia Cohort

Suman Jayadev, Malia Rumbaugh, Christopher Hale, David S. Hanna, Elaine Peskind, Debby Tsuang and Tom D. Bird. Seattle, WA

Education

M268. Ezio Sciammana, Early Progenitor of Cortical Mapping

Anthony L. Ritaccio and Sara Casciato. Albany, NY and Rome, Italy

Headache and Pain

M269. Burning Mouth Syndrome with Subjective Hyperosmia, Hyposmia, Hypogeusia

Sumit Kanwar, Manisha R. Chand, Malinda Walford and Alan R. Hirsch. Weston, FL; Willemstad-Curacao, Netherlands Antilles and Chicago

Health Services Research

M270. Association Between Counseling and Patient-Reported Treatment Adherence in Epilepsy

Lidia M.V.R. Moura, Emily L. Thorn, Thiago S. Carneiro, Michael P. Seitz, Andrew J. Cole, Barbara G. Vickrey and Daniel B. Hoch. Boston, MA and New York City, NY

M271. Role of Pre-Stroke Major Depressive Disorder in the High Prevalence of DNR (Do Not Resuscitate) Utilization in Acute Hemorrhagic Stroke

Zeeshan Mansuri, Achint Patel, Tapan Mehta, Girish Nadkarni, Uvesh Mansuri, Sarah Noble, Zabeen Mahuwala, Ashutosh Lodhi, Ruchir Goswami and Sanjeeva Reddy Onteddu. Philadelphia, PA and Fayetteville, AR

Neuromuscular Disease

M272. Ambulatory Blood Pressure Monitoring in Orthostatic Hypotension and Postural Orthostatic Tachycardia Syndrome

Jun-Sang Sunwoo, Do-Yong Kim, Jangsup Moon, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea

M273. Winged Scapula Secondary to Neuroborreliosis

Anna M. Bank, Matt T. Bianchi and Shibani S. Mukerji. Boston, MA

M274. Sensory and Autonomic Neuropathy in the db/db Mouse

Blessan Sebastian, Ben Liu, Baohan Pan, Yiyue Zhang, John Fissel, Ying Liu and Michael Polydefkis. Baltimore, MD

M275. "Tachycardia, Twitches and the Thymus: What's the Link?"

Ali Shebaryar, Anusha Edara, Aparna M. Prabhu, Sumeet S. Multani, Yongwoo J. Kim and Rabia Choudry. Philadelphia, PA

M276. Neurological Abnormalities in Cerebrotendinous Xanthomatosis: Case Series and Literature Review

Janice C. Wong, Kailey Walsh and Florian S. Eichler. Boston, MA

M277. Neurologic Involvement in V122i Familial Amyloidosis

Sami Khella, Brian Drachman, Patricia DiVito, Thomas Brannigan III and Michael Polydefkis. Philadelphia, PA

M278. Clinical and Electrophysiological Response to a Factor Xa Inhibitor in Distal Acquired Demyelinating Sensory Motor Neuropathy (DADS)

Alexis A. Lizarraga, Thomas I. Cochrane and Aaron L. Berkowitz. Miami, FL and Boston, MA

M279. Vasculitic Neuropathy in the Setting of Nivolumab Therapy for Metastatic Mesothelioma

Bing Liao, Wei Wang, Julie Hammack and Michelle Mauermann. Rochester, MN

Interventional Neurology

M280. Treatment of Complex Regional Pain Syndrome type II (CRPS-II) with Simultaneous Multi-Target Spinal Cord and Motor Cortex Stimulation: A Case Report

Faddi G. Saleh Velez, Juanita Duran, Erich T. Fonoff and William O. Contreras. Charlestown, MA; Sao Paulo, Brazil and Bucaramanga, Santander, Colombia

Autoimmune Neurology

M281. A Rare Case of Autoimmune Polyendocrine Syndrome Type 2 Associated with Anti-GAD Positive Ataxia and Seizure

Shri K. Mishra, Nastaran Rafiei, Hadi Mohammad Khanli and Parastou Tizro. Los Angeles, CA

Dementia and Aging

M282. Visual Hallucinations as the Initial and Predominant Presenting Symptom in an 83-Year-Old Patient with Posterior Cortical Atrophy

Erin L. Sadler and Hamid R. Okhravi. Norfolk, VA

Education

M283. The Curse of the Goddess

Sanam Anwer, Apoorv Prasad and Mihai Cornelia. Syracuse, NY

Headache and Pain

M284. Delayed Exacerbation of Burning Mouth Syndrome

Laila E. Ahmed and Alan R. Hirsch. Cane, Saint Vincent and the Grenadines and Chicago, IL

M285. Burning Mouth Syndrome; Induction by Quetiapine

Sumit Kanwar, Manisha R. Chand and Alan R. Hirsch. Weston, FL and Chicago, IL

Neuromuscular Disease

M286. Atypical Presentations of Vitamin B12 Deficiency in a Population of Northern Manhattan Clinic Patients

Elina Zakin and Susan Shin. New York, NY

M287. Novel NPC1 Gene Variant in Adult-Onset Niemann-Pick Disease Type C

Shri K. Mishra, Maren Schuner, Nasheed Jamal, Hadi Mohammad Khanli and Parastou Tizro. Los Angeles

M288. Familial Amyloid Polyneuropathy (FAP) Accompanied with Severe Post-Micturitional Abdominal Pain and Orthostatic Hypotension with Novel Transthyretin (TTR) Mutation (TTR, Lys80Arg)

Yuka Miyamoto, Motoko Ueda, Yukari Morita, Kohnosuke Furuta, Yasushi Osaki, Mitsuharu Ueda, Taro Yamashita, Yukio Ando and Hirokazu Furuya. Kochi, Japan and Kumamoto, Japan

M289. Genetic Analyses and Counselling of Sporadic Amyotrophic Lateral Sclerosis in Japan

Makito Hirano, Yusaku Nakamura, Kazumasa Saigoh, Hikaru Sakamoto, Shuichi Ueno, Hidekazu Suzuki and Susumu Kusunoki. Sakai, Osaka, Japan and Osakasayama, Osaka, Japan

M290. Reversible Cerebral Vasoconstriction and Posterior Reversible Encephalopathy in Guillain-Barre Syndrome

Armin Maghsoudlou, SeyedAli Hejazi, Avani Shah and Eufrosina Young. Syracuse, NY

M291. Temporal Trends in Guillain-Barre Syndrome at Assaf Harofeh Medical Center 2010-2015

Gilad Kenan, Mark Kushnir and Carmel Armon. Tel Aviv, Israel and Zerifin, Israel

M292. Focal Bioimpedance (BIA) and Its Superiority Over Total Body BIA

William H. Mays and Tulio E. Bertorini. Memphis, TN

Dementia and Aging

M293. Imaging and EEG Findings of the Heidenhain Variant of Creutzfeldt-Jakob Disease

William K. Jens, Sara Strauss and Aiesha Ahmed. Millersville, PA

Interventional Neurology

M294. Circadian Timing of Emergent Large Vessel Occlusion and Its Association with Efficacy of Mechanical Thrombectomy and Patient Outcomes

Bakhtier Nurmukhamedov, Sameer Sharma and Hesham Masoud. Syracuse, NY

Dementia and Aging

M295. "Serum MCI Screening Test" Is Correlated with CSF A β 40/A β 42 and Valuable for the Enrollment of MCI Patient to Clinical Trial

Yasuhiro Yoshii, Keiko Bouno, Kenichi Sakuta, Ken Ikeda and Yasuo Iwasaki. Kawasaki, Kanagawa, Japan; Minato-ku, Tokyo, Japan and Ota-ku, Tokyo, Japan

M296. Modeling the Impact of Neurogenesis and Cell Death on the Function and Structure of Neuronal Tissue

Yosef G. Tirat-Gefen. Fairfax/Vienna, VA

Education

M297. Charles Bonnet Syndrome Associated with Reversible Posterior Leukoencephalopathy Syndrome

Lucido L. Ponce Mejia, Hunaid Hasan, Trinh Nguyen and Alok Dabi. Galveston, TX

Headache and Pain

M298. Alliacious Burning Mouth Syndrome

Malinda Walford, Kebrina Bartley and Alan Hirsch. Willemstad-Curacao, Netherlands Antilles and Chicago, IL

Neuromuscular Disease

M299. Chemosensation in Charcot Marie Tooth Disease

Stephanie Espejo, Al-Mounawara A. Yaya, Feras A. Shalabi and Alan R. Hirsch. Willemstad, Curacao, Netherlands Antilles; Kralendijk, Bonaire, Netherlands Antilles and Chicago, IL

M300. Case Report of Giant Pseudomeningocele Masquerading as Monomelic Amyotrophy

William K. Jens, Rae Bacharach, Sandip Savaliya and Divpreet Kaur. Hershey, PA

M301. Treatment Related Effects of Anti-GAA Antibodies in Late Onset Pompe Disease

Marie A. Wencel, Claudia Shambaugh, Namita A. Goyal, Virginia E. Kimonis and Tabseen Mozaffar. Orange, CA

M302. Pharmacokinetic Profile of Edaravone: A Comparison Between Japanese and Caucasian Populations

Yoshinobu Nakamaru, Atsuhiko Kawaguchi, Shuji Kinoshita, Koji Takei and Joseph M. Palumbo. Tokyo, Japan and Jersey City, NJ

Traumatic Brain Injury

M303. Differential Expression of Cerebral Autonomic Function in Special Forces and Non-Special Forces Exposed to TBI

Thomas J. DeGraba, Kathy Williams, Melissa Rampino, Chloe LaRochelle and Geoffrey Grammer. Bethesda, MD; Olney, MD and Silver Spring, MD

M304. Parieto-Occipital delta alpha Spectral Power in Electroencephalogram Indexes Post-Traumatic Confusion and Predicts Recovery After Traumatic Brain Injury

Maliheb Mohamadpour, Sudhin A. Shah, Gulce Askin, Risa Nakase-Richardson, Dobrivoje S. Stokic, Mark Sherer, Stuart A. Yablon and Nicholas D. Schiff. New York, NY; Tampa, FL; Jackson, MS and Houston, TX

M305. Initial GCS and Laboratory Findings of Patients with TBI Are Associated with the GOSE and Mortality Rate at One Year, a Prospective Study

Elabe Bordbar, Shahram Paydar, Mehdi Taghipour, Hosseinali Khalili and Mehran Jafari. Baltimore, MD and Shiraz, Islamic Republic of Iran

M306. Screening for Novel Calpain-2 Selective Inhibitors

Shayan Torabi Moghaddam, Yubin Wang and Michel Baudry. Pomona, CA

M307. Pupillary Dysfunction in Post Traumatic Headache

Natalie A. Rea, Christopher E. Sciarretta, K.C. Brennan and Melissa Cortez. Salt Lake City, UT

M308. Etiologies of Concussion in Pediatric Population

Megan Edwards, Amanda Witt and Sara Dawson. Jackson, MS

M309. Efficacy of an Interdisciplinary Intensive Outpatient Program in Treating Combat-Related TBI and Psychological Health Conditions

Thomas J. DeGraba, Geoffrey Grammer, Kathy Williams and James P. Kelly. Bethesda, MD; Silver Spring, MD and Aurora, CO

M310. Post-Traumatic Dueling Synesthesias- Pathologic Gustatory vs Physiologic Retronasal Olfactory

Al-Mounawara Yaya and Alan R. Hirsch. Willemstad, Curaçao, Netherlands Antilles and Chicago, IL

Autoimmune Neurology

M311.WIP Stiff-Person Syndrome in Association with Cerebellar Ataxia: Overlapping Syndrome: A Case Report

Varun H. Chauhan and Abbas A. Jowkar. Detroit, MI

M312.WIP ARA 290 for Sarcoidosis and Painful Small Fiber Neuropathy

Daniel A. Culver, Jinny Tavee, Albert Dahan, Daiva Bajorunas, Maria Jeziorska, Monique Van Velzen, Leon Aarts, Martijn Tannemaat, Ann Dunne, Rita Kirk, Ioannis Petropoulos, Anthony Cerami, Rayaz Malik and Michael Brines. Cleveland, OH; Leiden, Netherlands; Tarrytown; Manchester, United Kingdom and Doha, Qatar

M313.WIP GABA-B Receptor Antibodies Inhibit GABA-B Receptor Signaling

Eric Lancaster, Elisabeth Burnor, Maxwell Greene, Ankit Jain and Sheena Baraton. Philadelphia, PA

M314.WIP CASE REPORT: A Case of Area Postrema Syndrome as a Debut of Neuromyelitis Optica Spectrum Disorder

Jimmy Palacios-Garcia and Brian J. Villafuerte-Trisolini. Lima, Peru

M315.WIP Spectrum of Zika Virus Associated Neurological Disease in Colombia

Paula Barreras, Laura Munoz, Beatriz Parra, Jairo Lizarazo, Jorge A. Jiménez-Arango, Andres F. Zea-Vera, Guillermo González-Manrique, José Vargas, Jorge A. Angarita, Gonzalo Zuñiga, Reydmir Lopez-Gonzalez, Cindy L. Beltran, Karen H. Rizcala, Maria T. Morales, Anupama Kumar, David R. Cornblath, Lyda Osorio and Carlos A. Pardo. Baltimore, MD; Cali, Colombia; Cucuta, Colombia; Medellin, Colombia; Neiva, Colombia and Barranquilla, Colombia

M316.WIP An iPSC Derived Human Minibrain to Study Zika Virus Associated Neurological Disease

Paula Barreras, David Pamies, Anupama Kumar, Laura S. Munoz, Beatriz Parra, Celina Abreu, Lucio Gamma, Helena Hogberg, Thomas Hartung and Carlos A. Pardo. Baltimore, MD; Cali, Colombia and Baltimore

Dementia and Aging

M317.WIP Relationship Between Obesity and Stroke vs Obesity and Cardiovascular Disease

Gargya Malla and Colin T. Farrell. Bowling Green, KY

M318.WIP Periodontal Disease as the Contributing as Well as Independent Risk Factor of Stroke and Cerebrovascular Diseases

Navdeep S. Lail, Gurleen K. Sohi, Ashkan Mowla, Robert N. Sawyer and Robert J. Genco. Buffalo, NY

M319.WIP Feasibility of a Tablet-Based System for Pre-hospital Neurological Assessment: The Improving Treatment with Rapid Evaluation of Acute Stroke via Mobile Telemedicine (iTREAT) Study

William M. Clark, Jason M. Lippman, Jack Cote, Brett J. Schneider, Timothy L. McMurry, Brian S. Gunnell, David C. Cattell-Gordon, Debra G. Perina, Nina J. Solenski, Sherita N. Chapman Smith, Bradford B. Worrall and Andrew M. Southerland. Charlottesville, VA

Education

M320.WIP Self-Administered Gerocognitive Examination (SAGE) Correlates to Montreal Cognitive Assessment (MOCA) in a Suburban Neurology Clinic

Ansh Bhammar, Heena Patel, Malini Nair and Anil Nair. Quincy, MA

M321.WIP Dementia Cost by Diagnosis and Geographic Location

Leslie Wilson, Yingjia Chen, Tracy Lin, Sutep Laohavanich, Kathrine Possin, Michael Schaffer, Paulina Ong, Winston Chiong, Stephen Bonasera and Bruce Miller. San Francisco, CA and Omaha, NE

Headache and Pain

M322.WIP Quality of Epilepsy Care of Native Americans Is at a Crisis Stage!

Miguel E. Fiol and Kirk Allison. Minneapolis, MN

M323.WIP Progressive Cardiac Dysautonomia Preceded Asystole with Sequential Electrographic Stages of Focal Status Epilepticus

Adeel A. Memon, Raima A. Memon, Sandipan B Pati and Chetan Nayak. Birmingham, AL and Bangalore, India

M324.WIP Characterizing Peri-Ictal Mood Changes in Psychogenic Nonepileptic Seizures

Katarina Vasiljevic, Erin Lanzo, Scott Thompson, Mark Kvarita and Jennifer Hopp. Baltimore, MD

Health Services Research

M325.WIP Neurological Complication Rates Associated with Epidural Injections

Byungkwan Hwang, Joongyub Lee and Byung-Joo Park. Lubbock, TX and Seoul, Republic of Korea

M326.WIP Abnormal Amygdala Volumes Predicted by Behavioral Measures in Patients with Chronic Daily Headache

Danielle D. DeSouza, Yohannes W. Woldammanuel, Meabh O'Hare, Bharati Sanjanwala and Robert P. Cowan. Palo Alto, CA

M327.WIP The Human Visual Cortex Responds to Isolated Melanopsin Stimulation

Geoffrey K. Aguirre, David H. Brainard and Manuel Spitschan. Philadelphia, PA

Interventional Neurology

M328.WIP A Rare but Costly Disease: The Case of Myasthenia Gravis

Jacklyn Omorodion, Jesse M. Pines and Henry J. Kaminski. Washington, DC

Traumatic Brain Injury

M329.WIP Loss of MUNC13-1 Function Causes Microcephaly, Cortical Hyperexcitability and Fatal Myasthenia

Andrew G. Engel, Duygu Selcen, Xinming Shen, Margherita Milone and Charles M. Harper. Rochester, MN

M330.WIP A Critical Period for Motor Skill Development in Rats: A Microgravity Study

Neeraj Singh, Kerry Walton and Shannon Harding. Albany, NY; New York, NY and Fairfield, CT

M331.WIP Retrospective Analysis of Effects of Edaravone on Functional Decline in Amyotrophic Lateral Sclerosis (ALS) Using ALS Milano-Torino Functional Staging System

Charlotte (Charley) Merrill, Ellen M. Dukes, Rebecca K. Bornheimer, Wendy Agnese, Pingping Ni, Marc Rivière and Gerry Oster. Jersey City, NJ; Brookline, MA; London, United Kingdom and Montreal, QC, Canada

M332.WIP Guillain-Barre Syndrome and Zika Virus: Epidemiological Surveillance in Puerto Rico

Carlos A. Luciano, Jose E. Arias-Berrios, Brenda Deliz, José R. Carlo, Gishlaine Alfonso and Brenda Rivera-García. San Juan, Puerto Rico and Houston, TX

M333.WIP Retrospective Analysis of Effects of Edaravone on Clinical Anatomic Progression in Amyotrophic Lateral Sclerosis (ALS) Using King's ALS Clinical Staging System

Wendy Agnese, Rebecca K. Bornheimer, Ellen M. Dukes, Charlotte (Charley) Merrill, Pingping Ni, Marc Rivière and Gerry Oster. Jersey City; Brookline; London, United Kingdom and Montreal, QC, Canada

M334.WIP A Randomized, Double-Blind, Placebo-Controlled Trial of L-Serine in Hereditary Sensory and Autonomic Neuropathy Type 1 (HSAN1)

Eichler Florian, Vera Fridman, William David, Peter Novak, Anne Louise Oaklander, Eric Macklin, Robert Brown and Hornemann Thorsten. Boston; Worcester and Zurich, Switzerland

M335.WIP Answer ALS: A Clinical and Comprehensive Multi-Omics Signature for ALS Employing Induced Pluripotent Stem Cell Derived Motor Neurons from 1000 Sporadic and Familial ALS Patients Nationwide

Jeffrey D. Rothstein, Clive N. Svendsen, Merit Cudkowicz, James Berry, Nicholas Maragakis, Alex Sherman, Dhruv Sareen, Steve Finkbeiner and Ernest Fraenkel. Baltimore, MD; Los Angeles, CA; Boston, MA and San Francisco, CA

Sleep Disorders and Circadian Rhythm

M336.WIP Genetic-Encoded Calcium Indicators in Mice to Monitor Whole-Cortex Activity During Sleep

Eric C. Landsness, Patrick W. Wright, Adam Q. Bauer, Andrew W. Kraft, Joe P. Culver and Jin M. Lee. Saint Louis, MO

Headache and Pain

M337.WIP Evaluating Peri-ictal Mood Changes in Patients with Epilepsy

Sharon R. Ong, Erin Lanzo, Mark D. Kvarta, Scott M. Thompson and Jennifer L. Hopp. Baltimore, MD

Autoimmune Neurology

CD540 The Effect of Vitamin D on Markers of Oxidative Stress in X-linked Adrenoleukodystrophy

Keith Van Haren, Emmanuelle Waubant, Gregory Enns, Ellen Mowry, Gerald Raymond, Patrick Aubourg and Lawrence Steinman. Palo Alto, CA; San Francisco, CA; Baltimore, MD; Minneapolis, MN and Paris, France

Headache and Pain

CD542 Psychosocial and Family Risk in Pediatric Chronic Migraine and Tension-Type Headache

Emily F. Law and Tonya M. Palermo. Seattle, WA

Autoimmune Neurology

CD544 Cognitive Function and Structural Neuroimaging in Behaviorally Acquired HIV+ Youth

J.L. McGuire, L. Hawkins, R. Datta, S. Narula, T. Benton, S.D. Douglas and B. Banwell. Philadelphia, PA

ANA 2016 Abstracts

Movement Disorder

S101. Dissociated Cognitive Impairments Associated with Midbrain and Hippocampal Microstructural Atrophy in Parkinson's Disease: A 7-Tesla MRI Study

Kathleen L. Poston, Michael Zeineh, Matthew A.I. Ua Cruadhlaioich, Jeffrey Bernstein, Sudarshan Ranganathan, Laura Santoso, Michelle Fenesy, Seoni Llanes, Gayle Deutsch, Brian Rutt and Geoffrey Kerchner. *Staford, CA and Stanford, CA*

Objective: Using ultra-high field 7 Tesla MRI, we investigated the relationship between midbrain and hippocampal microstructural atrophy and cognitive dysfunction in Parkinson's disease patients (PD).

Background: Unlike the cardinal motor symptoms of PD, the underlying pathophysiology of PD cognitive impairment is unclear. Several studies have suggested a dual-syndrome hypothesis, where different cognitive syndromes develop from distinct pathological processes. However, investigating the relationship between PD cognitive impairment and microstructural atrophy using conventional MRI is extremely difficult.

Design/Methods: We used susceptibility-weighted 3D 7 Tesla MRI to identify midbrain and hippocampal microstructural regions in 30 PD patients (age 65.4 $\pm$ 7.6, duration 4.1 $\pm$ 2.1 yrs), who completed comprehensive neuropsychological testing. The substantia nigra, subthalamic nucleus, and red nucleus were segmented both manually and semi-automatically using ITK-SNAP software. In addition, dimensions of hippocampal subfields (CA1 stratum radiatum/stratum lacunosum-moleculare and CA1 stratum pyramidale) were manually and semi-automatically measured with the FIRST tool in FSL (Kerchner 2014, Neurology). Due to the sensitivity of hippocampal subfield analysis to any head motion >0.5mm, only 14 participants were included in the hippocampal analysis. For all analysis the right and left sides were averaged.

Results: Mild Cognitive Impairment in PD (PD-MCI) Level-II diagnostic criteria (Litvan 2012, Mov.Dis.) were used to categorize 20 no-MCI and 10 MCI PD patients. Using a partial correlation analysis controlling for age, we found smaller substantia nigra volumes were associated with worse performance on tests of visuospatial and executive function; specifically the Hooper Visual Organization Test ($r=0.37$, $p=0.05$), Stroop color-word interference ($r=0.40$, $p=0.03$), and FAS word fluency ($r=0.37$, $p=0.04$). By contrast, smaller hippocampal subfield layer (CA1 stratum pyramidale) was only associated with worse CVLT-long delay free recall ($r=0.64$, $p=0.006$). In a subset of 12 patients (6 no-MCI/6 MCI), smaller CA1 stratum pyramidale was also associated with lower CSF α Beta ($r=0.57$, $p=0.053$).

Conclusions: In PD patients, we found a double dissociation between midbrain and hippocampal atrophy in relation to cognitive impairments in different cognitive domains. Specifically, within the midbrain only substantia

nigra atrophy predicted executive and visuospatial performance, whereas hippocampal atrophy predicted poor episodic memory performance and lower CSF α Beta. These findings provide valuable insight into the underlying pathophysiology of different cognitive impairments in PD and support the dual-syndrome hypothesis.

Cerebrovascular Disease

S102. Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis: CREST-2 Update

Thomas G. Brott, Brajesh K. Lal, George Howard, Gary Roubin, Robert D. Brown, Jr, Kevin M. Barrett, Seemant Chaturvedi, Marc I. Chimowitz, Bart M. Demaerschalk, Virginia J. Howard, John Huston III, Ronald M. Lazar, Wesley S. Moore, Claudia Scala Moy, Tanya N. Turan, Jennifer H. Voeks and James F. Meschia. *Jacksonville, FL*

Over 100,000 carotid revascularization procedures are done annually in the US for asymptomatic carotid arterial stenosis. The safety of carotid endarterectomy (CEA) and carotid stenting (CAS), and the efficacy of medical therapy in altering the progression of atherosclerosis have improved. Therefore, the applicability of prior randomized trials in asymptomatic carotid stenosis to current treatment decisions has been called into question. The aim of the NINDS-funded CREST-2 is to compare CEA and intensive medical therapy (IMT) versus IMT alone ($n=1240$), and CAS and IMT versus IMT alone ($n=1240$), through two parallel randomized clinical trials at approximately 120 medical centers, including collaboration with NIH-StrokeNet. The composite primary outcome is any stroke or death within 44 days after randomization or ipsilateral ischemic stroke thereafter up to 4 years. Secondary outcomes include cognitive function, which is assessed on a regular schedule through computer-assisted telephone interview. IMT is directed centrally and includes tight control of blood pressure (systolic target <140 mm Hg) and cholesterol (LDL target <70 mg/dl) as well as lifestyle coaching. As of March 18, 2016, 87 centers have been approved to randomize by the CREST-2 Site Selection Committee, and site selection is ongoing for up to 150 sites. 202 patients have been randomized. The Surgical and Interventional Management Committees have credentialled 261 surgeons and 98 interventionists. An additional 131 interventionists have been approved to submit additional cases via the CREST-2 Companion Registry which provides a CMS-reimbursed pathway for full credentialing in CREST-2. An update regarding the numbers of centers certified, surgeons and interventionists credentialled, and cases randomized will be provided.

S103. Burden and Outcomes of Acute Ischemic Stroke in Patients with Major Depression

Zeeshan Mansuri, Achint Patel, Zabeen Mahuwala, Uvesh Mansuri, Ruchir Goswami, Tapan Mehta, Sagar Patel, Kinsuk Chauhan, Sarah Noble, Girish Nadkarni and Sanjeeva Reddy Onteddu. *Philadelphia, PA; New York, NY; Dallas, TX; Storrs, CT and Fayetteville, AR*

Objective: To determine the trends and impact on outcomes of Acute Ischemic Stroke (AIS) in patients with pre-existing major depressive disorder (MDD).

Background: While post-stroke MDD has been extensively studied in the past, contemporary studies on the impact of pre-stroke MDD on AIS and post-stroke outcomes are largely lacking.

Methods: We used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) from years 2002-2012. We identified AIS and MDD as a primary and secondary diagnosis respectively using validated International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes. We used the Cochran-Armitage trend test and multivariate regression to generate adjusted odds ratios (aOR).

Results: We analyzed a total of 4,320,304 AIS hospital admissions from years 2002-2012 of which 8.6% had MDD. Proportion of hospitalizations with MDD increased from 6.4% in 2002 to 10.3% in 2012 (ptrend < 0.001). Utilization of thrombolysis was lower in patients with MDD (3.81% vs. 4.82%, $p < 0.001$). In-hospital mortality was significantly lower in patients with MDD (aOR 0.64; 95%CI 0.61-0.68; $p < 0.001$) but discharge to specialty care was higher (aOR 1.38; 95%CI 1.36-1.42; $p < 0.001$). In addition, median length of hospitalization (3.6 vs. 3.4 days; $p < 0.001$) was higher in hospitalizations with MDD.

Conclusion: Our study displayed an increasing proportion of patients with MDD admitted due to AIS in the last decade with lower mortality but higher morbidity post stroke. In addition, there was less utilization of thrombolysis in this population. There is a need to explore the reasons behind this disparity in outcomes and thrombolysis utilization in order to improve post-stroke outcomes in this vulnerable population.

Epilepsy

S104. Adjunctive Everolimus Therapy for the Treatment of Refractory Seizures Associated with Tuberous Sclerosis Complex: Results from a Randomized, Placebo-Controlled, Phase 3 Trial

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Background: Everolimus (EVE) is approved for the treatment of renal angiomyolipoma and subependymal giant cell astrocytomas in tuberous sclerosis complex (TSC). We now present results from the first randomized, placebo-controlled phase 3 adjunctive study of EVE for the treatment of refractory seizures associated with TSC (EXIST-3, NCT01713946).

Objective: To assess the efficacy/safety of EVE 3-7 (low trough [LT]) or 9-15 ng/mL (high trough [HT]) targeted trough concentration (Cmin) ranges vs placebo as adjunctive

therapy in patients with refractory seizures associated with TSC.

Design/Methods: Following an 8-week baseline phase, patients aged 2-65 years (stratified by age) with TSC and refractory seizures on 1-3 antiepileptic drugs were randomized to EVE LT or HT Cmin target ranges or placebo. Dose titrations (up to 3) were performed over weeks 1-6 and, as needed, during the subsequent 12-week maintenance period. The primary endpoints were change from baseline in average weekly frequency of seizures, expressed as response rate ($\geq 50\%$ reduction [RR]), and percentage reduction.

Results: Overall, 366 patients were randomized to EVE LT (n=117), HT (n=130), or placebo (n=119). The median percentage reduction in seizures was significantly greater with EVE LT (29.3%, $P=0.003$) and HT (39.6%, $P<0.001$) vs placebo (14.9%). RR was also significantly greater with EVE LT (28.2%, $P=0.008$) and HT (40%, $P<0.001$) vs placebo (15.1%). The most frequent $\geq 10\%$ all grade adverse events (AEs) reported with EVE LT/HT vs placebo included stomatitis (28.2%/30.8% vs 3.4%), diarrhea (17.1%/21.5% vs 5%), mouth ulceration (23.9%/21.5% vs 4.2%), nasopharyngitis (13.7%/16.2% vs 16%), upper respiratory tract infection (12.8%/15.4% vs 12.6%), aphthous ulcer (4.3%/14.6% vs 1.7%), and pyrexia (19.7%/13.8% vs 5%). Discontinuations due to AEs (5.1%/3.1% vs 1.7%) were low.

Conclusions: Adjunctive EVE therapy demonstrated a clinically and statistically significant reduction in seizure frequency with a tolerable safety profile compared with placebo in patients with TSC.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? J. French consults for Acorda, Adamas, Alexza, Anavex, BioPharm Solutions, Concert Pharmaceuticals, Eisai, Georgia Regents University, GW Pharma, Marinus, Monteris, Nestle-Health Science, Neurelis, Novartis, Pfizer, Pfizer-Neusentis, Pronutria, Roivant, Sage, SciFluor, SK Life Sciences, Sunovion, Takeda, UCB Inc., Upsher Smith, Xenon Pharmaceuticals, Zogenix and Zynerba. All consulting is done on behalf of the Epilepsy Study Consortium, and fees are paid to the consortium. NYU receives salary support from the consortium. J. French has also received personal compensation for serving as Associate Editor of *Epilepsia*, and received research funding from Acorda, Alexza, Eisai Medical Research, LCGH, Lundbeck, Pfizer, SK Life Sciences, Sunovion, UCB, Upsher-Smith and Vertex, as well as grants from the Epilepsy Research Foundation, Epilepsy Study Consortium, Epilepsy Therapy Project, and NINDS.

Movement Disorder

S105. Deep Brain Stimulation in Early Stage Parkinson's Disease: Long-Term Motor Benefit Through 5 Years

Mallory L. Hacker, Maxim Turchan, Lauren E. Heusinkveld, Amanda D. Currie, Sarah Millan, William Fisher, Madelyn Bollogh, Thomas L. Davis, Peter E. Konrad, Fenna T. Phibbs, Peter Hedera and David Charles. Nashville, TN

Background: A prospective, randomized pilot clinical trial of subthalamic nucleus deep brain stimulation (DBS) in early stage Parkinson's disease (PD) followed subjects through five years to collect long-term safety and clinical outcomes data. Motor symptom scores for early PD subjects who enrolled in the pilot trial with a medication duration of 1-4 years were compared five years after treatment with either optimal drug therapy (ODT) or DBS plus ODT (DBS+ODT).

Methods: After completing the initial two-year follow-up period, subjects in the DBS in early PD pilot trial were evaluated annually for three additional years to collect longitudinal safety and PD outcomes data (NCT#00282152, IDE#G050016, IRB#040797). Upon enrollment, subjects included in this analysis were age 50-75, with a medication duration of 1-4 years, and without dyskinesias or other motor fluctuations. Subjects randomized to ODT who received DBS during the extension period were excluded. Unified Parkinson's Disease Rating Scale (UPDRS) Part III ON motor assessments were rated by an independent, blinded neurologist at the conclusion of the extension study and compared between and within treatment groups (ODT n=8, DBS+ODT n=9).

Results: There was no difference in UPDRS Part III motor scores between the groups at baseline (ODT = 23.9 ± 10.3 ; DBS+ODT = 26.0 ± 12.2 ; $p=0.92$). Average scores for the DBS+ODT group were improved from baseline at each follow-up visit through five years. Conversely, the average ODT group motor scores were 27% worse than baseline at the five year visit ($p=0.04$). Average motor change from baseline scores at four- and five-years significantly favored the DBS+ODT group over the ODT group by -9.9 and -8.9 points, respectively ($p=0.04$ and $p=0.03$). This therapeutic advantage imparted by DBS in early stage PD exceeds a moderate clinically important difference in the UPDRS Part III motor score [1].

Conclusions: These results suggest that DBS applied in early stage PD provides long-term, clinically meaningful improvement in motor function over medical therapy alone. More investigation is needed to confirm these findings. The FDA has approved a phase III, pivotal, multicenter clinical trial evaluating DBS in early stage PD.

[1] Shulman et al., Arch Neurol. 2010 Jan;67(1):64-70.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Vanderbilt University receives income from grants and contracts with Allergan, Ipsen, Merz, and Medtronic for research led by David Charles. David Charles receives income from Allergan, Ipsen, Concert, and Medtronic for consulting and education services. Peter E. Konrad receives research funding and is on the speaker's bureau for Medtronic. Fenna T. Phibbs has done consulting work for Medtronic, Boston Scientific, St. Jude Medical, and Teva. Thomas L. Davis has done consulting work for AbbVie. There are no conflicts of interest for Mallory L. Hacker, Maxim Turchan, Lauren E. Heusinkveld, Amanda D. Currie, Sarah Millan, William Fisher, Madelyn Bollig, or Peter Hedera. This work has been

supported by: Vanderbilt CTSA grant UL1TR000445 from the National Center for Advancing Translational Sciences (NCATS), NCATS/NIH award UL1TR000011, NIH R01EB006136, Medtronic, Inc, and the Michael J. Fox Foundation for Parkinson's Research.

S106. Increased Dendritic Excitability and Calcium-Dependent PKC Activation: A Novel Mechanism Underlying Purkinje Neuron Dendritic Degeneration in Cerebellar Ataxias

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In degenerative cerebellar ataxias, Purkinje neurons undergo progressive simplification and degeneration of the dendritic arbor prior to cell loss. Although dendritic degeneration strongly correlates with motor impairment in many models of cerebellar ataxia, the mechanism behind this pathologic dendritic remodeling is not well understood. In a mouse model of the inherited ataxia spinocerebellar ataxia type 1 (SCA1), we investigated the hypothesis that Purkinje neuron dendritic degeneration is a result of a pathological increase in intrinsic dendritic excitability. Intrinsic dendritic excitability is a measure of neuronal dendrites' ability to regulate their membrane potential, and appropriate control of dendritic excitability is critical for protecting Purkinje neuron dendrites from toxic calcium loading. In our electrophysiologic recordings, we found that SCA1 Purkinje neurons show increased dendritic excitability throughout the course of dendritic degeneration, and we also found that this increased excitability is observed in association with reduced expression and function of several potassium channels. Enhancing activity of these potassium channels normalizes dendritic excitability and prevents dendritic degeneration, supporting a causal connection between increased dendritic excitability and pathologic dendritic remodeling. In our efforts to identify a downstream effector which might mediate excitability-dependent dendritic degeneration, we have found a progressive increase in protein kinase C (PKC) activity that correlates with dendritic degeneration in SCA1 Purkinje neurons. Increased PKC activity has been shown to cause Purkinje neuron dendritic degeneration in vitro and in vivo. Our studies found that increased PKC activity in SCA1 Purkinje neurons is linked to excitability-dependent calcium entry, suggesting that increased PKC activity might therefore be the mechanistic link between increased excitability and dendritic remodeling in SCA1 mice. We found evidence of increased PKC activity in Purkinje neurons in post-mortem tissue from patients with SCA1, as well as in post-mortem tissue from patients with multiple system atrophy, a sporadic cerebellar ataxia. These results indicate that increased PKC activity could underlie Purkinje neuron dendritic remodeling in diverse causes of cerebellar ataxia, and suggest that reducing dendritic membrane excitability and normalizing protein kinase C activity may represent a shared therapeutic strategy in degenerative ataxias. These results also provide evidence for dendritic ion channel activity being a critical determinant of dendritic structural integrity,

suggesting that dendritic ion channels may be a critical therapeutic target across a range of neurodegenerative diseases.

S107. Rare Recurrent *NRXN1* Deletions and *CNTN6* Duplications Increase Risk for Tourette Syndrome

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Background: Tourette Syndrome (TS) is a neurodevelopmental disorder with one of the highest familial recurrence rates among non-Mendelian neuropsychiatric diseases. Despite this high heritability, no genome-wide significant TS susceptibility genes have been identified to date. Given the presence of rare recurrent genomic deletions and duplications, i.e., copy number variants (CNVs), in other developmental neuropsychiatric disorders, we examined the role of rare CNVs in a large, European ancestry TS case-control sample.

Methods: 2,285 subjects meeting TS DSM-IV-TR diagnostic criteria and 3,821 ancestry-matched controls were genotyped on Illumina OmniExpress SNP arrays. CNVs were called based on the consensus of two Hidden Markov Model (HMM) algorithms, PennCNV and QuantiSNP. Sensitivity analyses across genotyping batches and case-control groups were conducted using 5,741 common CNVs identified in HapMap3 reference samples. Standard quality control metrics were applied to remove outlier subjects and poorly performing samples. In addition to a test of overall CNV burden of rare (<1% frequency), genic (spanning at least one exon) CNVs >50kb in size, segmental and gene-based association tests were performed to evaluate specific genes and/or genomic regions for association with TS. Results were subjected to a genome-wide correction using the max(T) permutation method.

Results: No increased burden of rare CNVs was present in cases, although a survival function analysis of CNV length indicated a nominal increase in deletion size between TS cases and controls ($p=0.02$). In both segmental and gene-based tests, two genome-wide significant CNV regions were identified, each conferring a significantly increased risk for TS: exonic deletions in *NRXN1* ($OR=20.2$, 95%CI (2.6-155.2), $P_{seg}=2 \times 10^{-5}$; $P_{corr}=9 \times 10^{-4}$) and exonic duplications in *CNTN6*, ($OR=6.0$, 95% CI (2.0-17.8), $P_{seg}=3 \times 10^{-5}$; $P_{corr}=7 \times 10^{-3}$). *NRXN1* deletions and *CNTN6* duplications were present in 0.56% ($n=12$) and 0.53% ($n=13$) of TS cases, respectively, compared to 0.03% ($n=1$) and 0.05% ($n=2$) of controls. Mutations in both genes have been found in other neurodevelopmental disorders, and both are thought to be involved in development of thalamic circuits.

Conclusions: Rare, exonic CNVs in *NRXN1* and *CNTN6* are significantly associated with Tourette Syndrome, representing the first genome-wide significant results for this disorder. Together, these structural rearrangements

are present in ~1% of TS patients and substantially increase disease risk. Future research will be needed to explore the role of these two genes in development of aberrant cortico-striato-thalamo-cortical circuits thought to underlie TS pathogenesis.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Scharf has received consulting fees from Nuvelation Pharma, Inc.

S108. Spatio-Temporal Analysis and Modeling of Gait in Parkinson's Disease

Christine E. Ashton, Catherine Tocci, Veronique G. Vanderhorst and Ludy C. Shih. Boston, MA

Background: Gait impairments associated with Parkinson's disease (PD) are complex and the neural circuitries responsible for gait problems are not well characterized. We have developed a model to capture changes in spatial and temporal gait parameters mediated by perturbations in distinct neural circuitries in mice. This model can also be applied to human gait, but it remains unclear to what extent this model can be used to measure various gait abnormalities in clinically well characterized PD subjects. Therefore, we sought to further develop this modeling approach in human subjects. Here, we utilize the model to analyze individual and grouped human data, with the goal of measuring subtypes of gait abnormalities in individual subjects as well as characteristics of PD gait in general.

Methods: We used a 16 x 2 foot Protokinetics Zeno walkway, with 18,432 under-foot pressure sensors, to record spatio-temporal aspects [step-by-step stride length, step length, swing duration, stance duration, stride velocity and averaged cadence] of gait in subjects diagnosed with PD and healthy age-matched controls, recruited from BIDMC movement disorders clinics and the Michael J. Fox Trial Finder. We measured gait in PD patients both on and off medications. In addition to gait measurements, we collected MDS-UPDRS, PDQ-39, FOG-Q, and cognitive measures [WAIS-IV digit span and letter number sequencing, Trails A and B, and Test of Premorbid Functioning]. For each gait parameter we plotted trial averages and step by step measures as a function of velocity and analyzed the data sets using regression analysis.

Results: Spatio-temporal gait measurements modeled as a function of velocity yield objective and reproducible means of quantifying gait characteristics in humans. We found significantly different regression curves for the PD and control cohorts in several, but not all gait parameters. Examination of step-by-step data within individuals allowed us to detect abnormalities that were not obvious from the averaged data sets, such as abnormalities that were prominent only in distinct ranges of velocity. This data also reflected clinically observed PD gait patterns, such as left-right asymmetries, freezing of gait, and levodopa influenced changes in gait.

Conclusion: Using a novel model to analyze spatio-temporal aspects of gait, we are able to make gait

measurements that parallel those in mouse models, distinguish PD from controls, and characterize specific elements of parkinsonian gait.

Multiple Sclerosis

S109. Vitamin D Genetic Risk Score Is Strongly Associated with Vitamin D Levels and Relapse Rate in Pediatric MS Patients

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Background: Low 25-OH vitamin D levels have been associated with increased risk to have MS and with greater disability and lesion burdens, but establishing a causal relationship has been challenged by multiple confounding factors.

Objective: We sought to determine if an instrumental variable of a genetic risk score for functional single nucleotide polymorphisms in vitamin D pathways is associated with vitamin D levels and relapse activity in pediatric MS subjects.

Methods: Consecutive subjects seen at two Pediatric MS Centers of Excellence between 2006 and 2011 were offered enrollment if they met published criteria for pediatric MS or clinically isolated syndrome with high risk of MS. DNA samples from enrolled subjects who were also followed for relapses were typed for 29 functional polymorphisms in vitamin D pathway genes identified through the literature to be associated with 25-OH vitamin D levels in human subjects. Linear regression models were used to compare genotype to 25-OH D level and Cox regression for association of a genetic risk score for low 25-OH D with relapse hazard.

Results: Six of the 29 polymorphisms were strongly associated with vitamin D levels in pediatric MS subjects ($n=181$) after Bonferroni correction ($p=0.0017$) for multiple comparisons. An unweighted risk score of these 6 SNPs was normally distributed and explained 12% of the variance of vitamin D level in these subjects. A five-unit change in the risk score for lower vitamin D (range 0 to 12), was associated with 5.4 ng/ml lower 25-OH D level (95% CI $-7.58, -3.14$, $p=0.0000018$). This risk score was associated with a 25% increase in the hazard to relapse (HR 1.25, 95% CI 1.03, 1.49, $p=0.017$).

Conclusion: A genetic score of six functional polymorphisms captures risk of hypovitaminosis D and identifies those who may be at greater risk of relapse related to this risk factor. These findings support a causal association of vitamin D with relapse rate.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Graves is supported by grants from Race to Erase MS, NMSS, Biogen, and Genentech.

Cerebrovascular Disease

S110. Hospitalization Risk Following Acute Stroke: The Atherosclerosis Risk in Communities (ARIC) Study

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Introduction: Hospitalizations among stroke survivors are common and contribute to a significant proportion of healthcare costs. The rates of all-cause and cause-specific hospitalization by stroke subtype are not well characterized.

Hypotheses: We hypothesized that rates of all-cause hospitalization after cardioembolic infarcts would be higher than for other stroke subtypes. We also hypothesized that persons with cardioembolic strokes would have higher rates of hospitalizations related to cardiovascular disease, infections, and procedure complications compared to other stroke subtypes.

Methods: Prospective analysis of 898 participants with incident stroke in the ARIC Study followed for a median (IQR) of 5.2 (1.7-10.3) years for hospitalizations (cause defined by primary ICD-9 code) occurring after incident stroke event. Stroke subtypes (thrombotic infarct; lacunar infarct; cardioembolic infarct; intracerebral hemorrhage) were defined by standardized criteria and adjudicated by physicians. Negative binomial models were used to calculate demographic-adjusted hospitalization rates.

Results: Mean age at time of incident stroke was 69 years, 50% were female, and 41% were black. Fifty-two percent of participants had a thrombotic infarct, 20% had a lacunar infarct, 21% had a cardioembolic infarct, and 7% had an intracerebral hemorrhage at baseline. Those with cardioembolic infarcts had the highest demographic-adjusted rate of all-cause hospitalizations (1056 [95% CI: 824-1288] per 1000 PY versus 724 [95% CI: 611-837] per 1000 PY for thrombotic infarcts [$p=0.005$], 652 [95% CI: 524-781] per 1000 PY for lacunar infarcts [$p=0.002$], and 607 [95% CI: 415-799] per 1000 PY for intracerebral hemorrhage [$p=0.005$]). For all stroke subtypes, cardiovascular disease was the most common cause of hospitalization, but those with cardioembolic infarcts had higher rates of cardiovascular disease related hospitalization compared to other stroke subtypes, all $p<0.001$. Persons with cardioembolic infarcts had higher rates of pneumonia (23.8 [95% CI 15.2-35.8] per 1000 PY) compared to those with thrombotic infarcts (13.6 [95% CI: 10.1-18.0] per 1000 PY, $p=0.032$) and compared to those with hemorrhagic infarcts (5.6 [95% CI: 0.9-18.5] per 1000 PY, $p=0.03$). Persons with cardioembolic infarcts had higher rates of procedure complications (14.8 [95% CI: 8.2-24.6] per 1000 PY) compared to those with thrombotic infarcts (6.8 [95% CI: 4.4-10.1] per 1000 PY, $p=0.02$).

Conclusions: Stroke survivors, especially those with cardioembolic infarcts, are at high risk of subsequent all-cause and cardiovascular disease-related hospitalizations. Further, a significant proportion of hospitalizations among those with

cardioembolic stroke are for pneumonia and procedure-related complications, which are potentially preventable.

S111. Burden and Outcomes of Acute Hemorrhagic Stroke in Patients with Psychosis

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Objective: To determine the trends and impact on outcomes of Acute Hemorrhagic Stroke (AHS) in patients with pre-existing psychosis.

Background: Although, post stroke psychosis has been extensively studied, contemporary studies on temporal trends and outcomes of pre-stroke psychosis on AHS outcomes are largely lacking.

Methods: We used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) from years 2002-2012. We identified AHS and psychosis as a primary and secondary diagnosis respectively using validated International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes. We used the Cochrane-Armitage trend test and multivariate regression to generate adjusted odds ratios (aOR).

Results: We analyzed 757,369 AHS hospital admissions from 2002-2012, of which 2.21% had psychosis. Proportion of hospitalizations with psychosis increased from 1.56% in 2002 to 2.93% in 2012 ($p_{trend} < 0.001$) on temporal trend analysis. Patients with psychosis had higher adjusted odds of discharge to specialty care (aOR 1.277; 95%CI 1.141-1.43; $p < 0.001$), but in-hospital mortality was significantly lower in patients with psychosis (OR 0.503; 95% CI 0.444-0.569; $p < 0.001$). In addition, median length of hospitalization (5.9 vs. 5.2 days; $p < 0.001$) and cost of hospitalization (\$11,929 vs. \$11,506; $p < 0.001$) were higher in hospitalizations with psychosis.

Conclusion: Our study displayed an increasing proportion of patients with psychosis admitted due to AHS in the last decade with lower mortality but higher morbidity after survival. There is a need to explore the reasons behind this disparity in outcomes and thrombolysis utilization in order to improve post-stroke outcomes in this vulnerable population.

Epilepsy

S112. Widespread Migration and Integration of Neurons in the Early Postnatal Human Frontal Cortex

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The first months of life are key to human brain development as a child begins interacting with its environment. The human frontal lobe has greatly increased in size and complexity compared to other mammals or non-human primates. To study the manner in which this region continues to develop postnatally, we followed young neurons from the

walls of the lateral ventricles and sub-ventricular zone (V-SVZ) to their final cortical destinations using high-resolution MRI, histology, and time-lapse confocal microscopy. We discovered a prominent and transient population of Doublecortin (DCX)+ migrating young neurons in a stream we refer to as the Anterior Arch. These cells were distributed widely throughout the frontal lobe invading multiple cortical areas in the first three months of life. DCX+ cells within the Arch were organized into four distinct regions (or tiers): 1) subventricular I, 2) subventricular II, 3) perivascular, and 4) in the developing white matter. The orientation of elongated DCX+ cells suggested that migratory neurons closer to the ventricular wall, in Tiers 1 and 2, were largely dispersing tangentially, while those in Tiers 3 and 4 have a more radial orientation. These young neurons expressed markers of interneurons and their entry into the anterior cingulate cortex (a major target of the Arch used for quantification) was correlated with the emergence of specific subtypes of GABAergic interneurons (NPY, Somatostatin and Calretinin). The distribution of Calbindin and Parvalbumin subtypes did not change with age in a similar fashion. DCX+ cells also expressed transcription factors associated with the ventral progenitor regions, the medial and caudal ganglionic eminences (MGE and CGE). Altogether, these data reveal a major migration of young neurons into the frontal lobe at periods of brain development that may contribute to changes to the neural circuit composition and its maturation during early infancy. The late development of neurons in the Arch may be related to plasticity in the developing human frontal lobe and defects in this migration could result in circuit defects that underlie neurodevelopmental disorders.

S113. Dynamic Participation Patterns of Superficial Cortex During Absence Seizures

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Absence epilepsy is a common childhood disorder featuring frequent cortical spike-wave seizures associated with behavioral arrest. The uniquely stereotyped EEG signature is assumed to reflect the global synchrony of neurons firing in unison among all cortical layers, disrupting complex patterns of synaptic integration. However, network activity of cortical neuronal populations in superficial layers has never been analyzed during seizures compared with the resting state. Using the calcium indicator Gcamp6 with in vivo 2-photon calcium imaging and simultaneous electrocorticography, we examined the collective temporal and spatial activity profiles of layer 2/3 neurons and neuropil during spike-wave seizure activity in the visual cortex of 9 stargazer mice, a monogenic absence epilepsy model. The calcium signal is an indirect but well-established surrogate measure of electrical activity in cortical neurons. With a mean $\pm$ SEM of 30.9 ± 4.3 neurons and 13.6 ± 1.3 patches of neuropil per dataset, we show that both neurons and neuropil in superficial layers of visual cortex are only sparsely and non-uniformly coupled to EEG synchronization. Unexpectedly, the majority of neurons ($81.2 \pm 3.5\%$, mean $\pm$ SEM) were

significantly less active in the ictal compared to the interictal state. Only a small proportion of cells were significantly more active during seizures ($4.1 \pm 1.5\%$). In contrast, $99.3\% \pm 0.7\%$ of neuropil patches had significantly reduced activity during the ictal state with only 1 patch of neuropil showing no significant change. When aligning the activity from all neurons and neuropil with the onset of seizures, the ictally suppressed neurons and neuropil show a significant but gradual reduction in activity several seconds before the first spike of the seizure. When aligned to the last seizure spike, activity returned to baseline within one second in the neuropil, while neurons lagged behind by 2-5 seconds. Furthermore, seizure-participation dynamics within this upper layer pool are not static, but fluctuate on a flexible (seconds to days) time scale within and across seizure episodes, indicating a loose and temporally transient community structure. Spatial patterns showed similar flexibility. Our results demonstrate that the conventional view of cortical neuronal ensemble behavior during a generalized spike-wave seizure as a fixed hypersynchronous unit overlooks a distinct separation of superficial cortical networks from stereotyped pathophysiological thalamocortical oscillations. This complex portrait of dynamic neuronal participation has major implications for deciphering cortical network excitability during hyperactive EEG states.

Movement Disorder

S114. To Study Falls in Parkinson Disease

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Objective: Why Do Patients with Parkinson Disease Fall?: A Single Center Experience.

Background: Falls are a major cause of disability in Parkinson disease (PD) patients. In this study, we investigated the risks associated with repeated falls in PD.

Design/Methods: Data were collected from 404 PD patients followed for one year in an outpatient setting.

Results: Of the 404 patients, 197 (49%) were non-fallers, 142 (35%) single fallers and 65 (16%) recurrent fallers. Single fallers (5.9 ± 2.5 yrs., 19.7 ± 8.3 UPDRS score) resembled non-fallers (5.4 ± 2.2 yrs., 18.9 ± 8.3 UPDRS score) in duration and severity of PD. Recurrent fallers differed significantly from single and non-fallers, having longer disease duration (12.6 ± 6.8 yrs., $P < 0.001$) and greater disease severity (32.3 ± 12.6 UPDRS score, $P < 0.001$). Recurrent fallers differed significantly from single and non-fallers in postural stability: "pull test" (23 (12%) of non-fallers, 19 (13%) of single fallers and 31 (48%) of recurrent fallers scored abnormally on this test) and one-leg stance test (11 (6%) of non-fallers, 22 (16%) of single fallers and 43 (66%) of recurrent fallers were impaired on this test). Recurrent fallers differed from single and non-fallers with a higher prevalence of Freezing of Gait, "FOG" (12 (6%) non-fallers, 19 (13%) single fallers, and 31 (48%) recurrent fallers received an abnormal score of greater than 1 on this test. The odds of obtaining an abnormal score on the FOG test were 2.4 times higher for single fallers in comparison to

non-fallers, 5.9 times higher for recurrent fallers in comparison to single fallers, and 14.1 times higher for recurrent fallers in comparison to non-P ($P < 0.001$).

Conclusions: Among fallers, postural stability was more impaired than locomotion. Strategies that improve the evaluation and treatment of postural stability should be emphasized in PD patients who fall.

S115. White Matter Abnormalities in Distinct Phenotypes and Putative Genotype of Spasmodic Dysphonia

Serena Bianchi, Giovanni Battistella and Kristina Simonyan.
New York

Spasmodic dysphonia (SD) is a form of focal dystonia characterized by involuntary spasms of the larynx impairing normal speech production. Two types of SD have been described, abductor (ABSD) and adductor (ADSD). In the former, the vocal folds hyper-abduct, making the voice breathy and weak; in the latter, the vocal folds abnormally adduct, making the voice strained or strangled. While the etiology of SD is unknown, evidence suggests that, similar to other forms of dystonia, SD may also have a hereditary basis.

In the brain, previous studies have shown that SD is associated with structural and functional abnormalities in cortical and subcortical regions underlying sensorimotor control. However, little is known regarding the neuroanatomical correlates of distinct SD phenotypes (ABSD, ADSD), and the genetic predisposition to this disorder. To address this limitation, the current study examined structural differences in white matter distribution between 1) ABSD and ADSD patients; and 2) SD patients with (familial) or without (sporadic) a family history of dystonia.

Diffusion-weighted images (DWI) of ABSD (N=30) and ADSD (N=30), as well as familial (N=22) and sporadic (N=23) SD patients were acquired on a 3T scanner. Following image pre-processing, phenotype and genotype-related differences in white matter distribution were measured as changes in fractional anisotropy (FA), and examined at the whole-brain level using Tract-Based Spatial Statistics analyses (TBSS).

Results showed differences in FA between ABSD and ADSD patients in the right cingulum, splenium, retrolenticular internal capsule, pre-supplementary motor area, precuneus, inferior frontal gyrus (Pars orbitalis), and left inferior temporal lobe. Differences in FA between familial and sporadic patients were found in the right inferior longitudinal fasciculus, and left superior longitudinal fasciculus.

These findings are consistent with previous neuroimaging studies of SD, indicating abnormalities in premotor and language-related regions. By revealing differences between ABSD and ADSD individuals, as well as familial and sporadic SD patients, moreover, these results suggest that SD is a heterogeneous disorder, with different neurological profiles underlying SD clinical phenotypes and putative genotype. Future neuroanatomical characterizations of SD phenotypes and genotype may contribute to the development of novel

diagnostic tools, as well as to identify neurological risk factors in families with one or more affected members.

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S116. A Translational Approach to Analyze Spatial and Temporal Gait Parameters: Normal and Parkinsonian Gait Signatures in Mice and Human

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Impairment of gait can manifest itself in various ways and be due to pathology at any CNS level. This implicates involvement of multiple CNS pathways in gait control, but these circuitries remain poorly understood. Powerful functional anatomical approaches are now available to unravel these circuitries in mouse models. However, a major hurdle for translating between mouse and human models involves the differences between quadruped gait in mice and biped gait in humans. We present a novel model to analyze spatial and temporal gait parameters as a function of velocity in both mouse models and human subjects.

To capture mouse data we used 8 cohorts C57Bl6J, VGaT-ires-cre, VGlut2-ires-cre, VGaT^{fl/fl} or VGlut2^{fl/fl} mice. In each group, we manipulated a distinct CNS target to study its role in the control of spatial and temporal gait parameters. This included 6OHDA microinjections into the substantia nigra or s.c. MPTP to induce parkinsonism, and selective modulation or loss of function of excitatory or inhibitory forebrain or pontomedullary cell groups using chemogenetic approaches or deletions. Each cohort served as its own control. We captured gait on a runway using high speed video gait analysis (Matlab). For human data, we used ground walking trials from healthy controls and subjects with Parkinson's Disease (PD) from Frenkel-Toledo et al, J NeuroEng Rehab, 2005 and Yogeve et al., Eur J Neurosci, 2005. Gait parameters were plotted as a function of velocity, and the best fit regression model was determined prior to comparing data sets.

In mice, each gait parameter behaves differently as a function of velocity. At walking speeds this can be captured using a simple linear or non-linear regression model. The human data shows remarkably similar relationships. Regression curves for gait parameters of the various experimental mouse cohorts shifted differentially, indicating region and cell-type specific control of gait parameters. Shifts in regression curves also occurred in PD subjects compared to control, resembling the MPTP and one of the pontomedullary reticular formation mouse models, but not the 6OHDA model.

This approach provides a powerful tool to reproducibly analyze behavior of distinct gait parameters as a function of velocity in various mouse models, as well as in human gait disorders. As such, it offers new and important translational opportunities to close the gap between mouse and human gait models.

S117. Distinct Synuclein Seeds in Parkinson Disease and Multiple System Atrophy

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Objective: To determine whether seeding activity of alpha-synuclein differs between Parkinson disease (PD) and Multiple system atrophy (MSA).

Background: There is growing evidence from both *in vitro* and *in vivo* studies that in many neurodegenerative diseases, including synucleinopathies, cell-to-cell transmission of a pathological protein occurs and may be a vehicle for spreading of pathology throughout the brain. This misfolded protein, or seed, further templates misfolding of native protein within the cell. Pathologic proteins may exist in diverse conformations with distinct cellular and biochemical properties.

Methods: We utilized a cell-based system which detects aggregation of synuclein as an increase in FRET signal (Holmes and Furman, *PNAS* 2013). We used this assay to measure seeding activity in detergent soluble and insoluble fractions of brains from PD and MSA patients. We then assessed the morphology of aggregated synuclein in the reporter cells by fluorescence microscopy.

Results: The FRET assay detects seeding from recombinant synuclein fibrils in the picomolar range ($p < 0.007$) while not detecting seeding of other amyloid types. Moreover, it is the first assay to robustly detect synuclein seeding activity in both synucleinopathies. While insoluble fractions showed seeding activity in both diseases ($p < 0.0005$), MSA showed robust seeding in the soluble fraction ($p < 0.0006$). Control samples of brains from non-synucleinopathy patients did not show significant seeding activity. Morphology of the seeded aggregates was also distinct between the two diseases; in PD a circumscribed form of aggregate predominated while in MSA, aggregates were more wispy and filamentous. On serial passage, only this latter type of aggregate was perpetuated.

Significance: We have found clear differences in synuclein seeding activity and aggregate morphology in MSA and PD, supporting the idea of a conformational difference between the pathologic synuclein found in these diseases.

Multiple Sclerosis

S118. Coordinated B Cell Compartmentalization with Antigen Presentation in a Murine Autoimmune Model of Multiple Sclerosis

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The mechanisms by which B cell antigen presentation directs the propagation of CD4 T cell auto-reactivity in an antigen-specific, major histocompatibility complex II (MHCII)-dependent manner during multiple sclerosis (MS) remain unclear. We have previously shown that antigen presentation exclusively by B cells can be sufficient to propagate CNS inflammatory demyelination in the animal model

of MS, experimental autoimmune encephalomyelitis (EAE). We hypothesized that the delay in onset of disease is observed when B cells are the exclusive antigen presenting cell during EAE is due to restrictions on B cells for access to central nervous system (CNS) antigens. We sought to determine the timing and capacity of B cells to capture and present antigen to propagate encephalitogenic CD4 T cell responses during autoimmune neuro-inflammation. We induced passive EAE using encephalitogenic CD4 T cell lines that target myelin oligodendrocyte glycoprotein (MOG). Experimental recipients included WT mice, mice with MHCII expression restricted to B cells that express a higher frequency of MOG-specific receptor (termed IgHMOGxBMHCI), and tamoxifen (TAM)-inducible MHCII expression exclusively by B cells that express a higher frequency of antigen receptor for MOG (termed IgHMOGxBTam-MHCI). Induction of MHCII expression by B cells following TAM administration was rapid and reached maximal expression within three days. IgHMOGxBTam-MHCI mice were resistant to passive EAE until TAM administration. Encephalitogenic T cells facilitate initiation of EAE by B cells independent of MHCII, as the number of days before onset of disease shrinks as the number of days T cells are present before TAM administration increases. This coincides with a build up of B cells in the meninges without B Cells infiltration into the spinal cord parenchyma during EAE. Based on our data, we conclude that B cells are capable of accessing CNS myelin targets via localization to the meninges and rapidly eliciting CD4 T cell-dependent neuro-inflammation upon cognate interactions. However, coordination of these interactions depends upon cognate-independent T cell signals that ultimately dictate the tempo of neuro-inflammation mediated by B cell antigen presentation during EAE.

S119. Macromolecular Proton Fraction (MPF) Mapping Strongly Correlates with Histologically Assessed White and Gray Matter Demyelination in the Murine Cuprizone Model

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Introduction: Cuprizone-induced demyelination is a widely used model in preclinical multiple sclerosis (MS) research. In MS, which is traditionally considered a white matter (WM) disease, the primary role of gray matter (GM) demyelination as a pathological substrate of disability progression has been recently recognized. A recently developed quantitative MRI method, fast macromolecular proton fraction mapping (MPF) has shown a promise as a biomarker of myelin in human and animal studies with a particular advantage of sensitivity to GM demyelination.

Purpose: Histologically validate the capability of MPF mapping to quantify myelin loss in WM and GM using the cuprizone-induced murine demyelination model.

Methods: Whole-brain three-dimensional (3D) MPF maps were obtained using an 11.7T small-animal MRI scanner with 100x100x500 μm resolution from 7 cuprizone-treated (0.3% solution in drinking water during 8 weeks) and 7 control C57BL/6 mice. MPF maps were reconstructed using the recently proposed single-point synthetic-reference method which requires only three source images for MPF determination. After scanning, brain sections were stained histologically using Luxol Fast Blue (LFB) for myelin quantification. MPF and LFB staining intensity were estimated in a series of WM and GM structures including corpus callosum, anterior commissure, internal capsule, thalamus, caudoputamen, and cortex. The differences between groups in MPF and LFB staining intensity were assessed using one-way ANOVA. Relationships between MPF and histology were examined using Pearson's correlation coefficient (r).

Results: Cuprizone-treated animals showed significant demyelination according to LFB staining ($p < 0.05$) and reduction in MPF ($p < 0.05$) in all WM and GM anatomical structures. MPF values across anatomical structures strongly correlated with quantitative histology in both the animal groups taken separately ($r = 0.95$, $p = 0.003$ for the treatment group and $r = 0.92$, $p = 0.009$ for the control group) and combined sample ($r = 0.93$, $p < 0.001$).

Conclusions: Fast 3D MPF mapping provides a robust and accurate clinically-targeted quantitative myelin imaging modality that showed the capability to detect demyelination in normal-appearing WM and GM in recent MS and mild traumatic brain injury studies. This study provides the first quantitative histological validation of the fast MPF mapping method in an animal demyelination model. Very strong correlation between histological myelin staining and MPF suggests that myelin loss is a major or even sole pathological substrate of MPF changes in both WM and GM in MS and other demyelinating diseases.

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S120. In Vivo Imaging of Cortical Demyelination and Remyelination in a Mouse Model of Multiple Sclerosis

Jennifer L. Orthmann-Murphy, Ethan G. Hughes, Peter Calabresi and Dwight Bergles. Baltimore, MD

People with progressive multiple sclerosis (MS) accumulate disability, developing difficulty with mobility, worsening fatigue and cognitive issues, as well as brain atrophy. These features are associated with cortical involvement, illustrating that damage in MS is not limited to the white matter. Cortical demyelination is a feature of MS pathology, but is undetectable on standard MRI sequences. To develop effective interventions for prevention or repair of progressive MS, it is critical to understand the dynamic relationship between cortical demyelination and remyelination, as well as the effect on underlying axons. We have developed a system to directly visualize the ongoing process degeneration and regeneration of cortical oligodendrocytes in an animal model of MS.

We performed craniotomies on 6-9 week old MOBP-EGFP transgenic mice (which express EGFP in mature oligodendrocytes), implanting chronic cranial windows over the somatosensory cortex. 8-12 week old mice are then fed 0.2% cuprizone-supplemented chow (or control chow) for at least 3 weeks to induce a toxic oligodendrocytopathy and demyelination in the cortex. We performed in vivo two-photon time-lapse imaging of the same region in the somatosensory cortex every 3 to 7 days on anesthetized mice prior to cuprizone supplementation (baseline), over the course of cuprizone-supplementation, and for up to 8-10 weeks after stopping cuprizone (recovery).

Preliminary observations show that 2 weeks of cuprizone supplementation are sufficient to detect oligodendrocyte loss and demyelination in layer 1 of the cortex. Loss of most of the oligodendrocytes present at baseline imaging continues through the duration of treatment and an additional 2 weeks following cessation of cuprizone. Most oligodendrocytes appearing on or after the last day of cuprizone supplementation remain as mature oligodendrocytes. Newly formed oligodendrocyte cell bodies appear in locations distinct from degenerated oligodendrocytes. During the time course of oligodendrocyte loss, myelin internodes fragment and form debris; these may be replaced by internodes from newly formed oligodendrocytes during the recovery period. In addition, new oligodendrocytes may form both remyelinated internodes as well as novel myelin internodes not present at baseline.

These findings demonstrate that we can successfully monitor the dynamics of demyelination and repair in the intact cortex of an animal model of multiple sclerosis. In future studies, this approach will allow us to test novel therapeutics targeting remyelination.

Cerebrovascular Disease

S121. Differences Between Lacunar Infarcts and Deep Intracerebral Hemorrhage: A Nested Case-Control Study from the Framingham Heart Study

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Introduction: Small vessel disease (SVD) is a precursor of clinical stroke and dementia. Two apparently diverse manifestations of SVD are lacunar ischemic stroke (LIS) and non-lobar intracerebral haemorrhage (NLICH), which share many epidemiologic and neuroanatomical characteristics: They affect primarily deep, subcortical areas, and 80% have concomitant hypertension. However, what predisposes some patients to ischemic stroke and others to haemorrhage is not well understood.

Materials and Methods: We performed a nested case-control study comparing two groups, persons with incident NLICH and those with LIS, to age- and sex-matched controls (1:3 matching) for baseline prevalence and levels of cardiovascular risk factors. Hypertension, diabetes, current smoking, atrial fibrillation and history of cardiovascular disease (coronary heart disease, clinical heart failure,

intermittent claudication) were examined as dichotomous variables. Systolic and diastolic blood pressure (SBP and DBP), body mass index (BMI), total cholesterol and high-density lipoprotein (HDL) were studied as continuous variables.

Results: We identified 118 LIS (mean age at matching 74 years, 51% male) and 108 NLICH (75 years, 46% male) events. Compared to their controls, LIS cases had higher prevalence of diabetes (33% vs 10%, $p<0.001$), hypertension (85% vs 62% $p<0.001$), smoking (21% vs 10%), higher SBP (150 vs 140 mmHg, $p<0.001$) and DBP (81 vs 76 mmHg $p<0.001$), lower HDL (44 vs 50 mg/dl, $p=0.004$) higher BMI (28 vs 27, $p=0.016$) and obesity (36% vs 23% $p=0.012$). Compared to their controls, NLICH were more likely to have hypertension (78% vs 67% $p=0.047$), higher mean SBP (150 vs 139 mmHg, $p<0.001$), mean DBP (80 vs 75 mmHg $p=0.01$) and lower BMI (26 vs 27 $p=0.013$). There was an overrepresentation of subjects with BMI <20 in the NLICH group compared to their controls (8% vs 2% $p=0.047$). Compared to LIS cases, NLICH cases had lower prevalence of diabetes (16% vs 33% $p=0.015$), higher HDL (52 vs 44 mg/dl $p=0.015$) and lower BMI (26 vs 28 $p<0.001$) and a significantly lower proportion of overweight (57% vs 75% $p=0.008$) and obese (15% vs 36% $p=0.001$) subjects.

Conclusion: Hypertension was more common in persons with both LIS and NLICH. Subjects with incident LIS were significantly more likely to be diabetic, obese and have lower HDL consistent with a metabolic syndrome. NLICH cases had lower BMI compared not only to LIS but to their controls as well; this finding is unexplained and merits further exploration.

S122. Large Vessel Occlusion Predicted by Stroke Screening Scales

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Objective: Patients with a large vessel occlusion (LVO) can benefit from thrombolytic therapy in conjunction with endovascular recanalization (Chen, Neurology, 2015). There are several screening tools to assess acute stroke patients and identify those with a LVO. The objective of this study is to compare the sensitivity and specificity of different stroke scales in detecting large vessel occlusion.

Methods: 113 patients presenting within 8 hours of symptom onset to two Midwest metropolitan tertiary care centers were retrospectively reviewed. Based on the initial National Institute of Health Stroke Scale (NIHSS) documented, the patients were scored using the Los Angeles Motor Scale (LAMS), the 3-Item Stroke Scale (3ISS), the Cincinnati Prehospital Stroke Scale, or FAST screen, and the Cincinnati Prehospital Stroke Severity Scale (CPSSS). Patients were then categorized based on presence or absence of a LVO based on radiologic contrast imaging. Sensitivity and specificity for LVO were calculated based on the following parameters based on literature: NIHSS ≥ 14 , FAST ≥ 2 , LAMS ≥ 4 , CPSSS ≥ 2 , 3ISS ≥ 4 (Sato, Neurology, 2008;

Nazliel, Stroke, 2008; Singer, Stroke, 2005; Kothari, Annals of Emergency Medicine, 1999; Katz, Stroke, 2015).

Results: In our cohort of patients, out of 113 patients evaluated over a 12 month period, 22 patients (19%, mean age 66 ± 22 years, mean NIHSS 13) were diagnosed with LVO. The NIHSS had a sensitivity rate of .27 and specificity rate of .95., FAST demonstrated a .86 sensitivity and .70 specificity, LAMS demonstrated a .05 sensitivity and .97 specificity, CPSSS had a .41 sensitivity and .96 specificity, and 3ISS had a .09 sensitivity and .99 specificity.

Conclusion: Stroke screening scales have high specificity to discern LVO when evaluated in a group of stroke patients seen by a neurologist in the ED or by telemedicine. In our population, the FAST screen was the most sensitive and specific tool for predicting LVO. Utilization of the most sensitive screening tool is important and can be particularly useful in the prehospital setting when triaging patients to a facility that can provide the most appropriate level of care. If a LVO is suspected, direct transportation to a facility capable of endovascular recanalization may provide the best outcome for these patients.

S123. Normalization of BUN/Creatinine Ratio in Acute Ischemic Stroke Patients Is Associated with Less Infarct Expansion

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Background: A volume contracted state (VCS) at the time of acute ischemic stroke may contribute to worsened short term clinical outcome. The potential mechanism for the effect of baseline volume status on outcome is not understood, but might include early infarct expansion. In this study we sought to investigate how changes in VCS influence infarct expansion within 24 hours of tPA administration.

Methods: Patients from the observational NIH Natural History of Stroke study who had MRI scans performed before, 2 hours after, and 24 hours after treatment with tPA were screened for inclusion. Those with a lesion on perfusion weighted imaging (PWI) thresholded at a time-to-peak of 4 seconds were included in this analysis. Blood chemistries were performed on admission and 24 hours later as per standard of care. A VCS was predefined as an elevated BUN/creatinine ratio > 15 . All MRIs were co-registered to a template atlas and stroke lesions measured by a stroke neurologist blinded to the patient's volume status. Stroke sizes using an apparent diffusion coefficient threshold of 600. Patients were considered to be tPA non-responders if infarcts expanded between the pre-treatment and 2 hour post-treatment MRI scans. Final infarct expansion defined as any increase in lesion size was measured at 24 hours relative to the pretreatment MRI.

Results: Of the 54 patients who met inclusion criteria, 32 (59%) demonstrated elevated BUN/creatinine ratio at the time of stroke presentation consistent with our definition of a VCS. Of these patients 21 (39%) were tPA non-responders. Patients in a VCS were more likely to

have a decrease in their BUN/creatinine ratio over the next 24 hours ($p=0.025$) compared with non-VCS patients who tended to have modest increases in BUN/creatinine ratio. tPA non-responders who were in a VCS had significantly less increase in their infarct size at 24 hours ($p=0.035$).

Conclusion: Stroke patients treated with tPA who present in a VCS demonstrate a decrease in their BUN/creatinine ratio during the subsequent 24 hours presumably due to more aggressive hydration. In the absence of early response to tPA, patients who normalize their BUN/Creatinine ratio also had less infarct expansion during the same time period. These findings suggest that fluid resuscitation may be a beneficial adjunct treatment to tPA for all patients. Further studies are needed to explore this hypothesis.

Epilepsy

S124. HLA-B*40:02 and HLA-DRB1*04:03 as Genetic Markers for Oxcarbazepine Induced Maculopapular Eruption

Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Korea

Oxcarbazepine (OXC) is a widely used antiepileptic drug for partial seizures, developed through structural variation of carbamazepine. Although it has a lower risk of cutaneous adverse drug reactions (cADRs) than carbamazepine, the cADRs ranging from maculopapular eruption (MPE) to the more severe Stevens-Johnson syndrome and toxic epidermal necrolysis still limits the use of OXC in some patients. A few human leukocyte antigen (HLA)-related genetic risk factors for carbamazepine-induced cADR have been identified. However, the HLA-related genetic risk factors associated with OXC-induced cADR are not yet well known.

We performed HLA genotyping in 110 Korean patients with epilepsy, including 40 patients presenting OXC-induced MPE and 70 OXC-tolerant patients. The HLA-B*4002 and HLA-DRB1*0403 alleles were significantly associated with OXC-induced MPE, in comparison with the OXC-tolerant group (odds ratio [OR] 4.33, $p = 0.013$ and OR 14.64, $p = 0.014$, respectively) and the general Korean population (OR 4.04, $p = 0.001$ and OR 3.11, $p = 0.013$, respectively). The frequencies of the HLA-B*1501 were significantly lower in the OXC-MPE group than in the OXC-tolerant group (OR 0.18, $p = 0.027$) and the Korean population (OR 0.22, $p = 0.04$). The allele frequencies of well-known HLA-related risk factors for carbamazepine-induced cADRs (HLA-B*1502, A*3101, and B*1511) were not different among the 3 groups.

This study is the first to demonstrate the association of HLA-B*4001 and HLA-DRB1*0403 with OXC hypersensitivity from the largest cohort of OXC-induced MPE patients. These findings need to be confirmed in future studies in different ethnic groups.

S125. Cyclicality and Clustering of Spontaneous Recurrent Seizures in Mouse Pilocarpine Model of Temporal Lobe Epilepsy

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Pilocarpine administration to mouse results in status epilepticus and after several weeks generates a model of temporal lobe epilepsy, characterized by spontaneous recurrent seizures (SRSs). In this study, we identified that SRSs in this mouse model appear in clusters with regular cyclicality.

The pilocarpine-induced temporal lobe epilepsy model was generated by single systemic injection of pilocarpine (330-400 mg/kg, i.p.) to 5-week old C57/B mice. The onset of status epilepticus (SE) was defined as the beginning of continuous tonic-clonic seizure after several discontinuous convulsive seizures and diazepam (5mg/kg, i.p.) was given 30-40 min after the onset of SE to interrupt prolonged seizures. The EEG surgery was performed between 3 to 6 weeks after induction of SE and continuous video-EEG monitoring was performed.

We continuously monitored 7 cases of pilocarpine-induced epilepsy mouse model for the average of 38.4 ± 7.1 days. The mean seizure frequency of the models was 2.64 ± 0.76 times per day. Over 90% of the seizures occurred in cluster, therefore it could be clearly divided as 'seizure-free' period and 'active seizure' period within a model. The median time of single seizure cluster was 6.5 days (range 2-13 days) and most of the seizure cluster displayed the unimodal curve in seizure frequency with a peak in the middle of the cluster. The average median cluster peak-to-peak interval was 18 days (range 12-20 days) and the median seizure free period was 9 days (range 2-14 days). Although the cluster intervals were slightly different among individuals, it displayed a regular interval within a model.

This is the first study to demonstrate cyclicality of SRSs in mouse pilocarpine model of temporal lobe epilepsy. This nature of SRSs should be considered when using the pilocarpine model to evaluate the antiepileptic effects of novel compounds, and it should be distinguished from the effect of seizure cycle *per se*. On the other hand, we suggest that pilocarpine model can be used as an appropriate model for studying the mechanisms of ictogenesis.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Staff

S126. Is Laser Ablation of Mesial Temporal Structures the New Surgical Treatment of Intractable Temporal Lobe Epilepsy?

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Rationale and Aims: MRI-Guided Laser Ablation (MRI-GLA) of mesial temporal structures is a relatively new minimally invasive surgical technique that has been used over the last three years in the management of patients with treatment-resistant temporal lobe epilepsy (TLE). The purpose of this study was to assess the post-surgical seizure

outcome and to assess the occurrence of neuropsychological and psychiatric complications in patients who had at least one year of post-surgical follow-up.

Methods: Nineteen patients (nine women), underwent a MRI-GLA at the Comprehensive Epilepsy Center of the University of Miami and had at least 12 months of follow-up (mean 19.2 ± 4.5 months). Ten were performed in the left and nine in right mesial temporal structures. Patients were seen in follow-up visit at one, 4, 8 and 12 weeks and every three months thereafter. At each visit, the seizure frequency, psychiatric and cognitive symptoms and adverse events of antiepileptic medications were established.

Results: Among the 19 patients, 11 (58%) had remained free of disabling seizures since the time of surgery and two (10%) had one breakthrough seizure after stopping the medication but became seizure free after restarting them (Engel Class I: 68%). Three patients (16%) had two seizures (Engel Class II), two (10%) had three to 5 seizures (Class III) and in one patient (5%), there was no change in seizure frequency (Engel Class IV). Post-surgical psychiatric complications requiring more than one pharmacologic intervention occurred in five patients (26.3%), three of whom had to be hospitalized in a psychiatric unit because of suicidal ideation (16%). All of these patients had a left sided ablation and a presurgical psychiatric history. Neuropsychological data were available in 10 patients. In four who underwent a left ablation there was a deterioration in verbal memory scores.

Conclusions: MRI-GLA appears to yield a comparable post-surgical seizure outcome to that of temporal lobectomies after at least one years of follow-up. Whether this seizure control is maintained overtime is yet to be established, however. MRI-GLA is associated with psychiatric complications particularly in patients with a presurgical psychiatric history who undergo a left sided ablation.

S127. Distinct Modes of Seizure-Like Hyperexcitability as Revealed in *Drosophila* Sodium Channel Mutants

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Mutations in genes encoding voltage-gated sodium (Nav), potassium (Kv), and calcium (Cav) channels are associated with a variety of heritable epilepsy syndromes. Interestingly, molecular lesions in homologous ion channel genes in the fruit fly *Drosophila melanogaster* lead to a variety of striking behaviors. Classic examples include many *Shaker* (*Sh*, Kv1) and *ether a go-go* (*eag*, Kv10) channel mutants displaying ether-induced leg shaking, and some *paralytic* Nav1 channel mutants showing high temperature-induced paralysis. Neurophysiological analyses of these mutants have linked ion channel gene mutations with altered cellular excitability and synaptic transmission properties, leading to aberrant circuit plasticity and motor pattern generation. This offers opportunities for systematic studies linking identified molecular lesions to functional modifications at both cellular and circuit levels in a genetic model system,

Drosophila, in which shorter generation time and high fecundity facilitates a high-throughput analysis.

In this report, we present a novel leg-shaking mutant, *Shaker-wings-down* (*Swd*) that displays severe ether-induced shaking and convulsions associated with seizure discharges. Surprisingly, we mapped *Swd* to a single non-polar amino acid substitution in the D3-S4 voltage sensor of paralytic, the only gene encoding Nav channels in *Drosophila*. At the larval neuromuscular junction, we demonstrated extreme excitability in motor axons reminiscent of the Kv double mutant *eag Sh*, but normal synaptic transmission properties. The observed neuronal hyperexcitability led to uncoordinated walking, abnormal motor program outputs, and aberrant spike discharges across the nervous system. To demonstrate that the entire functional consequences, from neuronal hyperexcitability to seizure behavior, arose from a single amino acid substitution in the Nav channel mutation, we adopted a CRISPR-based genome editing strategy. The characteristic behavioral and electrophysiological phenotypes of the *Swd* mutation, either generated in the original chemical mutagenesis screen or by CRISPR genome editing of the same amino acid replacement, rules out contributions from unknown genetic Background effects and defines a neomorphic mutation of the paralytic Nav channel gene that results in a unique hyperexcitability phenotype. Together, these findings represent a potentially important mechanism within the Nav channel that leads to specific neuronal hyperexcitability and neural circuit dysfunction as delineate by the *Swd* mutation.

Movement Disorder

S128. Disrupting Abducens Nerve Development Causes Duane Retraction Syndrome

Jong G. Park, Max A. Tischfield, Alicia A. Nugent, Long Cheng, Silvio Alessandro Di Gioia, Wai-Man Chan, Gail Maconachie, Thomas M. Bosley, Gail Summers, David G. Hunter, Caroline D. Robson, Irene Gottlob and Elizabeth C. Engle. Boston, MA; Durham, NC; Chevy Chase, MD; Cambridge, MA; Leicester, United Kingdom; Baltimore, MD and Minneapolis, MN

Duane retraction syndrome (DRS) is a congenital eye movement disorder defined by limited outward gaze of the eye, and retraction of the eye on attempted inward gaze. Previous MRI and EMG studies of patients with DRS found that the abducens nerve was absent or hypoplastic, and the lateral rectus extraocular muscle was aberrantly innervated by a branch of the oculomotor nerve instead of the abducens nerve. Although this pathology was well characterized, the developmental etiology of DRS remained unknown, in large part due to the lack of a robust animal model. In this study, we use a combination of human genetics and a new mouse model of DRS to provide evidence that the primary cause of the disorder is a failure of abducens nerve development. We identify three loss-of-function mutations in the gene *MAFB* in patients with DRS, and an additional dominant-negative mutation in *MAFB* causing both DRS and deafness. By using genotype-phenotype correlations in

humans and *Mafb* knockout mice, as well as *in vitro* studies of the dominant-negative mutation, we propose a threshold model for variable loss of MAFB function causing DRS and deafness. By performing embryonic whole mount preparations and orbital dissections in *Mafb* knockout mice, we demonstrate that selectively disrupting abducens nerve development is sufficient to cause secondary innervation of the lateral rectus muscle by aberrant branches of the oculomotor nerve. We observe that these aberrant branches of the oculomotor nerve form at developmental decision regions in close proximity to target extraocular muscles. Thus, we present genetic and developmental evidence that the primary etiology of DRS is failure of the abducens nerve to fully innervate the lateral rectus muscle in early development. This has important clinical implications, since our findings suggest that a wide variety of insults to the developing abducens nerve *in utero* can cause DRS.

S129. Framingham Risk Scores Predict a 2 Year Worsening in Motor Impairment in Parkinson Disease

Vikas Kotagal, Nicolaas I. Bohnen, Martijn L.T.M. Müller, Roger L. Albin and Kirk A. Frey. Ann Arbor, MI

Background: Parkinson disease (PD) progresses variably in different individuals for reasons that are not well understood. Vascular comorbidities may influence the rate of PD progression either by direct effects on nervous system integrity or through indirect effects mediated through other organ systems.

Methods: 32 subjects with PD underwent clinical testing at baseline and follow-up after approximately 2 years with the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor exam in the "off" state. Baseline testing also included vesicular monoamine transporter type 2 (VMAT2) [11C]DTBZ Positron Emission tomography (PET) to assess for nigrostriatal dopaminergic denervation and Pittsburgh Compound B [11C]PiB amyloid PET to assess for cortical amyloid plaque burden.

Results: 22 out of 32 subjects demonstrated a worsening of motor burden (increase in MDS-UPDRS motor exam score of >0) at follow-up (759.1 days $\pm$ 65.6). These subjects showed higher baseline 10-year General Cardiovascular Framingham risk (FR) scores (34.9% vs. 23.1%, $t=2.48$, $p=0.019$) compared to the 10 subjects who did not show a worsening. There were no differences between groups in age, baseline striatal DTBZ distribution volume ratio (DVR), or baseline cortical PiB DVR. In a posthoc logistic regression model controlling for baseline MDS-UPDRS motor score and disease duration, FR score still associated with motor progression status (Wald chi-square=3.93, $p=0.048$)

Conclusions: Vascular comorbidity burden may influence disease progression in PD, even in comparison to conventional measures of nigrostriatal and extranigral neuropathology burden.

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Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Kotagal

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S130. Use of Selective Serotonin Reuptake Inhibitors Does Not Improve Survival in Multiple System Atrophy

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Background: Loss of brainstem serotonergic neurons in multiple system atrophy (MSA) patients may cause respiratory dysfunction including stridor and increase the risk of sudden death. Augmenting serotonergic transmission through the use of selective serotonergic reuptake inhibitors (SSRIs) has been proposed to improve stridor and prolong survival in MSA.

Aim: To determine whether MSA patients who had taken SSRIs during their disease course had improved survival compared to those who had not taken an SSRI.

Methods: All patients diagnosed with MSA who completed standardized autonomic function testing between January 1998 and December 2012 at Mayo Clinic, Rochester were retrospectively reviewed. The use of SSRI medications, including name and dosage, was obtained from patient-provided medication lists in the electronic medical record. Clinical symptoms including motor, autonomic, and respiratory symptoms were collected from patient histories; the presence of stridor was obtained from clinical histories and polysomnogram, when available. Surviving patients were called to assess for development of stridor and initiation of an SSRI. Death data was recorded from the clinical record, Social Security Death Index, or via telephone contact. Survival analyses were performed using Kaplan-Meier Method.

Results: Of 685 MSA patients, 132 (19%) had used an SSRI during the disease course. Overall, median survival was 7.5 years (interquartile range 5.4 to 10.1 years) with no difference in survival in patients on an SSRI compared to those not on an SSRI ($p = 0.957$). SSRI users were more likely to be women compared to those who did not take an SSRI (64% versus 44%; $p = 0.0001$). While there was no difference in SSRI use between patients with MSA-

parkinsonism or MSA-cerebellar subtypes, 84% of SSRI users exhibited parkinsonism symptoms compared to 75% of non-SSRI users ($p = 0.027$). Falls were more common in SSRI users compared to those not on an SSRI (78% versus 64%; $p = 0.002$). Rates of stridor were similar in SSRI users (28%) compared to those not on an SSRI (25%; $p = 0.494$) based on patient report and in those who underwent polysomnography (53% versus 40%; $p = 0.181$).

Conclusions: SSRI use is not associated with improved survival in MSA. However, SSRI use was associated with higher rates of parkinsonism and falls, concerning for a negative effect on motor function in MSA.

S131. Preclinical Investigations of Sex-Specific Risk for Mild Cognitive Impairment in Parkinson's Disease: Androgen Effects on the Subthalamic Nucleus

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Clinical features of Parkinson disease (PD) differ in men and women. In addition to age of onset and motor phenotype, sex differences also characterize non-motor symptoms of PD including mild cognitive impairments. Numerous studies have explored mechanisms of estrogen protection in relation to these differences. However, using bilateral neostriatal 6-hydroxydopamine (6-OHDA) lesions to model the mild cognitive impairments of PD in rats, we discovered a link between circulating androgens and the ability of lesions to induce cognitive deficits. Specifically, in male rats and gonadectomized (GDX) male rats supplemented with testosterone (GDX-T) androgen levels are physiologic; while these subjects readily master cognitive demands in Barnes maze testing, after 6-OHDA lesions both groups show striking deficits in working memory and behavioral flexibility. In contrast, in GDX rats and GDX rats supplemented with E (GDX-E) androgen levels are low; while these subjects normally struggle with Barnes maze acquisition, following experimental DA lesions performance in both groups dramatically improves. Here we present parallel findings for group-specific effects of neostriatal DA lesions on neuronal firing in the subthalamic nucleus (STN)—a pivotal node in the frontostriatal circuits that mediate executive function and a key site of pathophysiology and therapeutic intervention in PD. Specifically, single units recorded in the STN of urethane-anesthetized male and GDX-T rats show normal patterns of slow, tonic firing; after 6-OHDA lesions mean frequencies and phasic bursting in STN neurons are significantly increased in these two groups. In contrast, in non-lesioned GDX and GDX-E rats STN firing is both faster than normal and often punctuated by high frequency bursting; after 6-OHDA lesions both measures of activity and reduced/restored to control values. Together, these data suggest that in male rats the ability of neostriatal 6-OHDA lesions to induce cognitive deficits and perhaps functionally related electrophysiological abnormalities in the STN is powerfully modulated by circulating androgen levels. Thus, while male vulnerability to aspects of PD including its cognitive signs has stimulated studies of potentially protective

effects of circulating estrogens, the present results suggest that examining roles for circulating androgens may be equally important for understanding PD. Further, androgens may prove especially relevant for managing cognitive impairments which are unaffected or exacerbated by most therapies used to treat PD, including deep brain stimulation of the STN.

S132. Apical Dendrite Degeneration, a New Cellular Pathology in Amyotrophic Lateral Sclerosis

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Upper motor neurons [corticospinal motor neurons (CSMN) in mice and Betz cells in humans] are important components of motor neuron circuitry because of their unique ability to initiate and modulate voluntary movement by receiving, integrating and conveying cerebral cortex input into spinal cord targets. Degeneration of Betz cells in amyotrophic lateral sclerosis (ALS) was documented as early as 1885, and has been accepted as a defining characteristic distinguishing ALS from other motor neuron diseases, the timing and the extent of Betz cell degeneration has been actively debated. Many studies suggested a degeneration starting from neuromuscular junction and moving towards cerebral cortex. This “dying-back” hypothesis diminished the importance of Betz cells as an important contributor to disease pathology, as it predicted that their death was a consequence of downstream events. We find that Betz cells of both familial and sporadic ALS as well as ALS/FTD patients display profound degeneration, especially at the site of their apical dendrite, whereas Betz cells of Alzheimer’s disease patients and healthy controls retain cellular integrity. The present study demonstrates the presence of apical dendrite defects in a broad spectrum of ALS, including sALS, fALS and FTD-ALS, but not in AD patients and controls. These profound cytoarchitectural defects in apical dendrites support the hypothesis that the cortical connectivity defects are an early event in ALS, and further suggest Betz cells as a novel cellular target for therapeutic interventions.

S133. If We Build It, Will They Come? Motivating Factors and Barriers for Participation in the DBS in Early PD Pivotal Trial

Lauren Heusinkveld, Mallory Hacker, Maxim Turchan, Christina Tamargo, William Fisher, Lauren McLaughlin, Adria Martig and David Charles. Nashville, TN and New York, NY

Introduction: Parkinson’s disease (PD) is a neurodegenerative condition for which no therapy is definitively proven to halt or slow the relentless progression of symptoms. Deep brain stimulation of the subthalamic nucleus (DBS) is effective in advanced and mid-stage PD for improving quality of life and motor symptoms and reducing medications. Preliminary data from a prospective, randomized pilot clinical trial suggests DBS in early stage PD reduces the relative risk of worsening for motor symptoms and complications of medical therapy compared to medication alone by 50-80% [1].

The FDA has approved a multicenter, phase III, pivotal clinical trial testing DBS patients with early stage PD (IDE#G050016). In collaboration with the Michael J. Fox Foundation for Parkinson’s Research (MJFF), we conducted a patient survey addressing motivating factors and barriers for considering participation in a future DBS in Early PD pivotal trial.

Methods: This IRB-approved survey (New England IRB#14-236) was distributed to early stage PD patients participating in Fox Insight, a virtual observational study led by the MJFF. Survey participants were provided with a description of the DBS in Early PD pivotal trial, the surgical procedure, and associated risks. Participants then indicated whether or not they would consider learning more about participating in a trial like this one and rated the importance of potential motivating factors and barriers on a five-point Likert scale.

Results: The survey was completed by 158 individuals with early stage PD who met basic inclusion criteria for the pivotal trial (age 50-70, disease duration <4 years, without dyskinesias or motor fluctuations). A large majority of early stage PD respondents (72%) indicated they would be interested in learning more about becoming a participant in a trial like this one. The most important motivating factors were possible slowing of PD symptom worsening (92%) and potential health benefits from DBS (84%). The greatest barriers were fear that participating in the trial could worsen one’s health (68%) and fear of risks associated with DBS surgery (61%).

Conclusions: A phase III, pivotal clinical trial evaluating DBS in 280 early stage PD patients has been approved by the FDA. The results of this inaugural Fox Insight external survey suggest patients will consider enrolling in a trial testing DBS in early stage PD.

[1] Hacker et al., *Parkinsonism Relat Disord.* 2015 Oct;21(10):1177-83.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Vanderbilt University receives income from grants and contracts with Allergan, Ipsen, Merz, and Medtronic for research led by Dr. Charles. Dr. Charles receives income from Allergan, Ipsen, Concert, and Medtronic for consulting and education services. There are no conflicts of interest for Lauren Heusinkveld, Mallory Hacker, Maxim Turchan, Christina Tamargo, William Fisher, Lauren McLaughlin, and Adria Martig. This work has been supported by the Michael J. Fox Foundation for Parkinson’s Research.

S134. Effects of Optimal Drug Therapy versus Deep Brain Stimulation on Employment in Early Stage Parkinson’s Disease

Christina L. Tamargo, Mallory L. Hacker, Taylor Hudson, Maxim Turchan, Sarah H. Millan and David Charles. Nashville, TN

Background: Parkinson’s disease (PD) progression is associated with increasing disability, often causing difficulty with work, early retirement, or unemployment. Many patients

who remain employed report disease-related complications at work. As a result, most PD patients reduce work or stop working within the first three years following a PD diagnosis [1].

Methods: The deep brain stimulation (DBS) in early stage PD pilot trial was a five-year prospective, randomized trial completed at Vanderbilt University (NCT00282152, IDEG050016, IRB #040797). Early stage PD subjects (age 50-75, medication duration between 6 months and 4 years, without dyskinesias or other motor fluctuations) were randomized to receive optimal drug therapy (ODT) or subthalamic nucleus DBS plus ODT (DBS+ODT). After study completion, subjects and their spouses or caregivers were invited to participate in a retrospective phone survey. This survey examined a variety of work-related topics, including employment status, employment history, demands faced on the job, and ways PD affected the ability to work. Statistics were carried out using a Chi-square test. Results are presented for subjects who were employed upon enrollment in the pilot trial.

Results: Twenty-one subjects or spouses/caregivers completed the survey. Of these, 12 study participants were employed upon enrollment in the pilot trial (6 ODT, 6 DBS+ODT). Almost everyone in the DBS+ODT group (5/6) was no longer working, ceasing employment $\sim 2.2 \pm 2.3$ years after enrolling in the study, versus 2 out of 6 in the ODT group ($\sim 2.5 \pm 1.8$ years after enrollment). None of the ODT subjects reported retiring on disability because of their PD, while a majority (4/6) of the DBS+ODT group did ($p < 0.05$). Slowness equally affected both groups' ability to work, with all subjects reporting this as a hindrance. Finally, while no DBS+ODT subjects reported handwriting as the factor that most contributed to their inability to work, 3 out of 6 in the ODT group did ($p < 0.05$).

Conclusion: These findings suggest that DBS+ODT in early PD may adversely impact employment. Limitations of this study include its retrospective nature and the small number of respondents in each group. Additional study is needed to confirm these findings, and employment data will be prospectively collected in the FDA-approved, phase III, pivotal clinical trial of DBS in early PD.

[1] Martikainen et al., *Mov Disord.* 2006;21(12):2187.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Vanderbilt University receives income from grants and contracts with Allergan, Ipsen, Merz, and Medtronic for research led by Dr. Charles. Dr. Charles receives income from Allergan, Ipsen, Concert, and Medtronic for consulting and education services. There are no conflicts of interest for Christina Tamargo, Mallory Hacker, Taylor Hudson, Maxim Turchan, or Sarah Millan. This work has been supported by: Vanderbilt CTSA grant UL1TR000445 from the National Center for Advancing Translational Sciences (NCATS), NCATS/NIH award UL1TR000011, NIH R01EB006136, Medtronic, Inc., and the Michael J. Fox Foundation for Parkinson's Research.

S135. Mass Spectroscopic Evidence for the Amine Inhibition of DOPAL Triggered Alpha-Synuclein Aggregation: New Neuroprotective Treatment Strategy for Parkinson Disease

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Objective: To inhibit 3,4-dihydroxyphenylacetaldehyde (DOPAL)-induced alpha synuclein (AS) aggregation and determine the molecular mechanism.

Background: AS aggregation contributes to Parkinson disease (PD) pathogenesis [JBC 289:21490, 2014]. DOPAL triggers AS aggregation and produces a rat PD model [Acta Neuropath 115:193,2008; PLoS One 5(12):e15251, 2010]. PD brains have high DOPAL [Europ J Neurol.1468.2010]. DOPAL triggers AS aggregation by forming Schiff-base adducts with lysine residues in AS [JBC 290:27660,2015].

Design/Methods: We determined if DOPAL forms Schiff-base adducts with amines in rasagiline and its metabolite, aminoindan, and inhibit DOPAL-triggered AS aggregation in vitro, and blocks DOPAL-induced PC-12 cell death. Various concentrations of rasagiline, aminoindan and dimethylaminoindan were incubated with DOPAL at 37°C for 10 minutes; then with 0.5 ug AS for 2 hrs. Controls contained drugs, DOPAL or alpha-synuclein alone. AS aggregates were separated on bis-tris gels, immunoblotted and quantitated by densitometry. PC-12 cells were cultured in the presence of 0.5-50 uM rasagiline or aminoindan in serum free medium for 2hrs and AS aggregation determined. PC-12 cells were cultured for 1-3 hrs with 1 uM DOPAL with or without 1uM rasagiline or aminoindan. Cell viability was determined using trypan blue exclusion. DOPAL (1.0mM) was incubated in the presence or absence of rasagiline, aminoindan or dimethylaminoindan (1.0-3.0mM) for 2hrs. Loss of DOPAL was measured by HPLC and adducts were identified by GC-Mass.

Results: Rasagiline and aminoindan reduced DOPAL-induced alpha-synuclein aggregates of all sizes (mono, di, tri, tetra, penta, hexa and polymeric forms) between 30-70% compared to DOPAL alone. Rasagiline or aminoindan (0.5 uM) inhibited DOPAL-induced AS aggregation in PC-12 cells. DOPAL killed 80-90% of PC-12 cells after 3hrs but in the presence of rasagiline or aminoindan 60-80% remained viable. DOPAL recovered was reduced with increasing time after incubation with rasagiline (79%+5.7 $p < 0.002$) or aminoindan (81% + 1.1; $p < 0.004$) but not with dimethylaminoindan. GC-MS demonstrated Schiff-base adducts between DOPAL+ rasagiline/aminoindan.

Conclusion: DOPAL forms a Schiff-base adduct with rasagiline and aminoindan. This adduct between DOPAL and amines in these drugs competes with the Schiff-base adduct between DOPAL and lysines in AS to inhibit DOPAL-induced AS aggregation in vitro and cell death associated with AS aggregation. We propose use of amines as a new neuroprotective therapeutic strategy in PD.

This research was supported by an investigator initiated grant from TEVA Pharmaceuticals, Kansas City, MO, USA.

S136. A Novel Spasticity Diagnostic Algorithm - A Case Study of the Kappa Paradox

Maxim Turchan, Taylor S. Hudson, Chandler Gill, Mallory L. Hacker, Amanda D. Currie, Anna L. Molinari, Thomas Davis, Fenna Phibbs, Christopher Tolleson, Candace Grisham, Daniel Byrne and David Charles. Nashville, TN and Chicago, IL

Background: Spasticity is a movement disorder that is both under-diagnosed and prevalent in vulnerable patient populations[1]. To improve the reliability of the diagnosis of spasticity, we developed a novel, flowchart-style, bedside algorithm that was tested by two neurologists at a long-term care facility.

Methods: Forty-three residents of a single long-term care facility provided informed consent and completed this study (IRB#090361, NCT01644123). Two neurologists with expertise in movement disorders independently performed brief neurological examinations using a flowchart-style algorithm that concluded with the determination of either presence or absence of spasticity. Cohen's kappa coefficient was used to evaluate the inter-rater reliability of this diagnostic algorithm.

Results: Raters agreed on the presence of spasticity in 7 subjects and the absence of spasticity in 31 subjects, representing an 88% observed proportion of agreement. Cohen's kappa was calculated to be 0.66 which represents substantial agreement between raters.[2] The Prevalence and Bias indices were 0.56 and 0.07, respectively. Consistent with the kappa paradox[3], this high Prevalence index and low Bias index depressed the maximum achievable kappa value to 0.80. Therefore, the raters' kappa reached 83% of the maximum attainable kappa value.

Conclusions: This novel, flowchart-style, bedside spasticity diagnostic algorithm demonstrated promising inter-rater reliability. Since the distribution of the raters' responses and the prevalence of the condition in the study population can artificially enhance or depress the apparent agreement, awareness of the kappa paradox is vital in interpreting the Cohen's Kappa statistic. Additional study is needed to validate and further enhance this bedside instrument. Improving the ease and efficiency of diagnosing spasticity will likely expand access to care for residents of long-term care facilities.

[1] Pfister et al., Archives of Physical Medicine and Rehabilitation 2003; 12: 1808–1812.

[2] Landis et al., Biometrics 1977; 33:159-174.

[3] Feinstein et al., Clinical Epidemiology 1990;43(6):543-9.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Vanderbilt University receives income from grants and contracts with Allergan, Ipsen, Merz, and Medtronic for research led by Dr. Charles. Dr. Charles receives income from Allergan, Ipsen, Concert, and Medtronic for consulting and education services. Dr. Phibbs has done consulting work for Medtronic. There are no conflicts of interest for Maxim Turchan, Taylor S Hudson, Chandler Gill, Mallory L. Hacker, Amanda

D. Currie, Anna L. Molinari, Thomas Davis, Christopher Tolleson, Candace Grisham, and Daniel Byrne.

S137. Statins and Risk of Parkinson's Disease: Insight Gained from a Large, National Claims Database

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Background: Using a large National Claims Database in the United States, we investigated the controversy surrounding the role of statins in Parkinson's disease.

Methods: The MarketScan Commercial Claims and Encounters database includes data from 30,343,035 subjects aged 40-65 years between January 1, 2008 and December 31, 2012. Parkinson's was identified via code for medical diagnosis, service procedures, or use of anti-parkinsonian medications. To provide a comparable neurodegenerative disease group, we also identified Alzheimer's disease patients via diagnosis code. First, we conducted a cross-sectional analysis to examine statin use in relation to Parkinson's prevalence. Second, the effect of statin use on Parkinson's incidence was assessed through a lagged matched case-control analysis of 2,458 pairs of Parkinson's cases and controls.

Results: In the cross-sectional analysis, usage of cholesterol-lowering drugs, statins or non-statins, was associated with higher Parkinson's prevalence (ORs=1.61-1.67, $p<0.0001$), but not with Alzheimer's disease (ORs=1.01-1.12, $p=0.055$) after adjusting for age, gender, and other comorbidities. Furthermore, the associations were strongest among patients with hyperlipidemia and similar across lipophilic and hydrophilic statins and other non-statin cholesterol-lowering drugs. The lagged case-control analysis confirmed the statin-Parkinson's association and showed "tolerance," namely, stronger effects in the earlier period after starting statins [the ORs and associated CIs for usage <1 , 1-2.5, ≥ 2.5 years are 1.93 (1.39-2.67), 1.83 (1.42-2.36), and 1.37 (1.15-1.64), respectively, with $P_{trend}<0.0001$].

Conclusions: Statin use was associated with higher risk of Parkinson's. The "tolerance" phenomenon suggests that statins may have an unmasking effect for an earlier onset of Parkinson's.

S138. Cognitive Impairment in Parkinson's Disease: Association Between Patient-Reported and Clinically Measured Outcomes in the Parkinson's Disease Biomarker Program

Kelly A. Mills, Jiangxia Wang, Angela Zhang, Emma Powers, Zoltan Mari, Catherine C. Bakker, Vanessa Johnson, Gregory M. Pontone, Alexander Pantelyat, Ted M. Dawson and Liana S. Rosenthal. Baltimore

Background: In Parkinson's disease (PD), cognitive impairment is subjectively assessed on the MDS-UPDRS in question 1.1 (Q1) by patient report, while the Montreal Cognitive Assessment (MoCA) is often used for objective assessment. Comparing objective and subjective measures of

cognition may provide insight into the patient's experience and relevancy of objective screening tools.

Methods: Clinical data from the NINDS Parkinson's Disease Biomarkers Program (PDBP), a longitudinal, multicenter biomarker study in PD, were extracted for analysis. We included 1186 individual PD patients, 42% of whom had data from at least two visits. Domain-specific composite scores were created from the MoCA by combining scores from individual tests that assess the same cognitive domain. A multinomial logistic regression analysis with robust standard error estimates adjusting for repeated measures from patients was fit using all MoCA composite domains as predictors of MDS-UPDRS Q1 to determine which domains had the largest impact on the relative risk of reporting a "1" (indicating slight cognitive impairment with no interference in daily function) rather than a "0" (indicating no cognitive impairment). Results are reported in relative risk ratios (RRR).

Results: Changes in visuospatial-executive performance (sequence alteration task, cube copy, and clock-drawing) and serial 7 subtractions had the largest degrees of impact on whether MDS-UPDRS Q1 was reported as "1" versus "0". The memory domain (delayed recall) had a smaller effect on chance of reporting a "1" versus "0". A 1-point increase in visuospatial-executive function decreased the chance of having a MDS-UPDRS Q1 score of "1 - slight" versus "0 - none" by 21.1% (RRR: 0.789, CI: 0.704, 0.885; $p < 0.001$) and decreased the chance of a MDS-UPDRS Q1 score of "2" rather than "0" by 43.4% (RRR: 0.565; CI: 0.475, 0.672, $p < 0.001$). A 1-point improvement in the serial 7 subtraction test decreased the chance of reporting "1 - slight" versus "0 - none" by 20.4% (RRR: 0.795; CI: 0.681, 0.928; $p = 0.004$).

Conclusions: Changes in visuospatial-executive and serial 7 subtraction performance on the MoCA are sensitive measures of change in patients' report of cognitive impairment on question 1.1 of the MDS-UPDRS. Conversion from a patient's report of "none" to "slight" cognitive impairment may depend on visuospatial-executive dysfunction and working memory more than other cognitive domains.

S139. Medullary Neuronal Loss and Alpha-Synuclein Burden in Multiple System Atrophy

Elizabeth A. Coon, Ann M. Schmeichel, Joseph E. Parisi, Phillip A. Low and Eduardo E. Benarroch. Rochester, MN

Background: Multiple system atrophy (MSA) is characterized by alpha-synuclein accumulation primarily as glial cytoplasmic inclusions (GCIs) and affects medullary autonomic and respiratory control areas, including the rostral ventrolateral medulla (VLM) and raphe nuclei. The relative neuronal vulnerability and its relationship to GCI accumulation in these areas are unknown.

Aim: To determine the extent of loss of adrenergic (C1) neurons in the rostral VLM and serotonergic neurons in the VLM, raphe pallidus, raphe obscurus and raphe magnus, and its relationship with GCI accumulation.

Methods: Sections of the medulla from 7 MSA (4 MSA-Parkinsonism and 3 MSA-Cerebellar) and 6 control subjects

were processed for tyrosine hydroxylase (TH), tryptophan hydroxylase (TrOH), and alpha-synuclein immunoreactivity. Neuronal counts were performed stereologically. GCI burden was quantified using object detection density (area/mm²). Co-staining with thionin and alpha-synuclein was used to assess for neuronal inclusions in all regions of interest.

Results: All MSA cases had orthostatic hypotension; 5 had laryngeal stridor. There was marked neuronal loss in the rostral VLM and medullary raphe in all cases. Most severely affected were TH-VLM (C1) neurons (83% reduction), followed by TrOH-neurons in the VLM (70%), raphe obscurus (56%), pallidus (57%), and magnus (47%). Alpha-synuclein density was highest in the raphe pallidus (0.0072), followed by the VLM (0.0056), raphe obscurus (0.0059) and magnus (0.0031). Alpha-synuclein density was less in the RMg nucleus compared to the VLM ($p = 0.035$) however alpha-synuclein density did not correlate with neuronal loss in any of the areas analyzed. There was no correlation between alpha-synuclein density and disease duration for any regions of interest. Alpha-synuclein accumulation occurred predominantly as GCIs with rare alpha-synuclein accumulation occurring within remaining neurons.

Conclusions: 1) There is severe neuronal loss in the VLM and medullary raphe which is consistent with previous studies and contributes to cardiovascular and respiratory dysfunction in MSA patients. 2) Adrenergic (C1) neurons may be more vulnerable than serotonergic VLM neurons. 3) Neuronal loss and alpha-synuclein (GCI) pathology may progress independently in medullary cardiorespiratory regions in MSA.

S140. The α -Synuclein Concentration in Plasma of Patients with Parkinson's Disease and Its Relation with Clinical Features as Well as with Mutation of Glucocerebrosidase

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The results of previous studies concerning the level of plasma α -synuclein (ASN) in patients with Parkinson's disease (PD) are controversial. There are only a few studies analysing the relation between plasma ASN level and heterogeneous symptoms of the disease.

The Aim: To investigate the relation between plasma ASN level and motor symptoms, cognitive functions, other non-motor symptoms as well as with the mutation of glucocerebrosidase (GBA) in patients with PD.

Methods: 138 patients with PD hospitalised in Neurology Department Medical College Jagiellonian University were performed sequencing the 8th and 9th exon of GBA gene. Next plasma ASN level was tested in 58 patients with sequenced GBA gene and in 38 healthy volunteers (HV). PD patients were assessed with the scales: UPDRS, Hoehn-Yahr, MMSE, MoCa, neuropsychological tests, Hamilton Depression Rating Scale, PD NMS Quest and SF-36. PiGD, TD and MIXED subtype were qualified on the basis

of UPDRS part II and III according to Jankovic method. The definition of early onset PD (EOPD) was the disease beginning before the age of 50 and late onset PD (LOPD) at or over 50 year old as.

The Results: There were 5 (3.6%) patients with N370S mutation and 11 (7.9%) with T369M polymorphism. The concentration of plasma ASN did not differ in PD patients and HV (median, respectively: 4.53 vs. 3.73 ng/ml, $p = 0.25$). Likewise plasma ASN level did not differ in PIGD, TD and MIXED subtype ($p = 0.46$). There was no relation between plasma ASN level and cognitive functions nor other non-motor symptoms. The level of plasma ASN did not differ between carriers of N370S mutation, T369M polymorphism, non-carriers and HV. There was inverse correlation between plasma ASN level and the disease severity in men ($R = -0.37$; $p = 0.047$), in PIGD subtype ($R = -0.33$; $p = 0.04$) and in patients with the disease lasting for ≤ 10 years ($R = -0.36$; $p = 0.049$). Patients with EOPD had higher plasma ASN concentration than patients with LOPD and healthy volunteers (median, respectively: 6.28 vs. 3.96 vs. 3.73 g/ml, $p = 0.019$). Ill male had higher ASN level than ill female (median, respectively: 4.96 vs. 3.13 ng/ml, $p = 0.013$).

Conclusions: There is relation between plasma ASN level and the severity of the disease in some subgroups of patients and with the sex.

S141. Alterations in 14-3-3 Protein Phosphorylation as a Biomarker for Neurodegeneration

Michael McFerrin, Xiaofei Chi, Leslie McClure, Gary Cutter and Talene A. Yacoubian. Birmingham, AL and Philadelphia, PA

Background: 14-3-3 proteins are a highly conserved family of proteins that play an important role in cell survival. 14-3-3s interact with key players implicated in Parkinson's disease (PD), including alpha-synuclein and LRRK2. We have shown that overexpression of certain 14-3-3 isoforms are protective in neurotoxin, alpha-synuclein, and LRRK2 models of PD, while inhibition leads to increased toxicity. Phosphorylation of 14-3-3s is a key mechanism for regulating 14-3-3 function. We recently observed that increased 14-3-3 phosphorylation is increased in several PD models and that phosphorylation of 14-3-3s reduces their neuroprotective effects.

Methods: In the current study we investigated 14-3-3 phosphorylation at three conserved sites, serine 58 (S58), serine 185 (S185) and serine 232 (S232), in postmortem temporal cortical samples from PD, Alzheimer's disease (AD), Lewy body dementia (DLB), progressive supranuclear palsy (PSP), and control subjects. Lysates from temporal cortices were fractionated into Triton X-100 soluble and insoluble fractions, and examined for 14-3-3 phosphorylation and total 14-3-3 levels by Western blotting.

Results: S58 phosphorylation was largely unchanged. S185 phosphorylation was elevated by 44% in Triton-soluble lysates in DLB. S232 phosphorylation was altered in several disorders, with a reduction in S232 phosphorylation in the soluble fraction by 44% and 34% in AD and DLB, respectively, and an increase in S232 phosphorylation by

37%, 42%, and 42% in PD, AD, and DLB, respectively, in the insoluble fraction. No phosphorylation changes were noted in PSP. Total 14-3-3 levels were dramatically reduced in the soluble fraction by 34% in AD and 37% in DLB.

Conclusions: Our data show that 14-3-3 phosphorylation is a marker of neurodegeneration, but these disorders differ in which phosphorylation sites are altered. These data point to the potential role of 14-3-3 phosphorylation in the pathophysiology of neurodegeneration and suggest that 14-3-3 phosphorylation may serve as a potential biomarker for neurodegeneration.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Talene Yacoubian declares that she has a US Patent #7,919,262 on the use of 14-3-3s in neurodegeneration.

S142. Repeat Associated Non-AUG Initiated Translation from GC Rich Repeats in Neurodegenerative Disease

Peter K. Todd. Ann Arbor, MI

Nucleotide repeat expansions underlie numerous human neurological disorders. Repeats can trigger toxicity through multiple pathogenic mechanisms, including RNA gain-of-function, protein gain-of-function, and protein loss-of-function pathways. Traditionally, inference of the underlying pathogenic mechanism derives from the repeat location, with dominantly inherited repeats within transcribed non-coding sequences eliciting toxicity predominantly as RNA via sequestration of specific RNA binding proteins. However, recent findings demonstrate that repeats outside of annotated open reading frames also trigger toxicity through a novel form of protein translational initiation known as repeat associated non-AUG (RAN) translation. RAN translation contributes to hallmark pathological characteristics in multiple neurodegenerative disorders, including ALS, Frontotemporal Dementia (FTD) and Fragile X-associated Tremor or Ataxia syndrome (FXTAS), by producing toxic homopolymeric or dipeptide repeat proteins. However, the specific sequence contexts and mechanisms underlying RAN translation remain largely unknown.

Using a series of reporter assays in vitro, in cells, and in cultured neurons, we have now defined some of the critical sequence and protein based factors required for RAN translation at two different repeats: the CGG repeat in FXTAS and the GGGGCC repeat in C9orf72 associated ALS and FTD. This work suggests that many aspects of canonical translational initiation are conserved in RAN translation, but that there are differences in the sites and modes of initiation across repeats and even at different reading frames of the same repeats. Importantly, specific mRNA sequence features and protein factors can selectively mitigate RAN, and targeting these processes suppresses toxicity in animal models. These results suggest a role for RAN translation in multiple neurodegenerative disorders and suggest specific targets for future therapeutics in repeat expansion diseases.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? I serve as a

consultant for and I have licensed technologies to Denali Therapeutics. As part of my compensation for this role, I receive stock options in the company.

Multiple Sclerosis

S143. Molecular-Based Diagnosis of Multiple Sclerosis and Its Progressive Stage

Peter Kosa, Christopher Barbour, Mika Komori, Makoto Tanigawa, Tianxia Wu, Kory Johnson, Ronald Herbst, Yue Wang, Keith Tan, Mark Greenwood and Bibiana Bielekova. Bethesda; Bozeman; Gaithersburg and Cambridge, United Kingdom

Background: Molecular taxonomy of cancers revolutionized oncology: biomarkers guide combination therapies specific for a patient's disease process and patient preselection leads to economical clinical trials. In contrast, polygenic central nervous system (CNS) diseases like multiple sclerosis (MS) lack a molecular diagnosis. Despite multifaceted pathophysiology and pathological heterogeneity, each MS patient is treated with a single drug without understanding what molecular mechanism(s) drive his/her disability. Therefore, we sought to develop a molecular signature of MS and its progressive stage(s) using reliable proteomic assay.

Methods: Using 1128 Slow Off-rate Modified DNA Aptamers (SOMAscan) and statistical modeling we identified in the blinded cohort of untreated patients with CNS diseases and healthy volunteers (n=225) a combinatorial biomarker of 17 cerebrospinal fluid (CSF) proteins that differentiates MS from other CNS diseases, including inflammatory, with an independent cohort (n=85)-validated area under the receiver operating characteristic curve (AUC) of 0.95.

Findings: Immunological biomarkers dominate the MS diagnostic test and over-representation of signaling lymphocytic activation molecule (SLAM) family members identifies these immunoregulatory molecules as a possible new therapeutic target. Primary- and secondary-progressive MS are biologically indistinguishable, with quantitatively comparable intrathecal inflammation to relapsing-remitting MS (RRMS). The molecular test that differentiates RRMS from progressive MS with a validated AUC=0.90 is based on 27 proteins and quantifies oligodendroglial and neuronal damage and LTA/LTB-related inflammation.

Interpretation: Validated molecular tests open opportunities for biomarker-supported drug development in MS, targeting processes poorly captured by imaging, such as neurodegeneration, compartmentalized inflammation in progressive MS and residual inflammation in partially-treated RRMS.

S144. Development of a Sensitive Outcome for Economical Drug Screening for Progressive Multiple Sclerosis

Peter Kosa, Danish Ghazali, Makoto Tanigawa, Irene Cortese, William Kelly, Blake Snyder, Joan Ohayon, Kaylan Fenton, Tanya Lehky, Tianxia Wu, Christopher Barbour, Mark

Greenwood, Govind Nair and Bibiana Bielekova. Bethesda and Bozeman

Background: There are no effective treatments for progressive multiple sclerosis (MS). Based on the transformative role magnetic resonance imaging (MRI) contrast-enhancing lesions had on drug development for relapsing-remitting MS, we consider the lack of sensitive outcomes to be the greatest barrier for therapeutic advancement in progressive MS. The purpose of this study was to compare 58 prospectively-acquired candidate outcomes in the real-world situation of progressive MS trials, to select and validate the best-performing outcome.

Methods and Findings: The one year pre-treatment period (i.e., before randomization) of adaptively-designed IPPoMS (NCT00950248) and RIVITaLise (NCT01212094) Phase II trials serves to determine the primary outcome for the subsequent blinded treatment phase by comparing eight clinical, one electrophysiological, one optical coherence tomography, seven MRI volumetric, nine quantitative T1 [qT1] MRI, and 32 diffusion tensor imaging [DTI] MRI outcomes in the first ≥ 30 subjects. Because the RIVITaLise trial was closed prematurely when only 29 patients finished pre-treatment baseline, the RIVITaLise cohort became one of two independent validation cohorts used. Fifteen outcomes demonstrated significant progression over one year (Δ) in the predetermined analysis of the IPPoMS trial and seven out of these have been validated in both independent cohorts. Validated MRI outcomes had limited correlations with clinical scales, relatively poor signal-to-noise ratio (SNR) and recorded overlapping values between healthy subjects and MS patients with moderate-severe disability. Clinical measures were better correlated, even though each reflects a somewhat different disability domain. Therefore, using statistical modeling, we developed a combinatorial weight-adjusted disability score (CombiWISE) that integrates four clinical scales: expanded disability status scale (EDSS), Scripps neurological rating scale, 25 foot walk and nine hole peg test. CombiWISE outperformed all clinical scales ($\Delta = 10.63\%$; $p = 0.0004$) and detected yearly changes in all three longitudinal progressive MS cohorts with comparable sensitivity to the best-performing MRI biomarkers. In contrast to MRI biomarkers, CombiWISE recorded no overlapping values between healthy subjects and disabled MS patients, had high SNR and predicted changes in EDSS in a longitudinal assessment of 98 progressive MS patients and in a cross-sectional cohort of 303 untreated subjects with MS, other neurological disorders, and healthy subjects. One point change in EDSS corresponds on average to 7.18 point change in CombiWISE with standard error of 0.11.

Conclusions: A novel validated clinical outcome CombiWISE has more than doubled sensitivity in detecting clinical deterioration in progressive MS in comparison to the scale currently utilized for regulatory approval, EDSS.

S145. Genetic Risk Factors May Have Larger Effect Sizes in Pediatric- Compared to Adult-Onset MS

Emmanuelle Waubant, Milena Gianfrancesco, Xiorong Shao, B. Rhead, Jennifer Graves, Tanuja Chitnis, Amy Waldman, Tim Lotze, Teri Schreiner, Anita Belman, Ben Greenberg, Bianca Weinstock-Guttman, Greg Aaen, Jan-Mendelt Tillema,

Jayne Ness, Yolanda Harris, Jennifer Rubin, Meghan Candee, Lauren Krupp, Mark Gorman, Leslie Benson, Moses Rodriguez, Soe Mar, I. Kahn, John Rose, Shelly Roalstad, Charlie Casper, L. Shen, Hong Quach, C. Metayer, Cathy Schaefer, Annette Langer-Gould and Lisa Barcellos. San Francisco; Berkeley; Boston; Philadelphia; Houston; Denver; NYC; Dallas; Buffalo; Loma Linda; Rochester; Birmingham; Chicago; Salt Lake City; Saint Louis; Washington DC; Oakland and Santa Monica

Background: Despite being rare, pediatric MS can inform on genetic and environmental risk factor combinations that lead to earlier disease onset.

Objective: To identify if adult genetic variants for MS are also associated with pediatric onset and have larger effect sizes.

Methods: Samples from 714 MS cases with onset <18 years (mean onset age 13.9 (+/- 3.5) years) and 29,235 controls. Genetic ancestry was used to identify population outliers and match cases and controls for association analyses of 110 non-MHC MS variants and HLA-DRB1*15:01. Adjusted logistic regression models were utilized.

Results: Results from Whites-only analysis (394 cases, 10,875 controls) showed HLA-DRB1*15:01 was as strongly associated with pediatric MS as reported for adults (OR=2.62, 95% CI: 2.23-3.07, $p=2.1 \times 10^{-32}$). Further, 36 of 110 non-MHC SNPs were significant with much larger effect size than reported in adults, with rs2744148 (chr 16) demonstrating the strongest evidence of association with pediatric MS (OR=2.94, 95% CI: 2.41-3.57, $p=5.2 \times 10^{-27}$). Results from GWAS showed at least three genomic regions harbored SNPs with $p < 10^{-7}$ not yet reported in adult MS. Replication work is ongoing.

Conclusions: Genetic effects may be stronger in pediatric MS overall.

S146. Convergent Effects of a Functional C3 Polymorphism on Cognitive Impairment, Brain Atrophy and Demyelination in Multiple Sclerosis

Tina Roostaei, Shokufeh Sadaghiani, Rahil Mashhadi, Masih Falahatian, Esmail Mohammadi, Aria Nazeri, Rozita Doosti, Abdorreza Naser Moghadasi, Mahsa Owji, Amir Pejman Hashemi Taberi, Ali Shakouri Rad, Amirreza Azimi, Arash Nazeri and Mohammad Ali Sahraian. Tehran, Islamic Republic of Iran and Toronto, ON, Canada

The complement system is a key component of the innate immune system that has been strongly implicated in the pathogenesis of multiple sclerosis (MS). Complement component 3 (C3) is a central element in the activation of both classical and alternative complement cascades. C3R102G (rs2230199) is a common coding variant in the C3 gene that affects the activity of C3 and is an established genetic risk factor for age-related macular degeneration.

Here we assessed the effect of rs2230199 on disease severity in 155 relapsing-remitting MS patients from the Cross-modal Research Initiative for Multiple Sclerosis and Optic Neuritis (age-range:18-57, F/M:121/34, EDSS≤6, in-remission) using clinical, cognitive and imaging outcomes. Clinical disability was assessed using Expanded Disability Status

Scale and Multiple Sclerosis Functional Composite. Cognitive function was indexed by averaging the standardized scores of Paced Auditory Serial Addition Test, Symbol-Digit Modalities Test and California Verbal Learning Test. Imaging was conducted at two sites using 1.5T MRI scanners. Genotyping was performed using PCR-RFLP technique. General linear models were used to assess the effect of rs2230199 on clinical and cognitive measures. Whole-brain gray matter voxel-based morphometry (VBM, using T1-weighted images), tract-based spatial statistics (TBSS, using diffusion-tensor imaging [DTI]), and white matter voxel-based analysis (using magnetization transfer ratio images) were performed using permutation testing and threshold-free cluster enhancement approach. Voxels with familywise error corrected $p < 0.05$ were considered significant. All analyses were performed while controlling for the effects of age, sex, and disease duration (and also imaging site in the imaging analyses).

While the C3 genetic variant showed no significant effect on clinical severity, rs2230199 minor-allele dosage was associated with worse cognitive performance ($t = -2.19$, $p = 0.03$). Moreover, the variant was associated with lower brain parenchymal fraction ($t = -2.96$, $p = 0.003$). Voxel-wise analyses showed significant inverse relation between rs2230199 minor-allele dosage and regional gray matter volume in subcortical structures and insular cortex ($n = 155$), fractional anisotropy in white matter skeleton of corpus callosum, posterior thalamic radiation, corona radiata, cingulum and short association fibers ($n = 105$) and magnetization transfer ratio in right periventricular white matter and corona radiata ($n = 90$).

We found converging evidence that carrying the C3 functional variant which is linked to enhanced complement activity is associated with greater cognitive impairment and white matter and gray matter damage in MS patients. Our findings support a causal role for complement system activity in the pathophysiology of MS.

S147. Relation between Fatigue Severity Scale (FSS) and Pupillary Indices in Patients with Multiple Sclerosis (MS)

Ye Hu, Hong Jiang, Byron L. Lam, Silvia Delgado, Jianhua Wang and Kottil W. Rammohan. Miami, FL

Objective: The hypothesis that alteration of central autonomic state is the basis of fatigue in MS was tested by examination of pupillary function. Miosis is mediated by the parasympathetic and mydriasis by the sympathetic nervous system. The resting pupillary tone is the sum of these opposing influences. We explored in this study the possibility that the resting and reacting pupil may serve as a marker for fatigue in MS patients. In preliminary studies, we examined the relationship of Fatigue Severity Scale and pupillary indices in patients with MS.

Methods: Eighteen eyes of 11 MS patients (4 males and 7 females; age: 40.1 ± 14.5 yrs) meeting inclusion and exclusion criteria were examined by automated pupillometer (Konan RAPDx pupillograph). Measurements included resting pupillary diameter, latency of constriction (LoC),

latency of maximal constriction (LmC), velocity of constriction (Vc), amplitude of constriction (Ac), percent change in amplitude of constriction, velocity of redilatation, and latency of redilatation. Severity of fatigue using the FSS was administered.

Results: Patients were categorized into those with severe ($n = 8$ patients: 13 eyes) or moderate to mild fatigue ($n = 3$ patients: 5 eyes). Severe fatigue was associated with significantly shorter LoC and LmC compared with the moderate to mild patients ($P = 0.049$, $P = 0.038$ respectively). Similarly, severe fatigue was associated with a trend of larger Ac ($P = 0.056$) and faster Vc ($P = 0.06$). FSS was inversely correlated to LoC ($r = -0.50$, $P < 0.05$) and LmC ($r = -0.48$, $P < 0.05$).

Conclusions: Our preliminary studies indicate that the pupillary function may serve as a biomarker for fatigue in MS. These early studies would suggest that the shortened latency of constriction of the pupils in severe fatigue may reflect a diminished sympathetic tone as the basis of fatigue in these patients.

This project is supported by NMSS pilot grant, NIH Center Grant P30 EY014801, Research to Prevent Blindness (RPB), and Department of Defense (DOD-Grant#W81XWH-09-1-0675).

S148. Increased Contact with Clinical Trial Participants May Improve Confirmed Multiple Sclerosis Relapse Detection

Kelsey Zorn, Augustus G. Calabresi, Sandra D. Cassard, Katherine C. Smith and Ellen M. Mowry. Baltimore, MD

Background: Relapses in people with multiple sclerosis (MS) contribute to long-term disability and often indicate the need to switch disease-modifying therapy. In clinical practice, new symptoms concerning for MS relapses, especially if mild, are under-reported. In phase 3 clinical trials in relapsing MS, relapse is usually the primary outcome and typically requires a documented worsening on neurologic exam. Study participants are asked to notify the research team promptly if new symptoms occur so that, when indicated, a neurologic exam can be performed to confirm a relapse has occurred. However, under-reporting of symptoms in clinical trials is also common, thus reducing relapse detection. This phenomenon is of concern as it leads to inflation of trial sample sizes, escalating costs and delaying availability of new treatments. New strategies are needed to improve MS relapse detection in clinical trials and in routine clinical care.

Methods: In an ongoing clinical trial of vitamin D supplementation as add-on to a standard MS therapy in people with relapsing-remitting MS, participants have routine study visits every 12 weeks. We evaluated the impact having a study coordinator check in with participants between these routine study visits (specifically, at weeks 4, 8, 18, 30, 42, 54, 66, 78, and 90) on the odds of confirmed MS relapse. Coordinators use a standardized script to ask about and characterize any new symptoms, subsequently providing the information to site principal investigators to assess if an unscheduled relapse visit is warranted.

Results: To date, 127 participants, 83 of whom have completed the trial, were available for analyses. Compared to the two-week period prior to the scheduled check-in, the odds of confirming a relapse in the two weeks afterwards were markedly increased (OR=3.51, 95% CI 1.42, 8.70, $p=0.007$).

Conclusions: Increased engagement of participants between regularly-scheduled visits may improve detection of examination-confirmed MS relapses in clinical trials. Further work is required to determine if the results are generalizable to the broader population of people with MS and to refine engagement strategies in the clinical trial and clinical settings.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Mowry receives research funding for an investigator-initiated trial from Biogen and free medication for a clinical trial from Teva Neuroscience. She is site PI of trials sponsored by Biogen and Sun Pharma.

S149. Effects of Intermittent Fasting in an Animal Model of Multiple Sclerosis

Francesca Cignarella, Claudia Cantoni, Laura Ghezzi, Yanjiao Zhou, Anne Cross and Laura Piccio. Saint Louis, MO and Farmington, CT

Background: Multiple sclerosis (MS) is a complex disease of unknown etiology involving central nervous system (CNS) inflammation, demyelination, and axonal damage. It is thought to be an autoimmune disease targeting CNS myelin. Strong evidence indicates that MS risk is impacted by environmental factors, including diet and obesity. Several recent studies showed that obesity during childhood/young adulthood confers increased risk of developing MS. The biological mechanisms relating obesity to MS is not known. These can include changes in serum levels of cytokines/adipokines controlling systemic inflammation as well as in the gut microbiome, which can affect immune responses. We have previously shown that a regimen of calorie restriction is able to ameliorate experimental autoimmune encephalomyelitis (EAE), the main MS animal model. An alternative approach to CR with similar metabolic effects is intermittent fasting (IF), which could be easier to translate to humans as demonstrated by an ongoing trial in our center.

Objectives: To test the effects of intermittent fasting (IF) clinical course, CNS pathology, serum adipokines, immune responses during EAE.

Methods: C57BL/6 mice were kept on a regimen of IF or ad libitum (controls) for a month prior to immunization with MOG35-55 and during EAE. Tissues were harvested at different time points after immunization to analyze CNS pathology, immune cell number and function in peripheral and gut associated lymphoid organs by flow cytometry.

Results: The IF group displayed a less severe EAE clinical course with a reduction of inflammatory infiltrates and demyelination in the spinal cord compared to controls. Levels of corticosterone and adiponectin were significantly increased in mice on IF compared to the control group.

Production of IL17, IFN γ and GM-CSF by T cells in the draining lymph nodes of the site of immunization was attenuated in IF mice. IF was also associated with an increased number of regulatory T cells in mesenteric lymph nodes, changes in the proportion of T cell subsets in the gut lamina propria (with an increase of naïve T cells and decreased memory T cells) and a different structure in the bacterial community.

Conclusions: This study demonstrates that IF is able to ameliorate EAE clinical course by modulating immune responses in many different ways including increasing corticosterone and adiponectin level and decreasing leptin level; affecting the composition of immune cells in gut associated lymphoid tissue and changing the composition of gut microbiome.

S150. Ovarian Age Is Associated with Gray Matter Volumes and Disability in Women with MS Independent of Chronological Age and Disease Duration

Jennifer S. Graves, Roland G. Henry, Bruce Cree, Marcelle Cedars, Ruth Greenblatt, Emanuelle Waubant, GERALYN Messerlian, Peter Bacchetti, Alyssa Zhu, UCSF EPIC, Steven L. Hauser and Jorge Oksenberg. San Francisco, CA; San Francisco and Providence

Background: Women with MS tend to have more benign initial course than men, but often transition to secondary progressive disease near menopause. It is not known if ovarian decline contributes to accumulation of disability in women with MS.

Objectives: To determine if ovarian decline as measured by levels of anti-Müllerian hormone (AMH) is associated with clinical disability or brain atrophy in women with MS.

Methods: Women with MS and healthy controls were included from a longitudinal research cohort with up to 10 years of clinical and MRI follow-up. AMH levels were measured in batch using a highly sensitive ELISA (pico AMH, Ansh labs) on plasma samples from baseline, year 3, year 5 and years 8-10 time-points. Logistic, linear and mixed model regression techniques were employed, with adjustments for age, disease duration, smoking, race, ethnicity, vitamin D level, disease modifying therapy (DMT), birth control, and hormone replacement therapy as appropriate.

Results: In models controlling for age, AMH levels were similar (1.01 fold difference; 95%CI=0.72,1.41;p=0.97) in women with MS (n=412, mean age 42.6) and healthy controls (n=180, mean age 44). In a multivariable model of women with MS, including rigorous adjustments for age and disease duration, ovarian reserve (per 2 fold lower AMH pg/ml) was associated with cortical gray matter volume (β =−2.24 mm³;95%CI=−4.39, −0.09; p=0.041), expanded disability status scale (EDSS) score (β =0.13; 95%CI=0.045, 0.21; p=0.0028) and multiple sclerosis functional composite (MSFC) z-scores (β =−0.076, 95%CI=−0.12,−0.029;p=0.0015) at baseline. In a multivariable random-intercept-random-slope model using all observations over time, two fold decrease in AMH (pg/ml) was associated with 1.95 mm³ decrease in total gray matter volume (95%CI=−3.9, −0.007; p=0.049), 0.96 mm³

decrease in cortical gray matter volume (95%CI=−2.06, 0.15; p=0.09), and increase in EDSS (β =0.079; 95%CI=0.034, 0.13; p=0.0007) over the follow-up period.

Conclusion: There is no reduction in follicular reserve in women with MS, implying normal fertility compared to healthy women. On the other hand, AMH was associated with total and cortical gray matter volumes and disability in MS patients independent of chronological age and disease duration.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Graves is supported by grants from the Race to Erase MS, National MS Society, Biogen, and Genentech. Dr. Cree has received personal compensation for consulting from Abbvie, Biogen, EMD Serono, MedImmune, Novartis, Genzyme/sanofi aventis, Teva and has received contracted research support (including clinical trials) from Acorda, Biogen, EMD Serono, Hoffman La Roche, MedImmune, Novartis and Teva. Dr. Hauser serves on the Scientific Advisory Boards for Annexon, Symbiotix, Bionure. Dr. Hauser also has received travel reimbursement and writing assistance from F. Hoffman-La Roche Ltd. for CD20-related meetings and presentations.

S151. Co-Production of GM-CSF, IL-22, or IL-17F Identifies a Pathogenic High IL-17A-Producing T Cell Subset from MS Patients That Is Steroid Resistant

Mark A. Jensen, Pretty Abraham, Anthony T. Reder and Barry G.W. Arnason. Rochester, MN and Chicago, IL

Steroids speed recovery during MS relapses but ultimate deficit is lessened minimally at best suggesting that some tissue damage participants may be steroid resistant. Multiple cytokines are implicated in the pathogenic response of MS relapses. We analyzed circulating CD4 cells in MS (n=11) and controls (n=10) by flow cytometry for expressed cytokine pairs that might identify a steroid insensitive subpopulation focusing on toxic IL-17A and IFN- γ and as partners, IL-22, IL-21, GM-CSF, IL-17F and IL-2. IL-17A cells that paired with GM-CSF, IL-22, or IL-17F produced 2 fold higher amounts of IL-17A than IL-17A cells not making these cytokines or IL-17A cells that paired with other cytokines (p<0.04 for each). Dual producers also made more IL-22 and IL-17F (p< 0.02 for each). IFN- γ -secretors that also made GM-CSF or IL-2 made twice as much IFN- γ as other subsets (p<0.001 for each). Conversely, the IL-17A- IFN- γ couplet made less IL-17A and IFN- γ than single producers and less than other couplets (p< 0.04 for each).

To determine steroid sensitivity, PBMC from MS patients (n=25) and controls (n=9) were cultured with PHA+/-methylprednisolone (MP) (10-6M), harvested at 48 hours and analyzed by flow cytometry. Cytokine pairs analyzed by flow included IL17A-GM-CSF and IL-17A-GM-CSF-IFN- γ (high IL-17A producers), IL-17A-IFN- γ (low IL-17A and IFN- γ producers), IL-17A-IL-21, IFN- γ -IL-2, and IFN- γ -GM-CSF. IL-17A- GM-CSF and IL-17A-GM-CSF-IFN- γ cells resisted MP totally. In contrast, IFN- γ cells, lacking IL-

17A, were very sensitive to steroid induced cell death, even those that made GM-CSF ($p < 0.001$ for each). Thus, the IL-17A- GM-CSF, IL-17A-IL-22 and IL-17A-IL-17F subpopulations share pathogenic T cell properties (i.e. high IL-17A production) and robust steroid resistance whereas IFN- γ and low IL-17A synthesizers, thought to be less pathogenic, are steroid sensitive.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Supported in part by a research grant from Mallinkrodt Inc. to the University of Chicago, Department of Neurology

Neurocritical Care

S152. Endovascular Therapy for Acute Stroke in the Mount Sinai Health System: The Role of Neurointensivist-Led System-Wide Triage

Stephan A. Mayer, Justin Mascitelli, Neha Dangayach, Natalie Wilson, Hazem Shoirah, Johanna T. Fifi, Srinivasan Paramasivam, Reade Deleacy, Errol Gordon, Joshua Bederson, J. Mocco and Stan Tuhirim. New York, NY

Introduction: Treatment of acute ischemic stroke (AIS) due to large vessel occlusion (LVO) is rapidly changing in the wake of RCTs demonstrating benefit with intra-arterial therapy (IAT). Mobilization of endovascular teams to deliver emergency IAT presents significant challenges. We describe the impact of a neurointensivist led emergency hotline for facilitating inter-hospital transfers for emergency IAT procedures within the Mount Sinai Health System.

Methods: The Mount Sinai Health System is composed of 6 hospitals that treat 530,000 ED patients and 1,520 AIS patients per year. On December 1, 2014, we instituted an neuro-emergency hot line staffed 24/7 by the on-call attending neuro-intensivist at The Mount Sinai Hospital for triaging all transfer requests. In February 2015 we instituted a secure group text mobile messaging app to facilitate real time communication between stroke neurology, emergency medicine, radiology, critical care, and interventional neuroradiology. IAT was provided by a team of three interventionalists at 4 of our 6 system hospitals, using a commando model (procedure performed at presenting hospital) when possible.

Results: In 2014 through November 32 patients were treated with IAT throughout the health system (2.9 per month), compared to 37 patients (7.4 per month) treated with IAT between December and April of 2015 (a 2.6-fold increase, $P = 0.04$). The number of inter-hospital transfers increased from 5 (16% of all IAT cases; 0.5 cases per month) in 2014 to 13 (35% of all cases; 2.6 cases per month, $P = 0.10$) after establishing the new triage strategy. The rate of TPA utilization was unchanged (53% vs. 54%). Door-to-puncture time overall decreased from 181 to 104 minutes overall (a 43% reduction, $P = 0.001$), and from 197 to 68 minutes among transfer patients (a 65% reduction, $P = 0.14$). Among all patients TICI 2b/3 rate did not change (87% vs. 81%), nor did the rate of symptomatic hemorrhage (9% vs. 11%) or the proportion of patients with a

discharge modified Rankin Scale Score of 0-2 (22% vs. 19%).

Conclusion: Armed with compelling new data, improved technology, and a team approach to delivering stroke care, we hypothesize that our neurointensivist staffed emergency hotline and use of a group messaging app helped to streamline care, resulting in a large increase in patients treated with IAT, including inter-hospital transfers, and a dramatic reduction in door-to-puncture times.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? SAM is a consultant for Stryker and Medtronic.

S153. Predicting Survival after Acute Civilian Penetrating Brain Injuries: The SPIN Score

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Objective: The aim of this study was to identify predictors associated with survival in a contemporary, large, diverse two-center penetrating traumatic brain injury (pTBI) cohort, and to develop a parsimonious survival prediction score for civilian pTBI.

Methods: Our cohort comprised 415 pTBI patients retrospectively identified from the local trauma registries at two U.S. level-1 trauma centers, of which one was predominantly urban and the other predominantly rural. Predictors of in-hospital and 6-month survival identified in univariate and multivariable logistic regression were used to develop the simple Surviving Penetrating Injury to the Brain (SPIN) Score.

Results: The mean age was 33 ± 16 years and patients were predominantly male (87%) and black (58%). Survival at hospital discharge as well as 6-months post pTBI was 42.4%. Motor Glasgow Coma sub-score, pupillary reactivity, self-inflicted injury, transfer from other hospital, female sex, Injury Severity Score and INR were independently associated with survival (all $p < 0.001$; model area-under-the-curve 0.962). Important radiological factors associated with survival were also identified but their addition to the full multivariable would have resulted in model overfitting without much gain in the area-under-the-curve.

Interpretation: We developed the SPIN Score, a logistic regression-based risk stratification scale estimating survival after pTBI. While external validation is warranted, this clinical survival prediction tool may provide important information to guide families and physicians during intervention- and goals-of-care decision-making after civilian pTBI.

Neuro-Oncology

S154. Impact of NEOD001 on Neuropathy and Organ Biomarkers in Patients with Light Chain Amyloidosis and Persistent Organ Dysfunction: Results from the Expansion Phase of a Phase 1/2 Study

Michaela Liedtke, Raymond L. Comenzo, Heather Landau, Vaishali Sancharawala, Brendan M. Weiss, Jeffrey Zonder,

Jackie Walling, Gene G. Kinney, Martin Koller, Dale B. Schenk, Spencer D. Guthrie, Enchi Liu and Morie A. Gertz. Stanford, CA; Boston, MA; New York, NY; Philadelphia, PA; Detroit, MI; Hillsborough, CA; South San Francisco, CA and Rochester, MN

Introduction: Patients with amyloid light chain (AL) amyloidosis experience multiorgan failure and peripheral neuropathy from abnormal deposition of misfolded light chain (LC) proteins. Current therapies limit LC production but do not directly target deposits underlying multiorgan failure and neuropathy. NEOD001, a monoclonal antibody, targets misfolded LC and is thought to neutralize circulating LC aggregates and clear insoluble deposits. In an interim analysis of a phase 1/2 dose-escalation study in patients with AL amyloidosis and persistent organ dysfunction (NCT01707264; EudraCT2012-002683-27), monthly infusions of NEOD001 were safe and well tolerated. Organ responses compared favorably with those of traditional chemotherapy (Gertz et al. *J Clin Oncol* 2016). We report updated results from the escalation phase and new results from the expansion phase of this study, which includes patients with peripheral neuropathy.

Methods: During the dose-escalation phase, 27 patients who completed ≥ 1 anti-plasma cell systemic therapy, had at least partial hematologic response to any previous therapy, and had persistent organ dysfunction received 0.5-24 mg/kg NEOD001 intravenously every 28 days (3 + 3 study design). Another 42 patients, including those with peripheral neuropathy, were enrolled and treated (24 mg/kg) in the expansion phase. We assessed neuropathy responses using the Neuropathy Impairment Score-Lower Limbs (NIS-LL), as well as safety/tolerability, pharmacokinetics, and immunogenicity.

Results: Twenty-seven patients (66.7% with cardiac involvement) were enrolled in the dose-escalation study. Another 42 patients, including 11 with peripheral nerve involvement, were enrolled in the expansion study. In the overall population, median age was 60 years, and 60.9% of patients were men. Median (range) time since diagnosis was 3.02 (0.4-16.0) years for the expansion patients and 2.85 (0.4-16.0) years for the overall population. In the expansion phase, best hematologic response (HR) to the most recent systemic treatment was complete response (CR) in 12 patients (28.6%), very good partial response (VGPR) in 13 patients (31.0%), partial response (PR) in 2 patients (4.8%), no response (NR) in 2 patients (4.8%), and unavailable in 13 patients (31.0%). Updated safety/tolerability and organ response data, including NIS-LL findings, will be presented for the expansion patients.

Conclusion: These updated results from the escalation phase and new results from the expansion phase may further elucidate our understanding of NEOD001 antibody therapy for patients with AL amyloidosis, including those with peripheral neuropathy.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? ML has served as consultant to and received research funding from

Prothena. RLC has served as consultant/advisor to Takeda, Prothena, GlaxoSmithKline, and Janssen, and received research funding from Takeda, Prothena, Karyopharm, and Janssen. HL has served as consultant/advisor to Takeda and Janssen, received research funding from Amgen, Takeda, and Prothena, and received honoraria from Takeda. VS has received research funding from Takeda, Celgene, and Prothena. BMW has served as consultant/advisor to Janssen, Takeda, and GlaxoSmithKline. JZ has served as consultant/advisor to Celgene, Bristol-Myers Squibb, Prothena, Seattle Genetics, Janssen, Takeda, and Array Biopharma, and has received research support from Celgene. JW is a stockholder in Amgen and BioMarin, has served as consultant/advisor to Corcept, Aduro, Prothena, Apex, Oxigene, Upsher Smith, Newgen, Exelixis, KaloBios, Stealth, NuMedii, Raptor, Pharm-Olam, Crown, Codexis, and Nektar, and holds intellectual property with Amgen and Upsher Smith. GKG is an employee of and holds stock in Prothena and has served as consultant to Amgen. MK is an employee of, holds stock in, has a leadership position with, and has received reimbursement for travel, accommodations, and/or expenses from Prothena. DBS is an employee of and holds stock in Prothena. SDG is an employee of and holds stock in Prothena. EL is an employee of Prothena. MAG has received honoraria from Celgene, Novartis, Millennium, Med Learning Group, Research to Practice, Onyx, Isis Pharmaceuticals, Sanofi, and Prothena, has served as consultant/advisor to Prothena, and has received reimbursement for travel, accommodations, and/or expenses from Prothena, Celgene, and Novartis.

S155. Clinical Features and Prognostic Factors of 476 Patients with Spinal Astrocytoma: An Integrated Analysis from Multi-Institutional Data and the Literature

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Objective: To perform a comprehensive integrative analysis on the prognostic factors, treatments, and survival of patients with spinal astrocytoma using primary cohort at four hospitals in the United States, China and Italy and published literature data.

Methods: Appropriate studies were identified per search criteria. The primary databases at Hospital of University of Pennsylvania (2005-2015), Duke University Hospital (1992-2012), University of Rome Sapienza (1976-2006), First Xiangya Hospital (2010-2016) were retrospectively searched to include a similar patient cohort. Patient demographics, presenting symptoms, tumor characteristics, treatments, and outcomes in terms of progression free survival (PFS) and overall survival (OS) were extracted for each individual patient. Univariate analysis was performed using the Kaplan-Meier method and multivariate analysis by Cox hazard analysis to identify prognostic factors for PFS and OS.

Results: A total of 476 patients were identified, including 98 who presented for initial treatment of spinal astrocytoma and 378 with available data from 80 published studies. All

baseline characteristics were similar between the institutional data and the literature data except for age (mean of 29.6 vs. 23.4 yrs, $p=0.002$), prior treatment (0 vs. 25%, $p<0.001$) and holocord involvement (0 vs. 4.6%, $p=0.001$). The median age was 20 and 42% were female. The median follow-up was 24 months (range: 0–480). The median PFS was 14 months (range: 0–239). The median OS was 24 months (range: 0–480). Significant prognostic factors for PFS on univariate analysis included WHO grade ($p<0.001$), location ($p=0.033$), extent of resection (EOR) ($p<0.001$), radiation therapy ($p<0.001$), and chemotherapy ($p<0.001$). Significant prognostic factors for OS on univariate analysis included age ($p<0.001$), prior treatment ($p<0.001$), WHO grade ($p<0.001$), extent of tumor involvement ($p=0.006$), EOR ($p=0.004$), radiation therapy ($p<0.001$), and chemotherapy ($p<0.001$). Independent prognostic factors for PFS on multivariate analysis included WHO grade (hazard ratio (HR) for low vs. high grade: 0.297–0.656), and EOR (HR for gross total resection (GTR) vs. subtotal resection (STR): 0.218–0.785). Independent prognostic factors for OS include age (HR for age<18 vs. age>18: 0.450–0.912), prior treatment (HR for no vs. yes: 0.127–0.350), WHO grade (HR low vs. high grade: 0.085–0.219), and EOR (HR for GTR vs. STR: 0.311–0.831).

Conclusion: In patients with spinal astrocytoma, WHO grade and extent of surgical resection were significant prognostic factors for both PFS and OS. Age>18 years and prior treatment were negative predictors of OS.

S156. MR Imaging Features Predict Survival and Molecular Profile in Diffuse Lower Grade Gliomas

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Background: Previous studies have shown that the Visually Accessible Rembrandt Images (VASARI) feature set can be used to predict survival and molecular profile of glioblastoma. However, no study of similar type has been performed on lower grade gliomas.

Objective: To conduct a comprehensive analysis of magnetic resonance imaging (MRI) visual features as they relate to genetic alterations, gene expression class, and patient survival.

Method: Presurgical MRIs of 165 patients with diffuse low-grade and intermediate-grade gliomas (WHO grades II and III) with genetic data in The Cancer Genome Atlas (TCGA) were acquired from the Cancer Imaging Archive (TCIA). Two neuroradiologists extracted the imaging features (F1–F25 and F29) according to the VASARI guidelines. Inter-rater agreements were assessed using the Kappa consistency test. Association between imaging features and survival were determined by Kaplan-Meier analysis followed by multivariate Cox regression models for those variables with $p<0.1$ on the univariate analysis; association between

imaging features and genomic clusters (RNASeqCluster, MethylationCluster, miRNA Cluster, CNCluster, RPPACluster, COCCluster)/genetic mutations (ARID1A, CIC, FUBP1, NOTCH1, PIK3CA, PIK3R1, ZBTB20, TP53, SMARCA4, PDGFRA, EIF1AX, ATRX, NF1, PLCG1, PTEN, PTPN11 and EGFR) were studied by using the chi-square test with Benjamini-Hochberg (BH) correction.

Results: Inter-rater analysis showed significant agreement in all imaging features scored ($k=0.703$ – 1.000). Four and nine imaging features were associated with progression-free survival (PFS) and overall survival (OS), respectively on univariate analysis. The multivariate cox regression analysis showed that enhancement quality (F4), definition of the non-enhancing margin (F13), the presurgical Karnofsky Performance Scale score and IDH1/1p19q subtype were significant predictors of PFS, while F13, age, grade and IDH1/1p19q subtype were significant predictors of OS, after taking into account gender, tumor location and histology. There were a total of 22 significant associations ($p<0.05$ after BH correction) between imaging features and genomic clusters involving 10 imaging features. Three imaging features had consistent associations (4 significant associations) across genomic clusters: enhancement quality (F4), proportion enhancing (F5), and proportion non-contrast-enhancing (F6). There were a total of 24 significant associations between VASARI imaging features and genetic mutations involving 14 imaging features. Genes that were most likely to have significant associations with imaging features include EGFR, NF1 and PTPN11.

Conclusion: Radiogenomic analyses of lower grade gliomas using VASARI feature set demonstrated that features related to tumor enhancement predicted survival and molecular profile.

Behavioral Neurology

S157. Cerebellar tDCS to Augment Chronic Aphasia Treatment

Rajani Sebastian, Amy Wright, Cameron Davis, Sadhvi Saxena, Kyrana Tsapkini, Donna C. Tippet, Pablo Celnik and Argye E. Hillis. Baltimore, MD

Background: Aphasia is one of the leading causes of disability following stroke. In recent years a number of studies indicate that transcranial direct current stimulation (tDCS) may help to facilitate language recovery in chronic aphasia. Prior investigators have mainly focused on the role of left hemisphere in language recovery, where the electrode is placed in the left frontal or temporal region (e.g., Baker, Rorden, & Fridriksson, 2010; Vestito et al., 2014). This study proposes a novel electrode placement for chronic stroke patients with aphasia with large left hemisphere lesions.

Aim & Methods: The aim of this study was to determine whether tDCS to the right cerebellum coupled with computerized naming therapy can improve naming performance in individuals with chronic aphasia with large lesions. Since beneficial cognitive effects from right cerebellar tDCS

have been found for both anodal and cathodal stimulation in healthy individuals, we will test the effect of anodal and cathodal stimulation in post-stroke aphasia. We hypothesized that Anodal tDCS (A-tDCS) or cathodal tDCS (C-tDCS) plus computerized naming therapy will result in improved naming performance for trained and untrained items from baseline to post-treatment compared to sham plus naming therapy. A randomized, double-blind, sham controlled, within-subject crossover trial design was utilized. Participants took part in 2 intervention periods of 15 computerized naming training sessions (3-5 sessions per week), with either tDCS + naming therapy or sham + naming therapy, separated by 2 months. 3 participants received Anodal tDCS (A-tDCS) + naming therapy and sham + naming therapy and the 3 participants received Cathodal tDCS (C-tDCS) + naming therapy and sham + naming therapy. 2 mA of A-tDCS or C-tDCS stimulation was induced between two 5 cm x 5 cm saline soaked sponges where one active electrode (anode in Group Anode or cathode in Group Cathode) was placed on the right cerebellum (1 cm under, and 4 cm lateral to theinion) and the reference electrode (cathode in Group Anode or anode in Group Cathode) was placed over the right shoulder.

Results/Discussion: tDCS treatment produced significant changes for both trained and untrained items for both the anode and cathode group, where as sham treatment produced only gains for trained items in 3/6 participants. The results, albeit preliminary, highlight the therapeutic potential of right cerebellar tDCS to augment naming therapy in individuals with chronic post stroke aphasia with large lesions.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Argye Hillis receives compensation from AHA for editorial activities for Stroke, and Elsevier for editorial activities for Practice Update Neurology.

S158. Differentiating between Subtypes of Primary Progressive Aphasia and Mild Cognitive Impairment on a Modified Version of the Frontal Behavioral Inventory

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Behavioral assessment has been investigated in frontotemporal lobar degeneration and Alzheimer's disease, but has not been explored extensively in subtypes of primary progressive aphasia (PPA). We explored the ability of a modified version of the Frontal Behavioral Inventory (FBI-mod) to discriminate between patients with distinct subtypes of PPA and patients with mild cognitive impairment (MCI). We hypothesized that individuals with nonfluent agrammatic PPA (nfaPPA) would have higher negative behavior scores than other groups and that individuals with semantic variant PPA (svPPA) would have higher disinhibition scores than other groups. Family members and/or caregivers of 87 individuals with PPA and MCI completed the FBI-mod (logopenic PPA, lvPPA n=29; mean age 70.55+ 6.73; nfaPPA n=20, mean age 66.65+ 10.94; svPPA n=15, mean age

67.60+ 5.74; unclassifiable PPA, UnCPPA n =7, mean age 70.29+ 7.06, MCI n=16; mean age 69.0+ 12.09). The groups were not significantly different in age, education, or disease duration. There were no significant differences between the groups on ANOVA for negative behaviors ($p=0.156$, $F=1.71$), although the svPPA and UnCPPA had the highest mean scores on this portion of the FBI-mod and individuals with MCI had the lowest mean score. The disinhibition scores were significantly different ($p=0.022$, $F=3.02$), with svPPA having the highest mean score. Multi-variable logistic regression analysis showed that the odds of having svPPA was significantly higher (OR 1.04 [1.01-1.09]) for every 1 point on the disinhibition score (but not negative behavior score; ns), independent of age, disease duration, and gender ($p=0.012$). When comparing negative and disinhibition scores (in percent), negative scores were significantly higher in all groups. The frequency of "severe" or "3" ratings revealed different negative behavioral profiles for each group which may have clinical and practical implications.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Argye E. Hillis, MD, MA receives compensation from AHA for editorial activities for Stroke, and Elsevier for editorial activities for Practice Update Neurology.

S159. Emotion Network Breakdown Relates to Baseline Autonomic Dysfunction in Behavioral Variant Frontotemporal Dementia

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Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease that impacts empathy, emotion, and social behavior. There is emerging evidence that patients with bvFTD have diminished parasympathetic and sympathetic nervous system functioning at baseline, deficits that may reflect deterioration of specific neural circuits that support emotion and autonomic nervous system physiology. We measured baseline respiratory sinus arrhythmia (RSA), a parasympathetic measure, and skin conductance level (SCL), a sympathetic measure, during a 6-minute resting period in 15 patients with bvFTD and 14 healthy controls who later underwent structural and task-free functional magnetic resonance imaging. The Neuropsychiatric Inventory was used to assess affective symptoms in the patients with bvFTD. Guided by a novel neuroanatomical model, we conducted whole-brain voxel-based morphometry analyses to identify regions where atrophy was associated with baseline autonomic deficits. We also extracted the functional connectivity time series from 21 emotion network nodes and used hierarchical multiple regression analyses to examine whether functional connectivity deficits in specific node-pairs related to baseline autonomic dysfunction. As expected, patients with bvFTD had significantly lower baseline RSA ($p<.05$) and SCL ($p<.05$) than healthy controls. Lower baseline RSA was associated with smaller left ventral anterior insula

volume, weaker functional connectivity between bilateral ventral anterior insula and anterior cingulate cortex, and stronger functional connectivity in predominantly right hemisphere hypothalamus- and amygdala-based nodes. Lower baseline SCL, in contrast, was associated with smaller volume in inferior temporal gyrus, dorsal anterior insula, hypothalamus, and periaqueductal gray; weaker functional connectivity between right hypothalamus/amygdala and anterior cingulate cortex; and stronger functional connectivity between dorsal anterior insula and periaqueductal gray. In bvFTD, higher irritability was correlated with weaker ventral anterior insula – anterior cingulate cortex connectivity whereas higher euphoria was correlated with weaker anterior cingulate cortex – hypothalamus connectivity. Our results suggest that baseline parasympathetic and sympathetic activity depend on the integrity of distinct nodes in a neural network that supports emotion. Resting autonomic physiology is the product of both strong and weak nodal connections, and deterioration of both types of connections is associated with baseline autonomic dysfunction and affective symptoms in bvFTD.

S160. Altered MicroRNA Expression in a Mouse Model of Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental syndrome characterized by the early dysfunction in social interaction and communication as well as the presence of repetitive and restrictive behaviors. Despite the high prevalence and the substantial socioeconomic burden of ASD, the exact pathophysiology of ASD has not been clearly defined. Increasing evidence points to a role for microRNAs (miR) as key regulators of gene regulation and neural development. This study aimed to determine miR expression profiles in the brain of ASD mice and to evaluate the effects of the antagomir treatment by inhibiting dysregulated miR. We employed a maternal immune activation model by injecting poly I:C (20 mg/kg) to pregnant mice at E12.5 period. Brain tissue of poly I:C-treated pups and saline-treated controls were obtained at 3 weeks of age. Genome-wide miR expression was analyzed by using Agilent Mouse miRNA 8 X 60K v19. Following the multiple comparison corrections by false discovery rate of 0.05, we identified 29 miR differentially expressed in ASD mice: 8 were upregulated (fold change > 2.0) and 21 were downregulated (fold change < 0.5). The most upregulated miR in ASD mice was miR-877-3p of which the fold change was 101.6. In silico prediction revealed that miR-877-39 targeted the GRIN2B gene encoding the NR2 subunit of N-methyl-D-aspartate receptor. Increasing evidence supported that genetic alteration in GRIN2B is associated with ASD. Our observations demonstrated that dysregulated miR expression occurred during the early postnatal period in an ASD mouse model. Further research is needed to evaluate the effect miR-based epigenetic modulation as novel therapeutics for ASD.

S161. Bismuth Neurotoxicity: A Rare Cause of Rapidly Progressive Dementia

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Introduction: Case of rapidly progressive dementia secondary to bismuth toxicity.

Discussion: A 52 year old woman was referred to Neurology for evaluation of a five month long sub acute onset progressive syndrome characterized by multi-modal cognitive decline, gait ataxia, and generalized myoclonus. Cognitive screen revealed moderate deficits in attention, recall, visuospatial tasks, and calculation. She was unable to continue her job as a finance analyst. She could no longer drive, cook or hold a coherent conversation. Planning daily activities, organizing tasks and decision making was severely impaired. Urine incontinence occurred episodically. Differential diagnoses included central nervous system infectious, inflammatory, neoplastic, para neoplastic and primary neuro-degenerative processes. Patient's EEG showed diffuse intermittent delta range slowing without epileptiform abnormalities. PET scan of the brain revealed generalized moderately diminished FDG uptake by both cerebral hemispheres, in a nonspecific pattern suggestive of encephalopathy. Abdominal X ray done due to a history of collagenous colitis showed punctate radiopaque material scattered throughout the colon. Vitamin B 12 was normal (332 ng/ml), TSH was normal (0.9 mIU/L), normal markers of systemic autoimmunity, spinal fluid analysis showed 4 nucleated cells, protein 21 mg/dL, glucose 60 mg/dL, negative IgG synthesis and oligo clonal bands, protein 14-3-3 was 9.0 ng/ml (<1.5 ng/ml), negative antibodies against NMDA, GABA-R, AMPA-R, GAD-65, CRMP-5, PCA, ANNA, AGNA, voltage gated potassium and calcium channels. Serum levels of cadmium, arsenic, lead, copper and zinc were normal. On further history it was discovered that the patient took bismuth subsalicylate for gastrointestinal symptoms at least 4 tablets of 262 mg each daily over the past two years. Bismuth levels were tested and revealed a whole blood bismuth level in the toxic range at 948 ng/ml (normal <50 ng/mL, toxic > 200 ng/ml), as well as a toxic urine bismuth level >406.5 ng/ml (normal < 50 ng/ml and toxic >200 ng/ml). Bismuth therapy was immediately discontinued. Upon follow up at 12 weeks the patient's cognitive screen was essentially within normal range with only a minimal deficit in calculation, myoclonus and gait ataxia resolved completely. Bismuth blood at this time was 9.5 ng/ml, and bismuth urine 8.6 ng/ml.

Conclusion: Bismuth neurotoxicity is characterized by rapidly progressive dementia, myoclonus and gait ataxia. This is rare but should be considered as a possible differential diagnosis for patients presenting with a rapidly progressive dementia and may mimic prion disease.

S162. Relevance of Inhibitory Control and Neurocognitive Function to Tactical Self-Regulation in the Context of Driving

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Epidemiologic data suggest that inexperienced young drivers and older drivers are at increased risk for crashes. Emerging evidence also shows that both at-risk groups evince large individual differences in their ability to self-regulate both tactically (e.g. increasing headway distance) and strategically (e.g. avoiding driving on bad weather days) to conserve safety. Our goal in this study was to quantify tactical self-regulatory processes across the lifespan in a driving simulator study; describe age differences and examine neurocognitive predictors of tactical self-regulation. Drivers who show large differences in fundamental driver skills/performance metrics including maintaining lane position, speed, and headway across varying but typical demand characteristics were argued to be poor at tactical self-regulation as they demonstrate larger lability in performance. We predicted that poor self-regulators would also show poorer performance in neurocognitive tests of functioning, may self-report lower levels of trait inhibitory control and higher levels of impulsivity especially novelty seeking. A better understanding of these issues can help identify those at-risk drivers who are the most vulnerable road users and shed light on remedial interventions that teach better tactical self-regulatory and compensatory behaviors to conserve safety. To that end, 88 participants from three age groups completed four drives that varied with respect to two within-subject factors: 1) easy vs. difficult drives and 2) presence or absence of a secondary distraction task. We operationalized tactical self-regulation as variability in lane position, headway and speed maintenance across the four drives. Both older drivers and younger drivers showed greater variability in maintaining lane position compared to middle-aged drivers across the four drives (p 's $< .05$). In addition, older drivers showed larger variability in speed maintenance (p 's $< .01$). Findings also showed that cognitive speed of functioning and executive function predicted variability in speed maintenance, memory predicted lane position maintenance while impulsivity but not inhibitory control predicted headway maintenance. These findings encourage an examination of both cognitive function and stable individual differences in specifying risk factors for poor versus better self-regulators.

Cerebrovascular Disease

S163. Early Changes in ADC Volumes Are Associated with Absolute Neutrophil Count During Ischemic Stroke

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Background: Patients with elevated absolute neutrophil count (ANC) carry a higher risk of future thrombotic events. Also, neutrophils have been shown to increase risk of hemorrhagic transformation after ischemic stroke and have been associated with poor clinical outcomes. Most associations of ANC or neutrophilic response to stroke have not examined possible associations with early changes in stroke lesion size (ECS), which can result in transient or even sustained changes in stroke lesion volume. We have previously reported early neurologic improvement and lower

rates of symptomatic intracerebral hemorrhage in patients with ECS. Here we compared ANCs in patients with ECS.

Methods: Between 2013-2014, we enrolled 58 acute stroke patients who received IV tPA or intra-arterial therapy and were scanned serially with MRI (pre-, 2 and 24 hours post intervention). We used image co-registry techniques to calculate ECS using $ADC < 600$ selected within perfusion lesions with $TTP > 4$ seconds. ECS was defined as ADC volumes between 2 hours – baseline and 24 hours – 2 hours. ANC was collected at baseline and on the following morning from admission. Of the 58 enrolled patients, 40 patients had ANC lab values measured at both time points. Data was analyzed using Chi-square and t -tests.

Results: Patients with stroke progression at 2 hours were more likely to have a 3 point elevation in ANC count on the second day of admission in comparison to patients that had a decrease in infarct size at 2 hours, including patients with sustained and transient 2 hour reversal (67% versus 20%, $p = 0.001$). Patients with stroke lesion progression at 2 hours had a greater change in ANC counts when follow up labs were compared to baseline in comparison to patients that had reversal in ADC volumes at 2 hours (2.9 ± 1.0 versus 1.0 ± 0.5 p value < 0.04). There were no significant differences in ANC between groups at baseline (5.4 ± 0.3 versus 4.9 ± 0.6 in patients with stroke progression).

Discussion: Here we show that early changes in stroke lesion volumes correlate with changes in ANCs, with early decreases in ADC volumes being associated with lower ANCs regardless of whether the decrease in stroke lesion volume is sustained or transient. This demonstrates that the dynamic changes that occur early after stroke treatment are also key in modulating the inflammatory response that occurs in stroke patients.

S164. Tumor Necrosis Factor-alpha Potentiates the Effect of Ischemic Brain Injury in Vascular Cognitive Impairment

Luther Creed Pettigrew, Christopher M. Norris and Richard J. Kryscio. Lexington, KY

Background: Tumor necrosis factor-alpha ($TNF\alpha$) is an inflammatory mediator that becomes elevated in ischemic brain. To complement its role as a determinant of cell survival after physiological stress, $TNF\alpha$ is also recognized as an important contributor to neurotransmission and synaptic plasticity.

Hypothesis: We tested the following dual hypotheses that constitutive upregulation of $TNF\alpha$ protein synthesis will: 1) alter long-term potentiation (LTP) as a measure of hippocampal synaptic integrity and 2) will affect cognitive performance after focal cerebral ischemia.

Methods: The $TNF\alpha$ -transgenic ($TNF\alpha$ -Tg) rat with selective overexpression of the murine $TNF\alpha$ gene in brain was used for all experiments. The effect of constitutive upregulation of $TNF\alpha$ protein synthesis on synaptic function was examined by LTP measured 60 min after 100-Hz stimulation of hippocampal slices. In separate experiments, $TNF\alpha$ -Tg rats underwent middle cerebral artery occlusion (MCAO) for 1 hr. Cognitive performance was assessed in a

Morris water maze before and 7 days after MCAO. Functional performance was examined in serial Rotarod tasks performed up to 28 days after MCAO.

Results: In naïve rat hippocampus, LTP was increased in TNF α -Tg animals compared to wild type (WT) littermates (n=5 per group; $p \leq 0.05$). During probe testing of reference memory retention 7 days after MCAO, only WT animals successfully employed differential search strategy (n=8 per group; $p \leq 0.03$ compared to random). After MCAO, TNF α -Tg rats performed inferiorly to sham-ischemic animals on 6 of 10 serial Rotarod task dates up to 28 days (n=5; $p \leq 0.05$ per comparison). Ischemic WT littermates performed inferiorly on only 3 dates ($p \leq 0.05$).

Conclusions: We conclude that upregulated synthesis of TNF α protein alters synaptic integrity, as shown in our LTP data, and amplifies cognitive impairment after focal cerebral ischemia.

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S165. Severe Stenosis of Internal Carotid Artery Is Associated with Higher Neutrophil-Lymphocyte Ratio: A Concept of Cerebrovascular Stress

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Background: The role of neutrophil-lymphocyte ratio (NLR) as bio-indicator for development and prognosis of intra-cranial misery perfusion is not well elucidated. We studied the relationship between NLR and the degrees of extra-cranial internal carotid (ICA) stenosis in patients who underwent carotid endarterectomy (CEA) as a surrogate marker of reduced cerebrovascular reserve.

Methods: We retrospectively reviewed the charts of 74 patients who underwent CEA during 2013-2014. Pre-operative NLR was calculated and compared to the degree of ICA stenosis (<90% and $\geq 90\%$), and the presence or absence of intracranial collateral circulation. Odds ratio (OR) was calculated by logistic regression analyses to investigate the relationship between NLR and degree of ICA stenosis. The model was adjusted for age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking, and atrial fibrillation. Patients with untreated coronary artery insufficiency and/or chronic systematic inflammation were excluded from the analysis.

Results: Out of the 74 patients total, the majority of the patients were male 53 (72%) and > 60 years-old 68 (92%). Severe degree of ICA stenosis ($\geq 90\%$) was confirmed in 29 (39%) of patients. NLR (mean $\pm$ SD) in patients

with $\geq 90\%$ vs. <90% stenosis of ICA were 4.3 ± 1.7 ; p 0.02 and 3.0 ± 1.6 ; p 0.02 respectively. NLR was higher (>4) for patient with ICA stenosis and associated stroke (mean $\pm$ SD 4.1 ± 0.8 ; p 0.04) vs. patients with ICA stenosis and transient ischemic attack (TIA) symptoms or asymptomatic (mean $\pm$ SD 2.9 ± 0.9 ; p 0.04 and 3.3 ± 1.7 p 0.04 respectively). OR and confidence interval for degree of stenosis ($\geq 90\%$) vs. <90%) were more significant when adjusted for age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking and atrial fibrillation (OR 4.3; 95% CI 1.2-15.4; p 0.03 vs. OR 3.3; 95% CI 1.2-9.1; p 0.03 respectively).

Conclusion: NLR could be use as an adjunct indicator of misery perfusion in patients with severe ICA stenosis at higher risk for stroke. NLR >4 is associated with established stroke when compared to ICA stenosis-TIA and ICA stenosis-asymptomatic patients.

Epilepsy

S166. Localized Hippocampal Knockout of TSC1 Gene in Mice Leads to In Vivo Cognitive Dysfunction and Electrophysiological Changes without Seizures

Paul R. Jarvis, Sean P. Flynn, Jeremy Barry and Gregory L. Holmes. Burlington, VT

Disruptions of the mTORC1 protein complex through heterozygous mutations of the TSC1 and/or TSC2 genes cause tuberous sclerosis (TSC). In humans, this disorder presents with a variety of neurologic symptoms including epilepsy, autism, and cognitive dysfunction. Genetic animal models of TSC with a heterozygous knockout of the TSC1 gene have been shown to have cognitive deficits in hippocampal dependent spatial learning and memory (Goorden, *Annals Neurol.* 2007). Complete knockout of the TSC1 gene leads to severe seizure burden and early death (Bateup, *Neuron* 2013). Meanwhile in vitro studies have suggested that localized knockout of TSC1 in the CA1 region of the hippocampus in mice has resulted in reduced synaptic inhibitory potentials, leading to a greater excitatory/inhibitory (E/I) ratio within the hippocampus (Bateup, *Neuron* 2013). However, the specific effects of localized TSC1 knockout in the hippocampus on cognitive function and oscillations in vivo have not been well studied. We therefore examined the effect of a bilateral localized knockout of the TSC1 gene in CA1 on spatial cognition and hippocampal oscillations in mice.

Localized knockout of TSC1 was achieved through stereotactic injection of cre-recombinase expressing adenovirus into bilateral CA1 of the hippocampus of TSC1tm1Djk/J strain mice, in which both alleles of TSC1 are floxed. Controls either received no injection or a saline injection, to control for possible effects of the surgery. All mice were then tested on spatial memory tasks including the Morris Water Maze and an active avoidance task on a rotating arena, as well as a task assessing sociability. Mice were also implanted with recording electrodes and local field potentials were recorded from the CA1 regions bilaterally. Compared to controls, mice with TSC1 gene knockout showed

cognitive deficits, having poorer performance in the Morris Water Maze task and receiving more total shocks per day during the active avoidance task. Electrophysiology recordings showed a slight but significant increase in the normalized power of theta range oscillations in the hippocampi of TSC1 gene knockouts. None of the mice had seizures. Our results suggest that a localized knockout of the TSC1 gene in the hippocampi is sufficient to generate cognitive dysfunction and changes in oscillatory patterns, but a broader network effect may be required to generate seizures seen in the disorder.

S167. Palinacousis

Madeline C. Fields, Lara V. Marcuse, Jenna Yoo and Saadi Ghatan. New York, NY

Palinacousis is the little well known but fascinating phenomena of auditory perseveration. Jacobs et al first coined the term in 1971 and since then there have been 25 cases in total reported in the literature. Palinacousis tends to occur in the ictal or peri-ictal period but has been well described during the brain mapping procedures of Penfield and Perot in the 1960's. Although the etiologies causing this phenomenon vary along the auditory pathway from strokes in the medial geniculate body to tumors in the temporal lobe the echoing of sounds or fragments of sentences recently emitted in the environment is the consequence. Often because of its location palinacousis at times occurs while the patient is aphasic making the diagnosis more difficult but we believe that it occurs much more often than reported. In the table below we describe 6 new cases of palinacousis.

In conclusion, the presence of palinacousis is not uncommon in our epileptic patients and can help identify seizure onset zones. In fact, the presence of auditory perseveration as described in schizophrenic patients as well as the ear worms we have all experienced after the overplayed song on the radio may further our understanding of the brain.

S168. Generalized Tonic Clonic and Psychogenic Non Epileptic Spells Audio Recordings in the Epilepsy Monitoring Units: Identification and Inter-Rater Agreement

Richa Tripathi, Hardik Doshi, Deepti Zutshi, Aashit Shah and Maysaa Basha. Detroit, MI

Introduction: Generalized tonic clonic seizures (GTCs) are associated with generalized convulsive movements. It is associated with vocalization, motor movements that consist of asymmetric clonic jerking, a diffuse tonic phase, and followed by clonic phase. GTCs can be easily identified and diagnosed by video EEG monitoring. Patients with frequent GTCs have an associated increased risk for Sudden Unexpected Death in Epilepsy (SUDEP), respiratory distress, and physical injuries. Concern over such events has prompted caregivers to look for detection aids which include bed alarms and EMG-based devices. Detection devices based on sound have not been explored yet which can differentiate GTCs from Psychogenic Non Epileptic Events (PNES).

Methods: Retrospective review of patients from Epilepsy Monitoring Unit between 2013 to 2016 was done and

events diagnosed as GTC or PNES were selected for review. The audio recording of 19 events were selected and 2- to 3-minute segments of each event was used for the study. Levels of training and practice was marked on four participants. Participants scored audio samples as GTC or PNES upon review on a standard computer based media player. They were blinded to the clinical information, the video clips and to the diagnosis corresponding to the events. Audio scores were compared to clinical diagnosis and analysis was done.

Results: The sensitivity for identifying GTCs was 72.50% (CI=56.11% to 85.40%) and specificity 75% (CI= 57.80%-87.88%). Positive Likelihood ratio is 2.90 (CI= 1.6-5.27) and Negative LR is 0.37 (0.21-0.63). Positive predictive value (PPV) for GTCs was 76.32% and negative predictive value (NPV) of 71.05%. For PNES events; the sensitivity was 75% (CI=57.80%-87.88%) and specificity 72.50% (CI= 56.11% -85.40%). A positive LR of 2.73 (CI=1.59-4.67) and negative LR of 0.34 (CI= 0.19-0.63). PPV of 71.05% and NPV of 76.32%. Inter rater reliability (Davies and Fleiss method) showed K value of 0.56 (moderate agreement) for evaluation of PNES and K value of 0.53 (moderate agreement) for evaluation of GTC seizures.

Conclusion: Audio analysis can be used to identify GTCs and can be used to differentiate from PNES, regardless of level of training. Further analysis to identify specific features that aid in the identification is needed and has a potential for creation of at-home or in-hospital audio recognition.

S169. Seizure Control Does Not Change Abnormal Functional Connections in Temporal Lobe Epilepsy

Mayra A. Lopez, Shaline Mylvaganam, Beau M. Ances, Robert E. Hogan and Luigi Maccotta. St. Louis, MO

Epilepsy has been associated with changes in the connectivity of human brain functional networks, such as the default mode network (1). It is unclear whether these changes reflect a chronic effect of the disease or whether they are an index of acute seizure burden, reflecting active disruption of functional networks (2,3). Epilepsy surgery is a therapeutic option for patients with medically intractable temporal lobe epilepsy (TLE) that can drastically reduce seizures or lead to seizure-freedom. To assess whether a significant reduction in seizure burden affects the abnormal connections of functional networks of epilepsy patients, we studied the preoperative and postoperative resting-state brain connectivity of 17 patients with intractable TLE before and after they underwent epilepsy surgery with Engel Class I outcome (i.e. seizure-free after surgery), as well as 17 age, gender and handedness-matched controls. We specifically focused on 264 nodes forming 12 distinct resting state subnetworks characterized in a large healthy control set. Participants were scanned in a 3T Siemens Trio MRI scanner with a resting state fMRI protocol. In patients the postoperative scan occurred a minimum of 8 months after surgery (mean 37 months, range 8-51 months). Strict artifact removal criteria according to recently published methods (4) were applied to the imaging data. Replicating prior studies (1), preoperative

TLE patients showed significant differences in connectivity from healthy controls, primarily involving the default mode network and the temporal/auditory subnetworks ($F = 12.2$, $p < .001$). Importantly, however, connectivity was largely unaffected by achieving seizure freedom, with abnormal connections remaining essentially unchanged postoperatively. This surprising result suggests that the abnormal network connectivity seen in intractable TLE reflects a history of abnormal connections, i.e. a chronic effect of the disease, rather than an acute index of seizure burden such as would be predicted by active disruption of brain networks by ongoing epileptic seizures.

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Movement Disorder

S170. Indirect Comparison of Tolerability of Deutetrabenazine and Tetrabenazine in the FIRST-HD and TETRA-HD Trials

Daniel O. Claassen, Benjamin Carroll, Lisa M. De Boer, Eric Wu, Rajeev Ayyagari, Sanjay Gandhi and David Stamler. Nashville, TN; Frazer, PA; Boston, MA and La Jolla, CA

Background: Deutetrabenazine (DTB) is a novel, selective vesicular monoamine transporter 2 inhibitor that contains deuterium, a naturally occurring, nontoxic form of hydrogen that extends active metabolite half-lives and minimizes drug concentration fluctuations. Tetrabenazine (TBZ) and DTB have not been compared in a head-to-head clinical trial.

Objective: To compare the tolerability of DTB as observed in the FIRST-HD (NCT01795859) and TBZ in TETRA-HD (NCT00219804) trials for the treatment of chorea associated with Huntington's disease (HD).

Methods: Aggregate data from the 12-week, parallel-group, phase 3 clinical trials FIRST-HD (N=90) and TETRA-HD (N=84), which were similar in design, were used to conduct an indirect comparison of the safety of DTB vs TBZ using the Bucher method, an accepted analytical approach. Serious adverse events (SAEs), discontinuation (all-cause and AE-related), and specific AEs that occurred in >10% of patients were included in the analysis. Placebo-adjusted risk differences in these outcomes were computed in each trial; the risk differences of these outcomes for DTB vs TBZ were estimated by subtracting the applicable placebo-adjusted risk in the TETRA-HD trial from the FIRST-HD trial. P values were obtained from z-tests.

Results: For patients in FIRST-HD and TETRA-HD trials, respectively, mean age was 53.8 (both trials), mean baseline chorea scores were 12.7 and 14.9, and percentage of female participants was 44% and 62%. DTB demonstrated statistically significant lower incidence of moderate to severe AEs ($P < .01$). Among specific adverse events, DTB had a statistically significant lower incidence of depression ($P < .01$), akathisia ($P < .01$), Parkinsonism ($P < .01$), drowsiness/somnolence ($P = 0.02$), insomnia ($P < .01$), and agitation ($P = 0.02$) compared with TBZ. No other analyzed estimates were statistically significant.

Conclusions: In this indirect comparison, DTB demonstrated statistically significantly better tolerability than TBZ on several safety and tolerability measures. Further analysis adjusting for demographic differences between trials should be conducted to confirm these findings.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Daniel O Claassen: Consulting/Advisory Board for Lundbeck, Teva

Benjamin Carroll: Employee of Teva

Lisa M De Boer: Employee of Teva

Eric Wu: Employee of Analysis Group, which received consulting fees from Teva for the conduct of this study

Rajeev Ayyagari: Employee of Analysis Group, which received consulting fees from Teva for the conduct of this study

Sanjay Gandhi: Employee of Teva

David Stamler: Employee of Teva

S171. KTKEGV-Motif Mutations in Alpha-Synuclein Cause Neuronal Death and Defects in Neurite Regrowth After Mechanical Injury

Nagendran Ramalingam, Ulf Dettmer, Dennis J. Selkoe and Oren A. Levy. New York, NY and Boston, MA

Alpha-synuclein (aSyn) accumulates in insoluble aggregates in several neurodegenerative "synucleinopathies," including Parkinson's disease, Lewy body dementia, and multiple system atrophy. Phosphorylation on serine-129 of aSyn is found almost exclusively, and in high abundance, in pathological aSyn aggregates. The functional role of phosphorylation at this site is controversial, as there are conflicting data regarding its role in aSyn-induced cell death. Mutations in aSyn account for rare cases of autosomal dominant PD. These mutations have been of limited value in understanding how aSyn can cause neurological disease because they have variable effects on putative pathogenic mechanisms. An alternative approach is to study rationally designed mutants of aSyn in order to understand the effect of alterations in defined regions or functions of the protein. aSyn contains highly conserved repeat motifs (KTKEGV) throughout the protein. Engineered mutations in these repeats lead to disruption of several aSyn functions, such as lipid binding and formation of aSyn multimers. In some cases, the effects of these KTKEGV-mutant proteins represent an enhanced or exaggerated version of changes caused by PD-linked mutations in aSyn. Therefore, these designed mutations may shed light on the pathogenic events caused by aSyn

dysfunction. We find that KTKEGV-mutants lead to rapid death of primary cortical neurons. Furthermore, KTKEGV-mutants impair neurite regrowth after mechanical injury in cultured neurons. Strikingly, each mutant is strongly phosphorylated on serine-129. In conclusion, KTKEGV-mutants may help to elucidate key pathophysiologic mechanisms, such as the role of phosphorylation on serine-129, involved in aSyn-mediated neuronal dysfunction and degeneration.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? DS is a director and consultant to Prothena Biosciences.

Multiple Sclerosis

S172. Claudin-4 is Required for Astrocytic Tight Junction Formation and Protects Against Inflammatory Lesion Size and Severity in the Central Nervous System

Sam Horng, Candice Chapouly, Anthony Therattil, Azeb Tadesse Argaw and Gareth John. New York, NY

Objective: To characterize molecular mechanisms that mediate the protective function of reactive astrocytes against inflammatory CNS lesion size and severity.

Background: A protective barrier restricts the passage of lymphocytes and soluble proteins from the bloodstream into the CNS parenchyma. This barrier has traditionally been characterized as a single layer consisting of tight-junction (TJ) bonds between CNS microvascular endothelial cells, a structure termed the blood brain barrier (BBB). However, recent work deleting the layer of astrocytes encircling the BBB revealed a protective role for this additional layer, termed the glia limitans, in delimiting lesion size and severity. We hypothesized that astrocytes form TJs themselves after inflammation, thereby, representing a second line of defense distal to the traditional BBB.

Design/Methods: We screened for changes in expression of TJ molecules in primary human astrocytes under control and inflammatory conditions, and positively identified three molecules, claudin-1, claudin-4 and JAM-A, in human astrocyte cultures exposed to inflammatory stimuli. Immunohistochemistry and immuno-EM of two in vivo mouse models of inflammatory CNS disease revealed that all three proteins localized to TJ between astrocytic endfeet at the glia limitans. In vitro co-culture assays of reactive astrocytes in which these genes were silenced using siRNA, and CD3+ T cells, demonstrated that all three proteins regulate the capacity of reactive astrocytes to limit migration of lymphocytes. An astrocyte-specific claudin-4 knock out mouse was found to have increased lesion size and severity in two models of inflammatory CNS disease, as well as significantly exacerbated clinical disability in EAE, a rodent model of multiple sclerosis.

Results: We report the presence of a second TJ barrier between the blood and the CNS, at the glia limitans, composed of claudin-1, claudin-4 and JAM-A, which are dynamically upregulated in response to inflammatory stimuli. In vitro, claudin-4 knock-down in reactive astrocytes limits their ability to restrict leukocyte dispersion. In vivo,

astrocyte-specific loss of claudin-4 leads to increased lesion size in inflammatory models, and worsened clinical disability in EAE.

Conclusions: Reactive astrocytes upregulate TJ molecules, claudin-1, claudin-4 and JAM-A, leading to the formation of TJs and a second barrier distal to the classical BBB at the glia limitans, which protects against the size and severity of inflammatory CNS lesions.

S173. Selection of First-Line Therapy in Multiple Sclerosis Using Risk-Benefit Decision Analysis

David Bargiela, Matt T. Bianchi, M. Brandon Westover, Lori B. Chibnik, Brian C. Healy, Philip L. De Jager and Zongqi Xia. Boston, MA and Pittsburgh, PA

Introduction: Selection of first-line therapy for multiple sclerosis requires consideration of long-term treatment risks and benefits. We aimed to integrate measures of disease-modifying drugs (DMDs) efficacy with risk of progressive multifocal leukoencephalopathy (PML) to guide long-term decision-making for multiple sclerosis patients.

Methods: We created a Markov decision model to evaluate disability progression and PML risk profile while on natalizumab (NTZ), fingolimod (FGL) or glatiramer acetate (GA) treatment across a 30-year disease course. Using published clinical trials, PML surveillance reports and the UK Multiple Sclerosis Risk Sharing Scheme, we integrated treatment utility, disability progression and risk of PML into quality adjusted life years (QALYs). Sensitivity analyses were performed to vary PML risk, PML survival, PML-associated morbidity and relative risk of disease progression across a wide clinically relevant range.

Results: Over the entire reported range of NTZ-associated PML risk, NTZ as first-line therapy is predicted to provide a greater net benefit (15.06 QALYs) compared to FGL (13.99 QALYs) or GA (12.71 QALYs) treatment over a 30-year period. NTZ treatment is associated with delayed progression to an Expanded Disability Status Scale score ≥ 6.0 versus FGL or GA treatment (22.7 years, 17.0 years and 12.4 years, respectively). When compared to untreated patients, NTZ-treated subjects have an increased relative risk of death in the early years of treatment that varies according to PML risk profile.

Conclusions: NTZ as a first-line treatment is associated with the highest net benefit across all ranges of PML risk profiles when compared to FGL or GA treatment, even after accounting for loss of QALYs due to PML or death (from all causes). Nevertheless, individualized patient counselling on the risk, morbidity and mortality of PML from NTZ or FGL treatment remains essential. Integrated modelling of long-term treatment risks and benefits informs stratified clinical decision-making.

S174. Longitudinal Spinal Cord Measurements in Neuroinflammatory Diseases

Shila Azodi, Emily Charlip, Winston Liu, Jeanne Billioux, Ashley Vellucci, Joan Obayon, Goavind Nair and Steve Jacobson. Bethesda, MD and College Park, MD

Background: Atrophy of the spinal cord is a prominent finding on MRI in inflammatory diseases including HTLV1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) and multiple sclerosis (MS). To date techniques to measure the spinal cord have looked only at specific levels of the spinal cord and required significant manual inputs.

Methods: MRI of the spinal cord was obtained in 15 healthy volunteers (HV), 40 HAM/TSP, 15 asymptomatic HTLV1 carriers (AC), 22 primary progressive, 10 secondary progressive, and 32 relapsing remitting MS patients. Of the HAM/TSP group, two patients were rapidly progressing clinically and had 5 MRIs over two years. Using a robust and semi-automatic quantification program analyzing the spinal cord cross-sectional area (SCCSA) we measured the diameter along the entire length of the spinal cord.

Results: Longitudinal data for the rapidly progressive HAM/TSP patients shows atrophy beginning in the thoracic cord and progressing cranially to the thoracic cord. Cross sectional data for the MS cohort shows a similar SCCSA for RRMS and HV while SPMS and PPMS shows significantly smaller cervical SCCSA and intermediate thoracic cord SCCSA compared to HV.

Conclusion: Neuroinflammatory diseases show unique patterns of spinal cord atrophy with time. The study findings suggest SCCSA may be used as a marker for disease progression in neuroinflammatory diseases.

S175. Polyprenols Stimulate Neurogenesis and Reduce Demyelination in the Murine Cuprizone Model of Multiple Sclerosis

Marina Yu Khodanovich, Valentina Yu Glazacheva, Edgar S. Pan, Andrey E. Akulov, Elena P. Krutenkova, Vladimir B. Trusov and Vasily L. Yarnykh. Tomsk, Russian Federation; Melbourne, Australia and Seattle

Introduction: Polyprenols are bioactive long-chain isoprenoid alcohols occurring in various plants. A pharmaceutical-grade preparation containing 95% polyprenols (isolated from the green verdure of *Picea abies* (L.) Karst) has hepatoprotective and immunomodulating properties. Its potential neuroprotective effect is under investigation.

Purpose: To evaluate the effect of pharmaceutical-grade polyprenols (Ropren®) on neurogenesis and demyelination in the cuprizone-induced murine model.

Methods: Demyelination was induced in 14 x 8-week-old male CD-1 mice by feeding with 0.5% cuprizone (mixed with a standard chow) for 10 weeks. Seven cuprizone-treated rats received intraperitoneal injections of polyprenols (12 mg/kg, once per day) from the sixth week of cuprizone treatment. The rest of the cuprizone-treated group (N=7) and the controls (N=7) received sham oil injections according to the same schedule. Brains were examined by MRI using an 11.7T small-animal MRI scanner with T2-weighted multi-slice acquisition sequence (in-plane resolution 100x100 µm, slice thickness 0.5 mm). Corpus callosum size was estimated using measurements in three adjacent cross-sections. Immediately after MRI and transcardial perfusion, brains were removed and frozen and sections stained for doublecortin (DCX), a marker of

immature neurons, and myelin basic protein (MBP). The number of DCX+ cells was counted for two neurogenic zones: the subventricular zone (SVZ) of lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus. Mean MBP staining intensity was measured in the corpus callosum, anterior commissure, internal capsule, thalamus, caudoputamen, hippocampus, and cortex. Groups were compared using independent t-test and ANOVA.

Results: Cuprizone administration reduced the estimated size of the corpus callosum by 19.5% compared to controls (p<0.01). MBP staining in the cuprizone-treated group was lower than controls in all brain structures (p<0.05) except for the anterior commissure and internal capsule. In contrast, mice treated with cuprizone and polyprenols did not show significant demyelination as shown by both MRI and MBP staining. Cuprizone treatment also reduced the number of DCX+ immature neurons both in the SVZ and SGZ (p<0.001). Ropren® administration restored neurogenesis to the level of controls.

Conclusions: This study suggests favorable effects of the pharmaceutical-grade polyprenols on cuprizone-induced demyelination. While the mechanism of action of polyprenols in this model is not fully studied, this substance should be considered for testing as a potential supplementary treatment in demyelinating diseases.

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Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Solagran Limited Biotechnology Company has Intellectual Property Rights to Ropren® substance

S176. HTLV-1 Viral Antigens Detected in Exosomes Isolated from HAM/TSP Patient CSF by Novel Nanotrap Technology

Monique Anderson, Maria Chiara Monaco, Ashley Vellucci, Ben Lepene, Yuetsu Tanaka, Joan Ohayon, Fatah Kashanchi and Steven Jacobson. Bethesda, MD; Manassas, VA; Nishihara-Cho, Okinawa, Japan and Charlottesville, VA

Human T-cell Lymphotropic Virus Type I (HTLV-1) is a delta retrovirus associated with Adult T-cell Leukemia and the progressively debilitating HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). As a demyelinating disease, there is significant damage to oligodendrocytes within the thoracic and cervical spinal cord although there has been a paucity of evidence for active infection of resident neural cells. There is much debate in the field concerning the cause of this damage, whether due to a bystander effect from elevated cytokines or through direct targeting of oligodendrocytes as HAM/TSP patients are noted for an increased presence of HTLV-1 specific T cells in the CNS. Exosomes, secreted microvesicles ranging from 30 to 100nm, have been shown to serve as a source of antigen in the immune system previously and accumulating evidence is pointing to the ability of viruses to hijack this system of

intercellular communication. Due to prior evidence of HTLV-1 components present in extracellular vesicles isolated from HTLV-1 infected cell lines, we sought to discover if this phenomenon was recapitulated in vivo. We tested HAM/TSP CSF and HTLV-1 seronegative Multiple Sclerosis CSF and found the presence of HTLV-1 Tax in exosomes isolated by a novel nanotrap technology from HAM/TSP CSF. Importantly, we could also find Tax in exosomes isolated from ex vivo culture of some HAM/TSP patient PBMCs that were positive for Tax in the exosomes from their CSF, although the relationship did not hold for all patients. Furthermore, in both normal donors (NDs) activated CD4+CD25+ and CD8+CD25+ T cells were the primary sources of these exosomes, but highest increase in exosome secretion occurred after activation of the CD4+CD25+ T cell subset. As, this subset serves as a viral reservoir in HAM/TSP and is noted for dysfunctional suppressive capabilities in HAM/TSP, we propose that they are a source of the Tax+ exosomes found in our patients and have undertaken experiments to validate this hypothesis.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? The nanoparticles used for trapping exosomes were kindly prepared and donated by Ceres Nanosciences

S177. Quantitative Assessment of Demyelination in the Medulla Oblongata in Multiple Sclerosis Using Macromolecular Proton Fraction Mapping

Vasily L. Yarnykh, James D. Bowen, Beena Gangadharan, Pavle Repovic, Angeli Mayadev, Peiqing Qian and Lily K. Jung Henson. Seattle, WA and Toms, Russian Federation

Introduction: Lesions in the medulla oblongata are frequently observed in multiple sclerosis (MS) and may be associated with significant morbidity. Despite the vital role of this anatomic structure, to the best of our knowledge, there were no systematic either imaging or pathological studies of medullary demyelination in MS. Fast macromolecular proton fraction (MPF) mapping is a recently developed MRI method enabling clinically-targeted quantitative imaging of brain myelination.

Purpose: Quantitatively characterize demyelination in the medulla oblongata and assess its clinical relevance in MS using fast MPF mapping.

Methods: Three-dimensional whole-brain MPF maps were obtained from 18 relapsing-remitting MS (RRMS) patients (EDSS range 1.0-6.5), 12 secondary-progressive MS (SPMS) patients (EDSS range 5.5-8.0), and 14 healthy controls using the fast single-point method. Source images were acquired on a 3T MRI scanner. The medulla oblongata was segmented using a semi-automated region-growing algorithm. Automatic whole-brain tissue segmentation was performed to determine global MPF values in white and gray matter. Groups were compared using one-way ANOVA. Pearson's correlation coefficient (r) and multivariate regression were used to test associations between imaging and clinical variables.

Results: MPF in the medulla oblongata nearly monotonically decreased from controls to RRMS patients and from SPMS to RRMS patients (mean $\pm$ SD: $12.0 \pm 0.5\%$, 11.2 ± 0.7 , and $10.2 \pm 0.7\%$, $P < 0.001$ for all comparisons). Relative changes in MPF translate into an approximate myelin loss in the medulla of about 10% in RRMS and 20% in SPMS. Medullary MPF strongly correlated with EDSS ($r = -0.67$, $P < 0.001$) and MSFC ($r = 0.75$, $P < 0.001$) scores and moderately with the disease duration ($r = -0.51$, $P = 0.004$). MPF in the medulla demonstrated modest correlations with global MPF values in white ($r = 0.64$, $P < 0.001$) and gray ($r = 0.57$, $P = 0.001$) matter and weakly correlated with the total lesion volume ($r = -0.40$, $P = 0.027$). In the stepwise multivariate linear regression analyses, only global MPF in gray matter and MPF in the medulla were retained in the models as significant predictors of EDSS ($r = 0.80$, $P < 0.001$) and MSFC ($r = 0.88$, $P < 0.001$) scores.

Conclusions: This study indicates that demyelination in the medulla oblongata is significant and strongly associated with disability in MS. The loss of myelin in the medulla cannot be completely explained by the trends of global demyelination in white and gray matter. Our results suggest that the medullary MPF value provides a promising clinical biomarker in MS.

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Epilepsy

S178. Prevalence and Character of Severe Epileptic Encephalopathy in Patients Affected by MECP2 Duplication Syndrome

Dana Marafie, Rebecca Schultz, Daniel Glaze, Bernhard Suter and Alica Goldman. Houston, TX

Objective: Epilepsy is a frequent, yet poorly understood neurological comorbidity of patients affected by MECP2 duplication syndrome (MDS). We aim to characterize the spectrum, severity, and treatment responsiveness of MDS associated epileptic syndromes.

Background: MDS is a rare X-linked neurodevelopmental disorder with an estimated prevalence of 1% in males with unexplained X-linked mental retardation and in 2% of males with encephalopathy and severe progressive neurological symptoms. Its main neurological manifestations include infantile hypotonia, severe intellectual disability, psychomotor regression, autism, and spasticity. About half of all MDS patients develop epilepsy in childhood with the prevalence reaching 90% by adolescence. Yet, epilepsy characteristics remain largely unknown. Epileptic encephalopathy (EE) has been reported in less than 10% of the published cases.

Methods: This study was approved by the Institutional Review Board of Baylor College of Medicine. A comprehensive health questionnaire was completed for 42 patients with MDS encountered at the Third Biannual MECP2 Duplication Syndrome Family Conference (Houston, September 2015) and at Texas Children's Hospital Blue Bird Clinic Rett Center.

Results: Epilepsy was identified in 50% cases with an average age of onset at 6 years and neurological regression coincided with the epilepsy onset or progression. Epilepsy was refractory and consistent with EE in 81% of patients and 90% of them were reported to have more than one seizure type. The most commonly reported seizure triggers were infections (33%) and sleep deprivation (29%). Epilepsy onset or worsening coincided with the onset of puberty in 5% cases. Lennox-Gastaut syndrome (LGS) was the most common EE syndrome, accounting for 65% of EE cases and affecting 1/4 of MDS patients. The other 35% of EE cases had EE of varied types. Levetiracetam, topiramate, and valproic acid were the most commonly prescribed anti-epileptic drugs. Parents reported that introduction of levetiracetam, clobazam, and clonazepam was most effective. Adjunct therapy with vagus nerve stimulator or ketogenic diet was implemented with a moderate effect in 5/21 and 7/21 patients, respectively.

Conclusion: Epilepsy in MDS is a common, often severe, medically refractory comorbidity which often coincides with developmental regression. Our findings inform the clinical care, prognostication, and family counseling with respect to early epilepsy diagnosis, specialty referral, and implementation of aggressive seizure control in order to minimize detrimental effect of uncontrolled seizures on pre-existing neurological deficits.

S179. Ultrahigh-Field MR Volumetry of the Endopiriform Nucleus in Temporal Lobe Epilepsy

David Ortiz, Bradley Nix, P-Pierre-Francois Van de Moortele, Julien Sein, Zhiyi Sha, Kamil Ugurbil and Thomas R. Henry. Minneapolis, MN

Background: The EPN has epileptogenic and seizure modulatory ("area tempestas") properties in experimental models. The EPN is evident in human cadaver studies, but not in current clinical MRI.

Design/Methods: We identified 11 TLE subjects who had unilateral ictal EEG onsets ipsilateral to hippocampal atrophy (N = 6) or to a malformation of cortical development (N = 5) on clinical 3 Tesla MRI. With IRB-approved consenting, we acquired 7T brain MRI in 18 healthy subjects and in the TLE patients, including T2-weighted turbo spin echo images (0.25 x 0.25 x 1.2 mm³) in contiguous coronal slices. We included only subjects whose 7T MRI data were of high contrast resolution, with little or no evidence of motion or other artifacts. We used a human brain atlas to locate expected EPN sites on clinical and 7T MR images. We then developed rules for EPN segmentation based on the brain atlas and landmarks visible on 7T MRI. One investigator (D.O.) manually segmented the EPNs on 7T MRI. The right EPN in each TLE subject was compared with the mean healthy right EPN, and the same comparisons were made on the left.

Results: Clinical MRI did not render distinguishable EPNs in any TLE subject. On high quality 7T MRI studies, the EPN was clearly distinct from adjacent amygdala, based on a narrow white matter band that was consistently detected between the EPN and the amygdala. In the healthy

group the right EPN had a mean volume of 156 mm³ (standard deviation of 44.9), and the left EPN had a mean volume of 140 mm³ (standard deviation of 41.4). Each individual TLE patient with hippocampal sclerosis had EPN volumes on the side ipsilateral to the atrophic hippocampus that were much smaller than the healthy subject mean volumes for that side. Each individual TLE patient with a malformation of cortical development located somewhere in the temporal lobe of ictal EEG onsets had EPN volumes on the side ipsilateral to the malformation that were larger than the healthy subject mean volumes for that side, even when the malformation was not located adjacent to the EPN.

Conclusion: Larger groups and reduced imaging artifacts will determine whether ultrahigh-field-strength MR imaging can consistently measure alterations in this small human nucleus, which has considerable pathophysiological significance in animal epilepsy models.

Movement Disorder

S180. Gender Differences in Symptom Manifestation and Survival Patterns in Multiple System Atrophy

Renee M. Nelson, Elizabeth A. Coon, David Sletten, Jay N. Mandrekar, Phillip A. Low and Wolfgang Singer. Rochester, MN

Background: Multiple system atrophy (MSA) is characterized by autonomic failure and predominant motor symptoms of parkinsonism (MSA-P) or cerebellar ataxia (MSA-C). Only few studies have explored the influence of gender on clinical features and survival, and reported findings have been conflicting.

Objective: To evaluate the influence of gender on clinical characteristics and survival in patients with multiple system atrophy.

Methods: All cases of patients diagnosed with MSA who completed standardized autonomic function testing between January 1998 and December 2012 at Mayo Clinic, Rochester were retrospectively reviewed. Clinical symptoms at onset and presentation were obtained from the electronic medical record and classified as either motor, autonomic, or combined (onset of both autonomic and motor symptoms within 1 month). Date of diagnosis and last follow-up were obtained from the electronic clinical record whereas death data was recorded from the clinical record, Social Security Death Index, or via telephone contact. Survival analyses were performed using Kaplan-Meier estimates.

Results: Of the 685 MSA patients in the cohort, 568 were deceased. Men accounted for 52% of patients. MSA-P was the most common subtype in both men and women (65% and 61% respectively, p=0.302). Median overall survival was 7.3 years for men and 7.6 years for women, p=0.040. Median survival from the time of diagnosis was 2.9 years in men and 3.8 years in women, p =0.001. Women were more likely to initially manifest motor symptoms (72%) compared to men (60%), p =0.001, while men were more likely to initially manifest autonomic symptoms (33%) compared to women (21%), p =0.001. Men were also more likely to require urinary catheterization within 3

years of onset (11% versus 6%, $p=0.019$) and experience orthostatic intolerance within 1 year of onset of symptoms (40% versus 30%, $p=0.006$). Women were more likely to experience falls within the first 3 years of disease compared to men (48% versus 57%, $p=0.014$).

Conclusions: In addition to a slight overall survival benefit, our data show longer survival of almost one year in women compared to men from the time of diagnosis. This would suggest that women tend to come to diagnosis at an earlier stage than men, which may be due to women initially manifesting motor compared to autonomic symptoms. The earlier and more severe autonomic symptoms in men may be contributing to their worse overall prognosis.

S181. Polygenic Risk of Spasmodic Dysphonia Is Associated with Functional Connectivity Alterations in the Sensorimotor Cortex

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Objective: To investigate the polygenic architecture in relation to abnormal functional brain networks and clinical characteristics of spasmodic dysphonia in order to identify the overall genetic risk and potential imaging markers of this disorder.

Background: Spasmodic dysphonia (SD) is an isolated task-specific dystonia of unknown causes and pathophysiology that selectively affects speech production. Although several reports indicated that up to 12% of SD patients have a family history of dystonia suggesting that genetic variants with reduced penetrance are likely involved in SD etiology, no causative genes for SD have been identified so far. Whether and how possible genetic risk factors may influence brain structure and function, and contribute to clinical symptoms of dystonia is largely unknown.

Methods: Using whole-exome sequence data in 57 patients with SD, we defined and computed polygenic risk scores from 1,804 genetic markers based on a genome-wide association study in another form of task-specific focal dystonia that shows similar functional brain alterations in neuroimaging studies, musician's dystonia. We examined resting-state brain activity in these patients compared to 30 healthy controls and assessed the relationship between the computed polygenic risk scores, resting-state functional connectivity (FC) abnormalities within the sensorimotor network, dystonia severity, and its age of onset. Gene set enrichment analysis was used to examine the genetic content of the polygenic risk score.

Results: Polygenic risk of SD was significantly associated with decreased FC in the left premotor/primary sensorimotor and inferior parietal cortices in SD patients. The abnormal connectivity of the inferior parietal cortex was further correlated with the age of dystonia onset. The polygenic risk score contained a significant number of genetic variants lying near genes related to synaptic transmission and neural development.

Conclusions: Collectively, our results bridge the genotype-phenotype gap in SD by showing that alterations of functional connectivity in the sensorimotor and inferior parietal cortices in SD patients are correlated with a polygenic risk score and may represent an intermediate endophenotype and imaging biomarker of SD, while genes involved in synaptic transmission and neuron development may be linked to the molecular pathophysiology of this disorder.

S182. Repurposing of Prostate Cancer Chemotherapeutics as a Brain Bioavailable Nurr1 Transactivator for Treatment of Synucleinopathies in Parkinson's Disease

Giulio Pasinetti and Kenjiro Ono. New York and Tokyo, Japan

IRX4204 is a second generation retinoid X receptor (RXR) agonist currently being tested for prostate cancer treatment with an excellent safety record. Nurr1-RXR heterodimer selective agonists have been actively pursued as a potential pharmacological target for Parkinson's disease (PD) due to their neuroprotective effects in models of PD. The objective of our study is to evaluate the effects of IRX4204 as a potential novel therapeutic in PD neuropathology. Primary rat mesencephalic cultures were used to study the role of IRX4204 on Nurr1-mediated neuroprotection. The 6-hydroxydopamine (6OHDA) induced rat model of PD was used to examine the potential neuroprotective role of IRX4204 on PD pathology. Nuclear magnetic resonance (NMR) and photo-induced cross-linking of unmodified protein (PICUP) were used to evaluate the role of IRX4204 on prevention of α -synuclein binding and oligomerization. We found that IRX4204 can selectively promote dimerization of the nuclear factor Nurr1-RXR at nM concentration in vitro and can promote expression of neurotrophic factors for the survival and maintenance of nigral dopaminergic (DA) neurons in a dose-dependent manner in vivo. This evidence is consistent with a significant attenuation of PD-type motor impairments following 6-OHDA lesions in response to IRX4204. Using a combination of NMR spectroscopy and PICUP assays, we found that IRX4204 shifts and prevents oligomerization of α -synuclein. Our data suggest that IRX4204 may benefit PD by providing neuroprotective support for DA neurons and by protecting DA neurons from α -synuclein neurotoxicity. We hypothesize that IRX4204 may neuroprotect DA neurons through Nurr1 mediated neuroprotective mechanisms intracellularly and possibly at more advanced PD-like states through inhibition of α -synuclein oligomerization.

S183. Development of a Brief Ataxia Rating Scale for Children (BARS-c)

Franziska Hoche, Winthrop P. Harvey, Bruna Olson-Bressane, Mark G. Vangel and Jeremy D. Schmahmann. Boston, MA

Objective: To develop a sensitive and reliable ataxia rating scale appropriate for use in children.

Background: Current ataxia rating scales are based on normative data in adults (International Cooperative Ataxia Rating Scale [ICARS] - Trouillas et al., 1997; Scale for Assessment and Rating of Ataxia [SARA] - Schmitz-

Huebsch et al., 2006; Brief Ataxia Rating Scale [BARS] - Schmahmann et al., 2009). The problem in children, however, is that healthy children <12 years score in the impaired range on these scales (Sival et al., 2009; Brandsma et al., 2014).

Methods: We administered the ICARS, SARA and BARS, the PEG board test, and novel developmentally adapted motor tasks for younger children (Bayley and Denver scales) to 133 healthy children (53 males) aged 11.0 months to 18.7 years, and 30 patients with cerebellar disease (age 15.0 months to 23.4 years). Using a two step approach: 1) we investigated the effect of age and gender on both established and novel tests in healthy children, 2) we selected or developed tests that differentiate typically developing children from those with cerebellar ataxia, and 3) we established normative values for these tests.

Results: ICARS, SARA, and BARS tasks and PEG-board scores were age-dependent, with younger healthy children scoring in the impaired range. Exceptions were Sitting and Oculomotor control, which separated patients from controls across the age span (both $p < .000$). Developmentally appropriate tasks for younger children included tracing Bayley figures (replacing Archimedes spiral), hand tapping (replacing dysdiadochokinesis), precision reaching (replacing finger to nose), and repeating syllables (replacing full sentences). We are currently developing novel norms for gait in each age group.

Conclusion: Ataxia rating scales need to be adjusted for use in children. We have developed the Brief Ataxia Rating Scale for children (BARS-c) that includes developmentally appropriate test items for use in the pediatric ataxia population.

S185. An Extragenic Safe Harbor Permits Suicide Gene Expression Serving as a Safety Switch for Cell Therapy of Neurological Disorders

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Background: Cell-based therapy using human induced pluripotent stem cells (hiPSCs) is an upcoming treatment of neurological disorders such as Parkinson's disease, ischemic stroke or ALS, although transplantation of neuronal cells obtained from hiPSCs still has concerns of adverse events including tumorigenesis. Selective elimination of wayward tumor-initiating cells with a suicide gene can be one of the most valuable approach to address this issue. Previous studies employed an approach with retroviral gene manipulation which left the possibility that transgenes could suffer silencing and/or dysregulate nearby genes.

Methods: We selected an extragenic region as a safe harbor which located far from any gene or microRNA loci. We knocked-in the herpes simplex virus thymidine kinase (HSV-TK) suicide gene into this safe harbor of hiPSCs using the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein (Cas) system. Precise integration of the transgene was confirmed by PCR

analysis and Southern blotting. Expression of HSV-TK was validated by RT-PCR and efficacy as a suicide gene was analyzed in vitro and in vivo.

Results: CRISPR/Cas9-mediated knock-in of HSV-TK was confirmed in HEK293T and iPSCs. Six out of 15 (33%) isolated iPS colonies possessed the knock-in allele and HSV-TK expression was detected in these cell lines. In vitro cytotoxicity assay revealed that IC50 of ganciclovir in the knock-in hiPSCs and its parent cells was 0.05 μ M and 200 μ M, respectively. Ganciclovir treatment also reduced the number of Ki67 positive cells from iPSCs carrying this suicide gene.

Conclusion: A suicide gene, HSV-TK, in an extragenic safe harbor could be a safety switch in future cell-based therapy for neurological disorders. Furthermore, this strategy can be applicable in therapeutic gene transfer for future regenerative medicine.

S186. Predicting the Optimal Stimulation Frequency for Deep Brain Stimulation Patients

Anahita Khojandi, Oleg Shylo, Brian H. Kopell and Ritesh A. Ramdhani. Knoxville, TN and New York

Purpose: Deep Brain Stimulation (DBS) is an effective therapy for patients with Parkinson's disease (PD) suffering from levodopa motor complications such as dyskinesia and motor fluctuations. It has been the prevailing notion that high frequency (130-180Hz) stimulation (HFS) is the driving force of clinical benefit, but recent studies have suggested the possible role of 60Hz stimulation for patients with gait disorder. Coupling these findings with growing physiological understanding of aberrant neuronal oscillations in the PD state underscores the idea that frequency – modulation may differentially influence various motor networks and symptoms. Therefore, the development of a computational model which stratifies patients a priori based on symptomatology into different frequency settings stands to improve the speed and efficiency by which programming optimization can be achieved. Here, we build a computational model that can accurately predict the patient-specific optimal frequency level after surgery (i.e., 60Hz or high frequency stimulation).

Methods: We retrospectively analyzed preoperative Unified Parkinson's Disease Rating Scale (UPDRS III) scores (32 indicators) collected from 20 PD patients implanted with bilateral Subthalamic nucleus (STN)-DBS patients at Mount Sinai Medical Center on either 60Hz stimulation or high frequency (130-185Hz) stimulation for at least six months. Predictive models using the Random Forest classification algorithm were built to associate patient/disease characteristics at surgery to the stimulation frequency. These models were evaluated objectively using well-developed statistical approaches, namely out-of-bag classification error and leave-one-out cross validation.

Results: Ten 60Hz patients and ten high frequency (130-185Hz) stimulation patients were included in the study. The computational models produced, stratified patients into 60Hz or high frequency (130-185Hz) stimulation with 90% accuracy. The best models relied on three or four indicators

out of the 32 analyzed for classification. Across all indicators, gait and rest tremor of the right hand were consistently the most important.

Conclusions: Computational models were developed using preoperative clinical indicators in PD patients treated with STN-DBS. These models were able to accurately stratify PD patients into 60Hz stimulation or high frequency (130-185Hz) stimulation groups a priori, offering a unique potential to enhance the utilization of this therapy based on clinical subtypes.

S187. Applying Natural Language Processing (NLP) to Verbatim Patient-Reported Outcomes

Jennifer L. Purks, Michael Harris, Karen E. Anderson and Ira Shoulson. Washington DC

Objective: To apply Natural Language Processing (NLP) to analyze verbatim patient-reported outcomes (PROs) among Huntington Disease (HD) research participants in the Phase 2 REACH2HD randomized-controlled trial examining safety and cognitive benefits of PBT2, an experimental modulator of metal ionophores.

Background: FDA and other regulatory agencies value PROs, but quantification and analytic approaches are lacking. The Huntington Disease Patient-Reported Outcome of Problems (HD-PROP) was developed to capture verbatim subject reports of patients' most bothersome problems and functional consequences. The HD-PROP was administered at baseline (BL), 12 weeks (W12) and 26 weeks (W26) of the REACH2HD trial to the 109 research participants who were randomly assigned 1:1:1 to PBT2 250 mg/day, PBT2 100 mg/day, or placebo.

Methods: Using NLP to extract relationships and meaning from large text-based resources, word clouds (images composed of words from a text where the size of the word indicates frequency or importance) were derived from HD-PROP data in the REACH2HD trial at BL and W26.

Results: The Problem Word Cloud showed that "BALANCE" (69 counts), "MEMORY" (66 counts) and "MOVEMENTS" (48 counts) were the most bothersome reported problems. There was a decrease from 8 "MEMORY" counts at BL to 4 "MEMORY" counts at W26 in the PBT2 250mg group. However the Functional Consequence Word Cloud did not show a clear or informative pattern.

Conclusion: The NLP word clouds for verbatim-reported problems and consequences help to quantify and visually depict patterns in the HD-PROP dataset of the REACH2HD trial. Verbatim problems are more uniformly informed by NLP than verbatim consequences, perhaps related to the complexity of the questions and replies. This may reflect lack of insight or impaired cause and effect reasoning between problem and its functional consequence in this patient population. Some PBT2 250mg treatment effect on MEMORY is suggested by these results. More advanced NLP may provide more informative analysis of PROs.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past

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S188. Predictors of Neurobehavioral Outcomes in Bilateral Subthalamic Nucleus Deep Brain Stimulation Surgery

Michelle E. Fullard, Diane S. Huss, Matthew J. Barrett, Carol A. Manning, Scott Sperling, Binit Shah, Jeffrey Elias, Eric Turkheimer and Madaline B. Harrison. Philadelphia, PA and Charlottesville, VA

Background: STN DBS for Parkinson's disease (PD) improves motor function, but can lead to adverse effects on mood and behavior. Postsurgical rates of neurobehavioral changes vary widely and large studies with well-characterized cohorts are lacking.

Methods: This single center retrospective study included patients with PD who underwent bilateral STN DBS between January 2000 and July 2012. The outcomes of interest were symptoms of emotional lability, including symptoms of hypomania and impulse control (category 1) and depression or apathy (category 2). Two blinded raters determined the presence of symptoms based on documentation at 1, 3 and 6 months post-operative. Potential predictors included gender, age at disease onset, age at surgery, education, disease severity (total UPDRS and Hoehn and Yahr stage), preoperative fluctuations or dyskinesias and preoperative medications. Statistical analysis was performed using classification and regression trees, a method that is robust to a high ratio of potential predictors to participants, missing data and non-linear and non-additive relationships. Prediction models were conducted separately for each outcome category.

Results: One hundred and twenty four patients met inclusion criteria (mean age 62.0 years; disease duration 10.8 years). Interrater reliability was >0.9 for both outcome categories. Of the 124 patients, 52 (42%) reported at least 1 symptom from category 1 (emotional lability) and 63 (51%) reported at least one symptom from category 2 (depression/apathy). Results suggest that age at surgery and age at PD onset interact in predicting symptoms of emotional lability. For patients over 50 at the time of surgery, 70% (26/37) of those with younger PD onset (<52) and lower total UPDRS scores (<56), reported symptoms in this category. Those with age of onset >52 reported post-operative symptoms of emotional lability less frequently (35%; 20/57). For depression, results suggested that patients at either end of the spectrum of severity (total UPDRS <30 or >82) were less likely to report symptoms (2/11 and 1/9 respectively). For the remaining patients with total UPDRS between 30-82, 61% of younger patients (age <70) reported symptoms in this category (57/93). Prediction accuracy for the models ranged from 70-80%.

Conclusions: In this retrospective case series, clinically useful predictors of adverse neurobehavioral outcomes in

bilateral STN DBS were identified using an empirically based analytic strategy.

S189. A Novel Presentation of Post-Surgical Edema Associated with DBS Implantation with Review of the English Literature

Nancy Song and Mary S. Feldman. Lebanon, NH

Objective: To report a novel presentation of post-surgical edema associated with Deep Brain Stimulation (DBS) implantation as well as review of the English literature.

Introduction: Transient, post-operative, noninfectious edema surrounding a surgically implanted DBS lead is a rare complication. Transient, post-operative, noninfectious symptomatic edema is even more uncommon^{1,4}. There have been case reports of this phenomenon in post-DBS patients presenting with neurologic symptoms including headache, seizure, behavioral changes, or worsening of pre-existing Parkinson's Disease (PD) symptoms^{1,2,3}. We report a novel presentation of post-surgical edema associated with DBS implantation presenting as acute homonymous hemianopia.

Description: A 58-year old female with PD s/p DBS implantation with an uncomplicated post-operative course presented 4 months after surgery with acute onset of right partial homonymous hemianopia. Her visual symptoms were preceded by fever, chills, and upper respiratory tract symptoms. Initial differential diagnosis was concerning for abscess or infarct.

Results: MRI revealed large area of signal alteration on T2 and FLAIR modalities surrounding the DBS lead. Area of signal alteration extended into the cerebral peduncle and posterior temporal lobe as well as the left optic tract, hypothalamus, and optic chiasm correlating with her clinical symptoms. Additional workup included infectious screen and vessel imaging. Serum studies including CBC, CMP, CRP, ESR, and blood cultures were obtained and were normal. Neurosurgery was consulted. Ultimately, the patient's clinical presentation and imaging findings were deemed most consistent with delayed onset idiopathic post-surgical edema. She was treated with Dexamethasone 4mg PO BID and discharged home with complete resolution of her symptoms after 3 weeks of steroids. Repeat MRI showed near complete resolution of T2 signal alteration.

Conclusion: Post-operative symptomatic edema associated with DBS is a rare surgical complication. We report this unique presentation of acute right homonymous hemianopia which resolved both clinically, as well as on repeat neuroimaging, after high dose steroid administration. Patients that develop neurologic changes after DBS should undergo evaluation to rule out emergencies such as infection, hemorrhage, or infarct. However, we recommend that post-operative non-infectious edema should be considered in the initial differential diagnosis. We concur with previous reports that caution against hasty removal of DBS electrodes in the absence of obvious signs of infection or intracranial mass effect¹.

1. Englot, *Stereotactic and Functional Neurosurgery*, 2011
2. Deogankar, *Journal of Clinical Neuroscience*, 2011
3. Lefaucheur, *Brain Stimulation*, 2013
4. Tong, *Neurosurgical Review*, 2014.

Neuro-Oncology

S190. Analysis of Glioblastoma Physical Characteristics in Patients Benefiting from Tumor Treating Electric Fields Therapy

Pyay P. San, Joshua Timmons, Edwin Lok, Kenneth D. Swanson and Eric T. Wong. Boston, MA and Lowell, MA

Background: Tumor treating electric fields (TTFields) therapy is an established treatment approved for patients with glioblastoma. It is frequency tuned to 200 kHz to disrupt cytokinesis of tumor cells during their transition from metaphase to anaphase. Two orthogonal arrays of TTFields transducers are applied to the shaved scalp of patients, but the contribution of anatomical and physical characteristics of the brain parenchyma and the tumor to treatment efficacy is poorly understood.

Methods: Three dimensional gross tumor volume (GTV) was contoured using ScanIP software (Simpleware Ltd) and bi-dimensional tumor size was measured according to the Response Assessment in Neuro-Oncology criteria on 5 patients with recurrent glioblastomas who benefited from TTFields (cohort 1) and 5 who did not (cohort 2). Surface area of the tumors and their geometric centroid distance (GCD) from the bilateral ventricles were computed using center-of-mass analysis. Wilcoxon rank sum test was then used to compare these physical parameters between the two cohorts.

Results: The respective median GTV was 11.6 (range 7.3-74.5) cm³ and 38.1 (range 2.2-55.8) cm³ (P=0.0591), while the respective median GCD was 5.0 (range 2.9-6.3) cm and 5.3 (range 4.1-6.4) cm (P=0.6761), in cohort 1 and 2. The bi-dimensional tumor size had a median value of 8.2 (range 5.5-42.3) cm² in cohort 1, as compared to a median of 53.9 (range 3.5-111.7) cm² in cohort 2 (P=0.0591). In addition, the surface area had a median value of 56.2 (range 31.6-510.0) cm² in cohort 1, as compared to a median of 214.0 (range 14.3-639.0) cm² in cohort 2 (P=0.4034). After removing an outlier from cohort 1 and another from cohort 2, the respective median GTV was 9.7 (range 7.3-14.3) cm³ and 41.3 (range 24.4-55.8) cm³ (P=0.1003), and the respective median surface area was 46.5 (range 31.6-83.0) cm² and 236.0 (range 214.0-639.0) cm² (P=0.0304). The respective median surface area/GCD was 13.3 (range 5.43-21.6) cm and 38.9 (range 37.0-119.5) cm (P=0.0304) and the respective median GTV/GCD was 2.7 (range 1.26-4.0) cm² and 8.5 (range 4.4-8.7) cm² (P=0.0304).

Conclusion: The ratio of surface area/GCD and GTV/GCD, which are proportional to the tissue capacitance, may be an important parameter for optimizing TTFields efficacy in the treatment of glioblastoma.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Novocure research grant

S191. Temporal Trends and Outcomes of Acute Ischemic Stroke in Patients with Cancer of Brain and Nervous System

Arpita Hazra, Achint Patel, Harshil Shah, Marwa Elnazeir, Tushar Mishra, Mihir Dave, Srilatha Thadur, Varun Shah, Geoffrey Barger and Abdul Samad Zahid. Detroit

Objective: To determine the temporal trends and outcomes of acute ischemic stroke (AIS) in patients with cancer of brain and nervous system (CBNS).

Background: Primary and metastatic CNS tumors are associated with increased risk for stroke due to either disease or treatment specific etiology. This population is also at disadvantage of underutilization of thrombolytic therapy due to higher risk of hemorrhage. National studies estimating the burden and outcomes of AIS in patients with CBNS are lacking.

Methods: We used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) from years 2002-2012. We identified AIS and CBNS using validated International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes. We used the Cochran-Armitage trend test and multivariate regression to generate adjusted odds ratios (aOR).

Results: We were total 822,076 all-cause hospitalizations in CBNS population from years 2002-2012. On trend analysis, proportion of hospitalizations due to AIS doubled from 5.8/1000 in 2002 to 11.1/1000 in 2012 (ptrend<0.001). AIS patients having CBNS were more likely to be female (52% vs. 46%, p<0.001) and white (80% vs. 70%, p<0.001). Patients with CBNS had higher odds of discharge to specialty care (aOR 1.38; 95%CI 1.36-1.42; p<0.001) as compare to AIS hospitalization without CBNS. However in-hospital mortality was similar to those without CBNS.

Conclusion: Our study displayed an increasing burden of AIS among patients living with CBNS. Given that CBNS is associated with greater need to post-discharge specialized care, our results emphasize the need for better risk stratification and early recognition/treatment in this population.

Behavioral Neurology

S192. Monogenic Disorders That Mimic the Phenotype of Rett Syndrome

Siddharth Srivastava, Sonal Desai, Julie Cohen, Kristin Baranano, Ali Fatemi and Sakkubai Naidu. Baltimore, MD

Introduction: Rett syndrome (RTT) is a rare neurodevelopmental disorder associated with a number of clinical features, including but not limited to postnatal microcephaly, seizures, loss of purposeful hand use and language, stereotyped hand movements, and apraxic gait. The disorder is caused by mutations in methyl-CpG binding protein 2 (MECP2), but defects in a handful of other genes (such as CDKL5, FOXP1, and MEF2C) can lead to presentations that resemble, but do not completely mirror, classical RTT. In this study, we attempted to identify other monogenic disorders that share features with RTT.

Methods: We performed a retrospective chart review on n = 319 patients who had undergone clinical whole exome sequencing (WES) for further etiological evaluation of neurodevelopmental diagnoses that remained unexplained despite extensive prior workup. From this group, we characterized those who (1) possessed features that were compatible with RTT based on clinical judgment (2) underwent MECP2 sequencing and/or MECP2 deletion/duplication analysis with negative results (3) ultimately arrived at a diagnosis other than RTT with WES.

Results: There were 7 patients with clinical features overlapping RTT who had negative MECP2 analysis but positive WES providing a diagnosis. These 7 patients collectively possessed mutations in 6 different genes. Two individuals had pathogenic variants in KCNB1; the remaining 5 individuals possessed pathogenic variants in the following genes: WDR45, FOXP1, MEIS2, TCF4, and IQSEC2. RTT associated features included the following: microcephaly (n = 3; WDR45, FOXP1, KCNB1); loss of hand or language skills (n = 3; KCNB1 × 2, IQSEC2); seizures (n = 5; KCNB1 × 2, WDR5, FOXP1, MEIS2); disrupted sleep (n = 4; WDR45, KCNB1, MEIS2, TCF4); stereotyped hand movements (n = 5; KCNB1 × 2, FOXP1, MEIS2, TCF4); bruxism (n = 3; KCNB1 × 2; TCF4); and hypotonia (n = 7).

Conclusions: Clinically-based diagnoses can be misleading, evident by the increasing number of genetic conditions associated with features of RTT with negative MECP2 mutations. In light of this, it may be prudent to restrict the definition of RTT to molecularly confirmed cases of MECP2 defect.

S193. Comparative Efficacy of Single-Agent and Combination Therapy with Midodrine and Pyridostigmine for the Treatment of Orthostatic Hypotension— Interim Analysis

Hye Rim Shin, Jung-Ick Byun and Jangsup Moon. Seoul, Republic of Korea

Orthostatic hypotension (OH) can cause presyncopal symptoms and produce considerable disability. Midodrine, a direct acting alpha1-adrenoceptor agonist, and pyridostigmine, a cholinesterase inhibitor are widely used for treatment of OH. However, their long-term efficacy and feasibility has not been fully evaluated. Also, whether combining these two agents would be superior to single-drug treatment is unknown. In this study, we tested the long-term efficacy of daily 5mg of midodrine, 60mg of pyridostigmine, and combination therapy by evaluating hemodynamics and symptom parameters at one and three months after treatment.

This was a single-blind randomized study (ClinicalTrials.gov, NCT02308124). Overall, 63 patients were randomly assigned to three treatment groups: Group 1, Midodrine single (n=22); Group2, Pyridostigmine single (n=19); Group 3, combination (n=22). Mean age was 55 (Range 18-92), 41.3% were male, and possible etiology of OH were MSA (n=3), Diabetes (n=10), paraneoplastic (n=5), unknown (n=45). Initial mean OH symptom assessment score was 20 (SD 12), and OH daily activity score was 11 (SD 10). There was no difference in demographic, OH

etiologies and symptom score between the groups. During follow up, 8 and 23 patients were lost at 1 and 3 months respectively, which was not different between the groups ($p=0.803$, 0.792 , respectively). Half of the patients (47.3%) still had OH at 1 month after treatment, and only 20% had OH at 3 months. Proportion of OH was not different between the treatment groups ($p=0.956$, 0.113 at 1, 3 months respectively). OH symptom parameters significantly improved during follow-up ($p < 0.0001$), and the improvement was similar between the treatment groups ($p=0.348$).

The result of our study suggests that patient with OH can benefit from long-term use of midodrine or pyridostigmine, however, we could not find superior effect from combination therapy.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Staff

S194. Baseline Aphasia Severity Determines the Effect of Right Pars Triangularis Theta Burst Stimulation on Naming

Joely A. Mass, Denise Y. Harvey, Rachel Wurzman, Priyanka Shah-Basak, Olufunsho Faseyitan, Daniela L. Sacchetti and Roy H. Hamilton. Philadelphia, PA and Toronto, ON, Canada

Following stroke, many patients suffer from aphasia - a chronic impairment in their abilities to produce and understand language. Noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) show promise in facilitating aphasia recovery, presumably by prompting neuroplastic changes in the language network. The current study used a form of TMS, called theta burst stimulation (TBS), to investigate the clinical utility of TBS for improving word retrieval in picture naming. Eight patients with aphasia due to left-hemisphere stroke received inhibitory TBS to right pars triangularis (rPTTr) vs. a control site (i.e., vertex) in separate sessions. Prior to stimulation, we obtained a baseline assessment of naming ability using a picture corpus of 520 common objects. We then compared naming accuracy prior to and immediately following stimulation of each site. We found that individuals varied in their responsiveness to TBS. We investigated whether naming impairment severity at baseline related to this variability by assigning subjects to groups based on a median split of baseline naming accuracy (median = 48%). We then explored within each group whether naming accuracy improved following TBS of rPTTr vs. vertex. We found that patients with less severe naming impairments (i.e., > 48% accuracy at baseline; $n = 4$) were more accurate following rPTTr stimulation when compared to pre-stimulation performance ($p = .002$), whereas this was not the case following vertex stimulation ($p = .52$). Language gains following rPTTr stimulation were significantly greater than changes in performance following vertex stimulation ($p = .05$). Conversely, patients with more severe naming impairments performed worse following rPTTr stimulation compared to pre-stimulation performance ($p = .025$), whereas accuracy did not change pre-

vs. post-stimulation of the vertex ($p = .41$). However, the decrease in naming accuracy following rPTTr stimulation for the more impaired speakers did *not* significantly differ from changes in naming accuracy that occurred following vertex stimulation ($p = .15$). We conclude that patients vary in their responsiveness to TMS, and the degree to which word retrieval is impaired may predict which patients are more likely to benefit from inhibitory TMS of the rPTTr. These findings have implications for predicting individual differences in responsiveness to TMS.

Cerebrovascular Disease

S195. White Matter Hyperintensity Patterns Associated with Atrial Fibrillation in Embolic Ischemic Strokes

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Background and Purpose: Among patients with a cardioembolic stroke, atrial fibrillation (AF) is a common comorbidity that is associated with a worse outcome. Mounting data indicates that AF may relate to stroke pathogenesis through mechanisms other than cerebral thromboembolic complications. This view is supported by observations that AF patients have an increased risk for cerebral small vessel disease related lesions such as greater white matter hyperintensity (WMH) lesion burden. Subcortical WMH spots as well as larger patches are commonly observed in clinical and research MRI but the significance of these different patterns is not known. We sought to identify different WMH patterns between patients with AF vs. non-AF related embolic ischemic strokes.

Methods: We retrospectively analyzed consecutive patients with acute anterior circulation embolic ischemic stroke included in an academic medical center's stroke registry. The stroke etiology was determined using the Causative Classification System of ischemic stroke. WMH lesion burden was assessed according to the Fazekas scale. An independent blinded examiner classified the different WMH-patterns, which included 5 categories: periventricular, subcortical spots, posterior subcortical patches, anterior subcortical patches, and severe confluent subcortical patches. Their association with AF was investigated using multivariable logistic regression (with backward elimination).

Results: Overall, 174 patients (94 with and 80 without AF) were included. In unadjusted analyses, patients with AF had a significantly higher rate of anterior subcortical patches ($p=0.018$) and a lower rate of a periventricular pattern ($p=0.022$). After adjusting for WMH lesion burden, presence of multiple infarcts, infarct volume, the CHA2DS2-VASc score as well as pertinent two-way and three-way interactions the presence of anterior subcortical patches (OR 2.41, 95%-CI 1.02-5.72, $p=0.045$) and a higher CHA2DS2-VASc score (per point, OR 1.28, 95%-CI 1.08-1.52, $p=0.005$) were independently associated with AF.

Conclusions: We found that AF is associated with specific WMH lesion patterns on MRI. The clinical significance of this observation remains to be clarified; yet it suggests that the well-established link between stroke and

AF extends beyond thromboembolism and may reflect an underlying cardiovascular pathology that can be characterized by WMH. If confirmed in future studies further investigation into the underlying pathophysiological mechanisms may provide novel avenues to AF detection and treatment.

S197. More Time Is Taken to Administer Intravenous Tissue-Plasminogen Activator (tPA) in Ischemic Stroke Patients with Earlier Presentations

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Background AND Purpose: In an acute ischemic stroke, administration of intravenous tissue plasminogen activator (IV tPA) within a 4.5 hour window from the time last known well (LKW) improves clinical outcomes, with better outcomes seen with earlier administration. We hypothesized that cases with a shorter LKW to stroke team activation ("stroke code") time will have a significantly longer stroke code to tPA administration time, possibly due to the perception on the part of evaluating physicians of sufficient time before the end of the tPA window.

Methods: There were 1865 ischemic stroke patients in the Mount Sinai Hospital Get with the Guidelines stroke database (2009-2015); 134 patients received IV tPA (including 10 patients ultimately discharged with TIA or non-stroke diagnoses); 12 were excluded due to incomplete data. The remaining 122 individuals were divided by time of "LKW to stroke code" into 3 groups: 0-59 minutes (n=38), 60-119 minutes (n=49), and ≥ 120 minutes (n=35). The mean time from stroke code to tPA administration was compared among these groups using ANOVA, pairwise t-tests, and linear regression analysis, adjusting for age, sex, NIH stroke scale score, and race-ethnicity.

Results: Average code to tPA administration time was 80 minutes in the 0-59 minute group, 67 minutes in the 60-119 minute group, and 52 minutes in the ≥ 120 minute group (ANOVA $p < 0.0001$). The inter-group differences were statistically significant with a 13 minute difference in means ($p = 0.021$) between the 0-59 and 60-119 groups and a 15 minute difference ($p = 0.003$) between the 60-119 and the ≥ 120 groups. In a fully adjusted model, there was an increase in code to tPA time of 1 minute for every 4 minute increase in LKW to code time.

Conclusion: There was a significant negative correlation between "LKW to code" time and "code to tPA" time, perhaps related to less perceived urgency to administer tPA with earlier hospital presentations. This relationship was independent of age, sex, NIHSS, and race-ethnicity. Given known improved outcomes with earlier administration of IV tPA, first responders to acute stroke codes must be mindful not to spend unnecessary time before administering tPA in cases with earlier hospital presentations.

S198. Intra-Arterial ALD401 Cell Therapy Is Associated with Reduction in Stroke Volume at 90 Days in a Subset of the RECOVER-Stroke Trial

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Huang, Jim Hinson, Sean Savitz and Dileep Yavagal. Miami, FL; Chapel Hill, NC; Nashville, TN and Houston, TX

Objective: to evaluate for stroke volume changes in stroke patients receiving ALD-401 cell therapy

Background: Stroke is a leading cause of major long-term disability worldwide. Despite availability of IV tPA and mechanical thrombectomy, over half of treated patients have significant disability. Cell based therapy is a promising in pre-clinical studies in improving stroke recovery. Final brain infarct volume is a major predictor of stroke outcome and may decrease with this treatment. We hypothesized that patients treated with intra-arterial stem cell therapy will have a significant reduction in stroke volume compared to non-treated patients.

Method: The RECOVER-Stroke trial is a randomized, sham-controlled study to determine the safety and efficacy of processed autologous bone marrow cells (ALD-401) injection via intracarotid infusion in ischemic stroke patients. Anterior circulation ischemic stroke patients were double-blind randomized into 2 groups, receiving ALD-401 injection or sham procedure between 9-19 days post stroke. All enrolled patients at 1 of 8 sites were included. Two blinded physicians used OSIRIX software to analyze stroke volume on DWI/24h CT brain and MRI at 90,180,365 days post intervention. Volumes were compared between the 2 groups at these timepoints.

Result: A total of 11 patients at our center(out of 48 multicenter patients) were included in this study, 6 patients receiving sham procedure and 5 patients receiving ALD-401. There was no significant difference in baseline variables. Mean baseline stroke volumes were not significantly different between ALD-401(102.6 ± 97.4 ml) and sham groups (65.56 ± 49.6 ml), $p=0.53$. The stroke volume reduction in the ALD-401 was 21.6 ± 19.3 ml vs. -0.62 ± 7.5 ml in the sham group ($p=0.0139$). On day 180 and 365, both groups did not show any further significant stroke volume reduction from day 90.

Conclusion: In this exploratory analysis from one center in the multi-center RECOVER-Stroke trial, intra-arterial stem cell injection with ALD-401 was associated with significant reduction in stroke volume at 90 days post therapy compared to sham procedure in subacute ischemic stroke patients.

S199. Reading and Naming Recovery After Left PCA Stroke

Charliem Long, Rajani Sebastian, Cameron Davis, Amy Wright and Argye Hillis. Baltimore, MD

Background: Functional reorganization of language networks after an acute left-hemisphere stroke may engage perilesional left brain areas as well as homologous right-hemisphere regions. It has been previously proposed in patients with MCA stroke that recovery of auditory comprehension involves a shift from bilateral activation patterns to left lateralized activation as patients recover their language skills. However, it is unclear whether this pattern would be applicable to other language tasks or strokes that affect PCA territory. Our aim was to examine longitudinal changes in

brain activation patterns in recovery of naming and reading in patients with PCA stroke.

Methods: 5 right-handed participants with acute ischemic left hemisphere PCA stroke (mean age: 55.6 years) and 1 normal control (age: 55) were enrolled in the study. Participants underwent language testing, structural and functional MRI at acute, sub-acute (2-5 weeks), and chronic (4-7 months) time points. Participants completed two fMRI tasks: a reading task and a naming task. In the reading task, participants were instructed to silently read 60 words. The control condition was viewing a checkboard pattern. The naming task consisted of 60 pictures and participants were instructed to overtly name each picture. Each picture was presented concurrently with an auditory cue, which was either: (i) a whole word (ii) an initial phoneme or (iii) auditory noise. The control task was viewing scrambled images.

Results: Language testing indicated that patients showed an improvement in reading and naming skills from the acute to the chronic time point. Imaging analyses for naming revealed a bilateral network including the frontal, temporal, parietal and occipital regions at the acute time point as well as the follow up time points. In contrast, activation for reading task was mostly restricted to bilateral occipital cortex during the acute time point with some intermittent activation in temporal/parietal regions. At the chronic time point, two patients showed a shift of fMRI activation to the left occipital cortex; this pattern was not observed for any of the patients during the naming task.

Conclusions: These preliminary data suggest that language recovery is dynamic, task dependent, and may have different time courses across individuals. Further understanding the differences in recovery of these two distinct language functions may yield a more detailed model of the recovery of different language processes in patients with PCA stroke.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Argye Hillis receives compensation from the American Heart Association for editorial activities for the journal *Stroke*. She also receives compensation from Elsevier for editorial activities for the journal *Practice Update Neurology*.

S200. Trends and Outcomes of Acute Ischemic Stroke in HIV-Positive Population (2002-2012)

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Background: The incidence of Acute Ischemic stroke (AIS) in HIV patients is on the rise in the United States, especially after the development of newer antiretroviral drugs. These drugs prolong the lifespan, however, are associated with an increased risk of stroke. This study determines the trends of stroke in HIV patients in the United States.

Design/Methods: Data from the Nationwide Inpatient Sample (NIS) and Healthcare Cost and Utilization Project (HCUP) were analyzed for years 2002-2012.

Hospitalizations with HIV-positive status were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 042, V08 and AIS by 433.xx-437.1. Cochran-Armitage trend test and multivariate regression were used to analyze temporal trends and the potential reasons for temporal changes over the years.

Results: A total of 2,584,548 hospitalizations with HIV status were made from 2002 to 2012. Of these, 22,889 (0.89%) admissions were due to AIS or developed AIS during hospitalization. Concurrent trend of AIS and HIV doubled from 0.7% to 1.2% in 2012 ($p<0.001$). This trend increased annually by 6% (OR 1.06; 95% CI 1.05-1.07; $p<0.001$). The temporal rise was partially (3%) explained by changes in demographics and an increase in concurrent comorbidities. Amongst HIV related hospitalizations, age (10-year increase) (OR 1.5; 95% CI 1.4-1.5) and African-American race (OR 1.2; 95% CI 1.1-1.3) were significantly associated with the development of AIS. HIV status showed a higher adjusted odds of in-hospital mortality (OR 1.5; 95% CI 1.2-1.8) and hospital stay 3.5 vs. 4.5 ($p<0.001$) in contrast to AIS in HIV-negative status.

Conclusions: These data suggest that the incidence of AIS among hospitalized adults with HIV infection continue to increase, and that HIV remains a significant predictor of in-hospital mortality in AIS population. These increasing AIS was partially explained by an aging HIV population and chronic comorbidities, but questions still remain regarding unexplained factors which merit in-depth study.

S201. Proportion of Strokes Missed with the FAST Algorithm

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Background: The FAST algorithm (Face, Arm, Speech, Time) is intended to help the public identify persons having an acute stroke to facilitate their rapid access to medical care. Stroke causing important disability may not present with these symptoms.

Objective: To determine the proportion of acute ischemic stroke patients with symptoms not captured by the FAST algorithm.

Design: Records of all patients admitted to the University of Kentucky Hospital between January 1 and December 31, 2014 with a discharge diagnosis of acute ischemic stroke were reviewed. Presenting symptoms and examination findings based on the NIHSS were abstracted. Those unresponsive or intubated were excluded.

Results: Of 950 consecutive ischemic stroke discharges, 753 met inclusion criteria; 14.3% did not have FAST symptoms at presentation (mean age 63.6 ± 1.3 vs 65.6 ± 0.6 years, $p=0.08$; NIH-SS 2.9 ± 0.4 vs 7.0 ± 0.3 , $p<0.001$; 44% vs 48% women, $p=0.41$; FAST negative vs positive, respectively). Of those who were FAST symptom negative, 25% had a gait abnormality, 43% visual loss and 57% had either a gait abnormality or visual loss; the proportion of stroke patients who would not have been identified by FAST was reduced to 6.2% with the addition of these

symptoms ($z=6.35$, 95%CI 4.59-8.17, $p<0.0001$). If face weakness, arm weakness or speech impairment on admission examination were considered in addition to a history of FAST symptoms, 10% of stroke patients would be missed (mean age 63.0 ± 1.5 vs 65.5 ± 0.6 years, $p=0.06$; NIH-SS 1.2 ± 0.1 vs 7.0 ± 0.3 , $p<0.0001$; 43% vs 48% women, $p=0.39$; FAST negative vs positive, respectively). Of the 10% who were FAST symptom and examination negative, the proportion of stroke patients who would not have been identified by FAST was reduced to 4.1% with the addition of visual loss and gait abnormalities ($z=5.40$, 95%CI 2.80-5.77, $p<0.0001$).

Conclusions: Although infrequent and having lower NIH-SS scores, a group of patients with ischemic stroke (14.3%) with potentially important deficits (gait impairment and visual loss) amenable to acute interventions are not identified using the FAST algorithm. The inclusion of these symptoms leads to a significant reduction in missed strokes. If validated in a prospective study, a revision of public educational programs may be warranted.

S202. Stent Retrievers versus Manual Aspiration for Treatment of Large Vessel Intracranial Occlusions: A Comparison Study

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Background: Neurointerventional techniques in patients with large vessel occlusions include stent retrievers and catheters to assist in aspiration of a thrombus.

Objective: Our objective was to compare 90-day clinical outcome in patients undergoing stroke thrombectomy with primary aspiration (PA) versus stent retrievers (SR).

Methods: With institutional review board approval, we retrospectively reviewed medical records of patients who underwent stroke thrombectomy between July 2012 and October 2015. The following data was collected: demographics, risk factors, intravenous tPA, treatment times, grade of recanalization, complications, and 3 month modified rankin scores (mRS). A favourable clinical outcome was defined as a mRS of 0-2 at 90 days.

Results: A total of 186 patients were included in this analysis with 97 (52.2%) women and 89 (47.8%) men, mean age 68 (26-94). There were 74 patients in the PA group and 112 in the SR group (96 solitaire device only). Baseline characteristics, imaging for procedure selection, patients receiving intravenous tPA, onset to groin puncture, and onset to recanalization times were comparable in both groups. Patients in the SR group had a higher number of passes, distal embolization, a longer procedure time, and were more likely to have more than one vessel occlusion at the onset of procedure; patients in the PA group were more likely to have a vessel vasospasm. Recanalization rates in the PA group were significantly higher, however when primary aspiration failed stent retrievers were used in combination. A total of 67 patients (36%) had a favourable clinical outcome, with no significant difference between the SR and PA group; fourteen patients were loss to follow up. Both groups

had comparable rates of arterial dissection, subarachnoid hemorrhage, and post-procedure intracerebral hemorrhage.

Conclusion: Stent retriever and aspiration thrombectomy are associated with similar rates 90-day clinical outcome in acute ischemic stroke patients.

Epilepsy

S203. Sabril Vision Study: Retinal Structure and Function in Adult Patients with Refractory Complex Partial Seizures (rCPS) Treated with Vigabatrin

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Objective: To evaluate visual-field (VF) and retinal-structure changes following adjunctive vigabatrin treatment in vigabatrin-naïve adults with rCPS.

Background: Visual deficits have been reported in retrospective, cross-sectional studies in vigabatrin-treated patients.

Design/Methods: Prospective, longitudinal, single-arm, open-label study (NCT01278173). Eligible patients (≥ 2 seizures/month who failed ≥ 3 therapies) performed reliable perimetry (Humphrey automated static) and retinal-structure assessment (spectral-domain optical coherence tomography) pre-vigabatrin exposure. Following vigabatrin initiation, testing occurred within 1 month (reference) and at 3, 6, 9, and 12 months. Endpoints included: mean change from reference in mean deviation (dB) and average retinal nerve fiber layer (RNFL) thickness, visual acuity (VA) changes from baseline, and number of patients who met pre-defined vision-parameter changes at 2 (confirmed) or 3 (persistent) consecutive visits.

Results: Sixty-five of 91 screened patients received ≥ 1 vigabatrin dose (all-patients-treated set [APTS]); 55 had ≥ 1 valid reference and post-reference assessment (full-analysis set [FAS]). Thirty-six APTS patients with valid pre-/post-reference values completed all planned visits (per-protocol set [PPS]). Thirty-eight (59%) APTS patients completed the study; 27 (42%) withdrew (none for VF changes); 32% and 15% had abnormal RNFL thinning and VA at baseline, respectively; 20% had abnormal near VFs vs reference. No significant mean near-VFs changes were observed (PPS); mean change in average RNFL thickness increased significantly (1-year data: Left-eye: $6.37\mu\text{m}$, CI:[4.66,8.09]; Right-eye: $7.24\mu\text{m}$ CI:[5.47,9.01]; PPS). No confirmed 3-line decreases in VA (FAS) were observed; 3 patients had pre-defined confirmed/persistent near-VF changes (FAS). All vision-related AEs were non-serious; the most common was vision blurred (9%).

Conclusions: Prior to vigabatrin initiation, rCPS patients may already exhibit vision deficits. Adjunctive vigabatrin treatment (up to 1-year) did not significantly change population near VFs (despite 3 patients meeting pre-defined near-VF-change criteria). RNFL thickening (unknown clinical significance) was observed. Limitations include: single-arm, open-label design; patients' inability to perform

ophthalmic/VF examinations; and short-term vigabatrin-exposure duration.

Funding: Lundbeck LLC.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? J. Isojarvi, Y. Dribinsky, J. Whittle, G. Feng, D. Lee are employees of Lundbeck LLC; R. Sergott has received personal compensation for activities with Biogen-Idec, EMDSerono, Teva, Lundbeck LLC, Pfizer, Thrombogenics, Sanofi-Aventis, Novartis, BioClinica, Covance, Basilea, Heidelberg Engineering, Merck & Co, Glaxo. C. Johnson has received personal compensation for activities and research support from Lundbeck LLC. R. Wechsler has received compensation for consulting and/or advisory boards and/or speaker bureau honoraria from Cyberonics, Eisai, Gerson Lehrman Group Inc., Lundbeck LLC, Sunovion, UCB, Upsher-Smith. K. Laxer has nothing to disclose.

S204. Sabril Vision Study: Pharmacokinetic and Pharmacodynamic Analysis of the Effect of Vigabatrin on Taurine Plasma Concentrations

Dwain Tolbert, Stine Timmermann, Johan Areberg, Deborah Lee and JoAnn Whittle. Deerfield, IL and Copenhagen, Denmark

Objective: Explore the relationship between vigabatrin plasma concentrations and (1) vision endpoints (Humphrey field analyzer [HFA] and retinal nerve fiber layer [RNFL]), and (2) taurine plasma concentrations. The relationship between taurine plasma concentrations and HFA and RNFL also was explored.

Background: Taurine is a naturally occurring amino acid that is essential for normal development and function of retinal rod photoreceptors. Reports suggest vigabatrin treatment may cause taurine deficiency in mice and humans.

Design/Methods: The vision study was a prospective, longitudinal, single-arm, open-label study (NCT01278173). Eligible vigabatrin-naïve adult patients (≥ 2 seizures/month who failed ≥ 3 therapies) performed reliable perimetry (Humphrey automated static) and retinal-structure assessment (spectral-domain optical coherence tomography) pre-vigabatrin exposure. Following vigabatrin initiation, vision testing occurred within 1 month (reference) and at 3, 6, 9, and 12 months. Sparse pharmacokinetic sampling to measure plasma concentrations of vigabatrin and taurine were performed during the study. The relationships between vigabatrin plasma concentrations and HFA and RNFL (change from reference), and taurine plasma concentrations, as well as taurine plasma concentrations on HFA and RNFL, were evaluated through mixed-effect analysis.

Results: Sixty-five of 91 screened patients received ≥ 1 vigabatrin dose (all-patients-treated set [APTS]); 38 (59%) APTS patients completed the study. Fifty-three patients from the APTS had at least one quantifiable vigabatrin plasma concentration measurement (PK population). No relationship was found between vigabatrin plasma concentrations and HFA and RNFL. A small but significant relationship ($P < 0.01$) with vigabatrin plasma concentrations

and taurine plasma concentrations (time-independent) was identified; taurine plasma concentrations decreased with increasing vigabatrin plasma concentrations. No relationship was observed between plasma taurine concentrations and HFA and RNFL.

Conclusions: Although concentrations of taurine in plasma decreased with increasing plasma vigabatrin concentrations, no relationship was found between plasma concentrations of vigabatrin or taurine and HFA and RNFL.

Funding: Lundbeck LLC.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? D. Tolbert, D. Lee, and J. Whittle are employees of Lundbeck LLC. S. Timmermann and J. Areberg are employees of H. Lundbeck A/S.

S205. Effect of Ketogenic Diets on Leukocyte Counts

Karisa C. Schreck, Roy E. Strowd, Bobbie J. Henry, Jaishri O. Blakeley and Mackenzie C. Cervenka. Baltimore, MD and Winston Salem, NC

Background: Ketogenic diets (KDs) have been used as an effective therapy for epilepsy since 1921. More recently they have been studied in a variety of diseases including rheumatoid arthritis, multiple sclerosis, Parkinson disease, and cancer. One potential mechanism of action is decreasing inflammation, in part by lessening NLRP3 inflammasome activation (Youm). Previous studies have shown that KDs modulate immune cell function (Youm, McMurray) and may decrease overall lymphocyte count (Fraser). Small human trials lasting 2-12 weeks have shown no adverse effect on white blood cell counts (Schmidt, Rafal). However, the data are inconclusive due to small sample size and short diet duration. The potential immune modulation raises concerns over risk of infection in immunosuppressed patients. Specifically, cancer patients with already low blood counts risk not receiving required chemotherapy if their white blood count (WBC) is insufficient. In this study we explore change in WBC over time in patients on KDs.

Methods: A retrospective review of 125 consecutive adults seen at our Adult Epilepsy Diet Center was conducted. Patients for whom laboratory data evidence of compliance with a ketogenic diet over serial visits (urine ketones $> 40\text{mg/dL}$ over serial visits) were included in the study, excluding patients for whom there was only one time point or no laboratory data to support compliance. Patients with glioma ($n=10$) were excluded due to the potential for chemotherapy that could impact WBC count.

Results: In 36 patients (12 male), mean age 33 years (SD14, range 18-61), there was no observed difference in overall white blood cell, neutrophil, or lymphocyte count at 3, 6, or 12 months after initiation of a ketogenic diet compared to pre-diet baseline ($n=32, 12,$ and 15 respectively). In eight patients with an absolute lymphocyte count < 1500 (ALC, $n=8, 22\%$) at baseline there was no significant decline in ALC at 3 months ($\Delta\text{ALC } 332, \text{SD } 479, P = 0.12$).

Conclusions: KDs do not appear to impact overall white blood cell counts or lymphocyte counts over the course of one year in a small, highly compliant cohort of adults with epilepsy. Further study, particularly in immunosuppressed patients, is necessary to fully elucidate the impact of KDs on immune function alone or with concurrent immunosuppressive medications.

S206. Brief Potentially Ictal Rhythmic Discharges (B(I)RDs) in the Non-Critically Ill Adults

Ji Yeoun Yoo, Lara V. Marcuse, Madeline C. Fields, Jillian Rosengard and Maria Traversa. New York, NY

Objective: Brief potentially ictal rhythmic discharges (B(I)RDs) have been described in neonates and recently in critically ill adults, and their association with seizures has been demonstrated. Their significance in non-critically ill adults remains unclear. We aimed to investigate the prevalence, electrographic characteristics and clinical significance of these discharges in non-critically ill adults.

Methods: We prospectively identified adult patients with B(I)RDs who received long term EEG recordings either in the epilepsy monitoring unit or in the ambulatory setting. Patients who had altered mental status, acute findings in imaging studies, or status epilepticus were excluded from the study. B(I)RDs were defined as very brief (<10 seconds) runs of focal or generalized rhythmic activity greater than 4 Hz, that was not consistent with any known normal or benign pattern. The clinical history, EEG findings and imaging results were retrieved. Each patient with B(I)RDs was matched to an age and etiology matched control group.

Results: We identified B(I)RDs in 15 patients (1.2%). The pattern most often consisted of 0.5-4 second runs of sharply contoured alpha, beta or theta activity without evolution. All patients with B(I)RDs had known epilepsy, and when compared to the patients with epilepsy without B(I)RDs, they had significantly higher association with medically refractory epilepsy (10 of 15 [67%] vs 3 of 15 [20%]; $p < 0.05$). Ten patients (67%) were non-lesional. Nine patients with B(I)RDs (60%) had seizures captured on EEG, and all seizure onsets co-lateralized to the B(I)RDs.

Conclusions and Relevance: B(I)RDs in non-critically ill patients were highly associated with refractory epilepsy and their location was correlated with the seizure onset area. Further electrographic and neurophysiologic studies are needed to better understand their significance in people with epilepsy.

S207. The Economic Impact of Epilepsy in Bhutan

Leah Wibecan, Veronica Bruno, Lhab Tshering, Sonam Deki, Damber K. Nirola, Megan B. Diamond, Chencho Dorji, Günther Fink and Farrah J. Mateen. Boston, MA and Thimphu, Bhutan

Objective: To assess the economic impact of epilepsy in Bhutan, a lower middle income country with a universal health care system.

Background: Epilepsy poses a significant health burden around the globe. However, less is known about the extent of epilepsy's economic impact in lower income countries, or

about the impact of specific models of health care on this burden.

Methods: We assessed the association of epilepsy with socioeconomic factors in a cross-sectional study at Jigme Dorji Wangchuck National Referral Hospital in Bhutan, from December 2015-March 2016. Data were collected on participants with epilepsy and controls (their sibling or neighbor from a separate household without epilepsy), via a tablet-based survey using Redcap. Survey themes included clinical features of epilepsy, cost of care, impact of epilepsy on work or school, and economic status. Frequencies were calculated and between group differences were assessed using a paired t-test.

Results: Of all participants surveyed, 109 participants out of 115 (92.7%) fulfilled criteria for epilepsy diagnosis (mean age 26.2 years, including 18 participants under age 18). Control information was collected for 101 (92.8%) of participants. Of participants with epilepsy, 49 (45%) had at least one seizure in the prior month. On average, epilepsy patients spent 8,402 Bhutanese ngultrum (BTN, approximately 126 USD) per year for direct costs related to medical care for epilepsy, constituting on average 4.6% of yearly reported household income. Of this total, the major component was transportation for epilepsy-related medical reasons (72.6%). Participants missed on average 8.9 days of work or school per year (range 0 to 60). Among participants with epilepsy, 40 (36.7%) were neither working nor attending school; 24 (60%) of whom had stopped working or attending school for reasons directly related to epilepsy. Households with an individual with epilepsy had a lower average monthly per-person income (5,131 BTN) compared to control households (8,920 BTN; $p = 0.0336$).

Conclusion: In this lower middle income country, even with universal health care offering free services and medication, people with epilepsy and their families are at an economic disadvantage. Costs related to transportation for medical reasons and missing or dropping out from school or work contribute significantly to the burden of epilepsy. This study suggests that household economic status is negatively impacted by the direct and indirect costs of epilepsy.

S208. Phase I Study to Determine the Pharmacokinetics, Pharmacodynamics, and Safety of IV Ganaxolone in Healthy Adults

Julia Tsai, Jeffrey T. Guptill, David B. MacLeod, Aatif Husain and Albenia Patroneva. Radnor, PA and Durham, NC

GNX (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one), a CNS-selective positive GABAA modulator, is a synthetic analog of the endogenous allopregnanolone and is in development for treatment of epilepsy and other neurological conditions. GNX allosterically modulates γ -aminobutyric acid type A (GABAA) receptors in the central nervous system and has sedative, anxiolytic and anticonvulsant effects. Two oral formulations are available. This IV formulation will expand treatment options for patients with status epilepticus.

The objective of this study is to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ganaxolone (GNX) IV administered as a bolus dose and

continuous infusion to healthy participants. This study is a single site, sequential cohort evaluation of IV GNX in healthy participants. The study consists of 2 stages and up to 6 cohorts. Stage 1 (up to 4 cohorts) will determine the PK, change in quantitative and qualitative EEG (PD), and safety (ECG, vital signs, physical examination findings, and adverse events) following single bolus doses of IV GNX. Stage 2 (up to 2 cohorts) will determine the PK, safety, and PD of bolus IV dosing followed by continuous infusion. The PK-PD model and data from the Stage 1 cohorts will determine the bolus dose and continuous infusion paradigm expected to achieve the goals of each cohort. The Sponsor and Data Safety Monitoring Team in consultation with the PK specialist will determine dosing in the Stage 2 cohorts. The study will consist of screening, dosing (36-48 hr), and follow up (clinic visit 7 days after IV GNX administration) periods. Subjects will be confined during the dosing period and an anesthesiologist will be present for all dosing to maintain participant safety.

This phase 1 study is intended to support the continued development of IV GNX for patients with acute seizures/status epilepticus or who are unable to take oral GNX. Results will be presented at the time of the meeting.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? salary and stock received as employee of the company for myself and those identified from Marinus.

The 3 Duke affiliations are receiving consulting fees or have some part of their salary paid by the Duke Research Institute a Academic Research Organization.

S209. Use of Interpreter and Test Duration During IAP in Non-Native English Speakers

Heidi A. Bender, Jessica S. Spat, Ann DeSollar, Madeline Fields, Lara V. Marcuse, Emily Roman, Evelyn Ramirez-Coombs, Rebecca Bind, Lindsay A. Whitman, William B. Barr, Blanca Vazquez, Orrin Devinsky and Chad E. Carlson. New York, NY and Milwaukee, WI

Confounds often preclude the standardization and generalization of intracarotid amobarbital procedures (IAP) to non-native English-speaking surgical candidates. Beyond immutable differences, such as the risk of atypical language representation, medical interpreters may extend the duration of the test which could artificially inflate memory scores. Sixty-two Spanish- and 62 English-speaking surgical candidates were matched by age, education, and gender. All patients had a confirmed diagnosis of epilepsy. All procedures were conducted in the patient's primary language, with an interpreter, if needed. No significant between-group differences emerged for age, education, gender and handedness ($p > 0.05$). The time of procedure ranged from 87- 440 sec, with a mean of 195.17 sec (SD = 74.30 seconds). Although the duration of the procedure at first injection did not significantly differ between English- and Spanish-speaking groups, the length of presentation was significantly longer in Spanish speakers during the second injection ($p = 0.044$). Memory scores did not differ between language groups. The

use of interpreters during the IAP introduce potential variability to the additional response delay, resulting in longer procedure durations. As a result, IAP data and interpretations should be evaluated with appropriate caution, especially in non-native English speaking surgical candidates.

Movement Disorder

S210. Measurement of Effect of Variable Deep Brain Stimulation Frequencies on Static Postural Control in Parkinson Disease (PD) Patients with Bilateral STN or GPi Stimulators by Employing Force Plate

Saulena Shafer, Abraham Lieberman, Aman Deep and Rohit Dhall. Phoenix, AZ

Objective: To Measure the effect of variable deep brain stimulation frequencies on static postural control in Parkinson Disease (PD) patients with Bilateral STN or GPi stimulators by employing force plate.

Background: Impairment of static postural control is one of the major contributory factors causing falls in PD patients. In this study we quantitatively measured the effect of low (LF-30 Hz), intermediate (IF-80 Hz) and high (HF >120 Hz) DBS frequencies in patients with bilateral STN and GPi stimulators using a force plate.

Methods: We tested 13 patients (7 bilateral STN and 6 Bilateral GPi). They were evaluated at HF, IF, and LF conditions in medication-off state in eyes open and eyes closed condition. IF and LF conditions were selected randomly. A minimum of 30-minute wait period was allowed before evaluation after changing stimulation frequency. All Patients were examined at all frequencies using MDS-UPDRS. Among the postural control parameters; Sway AP, Sway ML, area of ellipse, MPF_AP & ML (mean Power frequency in anteroposterior & mediolateral direction), RMS_AP & ML (root mean square anteroposterior and Mediolateral direction) were calculated.

Results: Data was analyzed using MANOVA ($p = 0.0041$). At HF UPDRS scores were better (29) when compared to IF (31) and LF (34). Among the UPDRS motor subsets at HF, arising from chair (0.52 vs 0.57 vs 0.63), gait (1.00 vs 1.23 vs 1.46), posture (1.42 vs 1.72 vs 1.77) and bradykinesia (1.65 vs 1.88 vs 2.06) were significantly improved as compared to IF and LF. Area of ellipse (mm^2) was significantly lower at HF (422 mm^2) vs IF (581 mm^2) and LF (509 mm^2). Mediolateral Sway (17mm vs 22 vs 19 mm), mean velocity (18 mm/seconds vs 16.8 mm/seconds vs 16 mm/seconds), mean power frequency in anteroposterior (0.26 Hz vs 0.24 Hz vs 0.22 Hz) and mediolateral directions (0.27 Hz vs 0.24 Hz vs 0.21 Hz) and root mean square in mediolateral direction (3.22 mm vs 3.79 mm vs 3.69 mm) were significantly improved when compared with IF and LF.

Conclusion: Our results indicate that HF (> 120 Hz) improved static postural control when compared with intermediate (IF-80 Hz) and Low frequency (LF-30 Hz). This suggests that HF stimulation may be more likely to lessen falls.

S211. How Long Is the Wait to See a Specialist in Parkinson's Disease in the United States?

Katherine Holmes, Karl Maki, Justin Martello and Stephen G. Reich. Baltimore, MD

Objective: To ascertain the wait time to see a PD specialist in the US.

Background: PD patients who see a specialist have better outcomes and are more likely to receive treatment in accordance with AAN recommendations. The United Kingdom's National Institute for Health and Care Excellence guidelines state that patients with mild PD should see a specialist within 6 weeks of referral and within 2 weeks for more advanced PD. In the US, there is no equivalent guideline. Prompted by hearing concerns by PD patients about the difficulty obtaining an appointment with a specialist, we investigated the wait time.

Methods: 144 US PD centers were identified from the Parkinson Disease Foundation's website and from the National Parkinson's Foundation's Centers of Excellence. Contact information and number of PD specialists at each center were identified from the internet. Each site was contacted by phone and asked about the next available appointment.

Results: One hundred and fourteen centers (79%) provided the next available appointment date; 30 (21%) refused to participate or were not able to provide the information. The average wait time was 2.2 months (SD=1.8) with a range of 1 day to 8 months. Fifty percent of centers (n=57) had wait times longer than 2 months and approximately one quarter (n=33) had wait times > 3 months. The wait time did not correlate with the number of PD specialists at a center ($r = -.09$, $p = .37$).

Conclusions: This study demonstrates great variability in the time to see a PD specialist in the US. For many centers, the wait was > 3 months and neither the variability nor duration was correlated with the number of PD specialists at a center. The long wait time at most PD centers makes it essential to develop novel methods to ensure that PD patients have easy and rapid access to specialty care.

S212. Medial Frontal 4 Hz Activity and Cognitive Symptoms of Parkinson's Disease

Nandakumar Narayanan. Iowa City, IA

Patients with Parkinson's disease can have cognitive symptoms, but the mechanism is unclear. We study the medial frontal cortex of patients with Parkinson's disease and animal models using a combination of EEG, single neuronal recordings, and brain stimulation techniques. We report three main findings. First, patients with Parkinson's disease have attenuated ~4 Hz rhythms in mid-frontal cortex during cognitive tasks. Second, this ~4 Hz rhythm synchronizes single neurons involved in cognitive processing in the human subthalamic nucleus and throughout frontal, cerebellar, and striatal brain areas in rodents. Third, optogenetically stimulating frontal neurons expressing dopamine receptors at 4 Hz in animal models can compensate for dopamine-dependent cognitive deficits. These data indicate that 4 Hz activity is a key mechanism of cognitive control that

malfunctions in Parkinson's disease, and could provide new insight into cognitive symptoms of Parkinson's disease.

S213. Application and Correlates of the Progressive Supranuclear Palsy Quality of Life Scale (PSP-QoL)

Lenora A. Higginbotham, Vanessa Johnson and Alexander Pantelyat. Baltimore, MD

Objective: To apply the PSP Quality of Life scale (PSP-QoL) within a cross-sectional PSP population and correlate these scores with those of the PSP rating scale (PSPRS).

Background: Despite the widespread recognition of PSP as a distinct disease entity with a well-defined set of disabling symptoms, there have been very few published scales dedicated specifically to the assessment of this disease. The PSP rating scale (PSPRS) has emerged as a useful and broadly validated measurement of disease severity. However, there is no widely used disease-specific QoL tool. The PSP-QoL, a 45-item questionnaire, is the only published PSP-specific QoL scale and has not been broadly applied. Furthermore, its interscale correlations with the PSPRS have not been explored. The utilization of the PSP-QoL within additional PSP populations and examination of its PSPRS correlates would help establish the PSP-QoL as a reliable clinical and research tool.

Methods: Descriptive statistics included means and standard deviations. Partial correlation analysis adjusted for age and disease duration was used to cross-sectionally evaluate the relationship between total and subscale PSP-QoL scores and total and subscale PSPRS scores, respectively.

Results: Among 19 PSP patients (10M:9W; 17 Caucasian, 2 African-American) seen in our multidisciplinary research clinic (mean(sd) age=73.1(7.7); disease duration=3.7(2.1) years), there was a significant positive correlation between total PSP-QoL and PSPRS scores ($r = 0.564$, $p = 0.018$) obtained within 1 month of each other. The mentation and physical subscales of each instrument also demonstrated significant positive interscale correlations ($r = 0.659$, $p = 0.004$; $r = 0.488$, $p = 0.047$). Of PSPRS subscale components, mentation demonstrated the strongest negative correlation with overall life satisfaction scores ($r = -0.498$, $p = 0.042$). In a subgroup analysis of patients with classic Richardson's syndrome (n=8), strong interscale correlations were also observed. However, among patients with other PSP predominance types (n=11), the total, mentation, and physical subscales were not significantly correlated ($r = 0.179$, $p = 0.645$; $r = 0.441$, $p = 0.235$; $r = 0.146$, $p = 0.708$).

Conclusions: Our results demonstrate significant interscale correlations between the total and subscale scores of the PSP-QoL and PSPRS, supporting the validity of the PSP-QoL and its broader application in PSP. However, subgroup analysis revealed few significant interscale correlations among patients without the classic Richardson's syndrome, likely reflecting the diversity of this population and its QoL determinants. Longitudinal studies utilizing the PSP-QoL are needed to further assess its utility in PSP.

Multiple Sclerosis

S214. Immunopathological Study of Glucose and Lactate Transporters in White and Gray Matter Lesions of Multiple Sclerosis and Neuromyelitis Optica

Katsuhisa Masaki, Satoshi O. Suzuki, Shotaro Hayashida, Mitsuru Watanabe, Takuya Matsushita, Ryo Yamasaki, Makiko Suzuki, Toshihiko Suenaga, Toru Iwaki and Jun-ichi Kira. Fukuoka, Japan; Hamamatsu, Japan and Tenri, Japan

Background: Recently, energy supply to axons via glial cells has received a lot of attention. Nutritional substances are transferred from blood vessel to axons via connexins (Cx) gap junction channels or glucose transporters (GLUTs) and monocarboxylate transporters (MCTs). We previously reported extensive loss of Cxs in active lesions of multiple sclerosis (MS), neuromyelitis optica (NMO) and Baló's disease (BD), suggesting early disruption of Cxs may cause extensive energy failure and contribute to the pathogenesis in demyelinating disorders. To obtain more precise understanding of metabolic conditions in demyelinating disorders, we studied the expression of GLUTs and MCTs in MS and NMO.

Methods: We pathologically evaluated GLUT1, 3, 5 and MCT1, 2, 4 expression relative to expressions of Cx43 and GFAP, extent of demyelination, expressions of neurofilament and amyloid precursor protein (APP), and lesion staging with CD68 staining for macrophages in autopsied samples from six cases with MS, eleven with NMO and 20 with other neurological diseases.

Results: In myasthenia gravis (control) case, GLUT1 and MCT1 were abundantly expressed in the microvascular endothelial cells. GLUT3 and MCT2 were mainly expressed in neuropil. GLUT5 was specifically expressed in resting microglia. MCT4 was expressed in astrocytes and perivascular foot processes. In the active demyelinating lesion of MS, despite of massive perivascular lymphocytic cuffing, endothelial MCT1 and GLUT1 were relatively preserved. By contrast, immunoreactivity for MCT4 was diminished in the perivascular foot processes in active lesion. Microglial GLUT5 was up-regulated in activated microglia and foamy macrophages in active lesion. GLUT3, MCT2 and MCT4 were preserved in cortical gray matter lesions of MS. In the active lesion of NMO, perivascular MCT4 was also extensively lost whereas endothelial MCT1 and GLUT1 were preserved even in the prominently hyalinized blood vessels. Immunoreactivity for APP was found in damaged axons and terminal ovoids in both MS and NMO. Similar to APP, immunoreactivity for GLUT3 was also enhanced in damaged axons of white matter and that was more obvious in NMO.

Conclusion: Our findings indicate that altered expression of GLUTs and MCTs could be seen in active MS and NMO lesions and may elicit energy failure in early stage of the demyelinating disorders. Particularly, extensive loss of MCT4 in astrocytic perivascular foot process may cause impaired transportation of energy from blood vessels to astrocytes followed by oligodendrocytic and axonal damages.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? J Kira serves as an editorial board member of Multiple Sclerosis Journal, Multiple Sclerosis and Related Disorders, BMC Medicine, PLOS ONE, Expert Review of Neurotherapeutics, Intractable and Rare Diseases Research, the Scientific World Journal and the Journal of the Neurological Sciences. He is a consultant for Biogen Idec Japan and Medical Review. He has received honoraria from Bayer Healthcare, Mitsubishi Tanabe Pharma, Nobelpharma, Otsuka Pharmaceutical and Medical Review. He is funded by a research grant for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare, Japan and grants from the Japan Science and Technology Agency and the Ministry of Education, Culture, Sports, Science and Technology, Japan.

S215. What Are Your Patients Not Telling You? Neurological Patients' Perspectives on the Role of Stigma vs. Coordination of Care Issues in the Sharing of Their Psychiatric Records

Alexis A. Adams-Clark, Alison Riehm, Caroline Franke, Steven Arenberg, Dominique Tosi, Kristen Hollinger, Kay Jamison and Adam Kaplin. Baltimore, MD

Prior research has indicated that increased accessibility by medical doctors of psychiatric electronic medical records is associated with improved clinical care for psychiatric patients (Kozubal et al., 2013). Despite this finding, many hospitals and healthcare providers are reluctant to share psychiatric information among physicians due to the perception of patients' elevated concerns about the privacy of their psychiatric information. The purpose of the present study is to clarify neurological patients' attitudes toward sharing medical and psychiatric information electronically among their clinicians, their feelings of stigma surrounding both medical and psychiatric illnesses, and their knowledge of the electronic medical record system. This study recruited via email members of MSAA (Multiple Sclerosis Association of America) who have a diagnosis of Multiple Sclerosis with or without an additional co-occurring medical or psychiatric disorder (N = 3614), and participants completed an online survey. Preliminary results indicated that most patients are willing to share both psychiatric (90 percent) and medical information (97 percent) with other doctors, and having a psychiatric illness predicted a higher willingness to share psychiatric records, ($p < .05$). Although 97 percent of participants believed that there were benefits to sharing medical records electronically, 77 percent of participants were not completely sure how the electronic medical records system works, and 82 percent of participants did not completely understand who can access their medical records. Ninety-seven percent of people surveyed also believed that they should have some say in whether their records, both medical and psychiatric, are shared with other doctors. These results suggest that, although most neurological patients are willing to have their information shared in the electronic medical record system, there is a lack of understanding about the

electronic medical record system, and more patient education is necessary.

S216. Cognitive Impairment in Primary-Progressive Multiple Sclerosis: A Role for Functional Connectivity and Neuronal Variability Changes of Resting-State Activity?

Maria Petracca, Catarina Saiote, Heidi A. Bender, Franchesca Arias, Colleen Farrell, Paola Magioncalda, Matteo Martino, Aaron Miller, Georg Northoff, Fred Lublin and Matilde Inglese. New York; Naples, Italy; Genoa, Italy and Ottawa, Canada

Cognitive impairment occurs in approximately 47% of patients with primary-progressive multiple sclerosis (PP-MS)¹ and it appears related to the disruption of brain functional connectivity (FC) as measured by resting-state functional MRI (rs-fMRI) and diffusion tensor abnormalities.² While the relationship between cognitive-related FC abnormalities and the damage of the connecting white matter (WM) tracts is well established in relapsing-remitting MS,³ it is not clear whether this holds true in PP-MS patients who are characterized by a relatively moderate WM lesion burden⁴ and a high burden of cortical lesions (CLs).⁵ Recent advances in rs-fMRI analysis have suggested that the measurement of FC in multiple frequency bands and the measurement of variability of BOLD signal amplitude provide a more comprehensive characterization of brain functional complexity.^{6,7}

We sought to determine FC and neuronal variability, as measured by standard deviation (SD) of BOLD signal amplitude, across multiple frequency bands in brain networks that underlie cognitive deficits in PP-MS and to investigate the impact of brain CLs on FC and SD abnormalities. FC and SD of resting state networks (RSNs) associated with cognitive deficits in different frequency bands (Standard, Slow-5 and Slow-4) were investigated in 25 PP-MS patients. The RSNs were compared voxel-wise amongst cognitively impaired and preserved patients and healthy controls. CL number was assessed on phase-sensitive inversion recovery images. We confirmed the presence of a widespread cognitive deterioration in PP-MS patients, with main involvement of visuo-spatial and executive domains. The presence of intracortical (IC) lesions was a relevant correlate of cognitive impairment in addition to diffuse WM injury. The functional analysis of the dorsal attention and executive networks (DAN and ECN) confirmed the presence of cortical reorganization presenting as increased variability and inter-network connectivity between ECN, DAN and other large-scale networks responsible for cognitive control. FC anomalies along the midline and deep gray matter regions were mainly observed in the lowest frequency band. We demonstrate, for the first time, that a maladaptive hyper-synchronization of large scale networks and an abnormal pattern of neural activity underlie cognitive dysfunction in PP-MS. The higher CL count in patients with cognitive impairment suggests they may contribute to FC and SD abnormalities.

1. Ruet, Neurology 2013

2. Rocca, Neurology 2010
3. Zhou, PLoS One 2014
4. Camp, Brain 1999
5. Calabrese, Neurology 2009
6. Buzsaki, Science 2004
7. Huang, Hum Brain Mapp 2014.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Maria Petracca has nothing to disclose. Dr. Catarina Saiote has nothing to disclose. Dr. Bender has nothing to disclose. Ms. Arias has nothing to disclose. Ms. Colleen Farrell has nothing to disclose. Dr. Magioncalda has nothing to disclose. Dr. Martino has nothing to disclose. Dr. Aaron Miller has served as a consultant and/or participant in advisory board meetings for Genzyme/sanofi-aventis, Biogen Idec, Glaxo Smith Kline, EMD Serono (Merck Serono), Novartis, ONO, Acorda, Nuron Biotech, Teva, Questcor and Accordant Health Services. He has received research support from Acorda, Novartis, Genentech, Genzyme/sanofi-aventis, Biogen Idec, Roche, and Questcor. He has served as Editor of Continuum, a continuing medical education publication of the AAN and currently serves as Editor of Continuum Audio. He is a member of the editorial board of Multiple Sclerosis and Related Disorders. He occasionally performs expert reviews of medical records or serves as an expert witness in medical malpractice cases.

Dr. Northoff has nothing to disclose.

Dr. Fred Lublin Sources of Funding for Research: Acorda Therapeutics, Inc.; Biogen Idec; Novartis Pharmaceuticals Corp; Teva Neuroscience, Inc.; Genzyme; Sanofi; Celgene; NIH; NMSS; Consulting Agreements/Advisory Boards/DSMB: Bayer HealthCare Pharmaceuticals; Biogen Idec; EMD Serono, Inc.; Novartis; Teva Neuroscience; Actelion; Sanofi-Aventis; Acorda; Questcor; Roche, Genentech; Celgene; Johnson & Johnson; Revalessio; Coronado Bioscience, Genzyme, MedImmune; Bristol-Myers Squibb, Xenoport, Receptos; Forward Pharma; Co-Chief Editor: Multiple Sclerosis and Related Diseases; Stock Ownership: Cognition Pharmaceuticals, Inc. Dr. Matilde Inglese has received research grants from NIH, NMSS, Novartis Pharmaceuticals Corp., Teva Neuroscience.

S217. DTI-Based Whole Brain Sulcal CSF Volume Is Associated with Cognitive Impairment in Multiple Sclerosis

Flavia Nelson, Zafer Keser, Benson Mwangi, Jerry S. Wolinsky, Ponnada A. Narayana and Khader M. Hasan. Houston, TX

Background: The human brain lateral ventricular (LV) cerebrospinal fluid (CSF) volume has been used as a neuroimaging marker of brain volume changes in health and disease. Brain atrophy measures based on LV size, estimated from T1 weighted (w) MR Images; correlate with multiple sclerosis (MS) related cognitive impairment (CI) (Benedict RH, Archives of Neurology. 2006). Diffusion tensor imaging (DTI) based whole brain sulcal CSF (WBsCSF) volume-to-intracranial volume percentage (ICV%) and total ventricular CSF volume (vCSF) to ICV%, have been

validated against T1w measures in healthy controls and MS patients (Hasan KM, MRI, 2014, Hasan KM, MRI, 2015) and present a different approach to assess central/cortical brain volume loss and may be accurate predictors of MS related CI.

Objective: To obtain WBsCSF (cortical, subarachnoid and cisterns) and vCSF (lateral [left & right], third and fourth ventricles) from a cohort of 46 MS patients with and without CI, and assess the correlation between WBsCSF, vCSF and CI, adjusted for age and T2 lesion volume (T2LV). Correlations between Total WBSCSF (WBSCSF = WBsCSF + vCSF) and CI were also obtained.

Methods: 46 MS patients [EDSS 0-7 mean (m) = 3.2, DD 1-37 m = 12; Ages 18-58 years m = 40, 41RR, 1PR, 4SP] were included in the study. Of those, 37 were diagnosed with CI and 9 with no CI based on the Minimal Assessment of Cognitive Function in Multiple Sclerosis (Benedict RH, the Clinical Neuropsychologist. 2002). CI was defined as impairment index (composite score) > 0.35. A semi-automated technique was used to obtain T2LV (Sajja BR, Ann Biomed Eng. 2006). Validated DTI-based methods were applied to estimate vCSF and WBsCSF (Hasan KM, MRI. 2014).

Results: Estimated WBsCSF correlated with CI ($r=0.49$; $p=0.004$). This association remained significant after adjusting for both age and T2LV. As expected, WBSCSF also correlated with CI ($r=0.51$; $p=0.0004$ age and T2LV adjusted). The vCSF did not correlate with CI, but correlated with T2LV in patients with CI ($r=0.64$, $p=0.004$).

Conclusion: Cross-sectional assessments of brain volume by DTI-based WBsCSF provide a significant correlation with CI. Longitudinal studies are needed to establish the potential predictive value of this measure on CI and disability outcomes.

Neurocritical Care

S218. High Compliance with Scheduled Nimodipine Is Associated with Better Outcome in Aneurysmal Subarachnoid Hemorrhage Patients Co-Treated with Heparin Infusion

Aaron Wessell, Matthew Kole, Neeraj Badjatia, Gunjan Parikh, David Schreiber and J. Marc Simard. Baltimore, MD

Object: In patients with aneurysmal subarachnoid hemorrhage, the hypotensive effect of nimodipine can lead to poor compliance with scheduled nimodipine administration. We sought to determine whether compliance impacted patient outcomes, with the intent of guiding future nimodipine management in patients who experience nimodipine-induced hypotension.

Methods: We performed a retrospective cohort analysis of 120 consecutive patients with aneurysmal subarachnoid hemorrhage, all of whom were treated with the Maryland Low-Dose IV Heparin Infusion Protocol between July, 2008 and July, 2015. Nimodipine compliance was calculated as the percent of nimodipine doses administered out of the total possible doses during one's hospital stay, up to a

maximum of 21 days. Using a receiver operating characteristic (ROC) curve, we identified an optimal threshold value for nimodipine compliance that would predict discharge to home. A multiple linear regression analysis was then conducted to determine predictors of discharge disposition in patients admitted with aneurysmal subarachnoid hemorrhage.

Results: The analysis included 120 patients (66% female; mean age of 55.9 ± 12.5 years) with a median Modified Fisher score of 3. Forty five percent of patients possessed a World Federation of Neurological Surgeons grade ≥ 3 . The mean percent compliance with scheduled nimodipine was $81.0 \pm 28.8\%$, with the average duration of treatment being 15.7 ± 5.7 days. ROC curve analysis revealed that 90.1% compliance with scheduled nimodipine was the most appropriate cutpoint value for predicting discharge to home (AUC 0.702; std. error 0.0472; $p<0.0001$). Subgroup analysis based on this cutpoint value revealed reduced rates of clinical vasospasm ($p=0.0114$), severe radiographic vasospasm ($p=0.0007$), and lower requirements for rescue therapy with vasopressor-induced hypertension ($p<0.0001$) or intra-arterial vasodilators ($p<0.0001$) in those with high nimodipine compliance. Patients who maintained high compliance with nimodipine had a greater rate of discharge to home (63% vs. 31%; $p=0.0012$). Multiple linear regression analysis revealed that age, duration of nimodipine treatment and percent compliance with scheduled nimodipine were the only statistically significant predictors of discharge to home.

Conclusions: Nimodipine compliance of 90% or more is associated with increased likelihood of a good outcome and discharge to home in patients with high grade aneurysmal subarachnoid hemorrhage who are co-treated with a low-dose heparin infusion. Our data suggest that, following subarachnoid hemorrhage, every effort should be made to maintain a high compliance with scheduled nimodipine, even if this requires the use of vasopressors to offset nimodipine-induced hypotension.

S219. Added Value of Imaging Characteristics at 12-36 Hours in Predicting Potentially Lethal Malignant Edema

Charlene J. Ong, Jeffrey A. Gluckstein, Osvaldo Laurido-Soto, Rajat Dhar and Jin-Moo Lee. Boston, MA and St. Louis, MO

Objective: Malignant edema occurs in up to 10% of ischemic stroke patients. While decompressive hemicraniectomy is the only therapy with conclusive efficacy, early recognition of surgical candidates is critical, as evidence suggests hemicraniectomy is most beneficial within 48 hours of onset. Information available at the time of admission is often insufficient in identifying these patients. The purpose of our study is to develop a model that incorporates radiographic features obtained in the first 36 hours of ictus to improve prediction of potentially lethal malignant edema (PLME).

Methods: To define our study population, we searched for patients admitted to Barnes-Jewish Hospital between 2006 and 2015 with diagnosis codes of "Cerebral Edema" and "Ischemic Stroke." Only patients with acute anterior circulation stroke and an NIHSS ≥ 8 who received a

baseline head CT within 24 hours of stroke-onset were included. Our primary outcome of PLME was defined as death with evidence of midline shift ≥ 5 mm or hemicraniectomy. We collected and performed univariate analyses on baseline data available on presentation and radiographic characteristics from head CTs obtained between 12 and 36 hours. Variables with p -values ≤ 0.15 were added in a step-wise fashion to construct a final multivariate model predicting PLME.

Results: 224 ischemic stroke patients with edema were included in the study of which 33% developed PLME. Sixty percent of the cohort was female. Median age was 68 (IQR 55-80) and median NIHSS was 18 (14-22). In the admission multivariate model consisting of age, previous stroke, diabetes, hypertension, glucose, WBC, NIHSS and ASPECTS score, no variables were independently predictive and the Area Under the Curve (AUC) was 0.68. The addition of neuroimaging characteristics obtained between 12 and 36 hours including midline shift, basal cistern effacement, any involvement of the anterior (ACA) or posterior cerebral artery (PCA) territories and 66% involvement of the middle cerebral artery (MCA) territory led to an improved model with an AUC of 0.89. Of all variables, basal cistern effacement remained an independent predictor with an odds ratio of 18 [2.4-403.3].

Interpretation: Early clinical variables are not sufficient to predict potentially lethal malignant edema. Information from head CTs obtained at 12-36 hours can add to the discriminatory power of a model for clinical decision making and potentially expedite surgery when necessary. Next steps include validation of this model in a separate cohort.

S220. Neurological Prognostication and Withdrawal of Life-Sustaining Therapy (WLST) Practices for Post-Cardiac Arrest Patients in a Single Academic Medical Center: A Retrospective Analysis

Mary M. Barden, Teddy S. Youn, Carolina B. Maciel, Sonya E. Zhou and David M. Greer. New Haven, CT

Background: Withdrawing life-sustaining therapy (WLST) because of perceived poor neurological prognosis is a common cause of hospital death after both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA). Recent guidelines recommend against WLST before 72 hours (WLST < 72 h). Early WLST perpetuates a self-fulfilling prophecy that may contribute to premature death in some patients who otherwise would have survived with good neurological prognosis.

Methods: Reviewing a retrospective cohort from January 2011 to December 2015 from a single, tertiary academic medical center, we evaluated all successfully resuscitated cardiac arrest patients for survival to hospital discharge, discharge outcome, as well as timing of and reason for WLST. We analyzed all neurological prognostic indicators in our cohort, including neurological examination, electrophysiology, and neuroimaging, and compared when findings were discrepant with early WLST.

Results: Of 113 patients, 54 had WLST due to poor neurological prognosis. Median day of WLST is 6. Of those patients, 70% (38/54) had been treated with targeted temperature management (TTM). The phrase "no meaningful chance for neurological recovery" was often used in documentation. 74.5% had an MRI that was interpreted as "global/diffuse/severe" anoxic injury. Of those that had WLST for poor neurological prognosis, 42.9% had a present pupillary light reflex.

Conclusion: Poor neurological prognosis is the most common reason for WLST in post-cardiac arrest patients. Early WLST in the setting of indeterminate neurological prognostic indicators is problematic for accurate neurological prognostication and perpetuates the self-fulfilling prophecy in post-cardiac arrest patients, especially in the era of TTM.

Cerebrovascular Disease

S221. Microvascular Brain Disease and Risk of Stroke: The Atherosclerosis Risk in Communities (ARIC) Study

Silvia Koton, Andrea L.C. Schneider, B. Gwen Windham, Thomas H. Mosley, Rebecca F. Gottesman and Josef Coresh. Tel Aviv, Israel; Baltimore and Jackson

Introduction: Microvascular brain disease may manifest as white matter hyperintensities (WMH) or as lacunar brain infarcts. Despite their similar pathophysiology and frequent co-occurrence, there are few reports on the clinical profile of the two entities in a single study, and their combined significance for the prediction of clinical stroke events has not been reported.

Hypotheses: We hypothesized that combined measures of WMH and lacunes would show stronger association with risk of stroke than their separate measures, and that progression of microvascular brain disease would be associated with increased risk of stroke.

Methods: Prospective analysis of 907 ARIC participants who underwent a brain MRI both at ARIC Visit 3 (1993-1995) and Brain MRI visit (2004-2006), and subsequently followed a median (IQR) of 8.0 (7.4-8.6) years for stroke incidence. We categorized WMH according to the Cardiovascular Health Study definitions and defined a 3-level combined WMH/lacune measure: WMH grade < 2 and no lacune; WMH grade ≥ 2 or lacune; WMH grade ≥ 2 and lacune. Progression was categorized as: no progression; increase of ≥ 1 unit in WMH grade or incident lacune; increase of ≥ 1 unit in WMH grade and incident lacune. Associations between microvascular brain disease and stroke incidence were studied with Cox proportional hazard models, adjusting for demographics and cardiovascular disease risk factors.

Results: At Brain MRI visit, mean age of participants was 72 years, 62% were female, and 49% were black. Distribution of the combined measure was 37% WMH grade < 2 and no lacune; 57% WMH grade ≥ 2 or lacune and 6% WMH grade ≥ 2 and lacune. No change from ARIC Visit 3 to Brain MRI visit was observed in 36% of participants, while 59% showed ≥ 1 unit increase in WMH

grade or new lacune, and 5% showed both increased WMH grade and new lacune. Risk of stroke associated with microvascular brain disease at baseline was HR 2.33, 95% CI 1.34-4.06 for prevalent WMH or lacune and HR 6.71, 95% CI 2.19-20.60 for the combined measure. Progression of microvascular brain disease was significantly associated with stroke risk in patients showing both higher WMH grade and new lacune (HR 3.85, 95% CI 1.36-10.89), but not in persons progressing to only higher WMH grade or new lacune.

Conclusions: Considerable progression of microvascular brain disease, manifesting as both new WMHs and lacunes, is related to substantial increase in risk of stroke.

S222. Is the Treatment Outcome from Thrombolysis for Acute Ischemic Stroke Different in Women versus Men?

Seung-Jae Lee and Cheryl Bushnell. Seoul, Korea and Winston Salem, NC

Several studies, but not all, have shown that women benefit more from thrombolysis (tPA) than men; none have accounted for pre-stroke mobility. Our aim was to determine whether there was an interaction between gender and thrombolysis treatment in 3 month modified Rankin score (mRS), after adjusting for pre-stroke mobility. Our design was a retrospective medical record review of consecutive ischemic stroke patients admitted to a comprehensive stroke center 10/2012 to 7/2015. We included 952 (469 women and 483 men) patients. Women were older (mean age 68 y vs men 65.8 y; $p=0.018$), less likely to be treated with IV tPA (15.8% vs 23.4% in men; $p=0.003$), and more likely to use walking aids pre-stroke (13.6% vs 8.3% in men; $p=0.008$). Women had worse outcomes (55.9% with mRS >3) than men (40.5%; $p<0.001$) in those with no tPA. In those who received tPA, there were no gender differences. In multivariable modeling, there was a significant interaction such that women responded with better outcome and men had worse outcome after tPA ($p<0.001$), even after adjustment for pre-stroke walking aids ($p<0.001$), age ($p=0.001$), NIHSS ($p<0.001$), diabetes ($p=0.001$), CHF ($p=0.049$), and prior stroke ($p<0.001$). Our results show that, unfortunately, women were less likely to be treated with IV tPA than men, but when treated, women received more benefit than men, even in the setting of prestroke mobility impairment.

Movement Disorder

S223. Characterization of Vitamin B12 Supplementation and Clinical Outcomes in a Large Longitudinal Study of Early Parkinson's Disease

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Development of vitamin B12 deficiency in chronic neurological conditions may increase morbidity. B12 deficiency may be more common in Parkinson's disease (PD) because of associated gastrointestinal changes. It is unknown whether B12 supplementation might reduce overall morbidity. We sought to characterize multivitamin and B12 use in a large

PD cohort to determine whether consumption of B12 either alone or as part of a multivitamin (MVI) supplement was associated with baseline or outcome features.

NET-PD LS1 was longitudinal study in which subjects with early treated PD were randomized to creatine or placebo. While more than 1,700 patients were randomized, because the study was halted prematurely due to futility, only 709 of these completed the 5 year main clinical endpoint. We reviewed medication logs to stratify subjects according to dose and duration to B12 exposure. Subjects predominantly fell in to 3 dose groups: those taking 6-25 $\mu\text{g/d}$ (typical of a MVI), those taking $\geq 100 \mu\text{g/d}$ (typical of a B12 supplement), and those taking no supplemental B12.

At baseline, 38% (640/1675) took a MVI, 3% took MVI+ B12, 3% took B12 alone while 56% reported no supplements. The mean age of subjects taking on MVI was 63 years, for MVI + B12 was 65.7, for B12 alone was 65.3 while for those not taking supplements it was 60.6 yrs. For the 709 who completed the 5 year visit, 34% took an MVI, 2.5% took MVI +B12, 2.8% took B12 alone (all for >4 years), and 42% took no supplement. At baseline, age, education level and income were significantly different for the four groups.

In NET-PD LS1, at baseline nearly 2/5 subjects took a MVI while only 6% took supplemental B12 of $>100\text{mcg/d}$. Subjects who took B12 or MVI supplements were significantly older. At 5 years, after adjusting for age, education, sex and treatment group, no benefit for cognitive or motor outcomes was observed in those who took MVI or B12 for more than 4 years during the study. This analysis does not show benefit of low dose B12 supplementation provided by an MVI (6-25 mcg dose). Because of the number of subjects treated with higher doses of B12 was small, this data does not exclude a benefit of higher dose B12 supplementation.

S224. Analysis of MSA Patient iPSC-Derived Neural Cells with COQ2 Mutation

Fumiko K. Nakamoto, Satoshi Okamoto, Jun Mitsui, Shoji Tsuji and Hideyuki Okano. Tokyo, Japan

Objective: Multiple-system atrophy (MSA) is a neurodegenerative disease characterized by autonomic failure in addition to various combinations of parkinsonism and cerebellar ataxia. We have reported that variants of COQ2 which cause functional impairment of COQ2 protein are associated with an increased risk of MSA. COQ2 protein is an essential enzyme for the biosynthesis of coenzyme Q10 (CoQ10) that plays critical roles in mitochondrial bioenergetics and antioxidative effect. The purpose of this research is to elucidate the significance of impaired mitochondrial bioenergetics in MSA pathogenesis by using induced pluripotent stem cell (iPSC) technology.

Methods: iPSCs were generated from two MSA patients carrying COQ2 mutations (compound heterozygous R387X/V393A mutations and a heterozygous V393A mutation) and two MSA patients without the mutations, and differentiated into neural cells in vitro.

Results: The established iPSC clones were evaluated based on the expression of pluripotent markers via immunocytochemistry, and were confirmed their normal karyotypes. Finally, three iPSC clones from each patient were selected for further analyses. The clones were confirmed the COQ2 gene mutations of their parental somatic cells. No significant differences were detected in either MSA iPSCs or controls with regard to neural cell differentiation efficiency. Eighty-six days after in vitro neural differentiation, glucose-free media supplemented with galactose were applied to force energy production through oxidative phosphorylation rather than glycolysis. After incubation for 1 week in glucose-free medium, percentages of apoptotic cells were higher in MSA iPSC-derived neurons (15-27%) than those in control iPSC-derived neurons (3-7%) ($P < 0.05$).

Conclusion: We generated iPSCs from MSA patients and differentiated them into neural cells. Our results indicate the evidence of mitochondrial respiratory-chain dysfunction in patients with MSA. In further study, we will measure CoQ10 levels and evaluate the effects of CoQ10 administration in MSA iPSC-derived neural cells and the potential of COQ10 administration as a therapy for MSA.

S225. The Astrocytic Transporter Slc7a10 (Asc-1) Mediates Glycinergic Inhibition of Spinal Cord Motor Neurons

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Objective: Slc7a10 (Asc-1) is a sodium-independent amino acid transporter known to facilitate transport of a number of amino acids including glycine, L-alanine, L-serine, and L-cysteine, as well as their D-enantiomers. Mice null for Slc7a10 display tremors, ataxia, rigidity, and seizure-like events that represent sustained myoclonus. This phenotype has been believed to reflect neuronal hyperexcitability arising from impaired transport of the NMDAR co-agonist D-serine. We examined whether this phenotype may in fact reflect hyperekplexia, attributable to a role for Slc7a10 in mediating glycinergic inhibition.

Background: Motor neuron activity is tonically regulated by inhibitory currents, mediated through spontaneous and evoked synaptic release of glycine and GABA. Glycinergic inhibitory neurons require glycine enrichment in order to maintain vesicular glycine pools. Finding that Slc7a10 is enriched in regions where glycinergic inhibitory neurons are abundant, knowing that Slc7a10 has a high affinity for glycine, and realizing that the myoclonus-like phenotype of Slc7a10-null mice could reflect hyperekplexia, we hypothesized that Slc7a10 may play a role in regulating glycinergic inhibitory activity.

Design/Methods: We conducted a careful examination of Slc710 distribution and cellular expression in the CNS, and examined glycinergic, GABAergic, and glutamatergic transmission in acutely prepared spinal cord motor neurons of Slc7a10-null, heterozygous, and wildtype mice.

Results: We find that Slc7a10 is enriched in a subset of astrocytes of the caudal brain and spinal cord in a

distribution corresponding to high densities of glycinergic inhibitory synapses. Spinal cord glycine levels are significantly reduced in Slc7a10-null mice and spontaneous glycinergic postsynaptic currents in motor neurons show substantially diminished amplitudes.

Conclusions: We propose that astrocytes play a crucial role in supplying and/or recycling glycine or its precursors to glycinergic neurons via Slc7a10. Our observations establish the etiology of sustained myoclonus and early postnatal lethality characteristic of Slc7a10-null mice, and implicate SLC7A10 as a candidate gene and auto-antibody target in human hyperekplexia and stiff person syndrome, respectively.

Neuro-Oncology

S226. The Folate Metabolism Pathway Polymorphism MTHFR C667T Increases the Risk of Methotrexate Myelopathy

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ObjectiveS: Myelopathy is a rare but devastating complication of the chemotherapy drug methotrexate (MTX). MTX inhibits dihydrofolate reductase resulting in a downstream depletion of S-adenosylmethionine, an essential substrate in the transmethylation of myelin. Previous reports of MTX myelopathy have found no clear dose relationship and individual susceptibility is unexplained. Polymorphisms in a key enzyme for folate metabolism, methylenetetrahydrofolate reductase (MTHFR) cause a substantial decrease in enzyme activity. The objective of this study was to explore the potential relevance of MTHFR polymorphisms for the development of MTX myelopathy.

Methods: 4 consecutive patients receiving methotrexate who developed unexplained myelopathy underwent extensive laboratory and electrophysiologic testing to excluded other causes of the clinical presentation. Each patient had PCR testing for MTRHF polymorphisms.

Results: Age was 49-62 years old and 50% were male. One patient each had B-cell lymphoma, Burkitt's lymphoma, acute myeloid leukemia and rheumatoid arthritis. 3 received intrathecal and 1 oral MTX. Each developed severe subacute quadriplegia and profound sensory loss. All patients had elevated CSF total and myelin basic protein. 3/4 had MRI findings of dorsal and/or lateral column T2 hyperintensity similar to subacute combined deficiency. B12, folate, MMA, homocysteine and copper levels were normal. 3 were found to be homozygous, and 1 heterozygous for the MTHFR C667T polymorphism. 3/4 patients improved with cessation of methotrexate and aggressive repletion of folate metabolites including SAM-e, folinic acid, cyanocobalamin, methionine, and/or 5-MTHF. 1 passed away from unrelated reasons prior to sufficient treatment.

Conclusions: This is the first report of an association between a polymorphism in a key step of folate metabolism (MTHFR C667T) and MTX myelopathy. Diagnostic testing is straightforward and should be considered in the

evaluation of myelopathy in those receiving MTX. Folate metabolite repletion may be an effective treatment. A future study is needed further investigate the relationship and to determine optimal treatment strategies.

S227. Postoperative Cognitive Status Testing in Brain Tumor Patients: A Review

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Introduction: Cognitive outcomes following brain surgery are an important component of quality of life (QOL) and long-term functional status. Increasingly, emphasis is placed on outcome measures to assess surgical quality. Postoperative cognitive status provides an objective, interrogable endpoint for clinical use. Despite this, information on postoperative cognitive outcomes of brain tumor patients remains sparse, and postoperative assessment of cognitive status is not part of routine follow-up care in these patients. Here we analyze and compare the quality of neuropsychological tests used in the assessment of postoperative cognitive outcomes of brain tumor patients.

Methods: PubMed and PsychInfo were queried for all publications related to or reporting cognitive outcomes in surgical neuro-oncology patients in order to identify all neuropsychological tests that have been used to assess cognitive outcomes in this patient group. Tests were included if they had evidence of being used to assess cognition in brain tumor patients following surgical tumor resection. 28 tests met all inclusion criteria. For each test, specific quality criteria were investigated and analyzed in order to evaluate its strengths and weaknesses, as well as its utility in assessing cognitive status of brain tumor patients postoperatively. Quality criteria included but were not limited to: number of cognitive domains assessed, depth of each domain tested, ease of use, time required for completion, performance compared to other tests, and a number of other factors such as sensitivity, specificity, PPV, NPV and ROC AUC. Overall assessment of quality and applicability of a test was based on weighted summative scores according to the above criteria.

Results: Among the 28 tests analyzed, the Modified Mini-Mental State Exam (3MS), Addenbrooke's Cognitive Exam – Revised (ACE-R), and the Neurobehavioral Cognitive Status Exam (NCSE) were found to outperform other tests in a number of key domains. Each test covered a broad range of cognitive domains with adequate depth and was widely accepted in the medical community. When compared to other tests under consideration, the 3MS, ACE-R and NCSE returned greater sensitivity/specificity and ROC AUC, and lower false negative rates for detecting cognitive impairment.

Conclusion: Neuropsychological testing is an important component of outcome tracking. And should be routine for brain tumor patients following surgery to better capture postoperative functional status and QOL. Future research may utilize cognitive outcome data to compare surgical approaches, identify best practices, and improve patient outcomes.

S228. Distinguishing Pineoblastoma from Medulloblastomas Using Tissue Mass Spectrometry Imaging

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Medulloblastoma (MB) is a common pediatric malignant primary brain tumor originating in the posterior fossa. There are 4 molecular subgroups of MB: Wnt, Shh, Group 3, and Group 4. Interestingly, MB was originally included in the primitive neuroectodermal tumor (PNET) class together with pineoblastoma. An approach that could accurately distinguish the MB tumors and pineoblastoma based on their molecular composition would bring additional information on these tumor types. MALDI mass spectrometry imaging (MALDI MSI) is a powerful technique to investigate the distribution of molecules within tissue sections. Studies have shown that MALDI MSI can be used to classify different tissue types by obtaining comprehensive molecular signatures.

Mass spectrometry imaging analyses were performed using a Fourier transform ion cyclotron resonance mass spectrometer on seven MB samples from different MB subgroups (Wnt, Shh, Group 3, and Group 4) and one pineoblastoma. The mass spectrometry analyses indicated that it is possible to distinguish the pineoblastoma and the medulloblastomas according to their lipid signatures. Lipidomics is an integral part of metabolomics, and constitutes the detailed analysis and global characterization, both spatial and temporal, of the structure and function of the lipidome within a living system. Our lipidomics data suggest that MB can be distinguished from pineoblastoma by MALDI MSI, however, more samples for each tumor type would be required to validate this work. The proposed research has the potential to pave the way for more comprehensive diagnostic approaches of MB, other pediatric brain tumors and can be extended to other neurological disorders.

Behavioral Neurology

S229. Immunoglobulin Class Switch of Anti-Glycolipid Antibodies in Neuroimmunological Diseases

Makoto Samukawa, Motoi Kuwahara, Miyuki Morikawa, Rino Ueno, Yukihiro Hamada, Kazuo Takada, Yoshiyuki Mitsui and Susumu Kusunoki. Osaka-Sayama, Osaka, Japan

Introduction: Anti-glycolipid antibodies are frequently detected in the acute-phase sera from patients with Guillain-Barré syndrome (GBS) and are used as diagnostic markers. In addition, they are sometimes detected in other neuroimmunological diseases. It remains to be determined whether the immunoglobulin class switch (CS) from IgM to IgG occurs in anti-glycolipid antibodies in neuroimmunological diseases. Herein we investigated this issue.

Methods: We enrolled patients with neuroimmunological diseases such as GBS, acute disseminated encephalomyelitis (ADEM), autoimmune encephalitis and others, who had IgM antibodies to glycolipids but did not have IgG

antibodies at onset. We repeatedly examined anti-glycolipid antibodies after four weeks or later from first examination.

Results: We found 20 patients with IgM antibodies to GM2 and/or GalNAc-GD1a (IgM-GM2/GalNAc-GD1a) in GBS (12 patients), Fisher syndrome (one patient), chronic inflammatory demyelinating polyneuropathy (CIDP) (two patients), neuralgic amyotrophy (one patient), multifocal motor neuropathy (one patient), Bickerstaff brainstem encephalitis (one patient), polyneuropathy (one patient) and ADEM (one patient), and 18 patients with IgM anti-Gal-C antibodies (IgM-Gal-C) in GBS (five patients), ADEM (two patients), autoimmune encephalitis (two patients), bilateral striatal necrosis (one patient), brainstem encephalitis (one patient), Fisher syndrome (one patient), CIDP (two patients), unknown (two patients), brachial plexus neuritis (one patient) and encephalitis and neuropathy (one patient). Among them, follow-up examinations of the antibody activities were performed in 14 patients with IgM-GM2/GalNAc-GD1a and six patients with IgM-Gal-C. None of the patients with IgM-GM2/GalNAc-GD1a had CS. Three of Gal-C group had CS (IgG1 in two patients; autoimmune encephalitis and bilateral striatal necrosis, IgG3 in one patient with encephalitis and neuropathy). All patients with CS were child of ages below 11 years and CSs were observed during recovery phase.

Conclusions: In this study, we detected IgM anti-glycolipid antibodies in several kinds of neuroimmunological diseases. CSs were observed in three child patients with IgM Gal-C antibodies. CS may occur when a patient is exposed to the pathogens for the first time. These three patients were convalescent when CSs were observed. It suggested that IgM anti-glycolipid antibodies could have pathological significance in those cases. Further studies should be performed to clarify the clinical significance of CS in anti-glycolipid antibodies.

S230. Adult Onset Leukodystrophy and Increased Survival as a Presentation of AARS2 Related Disease

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Defects in AARS2, encoding mitochondrial alanyl-tRNA synthetase, result in a spectrum of findings, ranging from infantile cardiomyopathy to progressive leukoencephalopathy. To date, there are 8 such reported cases. In this report, we present a 50-year-old man with progressive cognitive and motor decline, beginning in his fifth decade of life, as well as evidence of a leukodystrophy on brain MRI, found to have compound heterozygous AARS2 mutations. The patient presented for evaluation in Neurogenetics clinic at the age of 48 years. His childhood and early adulthood course were significant for two seizures (one between 2-4 years of age and another between 14-16 years of age), fine tremor which developed around 25 years of age, and anxiety attacks starting in his early 30s. His neurological deterioration commenced when he was 42 years old, when he developed fine motor difficulties, worsening tremor, depression, and unsteady balance. Thereafter, he progressively declined in cognitive and motor abilities. By around 46 years of age,

he had lost all speech, became immobile, and developed dysphagia. MRI at age 47 years showed bilateral, symmetric white matter changes in the frontal regions, occipital regions, and brain stem, as well as cortical and cerebellar atrophy; these findings were progressive compared to MRI at 42 years, which revealed prominent frontal white matter changes. After extensive prior genetic and metabolic testing, he underwent whole exome sequencing, which revealed compound heterozygous changes in AARS2: c.595C>T (p.R199C); c.2557C>T (p.R853W). The p.R199C variant has been previously reported in association with leukoencephalopathy and is predicted to impact synthetase function based on published structural modeling analysis. The p.R853W variant occurs at a position that is evolutionarily conserved, and in silico pathogenicity tools predict that this variant is probably damaging. Our case expands the clinical heterogeneity of AARS2 related disorders, as he is the oldest known survivor of this disease.

S231. A Novel PGRN Mutation Presenting as Progressive Aphasic Dementia and Evolving into Corticobasal Syndrome

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Background: Mutations in the progranulin gene (Chr 17) commonly result in behavioral variant frontotemporal dementia (FTD) or primary progressive aphasia (PPA), although a wide range of phenotypes have been described.

Case: A 60-year-old right-handed woman presented with difficulty expressing herself and trouble following multistep directions. She had significant word finding difficulty in conversational speech and marked involvement of her written language output, so much so that she was unable to convey a message in writing that she could easily convey in speech. Approximately a year into the illness she developed mild difficulty with object use, but did not have personality changes, memory complaints, hallucinations or visuospatial difficulties. Her family history was significant for Parkinson's disease in her mother and a sister passed away with a diagnosis of Pick's disease although an autopsy was not performed. Seven other siblings were cognitively normal. Initial neurologic examination revealed difficulty with calculation and digit span, but no trouble with naming, recall, registration or construction. Her repetition was spared, but she had difficulty following three step commands and her writing was significantly impaired. Picture description resulted in significant word finding pauses and semantic paraphasic errors. Formal neuropsychometric testing 18 months after symptom onset revealed impaired performance on attentional tasks, trail making, lexical and semantic fluency and logical memory, with relatively preserved audioverbal learning and recall, naming and construction. Her neurologic examination two years into the illness showed more generalized cognitive and language impairment, as well as ideomotor apraxia and hemiparkinsonism. Her initial MR imaging showed moderate to severe asymmetric left frontal-temporal-parietal atrophy. FDG-PET imaging showed a similar,

almost exclusively left sided pattern of intense hypometabolism. Amyloid PET imaging was negative. At follow up 16 months later both the left sided focal atrophy and hypometabolism had progressed, with little to no progression in the right hemisphere. Genetic testing revealed a previously unreported mutation in exon 12 of the GRN gene (c.1535delC, Pro512LeufsX5), resulting in a premature stop codon. Further evidence for pathogenicity was sought with quantification of serum progranulin levels.

Conclusion: We describe the clinical and imaging features in a novel, likely pathogenic progranulin mutation. The case is striking for the rapid progression and overlapping phenotypes, and although this has been described in other GRN mutations it remains poorly understood why this occurs.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr Boeve reported serving as an investigator for clinical trials sponsored by GE Healthcare and FORUM Pharmaceuticals; receiving royalties from the publication of Behavioral Neurology of Dementia (Cambridge Medicine, 2009); serving on the scientific advisory board of the Tau Consortium; serving as a consultant for Isis Pharmaceuticals; and receiving research support from the National Institutes of Health (grants U01 AG045390, U54 NS092089, P50 AG016574, UO1 AG006786, RO1 AG015866, RO1 AG032306, and RO1 AG041797) and the Mangurian Foundation. Dr Parisi reported serving on scientific advisory boards for the US Government Defense Health Board and the Subcommittee for Laboratory Services and Pathology; serving as a section editor for Neurology; receiving royalties from the publication of Principles and Practice of Neuropathology, second edition (Oxford University Press, 2003); and receiving research support from the National Institutes of Health as a coinvestigator (grant NS32352-13).

S232. Dynamic Evolution of Hepatic Encephalopathy Suggestive of a Cerebral Vascular Shunt Phenomenon

Hunaid Hasan, Divya B. Mella, Yun A. Coronado and Xiang Fang. Galveston, TX

Background: Hepatic encephalopathy (HE) has shown to impair function of protoplasmic astrocytes responsible for connecting with the perivascular, subpial and neuronal circuits with their endfeet. Studies have demonstrated HE causing disruption of numerous grey matter structures. Uniquely, our patient has demonstrated over many years progressive involvement of numerous grey matter structures such as the bilateral basal ganglia (BBG), dentate nuclei, midbrain and the subcortical white matter.

Aim/Objective: To perform a retrospective review of chronic HE with evolution of progressive worsening of MRI lesions of grey matter structures, as a function of the degree of protoplasmic astrocyte dysfunction leading to vascular function abnormalities.

Methods: Case study

Results: Fifty-one year old male presented with a past history of hepatitis C with cirrhosis (MELD score 10) for

which he has been admitted multiple times for HE presenting with confusion, dysarthria, tremor, unsteady gait and dizziness. On this admission the lab work showed an ammonia of 58. Liver enzymes were ALT 68 and AST 75. His earliest brain MRI without contrast in 2008 showed mild increased intensity of T2/FLAIR in the centrum semiovale, corona radiata and corticospinal tracts. Interval studies demonstrated new symmetric T2/FLAIR hyperintensities within BBG and cerebellar dentate nuclei. Recent MRI with/without contrast showed increased T2/FLAIR signal intensity within the BBG, cerebellar dentate nuclei and extending to the midbrain and subcortical white matter. EEG demonstrated diffuse slowing with low voltage fast Background.

Discussion: The progressive T2 hyperintensities as demonstrated, suggests that HE may affect populations of protoplasmic astrocytes in grey matter structures leading to cerebral vascular dysfunction. Adams and Foley in hepatic coma patients found that protoplasmic astrocytes increased diffusely in number and size with swelling of terminal processes, and folding of the basement membrane surrounding the capillaries, which affected the deeper layers of the cerebral cortex and the subcortical structures. Acutely, neurons were not affected; however, chronically, neuronal loss was seen. Therefore, the degree of cerebral vascular dysfunction of the structures could be correlated with the density of protoplasmic astrocytes in the particular grey matter structure. Therefore, successive involvement of grey matter structures could likely be due to increased destruction of the protoplasmic astrocytic function. We hypothesize that the progressive involvement of these grey matter structures could represent an analogous vascular shunt phenomenon similar to the portosystemic shunt of the abdominal vasculature, being regulated by protoplasmic astrocytic dysfunction.

S233. Burden and Outcomes of Acute Hemorrhagic Stroke in Patients with Major Depression

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Objective: To determine the trends and impact on outcomes of Acute Hemorrhagic Stroke (AHS) in patients with pre-existing major depressive disorder (MDD).

Background: While post-stroke MDD has been extensively studied in the past, contemporary studies on the impact of pre-stroke MDD on AHS and post stroke outcomes are largely lacking.

Methods: We used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) from years 2002-2012. We identified AHS and MDD as a primary and secondary diagnosis respectively using validated International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes. We used the Cochrane-Armitage trend test and multivariate regression to generate adjusted odds ratios (aOR).

Results: We analyzed a total of 757,369 AHS hospital admissions from years 2002-2012 of which 8.6% had

MDD. Proportion of hospitalizations with MDD increased from 4.46% in 2002 to 8.69% in 2012 (ptrend < 0.001). In-hospital mortality was significantly lower in patients with MDD (aOR 0.659; 95%CI 0.617-0.703; $p < 0.001$) but discharge to specialty care was higher (aOR 1.262; 95%CI 1.177-1.353; $p < 0.001$). In, addition, median length of hospitalization (5.24 vs. 5.30 days; $p < 0.001$) and cost of hospitalization (10,866 vs 11,574; $p < 0.001$) was slightly lower in hospitalizations with MDD.

Conclusion: Our study displayed an increasing proportion of patients with MDD admitted due to AHS in the last decade with lower mortality but higher morbidity post stroke. There is a need to explore the reasons behind this disparity in outcomes and thrombolysis utilization in order to improve post-stroke outcomes in this vulnerable population.

Cerebrovascular Disease

S234. Does Timing of Vessel Imaging for Suspected Large Vessel Occlusions Impact Reperfusion Time in Stroke Transfer Patients?

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Background AND Purpose: In acute ischemic stroke with large vessel occlusions (LVO), endovascular reperfusion within 6 hours from symptom onset improves long-term clinical outcomes. The Mount Sinai endovascular team receives transfers from community emergency departments (ED) at outside hospitals (OSH) within our health system and its affiliates. The optimal timing of diagnostic CT angiograms (CTA) is uncertain. Holding ambulance crews at the OSH while waiting to obtain CTA before departure can result in transfer delays. Conversely, obtaining CTA after arrival may result in unnecessarily transferring non-LVO patients. We sought to examine transfer practices and evaluate for differences in reperfusion times in relation to timing of CTA. We hypothesized: 1) reperfusion times would be similar 2) transferring patients without CTA results in the unnecessary transfer of non-LVO cases.

Methods: There were 57 emergency department transfers for endovascular treatment from January 2015 – March 2016, of which 39 underwent endovascular reperfusion. Among the 39 reperfusion patients, 56% (n=22) had CTA prior to transfer and 44% (n=17) had CTA on arrival. We calculated total travel time as arrival time minus OSH departure time. To adjust for differences in traffic and travel distances, we calculated door to puncture (DTP) time as the difference between groin puncture and OSH arrival time minus travel time. Mean DTP times between the two groups were compared using the t-test and the Wilcoxon rank sum test.

Results: Average age was 73 ± 13 years old and average NIHSS was 19 ± 5 . There was no significant difference in average DTP time between the two groups (191 minutes for CTA at OSH vs 190 minutes for CTA on arrival, $p=0.99$ for t-test and 0.69 for rank sum test). Among the 18 patients who were transferred but did not receive

endovascular intervention, 10 had no LVO, 5 had large established infarcts on arrival and 3 had post-TPA hemorrhage. Of the 10 non-LVO cases, only 1 had CTA at OSH but imaging was not definitive. Out of all transfers during this period, 15% (n=9) had CTA on arrival and were found to have no LVO.

Conclusion: Timing of CTA (before vs. after transfer) does not significantly impact DTP time. However, 15% of acute stroke transfers had no LVO, suggesting that it may be beneficial to obtain CTA at OSH to avoid unnecessary transfers.

S235. Hispanic Patients Have Longer Door-To-Needle Times Independent of Age, Gender and Stroke Severity

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Background AND Purpose: In acute ischemic stroke, administration of intravenous tissue plasminogen activator (IV-tPA) improves long-term clinical outcomes, with better outcomes seen with earlier administration. Prior research has demonstrated racial and gender differences in stroke care and outcomes. Black women have lower tPA administration rates due to late hospital arrival. 1 In those patients that receive tPA, there are higher hemorrhagic complications in Blacks and Asians, but tPA efficacy is not affected by race or ethnicity.2,3 There is limited data on whether race or ethnicity affect “door to needle” (DTN) times. We hypothesized that even among patients arriving within the tPA time window, there will be significant differences in DTN times based on race-ethnicity.

Methods: Out of 1557 ischemic stroke patients in the Get With The Guidelines stroke database of Mount Sinai Beth Israel Hospital (New York, NY) from 2010-2015, 209 received IV tPA (including 9 with transient ischemic attack and 21 with non-stroke diagnoses). Linear regression was used to test associations between DTN and race-ethnicity in univariate models as well as adjusted for age, sex and NIH stroke scale score.

Results: Out of 209 IV tPA cases, 113 (55%) were men, average age was 72 ± 15 years and average DTN was 60.5 ± 27.5 min. Race-ethnicity was divided into four groups: non-Hispanic White (n=108; 52%), non-Hispanic Black (n=25; 12%), Hispanic (n=35; 17%), and other (n=39; 19%). Compared to non-Hispanic Whites, Hispanic patients had an average longer DTN time of 12 minutes ($p < 0.021$). There was no significant difference in DTN time comparing non-Hispanic Whites and non-Hispanic Blacks. This finding remained consistent in the fully adjusted model.

Conclusion: There is a significant delay in DTN times for Hispanic ischemic stroke patients who received tPA with an average of 12 minute delay compared to non-Hispanic White patients. This relationship was independent of age, sex, and stroke severity. We speculate this may be due to language barriers. Further studies are needed to further explore this finding.

S236. Let7i Regulates Leukocyte Response in Patients with Acute Ischemic Stroke

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Background: The immune system responds rapidly following ischemic brain injury and can contribute to the final extent of brain damage. microRNA are differentially expressed in leukocytes following ischemic stroke and may regulate the immune response to ischemic brain injury. In this study we evaluate microRNA let7i-5p in ischemic stroke and its regulation of leukocytes.

Methods: A total of 212 patients were studied; 106 with acute ischemic stroke and 106 risk factor matched controls. Let7i-5p miRNA expression was assessed by Taqman qRT-PCR. Target gene expression was assessed by whole genome HTA Affymetrix microarray. Let7i-5p post-transcriptional regulation of target genes was evaluated by 3'UTR luciferase assay. Target protein expression was assessed by ELISA.

Results: Let7i-5p was decreased in patients with acute ischemic stroke (fold change -1.4, $p < 0.00001$). Let7i-5p inversely correlated with NIH Stroke Scale at admission ($r = -0.32$, $p = 0.02$), infarct volume ($r = -0.21$, $p = 0.04$) and plasma MMP9 ($r = -0.46$, $p = 0.01$). The decrease in let7i-5p was associated with increased expression of several of its messenger RNA targets including CD28/CD86, CXCL8 and HMGB1. In vitro studies confirm let7i-5p post-transcriptional regulation of target genes CD86, CXCL8 and HMGB1. Functional analysis indicate let7i-5p regulates pathways involved in leukocyte activation, recruitment, and proliferation including canonical pathways CD28 signaling in T helper cells, HMGB1 signaling, and CXCL8 signaling.

Interpretation: Let7i-5p is decreased in circulating leukocytes of patients with acute ischemic stroke. A modulation of leukocyte inflammatory response in relation to infarct severity was identified. Mechanisms by which let7i-5p may regulate inflammatory response in stroke include targeting CD28, CD86, CXCL8 and HMGB1.

S237. Predictors of In-Hospital Ischemic Stroke During Acute Myocardial Infarction Hospitalizations

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Objective: To determine the predictors of In-hospital Stroke during Acute Myocardial Infarction Hospitalizations.

Background: Acute Myocardial Infarction (AMI) and Ischemic Stroke are leading causes of morbidity and mortality in the United States. The lack of prompt response can mask In-hospital Ischemic Stroke (HIS) during a hospital stay. However, there is a limited data on trends and outcomes of HIS in acute AMI.

Methods: We reviewed the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (NIS) database from 2002 to 2012. We included adult hospitalization of AMI as a primary diagnosis using International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes 410.xx. HIS was defined as the presence

of secondary ICD-9-CM codes of 433.xx-437.1. Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) were identified by using ICD-9-CM procedure codes. We used Chi-square test and multivariate regression to analyze predictors.

Results: From 2002-2012, a total of 7,043,113 admissions with AMI occurred. Of these, 99,338 (1.4%) were complicated by HIS. In a multivariate regression analysis, age > 65 (Odds Ratio 2.28; 95% Confidence Interval 2.07-2.51; $p < 0.01$), female (OR 1.48; 95% CI 1.43-1.53; p -value < 0.01), African-American race (OR 1.32; 95% CI 1.25-1.40; p -value < 0.01) and increasing Charlson comorbidities index (OR 1.40; 95% CI 1.39-1.41; p -value < 0.01) have been associated with HIS. Patients undergoing PCI are less likely to develop HIS (OR 0.56; 95% CI 0.53-0.58; p -value < 0.01), however CABG is associated with higher odds of HIS (OR 1.47; 95% CI 1.38-1.57; p -value < 0.01).

Conclusion: The higher association of increasing age, sex and race with Ischemic Stroke is depicted. The patients who undergo CABG procedure are more likely to develop stroke. Therefore, further studies are warranted for improved risk stratification in AMI patients.

S238. Impact of Weekend Admissions on Mortality and Discharge Disposition in Acute Ischemic Stroke: A Nationwide Perspective

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Background: Stroke is the fourth most common cause of death worldwide. Previous studies have demonstrated differences in stroke mortality by time of the week, with increased mortality during the weekend compared to the standard workweek.

Methodology: We identified acute ischemic stroke (AIS) hospitalizations from the Nationwide Inpatient Sample database (years 2000-2011) using ICD-9-CM codes; the analytic cohort constituted all AIS hospitalizations. Weighted analysis to account for survey sampling was performed for categorical data with significance test by chi-square, for continuous data analysis using Student's t-test, and Cochran-Armitage test for trend. The primary comparison was mortality by time of week of admission (weekday versus weekend). Multivariate survey logistic regression was performed with primary outcome of mortality and the secondary outcome of discharge disposition (DD: discharge to skilled nursing facility/Intermediate care facility), comparing time of week of admission, adjusting for age, gender, race, hospital region, hospital academic status, and primary payer. Comorbidities were defined by Deyo's modification of Charlson's Comorbidity Index (CCI).

Results: A total of 5,224,074 hospitalizations for acute ischemic stroke were identified, of which 1,183,211 (22.7%) occurred on weekends. The mortality trend on weekend decreased from 7.2% in 2000 to 4.6% in 2011. In the crude analysis, all-cause in-hospital mortality (1.5% vs. 4.4%; $p = 0.01$) and DD (15.2% vs. 43.0%; $p < 0.01$) were

lower on weekends compared to weekdays. In multivariate analysis, weekend admissions were associated with higher mortality [odds ratio (OR) 1.023; confidence interval (CI) 1.001-1.045 ($p=0.04$)] and DD [OR 1.07; CI 1.06-1.08 ($p<0.01$)]. Large (>100 beds) hospital size [OR 1.05; CI 1.02-1.09 ($p<0.01$)], academic hospitals [OR 1.12; CI 1.10-1.15 ($p<0.01$)], and CCI >2 [OR: 1.84; CI: 1.80-1.89 ($p<0.01$)] were associated with higher mortality.

Conclusion: In a large administrative dataset, there was a decreasing trend over time for AIS-related mortality during the weekend. However, in adjusted models, weekend admission was associated with higher mortality. Further research would confirm these trends and explore causes for these differences.

Epilepsy

S239. Characterization of High Frequency Oscillations in One Patient with Epilepsy

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Objective: To further characterize the frequency components, pattern, and timing of pre- and postictal high frequency oscillations (HFOs; 80-500Hz) recorded through subdural EEG electrodes in patients with epilepsy.

Background: HFOs are considered electrographic biomarkers of epileptogenic focus (zone). Therefore, their characterization may help delineate their role in epileptogenic zone localization, seizure prediction, neurocognitive processing (Shum J, Journal of Neuroscience, 2013), and surgical outcome (Klooster, Neurology, 2015).

Methods: We analyzed 74 preictal and 81 postictal HFO events from 6 clinically similar seizures recorded over the course of 6 days of continuous video-EEG recording in a patient with drug-resistant temporal lobe epilepsy undergoing presurgical evaluation. The EEG was recorded at 512 Hz sampling rate (Natus, Nicolet). Interictal and ictal HFOs were analyzed (Wolfram, Mathematica) to characterize their frequency, wave shape, duration, timing, and spread pattern.

Results: Distinct pre- and postictal HFO patterns and frequency components were recognized. HFOs were found in greater abundance closer to the start and end of the ictal period. Higher frequency component (240Hz) HFOs were found closer to- while those of 120Hz were further from the start and end of the ictal period. Postictal HFOs had longer duration than preictal HFOs. A notable pattern in frequency, timing, location, and wave shape was found in postictal HFOs following shorter seizures (29s).

Conclusion: The localizing value of HFOs is clinically established. The areas under HFO-generating electrodes in this patient were included in surgical resection with excellent postsurgical outcome. Our findings suggest that HFOs can be further classified based on frequency and different patterns depending on the duration of seizures. Further characterization of HFOs in relation to the ictal event could uncover which types of HFOs are associated with certain types of seizures. This study is clinically significant since

HFOs may help with localization and timing of seizure onset, which in turn may improve seizure prediction and surgical outcomes of those patients undergoing epilepsy surgery.

References:

1. Shum J et al. A brain area for visual numerals. J Neurosci. 2013 Apr 17;33(16):6709-15.
2. Klooster et al. Residual fast ripples in the intraoperative corticogram predict epilepsy surgery outcome. Neurology. 2015 Jul 14;85(2):120-8.

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Disclosures: The authors have no disclosures.

S240. Intracranial Oscillatory Activity in Patients Performing an Object-in-Place Scene Memory Task

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Patients with medically refractory epilepsy are often considered for surgical intervention. Many of these patient as part of their seizure localization will undergo an intracranial electroencephalogram (EEG) with grids, strips, depths or stereo-EEG. Subjects undergoing intracranial EEG were tested using an object-in-place scene memory test, a task where the subject was required to recognize sets of correct targets on a colored Background. Their performance on this task was compared to the oscillatory activity in their brain. Spectral features associated with task parameters include theta/alpha band error signaling, high frequency spikes, attenuation of alpha and beta rhythm peri-selection, and late increase in alpha activity. Coherence between brain regions suggests a functional network supported by theta/alpha band coherence between the dorsolateral prefrontal cortex and the temporal lobe. Future analyses will attempt to further describe the spectral features associated with task performance and attempt to distinguish between the epileptogenic focus and unaffected tissue on the basis of oscillatory characteristics.

S241. The Epilepsy Transition Care Gap in Young Adults with Childhood-Onset Epilepsy

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Rationale: Many young adults with childhood-onset epilepsy require long-term epilepsy care as adults. There are not enough pediatric neurologists to care for these children as adults, and the extent to which epilepsy transition (process of preparation) occurs as adolescents transition into adulthood is unknown.

Methods: The Connecticut Study of Epilepsy is a prospective, community-based study of newly diagnosed childhood-onset epilepsy with 613 children (≤ 16 years old; recruited 1993-97). During the final exit interview, 308 young adults ≥ 18 years old (or parent-proxies) were asked, "Before you turned 18 years old, did your doctors or other

epilepsy care providers talk with you about how your epilepsy care needs might change as you get older?" ('transition discussion'). We explored whether or not sociodemographic and clinical characteristics were associated with reported care transition discussions using t-test, chi-square or Fisher's exact.

Results: For young adults with childhood-onset epilepsy (N=308; mean age 24 years, SD=4.0; mean age of epilepsy onset 5.4 years, SD=3.7), only 15% responded "Yes" to having had a "transition discussion". Of those with "active epilepsy" (N=130; seizure-free <5-years or on anti-seizure medication within 2 years of 18th birthday) at the time of transition (age 18), approximately one-third of young adults had "transition" discussions, compared to 4% of those with "inactive epilepsy" (N=178; $p<0.0001$); self- (N=95 active epilepsy) and proxy-reports (N=35 active epilepsy; 71% under guardianship) of "transition" discussions were comparable (31%). Transition discussions were significantly associated with neurodevelopmental comorbidity and current epilepsy physician type ($p<0.05$). Young adults with "active epilepsy" (at transition), identified the following physician types as currently managing their epilepsy: primary care (N=10; mean age 26 years; 10% had discussion), pediatric neurology (N=16; mean age 20 years; 38% had discussion), adult neurology (N=55; mean age 26 years; 47% had discussion), general neurology (pediatric and adult) (N=10; mean age 24 years; 30% had discussion), or care perceived as not required (N=39; mean age 27 years; 10% had discussion). There were no associations of having "transition" discussions with gender, race/ethnicity, high school graduation, parent insurance, or epilepsy syndrome for those with "active epilepsy" (at transition).

Conclusions: One-third of young adults with active epilepsy at transition followed since diagnosis reported having epilepsy care transition discussions with health care providers before age 18. Identifying barriers to successful delivery of epilepsy transition care is critical to remediating treatment care gaps and building effective future care models.

S242. Clinical Features of Geriatric Epilepsy: Does Age of Onset Make a Difference?

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Introduction: Although epilepsy is usually speculated as a disease of youth, it is the third most common neurological disorder of elderly population. Upon detailed history and demographic review of geriatric epileptic patients, we propose two distinct clinical entities in this group: Those who experienced their first seizure later in life versus at an earlier age. We hypothesized that clinical characteristics of geriatric patients with new onset seizures differ from similar aged patients with longstanding epilepsy.

Methods: Upon IRB approval of this study, we retrospectively obtained the list of all patients in our university outpatient practice age 65 years or older between January 2012 - July 2014 with the probable diagnosis of seizure and epilepsy utilizing ICD-codes 345/780. Age of onset of seizures

was identified, and 255 eligible patients were stratified into geriatric onset epilepsy (GOE, age of onset 55 or older) and non-GOE (age of onset less than 55) groups. Detailed collection of demographic and clinical data including but not limited to type and frequency of seizure, postictal phase, status epilepticus (SE) and associated neoplasms was performed.

Results: Regarding types of seizures, complex partial and complex partial with secondary generalization were most common in both groups ($p>0.05$) but generalized seizure had statistically significant higher percentage in non-GOE group in comparison to GOE group ($p<0.05$). Statistical analysis showed that GOE group had less number of epileptic patients with frequency of more than one seizure per month ($p<0.05$). Mean postictal duration in the GOE group was longer than in the non-GOE group ($p<0.05$). 92% of GOE patients presented with confusion compared to 72% of non-GOE patients in postictal phase ($p<0.05$). 15% of patients in GOE group had a history of SE that was higher than non-GOE group (2%) ($p<0.05$). Patients in GOE group were significantly more likely to harbor neoplasm in comparison to those of similar age with longstanding epilepsy (39.7% vs. 23.2%; $p<0.05$).

Conclusion: Stratifying elderly epileptic patients into GOE and non-GOE groups in our study demonstrates that geriatric patients with new onset epilepsy have distinct clinical characteristics versus similar aged patients with longstanding epilepsy. This finding emphasizes the need for careful investigation of elderly epilepsy in terms of clinical features and seizure control.

Movement Disorder

S243. Investigating the Plastic Effects of Rapid Paired Associative Stimulation in Dystonia

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Objective: To investigate the effects of rapid paired associative stimulation (PAS) in organic and psychogenic dystonia to see if this technique can differentiate them.

Background: PAS is an established measure of cortical plasticity that is obtained by pairing transcranial magnetic stimulation and peripheral nerve stimulation set to arrive at the same time to the motor cortex. Dystonia is a disease of abnormal muscle contractions, associated with abnormal cortical plasticity as measured by PAS. One study has previously shown promise in using the technique to differentiate organic from psychogenic dystonia, but this has not been reproduced. Rapid PAS decreases testing time, minimizing subject and investigator fatigue.

Design/Methods: We designed an internal pilot study of 18 participants, then repowering using the primary outcome measure of change from baseline of motor evoked potential amplitudes at 30 minutes after rapid PAS. Six patients with organic dystonia, six patients with psychogenic dystonia and six healthy volunteers underwent transcranial magnetic

stimulation using 5 Hz rapid PAS protocol. Motor evoked potentials were recorded at S50 intensity and over a range of stimulus intensities and a sigmoidal recruitment curve was fitted at four time points (baseline, immediately after, 30 minutes after, and one hour after rapid PAS). All subjects also had temporal discrimination thresholds (TDT) and short interval intracortical inhibition (SICI) measured.

Results: No significant group differences were found in the TDT, SICI, motor recruitment curve parameters or motor evoked potential amplitudes change from baseline at all time points in the study. Repowering produced an impractical number needed to proceed with the study, and the study was halted. One patient with organic dystonia had to be withdrawn from the study because no reliable motor evoked potential amplitudes could be obtained.

Conclusion: The present study shows that rapid PAS, TDT, and SICI do not easily differentiate between organic and psychogenic dystonia.

S244. In Parkinson's Disease Subcortical Connections Tighten as Impulsivity, Mood, and Dementia Worsen: A Network Study of Global and Local Efficiency in PD

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Parkinson's disease has been characterized as a "disconnection syndrome" reflecting the disruption of neural pathways. Network science analyses provide a promising way of further analyzing this characterization given the rich data they provide about the interrelationships between brain areas. In this study, network science graph theory based analyses were performed using the resting state data from 14 individuals with Parkinson's Disease.

The networks consisted of 90 nodes defined in natural brain space for each individual. Global efficiency, a measure of efficiency of transfer within the entire network (the inverse of path length or the average number of steps from one node to another), and local efficiency, a measure of the connectedness of the nodes that a node is connected to, were calculated. The mean global and local efficiencies for the 10 subcortical nodes and for the remaining 80 nodes were then correlated with an array of behavioral measures: the Barrett Impulsivity Scale (BIS), Beck Depression Inventory (BDI), and the Montreal Cognitive Assessment (MoCA).

Subcortical global and local efficiency were significantly correlated with all three scales; positively in the case of the BIS and BDI (in which higher scores imply worse symptomology) and negatively in the case of the MOCA (in which lower scores imply worse symptomology). Conversely no significant correlations existed between global or local efficiency and the behavioral measures across the remaining network. Further analyses of the BIS subscales revealed significant correlations with subcortical global efficiency for the motor, personal, and cognitive complexity scales. Subcortical local efficiency correlated significantly with the BIS attentional, nonplanning, personal, and self-control scales. In contrast, local efficiency for the remaining brain areas in the network without the subcortical nodes showed

significant negative correlations with the attention and personal BIS subscales, suggesting relatively decreased connectivity in these regions.

These preliminary analyses suggest further explorations of brain connectivity using the tools of networks science may enhance our understanding of what occurs in PD and how that is reflected in behavioral disruptions.

S245. The Role of Shooting Exposure in the Military and the Development of Progressive Supranuclear Palsy

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Objective: To investigate the role of shooting exposure in the military as a risk factor of progressive supranuclear palsy (PSP).

Background: The causes of PSP are not fully known, however, it is believed that inflammatory, environmental, and genetic components all contribute. It has been established that shooting and use of firing ranges leads to increased exposure to heavy metals, notably lead, a known neurotoxic agent. There have been studies investigating the potential role of lead in movement disorders; however, no studies have investigated its role in the development of PSP.

Design/Methods: In order to investigate the potential role of shooting exposure as a risk factor of PSP we recruited participants who had served in the military from a larger multi-center case control study. The final sample included 84 patients diagnosed with PSP and 74 controls. Participants were asked questions regarding their experiences in the military and their experience with shooting. For binary variables, Fisher's Exact test was performed and conditional odds ratios (OR) are reported. For continuous variables we performed two sample t-tests and report means.

Results: We found no significant difference in average amount of time spent in the military between cases, 4.7 years, and controls, 5.4 years (p -value=0.51). We found that 81.0% ($N=68$) of PSP cases and 63.9% ($N=46$) of controls reported that shooting was part of their job in the military. Compared to controls, PSP cases had an OR of 2.4 ($p=0.02$) for reporting shooting exposure as part of their job in the military. There was no difference between the number of reported hours of shooting monthly between cases, 3.1 hours, and controls, 3.5 hours, (p -value=0.69). We found no difference in the estimated total number of hours shooting over the course of the participants military service, with an estimated average of 135 hours for cases and 157 hours for controls (p -value=0.61).

Conclusions: Our study found that cases were over twice as likely to report use of firearms as part of their position in the military compared to controls. We believe this is the most accurate estimation of exposure, as general recall of using firearms in the military is likely more accurate than recall of average hours shooting monthly. This is the first study assessing firearm use and lead exposure as potential risk factors for PSP thus, further studies are needed to clarify this relationship.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past

12 months) with any commercial interests? Kristen Kelley is on a NIH TL1 grant, prior to September 1, 2015, Grant #TL1TR00098 and then beginning September 1, 2015, #1TL1TR001443.

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S246. Early Onset Parkinson's Disease and Chromosome 22q11 Deletion: Case Report

Kelly A. Mills and Stephen G. Reich. Baltimore

Objective: To call further attention to a recently recognized association between chromosome 22q11 deletion and young-onset PD [YOPD].

Background: The 22q11 deletion is the second most common cause of developmental delay and congenital heart disease, accounting for up to 15% of tetralogy of Fallot (Bassett AS et al. J Peds 2011). Its varied clinical expression also includes learning disability, palatal anomalies, facial dysmorphism, and schizophrenia. 22q11 deletion is now considered a risk factor for YOPD. The small number of cases reported thus far all demonstrate a clinical course, response to levodopa, and neuropathology typical for PD (Butcher NJ et al. JAMA Neurol 2013). While the 22q11 deletion region does not contain known PD risk factor loci, it does contain candidate genes that may directly interact with regulation of LRRK2 (Dweep et al. J Biomed Inform 2011) or the protein product of PARK2 (Zhang et al. PNAS 2000).

Results: A 39 year old man presented with decreased dexterity of the right hand, tremulous writing and a history of dyslexia, attention deficit disorder, and tetralogy of Fallot. Neuropsychological assessment at age 18 showed a full scale IQ of 83. He was previously found to have a 22q11 deletion which, at the time of the initial visit, was not known to be associated with parkinsonism. Examination showed mild, asymptomatic right hemiatrophy, right-sided bradykinesia, and rigidity. He was initially suspected of having hemiatrophy-hemiparkinsonism, but the clinical course became typical for PD with a beneficial, sustained response to levodopa, spread of signs to the left limbs, levodopa-related fluctuations and severe dyskinesias.

Conclusion: That the 22q11 deletion is now recognized as a risk factor for YOPD has several implications. First, neurologists should consider this deletion in a patient with YOPD and 22q11 syndrome features including learning disability, facial dysmorphism, congenital cardiac malformations, hypocalcemia, and velopharyngeal insufficiency. Second, patients with the 22q11 deletion should be monitored for parkinsonism. Third, patients with 22q11 are

often treated with antipsychotics and may be falsely assumed to have drug-induced parkinsonism rather than PD. Fourth, the 22q11 deletion may offer insights into the pathophysiology of PD. Lastly, the unexpected association between 22q11 deletion and YOPD demonstrates that potentially important insights may be gained by considering that seemingly unrelated clinical findings or other diseases in patients with PD may not be simply coincidental.

S247. Progression of Dysphagia in Spinocerebellar Ataxia Type 6

Chiharu Isono, Makito Hirano, Hikaru Sakamoto, Shuichi Ueno, Susumu Kusunoki and Yusaku Nakamura. Sakai, Osaka, Japan and Osaka Sayama, Osaka, Japan

Spinocerebellar ataxia type 6 (SCA6) is an autosomal dominant polyglutamine disease, characterized by a late-onset, slowly progressive disorder that mainly affects the cerebellum. Dysphagia is a common symptom in most neurodegenerative diseases and leads to aspiration pneumonia or suffocation, major causes of death in such patients. Characteristics of dysphagia in patients with SCA6 have been rarely reported. The aim of this study was to clarify progression patterns of dysphagia in patients with SCA 6 (N=12) and to compare them with those with SCA3 (N=6) using repetitive videofluoroscopic examination (VF). We revealed that the gross progression of dysphagia was apparently slower in patients with SCA6 than in those with SCA3. However four patients with SCA6 had earlier onsets of dysphagia (within 10 years from ataxia onset), with more rapid progressions than the rest of patients. A common clinical feature of the four patients was unexpectedly an older age at onset (> 60 y), though normally later onsets and milder phenotypes are linked in patients with shorter polyglutamine repeats. Nonetheless, in our study polyglutamine repeats did not parallel the dysphagia severities. One of the four patients had significant ischemic changes in the cerebral white matter and brainstem on MRI. Despite the small number of the patients enrolled, our findings suggests that clinicians should carefully monitor dysphagia in patients with SCA6 with older age at onset, since age-related factors might worsen dysphagia in such patients.

S248. Developmental Delay, Spasticity, and Progressive Generalized Dystonia in a Patient with Neurodegeneration with Brain Iron Accumulation Due to Mutations in COASY

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Objective: To describe clinical and genetic features of the third patient with mutations in COASY, a rare form of neurodegeneration with brain iron accumulation (NBIA).

Background: NBIA is a heterogeneous group of diseases characterized radiologically by iron deposition in the globus pallidus and occasionally in other basal ganglionic structures. Multiple causative genes have been identified, but approximately 30% of cases remain unexplained. In 2014, biallelic mutations in COASY, the gene coding for CoA synthase, were reported in two patients with early childhood

toe-walking, intellectual disability, progressive dystonia, and motor axonal neuropathy; these are the only cases reported to date (Dusi et al 2014). CoA synthase is involved in the last two steps of Coenzyme A biosynthesis. Another defect in Coenzyme A synthesis underlies the most common form of NBIA, pantothenate kinase-associated neurodegeneration (PKAN), which is caused by mutations in PANK2.

Case: Our male patient was born to consanguineous parents of Italian origin. Birth history and infantile development were reportedly normal. He walked at 16 months, but at 18 months he was referred for neurological evaluation due to deceleration in head growth, hypotonia, abnormal gait, and marked speech and language delay. At 6 years he was able to walk with supervision, however his motor function then deteriorated. He developed left arm dystonia and then progressive generalized dystonia over the next 3 years. Examination at 10 years revealed inability to walk, truncal hypotonia, lower limb spasticity, hyperreflexia, weakness, and generalized dystonia with marked involvement of the left arm and leg. Speech articulation became increasingly impaired. Trihexylphenidyl and clonazepam provided limited symptomatic benefit. Brain MRI at 12 years demonstrated symmetric abnormal pallidal susceptibility, consistent with iron deposition. There was T2 hyperintensity within the anteromedial region, and a small, round area of T1 hypointensity in the center of the globus pallidus bilaterally. No mutations in PANK2, FLT, or C19ORF12 were detected. Analysis of the COASY gene revealed the homozygous missense variant c.1222G>A (p.Glu408Lys), predicted to be pathogenic.

Conclusions: The NBIA syndrome associated with mutations in COASY is characterized clinically by spasticity and toe-walking in early childhood, intellectual disability, and slowly progressive generalized dystonia. The pallidal lesions seen on MRI are distinctive, and can be differentiated from similar lesions observed in PKAN.

Multiple Sclerosis

S249. Fingolimod Has Diverse Effects on Gene Expression by Differentiating Human Neuronal Progenitors

Micheline McCarthy, Ricardo Martinez and Rebeca Geffin. Miami, FL

Fingolimod (FTY-720), an analogue of sphingosine-1-phosphate, is an oral immunomodulatory medication for multiple sclerosis. Clinical studies suggest that this drug is neuroprotective; however, the cellular mechanisms underlying neuroprotection are not well understood. We adapted a human neuronal progenitor cell population (hNP1), derived from hESC WA09, to study how fingolimod affects neurons exposed to Human Immunodeficiency Virus (HIV). hNP1 cells were differentiated in medium alone (untreated), or in medium with added supernatants from mock-infected or HIV-infected lymphocytes, with or without daily added phosphorylated fingolimod. After 9 days and 12 days in culture, cells were lysed, and gene expression was measured using the Illumina HT12 microarray platform. Differences

in gene expression were evaluated according to both culture supernatant treatment and fingolimod treatment. The significance of these differences was assessed by ANOVA and Students t-test. By ANOVA, 189 genes were differentially regulated among untreated, mock-, and HIV-supernatant exposed cultures without added fingolimod, and 248 with added fingolimod after 9 days in culture (FDR adjusted value less than 0.25, p value less than 0.05). A larger number of genes were differentially expressed after 12 days in culture; 231 genes without fingolimod and 853 with fingolimod. Paired comparisons of untreated, mock-treated, and HIV-treated cultures with or without fingolimod revealed diverse genes showing statistically significant differences in expression with fingolimod treatment (absolute fold change value of 2.5 or more; p value less than 0.05). Differentially expressed genes reflected cell processes including neurogenesis, transcriptional regulation, apoptosis, DNA repair, RNA processing, and cell growth control. The effects of fingolimod could vary according to whether the differentiating neurons were exposed to mock or viral-containing supernatants. For example, in untreated cultures, expression of IL10 is unchanged by fingolimod exposure. In hNP1 cells differentiated with mock-infected supernatants, expression of IL10 is five fold higher with fingolimod exposure. In contrast, in hNP1 cells differentiated with HIV-infected supernatant, IL10 expression is reduced more than two fold with fingolimod exposure. Gene expression for the RNA helicase DDX3X was significantly upregulated in hNP1 cells differentiated with HIV-infected supernatant and fingolimod exposure. DDX3X has been implicated in anti-viral innate immune responses. These initial studies suggest that fingolimod can enhance neuronal anti-inflammatory or innate immune responses. Further studies on individual neuronal genes will help define the neuroprotective mechanisms this drug may promote.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Recipient of Investigator-initiated Research Grant from Novartis Pharmaceuticals to study the potential neuroprotective mechanisms of fingolimod in human neuronal cell cultures.

NO salary received from this research grant; it provides for research funds only.

S250. Brain Reserve in Multiple Sclerosis: Larger Maximal Lifetime Brain Growth Is Linked to Later Age of Multiple Sclerosis Diagnosis

James F. Sumowski, Maria A. Rocca, Matilde Inglese, Victoria M. Leavitt, Alessandro Meani, Korhan Buyukturkoglu, Paolo Preziosa, Giancarlo Comi and Massimo Filippi. New York, NY and Milan, Italy

Background: The brain reserve hypothesis states that persons with larger maximal lifetime brain growth (MLBG, estimated with intracranial volume, ICV) are better able to withstand neurologic disease without cognitive impairment or dementia. Several studies have supported the notion of brain reserve against cognitive decline in aging and multiple sclerosis (MS), and we have recently extended the brain

reserve hypothesis to physical disability in persons with MS. Herein we investigate a novel testable hypothesis of the reserve concept: that persons with larger MLBG will have an older age of MS diagnosis, consistent with the rationale that persons with larger MLBG can better withstand neurologic disease without/before suffering clinical symptoms precipitating medical attention and diagnosis.

Methods: A sample of 431 adult-onset Italian (n=341) and American (n=90) MS patients (288 women; 395 relapse-onset, 36 progressive-onset) underwent 3T MRIs of the brain to measure ICV, which was adjusted for sex and site (scanner), and divided into quintiles. Age of diagnosis was recorded, and adjusted for onset-course, site (country), sex, and socioeconomic status (years of education). Analysis of variance investigated differences in age of diagnosis across ICV quintiles.

Results: There was a medium-sized ($d=.04$) relationship between ICV and age of diagnosis ($F[4,426]=4.65$, $p=.001$), whereby patients in the largest quintile (Q5, mean age = 35.2 yrs; 95%CI: 33.4-37.1) were diagnosed at an older age than patients in Q4 (32.1, 95%CI: 30.3-33.9), Q3 (32.5, 95%CI: 30.7-34.3), and Q2 (32.4, 95%CI: 30.6-34.3, $P_s<.05$) and Q1 (29.5, 95%CI: 27.6-31.3, $p<.001$). Patients in Q1 (smallest ICV) were diagnosed at a younger age than patients in Q2, Q3, and Q4 ($P_s<.05$), and Q5 ($p<.001$). When Italian and American samples were analyzed separately, there was a reliable link between larger MLBG and older age of diagnosis in each sample ($P_s=.01$ to $.002$).

Conclusion: Consistent with the brain reserve hypothesis, persons with larger MLBG were diagnosed later (and persons with smaller MLBG were diagnosed younger), suggesting that larger brain reserve allows persons to better cope with MS disease burden before suffering clinical symptoms precipitating medical attention and diagnosis. This link between MLBG (ICV) and age of diagnosis was found in two independent samples. Data on lesion and clinical characteristics at diagnosis (e.g., lesion locations) were unavailable, but consideration of such factors in future research would ostensibly account for random error and improve power.

Neurocritical Care

S251. Subclinical Neuronal Injury in Good Grade Subarachnoid Hemorrhage

Halinder S. Mangat, Malik Fakhar, Xiangling Mao, Dikoma E. Shungu and Philip E. Stieg. New York, NY

Aneurysmal SAH causes devastating neurological injury with an overall 30-day mortality of 32-43%. However, patients who make a 'good neurological recovery' report significant psychosocial and neurobehavioral changes, which go undetected during the acute illness. Survivors suffer loss of motivation (50%), interests (47%), social relationships (39%), and concentration (70%). And up to 75% perform below the 25th percentile on neuropsychological testing. We utilized Magnetic Resonance Spectroscopy (MRS) to measure N-acetyl aspartate, a marker of neuronal integrity and

mitochondrial function, in frontal and temporal lobes, and CSF lactate, a marker of anaerobic metabolism, in survivors of good-grade SAH who had no neurological deficits and no evidence of infarction on MRI. MRI and MRS were performed between 5-14 days in patients who were neurologically intact.

Twelve patients with low-grade SAH underwent MRI. MRS data was obtained in these patients and compared to seven age-matched controls from our data library. Only patients who underwent endovascular aneurysm coiling were included, while surgically treated patients were excluded. Regions of interest (ROI) were placed in frontal and temporal lobes to include grey and white matter regions. Areas of non-specific white matter disease were excluded. In addition, if a patient had had an external ventricular drain, the tract was excluded from ROIs. Voxels with CSF and subdural spaces were also excluded. The measurement for each biochemical was averaged across all voxels in each hemisphere in each of the 3 imaging slabs. Measurements of CSF lactate were made by placing ROIs over the lateral ventricles. MR spectra demonstrated significantly decreased NAA peaks and NAA levels (area under the curve) in bilateral frontal lobes compared to controls whilst the profile in the temporal lobes was similar in the two groups. Frontal lobe NAA was 18.18 ± 6.55 in SAH patients and 21.49 ± 5.16 in controls ($p=0.03$). Temporal lobe NAA was 19.38 ± 6.04 in SAH patients and 19.36 ± 5.43 in controls ($p=0.98$). CSF lactate was significantly higher in SAH patients (7.81 ± 2.13 vs. 4.02 ± 0.76 in controls, $p=0.0005$).

Neurologically intact SAH patients have significant decreases in frontal lobe NAA and marked increase in CSF lactate. This preliminary data supports a mechanism of energy depletion and/or metabolic dysfunction associated with subclinical brain injury. In addition to validating this pilot data, in our future work we will explore whether these changes are associated with clinically relevant frontal lobe dysfunction and cognitive impairment that is seen in such patients.

Behavioral Neurology

S252. First Taste Syndrome

Nirmala Nagothu and Alan R. Hirsch. Willemstad, Netherlands Antilles and Chicago, IL

Introduction: In those with complaints of reduced or absent ability to taste, a common report is that of first bite of food having full or nearly full flavor followed by a rapid (less than one minute) decrement in flavor of the food to the baseline reduced or absent flavor. While clinically noted (Leopold, 2015 personal communication), this syndrome heretofore has not been described.

Methods: Six patients with first taste syndrome were evaluated with ages ranging from 44-63 yrs, 4 male and 2 female. Orthonasal smell ability ranged from anosmic (4) to hyposmic (1) to normosmic (1) and taste testing ranged from ageusic (5) to normogeusic (1). All had absent retro-nasal smell on Retronasal Smell Index testing. Half noted olfactory windows.

Discussion: All 6 patients demonstrate a consistent pattern with absent retronasal smell. This suggests that the origin for this phenomenon is a dysfunction in the olfactory system with misperception of loss of retronasal smell as loss of taste. The mechanism for this phenomenon may be pathological olfactory system with hyper-rapid adaptation (rapid shift on the exponential curve, Overbosch et al 1986). As such, one may anticipate that olfactory ability would not be totally absent, but rather severely reduced. Only half demonstrated the parallel phenomenon of hyper-rapid adaptation in orthonasal smell, as manifested by olfactory windows. Given the findings of gustatory deficit in 5 of 6 of these patients, true pathology of the gustatory system may be present and thus this may represent pathological hyper-acceleration of gustatory adaptation (Gent & McBurney 1978) or synergistic or additive hyper-acceleration of both olfactory and gustatory systems. Alternatively, first taste syndrome might represent an expectation with an associated projection with transient illusion of taste, the perceived flavor based on visual cues ("The first taste is always with the eyes", Van der Laan 2011). Such a transient hallucinatory phenomenon is seen in those suffering from cortical blindness as well as with haptic hallucinations with spinal cord injury and proprioceptive/kinesthetic hallucinations post amputation. Further investigation into the mechanisms of this syndrome is warranted.

S253. Abstinence from Drug Dependence After Bilateral Globus Pallidus Hypoxic Ischemic Injury

Khaled Moussawi and Jong W. Lee. Boston, MA

A 55 year-old female with a history of severe alcohol and opiate dependence was admitted after a methadone overdose. She was successfully resuscitated and gradually recovered. One month later, she was cognitively intact and her neurological exam was notable only for mild facial dyskinesias. A brain MRI revealed bilateral Globus Pallidus infarcts consistent with a hypoxic ischemic injury. Interestingly, her substance dependence remitted since the overdose. Her alcohol and opiate cravings and her compulsive drug seeking resolved. She resumed her career as an educator without any limitations and she continues to be abstinent after ten years. This case validates the addiction research literature in animal models where functional or structural lesions of the limbic striatum block relapse to drug seeking. In addition, this case highlights the Globus Pallidus as a new potential therapeutic target for deep brain stimulation (DBS) in the treatment of drug addiction.

S254. Sleep Spindle Activity in Children with Autism Spectrum Disorder (ASD)

Priyanka Chilakamarri, Cristian Farmer, Audrey Thurm, Susan Swedo, Scott A. Burroughs, Gregory L. Holmes and Ashura W. Buckley. Burlington, VT and Bethesda, MD

ASD is a neurodevelopmental disorder characterized by impaired social interactions and behavioral abnormalities. While there is increasing evidence of altered brain connectivity in autism, the degree and direction of these alterations in connectivity and their uniqueness to autism has

not been established. Sleep spindles in stage 2 of NREM sleep have demonstrated to be a robust measure of connectivity between the thalamus and cortex and play a critical role in neuronal plasticity and memory consolidation. We investigated spindle differences in density, frequency and duration in a large cohort of young children with ASD, developmental delay (without autism) and neurotypical development.

The study sample consisted of participants in an NIH natural history study of ASD approved by the NIH Combined Neurosciences Institutional Review Board. Spindle data were obtained from 135 children (ages 2 to 6) with ASD (n=85, 84% male), non-ASD developmental delay (DD; n=21, 62% male), or typical development (TYP; n=29, 72% male). EEG analysis of spindles were visually quantified in the first 5 minutes of stage 2 sleep.

Results of the Poisson regression showed a significant interaction between group and age in predicting spindle count ($\chi^2=37.68$, $p<.0001$). Probing of the interaction revealed spindle counts increased across ages in both the TYP and ASD groups, but decreased in the DD group. At younger ages, ASD had significantly fewer spindles than both DD and TYP ($p<0.0001$), while TYP had significantly fewer spindles than DD ($p=0.01$). At the mean age of about 4 years, ASD had significantly fewer spindles than both DD and TYP ($p<0.0001$), but DD and TYP no longer differed. At older ages, AUT had significantly fewer spindles than only TYP ($p<0.0001$). Among participants who had spindles (ASD, n=78; DD, n=20; TYP, n=28), frequency and duration were compared using ordinary least squares (OLS). The main effect of group was significant ($F=4.8$, $p=0.001$), and post-hoc analyses revealed significantly lower frequency in ASD compared to TYP ($p=0.02$). No significant differences in duration were observed.

In conclusion, this study strongly indicates that sleep spindles may be a biological marker that distinguishes young children with ASD from children with developmental delay without ASD and typically developing children and provides additional evidence for altered connectivity between thalamo-cortical regions in children with ASD. Future studies with longitudinal analyses exploring the stability of spindle findings with age may shed light on its role as a biomarker.

S255. Propranolol-Induced Psychosis in a Pediatric Patient

Ammar M. Alobaidy, Alicia Parker, Joseph R. Angelo and Lisa M. Nassif. Houston, TX

Objective: To describe a noteworthy case of propranolol-induced psychosis in a four year old male.

Design/Methods: A case report.

Background: This report demonstrates the importance of evaluating for propranolol-induced psychosis in pediatric patients with no past psychiatric history.

Results: The patient was a 4 years old male with history of hypertension secondary to renal art stenosis who presented to the emergency room with hallucinations following initiation of propranolol. Thirty minutes after his first dose

of propranolol, the patient developed transient visual hallucinations of turtles. After his third dose, hallucinations returned and were anxiety provoking, causing the patient to undress in an effort to rid himself of turtles. A recent history of poor sleep was elicited. Propranolol was stopped upon admission. The following day he had a third episode of anxiety and visual hallucinations. The differential diagnosis included occipital lobe seizures, autoimmune and infectious etiologies. EEG was within normal variation. MRI without contrast was without pathology.

Workup was unrevealing. Serologies performed included voltage-gated potassium channel antibodies, oligoclonal bands, aquaporin-4 antibodies, n-methyl-d-aspartate receptor antibodies, autoimmune encephalitis panel, thyroid antibodies, glutamic acid decarboxylase antibodies. CSF studies included voltage-gated potassium channel antibodies, herpes simplex virus PCR, Epstein-Barr virus PCR, cytomegalovirus PCR, varicella zoster virus PCR, West Nile IgG, enterovirus PCR, and oligoclonal bands and IgG index. Hallucinations ceased by the second day of admission. A diagnosis of propranolol-induced psychosis was established. He was discharged home without propranolol. At one-month followup, he was clinically at baseline without psychotic symptoms.

Conclusions: Psychosis is a significant, uncommon side effect of propranolol. To date, there have been four reported cases in adults of psychosis or hallucinations associated with propranolol. This is the first reported pediatric case of propranolol-induced psychosis. Clinicians would benefit from widening their differential diagnosis in cases of new-onset psychosis to monitor for this reversible condition. In the future, research to characterize whether these patients are at increased risk of psychiatric disorders would be beneficial.

S256. Axon Guidance Factors and the Development of Psychosis

James A. Wilcox and David Briones. Tucson, AZ and El Paso, TX

Netrin are axon guidance factors. Variation of netrin subtypes has been associated with changes in axon development related to psychosis. Such isoform changes in netrin NTNG1 have been associated with pre-pulse inhibition and reduced firing of NMDA receptor-mediated postsynaptic responses, associated with schizophrenia. Genetic information about formation of NTNG1 is located on chromosome 1p13.3, a linkage zone highly associated with psychosis in studies of schizophrenia. This study examines variations in isoforms of NTNG1 in an attempt to test the hypothesis that allelic variation in netrin subtypes contributes to risk for psychosis. We found a significant association of some subtypes of netrin NTNG1 and schizophrenia ($p < .001$), $n = 200$ compared to a subtypes in a healthy group of controls ($n = 200$) with no family history of mental illness. This suggests that variation in netrin isoforms may be associated with risk for psychosis.

S257. Factors Predicting Spontaneous Long-Term Recovery from Post-Stroke Aphasia

Denise Y. Harvey, Claire Healy, Myrna F. Schwartz and Roy H. Hamilton. Philadelphia, PA and Elkins Park, PA

Chronic stroke-induced aphasia affects approximately one million individuals in the US alone. It is widely assumed that most language improvements in persons with aphasia (PWA) occur spontaneously within three months post-stroke onset (MPO). This view of chronic aphasia as static directly impacts the availability of therapy and other supports for patients with persistent language deficits. Recently, however, we discovered that some chronic PWA made substantial recovery between 5 months to 8 years post-onset that cannot be ascribed to speech-language therapy (SLT). We examined the impact of demographic, psychosocial, and/or neurobiological factors on long-term aphasia recovery. We tested 18 chronic PWA secondary to left hemisphere stroke twice on the Western Aphasia Battery (WAB). We used WAB Aphasia Quotient (AQ) to assess changes in language impairment. Initial WAB assessments were performed from 5-133 MPO (mean: 40 months), and follow-up tests from 21-94 months after initial testing (mean: 61 months). We assessed psychosocial factors mediating aphasia recovery using a pictographic questionnaire rating the self-perceived burden of aphasia pertaining to quality of life and life participation. Lastly, we investigated the impact of lesion volume on aphasia recovery. Using a conservative benchmark of a > 7 point increase, 12 patients showed a clinically significant change in AQ. This "change" group did not differ from the "stable" group ($n = 6$) in mean age, education, and initial aphasia severity (p 's $> .2$). The "change" group reported marginally higher life participation satisfaction ($p < .065$) and more frequent technology use ($p = .02$) than those in the "stable" group. Correlational analyses across all patients revealed a significant relationship between AQ percent change across the two time points, and lesion volume and MPO at initial testing (p 's $< .05$). Additional analyses exploring whether these two factors independently contributed to changes in AQ scores revealed that lesion volume better predicts aphasia recovery; smaller lesions correlate with better recovery outcomes. This study demonstrates that PWA can recover long into the chronic period, and lesion volume appears to be a strong predictor of this potential. These findings highlight need for (1) acute stroke care centering on tissue preservation, whether through pharmacologic or procedural interventions minimizing ischemic burden or increased community awareness and education enabling early detection of and response to stroke symptoms; and (2) increased availability of resources such as SLT, aphasia centers, and assistive technologies to enhance long-term participation for PWA.

S258. Effects of Cigarette Smoke and Nicotine on Behavioral, Motor and Memory Function and Nervous System Inflammatory Responses in an Animal Model of HIV-1 Infection

Walter Royal III, Todd Gould, Adem Can and Joseph Bryant. Baltimore, MD

Objective: To examine cigarette smoke (CS) and nicotine (N) effects on cognitive, motor and proinflammatory responses in a HIV-1 transgenic (TG) rat model.

Background: Cigarette smoking has been linked to an increased risk of neurocognitive impairment in HIV infection.

Methods: TG and wild-type (WT) rats (3-6 month old) were either exposed 5 days/week for an average of 6 weeks to smoke from cigarettes containing either a regular amount (0.7 mg) or trace amount (0.03 mg) of N or, alternatively, injected with either 0.5 mg/kg/day of N tartrate or with saline. The animals were then daily transported to a separate facility and examined using the open field test (OFT), rotarod (RR) and novel object recognition testing (NORT). Subsequently, the brains of the animals were removed and frontal cortex and subcortical white matter were examined by PCR for analysis of TNF- α , IL-1 and IL-6 gene expression.

Results: There was an effect of animal genotype on both the RRT ($F=5.47$; $p<0.0001$) and OFT ($F=3.55$; $p=0.018$). In contrast, no treatment effects were noted for neither test and neither genotype nor treatment affected outcomes on the NORT. Levels of all cytokines were higher in non-exposed TG than in WT rat brains. Relative to non-exposed rats, TNF- α gene expression was increased in WT and decreased in TG brains by regular CS and increased in both TG and WT rat brains by exposure to low N smoke and by N alone. IL-6 gene expression levels in TG rat brain was increased by N-free smoke and by N alone. WT rat IL-1 gene expression was increased only by N alone.

Conclusions: Using the described treatment and testing paradigm, chronic exposure to CS and nicotine genotype specific behavioral and motor effects. In contrast, changes in proinflammatory cytokine gene expression can be observed to differ by genotype and type of exposure.

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Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? **Grant support:** Mallinckrodt; Biogen-Idec; Alexion; EMD-Serono; MedImmune

S259. Temporal Trends in Drug Abuse in Young Adults with Acute Ischemic Stroke

Zeeshan Mansuri, Achint Patel, Uvesh Mansuri, Ruchir Goswami, Kinsuk Chauhan, Girish Nadkarni, Zabeen Mahuwala, Tapan Mehta, Narendra Annareddy, Ashutosh Lodhi, Sanjeeva Reddy Onteddu and Sarah Noble. Philadelphia, PA

Objective: We sought to determine temporal trends, thrombolysis utilization and impact on outcomes of pre-stroke drug abuse on acute ischemic stroke (AIS) in young adults (YA).

Background: Drug abuse is an important risk factor for stroke. However, the national epidemiology of drug abuse on AIS outcomes in YA, a particularly vulnerable population, has not been yet delineated.

Methods: We used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) from years 2002-2012. We identified AIS and Drug Abuse as a primary and secondary diagnosis respectively using validated International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes. We defined YA as 18-49 years of age. We used the Cochrane-Armitage trend test and multivariate regression to generate adjusted odds ratios (aOR).

Results: We analyzed a total of 335,893 AIS hospital admissions in YA from years 2002-2012 of which 31,877 (9.49%) had drug abuse. Proportion of hospitalizations with DA increased from 7.38% in 2002 to 10.41% in 2012 ($p_{trend}<0.001$). Utilization of thrombolysis was lower in YA with drug abuse (5.06% vs. 5.64%, $p<0.001$). In-hospital mortality was lower in hospitalizations with drug abuse (aOR 0.89; 95%CI 0.72-1.10) but discharge to specialty care was higher (aOR 1.159; 95%CI 1.082-1.242; $p<0.001$).

Conclusion: We demonstrate that an increasing proportion of YA admitted with AIS have drug abuse. However, drug abuse has a paradoxical association with mortality in YA. Drug abuse is associated with lower thrombolysis utilization and higher discharge to specialty care. The reasons for the paradoxical association of drug abuse with mortality need to be explored in greater detail.

Cerebrovascular Disease

S260. Clinicopathologic Correlation in Lateral Medullary Stroke with Transient Ocular Motor Findings Mimicking Peripheral Vestibular Dysfunction

Jorge C. Kattah, Ali S. Saber-Tehrani, Sigrun Roeber, Meena Gujrati, Martin Sarah, David E. Newman-Toker and Anja K.E. Horn. Peoria, IL; Munich, Germany and Baltimore, MD

Background: Unilaterally decreased horizontal vestibulo-ocular reflex (h-VOR) gain occurs with peripheral vestibular (PV), vestibular fascicle and medial vestibular nucleus (MVN) lesions. The h-VOR is typically normal in lateral medullary strokes (LMS). We describe an unusual LMS with ocular signs mimicking a PV lesion. Initial DWI-MRI suggested caudal MVN infarction; however, nystagmus resolution and improved h-VOR gain favored transient ischemia (TI).

Methods: Clinicopathologic examination of a patient with an acute vestibular syndrome, aphonia and dyspnea. He had right-beating nystagmus and abnormal leftward horizontal head impulse test (h-HIT) confirmed by video-oculography and truncal lateropulsion (TL). MRI showed a left LMS extending rostrally near the MVN. The nystagmus subsided and the h-HIT normalized. Accordingly we hypothesized that the MVN neurons survived the TI and would be intact pathologically. Three weeks later he died and post-mortem analysis of the brainstem was performed.

Results: Neuropathological examination showed a left LMS whose extent matched that seen by imaging. Non-ocular motor signs correlated well with infarcted structures,

including the lateral vestibulo- spinal tract and lateral reticular nucleus responsible for TL. The MVN was spared.

Conclusion: We provide quantitative evidence of transiently abnormal h-VOR and nystagmus due to MVN ischemia surrounding the core of a LMS.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? GN Otometrics loaned us research equipment

S261. MRI Biomarkers of Blood-Brain Barrier Disruption in Patients with Cerebrovascular Disease

Richard Leigh, Christian Dias, Marie Luby and Lawrence Latour. Bethesda, MD

Background: Blood-brain barrier (BBB) disruption occurs in acute and chronic cerebrovascular disease. In the setting of acute stroke, gadolinium leakage into the CSF (GLCSF) can be seen on FLAIR MRI and is often referred to as hyperacute reperfusion marker (HARM). However GLCSF has been described in the absence of acute ischemia. Gadolinium leakage into the brain parenchyma (GLBP) can be measured using dynamic susceptibility contrast (DSC) MRI. The purpose of this study was to compare these two biomarkers in a population of stroke patients.

Methods: Patients needed to have an MRI with DSC imaging prior to the administration of IV tPA and have FLAIR imaging approximately 2 hours later to be included. GLCSF was rated visually on the 2 hour pre-contrast FLAIR thus reflecting leakage of the gadolinium administered during the pretreatment scan. GLBP was assessed with DSC permeability analysis at both time points. The average permeability was calculated within the acute lesion and in the white matter of the contralateral hemisphere. MRIs with poor curve fitting during the permeability analysis ($r^2 < 0.85$) were excluded. Only patients with an acute perfusion deficit were included in the analysis of the acute ischemic lesion and the percent reperfusion was calculated for patients who also had perfusion imaging at 2 hours. Analysis of contralateral BBB disruption was not restricted to patients with perfusion lesions.

Results: Of the 75 patients included in this analysis, 35 had evidence of GLCSF. The percent reperfusion between the two time points was strongly associated with GLCSF ($p=0.003$). In multivariate analysis of with reperfusion, pretreatment GLBP was not associated with GLCSF seen two hours later ($p=0.262$) but GLBP measured at the 2-hour time point was associated with GLCSF ($p=0.032$) detected at that time. GLBP measured in the contralateral white matter was associated with GLCSF classified as diffuse and severe ($p=0.032$).

Conclusions: In acute stroke patients treated with tPA, we found GLCSF was associated with both the amount of reperfusion and the degree of BBB disruption after reperfusion, consistent with prior descriptions of HARM. Diffuse GLCSF, on the other hand, may be due to BBB disruption in chronic white matter disease.

S262. Low Serum Vitamin D Levels in Patients Presenting with Acute Stroke, a Case-Control Study

Elahe Bordbar, Abbas Rahimi Jafari, Mehdi Taghipour, Aliasghar Karimi, Alireza Gholamigarei, Mojtaba Mahmoodi and Seyedeh Azra Shamsdini. Baltimore, MD; Shiraz, Fars, Islamic Republic of Iran; Baltimore, Fasa, Islamic Republic of Iran and Shiraz, Islamic Republic of Iran

Introduction: Stroke is a leading cause of death and disability worldwide. It is a global health problem and more helpful investigations into the prevention and treatment are essential. Vitamin D deficiency is shown to play an important role in hypertension, diabetes mellitus, carotid atherosclerosis, myocardial infarction and congestive heart failure, known as risk factors for stroke. The aim of this study was to evaluate vitamin D status in patients presented with acute stroke compared to the healthy individuals and to determine the association between vitamin D levels and patients' clinical characteristics.

Materials and Methods: The present case-control study included 394 patients (199 men, 195 women), admitted to our center with the diagnosis of acute ischemic or hemorrhagic stroke confirmed by a neurologist. The control group ($N=460$, 255 men, 205 women) was selected among healthy adults who had no previous history of any acute or chronic diseases or any relevant medication usage such as calcium or vitamin D supplements. Clinical relevant data (history, physical examination and laboratory data) were collected; 25-hydroxyvitamin D level was measured by an ELISA test in both groups.

Results: The case and control groups were comparable based on their age and gender. The mean $\pm$ SD age of the patients with stroke was 61 ± 12 years (30-79 y) and the mean $\pm$ SD age of healthy individuals was 60 ± 10 years (40-79). The prevalence of vitamin D insufficiency was high in our healthy population. Vitamin D deficiency was more common among patients with stroke compared to the normal group ($p<0.001$). The patients who smoked had significantly lower levels of vitamin D in their sera compared to non-smoker patients ($p=0.01$). Furthermore, we found significantly lower vitamin D levels in the sera of patients with hemiplegic gaits ($p=0.013$).

Conclusion: Vitamin D deficiency is more common in patients with stroke than normal population; however, further studies are needed to evaluate the mechanism by which vitamin D deficiency affects stroke disease.

S263. Focal Cortical Thinning in Unilateral Asymptomatic High Grade Carotid Artery Stenosis

Randolph S. Marshall, Iris Asllani, MaryKay A. Pavol, Alexander Farfad and Ronald M. Lazar. New York, NY and Rochester, NY

Objective/Background: Cortical thinning has been described in patients with cerebrovascular disease and degenerative dementia, but a relationship between cerebral blood flow (CBF) and cortical pathology has been difficult to establish because such patients typically already have brain infarction or global brain disease that could affect both processes. We examined the association between regionally-

specific CBF and cortical thinning in a cohort of patients with unilateral high-grade internal carotid artery (ICA) disease without history of stroke.

Methods: Twenty-seven patients age 74 ± 11 yrs, 10F, with unilateral ICA stenosis $\geq 80\%$ or occlusion underwent MRI, including high resolution T1 (MPRAGE) and tissue specific pseudocontinuous arterial spin labeling (ts-pASL) to assess cortical thickness and gray matter resting CBF. Cortical thickness was measured in each hemisphere in the primary motor cortex (M1–Brodmann Area 4) and primary visual cortex (V1–Brodmann Area 17) using Freesurfer software (<http://surfer.nmr.mgh.harvard.edu/>). Paired t-tests were used to compare cortical thickness on the occluded versus unoccluded hemisphere in M1 and V1, and gray matter CBF in the occluded versus unoccluded hemisphere.

Results: Cortex was significantly thinner on the side of ICA occlusion in M1 ($t=4.219$, $p=0.0003$), but not in V1 ($t=-1.112$, $p=.276$). Resting gray matter CBF was lower in the occluded hemisphere ($t=4.030$, $p=0.001$).

Discussion: Cortical thinning occurred in motor cortex but not in visual cortex in this cohort of “asymptomatic” unilateral ICA steno-occlusive disease, suggesting a direct pathological impact of asymmetrically reduced flow in the frontal lobes which are supplied by the ICAs. This finding adds specificity to our knowledge of the effects of reduced blood flow on brain pathology. Correlation with cognitive function is warranted.

S264. Dynamic Regulation of DNA Methylation Following Perinatal Hypoxic-Ischemic Brain Injury

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Background: Perinatal hypoxic/ischemic (H/I) brain injury and stroke are significant causes of neurologic disability throughout the lifespan. Abundant data suggests a crucial period of enhanced plasticity following such injuries that may represent an important therapeutic target for improving brain recovery and regeneration. The cellular and molecular mechanisms triggering this period of plasticity remain unclear. We hypothesized that epigenetic mechanisms, specifically DNA methylation, may be important regulators in this process. DNA methylation has long been considered a very stable epigenetic of gene expression, but recent evidence points to a more dynamic nature of this epigenetic mark. DNA is typically methylated at specific sites, most commonly cytosine-guanine dinucleotides (CpGs). The proposed mechanism by which these CpGs become demethylated involves hydroxylation of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) mediated by ten-eleven-translocase enzymes (Tet), followed by excision and replacement with unmethylated cytosine through base excision and repair mechanisms and the Gadd45 family of proteins.

Methods: We used a modification of the Rice-Vannucci model of right common carotid artery ligation followed by hypoxia to induce a hypoxic ischemic injury to the brain. At varying timepoints after injury, we sacrificed the animals and microdissected the dentate gyrus and subventricular

zones and isolated DNA and total RNA. Using quantitative real-time PCR we then examined changes in the mRNA expression of *Tet* and *Gadd45* genes. We measured relative levels of DNA methylation and hydroxymethylation with DNA dot blot analysis and immunohistochemistry.

Results: There was a reduction of 5-hmC expression in the ischemic hemisphere, but in the peri-infarct regions and within the subventricular zone the levels of 5-hmC appeared higher than in the contralesional hemisphere. Tet proteins were upregulated at 24 hours following perinatal H/I.

Conclusions: DNA methylation states are altered by H/I in the perinatal brain in a regionally specific fashion, with upregulation of genes involved in active demethylation of DNA. The presence of these changes within the neurogenic niche suggests a plausible role for DNA demethylation as a regulator of injury-induced plasticity. Future work will focus on further defining the time course of these changes, examining gene-specific methylation changes, and investigating the influence that these changes have on injury-induced neurogenesis.

S265. Modulation of Hippocampal Neurogenesis in the Global Brain Ischemia Model: Effects of p-tyrosol and Fluoxetine

Marina Yu Khodanovich, Alena A. Kisel, Galina A. Chernyshova, Vera I. Smol'yakova, Renata R. Savchenko, Mark B. Plotnikov and Vasily L. Yarnykh. Tomsk, Russian Federation and Seattle

Introduction: P-tyrosol is a small molecule contained in olive oil that has known antioxidant activity with possible neuroprotective properties. Adult neurogenesis is considered one of targets for post-ischemic brain recovery.

Purpose: Investigate the impact of p-tyrosol on neurogenesis in the rat model of global cerebral ischemia and compare it with the effect of fluoxetine that is known to stimulate neurogenesis.

Methods: Four groups of adult male Wistar rats were used: positive controls which underwent global ischemia by transient occlusion of the main branches of the aortic arch ($n=10$); two groups of animals after ischemia with fluoxetine ($n=11$) or p-tyrosol ($n=11$) treatment; and sham-operated animals without vessel ligation as negative controls ($n=10$). Fluoxetine or p-tyrosol was injected intraperitoneally in a dose of 20 mg/kg during 10 days after surgery. Positive and negative controls received saline injections. Half of animals from each group were euthanized on the 11th and 31st day after surgery. To evaluate neurogenesis, brain sections were immunostained for doublecortin (DCX) as a marker of immature neurons. DCX-positive cells were counted in the dentate gyrus (DG) as a neurogenic zone and in non-neurogenic zones of hippocampus outside DG. Groups were compared using two-way ANOVA.

Results: In DG, DCX-positive cell count in positive controls was higher ($p<0.001$) than in other groups on 11th day, and lower ($p<0.001$) than in other groups on 31st day after surgery. No significant distinctions were found between negative controls and both treatment groups except for fluoxetine-treated animals on 11th day after ischemia, which

showed even fewer DCX-positive cells than negative controls ($p < 0.01$). In the non-neurogenic zones, on 31st day after ischemia, the number of DCX-positive cells in positive controls was higher in CA1, CA2, and CA3 hippocampal regions compared to other groups ($p < 0.01$), probably due to migration. The most notable finding was an about four-fold increase of the number of new neurons, mainly in CA1 field, in the p-tyrosol-treated group on 11th day after ischemia.

Conclusions: P-tyrosol and fluoxetine similarly prevented an early pathological increase of neurogenesis followed by exhaustion of a limited stem cell pool in the neurogenic zone of hippocampus after global ischemia. P-tyrosol may induce formation of new neurons in non-neurogenic zones after ischemia thus providing a potential to restore brain damage.

Acknowledgements: Russian Science Foundation (project №14-45-00040) for immunohistochemistry, TSU Competitiveness Improvement Program for animal experiments.

S266. Trends and Outcomes for In-Hospital Ischemic Stroke in Acute Myocardial Infarction from 2002-2012: An Analysis of Nationwide Inpatient Sample Data

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Background: Acute Myocardial Infarction (AMI) and Ischemic Stroke are amongst the major causes of mortality and morbidity in the United States. However, there are limited data on trends and outcomes of in-hospital Stroke events in AMI hospitalizations.

Methods: We reviewed the Healthcare Cost and Utilization Project (HCUP) and National Inpatient Sample (NIS) database from 2002 to 2012 for admission of AMI as a primary diagnosis using International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes 410.xx. In-hospital Stroke was defined as the presence of secondary ICD-9-CM codes of 433.xx-437.1. Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) were identified by ICD-9-CM procedure codes. We used Cochrane-Armitage trend test and multivariate regression to analyze changes in trends and outcomes.

Results: From 2002-2012, a total of 7043113 admissions with AMI occurred and 99338 (1.4%) were complicated by in-hospital Stroke. In trend analysis, overall in-hospital Stroke incidence decreased modestly; however it increased notably in those who received PCI or CABG. Overall, In-hospital stroke was associated with increased odds for in-hospital mortality (Adjusted OR; 95% CI; p-value)(2.83; 2.71-2.96; $p < 0.01$) and discharge to specialized care (4.39; 4.16-4.63; $p < 0.01$). Also, In-hospital mortality trend due to in-hospital Stroke (adjusted OR increased from 2.79 to 3.47; $p < 0.01$) and discharge to specialized care (adjusted OR increased from 3.92 to 6.27; $p < 0.01$) were increased.

Conclusions: In-hospital Stroke is associated with significant mortality and morbidity, and its trend has increased in

patients receiving interventions. In-depth exploration of responsible factors is warranted.

S267. Infection Prior to Stroke—A Risk Factor or Trigger for Stroke?

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Introduction: Infection and inflammation have been implicated as risk factors or even as a potential trigger for stroke. We sought to determine how often first-ever stroke was preceded by an infection in two periods of the Greater Cincinnati/Northern Kentucky Stroke Study

Methods: As per routine in our population-based epidemiology study, all first-ever ischemic stroke (IS), intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) events in 2005 and 2010 in patients ≥ 20 years were ascertained by in-hospital ICD-9 codes 430-436. Potential events had detailed chart abstractions and then physician adjudication to confirm event and etiologic subtype. During chart abstraction, we collected all information regarding infection prior to incident event. WBC upon admission were examined for those with and without infection. We also looked at rates of immunizations preceding stroke.

Results: There were 3877 first ever strokes confirmed within the two study periods in patients 20 years and older; 56% female and 20% black, mean (SD) age 69 (15) years. 424 (11%) were reported to have an infection within the two weeks preceding the stroke event, more likely in the IS (12%) than ICH or SAH (7% and 6%, respectively). 1233 (32%) had an influenza vaccine within the year prior to the stroke and 1034 (27%) a pneumonia vaccine within the five years preceding the stroke. Median (IQR) WBC for those with infection was 9.8 (7.4, 13.4) vs. 8.3 (6.5, 10.7) without infection, $p < 0.001$. There was an increase in any reported infection with increasing age; those 20-44 years reported 9.5% and those 85 years and over 12.8% (test for trend $p = 0.001$). Females reported more infection than males (12.1% versus 9.4%, $p = 0.01$); white stroke patients reported more than black stroke patients (11.7% versus 8.1%, $p = 0.004$).

Conclusion: Infection was not uncommon prior to incident stroke, and was more common preceding IS than ICH or SAH, but was not so common as to suggest a large impact as a potential trigger for stroke.

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Epilepsy

S268. Temporal Coordination of Hippocampal Place Cells Reflects Cognitive Outcome Post Febrile Status Epilepticus

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The coordination of dynamic neural activity within and between neural networks is believed to underlie normal cognitive processes. Conversely, cognitive deficits that occur

following neurological insults may result from network discoordination. We hypothesized that cognitive outcome following febrile status epilepticus (FSE) depends on network efficacy within and between layers CA1 and CA3 to dynamically organize cell activity by theta phase. Control and FSE rats were trained to forage or perform an active avoidance spatial task. FSE rats were sorted by those that were able to reach task criterion (FSE-L) and those that could not (FSE-NL). FSE-NL CA1 place cells did not exhibit phase preference in either context and exhibited poor cross-theta interaction between CA1 and CA3. FSE-L and control CA1 place cells exhibited phase preference at peak theta that shifted during active avoidance to the same static phase preference observed in CA3. Temporal coordination of neuronal activity by theta phase may therefore explain variability in cognitive outcome following neurological insults in early development.

S269. Status Epilepticus in ITU: Epidemiology and 4 Year Follow Up in 39 Cases

Hina Khan and Violeta Sánchez Sánchez. Canterbury, United Kingdom

Background: Status epilepticus (SE) is a potentially life-threatening medical emergency. Often it requires admission to the Intensive Treatment Unit (ITU) for life support and management. Although considerable work is ongoing to establish the optimal algorithm for treatment of SE, to date there has been limited work looking at follow-up of cases. We therefore aimed to review the neurological follow-up of cases admitted to three local ITUs with SE.

Methods: Retrospective Case-Notes review of three ITUs. Cases were identified through the electronic patient record system WardWatcher of all admissions coded for SE from 1st January 2012 to 31st December 2012. Documents inspected included ITU discharge summary, neurology clinic documentation, imaging and EEG results as of 1st March 2016. Data was extracted for: patient identifier information, demographic data, duration of episode and ITU stay, anti-epileptic medication, intubation, imaging and EEG data, likely cause, co-morbidities, date of follow-up and confirmation of diagnosis.

Results: We identified 39 cases admitted to the ITU departments with SE over the period. These included both pediatric and adult cases. Full results are detailed in the poster. There was a significant proportion of cases of new onset SE secondary to focal brain lesions or medical concurrent issues (bacterial meningitis, brain tumours, cerebral infarctions, hypoxic brain injury due to cardiogenic causes, alcohol-related SE and metabolic induced SE). Complex multi-morbidity seemed quite prevalent, with learning disability/neurodevelopmental delay, obesity, sleep apnoea, psychiatric illness and substance misuse being among the most frequent. On neurological follow-up there were a few cases of non-organic seizure disorder identified, however these did not account for most patients with psychiatric comorbidity.

Conclusion: SE is a serious disorder which may have multiple causes. Follow-up of such patients can help elucidate underlying causal mechanisms and guide appropriate

treatment. In cases of multimorbidity a multi-speciality approach is recommended. Early EEG, preferably in ITU can help clarify diagnosis.

S270. Genome-Wide Long Non-Coding RNA Analysis in Mouse Pilocarpine Models of Temporal Lobe Epilepsy

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Long non-coding RNAs (lncRNAs) have received increasing attention for their capacity to modulate epigenetic regulation and their suggested role in various human diseases. Temporal lobe epilepsy is the most common form of partial epilepsy, and epigenetic regulations may take part in the process of epileptogenesis. However, comprehensive profiling of lncRNAs in temporal lobe epilepsy has been limited. Previously, we have proved dysregulation of lncRNAs in the brain of pilocarpine and kainate models.

In this study, we performed an extensive profiling of lncRNAs in the mouse pilocarpine models according to the brain regions and compared them to the control mouse. Hippocampus and cortex, the two main structures of the brain involved in the process of epileptogenesis, were used for microarray analysis (Arraystar Mouse lncRNA Expression Microarray V3.0). A total of 35,923 lncRNAs were analyzed. As a result, 22 and 83 lncRNAs were up- and down-regulated (≥ 2.0 -fold, $P < 0.05$) in the hippocampus of the epilepsy models, while 46 and 659 lncRNAs were up- and down-regulated in the cortex of the epilepsy models. Among these, 5 lncRNAs were up-regulated and 14 were down-regulated in both hippocampus and cortex of the epilepsy models.

This is the first study to identify dysregulated lncRNAs in the hippocampus and cortex of the pilocarpine-induced chronic epilepsy model. We believe that this finding will serve as a stepping stone in the emerging lncRNA research field.

S272. Cognitive, Behavioral and Social Functioning of a Child with Cardiofaciocutaneous Syndrome and Co-Occurring Leukemia: A Case Study

Jessica S. Spat, Hilary Murphy, Eva Keatley, Sarah Mandelbaum, Victoria Stein, Fawad Viqar, Erin Smity-Hyle, Jessica Suzuki, Amanda Bono, Caroline Martinez and Heidi A. Bender. New York, NY

The extant literature describing germline mutations of the Ras/Mitogen-activated protein kinase pathway known as RASopathies has expanded, including greater understanding of its role in childhood cancers. However, given their relative rarity, comparatively less is known about the cognitive, behavioral and social sequelae of children with co-occurring disorders. This case study describes the cognitive, behavioral and social functioning of a four year old child diagnosed with cardiofaciocutaneous syndrome (CFCFS), including craniofacial dysmorphology, congenital heart disease, dermatologic abnormalities, delayed acquisition of motor skills and slowed growth. Additional history included acute

lymphoblastic leukemia (ALL) diagnosed at 15 months of age treated with both chemotherapy and intrathecal radiation. Delayed motor development, profound distractibility and difficulty with peer relationships were also described. An extensive psychoeducational and neuropsychological test battery was administered to document the patient's unique pattern of strengths and weaknesses in order to inform diagnosis and treatment planning. Test results indicated that the child's current intellectual functioning was highly variable secondary to attentional deficits and poor fine-motor control. Despite these limitations, superior scores were received on measures of language, fluid reasoning, learning and memory. A screening of early academic functioning indicated that emergent reading and mathematics skills were also quite advanced for the patient's chronological age. Weaknesses included reduced processing speed, poor sustained attention and concentration, and diminished fine motor dexterity bilaterally. However, the patient did not present with the intellectual capacity disabilities often seen in individuals with CFCS. In terms of etiology, data were difficult to interpret, as prolonged response latency, diminished attention/concentration and reduced interest in peer relationships have been well documented in both individuals with CFCS, as well as in children receiving treatment for ALL. Given the elevated risk of childhood cancer, baseline and serial neuropsychological testing is vital to the clinical management of children with RASopathies in order to partition the cognitive, behavioral and social impact of acute complications (leukemia and related treatments) from the more chronic sequelae related to this rare constellation of disorders. Doing so would help clinicians recommend more targeted and individualized interventions which address the patient's long- and short-term symptoms.

Movement Disorder

S273. Comparison of Effect of Variable Deep Brain Stimulation (DBS) Frequencies on Gait and Balance in Parkinson Disease (PD) Patients with Either Bilateral GPi or STN Stimulators Employing Wearable Wireless Sensors

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Objective: Comparison of effect of variable Deep brain Stimulation (DBS) frequencies on gait and balance in Parkinson Disease (PD) patients with either bilateral GPi or STN stimulators employing wearable wireless sensors.

Background: Gait and balance abnormalities are major problems in PD patients. In this study we quantitatively studied the effect of low (LF-30 Hz), intermediate (IF-80 Hz) and high DBS frequency (HF >120 Hz) on gait and balance using wearable wireless sensors.

Methods: We tested 17 patients (8 bilateral STN and 9 bilateral GPi) employing wearable wireless sensors. Subjects were first tested in their usual HF DBS settings. They were reevaluated at IF, and LF conditions in medication-off state after random selection of the sequence of IF and LF conditions. A minimum of 30-minute wait period was allowed

before evaluation after changing frequencies. All Patients were examined at all frequencies using MDS-UPDRS. Among the gait parameters; UPDRS motor scores, Duration of gait cycle, Stride length, Stride velocity, cadence, double support, gait swing, stance, peak shank velocity, peak arm swing velocity and range of motion of arms were tested.

Results: Data was analyzed using Multivariate analysis of variance test (p value = .0193, Wilks lambda = .68027 with freedom of (20, 174) = 1.8482, Table 1). Motor part of UPDRS score was improved at HF (29) when compared with IF (31) and LF (37). Among the UPDRS motor subtests at HF; arising from chair (0.5 vs 0.58 vs 0.58), gait (1 vs 1.27 vs 1.48), posture (1.41 vs 1.75 vs 1.80) and bradykinesia (1.67 vs 1.95 vs 2.11) were significantly improved as compared to IF and LF. At HF; stride length measured in terms of % of subject height (76 vs 74 vs 75), Peak arm swing velocity (160 degrees/sec vs 151 degrees/sec vs 135 degrees/sec) and Range of motion arm RoM (20 degrees vs 18 degrees vs 17 degrees) were significantly improved. There were no significant difference between stride velocity, duration of gait cycle, cadence, double support, stance, gait swing and peak shank velocity among HF, IF and LF.

Conclusion: Overall HF improved some gait and balance parameters when compared with IF and LF. This improvement in these parameters may translate into a decrease in falls.

S274. Phenomenology and Treatment of Idiopathic Adult-Onset Truncal Dystonia

Debra J. Ehrlich and Steven J. Frucht. New York, NY

Objective: To characterize the phenomenology, natural history and treatment of adult onset idiopathic truncal dystonia.

Background: Focal dystonia is the most common type of adult-onset dystonia, however, apart from the neck, it infrequently affects axial musculature. Additionally, while truncal dystonia is frequently attributed to secondary etiologies such as Parkinsons Disease or neuroleptic exposure, idiopathic adult-onset truncal dystonia has only been previously described in case reports and small case series. We characterize 7 cases of adult-onset primary truncal dystonia and present them within the scope of the existing literature.

Methods: We conducted a retrospective chart review of medical records and patient videos for 7 adult patients with the diagnosis of idiopathic truncal dystonia.

Results: In our group of 7 patients, 85.7% were male and the mean age of onset of truncal dystonia was 47.6 years old. The most common direction of truncal movement was flexion in 57.1%, which was accompanied by lateral pulling of the trunk in 2 patients and right anterior shoulder movements in 1 patient. The dystonic movements occurred only with action in 57.1% and occurred at rest though worsened by action in 28.6%. Dystonic movements of the trunk were improved by use of a sensory trick in 71.4%. Most patients in this case series were refractory to multiple oral medications with 57.1% of patients who showed minimal or no benefit to at least 3 different oral treatments. All 7 patients were treated with trihexyphenidyl,

however only 2 patients exhibited mild improvement while the other 71.4% showed no benefit. Among the 5 patients treated with baclofen, a mild benefit was seen in 2 patients with no benefit in the other 3. A trial of carbidopa/levodopa was used in 3 patients with no improvement. Although all 7 patients were treated with botulinum toxin, only 2 exhibited appreciable functional improvement after injections.

Conclusions: Similar to previous reports of adult-onset truncal dystonia, our results showed that the majority of patients were male, exhibited truncal flexion as the primary direction of dystonic movements, and dystonia was action-induced or worsened by action. The analysis of treatment responses in our case series demonstrated that the majority of patients were refractory to multiple treatments, which illustrates the difficulty encountered in treating this rare but disabling condition and the need to find more effective treatment options.

S275. Myoclonus in Adult Onset Huntington's Disease

Robert Fekete. Valhalla, NY

Background: Chorea is the most common involuntary movement in adult onset Huntington's disease (HD), but rarely myoclonus is the main involuntary movement in adult onset HD.

Introduction: Published reports were evaluated with aim to review possible pharmacotherapies for adult HD related myoclonus.

Methods: Medline was searched for case reports and case series of adult onset HD with myoclonus. References inside publications were also followed.

Results: 8 manuscripts were identified which listed 18 patients. 11/18 were successfully treated with valproate, 4/18 were treated with valproate and a second medication, and 2/18 were treated with clonazepam alone.

Conclusion: In individual case reports and series of myoclonus in adult onset HD, valproate appears to be a successful and well tolerated treatment.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Robert Fekete is a consultant for Lundbeck NA Ltd., Merz Neuroscience, Inc., and Teva Neuroscience, Inc. He receives honoraria from Medlink, Inc. He has served on advisory boards of US WorldMeds, LLC., GE, and Teva Neuroscience, Inc.

S276. Five Year Follow-Up: BMI Increase Is Not Associated with Deep Brain Stimulation in Early Stage Parkinson's Disease

Sarah H. Millan, Mallory L. Hacker, Anna L. Molinari, Maxim Turchan, Amanda D. Currie, Lauren Heusinkveld and David P. Charles. Nashville, TN

Background: Previous studies have suggested that subthalamic nucleus deep brain stimulation (DBS) for Parkinson's disease (PD) causes weight gain. However, a two-year longitudinal analysis of BMI changes in patients with early stage PD showed that there was no significant difference between subjects treated with optimal drug therapy (ODT) and those treated with DBS and ODT. All subjects from the

DBS in early stage PD pilot trial were followed for three additional years to collect longitudinal safety and outcomes data. We present an analysis of the change in BMI from baseline to five years follow-up.

Methods: The DBS in early PD pilot was a prospective, randomized clinical trial (NCT#00282152, IDE#G050016, IRB#040797) that evaluated subjects with early stage PD (age 50-75, H&Y II off medication, treated with antiparkinsonian medications for ≥ 6 months but < 4 years, and without any history of dyskinesias or other motor fluctuations, or dementia). This analysis includes 24 subjects from the pilot trial (DBS+ODT=14, ODT=10) and excludes subjects randomized to ODT who received DBS during the extension period. Height and weight were recorded at each follow-up visit and used to calculate BMI following the conclusion of the study.

Results: There was no difference between the groups for average BMI at baseline (DBS+ODT 31.6 ± 5.1 ; ODT 28.6 ± 3.8 ; $p=0.14$). There was minimal change in BMI from baseline to 60 months for both groups (ODT = $+0.1 \pm 2.9$; DBS+ODT = -0.6 ± 2.9), and this difference between the two groups was not significant ($p=0.60$).

Conclusion: This five-year follow-up analysis suggests that DBS is not associated with weight gain in subjects with early stage PD. Additional studies with larger sample sizes are needed to confirm these findings. The FDA has approved (#G050016) a randomized, double-blind, placebo controlled, multicenter, phase III, pivotal clinical trial evaluating the safety and efficacy of DBS therapy in 280 subjects with early stage PD.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Vanderbilt University receives income from grants and contracts with Allergan, Ipsen, Merz, and Medtronic for research led by Dr. Charles. Dr. Charles receives income from Allergan, Ipsen, Concert, and Medtronic for consulting and education services. There are no conflicts of interest for Sarah H. Millan, Mallory L. Hacker, Anna L. Molinari, Maxim Turchan, Amanda D. Currie, and Lauren Heusinkveld. This work has been supported by: Vanderbilt CTSA grant UL1TR000445 from the National Center for Advancing Translational Sciences (NCATS), NCATS/NIH award UL1TR000011, NIH R01EB006136, Medtronic, Inc., and the Michael J. Fox Foundation for Parkinson's Research.

S277. Treating Orthostatic Tremor with Levetiracetam after Clonazepam Failure

Erin Feinstein, Winona Tse and Steven Frucht. New York, NY

Background: Orthostatic tremor (OT) is an uncommon tremor present only while standing and improves with walking, leaning, or touching surrounding objects, and fully resolves with sitting or lying down. Existing information is limited to case reports and case series, with few effective treatments. Clonazepam was the most commonly prescribed medication in a Mayo Clinic case series of 184 patients with OT. Of treated patients, 24.4% had mild tremor improvement and 15.3% had moderate improvement. 3

patients treated with levetiracetam had no to mild improvement. In a double-blind, placebo-controlled crossover study of 12 OT patients, levetiracetam provided no improvement of tremor or stance time (Hellriegel et al). We report 2 cases of effective symptomatic treatment of OT with low doses of levetiracetam in patients who previously failed clonazepam treatment.

Case 1: 84 year old woman presented with a 2 year history of leg tremors upon standing and a fear of falling while walking. On exam, 25 seconds after standing she felt unsteady with a fine fast palpable leg tremor. Holding the examiner's hand or lightly touching examiner's finger improved her standing stability, allowing her to walk without a fear of falling. Clonazepam was titrated to 0.25 twice daily, though was discontinued after 2 weeks when her symptoms worsened. She restarted levetiracetam, and slowly titrated to 250mg BID with improved tremor control and gait without side effects.

Case 2: 83 year old man with a 2 month history of leg tremors when standing from a seated position, associated with a fear of falling and feeling of eminent falling. Leaning on a wall fully alleviated his tremor and fear of falling. On examination, 15 seconds after standing he developed visible large amplitude leg tremors that disappeared when walking and improved when leaning against a wall. He was unable to tolerate treatment with clonazepam 0.25mg due to excessive somnolence. Treatment with levetiracetam 250mg twice a day modestly improved OT, however he experienced daytime sedation and dizziness. We decreased his evening dose to 125mg with fewer side effects and similar symptom control.

Discussion: Typically, with uncommon diseases, such as OT, the discovery of potential treatments is limited by low disease prevalence, potential for misdiagnosis, and unfamiliarity with the condition and previously attempted treatments. We demonstrate 2 cases in which treatment with clonazepam, the conventional treatment for OT, yielded unsatisfactory results while levetiracetam resulted in functional improvement.

S278. Analysis of the Minimum Data Set in a Long-Term Care Facility – Correlations with Spasticity Diagnosis

William S. Fisher, Taylor Hudson, Maxim Turchan, Amanda Currie, Chandler Gill, Anna Molinari, Fenna Phibbs, Christopher Tolleson, Mallory Hacker and David Charles. Nashville, TN and Chicago, IL

Background: Spasticity is a prevalent movement disorder in residents of long-term care facilities [1]. In this study, the prevalence of spasticity was evaluated in residents of a long-term care facility. These patients were also regularly assessed using the Minimum Data Set (MDS), a standardized, comprehensive assessment of each resident's functional capabilities that assists staff in identifying health problems. An analysis of this data was conducted to identify elements in the MDS that correlate with the presence of spasticity.

Methods: Any resident of the long-term care facility who provided informed consent was eligible to participate in this

IRB-approved study (IRB#090361, NCT01644123). Two neurologists conducted examinations for the presence of spasticity in 39 participants. MDS data was evaluated in patients with (n=12) and without (n=27) spasticity. The significance of the relationship between spasticity and other factors was determined using chi-squared tests of contingency and Mann-Whitney U Tests.

Results: The co-occurrences evaluated on the MDS were stroke, epilepsy, depression, dementia, pain presence/intensity, urinary incontinence, bowel incontinence, age and difficulty with activities of daily living. None of these factors were found to be significantly correlated with the presence of spasticity; however, there was a correlation between spasticity and history of stroke ($p=0.08$). Additionally, there was an inverse correlation found between spasticity and age, meaning spasticity was found more often in younger subjects (95% C.I.: Spasticity = 76.67 years old $\pm$ 2.94 years; Without spasticity = 79.79 years old $\pm$ 5.30 years; $p=0.14$).

Conclusion: Since spasticity is prevalent in residents of long-term care facilities, it could be informative to explore the nature of its relationship with other health factors. This analysis revealed a trend between stroke as well as lower age and the prevalence of spasticity. Although the rest of the conditions evaluated did not achieve clinical significance, a larger sample size may reveal trends and additional study is needed in order to make definitive correlations between the comorbidity of these conditions and spasticity. Further investigation into the relationship between spasticity and other conditions may improve care and quality of life for residents in long-term care facilities.

[1] Currie et al., *Movement Disorders* 2015; 30 Suppl 1: 1432.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Study supported by: Vanderbilt University receives income from grants and contracts with Allergan, Ipsen, Merz, and Medtronic for research led by Dr. Charles. Dr. Charles receives income from Allergan, Ipsen, Concert, and Medtronic for consulting and education services. Dr. Fenna T. Phibbs has done consulting work for Medtronic, Boston Scientific, St. Jude Medical, and Teva. There are no conflicts of interest for William Fisher, Taylor Hudson, Maxim Turchan, Amanda Currie, Chandler Gill, Anna Molinari, Christopher Tolleson, or Mallory Hacker. This work has been supported by Allergan and Merz.

S279. Comparison of Improvement in Swallowing Functions Between Patients with Parkinson's Disease Treated with Rotigotine and Those with Levodopa

Makito Hirano, Chiharu Isono, Hikaru Sakamoto, Shuichi Ueno, Susumu Kusunoki and Yusaku Nakamura. Sakai, Osaka, Japan and Osaka Sayama, Osaka, Japan

Parkinson's disease (PD) affects involuntary movements, including swallowing. Dopaminergic medicines including levodopa improve swallowing functions during the oral phase, mainly associated with voluntary movements, while improvement during the pharyngeal phase remains

controversial. Rotigotine is a dopamine agonist with non-oral administration, a transdermal patch, which may be suitable for dysphagic patients, but its effects on swallowing over the levodopa remain unknown.

In this retrospective study about treatments with rotigotine (2 mg/day) or levodopa (200 mg/day), we objectively evaluated swallowing functions with videofluoroscopic examination (VF) in 13 dysphagic patients with PD (rotigotine/levodopa=7/6) before and 1-2 weeks after treatment. The evaluation was based on the scale established by the Japanese Society of Dysphagia Rehabilitation, which can separately evaluate oral and pharyngeal phases. We also used widely-used measures, Pharyngeal Transit Duration (PTD) and Dysphagia Outcome Severity Scale (DOSS). UPDRS-III was additionally examined.

The results showed that the Japanese scale scores during the oral and pharyngeal phases and PTD, but not DOSS scores, significantly improved ($p < 0.05$, Wilcoxon signed-rank test) in the rotigotine group. By contrast, no measures significantly improve in the levodopa group, but with tendency of improvement. All patients had better scores of parkinsonism after treatment.

In conclusion, despite the small number of patients studied, our findings suggested that rotigotine transdermal patch improved better swallowing functions in patients with PD. Notably, the dose of rotigotine used was equivalent to only 50 mg of levodopa, suggesting that continuous dopaminergic stimulation may be important in swallowing.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Honoraria for lectures.

S280. Baseline Characteristics of STEADY-PD III: A Phase 3 Study of Isradipine as a Disease Modifying Agent in Patients with Early Parkinson's Disease

Kevin Biglan, Jillian Lowell, David Oakes, Karen Hodgeman, Rebecca Rockhill, Brittany Greco and Tanya Simuni. Rochester, NY and Chicago, IL

Objective: To evaluate the efficacy of isradipine 10 mg daily to slow progression of disability in early PD.

Background: Isradipine, a dihydropyridine calcium channel antagonist, is neuroprotective in in vitro/in vivo models of parkinsonism. Epidemiological data suggests a reduced risk of PD with chronic use of dihydropyridines. Our Phase II study found isradipine 10 mg daily to be safe and well tolerated in early Parkinson's disease (PD); a dosage that achieves serum concentrations found to be neuroprotective in animal models of PD.

Methods: The study is a 36-month, Phase 3, parallel group, placebo-controlled study of the efficacy of isradipine 10mg daily in 336 participants with early PD as measured by the change in the Unified Parkinson Disease Rating Scale (UPDRS) Part I-III score in the practically defined ON state. Secondary outcome measures include clinically meaningful measures of disability progression in early PD: 1) Time to initiation and utilization of dopaminergic therapy; 2) Time to onset of motor complications; 3) Change in

non-motor disability. Exploratory measures include global measures of functional disability, quality of life, change in the ambulatory capacity, cognitive function and pharmacokinetic analysis.

Results: The study was funded by NINDS and is being conducted at 55 Parkinson Study Group sites in US and Canada. A total of 336 subjects have been enrolled and there have been 3 premature withdrawals, 11 Serious Adverse Events (all unrelated to study drug) including 1 death. The cohort is 68.5% male ($n=230$) and 89.9% ($n=302$) are white non-hispanic. The mean (SD) age is 61.7 (9.6) years; the total UPDRS is 23.2 (8.6); and the MOCA is 28 (1.4). Enrollment was completed 6 months ahead of schedule with the last subject completing the study in approximately November 2018.

Conclusion: STEADY-PD III is fully enrolled and the population is similar to other early PD clinical trial cohorts. This study represents a unique opportunity to evaluate the potential impact of a novel therapy to slow progression of PD disability and provide clinically meaningful benefits.

Study supported by the NINDS U01NS080818 and U01NS080840.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Kevin Biglan

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Multiple Sclerosis

S281. Immunomodulatory and Neuroprotective Effects of Fingolimod Treatment in Multiple Sclerosis: Patients Modulation of the RAGE Axis

Zohara Sternberg, Channa Kolb, Kailash Chadha, Raphael Nir, Ryan George, Joseph Johnson and David Hojnacki. Buffalo, NY

Background: Multiple sclerosis (MS) pathophysiology involves dysregulation in the RAGE (receptor for advanced glycation end products) system. The interaction between the receptor RAGE and its ligands promotes inflammatory/neurodegenerative processes; whereas soluble RAGE (sRAGE) and endogenous secretory RAGE (esRAGE) isoforms down-regulate RAGE activity.

Objectives: Determine Fingolimod treatment effects on serum levels of sRAGE and esRAGE, and on RAGE ligands, high mobility group box (HMGB)1 and pentosidine.

Methods: 17 Relapsing-remitting MS patients (5 males) with EDSS of 3.6 ± 1.5 were treated with Fingolimod, and the variables were measured at baseline and 6 and 12 months post-Fingolimod treatment, by ELISA method.

Results: Fingolimod treatment of six months increased serum levels of sRAGE (from 2256 ± 165 pg/ml to 2700 ± 123 pg/ml), and esRAGE (from 290 ± 26 pg/ml to 383 ± 35 pg/ml), and reduced serum levels of HMGB1 (from 5359 ± 1531 pg/ml to 2639 ± 825 pg/ml) and pentosidine (from 102064 ± 31754 pg/ml to 75864 ± 26693 pg/ml). Similar results were observed at 12 months.

Conclusion/Relevance: Fingolimod may exert anti-inflammatory effects via upregulation of soluble RAGE isoforms and downregulation of the RAGE ligands. In addition, based on the notion that Fingolimod traverses the BBB and accumulates in the brain, the modulation of the RAGE system in the CNS may be among mechanisms contributing to Fingolimod neuroprotective effects.

S282. Superoxide Dismutase in Blood Plasma of Adrenoleukodystrophy Shows Phenotype Specific Reduction, Additionally Correlating with Cranial MRI Loes Score

Bela R. Turk, Ben Theisen, Mertz Christina, Carol Tiffany, Melissa Rosen, Xiao Hai Shi, Paul Watkins, Richard O. Jones, Joel Marx, Ann Moser and Ali Fatemi. Baltimore, MD

Background: Adrenoleukodystrophy (ALD) is an X-linked peroxisomal disorder, ABCD1 gene dysfunction leading to an accumulation of very long chain fatty acids (VLCFA) which in turn cause oxidative stress and cell death. Clinically ALD presents as multiple phenotypes with no known genotype correlation; A slow progressive spinal axonopathy adrenomyeloneuropathy (AMN), or rapid, deadly central demyelination as cerebral ALD (cALD) amongst others. No identified triggers for phenotype shift from AMN to cALD have been established bar cranial trauma in few cases. Superoxide dismutase (SOD) polymorphisms, an antioxidant enzyme has been associated with cALD. In this study, predictive values of antioxidant parameters including SOD were analyzed in human blood plasma and other tissues.

Method: Total radical antioxidant capacity (TRAP), Glutathione (GLT), Superoxide dismutase (SOD) 1 and 2, prostaglandin E2 and C/EBP homologous protein (CHOP) were measured in ALD patient blood plasma, monocytes, macrophages and fibroblasts.

Results: cALD patients monocytes, blood plasma and fibroblasts and show significantly lower ($p < 0.0003$) SOD activity and TRAP levels than AMN patients, who in turn show significantly lower levels ($p < 0.005$) than healthy controls. Phosphorylated CHOP is however significantly higher in cALD monocytes and macrophages than in AMN or control. SOD activity in cALD inversely correlates with cranial MRI Loes score severity ($p < 0.005$, $r^2 = 0.81$). SOD activity sees a reduction over time in individual patients, sharply dropping to very low activity around cerebral onset.

Discussion: SOD and antioxidant capacity reduction over time is unexpected in tissues undergoing oxidative stress, only active metabolite phosphorylated

CHOP increase showing large increase. Correlation to cMRI Loes score and individual patients over time may support future endeavour of determining prognostic value of SOD in determining cerebral disease onset.

Neuro-Oncology

S283. Motor Axonal Neuropathy During Pembrolizumab Treatment of Metastatic Melanoma

Maria Sepulveda, Eugenia Martinez-Hernandez, Nuria Solà-Valls, Jordi Casanova-Molla and Francesc Graus. Barcelona, Spain

Introduction: Pembrolizumab is a monoclonal antibody directed against the immune checkpoint PD-1 (programmed death-1 receptor) that has improved overall survival in patients with advanced melanoma. The immune activation caused by pembrolizumab may associate with autoimmune side effects but neurological complications other than single cases of myasthenia gravis have not been described.

Methods: We describe a 44-year-old man with metastatic melanoma who developed progressive muscle weakness while receiving pembrolizumab.

Results: Twelve months after starting treatment (10 mg/kg of pembrolizumab every 2 weeks), moderate transaminitis was detected on a routine blood test and, one week later, the patient developed proximal muscle weakness of the four limbs, mainly the left arm and right leg. The neurological examination revealed significant atrophy of the left shoulder girdle and right quadriceps and absent deep tendon reflexes. Cerebrospinal fluid examination demonstrated albuminocytological dissociation, without atypical cells. A spinal MRI showed contrast enhancement of the lumbosacral roots, and a brain MRI was unremarkable. Electrophysiological studies showed normal sensory and motor nerve conduction velocities and amplitudes, no conduction blocks, and no temporal dispersion of compound muscle action potentials (CMAP), with normal latencies of F-waves. Diffuse fibrillation on the four limbs and a reduction in the number of active motor unit potentials was detected by electromyography (EMG). The suspected diagnosis was acute motor polyradiculopathy and pembrolizumab infusions were stopped. Five weeks after symptoms onset intravenous immunoglobulins (0.4 g/kg for 5 days) plus oral prednisone (1mg/kg/day) were started. However, limb weakness progressively worsened, involving distal muscles, symmetrically, with amyotrophy and steppage gait. Two months from onset, ambulation was only possible with bilateral assistance. A new EMG showed marked reduction in the CMAP amplitude of the motor nerves and severe denervation in all groups studied, suggesting diffuse axonal motor damage. The patient was treated with plasma exchange (6 sessions), and two weeks later symptoms stabilized, starting intensive rehabilitation. At the last visit, 4 months from onset of symptoms, the muscle strength had improved in the proximal left arm and right leg.

Conclusion: To our knowledge, this is the first case of motor axonal neuropathy reported in a patient treated with pembrolizumab. The mechanism of action of

pembrolizumab suggests that the cause of the neuropathy may be immune mediated.

Behavioral Neurology

S284. Temporal Trends in Drug Abuse in Older Adults with Acute Hemorrhagic Stroke

Zeeshan Mansuri, Zabeen Mahuwala, Tapan Mehta, Ashutosh Lodhi, Girish Nadkarni, Uvesh Mansuri, Ruchir Goswami, Sanjeeva Reddy Onteddu, Sagar Patel and Sarah Noble. Philadelphia, PA

Objective: We sought to determine temporal trends impact on outcomes of pre-stroke drug abuse on acute hemorrhagic stroke (AHS) in older adults (OA).

Background: Drug abuse is an important risk factor for stroke. However, the national epidemiology of drug abuse on AHS outcomes in OA, a particularly vulnerable population, has not been yet delineated.

Methods: We used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) from years 2002-2012. We identified AHS and Drug Abuse as a primary and secondary diagnosis respectively using validated International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes. We defined OA as ≥ 50 years of age. We used the Cochrane-Armitage trend test and multivariate regression to generate adjusted odds ratios (aOR).

Results: We analyzed a total of 666,758 AHS hospital admissions in YA from years 2002-2012 of which 13,120 (1.97%) had drug abuse. Proportion of hospitalizations with DA increased from 0.95% in 2002 to 2.63% in 2012 (ptrend < 0.001). In-hospital mortality was higher in hospitalizations with drug abuse (aOR 1.042; 95%CI 0.935-1.16) but discharge to specialty care was higher (aOR 1.133; 95%CI 1.003-1.28; $p < 0.001$).

Conclusion: We demonstrate that an increasing proportion of OA admitted with AHS have drug abuse. Drug abuse is also associated with higher discharge to specialty care and increased mortality. The reasons for these trends in this vulnerable population need to be explored in greater detail.

Cerebrovascular Disease

S285. Long-Term MRI Evaluation of Nicardipine for Leucoaraiosis or White Matter Hyperintensities (WMH)

Senna William and Devathanan Gobinathan. Singapore, Singapore

Objective: As WMH is strictly an MRI diagnosis, we followed up and evaluated after a mean of 6 years, patients treated with nicardipine (N= 196) SR 40mg bd and those not administered but under standard care (N= 210) using repeat MRI.

Methods: Radiologists are blinded, even now, to this observational ongoing study started in 2002. Patients with MRI proven leucoaraiosis (using T2 flair 1.5T and same equipment for each subject) were offered nicardipine, a “forgotten” dihydropyridine anti-hypertensive with cerebral

anti-vasospastic action, and a calcium channel blocker. Patients were registered only if they return into two groups – those who persisted on the drug (N=196, SC Ni+) and those who elected standard care (SC) without nicardipine (N= 210, SC Ni-), the majority being under the care of cardiologists or internists. The 1st and 2nd MRIs ranged from 4 to 10 years. Deterioration was graded as $\Delta+$ using an arbitrary scale of grade 1 to 5 for the leucoaraiosis. Even slight deterioration was graded as $\Delta+$ or one grade down. Patients were evaluated in three consecutive cohorts when they returned after sufficient length of years to reduce unknown biasness. Atrophy deterioration ($\Delta A+$), global or regional, was also recorded.

Results: There were no statistical differences in age, sex, HbA1C, BP, antiplatelet usage, number of cases with cardiac stents (evidence of atherosclerotic risk) and use of angiotensin receptor blockers. More patients in SC group, as expected, were prescribed beta blockers, other calcium channel blockers, diuretics and aggressive statin therapy (AST-total cholesterol < 170 mg). There was strong MRI evidence of protection conferred by nicardipine to prevent 1 or 2 grade deterioration ($p < 0.001$ using both X2 and Z2 sample tests). The NNT is 2 for SC Ni+ vs NNT = 11 for SC Ni-. For 1st cohort of 140 patients difference in proportions = 0.70 (CI 0.60-0.92); 2nd cohort of 140 $p_2 - p_1 = 0.73$ (CI 0.62-0.83); 3rd cohort of 126 patients $p_2 - p_1 = 0.76$ (CI 0.6-0.92) and if total of 406 considered, $p_2 - p_1 = 0.73$ (CI 0.60-0.92). An incidental significant finding was AST did not confer protection and clearly accelerated atrophy (NNH=2 in 6 years).

Conclusion: Our MRI based study validates numerous early (1990's) clinical publications that nicardipine remains a unique cerebral vascular di-hydropyridine and should be used widely to prevent WHM or Leucoaraiosis.

Disclosure: nil.

S286. Geospatial Clustering of Patients Presenting to an Emergency Department with Known or Potential Ischemic Stroke

Daniel A. Dworkis and David A. Peak. Boston, MA

Ischemic stroke (iCVA) is common and carries significant morbidity and mortality; rapid identification of potential iCVA and transport to a recognized stroke center are key priorities for prehospital medical, emergency medicine, and neurology services. In an effort to target prehospital iCVA education and consider optimal resource deployment, we describe here a geospatial analysis of the home addresses of all patients presenting over a 36 month period with known or potential iCVA to the Emergency Department (ED) of Massachusetts General Hospital (MGH), a quaternary care stroke center in Boston, Massachusetts (MA). iCVA visits were selected by analyzing initial chief complaints, diagnoses on discharge from the ED and final diagnosis on discharge from the hospital. Patients self-reported home addresses were recorded on arrival to the ED as part of their routine medical care, and addresses in MA were geocoded using the United States Census Geocoder (geocoding.geo.census.gov) matched to the 2010 Census data. Mapping and spatial

analysis was performed with the open source geographic information system (GIS) software QIGS (www.qgis.org). Out of 313,085 total visits to the ED, we identified 3,261 visits for known or potential iCVA, including 2,780 visits from home addresses in MA. Of these, 2,401 were successfully geocoded to census level. iCVA patients were significantly older and more likely to be male than patients visiting MGH for other reasons. At the ZIP code level, iCVA visits generally originated from the north-east of MGH, likely reflecting the presence of other stroke center hospitals to the south-west of MGH. Using GIS based Jenks clustering analysis, we identified 12 census tracts with the highest number of iCVA visits, four of which remained important after adjusting for census tract population. These four census tracts represent hot spots of iCVA visits to MGH, and could be used for further research on community level iCVA risk and/or for targeting future iCVA education campaigns.

S287. Durability Over Time of Strategies to Reduce Door-to-Needle Times in Thrombolysis of Acute Ischaemic Stroke

Aimen Moussaddy, Bing Yu Chen, Mark Keezer, Yan Deschaintre and Alexandre Y. Poppe. Montreal, QC, Canada

Background: Clinical benefits of stroke thrombolysis depend on the timeliness of tissue plasminogen activator (tPA) bolus delivery. We implemented door-to-needle (DTN) time reduction strategies in our hospital's hyperacute stroke management protocol over a period of one month. Our aim was to assess the short- and long-term effects of these modifications on in-hospital delays and clinical outcomes.

Methods: Strategies were implemented in June 2013, including prenotification of stroke team by emergency medical services (EMS) via single-call activation system, priority access to point-of-care glycaemia measurement, use of international normalized ratio (INR) only if anticoagulation suspected, direct transfer from EMS to computed tomography (CT) upon hospital arrival, reserved access to elevator, presence of CT technician available 24/7 and directly accessible by stroke team, administration of tPA bolus and infusion on CT table, regular feedback to nursing and radiology personnel and a newsletter posting fastest times. We included all thrombolysed patients admitted directly to CHUM Notre-Dame Hospital between January 2012 and March 2015, excluding transfers from our hospital's in-patient units or from other hospitals. Included patients were categorized into the pre-modification phase (January 2012 - May 2013) and the post-modification phase (July 2013 - March 2015). The latter was subdivided into the early post-modification phase (July 2013 - December 2013) and the late post-modification phase (January 2015 - March 2015). In-hospital delays and clinical outcomes were compared between patients pre- and post-modification and between early and late post-modification phases.

Results: Forty-eight individuals were treated pre-modification, compared to 58 post-modification. The median DTN time was reduced from 75 (interquartile range:

60-93) minutes to 46 (33-59) minutes ($p < 0.0001$). The median DTN time in the early and late post-modification phases was not different (41 versus 46 minutes, $p = 0.4085$). The proportion of patients treated within 60 minutes of DTN time increased from 29.2% to 75.9% ($p < 0.001$), and this remained unchanged during the post-modification phase ($p = 0.161$). There was no significant change in regards to the in-hospital mortality ($p = 0.447$), intracranial hemorrhage ($p = 0.237$), NIHSS at three months post-stroke ($p = 0.244$), modified Rankin Scale at three months post-stroke ($p = 0.486$) or duration of hospital stay ($p = 0.066$).

Conclusions: We were able to decrease our door-to-needle time for treatment of acute stroke from a median of 75 minutes to 46 minutes by implementing simple modifications, and these improvements persisted over time.

S288. Acute Video-Oculography for Vertigo in Emergency Rooms for Rapid Triage

David E. Newman-Toker, Vahid Eslami, Kathleen B. Quinlan, David S. Zee, Daniel R. Gold, John P. Carey, Ari Blitz, Hardin Pantle, Daniel A. Herzka, William V. Padula, Richard E. Rothman, Richard E. Thompson, Zheyu Wang, Joshua Betz, Jorge C. Kattah, John Hafner, Kevin A. Kerber, William J. Meurer, Cindy Guede, Janet Obear, Jacob Reiss, Daniel McGillicuddy, Rachel Dlugash, Jennifer Houser, Maningbe Keita, Karen Lane, Vanessa A. Llewellyn, Ryan Majkowski, Steven W. Mayo, Nichol McBee, Andrew W. Mould and Daniel F. Hanley. Baltimore, MD; Peoria, Chicago, IL; Michigan, MI and Ann Arbor, MI

Background: Vertigo and dizziness lead to 4.4 million US emergency department (ED) visits annually at a cost of about \$10 billion. Of these, about 3.5% (130,000-220,000) are due to stroke. Roughly 35% of strokes are missed initially, resulting in treatment delays and patient harms. In addition, most of the 1 million patients with peripheral vestibular causes are over-tested, misdiagnosed, and undertreated. Accurate and efficient diagnosis will save lives and reduce costs through prompt and appropriate treatments.

Objective: To compare the impact of a novel, video-oculography (VOG)-guided diagnostic care pathway relative to standard diagnostic care on diagnostic accuracy, resource utilization, costs, treatments applied, and short-term health outcomes.

Design: This study is a multicenter (3-site), patient-level randomized, parallel design (1:1 ratio) Phase II clinical trial of VOG-guided vs. standard care to improve diagnosis and initial management for patients with vertigo or dizziness suspected to be of vestibular cause. We will recruit 226 adult ED patients with a chief symptom of new (< 7 days) vertigo or dizziness and at least one pathologic vestibular eye movement abnormality on pre-randomization VOG testing. We will perform VOG testing on all subjects using a portable device that measures eye movements quantitatively at the bedside. Patients will then be randomized to VOG-guided vs. standard care. In the VOG arm, patients will be diagnosed and treated according to a standard, predefined protocol guided by VOG results using automated, evidence-based decision rules. All patients will undergo follow-up

testing at one week that includes 3-Tesla MRI with contrast, laboratory-based vestibular function tests, and a neuro-otology exam. We will follow patients for 1 month for revisits and readmissions, reviewing records for stroke or related events. The diagnostic reference standard is a final diagnosis adjudicated by a masked, multidisciplinary panel of experts from neuro-otology, vascular neurology, neuroradiology, and emergency medicine.

Conclusion: We will evaluate the accuracy, safety, and efficiency of the VOG-guided rapid triage to differentiate peripheral from central vestibular disorders in ED patients presenting acute vertigo or dizziness.

S289. Segmental Arterial Mediolysis: A Rare Cause of Rapidly Progressive Intracranial Artery Dissections

David A. Lapides, Mazen S. Abusamaan, Jonathan J. Davick, Aditya M. Sharma, James W. Mandell, Kenneth C. Liu, Javier J. Provencio, Bradford B. Worrall and Andrew M. Southerland. Charlottesville, VA

Objective: To report an unusual case of rapidly progressive systemic arteriopathy involving the cerebrovasculature.

Introduction: Cervical and intracranial artery dissections (CeAD/IAD) often occur spontaneously, secondary to pathological degradation and weakening of the arterial wall. Approximately 10-20% of CeAD/IAD patients also show signs of fibromuscular dysplasia (FMD), a non-atherosclerotic, non-inflammatory vasculopathy with a variable but often benign natural history. We present a case of a devastating, rapidly progressive systemic arteriopathy resulting in multifocal dissections including the cervical and intracranial arteries.

Methods: Case report and review

Case Description: A 49yo RH woman presented with abdominal pain and was found to have a transaminitis and myocardial infarction. Abdominal imaging revealed bilateral renal infarcts and severe attenuation throughout the visceral vasculature, including hepatic, celiac, splenic, and bilateral renal arteries. Over a few days, she developed a severe headache, progressive encephalopathy, and T12 paraplegia. MRI brain and cervical spine revealed diffuse subarachnoid and intraventricular hemorrhage with C2-T11 cord compression and ischemia. CT angiogram revealed irregularity of the right vertebral and left subclavian arteries, as well as extensive multifocal irregularity of the intracranial arteries concerning for multifocal dissections. On day seven of her hospitalization, her neurological status further deteriorated with coma and loss of brainstem reflexes. MRI confirmed extensive infarctions involving multiple arterial territories. After family discussion, care was eventually withdrawn and she died. Temporal artery biopsy showed prominent intimal hyperplasia, medial degeneration, with no evidence of vasculitis. Post-mortem examination revealed multiple spontaneous arterial dissections of different ages involving the intracranial, cervical, coronary, and visceral arteries. Histological survey throughout demonstrated intramural hematoma, adventitial expansion, thinning of the medial layer with loss of smooth muscle fibers, and degradation of the elastic laminae.

Discussion: Segmental arterial mediolysis (SAM) typically presents in the 5th decade, manifesting with abdominal pain due to visceral artery dissections and hemorrhage. While it is histologically indistinguishable from fibromuscular dysplasia (FMD) as a non-inflammatory, non-atherosclerotic vasculopathy, the clinical syndrome is more rapidly progressive with a high mortality rate. Neurological deterioration stems from dissections in the cervical and intracranial arteries leading to ischemic stroke or subarachnoid hemorrhage. Further research is needed to better understand the pathogenetic mechanism of this rare entity, and to inform our diagnosis and management of cerebrovascular outcomes.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? BBW: Deputy Editor, Journal Neurology

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S290. Cerebral Vasoreactivity and Inflammation in Treated HIV Infection in Urban China

Joy Chan, Yanling Li, Yinghuan Hu, Huanling Wang, Weihai Xu, Farzaneh Sorond, Richard Price, Taisheng Li and Felicia Chow. San Francisco, CA; Beijing, China and Chicago, IL

Background: Several studies have demonstrated that rates of ischemic stroke are higher in HIV infection. Mechanisms underlying increased cerebrovascular risk in HIV are unknown. Chronic HIV-related inflammation may lead to impaired endothelial function and higher stroke risk. We compared cerebral vasoreactivity (VR), a measure of cerebrovascular endothelial function, between HIV-infected and uninfected individuals and investigated factors associated with lower cerebral VR in HIV, including inflammatory markers and antiretroviral therapy (ART).

Methods: We performed a cross-sectional study of participants from a longitudinal HIV cohort in Beijing, China. Uninfected partners were recruited as controls. All HIV-infected participants were on ART with undetectable plasma HIV RNA level. Cerebral VR, defined as the percentage change in middle cerebral artery mean flow velocity per second of breath-holding, was measured with transcranial Doppler ultrasound. We used mixed effects linear regression models (with a random person effect to account for within-person correlation of bilateral cerebral VR) adjusted for age, sex and candidate covariates chosen by forward stepwise selection to determine the association of HIV and other risk factors on cerebral VR.

Results: We studied 75 HIV-infected and 16 uninfected participants. There were fewer female HIV-infected participants than controls (44 vs 19%, $p=0.031$). Mean age was 41 years. We found no statistically significant difference by HIV status in prevalence of vascular risk factors, including hypertension and smoking. In an unadjusted model, HIV was associated with a trend toward a reduction in cerebral VR by 0.18% (95% CI -0.37% to $+0.02\%$, $p=0.079$). After adjusting for age, sex, coronary heart disease, smoking, statin and antiplatelet/anticoagulant use, the effect of HIV on cerebral VR was modified by total cholesterol ($p=0.015$ for interaction term). For individuals with lower total cholesterol (at or below mean), HIV was associated with significantly lower cerebral VR, whereas this effect was lost as total cholesterol increased. In a model restricted to HIV-infected participants, protease inhibitor use was associated with lower cerebral VR compared with efavirenz (-0.19% , 95% CI -0.41% to $+0.02\%$, $p=0.079$), as was an interleukin-6 (IL-6) >2.0 pg/mL among HIV-infected women (-0.09% , 95% CI -0.17 to -0.01% , $p=0.022$).

Conclusions: Among treated, virologically suppressed HIV-infected individuals with lower total cholesterol, HIV was a risk factor for worse cerebrovascular endothelial function. Further investigation into the potential negative impact of protease inhibitors on cerebral VR and association between greater inflammation and lower cerebral VR in HIV-infected women is merited.

S291. ABCD2 Score Use in Transient Ischemic Attack

Richa Tripathi, Waqar Hafeez, Deepmala Nandanwar, Maysaa Basha and Lakshmi Shankar. Detroit, MI

Objective: To assess the ease and utilization of ABCD2 scoring system in patients with Transient Ischemic Attack (TIA) presenting to an urban emergency department.

Background: The risk of stroke after Transient Ischemic Attack (TIA) is 3% to 10% at 2 days and 9% to 17% at 90 days. The ABCD 2 Score is a risk-assessment tool for the prediction of the short-term risk of stroke after a TIA. The score takes into consideration independent risk factors which include Age, Blood pressure, Clinical features, Duration of symptoms, and Diabetes mellitus; with risk categories assigned as low (0-3), moderate (4-5), or high (6-7). Although the use of ABCD 2 score is supported by American Heart Association/American Stroke Association guidelines to triage TIA patients for hospitalization, it's ease of implementation and actual utility in the decision tree at a busy urban emergency department is unknown.

Method: A retrospective review of patients diagnosed with TIA at an urban emergency room at a university hospital was done from July 2014 to July 2015. About 600 medical records were reviewed and 150 cases of Transient Ischemic Attacks were analyzed for the documentation of the ABCD 2 score and labeled as documented ABCD2 score (dABCD2). The clinical information was also reviewed and a calculated ABCD2 score (qABCD2) was tabulated by investigators. Additional information such as demographics, signs and symptoms and their duration, medications, laboratory findings, imaging studies,

disposition, length of stay (LOS). An intervention was made at 6 months in the form of an educational module disseminated to Neurology, Medicine and Emergency Departments residents. The modules covered topics on TIA, ABCD2 score, and its utility. Post intervention analysis of 150 patients was done to measure for change in frequency and accuracy of dABCD2 score and for change in medical intervention and disposition, as well as patient specific factors including LOS.

Results: The analyzed results so far gives an insight to utilization of ABCD2 score and its impact on variables mentioned above. We do not expect any difference in management of patients solely based on their ABCD2 scores. Further measures and plans will be devised to improve the efficacy of using alternate tools by the physicians for better patient care and resource use.

Conclusion: The use of ABCD2 score does not alter the patient course of treatment and its effect on hospital cost.

S292. Cerebral Infarction Secondary to Air Embolism Following Esophagogastroduodenoscopy

Gary P. Ho, Starane A. Shepherd and Steven K. Feske. Boston, MA

Objective: To report a case of cerebral air embolism resulting in multifocal ischemic infarcts and coma following esophagogastroduodenoscopy (EGD).

Background: Cerebral air embolism is an uncommon cause of ischemic stroke. Air may gain entry directly into the arterial circulation from extracorporeal bypass or decompression barotrauma. Alternatively, venous air may paradoxically enter the arterial circulation through a right to left shunt, such as a patent foramen ovale, or by overwhelming endogenous pulmonary filtration mechanisms. We report a case of multifocal ischemic strokes caused by air emboli following EGD.

Methods: Case Report

Results: A 71-year-old woman with a history of esophageal squamous cell carcinoma treated with chemotherapy and radiation, complicated by multiple esophageal strictures, presented with three days of dysphagia. The patient was taken for EGD under conscious sedation to evaluate for obstruction. Upon initiation of the procedure, she became unresponsive, bradycardic, and hypotensive, requiring intubation. An abbreviated EGD revealed an impacted almond, but this was not removed due to hemodynamic compromise. Computed tomography (CT) scan of the brain demonstrated pneumocephalus most prominent in the sulci of the right hemisphere. Chest CT showed pneumomediastinum. Brainstem reflexes, including pupillary light response, were intact. She was unresponsive to voice and had stereotyped, non-purposeful movements to noxious stimuli. Following transfer to a tertiary care center, the almond was removed by EGD. Magnetic resonance imaging (MRI) of the brain showed areas of diffusion restriction in both cerebral and cerebellar hemispheres and right pons. Due to her severe condition on arrival, hyperbaric oxygen was not administered. The following morning, forced downgaze was noted. Repeat CT showed right-sided cerebral edema,

effacement of the right frontal horn, and 3mm of midline shift. Hypertonic saline and mannitol were given. A trans-thoracic echocardiogram showed no evidence of a patent foramen ovale. She remained comatose, and died shortly after ventilatory support was withdrawn. Although the mechanism of the paradoxical emboli remained unclear, insufflation of the esophageal lumen probably allowed air to enter the venous system through scarred and friable mucosa. In the absence of an intracardiac shunt, a large enough quantity of air may have been sufficient to overwhelm endogenous pulmonary filtration mechanisms, allowing access to the arterial circulation. Alternatively, she may have had an undetected PFO or pulmonary arteriovenous malformation.

Conclusions: Our case highlights paradoxical air emboli following an endoscopic procedure as an unusual cause of ischemic stroke.

S293. Door-To-Needle Times for IV tPA in Acute Ischemic Strokes and Stroke Mimics and Related Complications

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Objective: We aimed to compare Door-to-Needle (DTN) time in treatment of stroke mimics (SMs) and acute ischemic strokes at our institution and identify complications associated with SMs treated with intravenous tissue Plasminogen Activator (IV tPA).

Background: There is ample evidence supporting improved outcomes with early IV tPA administration. Quality improvement initiatives aim to maximize efficiency in order to reduce door-to-needle times for eligible patients. This may lead to increased rates of IV tPA given to SMs. The risk of complications with thrombolytic treatment for SMs appears to be low; yet there remains concern for IV tPA associated adverse effects.

Design/Methods: We retrospectively reviewed charts of all patients treated with IV tPA for acute ischemic stroke at our institution during the year 2014. SMs were defined as patients who did not have findings consistent with acute stroke on MRI/CT head or were not diagnosed as acute stroke/TIA by stroke neurologists. We compared baseline characteristics, clinical outcomes and DTN times between SMs patients and patients discharged with a diagnosis of acute ischemic stroke/TIA. IBM statistical analysis tool SPSS was used for data analysis, considering P value of <0.05 as statistically significant. T-test and Mann-Whitney U test was used for comparison of variables.

Results: 67 cases were treated with IV tPA during the study period (11 SMs and 56 Acute Ischemic Stroke, 16.4% and 83.6% respectively). Their mean DTN time was 57 minutes in acute ischemic strokes and 67 minutes in SMs ($P > 0.23$). 7% of patients diagnosed with Acute Ischemic Strokes/TIA developed symptomatic ICH and none of the SMs cases developed ICH ($P > 0.36$). There were no cases of angioedema reported.

Conclusion: There was no significant difference in DTN time between SMs and Acute Ischemic Strokes at our

institution and even though there were no symptomatic ICH cases among SMs treated; the difference was not statistically significant. Administration of IV tPA seems to be safe in SMs. As such, our data further supports the rapid administration of IV tPA to eligible patients presenting with suspected AIS.

S294. Temporal Trends and Outcomes of Intracerebral Hemorrhage in Cirrhotic Patients

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Background: Intracranial Hemorrhage (ICH) is a feared complication in patients with cirrhosis. The incidence of ICH has been on the rise leading to increased hospital admissions in the US. We sought to determine the trend of ICH in cirrhotic patients over the period of 2002-2012.

Methods: Data from the Nationwide Inpatient Sample (NIS) and Healthcare Cost and Utilization Project (HCUP) were (was?) analyzed for years 2002-2012. Hospitalizations with ICH were identified using International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes 431.xx-432.9 as a primary diagnosis. Cirrhosis was defined by the presence of previously validated ICD-9-CM codes in secondary diagnosis fields. Cochran-Armitage trend test and multivariate regression models were used for analysis.

Results: There were a total of 769,221 ICH hospital admissions during the years 2002-2012. Of these 10,603 (1.38%) patients had cirrhosis. On temporal trend analysis, the proportion of patients with cirrhosis increased from 1.05% in 2002 to 1.81% in 2012 ($p < 0.001$). The proportion of in-hospital mortality was higher among cirrhotic patients 34% vs. 28% ($p < 0.001$). Even after adjusting for confounders and co-morbidities, patients with cirrhosis had higher odds of in-hospital mortality (OR 1.79; 95% CI 1.55-1.94; $p < 0.001$). In addition, the median length of stay was 7 days (cirrhosis) vs. 5 days (non-cirrhosis) ($p < 0.001$) and the median cost of hospitalization was 17074\$(cirrhosis) vs. 11494\$(non-cirrhosis)($p < 0.001$).

Conclusion: The burden of ICH is increasing in cirrhotic patients and associated with worse outcomes. Factors for this temporal change could be multifactorial, and this may continue to rise over the time. Further studies are warranted to identify possible factors and preventive strategies.

S295. Embolic Stroke and DVT in a Patient with May-Thurner Syndrome and Homozygous PAI-Gene Polymorphism

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May-thurner syndrome is a condition where the left iliofemoral vein is compressed by the crossing right iliac artery, commonly leading to left deep venous thrombosis (DVT), but rarely can manifest as right sided symptoms. Systemic anticoagulation may not be adequate to prevent thrombus formation. The anatomical variant is found in up to 20% of the population but responsible for only 2-3% of DVT

cases. Prior reports showed a significantly higher incidence of thrombotic events in patients with this syndrome.

A 51-year-old male with no other medical history presented with right-sided hemiplegia and global aphasia of unclear onset time. Intravenous alteplase was not administered as patient was outside of time window. CT head showed hypodensities in the territory of the left middle cerebral artery and head CT Angiogram (CTA) showed distal left M1 occlusion. He was found to have a patent foramen ovale (PFO) as well as a right popliteal DVT. Due to risk of hemorrhagic transformation with systemic anticoagulation, an inferior vena cava (IVC) filter was placed and anticoagulation was deferred. Two days later, he developed new-onset hypoxia and the subsequent chest CTA revealed bilateral pulmonary emboli. He was then started on systemic anticoagulation to limit progression of PE. He underwent PFO closure and was found to have massive clot burden extending from the right iliac vein to IVC and the IVC filter was completely filled with clot. CT abdomen and pelvis was obtained and revealed no signs of malignancy but showed complete occlusion of bilateral internal iliac veins and partial occlusion of the external iliac veins. The patient underwent an Angiovac procedure for clot removal during which the left iliac vein demonstrated extrinsic compression with marked collateral filling, compatible with May-Thurner syndrome.

The patient underwent hematologic workup which revealed homozygosity of PAI-1 4G allele. The 4G allele is associated with increased PAI-1 plasma activity levels and confers a mild risk for venous thromboembolism in individuals having no other thrombophilia. In individuals with other thrombotic risk factors, this genotype confers a significant risk for venous thromboembolism.

We report a rare case of May-Thurner syndrome in a homozygous PAI-1 4G individual who presented with an embolic L middle cerebral artery stroke. He was initially found to have contralateral (right popliteal) DVT with subsequent clot burden progression despite systemic anticoagulation, and ultimately required angiographic clot removal.

S296. Do Language Barriers Cause a Delay in IV t-PA Treatment in Acute Stroke?

Hugo J. Aparicio, Shefali Dujari, Helena W. Lau, Judith Clark, Thanh N. Nguyen, Viken L. Babikian, Carlos S. Kase and Rafael J. Romero. Boston, MA

Background: Limited English proficiency (LEP) and English spoken as a non-native language may limit a patient's ability to speak or understand English at a level sufficient to communicate effectively with healthcare providers. We hypothesized that patients with language barriers presenting with acute ischemic stroke would experience a delay in acquisition of initial brain imaging and prolonged door-to-needle (DTN) times for administration of IV tissue plasminogen activator (t-PA).

Methods: Electronic medical records were reviewed to determine LEP status on all patients who received IV t-PA in the emergency department (ED) of a safety-net academic medical center in Boston, MA. LEP was defined as a

language preference other than English, use of a professional healthcare interpreter, or ad hoc interpretation by a family member or bilingual staff. We abstracted and compared data on age, sex, race, presentation during work day hours (Mon-Fri, 7AM-7PM), stroke severity (by NIHSS), blood pressure, time last known well, time of head CT (HCT), and DTN times. Door-to-HCT and DTN times for LEP patients and fluent English speakers were compared in crude and adjusted models controlling for demographic factors, NIHSS, blood pressure, arrival during work day, and year.

Results: Between January 2009-June 2015, 120 patients presenting with acute stroke received IV t-PA in the ED (44% female, mean age 65[SD+16] years, mean DTN time 69[SD+32] minutes). The proportion meeting LEP criteria was 27.5%, speaking preferred languages of Haitian Creole (27%), Portuguese Creole (24%), Spanish (21%), and other (28%). LEP and non-LEP patients were similar by age, sex, NIHSS, work day arrival, blood pressure, and pre-hospital delay ($p=n.s.$). DTN times were longer for LEP compared to non-LEP patients (77[SD+36] and 66[SD+30] minutes, $p=0.07$), reaching borderline significance. One outlier (LEP patient, DTN time 186 min) was removed for the analysis using the adjusted model. LEP status was associated with increased door-to-HCT time, causing a 6 minute delay (95% CI 0.5-11.5 minutes, $p=0.03$), and a delay in DTN time of 11.6 minutes (95% CI -0.5-24 minutes, $p=0.06$), after adjusting for covariates.

Conclusion: In the setting of acute stroke, language barriers were associated with a delay in initial imaging acquisition. We found longer DTN times for patients with LEP in comparison to non-LEP patients, with trending significance. Research using a larger sample size or a multi-center study is needed to clarify the role of LEP as a barrier for acute stroke care.

S297. Neurosyphilis and Antiphospholipid Antibodies in a Patient with Moyamoya Syndrome

Roman Kassa, Gauhar Chaudhary and Jessica Lee. Lexington, KY

Background: Moyamoya is a progressive occlusive disease of the distal internal carotid arteries and proximal middle and anterior cerebral arteries.

Objectives: To describe antiphospholipid antibodies and neurosyphilis in association with Moyamoya syndrome.

Methods: Single case report.

Results: We report a case of a 26 yo Caucasian male who presented with acute onset of left hemiparesis and dysarthria. Vascular risk factors included smoking and history of DVT. Exam revealed left hemiparesis, arm > leg and dysarthria. CT head without contrast showed no areas of hypodensity or hyperdensity. CT angiography revealed irregular lumen of the right supraclinoid internal carotid artery, right anterior cerebral artery A1 segment and bilateral middle cerebral arteries M1 segments, consistent with Moyamoya syndrome. MRI head showed foci of restricted diffusion in a watershed distribution over the right cerebral hemisphere. Catheter angiography showed severe stenosis of the supraclinoid segment of the right internal carotid artery with pial

collaterals in the lenticulostriate branches of the distal posterior and anterior cerebral arteries as well as mild narrowing of the supraclinoid left internal carotid artery. Routine laboratory tests were normal. Anticardiolipin antibodies IgM and IgG were elevated. Lupus anticoagulant, ANA, cANCA, pANCA and Factor V Leiden mutation were negative. Protein S, protein C, antithrombin and prothrombin time were within normal limits. MHA-TP was reactive; CSF VDRL was also reactive (1:2). Patient was treated with penicillin G 24 million units/day for 14 days and was also started on ASA. Repeat catheter angiogram 2 months later showed interval worsening of the right supraclinoid internal carotid artery stenosis. Patient underwent encephaloduroarteriosynangiosis (EDAS) for the treatment of right Moyamoya.

Conclusions: Various hypotheses for the pathogenesis of Moyamoya syndrome have been proposed, including autoimmune disease. Antiphospholipid antibodies may be associated with vascular endothelial or subendothelial damage. Anticardiolipin antibodies have been implicated in the acute occlusion of narrowed intracranial vessels. Interestingly, the patient had been on immune suppressive therapy for three years due to plaque psoriasis, another autoimmune condition. Whether or not this led to expedited development of neurosyphilis is unclear. Narrowing of proximal portions of internal carotid artery and middle cerebral artery from neurosyphilis compounded by predilection for thrombosis from antiphospholipid antibodies in our patient may have accelerated the natural course of Moyamoya appearance.

Epilepsy

S298. Comparison of Serial Electroencephalography in Creutzfeldt-Jakob Disease and Voltage-Gated Potassium Channel Autoimmune Encephalitides

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Background and Purpose: Differentiating the family of Voltage-Gated Potassium Channel antibody associated Autoimmune Encephalitides (VGKC AE) and Creutzfeldt-Jakob Disease (CJD) can be vitally important in the evaluation of rapidly progressive dementia. EEG is commonly used as a diagnostic tool. EEG abnormalities feature among diagnostic criteria for CJD and AE. While MRI findings in some cases of VGKC AE have been shown to be similar to CJD, studies comparing EEG findings initially and over time have yet to be performed. Here we describe serial EEG findings in patients with definite CJD and seropositive VGKC AE.

Methods: Retrospective review of clinical data and EEG recordings in autopsy confirmed CJD and seropositive VGKC AE patients treated at two tertiary medical centers over a seven year period. Two board-certified epileptologists blinded to patient diagnoses performed standardized review of initial and final EEG recordings.

Results: Nine patients with definite CJD (5 female; 8 sporadic, 1 familial, median age 65) and nine patients with seropositive VGKC AE (1 LGI1; 6 female, median age 67, median titer 0.24 nmol/L) were identified. Initial EEG

was performed after a median of 9 weeks of symptoms (10 weeks in CJD, 8 weeks in VGKC, no significant difference (NS)). Fourteen patients underwent repeat EEG (8 CJD, 6 VGKC), the final EEG occurring a median of 10.5 weeks after symptom onset (10 weeks in CJD, 11.5 weeks in VGKC, NS). Initial EEG demonstrated periodic sharp wave complexes (PSWCs) in 4/9 CJD patients and 0/9 VGKC patients (NS), and on final EEG 4/6 CJD and 0/8 VGKC patients ($P=0.02$). Focal slowing was seen in 7/9 CJD and 5/9 VGKC patients initially (NS), but 6/6 CJD and 2/8 VGKC on final EEG ($P=0.01$). Epileptiform discharges were noted initially in 5/9 CJD patients and 2/9 VGKC patients (NS), and on final EEG in 4/6 CJD and 1/8 VGKC (NS).

Conclusions: The presence of PSWCs, well-defined in CJD, was a specific initial finding in this group. Repeat EEG did not increase the yield of identifying PSWCs. Epileptiform discharges and focal slowing were common initial findings in both CJD and VGKC AE. Further analysis of EEG characteristics and comparison at different times in the disease course is necessary to better understand its use as a diagnostic tool in assessing patients with rapidly progressive dementia.

Movement Disorder

S299. An Updated Flowchart for the Diagnosis of Chorea

Ruth H. Walker. Bronx, NY and New York, NY

Background: Chorea is a common movement disorder, the etiology of which is rarely identifiable from its appearance. The identification of genetic causes for some of the inherited choreas has facilitated their diagnosis, in addition to increasing the spectrum of phenotypes for other genetic disorders in which chorea may occur less frequently. A number of clues in the family and medical history, clinical examination, and laboratory findings, may inform the diagnosis. Whilst we often consider these factors simultaneously when evaluating the patient with chorea, there is a need for an algorithm to generate consideration of some of the rarer etiologies.

Methods: I present an updated version of the flowchart, initially developed and presented eight years ago, to facilitate the diagnosis of patients with chorea. I highlight the various factors which may facilitate making the correct diagnosis, and the appropriate testing to consider depending upon previous test results. These include inheritance patterns, additional neurological and non-neurological clinical features, neuroimaging results, routine and specialized laboratory testing.

Results: The flow chart is presented as a poster, and conference attendees are encouraged to comment upon and amend it in the light of additional information from their own experience.

Conclusions: The list of differential diagnoses of chorea is ever-evolving with advances in the molecular biology of movement disorders. Recent additions include chorea due to mutations of C9ORF72, ADCY5, and RNF216, and due

to auto-antibodies, in both paraneoplastic and non-paraneoplastic settings. I present an updated algorithm which is open to further development in the light of new knowledge. This flow chart does not necessarily indicate the temporal course of the diagnostic work-up of chorea, but should be used a guideline to generate the consideration of various clinical entities in light of the available information.

S300. Dried Blood Spot Glucocerebrosidase Measurement Is Reliable in Controls When Adjusting for White Blood Cell Count

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Background: The glucocerebrosidase1 gene (*GBA1*) encodes the lysosomal enzyme glucocerebrosidase (GCase), which has markedly reduced activity in Gaucher disease. Heterozygous mutations of the *GBA1* gene are the most commonly known genetic risk factor for Parkinson disease (PD), and reduced peripheral GCase activity has been shown to be a possible marker for PD, both in *GBA1* mutation carriers as well as in non-*GBA1* mutation PD. Further, GCase activity may be a pharmacologic target in treatment of *GBA1* mutation PD. However, the reliability of GCase activity across multiple samples has not been evaluated. Herein, we assess the reliability of GCase activity in a control group and determine the relationship between two methods of measuring GCase activity, dried blood spot (DBS) vs. plasma.

Methods: Both DBS and plasma samples were collected from 10 controls over 10 days (100 total samples) for assessment of GCase activity and white blood cell count (WBC) at the time of blood draw. GCase activity was assessed using tandem mass spectroscopy (MS/MS). The stability of GCase activity was quantified and the relationship between GCase activity when assayed using DBS vs. plasma was measured. Random intercept mixed effect models were constructed and a post estimation of intraclass correlation coefficients (ICC) were utilized.

Results: Reliability of DBS GCase activity was poor when participants were used as a random effect (ICC=0.22, 95%CI: 0.08-0.50). However, reliability was strong (0.71, 0.43-0.89) when WBC was added to the model as a random effect. In assessing the relationship between DBS and plasma GCase activity, an increase of 1 umol/L/h in DBS GCase activity is associated with an increase of 0.08 umol/L/h in plasma GCase activity (b=0.08, 95%CI: 0.03-0.14).

Conclusions: *DBS reliability:* Among 10 controls in a test-retest sample occurring over 10 days, we demonstrate that the reliability of GCase activity in DBS is good when accounting for WBC at the time of blood draw. As approximately 50% of the GCase activity may be present in white blood cells, it would be expected that WBC accounts for variability in total GCase activity. An assessment of reliability of GCase activity in plasma is ongoing. *DBS vs. plasma:* The preliminary results provide an estimated linear

relationship between two different methods of assessing GCase activity (DBS and plasma).

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? OA Bodamer: research support and honoraria for lectures from Genzyme and Shire. S. Bressman: US WorldMeds, consulting.

Multiple Sclerosis

S301. Multiple Sclerosis with Hypothalamic Involvement: A Cold Diagnosis

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Objective: Increase awareness of hypothalamic dysfunction as a potential, yet uncommon manifestation of multiple sclerosis (MS).

Background: MS is a common immune-mediated demyelinating disease of the CNS. Hypothalamic involvement has been confirmed by neuropathological studies; however reports of symptomatic hypothalamic dysfunction due to MS are limited.

Case Description: A 46 year old wheel-chair bound, African American male, managed on dimethyl fumarate for a history of MS, presented with worsening weakness and fatigue marked by refractory bradycardia, hypotension, and hypothermia (91.0 F). Physical examination lacked signs of infection or new focal neurological deficits. He was initially treated in the ICU with vasopressors, warming blankets, and empiric antibiotics for presumed sepsis. Investigation for adrenal insufficiency was initiated after sepsis work up failed to identify an infectious source, and there was no clinical improvement after two days. Serum AM cortisol level was 7.6mcg/dL. Functional adrenal glands were indicated by a pretest cortisol of 11.9mcg/dL, increasing to 24.1mcg/dL an hour after cosyntropin administration. Clinical suspicion for adrenal insufficiency as the etiology of severe malaise and hypotension remained. Persistent hypothermia made hypothalamic dysfunction strongly suspected as the underlying cause. Further pituitary function tests revealed a low ACTH <1.1pg/mL, prolactin 3.1ng/mL and growth hormone 0.10ng/mL while TSH 4.16mIU/mL, FSH 3.7mIU/mL, and LH 5.9mIU/mL were normal. With a past medical history of MS, brain MRI was obtained in an attempt to confirm hypothalamic MS involvement. MRI demonstrated multiple foci of abnormal enhancement consistent with active demyelinating plaques, however none within the hypothalamus. Maintaining a strong clinical suspicion for hypothalamic MS, and given the low sensitivity of imaging studies to identify such lesions, methylprednisolone was administered for five days. Hemodynamic instability rapidly resolved while temperatures increased gradually. Upon discharge, the patient completed a six week prednisone taper. Marked clinical improvement was evident 7 weeks post hospital discharge, as temperature and heart rate normalized, and he endorsed more energy, strength and clarity of thought than he had over the past 1 1/2 years.

Conclusion: Hypothalamic involvement of MS has gained recognition in neuropathological studies yet reports

of symptomatic hypothalamic dysfunction are limited. Signs and symptoms of adrenal insufficiency are nonspecific yet concomitant hypothermia, in the absence of sepsis, should prompt a consideration of hypothalamic dysfunction. Absence of MS lesions on brain MRI should not preclude a diagnosis of hypothalamic MS, while clinical response to steroids may be diagnostic.

S302. Helping MS Patients Find Their Purpose in Life: A Pilot Study of the Effect of Participation in an Online Community

Laura Anzaldi, Alexis Adams-Clark and Adam Kaplin. Baltimore, MD

A person's sense that their life has meaning and that they have the ability to make and achieve future goals has been associated with a number of positive neurologic health outcomes, although it is not clear whether this relationship is causative or merely a correlation. In an effort to begin to test this relationship we first set out to see if an individual's purpose in life (PIL) can be increased through an intervention. In this pilot study, we (1) looked at the effect of an online Multiple Sclerosis (MS) support network (myCounterpane.com) on PIL and (2) tested the feasibility of using an integrated survey with feedback system to measure PIL. Sixty-seven myCounterpane users were consented to the study between January 2015 and January 2016, though the availability of longitudinal PIL survey data was available on a subset of 29 users with multiple sclerosis that was ultimately analyzed. We found that, among MS patients who were able to see feedback from their prior responses, experienced members of myCounterpane were more likely to have an increase in their PIL ($+12 \pm 4$ SE) over the study period while new members of myCounterpane were more likely to experience in their first 2 months a decrease in their PIL (-10 ± 5 SE) ($p = 0.005$). We also found that with the integrated survey system, 49.3% of all consented participants completed more than one survey, and the implementation of a feedback system did not significantly improve response rates ($32.3 \pm 29.0\%$ without feedback vs. $24.9 \pm 21.7\%$ with feedback; $p = 0.238$). Our findings imply (1) there is an adjustment period associated with joining a support group, though eventually such an environment benefits PIL, and (2) the integrated survey system provides a convenient means to assess PIL in members of MCP, however alternate strategies or implementations of feedback should be considered to increase response rates and retention.

S303. The Pharmacokinetics of Lipoic Acid at Baseline and 48 Weeks in Secondary Progressive Multiple Sclerosis Patients

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Lipoic acid (LA) is a water and fat soluble oral anti-oxidant with anti-inflammatory properties. It has demonstrated benefit in animal models of multiple sclerosis (MS) (Chaudhary Journal of Neuroimmunology 2011) and is being evaluated for MS relapse prevention and neuroprotection.

There are relatively few data on pharmacokinetics (PK) in elderly populations, and changes in LA pharmacokinetics over time. The current study gives results on PK data at baseline and again at 48 weeks in a group of patients with secondary progressive MS (SPMS) enrolled in a randomized placebo controlled trial of LA.

PK blood draws were conducted at the baseline visit and 48 weeks. Patients arrived in the fasted state for the prior 10 hours, and a pre-dose level taken. Patients then ate a meal immediately followed by 1200mg LA. Additional blood draws occurred at 30, 60, 90, 120, and 240 minutes post dose. Blood was allowed to clot at room temperature, serum separated by centrifugation, and stored at -80°C until analysis by mass spectrometer.

Of the 54 randomized patients, 27 patients took at least 1 dose of LA and were included in PK analysis. Average age was 57.9 (SD 6.7) years, 59% were female, and 96% Caucasian. Average disease duration was 30.9 (SD 9.3) years and median Expanded Disability Status Scale 5.5. Mean baseline peak concentration (C_{Max}) was 2892 ± 2203 nanograms/milliliter with no significant difference at 48 weeks. While T_{max} was not calculated, the largest proportion had C_{max} values at times later than previously reported T_{max} values, at baseline and 48 weeks. Subjects demonstrated $>80\%$ compliance by pill counts. LA achieved blood levels comparable with those previously reported. Four (7.8%) patients taking LA terminated early (1 each of glomerulonephritis, testicular cancer, renal failure, MRI intolerance). Adverse events were comparable between study arms (81 in LA, 69 in placebo, $p=0.37$) with significantly more GI upset ($p=0.004$) and fewer falls ($p=0.03$) in the LA cohort.

The significance of this data is that it adds the largest set of MS patient-specific PK data on LA to the existing information regarding the safety and reliability of LA, and indicates stability in the bioavailability of orally administered LA over 48 weeks of administration, data which will be useful for further study of LA in MS populations.

Support: Support: Dept. Veterans Affairs (B7493-W), NIH (UL1TR000128), and Pure Encapsulations, Sudbury, MA.

Cerebrovascular Disease

S304. The Utility of INR to Predict Ischemia in Patients on Warfarin

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Background: Stroke can occur in patients on warfarin despite anticoagulation. A therapeutic INR is typically defined as 2-3. Patients with low INRs should theoretically be at greater risk of an ischemic event, and those therapeutic at lower risk; however data is scarce regarding the utility of INR to predict ischemia over ischemic stroke mimics in patients on warfarin presenting with acute neurologic symptoms.

Objectives: This study was designed to evaluate the association between INR and likelihood of ischemic stroke in patients presenting to the Emergency Department with

acute neurologic symptoms who were on warfarin prior to admission. We further evaluated the predictive value of INR in determining the likelihood of ischemic stroke.

Methods: Patients were identified using the acute stroke registry at our Primary Stroke Center from January 2013 to December 2014. All adult patients undergoing evaluation for acute stroke with prior documented use of warfarin and an INR level at presentation were included. Data were collected regarding patient demographics, medical comorbidities, stroke severity, reason for anticoagulation, and laboratory studies including INR. Student's t-tests and chi square analysis were used to evaluate factors associated with increased likelihood of ischemia (stroke or transient ischemic attack) versus mimic. Significant results were entered into a multivariable regression analysis. Sensitivity and specificity analyses were conducted to determine the positive predictive value of INR for ischemic stroke risk.

Results: 116 patients were included; 46 were diagnosed with ischemia, 70 were diagnosed as mimics. 75% of patients were on warfarin for atrial fibrillation versus 25% for venous thrombosis. There was a significant difference in mean INR for ischemic patients versus mimic patients (1.7 (subtherapeutic) versus 2.8 (therapeutic); $p < 0.001$). In multivariable analysis, subtherapeutic INR ($p < 0.001$) and atrial fibrillation as an indication for anticoagulation ($p = 0.014$) were both statistically significant predictors of ischemia. In patients with an $\text{INR} \geq 2$ the chances of not having ischemia was 79%. No ischemic events were observed at INR values of ≥ 3.6 . The area under the curve for predicting ischemia using INR and indication for anticoagulation was high at 0.77.

Conclusions: Initial subtherapeutic INR and atrial fibrillation as an indication for warfarin are strongly associated with ischemic events in patients on warfarin presenting with acute neurologic symptoms. We conclude that ischemia is uncommon in patients on warfarin when the INR is therapeutic and highly unlikely with an INR greater than 3.6.

S305. Amphetamines Use in Adults with ADHD and Embolic Strokes of Undetermined Source; a Casual or Causal Relationship?

Karen Orjuela, Rochelle Sweiss and Jose Biller. Maywood, IL

*Nearly 2.7 million children in the United States are prescribed amphetamines to treat ADHD. Amphetamines are now increasingly prescribed to adults for maintenance therapy of ADHD and narcolepsy. Reports of sudden death, myocardial infarction, and stroke have raised concern about their safety profile. Amphetamines produce their effect by increasing the synaptic levels of dopamine, biogenic amines, norepinephrine, and serotonin. The association between amphetamines and ischemic or hemorrhagic stroke is based solely on case series. Amphetamine-associated stroke is postulated to occur due to a rise in catecholamine levels, vasoconstriction of extra- and intra-cerebral vasculature, or cerebral vasculitis.

*To report 3 patients with ADHD on dextroamphetamine/amphetamine and lisdexamfetamine presenting with ischemic strokes.

Patient 1: 37 year old right handed male with hypertension (HTN), hyperlipidemia, and ADHD on dextroamphetamine/amphetamine 15 mg daily who developed sudden onset of right monocular visual loss, right parietal headache, and emesis. MRI brain showed multiple right cerebellar and vermian infarcts. MRA of the extra- and intra-cranial vasculature showed no stenosis or occlusion. No evidence of cardio-embolic source, hypercoagulable and malignancy work up were negative.

Patient 2: 35 year old left handed woman with history of uncontrolled HTN, iron deficiency anemia with reactive thrombocytosis (normal bone marrow biopsy), ADHD on dextroamphetamine/amphetamine 30 mg daily, obesity, and 20 pack year tobacco use who developed sudden onset vertigo, dysarthria, right hemi-body numbness, hemi-paresis and incongruous right superior quadrantanopia. MRI brain demonstrated right thalamic and right medial temporal and occipital lobe infarctions. CT angiogram showed no extra- nor intra-cranial stenosis or occlusion. Cardiac work up negative for an embolic source.

Patient 3: 23 year old man with history of ADHD on lisdexamfetamine and major depressive disorder who developed sudden onset right occipital headache followed by left hemi-body numbness and congruous left homonymous hemianopia. MRA brain revealed mild stenosis of the distal P1 segment of the right posterior cerebral artery. MRA of the extracranial circulation was normal. Cardiac work up was unremarkable; event monitor showed brief episodes of atrial tachycardia.

*Two of three of our patients had risk factors for stroke but in all three patients, no clear etiology was discovered. Amphetamine use may have been an actual cause or potentiated other underlying risk factors, leading to ischemic stroke. Further population-based studies are needed to assess the link between prescription amphetamine use and ischemic stroke.

Movement Disorder

S306. TOR1A Mutations Are Not Frequent in a Cohort of Parkinson's Disease Patients

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Background: Pathological studies have demonstrated high levels of TOR1A mRNA in dopaminergic neurons of the substantia nigra. Non-mutated TorsinA protein has also been found in Lewy Bodies of pathologically confirmed cases of Parkinson's Disease (PD). While parkinsonism is known to be an expression of dopa-responsive dystonia, the relationship between DYT1 mutations and parkinsonism is less well known. Multiple studies have looked for TOR1A mutations among cohorts of multiple movement disorders, including PD, but none have shown coincident TOR1A mutation among patients with PD.

Design/Methods: We report a patient with PD and a TOR1A mutation who had symptomatic writer's cramp in his 20s, as well as a systematic examination for TOR1A

mutations in a cohort of 85 patients with Parkinsonism as part of whole exome sequencing.

Results: A 61 year old Ashkenazi Jewish (AJ) man presented with asymmetric right hand rest tremor, bradykinesia, and rigidity diagnosed as PD. His exam also showed marked left arm writer's cramp, which he reported began at age 25, and led him to write with his non-dominant hand. Genetic testing showed the GAG deletion mutation in the TOR1A gene, consistent with DYT1 dystonia. 85 patients (from 82 families) with Parkinsonism (mean age onset 57.9 years; range 17-95) were studied from an existing cohort. None harbored the TOR1A GAG deletion. Of this cohort, 63 patients were AJ, 6 Sephardic, 2 Italian, and 14 of Hispanic and/or Afro-Caribbean Background. 75 were diagnosed with PD, 4 with Lewy Body Dementia, 2 with MSA-C, 1 with MSA-P, 1 with drug-induced Parkinsonism, and 2 with Fronto-Temporal Dementia (1 with a Primary Progressive Aphasia subtype).

Conclusions: Our clinical case supports that TOR1A GAG deletions may be coincident with parkinsonism. The lack of mutations in a systematically studied group of parkinsonian patients, including a sample of PD of Ashkenazi heritage, suggests that this may have occurred by chance rather than as an expression of DYT1 dystonia. The frequency of the TOR1A mutation is between 1:1000-1:3000 individuals in the AJ population, thus, assessment in a larger population of PD cases of AJ Background is needed to establish whether an association is greater than expected by chance.

Multiple Sclerosis

S308. Internuclear Ophthalmoplegia Is a Potential Clinical Marker for Progression in Multiple Sclerosis

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Objective: To examine the association of progressive disease in patients with established unilateral or bilateral internuclear ophthalmoplegia (INO)

Background: The observation was made that patients with INO often manifested significant physical disability. The significance of INO as a predictor of disability in Multiple Sclerosis (MS) is unknown. The hypothesis was that when present, INO is a marker of significant disability and progressive disease in patients with MS.

Methods: INO was defined as a failure of adduction during conjugate gaze with presence of nystagmus in the abducting eye and preserved convergence. Thirty consecutive patients with INO seen in our center were eligible for evaluation. The EDSS and MR imaging of the brain were examined.

Results: The 30 patients were comprised of 14 males and 16 females. Ages ranged from 21 to 74 years. The median duration of disease was 12.3 years. Amongst functional domains, in addition to the elevated brain stem scores due to the INO, increased scores were also observed in motor, sensory, cerebellar and cognitive domains. The maximum EDSS was 8.5 with 17 patients requiring cane, walker or

wheelchairs. MRI was available in 28 patients. 20 patients showed T2 lesions in the brainstem, but not all patients had abnormalities in the medial longitudinal fasciculus (MLF). The absence of lesions in the MLF in some patients raised concerns if the pathology was predominantly an axonopathy rather than demyelination. A single patient with INO who also had MR studies died and the brain-stem was available for examination. A lesion in the MLF was not evident in this patient by MRI, and studies are under way to define the abnormalities in the brainstem that may have contributed to the occurrence of INO.

Conclusion: In a cross sectional unselected population of MS patients with INO the presence of high disability was noted to be significant. The finding that not every patient with INO had a corresponding lesion in the MLF invoked concerns of axonopathy as the basis of INO. Spectroscopy of the MLF in patients without T2 lesions will help to clarify if axonal injury is the basis of this clinical entity. Our studies would suggest that the identification of uni- or bilateral NMO should be viewed with concern since this may be a harbinger for future progression of MS.

Neurocritical Care

S309. Fulminant West Nile Virus (WNV) Encephalitis in a Double Bilateral Lung Transplant Recipient: Case Report

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Background: Neuroinvasive WNV disease has a prevalence up to 40% in transplant recipient patients compared to <1% in the general population. Overall mortality rate of neuroinvasive WNV is approximately 6-9% but reaches 30% in immunosuppressed patients. Few cases of fatal WNV encephalitis in renal, heart, and bone marrow transplant recipients have been reported, but to our knowledge, this is the first reported case of rapidly fatal WNV encephalitis in a patient with double, bilateral lung transplant.

Design/Methods: A 51-year-old woman with history of cystic fibrosis, status post double bilateral lung transplant in 1996 with redo in 2006 due to bronchiolitis obliterans, maintained on immunosuppressive therapy consisting of prednisone, mycophenolate, and cyclosporine, presented with acute onset of emesis, fevers, and altered mental status. Initial examination was pertinent for agitation, bilateral sixth cranial nerve palsies without papilledema, and absent meningeal signs. Admission brain MRI showed patchy irregular, left thalamic T2/FLAIR hyperintensities without contrast enhancement, leptomeningeal enhancement, nor signs of parameningeal infection. Brain MRV was negative for cerebral venous sinus thrombosis. CSF studies showed lymphocytic pleocytosis, mild elevation of protein content, and normal glucose. She was started on broad spectrum intravenous antibiotics with meningeal dosing and acyclovir. By hospital day two, due to worsening encephalopathy, patient was intubated for airway protection. Brain MRI repeated on hospital day 5 showed marked extension of T2/FLAIR hyperintensities of both thalami and brainstem with patchy

contrast enhancement consistent with hyperacute rhomboencephalitis/diencephalitis. Examination demonstrated absent brainstem reflexes and subsequent apnea testing confirmed brain death. CSF was positive for West Nile RNA PCR. All other bacterial, viral, and fungal studies were normal. Autopsy findings were consistent with viral encephalitis. Paraffin embedded tissue sent to the Center for Disease Control (CDC) who performed PCR assay on RNA extracts of brain tissue, was positive for WNV.

Results: Delineating the etiology of encephalitis in the immunocompromised patient poses a challenging task given the multitude of pathogenic culprits. Hyperacute rhomboencephalitis with diencephalitis and rapid brain MRI progression should raise suspicion for WNV infection especially in the immunocompromised host.

Neuro-Oncology

S310. Comparison of the Use of Volumetry vs Linear Height Measurements to Detect Changes in the Pituitary Gland Using 3D-T1W Non-Contrast MRI

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Background: MRI with contrast is the imaging method of choice for examining the pituitary gland, sella, and parasellar region. Although assessment of pituitary function on MRI is best done through the determination of the volume of the gland, height in the sagittal plane has traditionally been used as the method to evaluate gland size.

Hypothesis: There is a lack of correlation between pituitary gland height and volume.

Methods: Twenty four astronauts were scanned in a 3 Tesla MRI using isovolumetric T1 weighted images in the sagittal plane with 1 mm voxel size (3D-T1W MPRAGE). Height and volume measurements of the pituitary gland were made using Analyze 11 software.

Specific Aim: Using Analyze 11 software, retrospectively measure pituitary gland heights and volumes and determine if a correlation exists between the two.

Results: Twenty four cases were evaluated with average age of 46 years (SD = 4.4). The average height was 5.5 mm with SD of 1.3 mm ranging between 3.5 mm to 9.4 mm. The average volume was 0.74 mm³ with SD of 0.11 mm³ ranging between 0.52 mm³ to 0.92 mm³. There was no correlation between the volume and height (correlation coefficient $r = 0.11$, $p = 0.60$).

Conclusion: Use of midsagittal height for screening of pituitary gland abnormalities may not be a suitable surrogate for pituitary gland volume.

S311. Status Epilepticus Secondary to Abrupt Diffuse Parenchymal Hemorrhage in a Patient with Miliary Cerebral Melanoma

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Introduction: Malignant melanoma (MM) is the third most common cause of brain metastases (after carcinoma of the lung and breast). Up to 75% of patients with MM are

found to have brain metastases at autopsy and brain metastases are a major cause of death in MM. Miliary cerebral metastases or carcinomatosis encephalitis from melanoma represents an exceedingly rare pattern of metastasis. This case report highlights the imaging and pathologic findings of miliary cerebral melanoma.

Methods: Case Report

Results: A 35 year-old man with melanoma complicated by cerebral parenchymal and leptomeningeal metastases was hospitalized after two generalized tonic clonic seizures. Brain MRI on admission revealed the known metastases as well as hundreds of micro- and macro-hemorrhages that were new since out-patient MRI obtained 3 days earlier. On hospital day two his neurologic exam deteriorated with episodes of bradyarrhythmia requiring atropine. Head CT revealed a new large hemorrhagic lesion in the right temporal pole with mass effect and uncal herniation. The patient was transitioned to comfort measures and passed away the following day. On autopsy, there were innumerable punctate nodules of hemorrhagic melanoma metastases involving the parenchyma, leptomeninges and perivascular spaces as well as marked cerebral edema with bilateral transtentorial and cerebellar tonsillar herniation. The patient's catastrophic decline was attributed to rapid disease progression.

Conclusions: Brain metastases, which are a major cause of death in malignant melanoma, can progress rapidly especially when disseminated throughout the CSF. In melanoma, this can lead to vasculature involvement and development of hemorrhage. This case demonstrates a rare pattern of metastasis, miliary cerebral metastases, which rapidly evolved from normal imaging and resulted in a catastrophic clinical decline.

S312. Lower Extremity Spasms Resulting in Bilateral Femoral Fractures in Stiff Person Syndrome Patient

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Introduction: In Stiff Person Syndrome (SPS), affected extremities are painfully locked at the joints, unable to flex or extend. This is often accompanied by painful muscle spasms, but rarely do these spasms impose enough stress to test the integrity of the bone. We present a case of paraneoplastic SPS in which the patient sustained bilateral femoral neck fractures.

Case: A 47-year-old female with history of invasive ductal cancer of the left breast, status post neoadjuvant chemotherapy, mastectomy and radiation presented with a three-week history of progressive stiffening of the lower extremities until she had become bedbound. Physical exam revealed stiff lower extremities fixed at 180° at the knees and 90° at the ankles. Electromyogram was overall normal but a trial of diazepam provided some symptom improvement. Lab work was positive for elevated glutamic acid decarboxylase (GAD65) autoantibody level of 1128 nmol/L but paraneoplastic antibody panel was otherwise negative. Symptoms improved further with a course of IVIG and she was able to ambulate with a walker prior to discharge. Workup for

cancer recurrence was negative. Relief was only temporary and she required inpatient admissions twice more in a six-month period. On the third admission, she experienced an intense bout of lower extremity spasms that culminated in a painful “popping” sensation in her left hip which x-ray confirmed to be a femoral neck fracture. One week after arthroplasty of the left femur, she had the same painful sensation in the right hip during spasms and x-ray showed a new right femoral neck fracture which was not present when the right hip was imaged during the initial (left-sided) fracture. While imaging had suggested that there may have been metastatic lesions weakening the fractured bones, pathology taken from both surgical cases was negative for pankeratin and GATA3; markers for breast cancer.

Discussion: Spasms are a frequent complication of the rare condition of Stiff Person Syndrome that can occur spontaneously or triggered by a variety of stressors. Patients can subjectively report the severity of pain, but the clinician rarely gets an objective glimpse into the intensity of the force the spasms exert on the body as in this case where new fractures are documented in the setting of spasm. This case stresses the importance of aggressive symptom management in SPS.

Cerebrovascular Disease

S313. Cofilin-1 as a Possible Therapeutic Target to Prevent Cognitive Sequelae in Cerebral Malaria

Simhadri Praveen Kumar and Prakash Babu Phanithi. Hyderabad, Telangana, India

Malaria is a life threatening disease of humans caused by protozoan parasite *Plasmodium falciparum* and *Plasmodium vivax*. Indeed, poor diagnosis or treatment for malaria often leads to Cerebral Malaria (CM). Consequently, CM is serious form of malaria characterized by seizures, coma and even death. Experimental CM using *Plasmodium berghei ANKA* infected C57BL/6 mice being widely accepted model that re-iterate major symptoms of human cerebral malaria. Underlying mechanisms of CM pathogenesis includes sequestration of infected RBC, migration of phagocytic cells, release of microparticles and hemozoin via disruption of blood-brain barrier. However, precise mechanism of CM pathogenesis is not completely understood. Those who survived from CM, approx 5-15% of adults and 30% of children suffer from long term cognitive deficits. It appears that excitotoxicity, oxidative stress, hypoxia and recurrent seizures affect the micro environment of brain that alters actin dynamics of dendritic spines in neurons. Neuronal morphology, in terms of its intact arborization pattern and dendritic spine density is critical in maintaining synaptic transmission. Cofilin-1 which is ubiquitously expressed in the brain, plays key role in maintaining the actin dynamics in dendritic spines and thus executing learning and memory functions. In this study, we assessed the morphology of neuronal arborization and its dendritic spine density using Golgi cox staining method. Further, the expression of the cofilin-1 was studied in whole brain lysates of experimental groups i.e. CM, asymptomatic, anemic and control. The

results showed loss of dendritic spine density, reduced dendritic arborization and extensive dendritic beadings (pathological feature of altered dendrite) in the neurons of CM infected brains. The expression of cofilin-1 was significantly reduced in the CM infected brain which is the hallmark of imbalance of the actin dynamics during the pathology. These findings suggest that altered morphology of neurons at ultra structural level could be attributed to cofilin-1 levels in the brain after experimental CM. This may help to establish newer therapeutic strategies aiming long term cognitive impairment after CM.

S314. Pseudomastoiditis Secondary to Lateral Cerebral Sinus Thrombosis in the Setting of Norgestimate/Estradiol Oral Contraceptive (OCP) Use

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Objective: To describe a case in which non-infectious lateral cerebral sinus thrombosis masquerades as infectious cerebral sinus thrombosis due to imaging results concerning for mastoiditis.

Background: A 33-year-old woman taking oral contraceptive pills presented to an emergency department with right ear pain. She was diagnosed with otitis externa and treated with antibiotics. One week later, she presented to the otolaryngology clinic complaining of intermittent vertigo and nausea associated with severe pain around her right ear. She was afebrile. Neurological examination and examination of the right ear were normal. An audiogram was normal. Magnetic resonance imaging of the internal auditory canal with contrast was requested.

Design/Methods: Information was obtained from the patient and medical record.

Results: The MRI showed right lateral sinus thrombosis and fluid in the adjacent mastoid air cells; there was no abscess or meningeal enhancement. CT head with angiogram confirmed thrombosis of the right transverse sinus, sigmoid sinus, and internal jugular vein without mastoid air cell opacification or osseous destruction. The patient was treated with anticoagulation. Fundoscopy revealed papilledema in the right eye and she was started on acetazolamide. She received empiric antibiotics due to concern for otomastoiditis. CRP, ESR, fibrinogen, blood cultures, and hypercoagulable studies were unremarkable.

Conclusions: Repeat MRI after six weeks of anticoagulation showed improvement of right lateral sinus thrombosis and stable signal abnormality in the right mastoid air cells. Compared to women not taking OCPs, women taking OCPs have a seven-fold greater risk of developing cerebral sinus thrombosis. MR evidence of mucosal edema in mastoid air cells ipsilateral to a thrombosed lateral sinus suggests congestion of mastoid veins rather than infectious mastoiditis, unless clinical and radiographic features strongly support the latter. A CT scan has a sensitivity of 97% for infectious mastoiditis, the hallmark finding being osseous destruction of the mastoid air cells.

S315. Cardiac Autonomic Dysfunction After Lacunar Stroke: Does Side Really Matter?

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Background: Sudden cardiac death due to arrhythmia and associated electrocardiographic (E.C.G) abnormalities are common among stroke survivors. Stroke is known to damage the central autonomic pathway which in turn causes significant cardiovascular dysfunction and arrhythmogenesis. Heart Rate Variability (H.R.V) is a commonly used measure for studying cardiovascular autonomic modulation. Therefore we felt studying H.R.V could throw some light on cardiovascular autonomic balance post stroke. Thus H.R.V and cardiovascular reflex autonomic function tests were compared between right hemispheric and left hemispheric lacunar stroke patients.

Materials and Methods: It was a cross sectional study involving 50 patients (left = 26, right = 24) after various duration post lacunar stroke ranging from 3 to 6 months. The stroke was verified by C.T scan and or M.R.I scan. Inclusion criteria were: age group 45-75, first stroke, absence of significant carotid stenosis, absence of intracranial haemorrhage. Patients with major concurrent medical illness and those on drugs affecting the A.N.S were excluded. E.C.G was recorded for 5 minutes after 10 minutes of rest with the patients lying in supine position according to task force guidelines. Time domain, Frequency domain and Non linear analysis of H.R.V was conducted. Standard battery of autonomic function tests were carried out on all patients.

Results: Among the frequency domain parameters Very Low Frequency, Low Frequency(L.F) and Total power were significantly reduced on left sided stroke patients. Though there was no significant difference in time domain parameters between right and left hemispheric ischemic stroke, Root Mean Square of Successive Deviation (RMSSD) was reduced and Standard Deviation of successive N-N intervals (SDNN) was higher after right sided stroke. However there was no effect of lateralization of stroke on the standard reflex cardiac autonomic function tests.

Conclusion: There is a higher sympathetic tone after right stroke as denoted by a higher L.F, Total Power and a higher LF/HF(low/high frequency) ratio. Clinical autonomic tests did not show any significant difference between left and right groups.

S316. Vertebrobasilar Dolichoectasia- An Incidental Finding of a Rare Cause of Obstructive Hydrocephalus

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Introduction: Vertebrobasilar dolichoectasia (VBD) is a well-recognized arteriopathy characterized by elongated, dilated and tortuous vertebrobasilar vasculature. VBD is asymptomatic in 90% of the cases. When symptomatic, clinical manifestations are those related to ischemia, mass effect primarily on cranial nerves and brainstem, hydrocephalus and hemorrhage.

Case: A 58 year old female presented with one year history of multiple falls associated with syncope. A non-

contrast CT head performed as part of the workup showed diffuse ventriculomegaly with the 3rd and the lateral ventricles dilated more than the 4th. CT angiography revealed tortuous course of the vertebrobasilar vasculature with a dilated and elongated basilar artery extending into the suprasellar space, directly abutting the third ventricle. The compression of the 3rd ventricle with this dolichoectatic basilar artery was the likely etiology of the observed obstructive hydrocephalus. The patient denied any headaches or visual symptoms and had an unremarkable gait. Further focused history and examination did not reveal any clinical features to suggest symptomatic hydrocephalus. After consultation with neurosurgery decision to perform shunting was deferred and close follow up ensured to evaluate for progression and development of any concerning symptoms.

Conclusion: Obstructive hydrocephalus is a rare complication of VBD. Management of VBD depends on symptomatic manifestations. Ventriculo-peritoneal shunting is the current standard of care for VBD induced hydrocephalus. The benefits of surgery in asymptomatic individuals is unclear. However, close observation is advised to evaluate for occurrence of vascular events and other clinical manifestations associated with VBD.

S317. The Dilemma of Anticoagulation in Patients with Left Ventricular Assist Devices and Warfarin-Associated Intracerebral Hemorrhage

Chandler E. Gill, Rochelle Sweis and Jose Biller. Maywood, IL

The use of left ventricular assist devices (LVADs) is increasing as a bridge-to-transplant or destination therapy in patients with advanced heart failure. Anticoagulation and often antiplatelet therapy are needed to prevent thromboembolic events and pump failure. However, these therapies, in addition to acquired von Willebrand's syndrome associated with LVADs, increase risk of intracerebral hemorrhage (ICH). Patient prognosis after spontaneous ICH, in particular, is poor and few studies exist to guide treatment decisions regarding anticoagulation reversal and duration of withholding anticoagulation.

A 47 year-old woman with history of stage IV chronic kidney disease secondary to polycystic kidney disease, awaiting renal transplant, and non-ischemic cardiomyopathy due to viral myocarditis presented with a 24-hour history of fluctuating consciousness and nonsensical speech. She had undergone placement of Heartware LVAD 10 months prior, was listed for heart transplant (UNOS status 1A), and remained compliant with warfarin therapy. Examination was remarkable for fluent aphasia and mild right hemiparesis. Non-contrast CT head showed a large left temporo-parietal ICH with INR of 2.1 (ICH score 2, GCS 11, FUNC score 11). Anticoagulation was held, and she was treated with vitamin K in addition to prothrombin complex concentrate (PCC). Serial CT scans confirmed stability of hemorrhage size at 30cc with 5mm of left-to-right midline shift.

Selective angiogram with minimal contrast use due to renal insufficiency did not show underlying aneurysm or other vascular anomaly. APOE variants 2 and 4 were negative. Daily device interrogations were performed but did not

reveal increasing power spikes, and serial LDH remained normal, suggesting absence of pump thrombi. Neurologic examinations demonstrated stable aphasia with improving right hemiparesis. The patient was transferred to acute rehabilitation on hospital day 8. Warfarin was restarted on post-ICH day 10 with an INR goal of 2.0-2.5 without increase in ICH size.

We report a case of anticoagulation-associated ICH in a patient with LVAD and therapeutic INR, who tolerated warfarin reversal with PCC and vitamin K. Warfarin re-initiation 10 days after ICH resulted in no adverse events. Although there is no definite data to guide treatment of ICH in patients with LVADs, this clinical observation may guide neurologists faced with the dilemma of anticoagulation reversal and timing of re-initiation of oral anticoagulant therapy. APOE epsilon 2/4 variants and acquired von Willebrand's multimers are important risk factors for re-hemorrhage that should be considered.

S318. Hypothyroidism Presenting with Dysarthria and Intermittent Weakness of the Extremities

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Objective: To describe a rare case of hypothyroidism presenting with dysarthria and extremity weakness.

DESIGN: A case report.

Background: Uncontrolled hypothyroidism can affect the central and peripheral nervous systems causing a range of neurological symptoms including cognitive dysfunction and peripheral neuropathy. Hypothyroid myopathy may occur. This report demonstrates the importance of evaluating for hypothyroidism in patients presenting with dysarthria and extremity weakness.

HOSPITAL COURSE: The patient was a 56 year-old right-handed male with a history of carotid stenosis, hypothyroidism, hyperlipidemia, and obstructive sleep apnea who presented with the complaint of dysarthria. He reported the gradual development of slurred speech two weeks prior to admission. Within a week, he developed intermittent weakness of his left hand followed by intermittent weakness of both legs. On admission, he endorsed persistent dysarthria, generalized fatigue and improvement in extremity weakness. General examination was notable for bradycardia with pulse in the 50s and lack of edema. Neurologic examination was remarkable for moderate dysarthria and distal sensory loss in all extremities. He was alert, oriented to time, place and reason for hospitalization, with fluent speech and intact comprehension. Initial labwork revealed a CK of 2314 U/L which was treated with fluids. Imaging of brain structure and vessels with MRI and CTA was unremarkable. Telemetry revealed asymptomatic bradycardia in the 30s during sleep prompting a Cardiology consultation, with recommendation of outpatient evaluation. Serologies were remarkable for TSH of 126 U/ml and undetectable free thyroxine (fT4). The patient noted that he had exhausted his levothyroxine supply a month previously and had not called for a refill. The Endocrinology service

recommended levothyroxine 175 mcg daily and IV hydrocortisone 50 mg every six hours. On the third day of admission, his fatigue and dysarthria had improved. He was discharged home with a steroid taper and levothyroxine 175 mcg daily. After three months on levothyroxine, his TSH was within normal range. On clinic followup at that time, his dysarthria and fatigue had resolved. Stocking-and-glove sensory loss persisted.

Conclusions: Hypothyroidism can mimic cardiovascular disease and other neurologic syndromes. Hypothyroidism has been sparsely described as presenting with dysarthria, with two reported cases to date. This case illuminates the importance of evaluating for reversible causes of dysarthria and weakness, including endocrine disorders such as hypothyroidism.

S319. An Interesting Case of Unilateral Central Retinal Vein Occlusion Leading to Cilio Retinal Artery Occlusion

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Introduction: Central retinal vein occlusion (CRVO) is a common cause of permanent visual loss in adults. CRVO occurs due to thrombus within the central retinal vein at the level of the lamina cribrosa of the optic nerve, leading to involvement of the entire retina. Work up and laboratory evaluation of patients requires the clinician to rule out hypertension, diabetes, hyperlipidemia, and glaucoma and testing for primary and secondary thrombophilias in selected patients.

Case presentation: We present a case of CRVO leading to cilio retinal artery occlusion in a 49-year-old man with history of untreated HTN. He presented to the emergency department with complaints of sudden unilateral vision loss. He developed a blind spot in the center of his vision in his left eye (OS) which rapidly progressed to involve lower visual fields. On arrival, he had visual acuity of 20/70 in OS and 20/20 in right eye (OD), funduscopic examination was done and macula OS showed superior pallor along cilioretinal artery and engorged veins, attenuation of cilio retinal artery and mildly elevated intra ocular pressure OS. Rest of the neurological exam was non focal. He was admitted to stroke service for further management. He underwent contrast angiography of the neck and brain vessels, magnetic resonance imaging and lab work including complete hypercoagulability work up which were noncontributory. Patient was started on Aspirin (ASA) and statin therapy. He was diagnosed with CRVO with cilio retinal artery occlusion. Risk factors were highly suspected to be hypertension and mildly elevated intraocular pressure in the OS.

Conclusion: CRVO is a lethal and debilitating disease process that leads to ischemia and hypoxia. Macula develops edema and neovascularization is usually seen in the retina. However sometimes it leads to retinal artery occlusion resulting in visual loss. Our case illustrates an interesting presentation of unilateral CRVO leading to cilio retinal artery occlusion, where hypertension and glaucoma were found to be the main risk factors. It is important to have

close follow up, to monitor for Neo Vascular Glaucoma (NVG) and strict blood pressure control to prevent further morbidity.

S320. Procedures Requiring General Anesthesia in Patients with Unruptured Intracranial Aneurysms

Vijayalekshmi V. Nair, Sameer Sharma, J. Thatcher, T. N. Nguyen and Hesham Masoud. Syracuse, NY and Boston, MA

Background: The role of general anesthesia in precipitating aneurysm rupture is not clearly defined. In this study we aimed to estimate the risk of aneurysm rupture in patients undergoing non-aneurysm related procedures requiring general anesthesia.

Methods: Retrospective review of consecutive patients with untreated intracranial aneurysms that underwent unrelated surgery with operative note documentation of general anesthesia. Events of intraoperative and postoperative subarachnoid hemorrhage were recorded to calculate risk of rupture.

Results: 85 patients harboring 107 unsecured aneurysms were studied. The mean age was 59.2 (range 18 - 81 years old) and 72% were women (n=61/85). Mean aneurysm size was 3.4 mm (range 1.5 - 16). A total of 177 procedures were performed under general anesthesia. There were no events of subarachnoid hemorrhage in 7526.7 months of follow up.

Conclusion: In our study, general anesthesia did not precipitate aneurysm rupture and there were no instances of subarachnoid hemorrhage during the follow-up period. Our results should be interpreted with caution given the small sample size and retrospective design.

S321. Use of the Computerized Causative Classification System for Ischemic Stroke in the Population-Based Framingham Study

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Objective: Describe our experience using the online Causative Classification System (CCS) for ischemic stroke subtyping in the Framingham Heart Study (FHS). We will estimate the level of agreement between CCS and on-going, prospective stroke event determination using modified TOAST (Trial of ORG10172 in Acute Stroke Treatment) criteria.

Methods: Study neurologists were trained and certified for CCS using an online module. Quality control was provided through separate CCS subtyping on a subsample of cases by independent and expert evaluators (JWC,MH). These evaluators were among the key classifying neurologists for the NIH Stroke Genetics Network (SiGN) study. Major stroke subtypes will be analyzed for agreement.

Results: Study participants included 67 adults (mean age 59.2 years, 49% women) followed prospectively, with the earliest stroke adjudicated in 1953. CCS classification in most of the cases (75%) was performed for an AHA-Cardiovascular Phenome-Genome Study grant investigating rare gene variants in young stroke age<55, accounting for

the younger mean age of our sample. Disagreement occurred in 2/23 cases during quality control. CCS subtyping classified, as evident/possible/probable, 21(31%) cardio-aortic embolism, 4(6.0%) small-artery occlusion, 4(6.0%) large-artery atherosclerosis, 12(18%) other causes, 4(6.0%) cryptogenic, and 22(33%) undetermined cause. FHS classification determined, as definite/probable, 19(28%) cerebral embolism, 11(16%) lacunar, 5(7.5%) large-artery atherosclerosis, 21(31%) atherosclerotic brain infarctions (mechanism unspecified), 1(1.5%) TIA with positive imaging, 7(10%) other CVA, and 3(4.5%) questionable CVA/type unknown.

Conclusions: Using CCS for subtyping of FHS stroke cases presents unique challenges, due to the longitudinal, multi-generational, and prospective nature of the data source. Some of these challenges are common across prospective cohorts, a setting in which CCS has had limited application. Other challenges are unique to FHS. For example, in the earliest epochs, strokes were investigated using different technology, including pneumoencephalography, angiogram, and LP. CT scanning was unavailable before 1976 and brain MRI before 1990. Lifetime pre- and post-stroke information is available using cohort data and CCS is ambiguous about how this additional information should be incorporated. Examples of such data include multiple EKG's or ambulatory recording for atrial fibrillation, multiple echocardiograms and carotid ultrasounds, and cardiac CT/MRI. Review of delayed brain MR imaging can localize strokes not visualized on acute imaging. Despite these caveats, the CCS proved applicable to the FHS cohort with high inter-observer concordance. Agreement between current FHS and CCS subtypes is predicted to be moderate, and will be analyzed with a larger sample.

S322. The First Sign of Loss of Consciousness

Typ Whinnery and Estrella M. Forster. Oklahoma City, OK and Mustang, OK

Introduction: Determination of loss of consciousness (LOC) is dependent on signs induced by a critical level and duration of cephalic nervous system (CPNS) ischemia. The initial signs of LOC onset were determined from 212 healthy individuals exposed to acceleration (head-to-foot) +Gz-stress.

Methods: Two different types of acceleration onset rates (gradual onset rate (GOR) and rapid onset rate (ROR)), which determine the rate of CPNS ischemia induction, were employed to induce LOC. The onset rate range for LOC induction was gradual (GOR) (0.0625-0.25 G/s) for 114 of the LOC exposures and rapid (2.00-7.67 G/s) for 98 of the exposures.

Results: The mean maximum +Gz-level for all LOC exposures was +8.07 Gz $\pm$ 1.08 SD. Five initial signs were found to specify the earliest indication of LOC onset. They included eye fixation in the primary position, upward eye deviation, eyelid closure, loss of muscle control, and muscular twitching. Close temporal association of these initial individual signs made it preferable to develop sign complexes heralding the onset of LOC rather than individual signs. The sign complexes were defined by the onset of two

or more signs occurring simultaneously and/or within one second of each other. The sign and sign complex distributions were established for the entire group as well as the distributions for the LOC episodes induced by different onset rates (GOR and ROR) episodes. The most frequent individual sign associated with onset of LOC was loss of postural muscle control occurring as the initial sign in 84% of the LOC episodes followed by eye fixation in 8.5% and upward eye deviation in 6.1%. The most frequent sign complexes were: 1) loss of postural motor control and eyelid closure occurring in 53.3%, 2) loss of postural motor control with upward eye deviation in 12.3%, and 3) loss of postural motor control with eye fixation in 11.8% of the episodes.

Conclusions: Signs and sign complexes remained similar for GOR and ROR exposures indicating that the onset rate of CPNS ischemia induction, well above relaxed acceleration tolerance, did not alter the first sign or signs of LOC. Establishing the first sign and sign complex associated with the onset of LOC provides a common method for defining what is measured when determining experimental or clinical LOC, the precise time of LOC onset, and the kinetics of the incapacitation resulting from ischemic LOC induction.

S323. Burden and Outcomes of Acute Ischemic Stroke in Patients with Psychosis

Zeeshan Mansuri, Achint Patel, Zabeen Mahuwalla, Uvesh Mansuri, Ruchir Goswami, Tapan Mehta, Sagar Patel, Sarah Noble, Ashutosh Lodhi, Girish Nadkarni and Sanjeeva Reddy Onteddu. Philadelphia, PA; New York, NY; Dallas, TX; Storrs, CT; Cleveland, OH and Fayetteville, AR

Objective: To determine the trends and impact on outcomes of Acute Ischemic Stroke (AIS) in patients with pre-existing psychosis.

Background: Although, post stroke psychosis has been extensively studied, contemporary studies on temporal trends and outcomes of pre-stroke psychosis on AIS outcomes are largely lacking.

Methods: We used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) from years 2002-2012. We identified AIS and psychosis as a primary and secondary diagnosis respectively using validated International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes. We used the Cochrane-Armitage trend test and multivariate regression to generate adjusted odds ratios (aOR).

Results: We analyzed 4,320,304 AIS hospital admissions from 2002-2012, of which 2.7% had psychosis. Proportion of hospitalizations with psychosis increased from 1.89% in 2002 to 3.47% in 2012 ($p < 0.001$). Thrombolysis was lower in patients with psychosis (3.27% vs. 4.11%, $p < 0.001$). Patients with psychosis had higher adjusted odds of discharge to specialty care (aOR 1.64; 95%CI 1.58-1.71; $p < 0.001$), but in-hospital mortality was significantly lower in patients with psychosis (OR 0.66; 95% CI 0.60-0.718; $p < 0.001$). In addition, median length of hospitalization (4 vs. 3.4 days; $p < 0.001$) and cost of hospitalization (\$8665 vs. \$8140; $p < 0.001$) were higher in hospitalizations with psychosis.

Conclusion: Our study displayed an increasing proportion of patients with psychosis admitted due to AIS in the last decade with lower mortality but higher morbidity after survival. In addition, there was less utilization of thrombolysis in this population. There is a need to explore the reasons behind this disparity in outcomes and thrombolysis utilization in order to improve post-stroke outcomes in this vulnerable population.

S324. Midbrain Stroke Mimicking Diabetic Third Nerve Neuropathy

Parvinder Kaur, Jared Noroozi, Adil Iqbal, Marks J. Stephens and Brij Ahluwalia. Valhalla, NY

Purpose: We present a case of a diabetic patient with pupil sparing, oculomotor palsy, with unilateral ptosis secondary to a midbrain infarct affecting the fascicles of the third nerve.

Background: Pupil sparing third nerve palsy is seen in diabetics due to extra-axial microvascular changes confined to the core of the oculomotor nerve. Peripherally located unmyelinated pupillary fibers are resistant to ischemia, sparing the pupil. In nuclear lesions, there is complete ipsilateral third nerve palsy with bilateral ptosis and contralateral superior rectus involvement. Fascicular lesions manifest as ipsilateral oculomotor palsy with sparing of the opposite ocular muscles. In literature, there are only a few cases described where isolated fascicles of third nerve were affected without any involvement of other brainstem structure.

Design/Methods: A 69-year-old diabetic African American male experienced acute onset of vertical diplopia. He had bilateral equal and reactive pupils, left unilateral ptosis, impaired adduction, elevation, depression and without any contralateral eye pathology. No weakness, sensory deficit, tremor, ataxia was observed.

Results: MRI of the brain demonstrated an acute mesial caudal midbrain ischemic infarct involving the fascicles of the third nerve with sparing of the pupillomotor fibers innervated by the superiorly located Edinger-Westphal nucleus. Hemoglobin A1c was 8.2. CT angiogram ruled out any vessel occlusion or aneurysm.

Conclusion: Ipsilateral pupil sparing oculomotor palsy due to fascicular involvement in caudal midbrain due to ischemic stroke can mimic diabetic extraaxial neuropathy. MRI of the brain is warranted due to the similar presentation of these two different etiologies. Ischemic lesion of the midbrain would necessitate implementation of secondary stroke prevention.

Epilepsy

S325. Obesity in Adult Patients with Psychogenic Non-Epileptic Seizures

Abubuzelfa Abubakar and Ilse P. Wambacq. Jackson, MS and Montclair, NJ

Purpose: we assessed the incidence of obesity in PNES.

Methods: Retrospective chart reviews of all patients admitted to the EMU between 2010 and 2012 were conducted. Patients with the diagnosis of PNES were

ascertained. All patients underwent prolonged video EEG recording to confirm the diagnosis of PNES. Demographic characteristic, body weight and height were collected. The body mass index (BMI) was calculated and defined as follows; BMI 25-29 overweight, 30-39 are obese and >40 are very obese.

Results: There were 118 patients with diagnosis of PNES. 66 out of 118 had documented weight and height and were included in the evaluation. There were 29 males with an age range 18 to 64 years and 9 of them were Afro-Americans. There were 37 females with an age range 18 to 70 years and 12 of them were Afro-American. Forty-seven out of 66 patients with PNES were overweight/obese, representing 71% of the sample. Twenty-three patients are overweight representing 34.8%, 16 patients are obese representing 24.1% and 8 are very obese (BMI >40) representing 12.1%. Overall, the occurrence rate of being overweight was more common in Afro-American (42.1%) than Caucasian patients (31.9%). However the combined rate of obese/very obese was significantly higher in Caucasian 40.4% compared to Afro-American 26.3% ($P=0.0027$). Men were more commonly overweight than women (41.4% vs. 29.7%) however the combined rate of being obese/very obese was more common in women (40.5%) than men (31%).

Conclusion: This study demonstrates that the frequency of being overweight/obese is high in patients with PNES. There is a higher rate of morbid obesity in females, especially Caucasian women, which may give insight into the causation of PNES.

S326. New-Onset Epilepsy and Vitamin D Deficiency: A Case-Control Study

Riwaj Bhagat, Samyog Khatriwada and Ritesh Neupane. Bharatpur, Nepal; Biratnagar, Nepal and Chittagong, Bangladesh

Purpose: Vitamin D deficiency is associated with various neurological diseases¹. It can also play a role in the etiopathogenesis of epilepsy². However, there are only a few number of studies to support this fact. So, we tried to find out the association between new-onset epilepsy and Vitamin D deficiency.

Method: A case-control study was conducted in the tertiary care center, Chitwan, Nepal to evaluate the relationship between new-onset epilepsy and Vitamin D deficiency. 100 patients diagnosed with epilepsy were identified between 2013 and 2015 from the hospital records. A control of 100 non-epileptic people were randomly selected from Nepal and approximately matched to age, sex, geographic distribution, past illness and current medication of the epileptic patients. Vitamin D level of the cases and controls were tabulated. Vitamin D 25-OH level was categorized as inadequate (< 20 ng/ml) and normal (20-50 ng/ml). Finally, descriptive and inferential statistics were employed.

Results: With 100 cases and 100 controls ($N=200$), mean age of 26.30 years ($SD=12.74$; range=6-64), male 109(54.5%) and female 91(45.5%), mean Vitamin D level was 30.57 ng/ml ($SD=10.170$; range=14-48). Vitamin D

deficiency was seen in 87.5% of cases compared to 12.5% controls. OR for inadequate Vitamin D level was 14.636 (95%CI: 6.425-33.34) ($p=0.000$ ($p<0.05$), Pearson chi-square).

Conclusion: New-onset epilepsy is associated with vitamin D deficiency. More study should be conducted to support the evidence.

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S327. Isolated Transient Forced Gaze Deviation as Initial Presentation of Anaplastic Oligodendroglioma

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Objective: To review a clinical case of a patient with isolated intermittent gaze deviation that is associated with anaplastic oligodendroglioma in the right frontal area.

Background: Forced gaze deviation coupled with versive head deviation is a common ictal phenomenon in complex partial seizures. However, isolated episodic forced gaze deviation is a rare manifestation of a simple partial seizure in adults.

Methods: Retrospective review of a clinical case with clinical course, diagnostic procedures, and treatment approaches.

Results: A 48 year old Caucasian male presented with an 18-month history of isolated, forced intermittent, involuntary eye deviation. The events occurred several times a day; most lasting for only a few seconds each. The events were not associated with loss of consciousness, convulsion, headache, nausea/vomiting, dizziness, vertigo, weakness or numbness. Prior to his evaluation in clinic, he had noticed that the events had increased in frequency to 6-7 times a day. Brain MRI revealed a space occupying cortical and subcortical lesion with no significant enhancement in the area of the right frontal eye field. He was started on Keppra 500 mg BID with significant reduction in frequency of episodes. Interictal EEG showed epileptiform sharp and slow wave activity in the right frontal region. Carbamazepine was added with complete cessation of attacks. Patient underwent a completed resection of the mass, and pathological studies were consistent with anaplastic Oligodendroglioma, WHO Grade III and Co-Deletion of 1p and 19q with polysomy detected. He had a fairly unremarkable post-operative course and has been seizure free since the resection.

Conclusions: Transient forced saccadic eye movements are a unique semiology of partial seizures affecting the frontal eye fields in a patient with large frontal oligodendroglioma. Early recognition of this unique presentation and prompt initiation of anti-epileptic and work-up are critical in reducing morbidity and mortality associated this disease entity.

Movement Disorder

S328. Symptomatic Isolated Tongue Tremor of Cortical Origin Due to Stroke

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Isolated tongue tremor is an uncommon neurological symptom. A limited number of cases have been reported in association with pilocytic brainstem astrocytoma, post-radiosurgery, electrical injury, liver cirrhosis, Wilson's disease and drug use. Moreover, tongue tremor can be a rare initial presentation of essential tremor and Parkinson's disease. However, isolated tongue tremor has to our knowledge not yet been reported as a manifestation of acute stroke. Herein, we describe an unusual case of transient, isolated tongue tremor caused by an ischemic cortical lesion.

A 82 year-old right-handed Caucasian male with past medical history of recurrent strokes, diabetes, hypertension, atrial fibrillation and chronic kidney disease who presented to the ER with difficulty speaking and abnormal tongue movement after waking up.

On neurological examination, tongue tremor was observed both at rest and upon protrusion, without weakness of tongue muscles, tongue deviation or atrophy. No tremor or other hyperkinetic movement of palate, mandible, or other parts of body were observed. Other than mild dysarthria, the remainder of the neurological exam was normal.

MRI brain showed evidence of acute ischemic stroke involving the left fronto-parietal region which includes the area representing the motor function of the tongue on the cortical homunculus. No imaging abnormalities were detected in brainstem, cerebellum, or basal ganglia.

In this patient, the tremor had a sudden onset and the patient had many risk factors of stroke. Additionally, there was no recent initiation or adjustment of medication. None of his current medications (warfarin, aspirin, simvastatin, glipizide, metformin, amlodipine and metoprolol) has been reported to cause tremor. Therefore, the most likely etiology of tremor in this case would be cerebrovascular accident.

The tremor gradually improved over a few days without any additional treatments. Difficulty speaking resolved. Patient was able to eat without swallowing problem. He was discharged after 2 days of hospitalization.

In conclusion, this report provides evidence that isolated tongue tremor can develop after unilateral cortical lesion, especially from acute infarction. Since cortical origin of symptomatic palatal tremor (SPT) has been described, this patient, presenting with isolated tongue tremor but without palatal tremor might constitute an abortive form of SPT.

Multiple Sclerosis

S329. Medication Use Patterns of Glatiramer Acetate 40 mg/mL in Patients with Multiple Sclerosis

Debra Irwin, Ying Wu, Katherine A. Cappell, Brian M. Davis, Augusto Grinspan and Sanjay K. Gandhi. Chapel Hill, NC; Frazer, PA; Ann Arbor, MI and Weston, FL

Background: Multiple sclerosis (MS) is a leading cause of disability in adults. Disease-modifying therapy (DMT), such as glatiramer acetate 40 mg/mL (GA40), aims to reduce the frequency and intensity of relapse episodes. Adherence to DMT is a key variable to ensure treatment success.

Objective: This analysis examines medication use patterns and adherence to GA40, introduced in the United States in January 2014.

Design/Methods: A retrospective cohort study using MarketScan Commercial and Medicare Databases (January 2014–January 2015) was conducted in adult patients with MS newly initiating GA40. Patients were required to have 9 months of medical and pharmacy enrollment prior to and 6 months following GA40 initiation. Outcomes included medication use patterns, such as switch to another DMT, discontinuation for at least 30 days, and adherence measures (proportion of days covered [PDC]; medication possession ratio [MPR]).

Results: Of the 4393 GA40 patients qualifying for the analysis, 14.1% had no prior DMT treatment, 80.6% switched from daily glatiramer acetate 20 mg/mL, 3.1% switched from dimethyl fumarate, and 2.1% switched from other DMTs. Approximately 87% of patients remained on therapy during the 6-month follow-up period. Approximately 7% of patients switched to another DMT, and 6% discontinued without re-initiation of another DMT. The adherence to medication was high, with PDC of 0.84 (standard deviation [SD] 0.22) and MPR of 0.94 (SD 0.12).

Conclusions: In this largest study to date evaluating adherence among patients newly initiating GA40, a large proportion of patients remained on GA40 throughout the study period and demonstrated high levels of adherence. This highlights a greater likelihood for GA40 treatment to deliver clinical benefits to patients in real-world clinical practice, as high adherence is an important factor contributing to treatment success.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? YW, AG and SG are employees of Teva Pharmaceuticals. KC, DI and BD are employees of Truven Health Analytics. Truven Health Analytics received funding to conduct research studies.

S330. Patient-Reported Treatment Satisfaction with Multiple Sclerosis Therapy After Switching from a More Frequent to a Less Frequent Injection Administration

Natalia M. Flores, Gary R. Cutter, Ying Wu, Sanjay Gandhi, Lulu K. Lee, Adriana J. Carra, Antonella Veneziano and Augusto Grinspan. Foster City, CA; Birmingham, AL; Frazer, PA; Buenos Aires, Argentina; Assago, Milan, Italy and Weston, FL

Objective: To assess patient-reported treatment satisfaction with multiple sclerosis (MS) therapy after switching from a more frequent to a less frequent injection administration.

Background: Little is known about treatment satisfaction of patients with MS who switch from a more frequent to a less frequent injection therapy. This study examined the treatment satisfaction of patients who switched to a 3-times-a-week injection (40 mg dose) of glatiramer acetate (GA)

from a once-daily injection (20 mg dose) of GA in the United States.

Design/Methods: Data from a cross-sectional, internet-based survey of adult MS patients (aged 18 years and older) were used to identify those who self-reported currently receiving GA 40 mg for treatment of MS (N=275). Measures included demographics and health characteristics (e.g., age, comorbidities), clinical characteristics (e.g., MS severity), reasons for choosing the 40 mg dose, Medication Satisfaction Questionnaire (MSQ; 7-point scale [1=extremely dissatisfied to 7=extremely satisfied; 4=neither satisfied nor dissatisfied]), and Treatment Satisfaction Questionnaire for Medication (TSQM-9; 3 scores assessing medication effectiveness, convenience, and global satisfaction [1=lowest to 100=highest satisfaction; midpoint=50]). Descriptive statistics (means and standard deviations [SDs] for continuous variables, percentages and frequencies for categorical variables) were used to describe patient characteristics and treatment satisfaction.

Results: MS patients using GA 40 mg were, on average, 48.2 years old, 78.9% female, and 78.9% white, with the majority characterizing their MS as mild (51.3%) or moderate (41.8%); 89% had switched from GA 20 mg (n=245). Among those who switched from once-daily injection GA to 3-times-a-week GA, the mean MSQ score was 5.23 (SD=1.65). The majority (77.6%) of patients indicated satisfaction (scores 5-7) and only a minority of patients (15.5%) indicated dissatisfaction (scores 1-3) with treatment. Mean TSQM effectiveness score was 66.76 (SD=21.98), convenience was 70.57 (SD=20.82), and global satisfaction was 71.40 (SD=22.54), indicating satisfaction with GA 40 mg. The most common reason reported for choosing the 40 mg dose was "I prefer the less frequent injections with the 40 mg 3-times-a-week injection" (64.1%).

Conclusions: Less frequent injections of the 40 mg dose may be the main driver for high treatment satisfaction. Among those who switched from 20 mg, treatment satisfaction with GA 40 mg was high, as expected and indicated by the validated MSQ and TSQM instruments.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? YW, AG and SG are employees of Teva Pharmaceuticals. NF and LL are full-time, paid employees at Kantar Health. Teva paid Kantar Health for study design, analyses, and publication preparation. GC is DSMB member and/or consultant.

S331. Positive Effect of Natalizumab on Depression, as Assessed by BDI-II Scores in the SENTINEL Trial

Dominique M. Tosi, James Potts, Ryoko Susukida, Denise Campagnolo, Alexis A. Adams-Clark, Richard Rudick, Kristen Hollinger, Gisele von Buren and Adam I. Kaplin. Baltimore, MD and Cambridge, MA

Background: The incidence of clinical depression in patients with multiple sclerosis (MS) is 5-fold greater than that of the general population (25% vs 5%, respectively). Natalizumab inhibits the migration of leukocytes across the blood-brain barrier (BBB) by acting as an $\alpha 4$ integrin antagonist, reducing inflammation within the central nervous

system (CNS). SENTINEL, a randomized, double-blind, placebo-controlled, phase 3 clinical trial, was completed in 2005 to evaluate the efficacy and safety of natalizumab vs placebo in combination with IFN β -1a in relapsing remitting MS patients who presented with at least one relapse in the prior 12 months. The primary aim of this study was to explore whether natalizumab reduced the severity of depression in depressed patients with MS who participated in the SENTINEL trial.

Methods: In this study we used data from the SENTINEL trial in which participants were randomized to receive IFN β -1a+natalizumab or IFN β -1a+placebo. The investigators collected Beck Depression Inventory (BDI)-II scores at baseline and at weeks 24, 52, 76 and 104. Among the 749 subjects with BDI-II data collected at baseline (63.9% of 1171 total subjects), 50/376 (13.3%) in the natalizumab+IFN β -1a group and 54/373 (14.5%) in the placebo+IFN β -1a group were judged clinically depressed based a BDI-II cutoff score of 19. A mixed effects model, adjusting for baseline differences including baseline BDI-II score and disease duration (>5 years vs $\leq$ 5 years), was used to evaluate a natalizumab treatment effect in the temporal dynamics of BDI-II among patients with depression at baseline.

Results: Eighteen patients (36%) in the natalizumab+IFN β -1a group and 10 patients (18%) in the placebo+IFN β -1a group had a predicted improvement in BDI-II score of $\geq$ 50% between baseline and week 104 (P<0.05). At week 104, the estimated difference in adjusted mean change in BDI-II scores from baseline was 4.77 points better in the natalizumab+IFN β -1a arm compared to the placebo+IFN β -1a arm and was statistically significant (p<0.01).

Conclusions: MS patients who were depressed at baseline given natalizumab+IFN β -1a had a statistically significant, four-fold greater depression treatment response than those given placebo+IFN β -1a. This suggests that natalizumab has an antidepressant effect on MS patients, consistent with the research suggesting that inflammation is etiologically related to depression. The possible use of natalizumab in severe, refractory depression would be a plausible next avenue of investigation.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? James Potts: Employee of Biogen and holds stock and/or stock options in Biogen

Denise Campagnolo: Employee of Biogen and holds stock and/or stock options in Biogen

Richard Rudick: Employee of Biogen and holds stock and/or stock options in Biogen

Gisele von Buren: Employee of Biogen and holds stock and/or stock options in Biogen

Neurocritical Care

S332. Reemergence of Japanese Encephalitis in South Korea, 2010-2015

Jun-Sang Sunwoo, Jangsup Moon, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea

Following the introduction of the national immunization program for children in 1983, Japanese encephalitis (JE) was nearly eliminated in South Korea; over the past 3 decades fewer than 0.02 cases per 100,000 population have been reported annually. However, JE has reemerged since 2010, and we herein presented the epidemiological data focusing on the recent increase of JE cases in South Korea. From 2010 to 2015, 129 JE cases were reported. The median age of the patients with JE was 53 years and 43.4% were female patients. On an average, affected female patients were older than male patients ($p = 0.017$). Patients aged 50–59 were the most affected group (37.2%), followed by those aged 40–49 (24%), whereas the patients aged under 19 accounted for only 3.1% cases. Regarding the geographical distribution, 45% of cases originated in Seoul, the capital of South Korea, and Gyeonggi Province, the area surrounding Seoul. The case fatality rate for JE increased from 9.1% (1985–2009) to 21.3% (2010–2014) ($p = 0.055$). It is suggested that the reemergence of JE not only represents a numerical increment of cases, but also represents an association with increased disease severity. Although epidemiology of JE is largely contingent on the ecology of vectors and amplifying hosts, total numbers of mosquitoes, and the individual numbers of *Culex Tritaeniorhynchus*, collected every year have been gradually declining since 2010. In addition, seropositive rates for Japanese encephalitis virus (JEV) in swine have steadily decreased, reaching 10.2% in 2015. The surveillance data indicate that additional factors may have contributed to recent outbreaks of JE. In terms of public health, close attention is required concerning the gradual increase in cases of JE and policies regarding adult vaccination against JEV.

S333. Confirming Smear-Negative Central Nervous System Tuberculosis in a Comatose Patient: Case Report and Review of Literature

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Introduction: Confirming *Mycobacterium tuberculosis* (MTB) infection in the central nervous system (CNS) is challenging because cerebrospinal fluid (CSF) smears for acid-fast bacilli (AFB) can be insensitive and AFB cultures are slow-growing. We report a case of a comatose patient with CNS MTB infection whose initial workup revealed nonspecific meningoencephalitis with multiple negative CSF and sputum AFB stains.

Case report: A 46 year-old HIV-negative man from Guyana with diabetic nephropathy presented with subacute headache and confusion, followed by rapid deterioration into coma requiring intubation. CSF analysis revealed 20 erythrocytes/cmm, 123 neutrophils/cmm, glucose 106 mg/dl, and protein 433 mg/dl. Noncontrast brain MRI revealed only a limited area of restricted diffusion in the orbitofrontal lobes, with mild hydrocephalus and ventriculitis. Despite empiric antimicrobial therapy for meningitis and placement

of a ventriculostomy with aggressive drainage, the patient's comatose state did not improve. Bacterial and fungal cultures from CSF remained negative.

Results: Multiple AFB smears of the patient's CSF and sputum were negative, and an initial QuantiFERON®-TB Gold In-Tube test (QFT-G) was indeterminate. A CT scan of the patient's chest, abdomen, and pelvis was nondiagnostic. Repeat QFT-G returned positive, indicating either active or latent MTB, and drug therapy for MTB was initiated. Bone marrow biopsy revealed non-caseating granulomas, consistent with but not definitively diagnostic of MTB. A confirmatory CSF Xpert MTB/RIF test (real-time PCR for MTB) for active MTB subsequently did return positive with a rapid turnaround time. Despite initiation of MTB therapy, the patient was eventually made comfort measures due to multi-organ dysfunction. A diagnosis of disseminated MTB was later reconfirmed by positive CSF and sputum AFB cultures, two weeks following presentation.

Conclusion: This case demonstrates the challenges of rapidly diagnosing CNS MTB infection in a neurocritically ill patient and highlights the role of Xpert MTB/RIF testing of CSF as a confirmatory tool.

S334. Improvement in Midline Shift Is Associated with Survival after Decompressive Hemicraniectomy in Large Hemispheric Infarctions

Joanna I. Ramiro, Rajat Dhar, Eliahu Feen and Abhay Kumar. Saint Louis, MO

Background And Purpose: Patients with malignant edema after large hemispheric infarction (LHI) may remain at risk of death despite decompressive hemicraniectomy (DHC). We investigated factors associated with in-hospital mortality in these patients.

Methodology: This retrospective cohort study identified 29 patients over six years. Patient demographics with pre- and post-DHC data were analyzed in relation to in-hospital mortality.

Results: DHC was performed at a median of 52 hours. Mortality was 28% (8/29); postoperative survival was significantly lower for dead vs alive (3 ± 1 vs 12 ± 2.5 days), $p = 0.001$. The cause for death was herniation in only two patients, while remaining died due to withdrawal of care. None of the dead had any neurological improvement. Patients had an average preoperative midline shift (MLS) of 10 ± 3 mm. Improvement in MLS on first postoperative imaging (POI₁) to preoperative imaging (PreOI) was significant in survivors (-2.8 ± 4.0 mm) compared to nonsurvivors (2.6 ± 3.5 mm), $p = 0.002$. Patients going to rehab were significantly younger (48 ± 11 vs 62 ± 13 yrs, $p = 0.005$), and also had significant improvement in POI₁ to PreOI MLS (-3.8 ± 3 vs 1 ± 4.5 mm, $p = 0.002$). Other variables (NIHSS, age, ICP) did not have any significant contribution to patient outcomes.

Conclusion: Immediate improvement in MLS when seen on POI₁ after DHC could predict survival as well as favorable disposition. Prospective, larger studies are needed to validate our findings.

S335. Gabapentin Use to Decrease the Requirement of Intravenous Infusion Sedatives Among Patients with Acute Brain Injury in the Neurocritical Care Unit: A Case Series

Christa O'Hana V. San Luis and Xin Qi. Jackson, MS

Background: Gabapentin classically has been used to treat neuropathic pain. In the neurocritical care unit (NCCU), its use has been limited to patients with neuropathy and spinal cord injury. We report 3 patients with acute brain injury with neither neuropathic symptoms nor spinal cord injury (SCI), who required multiple intravenous infusions for sedation and intracranial pressure control, for which gabapentin was used as an adjunct to decrease intravenous infusion medication requirements.

Methods: Retrospective observational case series

Results: Three patients, 1 with post-operative bithalamic infarction and 2 with severe traumatic brain injury was admitted in the NCCU for further evaluation and management. All patients had intracranial pressure monitors upon admission to the NCCU. One patient had an intraventricular tumor resection that was complicated by bithalamic infarction and he subsequently had clinical paroxysmal sympathetic hyperactivity with associated intracranial hypertension while the 2 patients presented with GCS 3 and 5 after motor vehicular accidents and they both subsequently developed intracranial hypertension requiring high and multiple doses of intravenous infusions of sedative medications along with osmolar therapy with hypertonic saline and mannitol. All patients were less than 30 years old at presentation. Gabapentin was continued for two patients until discharge while it was discontinued by the primary team on one patient prior to discharge. Intravenous infusion of sedatives were discontinued within a mean of 7 days after the first dose of gabapentin was started. All patients were weaned off from the ventilator and transferred to rehabilitation.

Conclusion: To our knowledge, this is the first reported series of gabapentin use as an adjunct to decrease intravenous infusion of sedative medications among patients with acute brain injury. All patients tolerated the medications with no reported complications. Larger prospective studies should be done to further support its use in this setting.

S336. Low Cumulative Dose Propofol Precipitating Propofol Infusion Syndrome in an Intra-Cranial Hemorrhage Patient

Alok Dabi and Nicholas R. Metrus. Galveston, TX

Introduction: Symptom constellation that constitutes Propofol infusion syndrome (PRIS) is a rare but potentially fatal condition, usually associated with a large cumulative dose of Propofol (above 5milligram/kilogram body-weight). We present a case of Propofol infusion syndrome that developed at much lower cumulative dose (3.6milligram/kilogram body-weight) and in a relatively short duration (just over 48 hours) of its infusion.

Case presentation: A 46 years old gentleman, weighing 91 kilograms, with past history of untreated hypertension, was admitted with acute left hemiplegia and hemineglect, secondary to right basal ganglia hemorrhage. Few hours post

admission, he needed intubation for depressed sensorium, with subsequent sedation by Propofol infusion. The range of Propofol infusion used was 50 to 80 micrograms/kilogram/hour with aim for sedation and to control focal epileptiform discharges found later on electroencephalogram. By day 2 of admission, he developed acute renal dysfunction, progressing to high anion-gap metabolic acidosis, episodic bradycardia, elevated troponin, rhabdomyolysis and hypertriglyceridemia by day 3 of admission. The Propofol infusion was discontinued on day 2 with total duration of about 48.5 hours of its use, resulting in a cumulative dose of 3.66milligram/kilogram. Subsequent hospital course was complicated by sepsis, acute respiratory distress syndrome and refractory intra-cranial hypertension needing decompressive hemicraniectomy, with transfer to in-patient rehabilitation upon recovery.

Discussion: Symptom constellation that makes Propofol infusion syndrome includes high anion-gap metabolic acidosis, arrhythmia/other electrocardiogram changes, acute kidney injury, rhabdomyolysis, hypotension, hypertriglyceridemia, cardiac failure, fever etc. Our patient developed all of these symptoms except hypotension and cardiac failure. Most of his symptoms improved after discontinuation of the Propofol infusion, hence supporting this clinical diagnosis. Most of the PRIS cases described in literature occur at cumulative Propofol dose above 5milligram/kilogram, sometimes after over 96 hours of infusion, but our patient developed this syndrome at 3.66 milligram/kilogram cumulative dose (within just 48.5 hours of use). An awareness of this possibility is critical as this syndrome still carries an unacceptably high mortality rate of at least 35%. Presence of sepsis possibly delayed the diagnosis of PRIS in our patient. A watchful observation for PRIS symptoms in daily clinical practice in presence of confounding/overlapping syndromes like sepsis, shock etc. can be challenging. In absence of specific investigative tests and bio-markers, high clinical suspicion remains the crux of early diagnosis of this potentially lethal complication.

Cerebrovascular Disease

S337. Post-Stroke Cognitive Impairment Predicted by Lesion and Functional Status

Richa Sharma, Wendy Chen, Rafael H. Llinas and Elisabeth B. Marsh. Baltimore, MD

Background: Cerebrovascular disease is a major risk factor for cognitive decline. Nearly 2/3 of stroke patients develop some degree of cognitive impairment, and 1/3, dementia. Prior studies have shown that age, education, depression, and pre-stroke cognitive and functional status are predictors of long-term cognition after stroke; however, there is little data regarding cognition and stroke severity in the subacute phase of recovery. The purpose of this study was to investigate factors associated with post-stroke cognition.

Methods: Over a 16-month period, 78 patients returning for follow-up after acute ischemic stroke were administered the Montreal Cognitive Assessment (MoCA). Patient demographics, medical variables (vascular risk factors and medical

co-morbidities), and stroke characteristics (size and location of infarct, Cardiovascular Health Studies (CHS) score of white matter disease, admission and follow-up NIHSS, modified Rankin Scale) were obtained. Student's *t*-tests, Chi-squared analyses, and multivariable linear regressions were used to determine factors associated with poor cognitive performance compared to a control group (*n*=32) presenting after transient ischemic attack or stroke mimic.

Results: One hundred and ten patients (stroke and non-stroke) were seen in follow-up a median of 60 days post-event. The mean age was 62.5 years; 24% were black, 56% were women, and 95% had a high school education or greater. Forty percent had a prior stroke, 8% prior dementia, and 34% took an SSRI. Among stroke patients, the mean admission NIHSS was 4.4, follow-up NIHSS 1.8, and follow-up mean Rankin 1.8. The average infarct size was 17.3cm³ with a CHS score of 3.9.

The average MoCA score for the total sample was 23.7. Stroke patients scored 6 points lower than controls (22 versus 28; *p*<0.01). Among stroke patients with low NIHSS (<5; *n*=46), the mean MOCA score was 23.6, higher than larger NIHSS scores (mean 19.23), but lower than controls (mean 27.8). The greatest differences were noted in executive function, attention, orientation, and abstraction, with no difference in language or recall. After stroke, MoCA scores were most significantly associated with prior dementia (*p*=0.0003), cortical infarct (*p*= 0.0158), NIHSS on follow-up (*p*= 0.0121), and CHS score (*p*=0.0008).

Conclusion: Patients post-stroke are significantly more likely to exhibit cognitive impairment in the weeks following infarct compared to controls. Degree of impairment is dependent on stroke severity, but seen even in mild stroke. The natural history of cognitive recovery and factors predicting permanent impairment require further study.

Movement Disorder

S338. Remembering James Parkinson (1755-1824): His Historic Essay on the Shaking Palsy, and His Prodigious Eclectic Career as a "Physician for All Seasons"

David Roby, Alison Roby, Anusha Edara and Gary Horowitz. Philadelphia, PA and University Park, PA

In 1817 James Parkinson published his essay describing six patients with resting tremor, flexed body posture and festinating gait which began insidiously around 60 years of age. The senses and intellect were normal. However, over time patients showed progressive deterioration including speech and swallowing dysfunction, sleep disturbance, constipation, delirium, and depression. Parkinson reviewed prior literature on similar conditions, apologized for lack of anatomic information, but urged his readers to study such patients. In 1884 Charcot proposed that the condition be referred to as "Parkinson's disease."

While many are familiar with Parkinson's contribution to movement disorders, an appreciation of Parkinson's diverse interests and accomplishments is generally lacking. In 1795, he attended a series of anatomic lectures by John Hunter and transcribed them using short hand. In 1800 he

published the Hospital Pupil which summarized attributes important for a medical career and offered suggestions for a medical school curriculum. He recommended oversight of drug production and sales. He authored guides to topics of interest to the lay public such as the Villager's Friend and Physician. He was also highly critical of political and social inequities and published essays under the pseudonym of "Old Hubert." This political radicalism nearly led to him being imprisoned. Parkinson urged good childrearing, and avoidance of dangerous sports. He proposed reform in mental health care and the process of incarceration. In his later years, he devoted attention to his longstanding interest of geology and paleontology. In 1978, Melvin Yahr noted that "in all of his activities, Parkinson brought the approach of keen astute observation, good deductive reasoning, and above all, an empathy for and desire to benefit mankind. By every criterion, he was truly a physician for all seasons."

Neuro-Oncology

S339. Leptomenigeal Carcinomatosis: A Rare Complication of Gastric Carcinoma

Aashrai Gudlavalleti, Siddharth Shah, Dalvir Gill, Ryan Asterita, Nibaal Saad and Sheila Lemke. Syracuse, NY

Background: Leptomenigeal carcinomatosis[LMC] is characterized by infiltration of the pia mater and arachnoid membrane by malignant cells. It is estimated to occur in 5%-8% of cancer patients and represents an advanced stage of cancer. While seen in all malignancies, it is quite rare in solid tumors, especially in those of gastric origin. It is important to recognize LMC early as it has a poor prognosis and treatment options are limited. We describe a case of LMC presenting with headache in a patient with gastric cancer.

Case report: A 64 year old male with signet ring cell gastric adenocarcinoma with metastases to the pelvis (diagnosed 7 months earlier), presented with occipital headaches, nausea and vomiting for a week following a whiplash injury to his neck. He had completed 6 cycles of chemotherapy with DCF(Docetaxel, Cisplatin and 5-Fluorouracil). Magnetic Resonance Imaging (MRI) of the head (with Gadolinium contrast) was remarkable for abnormal signal hyperintensity in the subarachnoid spaces, consistent with subarachnoid hemorrhage, carcinomatous meningitis or infectious meningitis. Cerebrospinal Fluid (CSF) analysis and cytology were consistent with metastatic adenocarcinoma, indicating leptomenigeal carcinomatosis (LMC) of gastric adenocarcinoma. Intrathecal methotrexate was started, but the patient started experiencing non-focal neurological symptoms due to elevated intracranial pressures. CSF drainage via intrathecal reservoir only provided transient relief. Given his poor prognosis, the patient was discharged home with hospice care. He expired within a month of discharge.

Discussion: LMC is very rare in gastric cancer. It is estimated to occur in 0.16-0.69% of all gastric cancer, which is lower than that of breast cancer, lung cancer and malignant melanoma. LMC is associated with features such as disseminated disease, undifferentiated carcinoma or signet-ring cell

gastric adenocarcinoma. The most common presentation of LMC is headache or altered mental status. Gadolinium enhanced MRI can be used to diagnose LMC. However, the gold standard is a positive cytology on cerebrospinal fluid studies. Overall survival in LMC is short with a median survival of 4-5 weeks without treatment, and 2-4 months with treatment. Treatment options include intrathecal chemotherapy, systemic chemotherapy and best supportive care. Methotrexate is the most widely studied and the most commonly used intrathecal agent, but cytosine arabinoside has been used for the same as well. Clinicians should have a high suspicion in patients with advanced gastric cancer presenting with features such as headache, nausea, vomiting or altered mental status of undetermined etiology.

S340. A Rare CNS Infection in an Immunocompetant Adult Masquerading as a Metastatic Brain Tumor

Ali Sheharyar and Aparna M. Prabhu. Philadelphia, PA

Introduction: Differentiating brain abscesses from cystic or necrotic tumors by CT/MR imaging can be challenging. Difficulties encountered are mainly due to the combination of non-specific clinical findings and similarities in the morphologic appearance on imaging of intracranial mass lesions, such as cystic gliomas, metastases, and brain abscesses. Of all cerebral abscesses, only 2% are due to *Nocardia* species.

Case report: A 51-year-old previously healthy male presented with a two week history of bi-temporal headaches. History and review of systems was otherwise non-contributory. His initial neurological exam was benign. Non contrast CT head revealed left temporal mass lesion with surrounding vasogenic edema. Contrast enhanced CT head and CT perfusion imaging were consistent with brain neoplasm with increased cerebral blood volume in the surrounding rim of enhancement. Evaluation for the primary tumor revealed a nodule in the left lung suspicious for small cell cancer. He was empirically treated with intravenous steroids.

He underwent craniotomy for possible resection of the mass and "pus" was encountered intra-operatively. Pathology revealed filamentous gram positive, partially acid-fast rods later confirmed as *Nocardia farcinica*. Therapy was initiated with intravenous Amikacin and Bactrim; later switched to oral Bactrim and Augmentin.

Conclusion: This case reflects that differentiating pyogenic brain abscess from a brain neoplasm can be challenging despite advanced imaging. Tissue diagnosis remains the gold-standard. Aggressive management to investigate for a potentially treatable pathology is essential for a better outcome particularly in the case of cerebral Nocardiosis where prognosis is dependent upon an early initiation of appropriate antimicrobial therapy.

S341. Extra-Cranial Metastatic Glioblastoma Presenting with Lhermitte's Phenomenon, Torticollis and Quadriparesis

Michael Ruff and Sean Pittock. Rochester, MN

Objective: Illustrate a case of extracranial glioblastoma metastasis presenting with a cervical myelopathy, torticollis and Lhermitte's phenomenon.

Background: Extracranial glioblastoma metastases are exceedingly rare, though described in the literature. Epidural glioblastoma metastasis presenting as a cervical myelopathy with torticollis and Lhermitte's phenomenon has not previously been described in the English literature.

Case: A 20-year-old male status post subtotal bifrontal "butterfly" glioblastoma resection complicated by perioperative left ACA infarction developed unsteadiness, progressive quadriparesis, urinary retention, and lethargy over 48 hours. He was six months postoperative status post radiotherapy with concomitant and adjuvant temozolomide. Physical exam was notable for flattened affect, environmental dependence, and neck stiffness with rightward torticollis. Motor examination revealed prominent gegenhalten, and moderate weakness of the deltoid, triceps, biceps, wrist extensors and finger extensors with lateralization of weakness to the left. There was an upper motor neuron pattern of weakness present in the bilateral lower extremities, this again lateralized to the left. Rectal tone was preserved. Reflexes were pathologically brisk in the bilateral upper extremities with extensor response to plantar stimulation on the right, and equivocal response on the left. The patient was able to sit upright with assistance; he was unable to stand unassisted. There was decreased pinprick sensation in the lower extremities and chest relative to the upper extremities. Inflammatory markers were markedly elevated. CT head did not show a significant change from prior imaging. Broad spectrum antibiotics were started at meningeal doses. LP was not performed. Emergent cervical MRI was obtained which revealed a mass lesion compressing the cervical spine at C2-C5 (In retrospect the lesion could be seen months prior on surveillance imaging). The patient underwent urgent posterior decompression with debulking of the mass. Due to a strong initial suspicion for abscess, no intra-operative pictures were taken, however final pathology was consistent with metastatic glioblastoma. The patient made minimal recovery post-operatively and unfortunately continued to have progression of both intracranial and extracranial disease. Palliative spinal radiation was pursued. The patient was discharged to hospice and passed within six weeks of presentation.

Conclusion: Extracranial glioblastoma metastases are exceedingly rare, though described in the literature. Subacute onset of neck pain and torticollis with Lhermitte's phenomenon in a patient with Glioblastoma may represent epidural cervical spine metastases. As treatments and patient survival improve glioblastoma metastasis may become more common.

Cerebrovascular Disease

S342. A Rare Case of Cerebral Venous Sinus Thrombosis Secondary to Danazol Therapy

Gobind P. Singh, Apoorv Prasad, Seyedali Hejazi, Armin Maghsoudlou and Carmen M. Martinez. Syracuse, NY

Introduction: Cerebral venous sinus thrombosis (CVST) is an infrequent disease with a variety of causes that predispose to hypercoagulability and can present with non specific

symptoms like headache, focal weakness and seizures. Estrogen containing formulations such as oral contraceptive pills have been documented to produce hypercoagulable state causing CVST. However, there are very few reports of CVST in patients due to androgenic drugs. In this case report we present a case of deep cerebral venous thrombosis secondary to Danazol therapy.

Case: A 54 year-old female with no vascular risk factors presented with confusion and inability to express herself for a day. Her medical history was significant for dysfunctional uterine bleeding for which she was prescribed Danazol 100 mg BID about four months ago. Neurological examination revealed expressive aphasia and right sided weakness. CT head showed hypo attenuation in the left thalamus region. MRI brain revealed parenchymal edema within the left thalamus, basal ganglia and a small associated infarct could not be excluded. CT venogram was performed which revealed acute thrombosis of the straight sinus, vein of Galen, internal cerebral veins and left thalamostriate vein. Patient's hypercoagulable workup was negative. Danazol was discontinued after discussion with her gynecologist. She was started on Coumadin with goal INR of 2-3 for three months. She improved remarkably during her hospitalization and was later discharged home.

Discussion: Danazol is a synthetic androgenic steroid which is used for the treatment of endometriosis and fibrocystic breast disease. It induces a pro-thrombotic state by increasing thromboxane A2 or decreasing production of prostacyclin due to its androgenic activity. This enhances platelet aggregation, thereby increasing the risk of thrombotic events. In addition, it may also cause increase in coagulation factors but is not fully understood. Aforementioned case developed thrombotic complications from therapeutic dose of Danazol for four months.

Conclusion: Androgen administration may predispose to hypercoagulable state leading to arterial and venous thrombosis. It is thus prudent to consider diagnosis of CVST with androgens as underlying cause in differentials for a patient who is on exogenous androgen therapy presenting with central neurological symptoms. The treatment can then be initiated in a timely fashion to prevent serious long term complications.

S343. Cerebral Venous Sinus Thrombosis (CVST) Associated with Methylenetetrahydrofolate Reductase (MTHFR) A1298C Mutation During Early Pregnancy: Case Report and Literature Review

Yongxing Zhou, Abhishek Anand, Faranak Najibi, Shariff Dunlap, Roger Weir and Annapurni Jayam-Trouth. Washington, DC

Background: CVST accounts for 0.5-1.0% of all strokes. CVST is known to occur in a variety of systemic conditions. Gowers (1888) suggested an association of CVST with pregnancy. In late pregnancy and in the puerperium such an association is well recognized. Often it is found to occur in pregnancy with obstetric complications, but it is exceedingly rare in the first trimester of pregnancy, only a few cases of CVST have been reported. MTHFR plays a central role in

the folate cycle and mutations of MTHFR are associated with vascular disease. Upon literature review, there has been no reported case of CVST associated with MTHFR A1298C mutation during early pregnancy. Herein, we report the first case of patient who developed CVST in her eighth week of pregnancy was found to have MTHFR A1298C mutation.

Case Presentation: This is a 29-year-old female with past medical history of migraine, CVST, 8 weeks pregnancy, and a strong family history of vascular thromboembolism who presented with left-sided tempero – occipital headache. The pain was throbbing, intensity of 9 to 10/10, related to postural changes. The headache was associated with nausea, vomiting, and photophobia. She went to the Laurel Regional Hospital ER on 05/22/15 and was discharged home with pain medications. Because of persistent, severe headache she went back to the same ER on 05/24/15. CT head, MRI brain done, and patient was transferred to Howard University Hospital (HUH) for further management. Medical records showed that the patient was admitted to HUH in February 2012, with the complaint of severe headache. At that time, she was using a topical contraceptive patch (Ortho Evra) for approximately 1 year. She was diagnosed with CVST, treated with anticoagulation and discharged on Coumadin for a year. Her hypercoagulable workup showed a MTHFR A1298C mutation. During her hospitalization, repeated MRI showed acute left occipital hemorrhagic infarction and the MRV confirmed left-sided transverse CVST. She was started on a heparin drip initially, followed by Lovenox 100 mg subcutaneous once daily. Her symptoms, imaging studies improved, discharged with Lovenox and was instructed to follow up with neurology, hematology, and OB/GYN.

Conclusion: Diagnosis of CVST during early pregnancy is important and should be differentiated from other disorders presenting as headache. Timely diagnosis is important as these patients are shown to benefit from anticoagulation therapy.

S344. Postpartum Cerebral Angiopathy Presenting with Intracerebral Hemorrhage-Possibly an Under Diagnosed Condition

Syed W. Abbas and Oleg Y. Chernyshev. Shreveport, LA

Objective: To report an unusual case of postpartum cerebral angiopathy presenting with thunderclap headaches and intracerebral hemorrhage (ICH)

Introduction: Reversible cerebral vasoconstriction syndrome or RCVS is a rare condition associated with transient but multifocal cerebral vasospasm resulting in multiple areas of ischemic and hemorrhagic strokes. About 7-8% cases of RCVS can present in immediate postpartum period also known as postpartum cerebral angiopathy (PPA). Clinical information about this condition is limited to case reports showing median age of onset at 32-years mostly within 5-7 days postpartum. Symptoms include thunderclap headaches, seizures, focal neurological deficits and coma. Likely mechanisms include female hormonal changes, exposure to ergot alkaloid derivatives and use of antidepressants. Other causes

of postpartum thunderclap headaches include subarachnoid hemorrhage and cerebral venous sinus thromboses.

Case Description: We report a 27-years old female who presented on day-5 postpartum with thunderclap headaches. It was followed by rapid onset confusion, weakness of the upper and lower extremities on the right side and inability to speak. She had an uneventful gestational period and delivered a healthy baby boy at 38 weeks. Neurological examination showed a lethargic female patient with global aphasia, right sided hemiparesis and sensory impairment. Laboratory tests revealed ESR of 35 mm/hr and unremarkable urine drug screen, infection and autoimmune panels. Spinal fluid analysis was also normal. CT head showed left frontal and parietal region hematoma. CTA head and neck revealed the presence of the cerebral vasospasm. Conventional four vessel angiogram confirmed the presence of cerebral vasoconstriction. MRI Brain demonstrated focal areas of hemorrhagic infarcts most of which co-incided with areas of vasospasm. Serial transcranial doppler scans were used to monitor the course of severity of the disease showing progressive resolution of vasospasm. She was started on oral verapamil with remarkable improvement in her neurological deficits over next 2 weeks.

Discussion and Conclusion: Intractable headaches in postpartum period may be the harbinger of reversible cerebral angiopathy which may be a life threatening and possibly under diagnosed condition. Physicians should be aware of this condition as early angiographic evaluation and appropriate treatment would lead to favorable clinical outcome.

S345. Management Dilemmas Among Anticoagulated Patients with Intracranial Bleeding and Mechanical Heart Valves

Jorge Ortiz, Rochelle Sweis and Jose Biller. Maywood, IL

Objective: To review optimal timing of reinstating antithrombotic therapy for patients with mechanical heart valve prostheses and warfarin-induced major bleeding.

Background: Life-long oral anticoagulation is recommended in patients with mechanical heart valve prostheses but poses risk of major bleeding. Management dilemmas arise in patients with mechanical heart valves and warfarin-induced intra-cranial bleeding. Without anticoagulation, risk of major embolism reaches 4% per patient year. Warfarin reduces this incidence by approximately 75% to an annual risk of 1%. Duration of holding anticoagulation and optimal timing of recommencing therapy remains controversial but should balance the risk of thromboembolic complications versus further life-threatening bleeding.

Methods: Case report and literature review

Results: 62-year-old man with history of rheumatic fever, status post mechanical aortic valve replacement (AVR) and mitral valve replacement (MVR), and chronic atrial fibrillation (CHA2DS2-VASc Score = 2, HAS-BLED Score = 1) on warfarin and aspirin presented with acute on chronic right subdural hematoma (SDH) in the setting of supratherapeutic INR. Phytonadione was administered and burr hole drainage performed but a fronto-parietal craniotomy was required due to expanding SDH. In order to avoid lifelong

anticoagulation, bioprosthetic valve replacement and MAZE procedure were considered but timing was uncertain. Delaying surgery increased risk of valve thrombosis and thromboembolism but prompt intervention requiring heparinization during cardiopulmonary bypass could exacerbate intracranial bleeding. Patient remained off anticoagulation and antiplatelet therapy for four weeks after which he underwent redo of AVR with #21 Magna Ease valve and MVR with #29 Mosaic valve and MAZE procedure without intraoperative nor postoperative hemorrhagic complications. He was discharged home on aspirin.

Conclusion: In patients with warfarin-induced major bleeding and mechanical heart valves, the safe period of holding anticoagulation for intracranial bleeding varies from 7-14 days and 48-72 hours for extra-cranial bleeding after the onset of bleeding.

S346. Amphetamine Use Presenting as Bilateral Basal Ganglia Hemorrhage

Alyssa E. Bautista, Ima M. Ebong, Erika Marulanda-Londoño and Sebastian Koch. Miami, FL

Introduction: Hemorrhagic stroke is considered less common than its ischemic counterpart, more so bilateral intracerebral hemorrhage (ICH) which is rare. Bilateral ICH has been associated with hypertension, amyloid angiopathy, hemorrhagic infarction, coagulation defects, and sinus thrombosis. Amphetamine abuse has been implicated in hemorrhagic stroke, but rarely bilateral as in this case.

Presentation of Case: We report a case of bilateral basal ganglia ICH related to dextroamphetamine/amphetamine abuse, in the absence of hypertension, infarction, coagulopathy, or sinus thrombosis. A 36-year old male with dextroamphetamine/amphetamine use by history, presented with seizures and was brought in with a blood pressure of 120/66, comatose with ocular clonus, deep tendon hyperreflexia, inducible clonus, muscle rigidity, mydriasis, and diaphoresis. Urine was positive for amphetamines. Computed tomography showed bilateral large putaminal hemorrhages.

Discussion: Significant increases in blood pressure and cerebral arterial spasm related to adrenergic surge, and cerebral vasculitis have been proposed mechanisms of amphetamine-related ICH in literature. The nature of bilaterality has been poorly understood. Amphetamine-related damage to striatal dopamine transporter axons have been variously described, but it is unknown if this is coincidental or if there exists a curious link to the susceptibility of bilateral basal ganglia to amphetamine-related ICH, owing to this rarity.

Conclusion: With drug use often presenting as ICH in young individuals, awareness of this unusual radiographic finding in the absence of hypertension should lead to suspicion of amphetamine abuse.

S347. Thalamic Venous Infarcts: Etiology, Therapy and Outcome

Elina Zakin, John Liang, Gordon Cantor and Stanley Tuhim. New York, NY and Elmhurst, NY

Background: The presentation of bilateral thalamic venous infarctions is often under-recognized. Venous drainage of

the thalamus occurs via the thalamo-striate veins, which come from the internal cerebral veins, ultimately draining into the straight sinus. Thus, thrombosis of a common point of drainage can result in bilateral thalamic venous infarction (Hoitsma 2002). Clinician awareness of this condition is important for prompt diagnosis and has important therapeutic implications.

Methods: We present two cases of deep CVST (cerebral venous sinus thrombosis) with thalamic venous infarction with different time courses of presentation and etiologies.

Case report: The first case is of a 60 year-old engineer with hypertension, hyperlipidemia and diabetes who presented with several months of progressive cognitive impairment and gait unsteadiness, without complaint of headache. Examination revealed poor attention and memory, bradykinesia, dysarthria and mild left hemiparesis. Imaging showed bi-thalamic hypodensities on CT with corresponding T2-FLAIR hyperintensities in bilateral thalami with diffusion restriction and contrast enhancement on MRI. Vessel imaging revealed straight sinus thrombosis and cerebral angiography elucidated a complex dural arterio-venous fistula (dAVF) at the vein of Galen and straight sinus. The patient underwent staged embolization of the dAVF arterial feeders with good neurologic outcome. The second case is of a 30 year-old female with microcytic anemia (hemoglobin 7.3g/dL) who presented with right sided throbbing headache and hypersomnolence. Examination revealed lethargy and global aphasia without other focal deficits. MRI brain showed T2-FLAIR hyperintensities involving bilateral thalami, bilateral basal ganglia and the left cerebellar hemisphere with diffusion restriction. MR venography showed extensive venous sinus thrombosis involving the vein of Galen, straight sinus and right transverse sinus. Cerebral angiography showed incomplete recanalization of the straight, left transverse and left sigmoid sinus with persistent thrombosis of the right deep venous system. Due to the extent of high grade narrowing of the straight sinus, endovascular recanalization was unsuccessful and the patient received systemic anticoagulation with improvement in mental status and headache resolution.

Conclusion: CVST can have both acute and insidious courses of presentation with distinct etiologies. The first case presented with a subacute course of cognitive decline without headache, found to have CVST, whose etiology was a complex dural AVF. The second case of CVST presented with acute headache and lethargy and was found to have microcytic anemia, which has previously been reported as a risk factor for CVST (Balci 2007).

S348. A Peculiar Case of Acute Vertebral Artery Dissection in the Setting of Newly Diagnosed Multiple Myeloma

Syedali Hejazi, Gobind Singh, Armin Maghsoudlou and Gaganjot Singh. Syracuse, NY

Introduction: Multiple myeloma (MM) is a neoplastic disorder caused by monoclonal proliferation of plasma cells derived from immunoglobulin-secreting B cells, with cervical spine fracture causing vertebral artery dissection being a

very rare complication. We report a case of acute vertebral artery dissection in a patient with newly diagnosed MM, who presented with vertigo and headache.

Case: A 57-year-old female was admitted to our institution for a new sudden onset of headache, vertigo, and left-sided neck pain of 2-hour duration. Physical examination revealed normal vital signs, tenderness over the neck posteriorly, and right-beating horizontal nystagmus in both eyes. CT head was unremarkable. CTA head and neck showed multiple lytic lesions causing acute pathological fracture of C1 cervical vertebrae and left vertebral artery dissection at that level. MRI brain revealed acute left cerebellar infarct. Laboratory tests were significant for normochromic normocytic anemia, elevated erythrocyte sedimentation rate, serum total protein of 11.6 gm/dL, and monoclonal band in gamma region on serum protein electrophoresis. Bone marrow biopsy demonstrated 34% plasma cells consistent with MM. The patient was started on anticoagulation therapy with warfarin as well as on a chemotherapy regimen consisting of vincristine, doxorubicin, and dexamethasone. The patient has been doing well in the last two years of follow up.

Discussion: MM is characterized by malignant clonal proliferation of immunoglobulin secreting differentiated B-lymphocytes and plasma cells. Pathological fracture of cervical spine due to MM is very rare. Vertebral artery is susceptible to injury or occlusion at C5-C6 vertebral level, atlanto-axial joint, and atlanto-occipital joint secondary to stretching or tearing of intima or compression of the artery following cervical fracture or dislocation. Intima tear can trigger platelets aggregation and clot formation which can lead to embolic stroke. CTA and MRA are non-invasive diagnostic techniques that can be used to evaluate vertebral artery dissection, whereas cerebral angiography is reserved for cases in which these modalities are non-diagnostic. Treatment with anticoagulants is recommended for six months in patients who have neurological symptoms from extracranial dissection. For patients with recurrent ischemic events despite anticoagulation therapy, stent placement or surgical treatment may be considered.

Conclusion: Vertebral artery dissection is a potentially life-threatening complication of MM which needs prompt diagnosis to initiate therapy in a timely fashion.

S349. A Rare Presentation of Disseminated Cryptococcal Infection as Acute Stroke

Gobind P. Singh, Yi Mao, Varada Nair and Antonio Culebras. Syracuse, NY

Introduction: Cryptococcosis is an invasive fungal infection which is acquired through inhalation and may become disseminated to lungs, brain, skin in immunocompromised host. Involvement of the brain causes meningoencephalitis which typically presents with indolent symptoms of headache, fever, malaise and altered mental status. There are very few cases reported where the presenting symptom is an acute stroke. In this case report we present a case of immunocompromised patient where disseminated cryptococcosis presented with multiple strokes.

Case: A 56 year old Asian male with history of hypertension, end stage renal disease status post kidney transplantation on immunosuppression therapy presented to our stroke service with sudden onset binocular diplopia and right eyelid droop. In addition, there was history of recent weight loss and 2 week old skin lesion on the back. Neurological exam revealed right pupillary sparing third nerve palsy with right eye down and out in resting gaze with inability to adduct. CT head revealed hypodensity in the paramedial right midbrain and periaqueductal area. MRI Brain without contrast was positive for infarct in the right midbrain and along the course of right third nerve and small acute infarct in ventromedial left thalamus. MRA head and neck did not reveal significant stenosis of major vessels of head and neck. Lumbar puncture was significant for 55/mm³ WBCs, Glucose 6mg/dl, Protein 253mg/dl and was positive for Cryptococcal Ag in CSF. Xray chest showed round, 2.5 cm left upper lung field opacity which was confirmed with CT Thorax. CT guided lung biopsy was positive for Cryptococcus. Treatment plan involved initiating Amphotericin and Flucytosine for 2 weeks followed by Fluconazole.

Discussion: Cryptococcus infection has been postulated to induce vasculitis in the host although the exact mechanism is not clear. Direct response to fungal antigen causing inflammation in the walls of blood vessels is the most likely explanation. Vasculitis as well as brain tissue inflammation can thus predispose the patients with chronic cryptococcal meningitis to infraction. Hence, in some instances stroke may follow the typical presenting symptoms of meningitis, very rarely is the stroke itself a presenting symptom. Aforementioned case presented with an acute stroke and was found to have disseminated cryptococcus on further investigation.

Conclusion: In immunocompromised patients with very few vascular risk factors, cerebral infarction secondary to opportunistic infections like cryptococcus should be an important consideration in the differential diagnosis of stroke of unknown origin.

Movement Disorder

S350. Enlarged Perivascular-Like Spaces at 3T as an MRI Sign of Multiple System Atrophy

Abhimanyu Mahajan and Christos Sidiropoulos. Detroit

Objective: To present Enlarged perivascular-like spaces at 3T as an MRI sign of multiple system atrophy.

Background: The ante mortem diagnosis of multiple system atrophy (MSA) remains largely clinical although Magnetic Resonance Imaging (MRI) criteria have been developed as a surrogate diagnostic tool. Putaminal changes such as atrophy and posterior putaminal slit like hyperintensity on T2 weighted images have been proposed to be highly supportive of a diagnosis of MSA. A recent study on 12 MSA-P patients with MRI signs preceding diagnostic criteria by Mestre et al. showed imaging diagnosis of these patients at 25 months, compared to a clinical diagnosis of "possible MSA" at 30 months.

Methods/Design: Two patients presented to our center for evaluation and further management of "Parkinson's-like" features: A 56 year old male with a 36 month long history of tremor dominant parkinsonism and erectile dysfunction and a 65 year old female with a 48 month long history of parkinsonism, severe postural instability, nighttime stridor and sleep apnea. They both had been treated with and had a poor response to Levodopa. Based on the second consensus statement on the diagnosis of MSA, the patients presented with a clinical diagnosis of "probable MSA-P". As part of their further work up, we decided to proceed with 3T MRI Brain imaging.

Results: The 3T MRI Brain images were consistent with atypical and enlarged ovoid perivascular-like T2 hyperintensities in the globus pallidus and posterior putamen.

Conclusions: We hypothesize that this finding may represent a variation of the putaminal hyper intensity sign. These findings should be carefully sought for in cases of atypical Parkinsonism for correlation with clinical criteria for diagnosis of MSA.

S351. Identification a Novel De Novo Mutation of PRKCG in a Patient with SCA14 by Targeted Next-Generation Sequencing Technology

Wei Song, Yafang Hu, Xiaojia Liu and Suyue Pan. Guangzhou, China

Introduction: Spinocerebellar ataxia type 14 (SCA14) is a rare form of autosomal dominant cerebellar ataxias caused by mutations in the protein kinase Cγ gene (PRKCG). Mild, slowly progressive ataxia is a predominant feature of SCA14, sometimes accompanied by myoclonus, cognitive impairment, extrapyramidal signs, and sensory disturbance.

Case report: A 19-year-old Chinese man visited our hospital with a 2-year history of irregular intermittent tremulous movements. The tremulous movements particularly affected the head and trunk, occasionally involved the extremities. These movements were triggered or aggravated by action or tension, usually lasted from minutes to hours, and alleviated by relaxation. He recalled clumsiness while running at approximately age 15 during school sports. His family history was negative. Neurological examination revealed wide-based gait ataxia with inability to tandem walk, dysmetria on finger-to-nose testing, bilateral gaze-evoked horizontal nystagmus, and mild cerebellar dysarthria. Multifocal myoclonus was observed predominantly in the trunk and arm. A trunk tremor was present in the supine position or during walking. A cerebral MRI in this patient showed cerebellar atrophy, most pronounced in the vermis. EEG monitoring revealed no focal disturbances or epileptic phenomena. Targeted exome sequencing of the patient DNA revealed a c.401G>A (p.Cys134Tyr) variant in exon 5 of PRKCG, which was predicted to be pathogenic using in silico prediction algorithms (SIFT and PolyPhen-2). In addition, this mutation was not found in 128 controls of Chinese, the Single Nucleotide Polymorphism database and the 1000 Genomes Project. Combined with the absence of the c.401 G>A variation in his parents, we concluded that this PRKCG variant was a pathogenic de novo mutation,

originating in the index patient or possibly in the (germ-line) cells of one of his parents. For symptomatic treatment, the patient was started on an increasing dose of clonazepam 1 mg at night for three days, building up to a treatment dose of between 2-4 mg in divided dose daily. He found that clonazepam relieve with his symptoms with no side effects.

Conclusions: To our knowledge, this is the first report of a Chinese patient with SCA14 carrying a novel de novo mutation in PRKCG (c.401G>A). Our case expands the spectrum of mutations associated with this condition.

Multiple Sclerosis

S352. Psychometric Evaluation of the Medication Satisfaction Questionnaire (MSQ) to Assess Satisfaction with Glatiramer Acetate Among Patients with Multiple Sclerosis

Lulu K. Lee, Ying Wu, Gary R. Cutter, Jeremy C. Hobart, Natalia M. Flores, Adriana J. Carra, Augusto Grinspan and Sanjay Gandhi. Foster City, CA; Frazer, PA; Birmingham, AL; Plymouth, Devon, United Kingdom; Buenos Aires, Argentina and Weston, FL

Objective: To examine the measurement performance of the Medication Satisfaction Questionnaire (MSQ) for assessing glatiramer acetate (GA) treatment satisfaction among patients with multiple sclerosis (MS).

Background: MSQ was previously developed to assess treatment satisfaction among people with schizophrenia. It has not been examined in people with MS.

Design/Methods: Data from a cross-sectional, internet-based survey of adults (aged 18 years and older) were used to identify those self-reporting an MS diagnosis and currently receiving GA for treatment of MS (N=400). Measures used in the survey included demographics and health characteristics (e.g., age, gender, comorbidities) and satisfaction instruments including the single-item MSQ, the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9), health-related quality of life (SF-12v2), and Hospital Anxiety and Depression Scale (HADS). Pearson correlations were used to assess convergent and discriminant construct validity. Analysis of variance was used to assess known-groups construct validity by examining MSQ score differences across treatment satisfaction groups (low, medium, high) from TSQM item 9 ("Taking all things into account, how satisfied or dissatisfied are you with this medication?").

Results: The moderate and significant correlation between MSQ and TSQM-9 global scores ($r=0.531$) provided evidence to support convergent construct validity. The lower correlations between the MSQ and measures of other variables supported discriminant construct validity [HADS depression subscale ($r=-0.294$), HADS anxiety subscale ($r=-0.186$), SF-12 physical component summary ($r=0.158$), SF-12 mental component summary ($r=0.201$), health utilities ($r=0.206$)]. Known-groups construct validity was supported by the finding that mean MSQ scores were significantly different for people with high (MSQ=5.87),

medium (MSQ=4.81) and low (MSQ=2.77) satisfaction on TSQM item 9, all $P<0.05$.

Conclusions: This study provides evidence to support the measurement performance of the MSQ for assessing treatment satisfaction in this sample of people with MS. Future research could examine an evaluation of predictive validity using a longitudinal study design.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? YW, AG and SG are employees of Teva Pharmaceuticals. NF and LL are full-time, paid employees at Kantar Health. Teva paid Kantar Health for study design, analyses, and publication preparation. JH institution/hospital received clinical service and/or research support from Acorda, Actelion, Biogen, Merck Serono, Genzyme, and Teva. GC is DSMB member and/or consultant.

S353. Understanding Seroconversion and Variability of Indices when Performing Serial JC Virus Testing in Patients with Multiple Sclerosis

John J. Peters and Eric M. Williamson. Philadelphia, PA

Objective: To examine results of serial JC Virus (JCV) index measurements in patients with multiple sclerosis (MS) in hopes to better understand how to assess risk using this test. We have investigated relationships between age, gender, length of therapy, current disease modifying therapies (DMT) and JCV index levels and noticed great variability between repeat JCV index measurements. Rates of seroconversion from negative to positive will be reported, and we aim to demonstrate what happens if alternative values are used as a cutoff for identifying risk.

Background: Positive titers of antibodies against JCV have been shown to be a risk factor for development of progressive multifocal leukoencephalopathy (PML) in patients with MS on natalizumab and hypothesized to be helpful in assessing risk with other DMTs. JCV indices are currently used by clinicians and patients to make decisions on continuing or stopping treatment and there are arguments that higher titers may carry increased risk for PML. Collecting serial indices and establishing relationships between indices and various clinical measures may provide physicians with a better understanding of JCV testing and allow them to better interpret a patient's risk for PML.

Methods: Medical records of patients diagnosed with MS were reviewed and results of serial JCV indices were analyzed over time. Date of diagnosis, age, gender, length and type of current and past DMTs were also collected.

Results: Serial JCV indices of nearly 200 patients were examined, noting many patients had multiple values in time. Using the current cutoff of 0.2, over 15% of patients who previously tested negative seroconverted to a positive result. The variability and chances of having a subsequent test go from below to above or the opposite when using higher cutoff values, including 1 and 1.5, yielded even greater rates of seroconversion than with lower cutoff values.

Conclusions: Given the propensity to fluctuate, our results indicate that repeat testing may be needed to better

interpret JCV status. The variability of JCV indices over time was marked and more pronounced at high titers. Using alternate seroconversion cutoff values, our results seem to make interpretation of this test more complex. This is not yet a proven strategy to assist in predicting risk of PML and given these findings, using the value of the index rather than simple positivity should perhaps be interpreted with caution.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Eric Williamson: Received compensation for consulting for both Teva Neuroscience and EMD Serono

Neurocritical Care

S354. Septic Cavernous Sinus Thrombosis Secondary to Chronic Corticosteroid Use in a Cancer Patient

Narges Moghimi and Mary Chen. Galveston, TX and Houston, TX

Objective: Septic thrombosis of the cavernous sinuses is a potentially lethal illness. We report a patient with lymphoma on long term steroids with septic fungal cavernous sinus thrombosis (CST) and subsequent fatal complications.

Background: 47-year-old female with aggressive T-cell lymphoma as well as autoimmune hepatitis on long term high-dose oral steroids presents to the Emergency Department with neutropenic fever. She is admitted to the Intensive Care Unit where she is managed for acute respiratory failure and septic shock. She is subsequently found to have fungal pneumonia and is started on antifungal medication. Later on, she develops multiple open skin wounds throughout her body as well as right facial cellulitis which is confirmed with Magnetic Resonance Imaging (MRI) of the brain and orbits. Neurology is consulted for acute onset anisocoria. On physical exam she has right ophthalmoplegia. Magnetic resonance venogram (MRV) of the brain shows right cavernous sinus thrombosis and Internal Carotid Artery (ICA) occlusion. Despite aggressive medical management, she develops a new left cavernous sinus thrombosis as well as right middle cerebral artery infarction with hemorrhagic transformation. She is later transitioned to comfort care.

Results: Long-term steroids have immunosuppressive role and increases the risk of opportunistic infections. Fungal septic CST is a rare and potentially life-threatening condition mostly caused by facial, ear or nose infections. Septic CST can be a rare cause of ischemic stroke when complicated by ICA occlusion because of septic arteritis. Even in the era of antibiotics, septic thrombosis of an intracranial venous sinus remains a potentially life-threatening condition.

Conclusions: Long term corticosteroids can weaken immune system and put patient at risk for fungal infections particularly in immunocompromised patients with malignancies. CST is a rare and serious complication secondary to invasive fungal infection with significant morbidity and mortality.

Cerebrovascular Disease

S355WIP. The Importance of Anticoagulation to Prevent Strokes in Patients with Atrial Myxomas

Neeraj Singh and Kathleen Ward. Albany, NY

Left atrial myxomas are thrombogenic and can cause ischemic strokes, but there are no guidelines on whether patients with myxomas should be anticoagulated. We report three cases that reveal the importance of starting anticoagulation in such patients. N.C. was a 72-year-old woman with dysequilibrium causing falls. MRI Brain revealed old bilateral cerebellar infarcts and an acute right corona radiata infarct. She had a known left atrial myxoma, but was only on full-dose aspirin. A.T. was a 21-year-old woman with left monocular vision loss, left hand clumsiness, and expressive aphasia. MRI Brain revealed bilateral subacute infarcts and Echocardiogram revealed a left atrial myxoma. She was started on warfarin and low-dose aspirin. T.A. was a 38-year-old woman with right homonymous hemianopia and vertigo. MRI Brain revealed acute and subacute infarcts at the left cerebellum and parietal and occipital lobes, and Echocardiogram revealed a left atrial myxoma. She was started on warfarin. In all cases, the myxomas were resected promptly, but head imaging had revealed old asymptomatic infarcts. These cases support initiating anticoagulation and promptly resecting myxomas once discovered, to prevent embolic phenomena that may be subclinical, such as ischemic strokes.

S356WIP. Pseudobulbar Affect Associated with Autoimmune Encephalitis

Neeraj Singh and Matthew Murnane. Albany, NY

Pseudobulbar affect (PBA) is seen secondary to neurological conditions, such as stroke and traumatic brain injury, but has not previously been seen with autoimmune encephalitis. We present a case of PBA with autoimmune encephalitis. A 49-year-old man presented with severe leg spasms and myoclonic jerks, causing dysequilibrium and falls. A neurological exam revealed inducible bilateral lower extremity myoclonic jerks, diffuse hyperreflexia, inability to look leftward past midline, and crying episodes without sadness. A MRI of the brain and entire spine with and without gadolinium showed no parenchymal changes or meningeal enhancement. A lumbar puncture revealed elevated leukocyte and protein levels, with normal glucose level and no viral or bacterial infection. A paraneoplastic panel was normal, but an autoimmune panel revealed anti-glycine receptor antibodies. The patient received intravenous methylprednisolone over five days, with diazepam for spasms and dextromethorphan/quinidine for PBA. Within three weeks, his spasms were controlled and he could ambulate with a walker. Six months later, he could walk independently and his PBA and spasms resolved, requiring no more symptomatic treatment. This case reveals autoimmune encephalitis as a new type of neurological condition that should be considered when a patient presents with PBA.

Multiple Sclerosis

S357WIP. Cerebral Peduncle Angle: Unreliable in Differentiating Progressive Supranuclear Palsy from Other Neurodegenerative Diseases

Philip W. Tipton, Takuya Konno, Daniel F. Broderick, Dennis W. Dickson and Zbigniew K. Wszolek. Jacksonville, FL

Introduction: The significant symptom overlap between progressive supranuclear palsy (PSP) and other parkinsonian neurodegenerative diseases frequently results in misdiagnosis. However, neuroimaging can be used to quantify disease-related morphological changes and specific markers. The cerebral peduncle angle (CPA) has been shown to differentiate clinically diagnosed PSP from other parkinsonian diseases but this result has yet to be confirmed in autopsy-proven disease.

Methods: Magnetic resonance imaging (MRI) scans were obtained for 168 patients representing 69 medical facilities. Following randomization, the images were divided into two groups (Type 1 and Type 2) based upon midbrain morphological differences. Two readers were blinded and independently measured the CPA of 146 patients with autopsy-proven progressive supranuclear palsy (PSP; n=54), corticobasal degeneration (n=16), multiple system atrophy (MSA; n=11) and Lewy body disease (n=65).

Results: Applying two separate measurement techniques revealed no statistically significant differences in CPA measurements among any study groups regardless of classification measurement approach. The interobserver agreement showed significant differences in measurements using the Type 2 approach.

Conclusion: Measuring the CPA on MRI is not a reliable way of differentiating among patients with PSP, corticobasal degeneration, MSA, or Lewy body disease.

S358WIP. Efficacy of IncobotulinumtoxinA in the Treatment of Equinovarus Foot in Adults

David M. Simpson, Djamel Bensmail, Astrid Scheschonka, Birgit Flatau-Baqué, Olivier Simon and Jörg Wissel. New York, NY; Garches, France; Frankfurt, Germany and Berlin, Germany

This post-hoc analysis assessed the effectiveness of incobotulinumtoxinA for treating lower limb (LL) spasticity.

155 adults with UL and LL spasticity received 400, 600 and 800U incobotulinumtoxinA, respectively. Outcomes 4 weeks post-injection included muscle tone (Ashworth Scale; AS), responder rates (≥ 1 point improvement on the AS), and Resistance to Passive Movement Scale (REPAS). 100 patients received equinovarus foot treatment (mean $\pm$ standard deviation [SD] dose 166.3 ± 94.9 U) while 55 patients did not receive a treatment in the first cycle. The mean $\pm$ SD improvement in ankle joint AS score was 0.63 ± 0.76 in patients treated for equinovarus foot and 0.16 ± 0.63 in patients not treated for equinovarus foot. Analysis of covariance (ANCOVA) with AS baseline value as covariate revealed a significant effect of the dose on AS improvement ($p=0.0096$). AS responder rates were 55.0% in treated and 12.7% in untreated patients ($p<0.0001$;

Mantel-Haenszel Chi-Square test). Mean $\pm$ SD improvement in REPAS LL scores was 1.6 ± 2.0 in patients with LL treatment and 0.3 ± 1.5 in patients without. ANCOVA with LL REPAS baseline value as covariate revealed a significant influence of LL dose ($p=0.0022$). Safety described elsewhere. Results demonstrate the efficacy of incobotulinumtoxinA for treating LL spasticity.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Consulting fees: Allergan, Ipsen, Merz

Speakers' bureau: Allergan

Research grants: Allergan, Ipsen, Merz

Have you received funding or in-kind support/will your presentation be supported/sponsored (in any way whatsoever, including grants) by a commercial interest? Travel to the congress to present the data

S359WIP. Jerky Dystonic Shoulder After Posterior Thalamic Infarction: Two Cases Report and Literature Review

Yongxing Zhou, Michael H. Pfeiffer, Amal Elhaj, Mohamed Ali-Eltom, Derrick Fox, Marshall S. Balish, Roger Weir and Annapurni Jayam-Trouth. Washington DC

Focal brain lesions can induce several types of abnormal involuntary movements (AIM) such as dystonia, chorea, hemiballism, tremor, myoclonus, and parkinsonism. The most frequent cause is stroke, followed by tumor, trauma, anoxia, vascular malformation, or multiple sclerosis. Among these AIM, dystonia, which is particularly common, the lesions usually located within the striatopallidal complex, the mesencephalon, and the thalamus. Most of the striatopallidal lesions are located in the lentiform nucleus, especially the putamen, whereas the thalamic lesions were centered on the ventral intermediate and ventral caudal nuclei. Compared with the clinical features of dystonia observed after lesions of the striatopallidal system, dystonia in patients with thalamic lesions was characterized by action and posture myoclonus and dystonia of the hand. Upon literature review, all patients with jerky dystonia due to thalamic infarction, affected hand (jerky dystonic hand), except only one patient who reported jerky dystonia with shoulder involvement. Herein, we report two patients with multiple risk factors for stroke, who developed jerky dystonic shoulder movements in one month and 8 months respectively, after posterior thalamic infarctions. The cause for the proximal, rather than distal, upper limb involvement, is unclear.

S360WIP. Associations Between Brain Structure and Executive Function in Patients with Rapid-Onset Dystonia-Parkinsonism

Christopher T. Whitlow, Jared F. Cook, Beverly M. Snively, Kathleen J. Sweadner, Ihtsham U. Haq, Mark Stacy, Laurie J. Ozelius and Allison Brashear. Winston-Salem, NC; Boston, MA and Durham, NC

Rapid-onset dystonia-parkinsonism (RDP) is caused by ATP1A3 gene mutations and has been recently shown to affect several cognitive domains, including executive

function. This study aims to investigate the neuroanatomical substrates underlying RDP-associated effects on executive function. We hypothesized that RDP may affect components of the cerebello-thalamo-cortical (CbTC) pathway thought to be affected in other movement disorders and known to play a role in executive function.

In this preliminary investigation, standard brain MRI voxel-based morphometry was used to measure gray matter (GM) volume in prefrontal cortex, thalamus and cerebellar structures among 6 RDP patients (age: mean $\pm$ SD = 37 $\pm$ 20 years; 50% female) in an ongoing study of brain structure and cognitive function. Wisconsin Card Sort Task (WCST) age- and education-specific percentile scores of total and perseverative errors were used for analyses.

Pearson correlation demonstrated statistically-significant ($p \leq 0.05$) correlations (range: $r = 0.80$ - 0.86) between WCST and GM volume in thalamus and cerebellar structures, but not prefrontal regions.

These data suggest that RDP-associated abnormalities of executive function may be mediated by thalamic and cerebellar portions of CbTC pathway rather than prefrontal regions that are more commonly ascribed to executive dysfunction in other central nervous system diseases.

Neuro-Oncology

S361WIP. High Energy Intake from Dietary Fat Increases Relapse Rate in Early Pediatric Multiple Sclerosis

Saeedeh Azary, Teri Schreiner, Jennifer Graves, Amy Waldman, Anita Belman, Bianca Weinstock Guttma, Gregory Aaen, Jan-Mendelt Tillema, Soe Mar, Janace Hart, Jayne Ness, Yolanda Harris, Lauren Krupp, Mark Gorman, Leslie Benson, Moses Rodriguez, Moses Rodriguez, Tanuja Chitnis, John Rose, Lisa F. Barcellos, Tim Lotze, Shelly Roalstad, Charles Casper and Emmanuelle Waubant. San Francisco, CA; Aurora, CO; Philadelphia, PA; Stony Brook, NY; New York, NY; Loma Linda, CA; Rochester, MN; St. Louis, MO; Birmingham, AL; Boston, MA; Salt Lake City, UT; Berkeley, CA and Houston, TX

A high-fat diet has been associated with worse disease phenotype in Experimental Autoimmune Encephalomyelitis (EAE). Contribution to the severity of the human disease is unknown. This analysis is the product of an ongoing case-control study at 16 US centers of environmental risk factors in pediatric MS (18 years at onset). Patients who had available prospectively collected relapse data included in this analysis. Multivariate Cox proportional hazard model was used. The model was adjusted for age, gender, race/ethnicity, body mass index, and presence of disease-modifying treatment at enrollment. 219 patients with pediatric relapsing-remitting MS were included in this study. In multivariable analyses, each 1% increase in energy intake from fat increased the hazard of relapse by 4% (adjusted hazard rate (HR) 1.04, CI:1.0-1.09, $p = 0.04$). In contrast, patients with high vegetable intake had a lower hazard of relapses (adjusted HR: 0.58, CI:0.35-0.96, $p = 0.03$). These associations remained with mutual adjustment and persisted when adjusted for baseline 25(OH) vitamin D serum level. This

study suggests that high energy intake from fat may increase the hazard to relapse in children while vegetable intake may be protective.

S362WIP. Investigating the Role of Fibrinogen in Inflammatory Demyelination Using Combined MRI and Histopathology in the Marmoset Experimental Autoimmune Encephalomyelitis Model

Nathanael J. Lee, Seung-Kwon Ha, Nicholas J. Luciano, Emily Leibovitch, Jennifer Lefevre, Matthew K. Schindler, Pascal Sati, Afonso C. Silva, Katerina Akassoglou, Steven Jacobson and Daniel S. Reich. Bethesda, MD and San Francisco, CA

Multiple sclerosis (MS) is an inflammatory demyelinating disorder, where patients develop characteristic lesions in the central nervous system whose pathological features differ depending on the stage of lesion development. However, MS tissue is not routinely available for pathological analysis. Experimental autoimmune encephalomyelitis (EAE) in the common marmosets (*Callithrix jacchus*) recapitulates many radiological and pathological features of focal white matter MS lesions, providing opportunities to investigate how such lesions develop and the timing of pathogenic factors involved. Using serial MRI, we tracked lesion development, and further characterized lesions using histopathology targeting various markers, including fibrinogen. Fibrinogen is a marker for blood-brain-barrier leakage, and also has been investigated for its pathogenic role in MS lesion development. Our data show that fibrinogen leaks from blood vessels in early, active lesions, and its distribution pattern depends on lesion age. Lesions that are up to two weeks old show patchy fibrinogen deposition around the central vein, whereas fibrinogen is cleared from older lesions by phagocytes. In conclusion, our results show that fibrinogen is a reliable marker of the early, active stage of EAE lesion development.

Behavioral Neurology

CD502. Clinicopathological Features of NCL Occur in Humans with Progranulin Haploinsufficiency

Michael E. Ward, Robert Chen, Hsin-Yi Huang, Connor Ludwig, Maria Telpoukhovskaia, Alice Taubes, Helene Boudin, Sakura Minami, Meredith Reichert, Philipp Albrecht, Jeff Gelfand, Andres Crus-Herranz, Marcel Alavi, Shannon Leslie, William Seeley, Bruce Miller, Eileen Bigio, Marsel Mesulam, Matthew Boggy, Ian Mackenzie, John Staropoli, Susan Cotman, Eric Huang, Li Gan and Ari Green. Bethesda; San Francisco; Chicago; Palo Alto; Boston and Vancouver, Canada

Heterozygous GRN mutations lead to progranulin (PGRN) haploinsufficiency and cause frontotemporal dementia (FTD), a neurodegenerative syndrome of older adults. Homozygous GRN mutations, on the other hand, lead to complete PGRN loss and cause neuronal ceroid lipofuscinosis (NCL), a lysosomal storage disease usually seen in children. Since the predominant clinical and pathological features of FTD and NCL are distinct, it is controversial whether the disease mechanisms associated with complete and partial PGRN loss are similar or distinct. Here, we show that PGRN haploinsufficiency leads to NCL-like features in humans, some occurring before dementia onset.

Non-invasive retinal imaging reveals pre-clinical retinal lipofuscinosis in heterozygous GRN mutation carriers. Increased lipofuscinosis and intracellular NCL-like storage material also occurs in post-mortem cortex of heterozygous GRN mutation carriers. Lymphoblasts from heterozygous GRN-mutation carriers accumulate prominent NCL-like storage material, which can be rescued by normalizing PGRN expression. Fibroblasts from heterozygous GRN-mutation carriers have impaired lysosomal protease activity, and GRN mutation iPSC-derived neurons have enlarged lysosomes. Our findings indicate that progranulin haploinsufficiency causes accumulation of NCL-like storage material and early retinal abnormalities in humans, implicating lysosomal dysfunction as a central disease process in GRN-associated FTD and GRN-associated NCL.

Cerebrovascular Disease

CD503. Accuracy of Wearable Cameras to Track Social Interactions in Stroke Patients

Amar Dhand, Alexandra E. Dalton, Douglas A. Luke, Brian F. Gage and Jin-Moo Lee. St. Louis, MO and Hanover, NH

Background: Social isolation after a stroke is related to poor outcomes. Typical measures of social networks rely on self-report, which is vulnerable to response bias and measurement error. We aimed to test the accuracy of an objective measure—wearable cameras—to capture face-to-face social interactions in stroke patients.

Methods: In this prospective study, ten stroke survivors each wore two wearable cameras (Autographer and Narrative Clip) that automatically took a picture every 20-30 seconds. Patients mingled with healthy controls for five minutes of one-on-one interactions followed by five minutes of no interaction for two hours. After the event, two blinded judges assessed whether photograph sequences identified interactions or non-interactions. Diagnostic accuracy statistics were calculated.

Results: 8776 photographs were taken and adjudicated. In distinguishing interactions, the Autographer's sensitivity was 1.00 and specificity was 0.98. The Narrative Clip's sensitivity was 0.58 and specificity was 1.00. The receiver operating characteristic curves of the two devices were statistically different ($Z=8.26$, $p < 0.001$).

Conclusions: Wearable cameras can accurately detect social interactions of stroke patients. Likely due to its large field of view, the Autographer was more sensitive than the Narrative Clip for this purpose.

CD504. New Diagnosis of Cancer and the Risk of Subsequent Stroke

Babak B. Navi, George Howard, Virginia Howard, Hong Zhao, Suzanne E. Judd, Mitchell S.V. Elkind, Costantino Iadecola, Lisa M. DeAngelis, Hooman Kamel, Peter Okin, Susan G. Lakoski, Elsayed Z. Soliman, Mary Cushman and Paul Muntner. New York; Birmingham; Houston; Winston-Salem and Burlington

Background: The risk of stroke associated with cancer is uncertain.

Methods: We analyzed participants, 66 years and older, in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study with Medicare coverage. Participants with history of cancer were excluded. A new diagnosis of malignant cancer after baseline was identified through Medicare claims, and modeled as a time-dependent exposure. Participants were prospectively followed from their baseline REGARDS visit in 2003-2007 through 2013 for the primary outcome of a neurologist-adjudicated stroke. Cox regression was used to evaluate the association between cancer diagnoses and subsequent stroke. Follow-up time was modeled in discrete time periods to fulfill the proportional hazard assumption.

Results: Among 5,743 eligible REGARDS participants, 984 were diagnosed with cancer during follow-up. There was a markedly increased risk for incident stroke in the first month after a cancer diagnosis (HR 5.1, 95% CI 1.9-13.8). This association persisted after adjustment for demographics, geographic region, and stroke risk factors (HR 6.9, 95% CI 2.5-18.5). There was no association between cancer diagnoses and incident stroke beyond one month.

Conclusions: A new diagnosis of cancer is associated with a substantially increased short-term risk of stroke.

CD507. A Time Window of Heightened Plasticity to Training After Ischemic Stroke

Steven R. Zeiler, Kwan Ng, Robert B. Hubbard, Ellen M. Gibson, Tony Zheng, Richard J. O'Brien and John W. Krakauer. Baltimore, MD; Sacramento, CA and Durham, NC, United Kingdom

Data in humans suggest that most recovery from motor impairment occurs in the first 4 weeks after stroke and is mediated in part by increased responsiveness to training in this short time period which we call the sensitive period. Based on these data, we tested three hypotheses. First, that there is a gradient of diminishing responsiveness to training in the first week after stroke in the mouse. Second, the counterintuitive prediction that a second stroke should reopen the sensitive period and lead to paradoxically enhanced recovery from a first stroke with incomplete and plateaued recovery. Third, that fluoxetine can extend the sensitive period. Using a skilled prehension task, we show that training-associated recovery of prehension was complete if training was initiated after a 1-day, post-stroke delay but incomplete if training was initiated after a 7-day, post-stroke delay, even with additional training days. At post-stroke day 21, induction of a second focal stroke in the medial premotor area of mice with plateaued recovery led to a dramatic response to early post-stroke training with recovery to normal performance. Daily fluoxetine administration post-stroke was associated with complete recovery of prehension.

CD508. Cellular and Molecular Disruption of the Oligovascular Unit in Metabolic Syndrome and White Matter Stroke

Guanxi Xiao, Stefanie Nunez and Jason D. Hinman. Los Angeles, CA

Cerebral microvascular disease is a leading cause of stroke and vascular dementia causing diffuse and focal ischemic lesions predominantly within brain white matter. Both lesions are progressive, implying cascading biologic pathways, driven by chronic risk factors including metabolic syndrome (MetS) that impact multiple cell types. To better characterize the effect of MetS on the oligovascular unit and the response to focal white matter stroke, we utilized a variety of transgenic, molecular, and stroke modeling approaches. MetS is associated with a decrease in microvascular volume in the corpus callosum, altered axonal microdomain organization, lost axoglial contact, and ultrastructural disruption of myelin. In part, these changes result from MetS-induced changes in the oligodendrocyte lineage. To determine the effect of MetS on the transcriptional profile of diseased cerebral endothelia within the white matter, we used cell specific RiboTAG and RNA-seq to identify a number of disease-induced vascular signaling pathways including the IL-17/CXCL5 inflammatory chemokine pathway that may exert its action on the oligovascular unit. Together, these results identify the basic cellular mechanisms that mediate cerebral microvascular disease and identify new therapeutic targets for vascular and white matter repair.

CD510. ABCD1 Deficiency Causes White Matter Microvascular Perfusion Abnormalities

Patricia L. Musolino, Arne Lauer, Xiao Da, Mikkel Bo Hansen, Jayashree Kalpathy-Cramer, Kim Mouridsen, Bruce Rosen and Florian S. Eichler. Boston, MA; Charlestown, MA and Aarhus, Denmark

X-linked Adrenoleukodystrophy (ALD) is a devastating neurodegenerative disorder that results from mutations in the ABCD1 gene. Sixty percent of males are at risk for rapidly progressive cerebral inflammatory demyelination (Eichler et al. 2007; Moser et al. 2007). A major challenge facing clinicians is the lack of biomarkers to determine which patients carrying the mutation will develop cerebral disease. Selective brain endothelial dysfunction (Musolino et al. 2015) and increased permeability of the blood brain barrier (BBB) as indicated by contrast extravasation on brain MRI (Loes et al. 2003) suggest that white matter microvascular dysfunction contributes to the phenotypic conversion. Using dynamic susceptibility contrast (DSC) MR perfusion imaging we analyzed a cohort of ALD patients and found that ABCD1 deficiency causes high microvascular flow heterogeneity in the white matter regions and developmental stages with highest susceptibility for conversion to cerebral disease. When this is followed by an increase in BBB permeability lesion progression ensues. These abnormalities normalize one year after treatment with hematopoietic stem cell transplantation. Here we report for the first time in-vivo the effect of ABCD1 upon microvascular flow physiology in white matter at risk of inflammatory demyelination.

CD511. Differential Sex Response to Aspirin in Decreasing Aneurysm Rupture in Humans and Mice

David Hasan. Iowa City, IA

We previously found that aspirin decreases the risk of cerebral aneurysm rupture in humans. A nested case-control analysis

from the ISUIA was performed to assess whether a sex differential exists in the response of human cerebral aneurysms to aspirin. Aneurysms were induced in mice using hypertension and elastase injection into mice basal cisterns. Aspirin decreased the risk of aneurysm rupture more significantly in men than in women in the ISUIA. In mice, aspirin and COX-2 inhibitor significantly decreased the incidence of rupture. The incidence of rupture was significantly lower in male versus female mice on aspirin. PCR of cerebral arteries showed higher 15-PGDH levels in male mice. The rate of cerebral aneurysm rupture was similar in male mice receiving aspirin and 15-hydroxyprostaglandin dehydrogenase inhibitor compared with females receiving aspirin and 15-PGDH agonist, signaling a reversal of the sex-differential response to aspirin. Aspirin decreases aneurysm rupture in human and mice, in part through COX-2 pathways. Evidence from animal and human studies suggests a consistent differential effect by sex. 15-PGDH activation in females reduces the incidence of rupture and eliminates the sex-differential response to aspirin.

Epilepsy

CD512. Pathologic Mechanisms Underlying Hypomyelination Following Loss of TSC2 from Oligodendrocytes

Robert P. Carson, Mark D. Grier, Birtany Parker, Keliene Verdier and Kevin C. Ess. Nashville, TN

Objective: A positive link between PI3-K/mTORC1 signaling and myelination has been established, though a paradoxical hypomyelination is seen following loss of Tsc1 or Tsc2 from oligodendrocytes. The objective of this study is to determine mechanisms and pathways leading to hypomyelination following loss of Tsc2.

Methods: To inactivate the Tsc2 gene in oligodendrocytes, we generated a conditional knock-out (CKO) mouse using Cre-recombinase driven by the Olig2 promoter. From these animals, primary mixed glial cultures were derived and underwent a shaking protocol to enrich cultures of OPCs and astrocytes, followed by differentiation into mature oligodendrocytes.

Results: To assess the requirement for Tsc2 in oligodendrocyte development, maturation of OPCs deficient for Tsc2 was characterized. A 90% reduction in mature oligodendrocytes was seen after 6-9 days in culture. CKO astrocytes and oligodendrocytes were larger and demonstrated altered morphology as compared to control cells, consistent with loss of Tsc1 or Tsc2.

Conclusions: Homozygous loss of Tsc2 in oligodendrocytes results in hypomyelination likely due to loss of oligodendrocyte precursors. Understanding the mechanisms for the cell loss may provide novel molecular targets for improving myelin integrity in human disease.

CD514. Neuronal Chloride Concentration Developmental Decrease Is Independent of Slicing Trauma in Thalamo-Cortical Brain Slices

Joseph Glykys and Kevin J. Staley. Boston, MA

Intraneuronal chloride concentration ($[Cl^-]_i$) is critical in determining the polarity of GABA_A receptor currents.

Elevated $[Cl^-]_i$, associated with depolarizing action of GABA, is observed in early brain development and in pathological conditions. We evaluated whether acute trauma increases $[Cl^-]_i$ in the neocortex and thalamus and if it is also affected by development. Neuronal $[Cl^-]_i$ was imaged by multiphoton microscopy in acute thalamo-cortical brain slices from Clomeleon mice at post-natal days 5 to 20. We observed: 1) $[Cl^-]_i$ is higher in the most superficial areas, close to the cutting edge, in both neocortical and thalamic brain slices at all ages and, 2) there is a developmental decrease in $[Cl^-]_i$ independent of acute trauma caused by brain slicing. We conclude that $[Cl^-]_i$ has a developmental progression during P5-20 in both the neocortex and thalamus independent of brain trauma. However, in both brain regions and during development, neurons closest to the slicing trauma have an elevated $[Cl^-]_i$. Trauma induced changes in $[Cl^-]_i$ are key to the understanding of the effects of GABA_A receptor allosteric modulators on injured tissue.

CD515. Widespread Migration of Neurons in the Postnatal Human Frontal Cortex

Mercedes Paredes, David James, Sara Gil-Perontin, Hosung Kim, Jennifer Cotter, Carissa Nguyen, David Rowitch, Duan Xu, Jose Manuel Garcia-Verdugo, Eric Huang and Arturo Alvarez-Buylla. San Francisco, CA; Valencia, Spain and San Francisco, CA

The human frontal lobe has greatly increased in size and complexity compared to other mammals. To study the manner in which this region continues to develop postnatally, we followed young neurons from the walls of the lateral ventricles and sub-ventricular zone (V-SVZ) to their final cortical destinations using high-resolution MRI, histology, and time-lapse confocal microscopy. We discovered a prominent population of Doublecortin (DCX)+ migrating young neurons in a stream we refer to as the Anterior Arc. These cells were distributed widely throughout the frontal lobe invading multiple cortical areas in the first three months of life. These young neurons expressed markers of interneurons and their entry into the anterior cingulate cortex was correlated with the emergence of specific subtypes of inhibitory neurons (NPY, Somatostatin and Calretinin). DCX+ cells expressed transcription factors associated with ventral progenitor regions, the medial and caudal ganglionic eminences (MGE and CGE). Altogether, these data reveal a major migration of young neurons into the frontal lobe that may contribute to changes to the neural circuit composition and its maturation during early infancy. Defects in this migration could result in circuit defects that underlie neurodevelopmental disorders.

CD516. Multimodal Biomarker Discovery in Childhood Epilepsy

Catherine J. Chu, Dan Song, Emily L. Thorn, Wenting Xie, Sydney S. Cash, Kevin Staley and Steven M. Stuffelbeam. Boston, MA

Benign epilepsy with centrotemporal spikes (BECTS) is the most common childhood epilepsy syndrome and characterized by a transient period of seizure susceptibility of

uncertain duration in school-age children. A biomarker of epilepsy remission would provide invaluable prognostic information for these children and guide decisions regarding anticonvulsant drug treatment. In addition, identification of clinically accessible biomarkers to track epileptogenicity in childhood epilepsy may provide candidate biomarkers to target in other populations at risk.

A characteristic feature in BECTS are epileptic spikes arising from the rolandic cortex. This abnormal physiology overlaps with a stereotyped sequence of complex brain maturational processes. We hypothesize that focal processes of cortical expansion and contraction and white matter myelination contribute to abnormal neuronal excitability and network synchronization in children with BECTS and that objective measures of these properties using established and novel techniques will provide robust, clinically relevant biomarkers of seizure risk and remission.

We have begun enrollment for a cross sectional multimodal imaging study of children with active BECTS, remission, and healthy controls.

Our preliminary results suggest that targeted physiological and anatomical measures of neuronal excitability and cortical maturation may provide robust biomarkers that track with disease in childhood epilepsy.

CD517. Using In Vivo Two-Photon Calcium Imaging to Probe the Dentate Gate Hypothesis of Epilepsy

Matthew Shtrahman, Thanh Tran, Shannon H. Kee, Bloyd Cooper, Johnston T. Stephen, Goncalves J. Tiago and Fred H. Gage. La Jolla, CA

We utilize red-shifted genetically encoded calcium indicators to perform deep two-photon imaging of network activity within multiple hippocampal subfields including CA1, DG, and the hilus in awake behaving mice for the first time. We use this approach to compare excitability and synchronization in these networks between healthy and pilocarpine treated epileptic mice. We demonstrate that network activity within each of these three regions can be recorded in awake animals with single cell resolution and excellent signal to noise ratio, which reveals marked differences in synchronous activity among the different these cell types between healthy and epileptic animals.

Movement Disorder

CD519. Precisely Timed Optogenetic Inhibition of Dopaminergic Neurons During Motor Skill Acquisition in Rats

Damien J. Ellens, Matt Gaidica, Amy Hurst and Daniel K. Leventhal. Ann Arbor, MI

Striatal dopamine loss is the most prominent neurochemical finding in Parkinson Disease (PD), and dopamine replacement improves motor function in PD. Standard basal ganglia models and the short duration response to levodopa suggest that striatal dopamine acutely influences motor function. It is also clear, however, that striatal dopamine influences implicit learning processes. How these dual functions of dopamine relate to clinical parkinsonism is unclear,

and difficult to determine with interventions that operate over hours (e.g., pharmacology) or longer (e.g., lesions). Precisely timed optogenetic inhibition of midbrain dopaminergic neurons during acquisition and performance of fine motor skills allows us to separate “learning” and “performance” roles of striatal dopamine. We employed a rat skilled reaching task with real-time computer vision to precisely time optogenetic suppression of dopamine neurons during reaches. Our preliminary results suggest that dopamine neuron suppression at reach onset does not influence reach trajectory, but reduces the likelihood that rats will perform future reaches. Ongoing studies aim to distinguish motor from motivational effects of dopamine neuron suppression, define functional subpopulations of midbrain dopamine neurons, and examine how the timing of dopaminergic neuron activity influences motor skills.

CD520. Contact Location and Non-Motor Outcomes in Subthalamic Deep Brain Stimulation for Parkinson Disease

Darlene P. Floden, Caio M. Matias, Conor A. Wathen, Grace E. Ozinga and Andre G. Machado. Cleveland, OH and Sao Paulo, Brazil

There are a host of influences that contribute to cognitive and behavioral changes following Deep Brain Stimulation. The location of the active cathode relative to the Subthalamic Nucleus and other neighboring structures is likely an important variable but one that has received little attention. Here, we measured contact location and examined associations with a range of outcomes in 46 patients (mean age = 60.9 +/- 8.1, 38 males) who underwent unilateral or bilateral Subthalamic Nucleus Deep Brain Stimulation for treatment of idiopathic Parkinson disease. Correlational analyses indicated that medial/lateral and anterior/posterior contact locations in the left hemisphere were particularly influential for depression, semantic fluency, and phonemic fluency outcomes. Memory outcome, on the other hand, was related to right-hemisphere stimulation voltage, which is likely a proxy for variable electrode location. These findings have implications for understanding the functional divisions of the Subthalamic Nucleus as well as for surgical targeting and intraoperative testing procedures.

CD521. Synergistic Effects of Botulinum Toxin and Physical Therapy in Primary Cervical Dystonia

Aparna Wagle Shukla, Shanker Kulkarni, Jon Shuster, Michael Okun and David Vaillancourt. Gainesville

Objective: To compare standard botulinum toxin (BoNT) versus BoNT combined with physical therapy (PT) in primary cervical dystonia (PCD).

Background: BoNT is the gold standard treatment for PCD however response can be suboptimal and effects wear off between doses even with good response. PT in PCD is potentially promising but never tested.

Design/Methods: PCD subjects with suboptimal benefits on BoNT (10 weeks or lesser) were enrolled. Subjects either received PT and BoNT (PT group) or BoNT alone. Toronto Western Spasmodic Torticollis Scale (TWSTRS) scores and

SF-36 quality of life scores were obtained at baseline, at peak BoNT benefits (approximately 3-6 weeks), and 12 weeks post BoNT. A PT program was initiated at baseline visit followed by a home exercise program was performed for six weeks.

Results: Fifteen subjects (7 male, 8 female), mean age 64.5, mean disease duration 14.4 were recruited. The change in TWSTRS pain score at 6 weeks peak BoNT benefits in PT group was significantly greater than non-PT group. Improvement in SF-36 scale approached significance in the PT group.

Conclusions: Preliminary results suggest BoNT combined with PT improve pain and quality of life greater than BoNT alone.

CD522. Connectivity and Behavioral Changes in Patients with Parkinson's Disease and Freezing of Gait

Gonzalo J. Revuelta, Rachael Deardorff, Aaron Embry, Clifford Chan, Shonna Jenkins, Logan Dowdle, Leonardo Bonilha, Daniel Lench, Steve Kautz and Jens Jensen. Charleston, SC and Charleston

Objective: To determine structural and functional connectivity, gait and cognitive changes in Parkinson's disease (PD) freezers compared to non-freezers.

Background: Freezing of Gait (FoG) is a debilitating, progressive and common phenomenon in PD. We propose that a loss of automaticity of gait results in increased cortical control of gait.

Methods: 20 PD patients with and 19 without FoG underwent MRI (diffusional kurtosis imaging (DKI) and RS-fMRI protocols). A deterministic fiber-tracking algorithm based on DKI was used, with a seeding region placed from the PPN to the SMA. Cognitive assessments aimed at executive and attentional functions were administered. Gait analysis was available on 8 freezers and 4 controls.

Results: PD non-freezers had mean age of 70 years (79% male), while freezers had mean age of 65.7 years (69% male). Freezers had increased fiber count (mean: 1099 ± sem: 125) compared to non-freezers (mean: 776 ± sem: 114), p=0.049.

Conclusions: This data supports the notion that there is increased cortical control of gait in patients with PD freezers compared to non-freezers. Further studies to support this notion include functional connectivity analysis, gait and cognitive data.

CD523. Olfactory Deficits Predicts Abnormal Forebrain White Matter in Early PD: Support for the Braak Hypothesis of Spreading Pathology

Frank M. Skidmore, Glenn Brook, Thomas Anthony, Jon Marstrand, Yuliang Liu, Mitchel Horton, Chad Burdyslaw, Lonnie Crosby, Junqi Yin, Gary Cutter and David Standaert. Birmingham, AL and Oak Ridge, TN

The rhinencephalon (“nose brain”) has the distinction of being the only sensory region of the brain that does not relay through the thalamus, instead projecting diffusely, including into the forebrain and brainstem. Braak found early olfactory pathology in some individuals with PD.

Approximately 2/3 of individuals with PD in the Parkinson's Progressive Markers (PPMI) dataset have altered olfaction at baseline. We evaluated the relationship between olfaction and forebrain gray and white matter in PD. Fractional Anisotropy (FA), Mean Diffusivity (MD), T1 signal, and novel measure, white matter atrophy, were measured in 95 individuals with PD and 56 healthy adults in the PPMI dataset. In PD (but not in healthy adults), poor olfaction was associated with diminished FA and MD in hypothalamic regions, as well as white matter atrophy. No T1 signal changes were noted. Combining olfaction and MRI, we could exclude 100% of healthy controls at a PD detection rate of 60%, suggesting the possibility of using a combined olfaction and imaging tool for screening. Overall area under the ROC curve exceeded 90%.

CD524. Medial Frontal 4 Hz Activity and Cognitive Symptoms of Parkinson's Disease

Nandakumar Narayanan. Iowa City, IA

Patients with Parkinson's disease can have cognitive symptoms, but the mechanism is unclear. We study the medial frontal cortex of patients with Parkinson's disease and animal models using a combination of EEG, single neuronal recordings, and brain stimulation techniques. We report three main findings. First, patients with Parkinson's disease have attenuated ~4 Hz rhythms in mid-frontal cortex during cognitive tasks. Second, this ~4 Hz rhythm synchronizes single neurons involved in cognitive processing in the human subthalamic nucleus and throughout frontal, cerebellar, and striatal brain areas in rodents. Third, optogenetically stimulating frontal neurons expressing dopamine receptors at 4 Hz in animal models can compensate for dopamine-dependent cognitive deficits. These data indicate that 4 Hz activity is a key mechanism of cognitive control that malfunctions in Parkinson's disease, and could provide new insight into cognitive symptoms of Parkinson's disease.

CD525. Neurodegeneration in a Novel PARK9/CLN12 Knockout Mouse

Michael C. Kruer, Helen Magee, Nadia Sahir, Lauren McBeth, Joshua Doorn, Elizabeth Jones, Marianna Madeo, Tyler N. Jepperson, Anna Yarrow, Chun-hung Chan, David A. Pearce and Jon Cooper. Phoenix, AZ; Sioux Falls, SD and London, United Kingdom

Mutations in ATP13A2 have been shown to lead to both juvenile Parkinson disease (PARK9) and a form of neuronal ceroid lipofuscinosis (CLN12). We generated a novel Atp13a2 knockout mouse and characterized phenotypic and neuropathologic features of this PARK9/CLN12 model. Knockout animals showed impaired neuromotor performance and decreased survival compared to wild-type littermates, with a significantly larger proportion of spontaneous deaths. Neuropathology revealed age-dependent accumulation of autofluorescent and Periodic Acid Schiff-positive storage material in the brains of knockout animals. Both astrocytic activation and microglial activation were observed in Atp13a2 $-/-$ mice, along with Purkinje cell dropout. Our

data indicate that these Atp13a2 $-/-$ mice recapitulate many of the core features of the human disease.

Multiple Sclerosis

CD527. Leptomeningeal Enhancement on 7T MRI in Multiple Sclerosis Is Associated with Cortical Gray Matter Atrophy

Daniel M. Harrison, Kevin Wang, Julie Fiol, Walter Royal III, Jun Hua and Izlem Izbudak. Baltimore, MD

Background: We have previously reported 7 Tesla (7T) post-contrast MPFLAIR MRI as a potential marker of meningeal inflammation in MS. Here we explore the relationship between this finding and cortical GM pathology.

Methods: 29 participants with MS underwent 7T brain MRIs. Post-contrast leptomeningeal hyperintensities were identified on MPFLAIR. Automated segmentation volumes were normalized to intracranial volume.

Results: A total of 78 foci of leptomeningeal enhancement were noted in 26 (90%) cases with MS. Two patterns of enhancement were seen: spreading (42 foci, 69%) and nodular (36 foci, 59%). Mean cortical GM fraction was lower in cases with >1 enhancing focus (0.312, SD 0.021) than those without (0.329, SD 0.019, $p = 0.043$). Mean cortical GM fraction was also lower in those with spreading enhancement (0.309, SD 0.019) than those without (0.334, SD 0.017, $p = 0.002$). No significant relationships were found between leptomeningeal enhancement and white matter (WM) fraction or WM lesion volume.

Discussion: Leptomeningeal enhancement in MS was associated with cortical GM atrophy, but not with WM atrophy or lesions. This supports pathologic data linking meningeal lymphoid follicles in MS to local cortical atrophy and subpial demyelination.

CD529. Determining the Natural History of Alexander Disease: A Pilot Study

Amy T. Waldman, Geraldine Liu, Amy Lavery, Albee Messing and Adeline Vanderver. Philadelphia, PA and Madison, WI

Background: Future clinical trials in Alexander disease (AxD) are being considered based on novel studies in murine models; however, translating these findings into effective treatments is limited by the lack of natural history studies.

Objective: To obtain preliminary data on disease severity to inform the selection of clinical outcome assessment tools for future prospective natural history studies in AxD.

Methods: We performed a retrospective chart review, supplemented by telephone interviews, for patients with AxD to determine the rate of functional decline and feasibility of gross and fine motor, speech and language, and swallowing testing in affected individuals.

Results: We will present details on 38 patients (Type I, N=32, mean age at symptom onset 1.5 years, range 0.3 – 3.3 years; Type II, N=6, mean age 27.7 years, range 14.8 – 47 years). Language was the most affected domain across the age span, followed by swallowing difficulties. Most were

still ambulatory or required an assistive device whereas fine motor skills were not impacted.

Conclusion: Based on these results, we have selected clinically relevant, robust, and quantifiable outcome measures that are currently being evaluated prospectively in AxD patients.

Neuro-Oncology

CD532. Investigating Histone H3 Post-Translational Modifications Using Paraffin-Embedded Pediatric Glioma Tissue Samples

Amanda M. Saratsis, Tina Huang, Andrea Piunti, Rintaro Hashizume, Elizabeth Bartom, Tadanori Tomita, C. David James and Ali Shilatifard. Chicago, IL

Histone H3 is increasingly thought to play a role in pediatric gliomagenesis. Chromatin immunoprecipitation sequencing (ChIP-Seq) is a powerful method for studying epigenetic control of gene expression by histone proteins. However, the paucity of fresh tissue from rare or surgically-inaccessible tumors, like pediatric brainstem glioma, limits application. Since cell culture conditions may alter the tumor epigenome, ChIP-Seq of formalin-fixed, paraffin-embedded (FFPE) tumor, derived via biopsy or autopsy, could serve as a reasonable alternative approach. We performed the first successful ChIP-Seq of FFPE pediatric brain tumor tissue, to our best knowledge, as an alternative to fresh tissue analysis. Genomic deposition of H3K27M, H3K4me3 and H3K27ac was determined via ChIP-Seq of FFPE pediatric glioma tissue (n=8) using the KAPA HTP Library Preparation Kit and Illumina NextSeq 500. H3K27M was determined via Sanger Sequencing. Genomic enrichment of H3K4me3 and H3K27ac was detected in chromatins extracted from H3K27 wild-type FFPE glioma, consistent with ChIP-Seq of pediatric glioma cell lines (n=3). Analysis of H3K27M mutant glioma specimens is currently underway. ChIP-Seq of FFPE pediatric glioma tissue is technically feasible, and may provide new insight into the biology of these rare, highly aggressive tumors.

Neurocritical Care

CD534. NMNAT3 Protects Neurons Against Neuronal Degeneration Following Neonatal Cerebral Hypoxia-Ischemia

Rafael Galindo, Marianne B. Greenberg, Toshiyuki Araki, Yo Sasaki, Nehali Mehta, Jeffrey Milbrandt and David M. Holtzman. St. Louis, MO and Kodaira, Tokyo, Japan

Neonatal cerebral hypoxia-ischemia is a major cause of newborn death and chronic neurodevelopmental disability in children, although limited therapies are available for its prevention and treatment. The family of NAD⁺ biosynthetic enzymes, nicotinamide mononucleotide adenylyltransferases (NMNATs) are known to protect injured peripheral axons from degeneration. However, the role that the other NMNAT isoforms play in immature neuronal survival after cerebral injury remains unexplored. Utilizing a NMNAT3-overexpressing mouse line and adeno-associated viral vectors we demonstrate that the mitochondrial-associated NMNAT

isoform, NMNAT3, protects the immature brain from the degenerative effects of neonatal H-I. NMNAT3-neuroprotective mechanism involves a decrease in the degradation of calpastatin, and a concomitant decrease in caspase-3 activity and calpain-mediated cleavage. Conversely, NMNAT3 knockdown in cortical and hippocampal neurons in vitro promoted neuronal fiber degeneration and increased glutamate-dependent excitotoxic neuronal cell death. The effects of NMNAT3 knockdown on neurodegeneration were significantly reduced by exogenous upregulation of NMNAT3 suggesting that endogenous NMNAT3 is important for sustaining neuronal survival during baseline conditions and following excitotoxic injury. Understanding the neuroprotective properties of NMNATs in the injured developing brain may offer new therapeutic targets against the effects of birth asphyxia in humans.

CD535. Sarm1 Knockout Attenuates Traumatic Axonal Injury and Improves Functional Outcome After Traumatic Brain Injury in Mice

Nils Henninger, James Boley, Elif M. Sikoglu, Jiyan An, Constance M. Moore, Jean A. King, Robert Bowser, Marc R. Freeman and Robert H. Brown. Worcester, MA and Phoenix, AZ

Axonal degeneration has been consistently observed after traumatic brain injury (TBI). However, molecular pathways underlying the pathology of TBI-related axonal injury remain poorly understood and there is no efficacious treatment for TBI. We show that mice lacking the mouse Toll receptor adaptor Sarm1 (sterile α /Armadillo/Toll-Interleukin receptor homology domain protein) gene, a key mediator of Wallerian degeneration, demonstrate multiple improved TBI-associated phenotypes after mild TBI. Strikingly, Sarm1 knockout mice had significantly fewer beta amyloid precursor protein-stained axon profiles in the corpus callosum after TBI when compared to wild type mice. Furthermore, plasma concentrations of the phosphorylated axonal neurofilament subunit H were reduced in knockout mice indicating preserved axonal integrity after TBI. Importantly, there was a strong early preservation of neurological function in Sarm1 knockout mice when compared to wild type animals. Last, proton magnetic resonance spectroscopy tissue signatures were consistent with preserved neuronal energy metabolism in knockout animals compared to wild type mice early after TBI. In summary, our results indicate that the Sarm1-mediated prodegenerative pathway promotes pathogenesis in TBI. Exploring anti-Sarm1 therapeutics may represent a novel viable approach for preserving neurological function after TBI.

Autoimmune Neurology

M101. New Clinical and Immunological Features of Anti-GABAA Receptor Encephalitis

Marianna Spatola, Mar Petit-Pedrol, Myrna Rosenfeld, Francesc Graus and Josep Dalmau. Barcelona, Spain; Lausanne, Switzerland and Philadelphia, PA

Background: We recently reported a novel autoimmune encephalitis with prominent seizures and antibodies to the

$\alpha 1\beta 3$ subunits of the GABA_A receptor (GABAAR) (Petit-Pedrol et al., *Lancet Neurol*, 2014). Two recent studies suggested that the $\gamma 2$ subunit was also a target, but the associated clinical features were unclear (Pettingill et al, *Neurology*, 2015; Ohkawa et al. *J Neurosci* 2014). We examined for GABAAR antibodies 2916 samples from patients referred to our laboratory for antineuronal antibody studies and analyzed their GABAAR subunit specificity.

Methods: Clinical information was obtained from questionnaires completed by the physicians. Antibodies to $\alpha 1$, $\beta 3$ and $\gamma 2$ GABAAR subunits were determined using cell-based assays (CBA).

Results: We identified 15 new patients with GABAAR encephalitis (April 2013-January 2016). The median age was 53 years (range 0.16-88). The main clinical features were seizures, alteration of consciousness, neuropsychiatric symptoms and movement disorders. In a 10-month-old baby the clinical picture resembled anti-NMDAR encephalitis. Comorbidities included 7 tumors (4 thymoma, 1 lung, 1 rectal and 1 multiple myeloma), and 2 herpes virus encephalitis (1 HSV1 and 1 HHV6). Treatment was available for 13 patients: 9 received 1st line immunotherapy (corticosteroids, plasmapheresis, IVIg), 3 received 1st and 2nd line (rituximab, azathioprine, cyclosporine), and one was not treated. 11/12 treated patients had partial or complete recovery, 1 died of sepsis. Pooled analysis of 33 patients (the current 15 and our 18 previously published cases) showed that, compared to adults, children had more seizures ($p=0.029$) and movement disorders ($p=0.005$), and showed a more severe clinical condition ($p=0.05$). However, response to immunotherapy was similar ($p=0.07$). Patients with tumor were older than those without tumor (62 vs 21 years, $p=0.004$), but had the same outcome. Of the 27 patients with encephalitis, (the other 6 had stiff-person syndrome or opsoclonus-myoclonus), 63% had extensive multifocal MRI abnormalities. All patients' antibodies recognized the $\alpha 1$ and/or $\beta 3$ subunits. The $\gamma 2$ was recognized by 8 patients' antibodies but always in combination with $\alpha 1/\beta 3$, without any syndrome specificity.

Conclusions: Anti-GABAAR encephalitis is characterized by prominent seizures and multifocal MRI abnormalities. Seizures and movement disorders occur more frequently in children than adults, and can mimic anti-NMDAR encephalitis. The main GABAAR antibody targets are $\alpha 1$ and $\beta 3$ subunits; $\gamma 2$ subunit has no additional diagnostic value.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr J. Dalmau receives royalties from licensing fees to Athena Diagnostics for a patent for the use of Ma-2 as an autoantibody test; licensing fees to Eurimmun for patents for the use of NMDA receptor and GABAB receptor as autoantibody tests; licensing fees for the use of DPPX, GABA_A receptor, and IgLON5 antibodies as diagnostic tests; and has received a research grant from Eurimmun.

Dr F. Graus receives royalties from licensing fees to Eurimmun for the use of IgLON5 as a diagnostic test.

Dr M. Spatola has received financial support for research from the Pierre Mercier Foundation for Science (Lausanne, Switzerland) and the Academic Society of Vaud (Switzerland).

Drs Petit-Pedrol and M. Rosenfeld report no disclosures.

M102. Antiglycolipid Antibodies in Neurological Diseases Subsequent to Mycoplasma Pneumoniae Infection

Susumu Kusunoki, Motoi Kuwahara, Makoto Samukawa, Miyuki Morikawa, Rino Ueno and Yukihiko Hamada. Osaka-Sayama, Osaka, Japan

Neurological diseases, including Guillain-Barre syndrome (GBS) and acute disseminated encephalomyelitis (ADEM) sometimes develop after Mycoplasma pneumoniae (M.pneumoniae) infection. It has been reported that IgM and/or IgG antibodies to galactocerebroside (Gal-C), a glycolipid antigen specifically localized in myelin of both central and peripheral nervous systems, are frequently detected in acute phase sera from patients with neurological diseases subsequent to M. pneumoniae infection. The anti-Gal-C antibodies may be involved in the pathogenetic mechanisms in GBS and ADEM. To study the spectrum of clinical characteristics and the antibodies to glycolipids including Gal-C in such neurological diseases, we retrospectively investigated the IgM and IgG antibodies to nine glycolipids (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b and Gal-C) and clinical features in neurological diseases subsequent to M.pneumoniae infection diagnosed in multiple hospitals throughout Japan. Diagnosis of M.pneumoniae infections was made by particle agglutination (PA) test. We had 46 patients with neurological diseases subsequent to M.pneumoniae infection. Among them, 27 patients were affected with GBS, two with Fisher syndrome (FS), 16 with central nervous system (CNS) diseases including ADEM, and one with both GBS and CNS diseases. Anti-glycolipid antibodies were detected in 27 patients (59%). In particular, anti-Gal-C IgM and/or IgG antibodies were most frequently detected (23/46, 50%). A significant correlation was observed between the titers of anti-Gal-C IgM antibody and M.pneumoniae PA ($p = 0.005$). Patients affected with CNS diseases were younger than GBS and FS patients ($p = 0.003$). IgM antibodies to Gal-C were more frequently detected in the patients with CNS diseases (41%) than in those with GBS or FS (13%). Of the nine patients who had IgM, but not IgG, antibody activities to Gal-C, we found the class-switch of anti-Gal-C antibody from IgM to IgG in two patients. The IgG antibodies appeared during their recovery phases. They were of IgG 1 subclass. We confirmed that presence of the anti-Gal-C antibodies is closely associated with neurological diseases subsequent to M.pneumoniae infection. Anti-Gal-C IgM antibodies are more frequently present in younger patients with CNS involvement.

M103. Anti-AQP4 Titer Is Not Predictive of Disease Course in Neuromyelitis Optica Spectrum Disorder

Remi A. Kessler, Maureen A. Mealy and Michael Levy. Baltimore, MD

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease associated with a serological antibody to aquaporin-4 (AQP4) detectable in up to 80% of patients. The enzyme-linked immunosorbent assay (ELISA) is one of the most popular methods of testing for anti-AQP4 antibodies in the US that results with a titer in which <3 Units is negative, 3-5 is borderline and 5+ is positive. The value of the positive titer in predicting long term disease course is currently unknown.

Methods: This is a retrospective analysis of NMOSD patients at three centers around the world: Baltimore, USA, Shanghai, China and Medellin, Columbia, where ELISA titers on anti-AQP4 testing is available. Inclusion criteria include a diagnosis of NMOSD and a seropositive anti-AQP4 antibody test with titer. Patients were stratified into three groups by titer: 3-10 Units, 11-100 Units, and 101+ Units. Demographic factors such as age at onset, race and sex were collected along with clinical features such as annualized relapse rate, duration of disease, location of relapses and treatment history were compared.

Results: A total of 47 NMOSD patients met criteria for inclusion in this study, stratified into three groups by titer: 14 subjects with titers of 3-10 Units, 12 subjects with titers of 11-100 Units and 21 subjects with titers of 101 or greater Units. The average age of onset, sex and race distribution were significant different among the groups. The number of patients treated in each group was similar (< 5%) as was the average annualized relapse rate (0.37 – 0.42 relapses/year). With an average of 10 years follow up, the average disability level is not different among the three titer groups (EDSS range 3.8 – 5.3). The distribution of lesions, as well as their acute and preventive treatment regimens did not differ significantly.

Conclusions: Beyond a positive/negative result, the titer of the anti-AQP4 ELISA assay is not predictive in the disease course for patients with NMOSD. Low titer patients experience the same disease course as mid-titer and high titer anti-AQP4 patients with NMOSD.

Dementia and Aging

M104. Effect of Sleep Deprivation and Sodium Oxybate on CSF A β 40 and A β 42 Kinetics

Brendan P. Lucey, Terry J. Hicks, Jennifer S. McLeland, Cristina D. Toedebusch, Jill Boyd, Robert Swarm, Kwasi G. Mawuenyega, Vitaliy Ovod, Tom Kasten, John C. Morris and Randall J. Bateman. St Louis, MO

In rodents and humans, amyloid- β (A β) concentration fluctuates with the sleep-wake cycle as a diurnal pattern. Animal studies suggest that A β concentration and deposition may be modifiable through manipulation of the sleep-wake cycle. The purpose of this proof-of-concept study is to determine if A β concentrations in the human central nervous system are modifiable through manipulation of sleep. We collected serial cerebrospinal fluid (CSF) samples via indwelling lumbar catheter every 2 hours for 36 hours in adults 18-60 years old during behavioral sleep deprivation (N=12), pharmacologic sleep induction with sodium oxybate (N=12),

and control (N=12). All participants were infused with ¹³C6-leucine to measure A β kinetics via isotopic enrichment. A β 40 and A β 42 isoforms were quantitated by mass spectrometry. Sleep-wake activity was monitored with polysomnography. We found that concentrations of A β 40 and A β 42 increased 25-30% during sleep deprivation compared to control. This increase occurred during the sleep period, hours 18-24 or 01:00-07:00. Participants treated with sodium oxybate were found to have a greater decrease in A β 40 and A β 42 area under the curve compared to control (p<0.05). Sleep is hypothesized to be the primary driver of the A β diurnal pattern. Since changes in A β concentration of 25-40% have been associated with causing or preventing Alzheimer's disease, manipulation of sleep has potential as a preventive therapy. Future investigations will be needed to assess if A β concentrations are increased in individuals with poor sleep quality compared to controls and if this increase can be normalized with a sleep-inducing medication.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Brendan P. Lucey: Dr. Lucey has consulted for AbbVie and Neurim Pharmaceuticals

Randall J. Bateman: Dr. Bateman receives grants from the DIAN Pharma Consortium (Amgen, AstraZeneca, Biogen, Eisai, Eli Lilly and Co, FORUM, Hoffman La-Roche, Pfizer, and Sanofi) and a tau consortium (AbbVie and Biogen), has received honoraria from Roche, OECD, and Merck as a speaker, and from IMI, Sanofi, and Boehringer Ingelheim as a consultant. Dr. Bateman, Dr. Holtzman, the Chair of Neurology, and Washington University in St. Louis have equity ownership interest in C2N Diagnostics and may receive royalty income based on technology licensed by Washington University to C2N Diagnostics. In addition, Dr. Bateman and Dr. Holtzman receive income from C2N Diagnostics for serving on the Scientific Advisory Board. Washington University, with R.J.B. and D.M.H. as co-inventors, has also submitted the U.S. nonprovisional patent application "Methods for measuring the metabolism of CNS derived biomolecules in vivo," serial #12/267,974

John C. Morris: Neither Dr. Morris nor his family owns stock or has equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company. Dr. Morris has participated or is currently participating in clinical trials of antidementia drugs sponsored by the following company: A4 (The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease) trial. Dr. Morris has served as a consultant for Lilly USA and Takeda Pharmaceuticals. He receives research support from Eli Lilly/Avid Radiopharmaceuticals and is funded by NIH grants # P50AG005681; P01AG003991; P01AG026276 and UF01AG032438.

Tom Kasten: Dr. Kasten received a royalty from C2N for the CSF A β patent/protocol.

Vitaliy Ovod: Mr. Ovod may receive royalty income based on technology licensed by Washington University and tied to AGREEMENT 010395-0001.

Kwasi G. Mawuenyega: Dr. Mawuenyega may receive royalty income based on a patent: Methods for

simultaneously measuring the in vivo metabolism of two or more isoforms of a biomolecule licensed by Washington University to C2N Diagnostics.

Terry J. Hicks, Jennifer S. McLeland, Cristina D. Toedebusch, Jill Boyd, Robert Swarm: Nothing to disclose.

Health Services Research

M105. Trends and Regional Patterns of Care Associated with Hospice for US Stroke Inpatients, 2002-2011

Benjamin P. George, Adam G. Kelly, Bogachan Sahin, Eric B. Schneider and Robert G. Holloway. Rochester, NY and Boston, MA

Objective: The decline in inpatient mortality among patients with acute stroke in the US over the past decade parallels a national campaign for palliative care. We sought to determine trends in discharge to hospice for acute stroke and examine patient and regional characteristics associated with hospice discharge.

Methods: From the Nationwide Inpatient Sample, US adult (≥ 18 years) acute ischemic stroke discharges were selected from 2002-2011. Trends in hospital discharge rates were examined using hospitals with at least 50 stroke admissions annually and complete detailed reporting of patient disposition ($n=3,664$ hospitals). Hospitals were linked to selected measures of inpatient utilization during the last six months of life for all Medicare Beneficiaries as reported by Hospital Referral Region in the Dartmouth Atlas of Healthcare. Patient and region-level predictors of hospice discharge after stroke were evaluated using multivariable logistic regression on a subset of data with complete availability of race/ethnicity and reported hospital name ($n=1,075$ hospitals).

Results: The average rate of discharge to hospice by individual hospitals increased from 0.9 to 4.6 per 100 hospitalizations, 2002-2011 (95% CI, 0.7-1.0 in 2002 vs. 4.2-4.9 in 2011). Subgroup analysis demonstrated the largest increases among the oldest old (≥ 85 years), women, white patients, and Medicare beneficiaries. On average, hospice discharges had longer length of stay compared to no hospice (6.3 vs. 5.7 days, $p<0.01$), and fewer hospital charges (\$46,000 vs. \$55,000 2014 US dollars, $p<0.01$). After adjustment in a multivariable model, age ≥ 85 years (Odds Ratio [OR] 11.20 vs. 18-54 years), and female (OR 1.35 vs. male) were associated with hospice discharge. Black patients were less likely to be discharged to hospice (OR 0.53 vs. white). Hospitals within regions with a high proportion of Medicare beneficiaries hospitalized (OR 0.56, 95% CI: 0.47-0.68, 1st vs. 4th quartile), dying inpatient (OR 0.35, 95% CI: 0.31-0.40, 1st vs. 4th quartile), with ICU stays >7 days (OR 0.67, 95% CI 0.50-0.90, 1st vs. 4th quartile), or with high ICU charges (OR 0.74, 95% CI 0.63-0.86, 1st vs. 4th quartile) in the last 6 months of life, had decreased odds of hospice discharge.

Interpretation: There was an increasing trend of hospice discharges over the past decade among acute stroke inpatients. Further research is needed to understand patterns and

optimal approaches to end-of-life care and hospice use for patients with acute stroke.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? The authors have no relevant relationships to disclose.

Neuromuscular Disease

M106. Alpha-M Integrin (CD11b) Facilitates Pathogenic Leukocyte Trafficking in the Acute Inflammatory Demyelinating Polyradiculoneuropathy Variant of Guillain-Barré Syndrome

Eroboghene Ubogu, Steven Palladino, Rebecca Beacham, Eric Scott Helton and Chaoling Dong. Birmingham, AL

The molecular determinants, signaling pathways and mechanisms involved in pathogenic mononuclear leukocyte trafficking from circulating blood across the blood-nerve barrier (BNB) in the Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)-variant of Guillain-Barré syndrome are being elucidated. Prior work using untreated AIDP patient mononuclear leukocytes in a real-time flow-dependent trafficking model demonstrated a crucial role for leukocyte integrin, alpha M integrin (CD11b) in adhesion and transmigration at the cytokine stimulated human BNB in vitro. In order to ascertain the pathogenic relevance of this integrin to AIDP, we demonstrated large clusters of CD11b+ leukocytes associated with demyelinating axons within the sural nerve endoneurium of three AIDP patients by immunohistochemistry.

Using a representative animal model of AIDP, bovine peripheral nerve myelin-induced severe murine experimental autoimmune neuritis in 8-12 week old female SJL mice, we sought to determine the functional role of CD11b in leukocyte trafficking across the BNB in vivo and determine its effect on disease severity, peripheral nerve inflammation and demyelination using a published neuromuscular severity score (NMSS) scale, motor nerve electrophysiology and histopathological assessments. 5 mg/kg of a depleting, function-neutralizing monoclonal rat-anti mouse CD11b antibody was administered daily for 5 days starting a week after disease onset. CD11b antibody antagonism reduced NMSS to near normal levels. This was associated with a statistically significant increased mean dorsal caudal tail nerve (DCTN) amplitude, and increased mean DCTN and sciatic nerve conduction velocities and reduced mean DCTN and sciatic nerve total waveform durations compared to vehicle-treated (phosphate buffered saline) and isotype antibody-treated mice. Histopathological assessments showed statistically significant reductions in the mean numbers of F4/80+ monocytes/macrophages, CD3+ T-cells and total CD11b+ mononuclear leukocytes, as well as the mean percentage demyelinated area per axial section. Compared to 2 g/kg human IVIg given over 5 days, CD11b treatment resulted in more favorable NMSS, motor nerve electrophysiology demyelination parameters and histopathological assessments of inflammatory demyelination.

Consistent with in vitro observations of AIDP patient leukocyte trafficking at the BNB under flow, electron photomicrographs of active leukocyte transmigration in sural nerve biopsies of AIDP patients demonstrated paracellular leukocyte infiltration with intact electron-dense intercellular junctions between endoneurial endothelial cells and between these cells and infiltrating leukocytes. This study supports a crucial pathogenic role of CD11b in leukocyte trafficking at the BNB in AIDP, providing a target for therapeutic modulation.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Eroboghene Ubogu: Royalty for marketing SV40 large T antigen immortalized human endoneurial endothelial cells from Baylor Licensing Group. Royalty from Springer Science + Business Media for a book titled "Chemokines: Methods and Protocols" that describes the BNB leukocyte trafficking assay.

Other co-authors have nothing to disclose.

M107. Knockdown of a SMN-Associated Long Non-Coding RNA as a Novel Therapeutic Strategy for SMA

Constantin d'Ydewalle, Noah J. Pyles, Daniel Ramos, Celeste M. Pilato, Frank Rigo, Frank Bennett and Charlotte J. Sumner. Baltimore, MD and Carlsbad, CA

Several studies and our own data indicate that SMN expression is developmentally regulated with decreasing levels during neuronal differentiation. However, little is known about the molecular mechanisms that regulate the dynamic expression of SMN. Long non-coding RNAs (lncRNAs) have recently been shown to be powerful regulators of protein-coding gene expression. Many lncRNAs that transcriptionally regulate gene expression bind to the epigenetic modifier Polycomb repressive complex-2 (PRC2), which represses gene expression. Many lncRNAs exhibit regionally specific expression in the central nervous system, and some have been associated with neurodegenerative disorders. Given their role in neuronal development, lncRNAs could represent promising targets for therapeutics.

Results: We identified a 1.6 kb long antisense transcript arising from the SMN locus that we named SMN-AS1. This nuclear transcript is enriched in the central nervous system in humans and in SMA mice. SMN-AS1 expression levels are developmentally regulated and inversely correlate with SMN levels. SMN-AS1 recruits PRC2 to the SMN promoter to repress its transcription. SMN-AS1 knockdown in human SMA fibroblasts and in primary neurons isolated from SMA mice increases SMN expression in a dose-dependent manner. Interference with SMN-AS1 expression in SMA mice results in increased SMN expression, improves motor behavior and increases lifespan when combined with a low, sub-optimal dose of SMN2 splicing oligonucleotide.

Conclusions: In this study, we have implicated a long non-coding RNA in the regulation of SMN expression during neuronal development. Our data indicate that SMN-AS1 knockdown increases SMN expression in SMA cell culture models and in SMA mice. Our recent work also suggests that interference with SMN-AS1 is a novel and

promising approach to treat SMA. Future experiments will continue to evaluate whether this approach has additive effects with SMN2 splicing strategies.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Frank Rigo and Frank Bennett are employees of Ionis Pharmaceuticals, a company developing treatments for SMA.

M108. Mechanism of Cytoplasmic Protein Aggregation and Neurodegeneration in Drosophila Models of C9-ALS/FTD

Ke Zhang, Kathleen Cunningham, Jonathan Grima, Jeff D. Rothstein and Thomas E. Lloyd. Baltimore, MD

Expansion of GGGGCC (G4C2) hexanucleotide repeats in the first intron of the C9orf72 gene is the most common genetic cause of ALS/FTD spectrum disorders (C9-ALS/FTD). To gain insight into the pathogenesis of C9-ALS/FTD, we utilized a Drosophila model that replicates many of the key features of this disease including age-dependent neurodegeneration, ubiquitinated protein inclusions that label with p62/SQSTM1 (Sequestosome-1), and axonal transport disruption. This screen has identified at least three important cellular pathways that regulate G4C2 repeat-mediated neurodegeneration including: nucleocytoplasmic transport, the ubiquitin-proteasome system (UPS), and endoplasmic reticulum (ER) stress. Disruption of each of these cellular pathways may cause cytoplasmic accumulation of misfolded proteins and has been implicated in ALS. Importantly, in collaboration with the Rothstein laboratory, we have validated nucleocytoplasmic transport disruption in iPS neurons and brain tissue from patients with C9-ALS. Our data suggest that the toxic cytoplasmic accumulation of TDP-43 seen in almost all forms of ALS may be caused by an impairment in nuclear import.

Some of the most potent suppressors found in our screen are genes that regulate selective autophagy of ubiquitinated protein aggregates (aggrephagy). Using genetic epistasis experiments, we propose a model for pathogenesis in which p62-containing protein aggregates inhibit the proteasome and induce ER stress. Interestingly, neurodegenerative phenotypes are suppressed by knockdown of p62, suggesting that this ubiquitin-binding protein mutated in rare forms of familial ALS is required for neurotoxicity downstream of G4C2 repeat expression. Ongoing experiments are investigating the mechanism of this toxicity and the interrelationship between protein aggregate formation and nucleocytoplasmic transport disruption.

Autoimmune Neurology

M109. Pathological Mechanisms of Glycine Receptor Antibodies

Sarah J. Crisp, John Rothwell, Angela Vincent and Dimitri M. Kullmann. London, United Kingdom and Oxford, United Kingdom

Antibodies against glycine receptors (GlyRabs) have been found in some patients with progressive encephalomyelitis

with rigidity and myoclonus (PERM), and in patients with related acquired neurological syndromes (Carvajal-Gonzalez, 2014). The clinical features of PERM, which include muscle rigidity, exaggerated startle responses, oculomotor and autonomic disturbance, are consistent with a disruption of spinal and brainstem inhibitory circuits. However, the relationship between the identified antibody and neurological disease is based largely on circumstantial clinical evidence.

Using whole-cell patch-clamp we have recorded spontaneous miniature inhibitory postsynaptic currents (mIPSCs) from motoneurons in rat dissociated spinal cord cultures. GABA and glycine are co-released at interneuron-motoneuron synapses, both contributing to mIPSCs (Jonas, 1998). Pharmacologically isolated glycinergic currents have a shorter decay time than GABAergic currents. We use this difference in time course to separate the two components, in the absence of pharmacological blockade, to quantify the contribution of glycinergic neurotransmission to mIPSCs. We compare the contribution of glycinergic neurotransmission to mIPSCs recorded from neurons incubated in patient IgG or control IgG for up to 24h prior to recording. Our preliminary results indicate a significant decrease in the glycinergic contribution to mIPSCs for motoneurons incubated in patient compared with control IgG from 41% to 12% ($p < 0.005$).

These results show that not only do the GlyRABs detected in these patients bind to glycine receptors in cell based assays, and to motoneurons in slices of rodent brain tissue, but they also result in a reduction in glycinergic neurotransmission onto motoneurons. A reduction in glycinergic neurotransmission would be consistent with many of the clinical phenotypes seen in patients with GlyRABs. The electrophysiological findings presented here, therefore, provide strong evidence that the antibodies in these cases are pathogenic.

Alongside the in vitro investigations we are using clinical neurophysiology to identify affected circuits in GlyRAB patients. Findings are compared to patients with genetic defects in glycinergic pathways (hereditary hyperekplexia), and healthy controls.

References:

- Carvajal-Gonzalez A et al. (2014). *Brain* 137:2178-92.
Jonas P et al. (1998). *Science* 231:419-24.

M110. A Novel Type of Autoimmune Encephalitis Associated with Neurexin-3 α Antibodies

Eugenia Martinez-Hernandez, Núria Gresa-Arribas, Jesús Planagumà, Mar Petit-Pedrol, Thaïs Armangué, Francesc Graus and Josep Dalmau. Barcelona, Spain; Stockholm, Sweden; Madrid, Spain and Philadelphia, PA

Objective: To report a novel autoimmune encephalitis in which the antibodies target neurexin-3 α , a cell-adhesion molecule involved in the development and function of synapses.

Methods: Five patients with encephalitis of unclear cause and antibodies with a similar pattern of brain reactivity were selected over a 10 year period in our center. The target antigen was characterized, and a cell-based assay (CBA) was developed to test for these antibodies. The antibody effects on cultured rat embryonic neurons were analysed with

confocal microscopy. The study included 200 control samples of patients with different neurological disorders or healthy blood donors.

Results: The serum and CSF of the 5 patients showed an identical pattern of immunostaining on the hippocampus that was different from other known neuronal cell-surface antibodies. Studies with cultures of hippocampal neurons demonstrated that the epitopes were on the cell-surface, and immunocompetition experiments confirmed that patients' antibodies recognized the same antigen. Immunoprecipitation and CBA identified neurexin-3 α as the autoantigen of patients' antibodies. None of the 200 controls showed reactivity with neurexin-3 α . All 5 patients (median age 44 years, range 23-50; 4 female) presented with prodromal fever, headache, or gastrointestinal symptoms, followed by confusion, seizures, and decreased level of consciousness. Two patients developed mild orofacial dyskinesias, 3 needed respiratory support and 4 had laboratory findings suggestive of systemic autoimmunity. The CSF was abnormal in all patients (4 moderate pleocytosis, 1 elevated IgG index), and brain MRI was abnormal in 1 (increased FLAIR/T2 in medial temporal lobes). All 5 patients received steroids, 1 also received IVIg, and 1 cyclophosphamide. Two patients died, 1 had complicated sepsis while recovering from the encephalitis, and the other had a rapidly fatal progression (the autopsy showed substantial brain edema without evidence of inflammatory infiltrates). Three patients partially recovered after follow-up of 2, 24 and 36 months; all 3 remained with cognitive deficits, 1 had seizures, and 1 respiratory problems. Cultures of neurons exposed during days in vitro 7-17 to patients' IgG, showed a decrease of neurexin-3 α clusters as well as the total number of synapses.

Conclusion: Neurexin-3 α antibodies associate with a severe but potentially treatable encephalitis in which the antibodies cause a decrease of neurexin-3 α and alter synapse development.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Dalmau receives royalties from licensing fees to Athena Diagnostics for a patent for the use of Ma2 as an autoantibody test; licensing fees to Euroimmun for patents for the use of NMDA receptor and GABAB receptor as autoantibody tests; licensing fees for the use of DPPX, GABAA receptor, and IgLON5 antibodies as diagnostic tests; and has received a research grant from Euroimmun.

Dr. Graus receives royalties from licensing fees to Euroimmun for the use of IgLON5 as a diagnostic test.

Drs. Martinez-Hernandez, Gresa-Arribas, Planagumà, Petit-Pedrol and Armangué report no disclosures.

M111. Phase II, Placebo-Controlled, Double-Blinded, Crossover Study of Extended-Release Dalfampridine in Monophasic Transverse Myelitis

Kathleen Zackowski, Kateryna Schwartz, Nicholas Wymes, Hua Huang, Allen Jiang, Daniel Becker, Pablo Celnick, Carlos A. Pardo, Maureen A. Mealy and Michael Levy. Baltimore, MD

Background: Transverse myelitis is an inflammatory disorder of the spinal cord that leads to disabilities of gait. Dalfampridine, a sustained-release potassium channel blocker that has been shown to be effective in improving gait and other neurologic functions in multiple sclerosis, has the potential to improve gait and neurologic function in patients with transverse myelitis as this rare disorder shares a similar pathogenic process with multiple sclerosis.

Methods: This is a randomized, double-blind, placebo-controlled cross-over study of extended release dalfampridine (Ampyra®) versus placebo. Twenty-four study participants with monophasic transverse myelitis confirmed by MRI, aged 18-70, with no history of multiple sclerosis were enrolled. After a 2-week placebo lead-in, subjects were randomized to receive either 10 mg twice-daily doses of dalfampridine or placebo control for 8 weeks. Following a 2-week washout and 2-week lead-in, participants crossed over to the second arm of dalfampridine or placebo for 8 weeks. The primary outcome measure was timed 25-foot walk and second outcomes included strength, balance assessments, spasticity and Expanded Disability Status Scale (EDSS) score. Single pulse transcranial magnetic stimulation (TMS) was applied to participants at baseline and end of each arm to measure objective changes in neuronal conduction.

Results: Of 24 enrolled participants, 2 screen failed, 3 withdrew and 19 completed the trial. Among the 19 completers, 10 were women, 17 were white and the average age was 43 years. Timed 25-foot walk improved in 11 of 19 completers by an average of 22%. In the responder group, strength in grip and hips improved. TMS demonstrated increased latencies in TM participants compared to healthy controls; the analysis of dalfampridine on neuronal conduction is underway.

Conclusions: Extended-release dalfampridine improves walking speed in 55% of participants with monophasic TM by an average of 22%. The responder rate in TM is somewhat higher than multiple sclerosis (40%), and the average degree of improvement is comparable.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Michael Levy receives research support from NIH, Guthy Jackson Charitable Foundation, Shire, Alexion, Acorda, Sanofi/Genzyme, Alnylam, NeuralStem and Genentech, and serves as a consultant for Chugai Pharmaceuticals, Shire, GlaxoSmithKline, Quest Diagnostics and Alexion Pharmaceuticals.

M112. Tocilizumab Is Effective in Autoimmune Limbic Encephalitis Refractory to Weekly Rituximab

Jung-Ah Lim, Woo-Jin Lee, Soon-Tae Lee, Jun-Sang Sunwoo, Jung-Ick Byun, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Seon-Jae Ahn, Hye Rim Shin, Yoon Hyuk Jang, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea

We aimed to determine the efficacy of tocilizumab treatment in rituximab-refractory autoimmune limbic encephalitis (ALE) as compared to other treatment options.

Furthermore, we aimed to determine predictors for a good clinical response to tocilizumab.

Ninety-one patients with ALE, who had inadequate clinical response to first-line immunotherapy and following rituximab treatment, were recruited from the Korea Autoimmune Synaptic and Paraneoplastic Encephalitis Registry (KASPER). Patients were grouped according to their further immunotherapy strategies. Intergroup analyses of demographic, clinical, laboratory, treatment profiles, and outcomes were performed. Main outcomes were defined as the favorable modified Rankin-Scale (mRS) score (0–2) at 1 and 2 months from the initiation of each treatment strategy and at the last follow-up. Achievement of favorable clinical response at the last follow-up was also analyzed.

Thirty (33.0%) patients were included in the tocilizumab group, 31 (34.0%) in the additional rituximab group, and 30 (33.0%) in the observation group. The tocilizumab group showed more frequent favorable mRS scores at 2 months from treatment initiation and at the last follow-up, compared to those at the relevant time points of the remaining groups. The majority (89.5%) of the patients with clinical improvement at 1 month from tocilizumab treatment maintained a long-term favorable clinical response. No serious adverse effects of rituximab or tocilizumab were reported.

Tocilizumab is effective and safe for the treatment of ALE with inadequate responses to first-line treatment and the second-line standard-regimen, rituximab. The tocilizumab-mediated clinical improvement manifested as early at one month after treatment initiation.

M113. Tolerization Therapy Reduces Disease Frequency and Severity in Mouse Model of Neuromyelitis Optica

Melina V. Jones, Anne Semon and Michael Levy. Baltimore, MD

Background: We previously discovered that T cells from aquaporin-4 (AQP4) knockout mice immunized with the second extracellular loop of AQP4(135-153). These T cells do not cause disease in AQP4 knockout mice as these mice lack the AQP4 target. However, when adoptively transferred to wild-type mice, these AQP4-reactive T cells mount an inflammatory attack in the spinal cord and optic nerves very similar to human NMO disease. Thus, AQP4-reactive T cells alone are sufficient to recapitulate NMO in mice. We tested the ability to block AQP4-reactive T cells using a peptide tolerization strategy.

Design/Methods: Wildtype recipients of pathogenic AQP4-reactive T cells were treated with subcutaneous injections with a range of doses of AQP4(135-155) from 10 M – 1 mM on days 1, 3 and 5 post-transfer and monitored for changes in weight and neurological behavior on the standard EAE scale. Pathological examination of spinal cord and optic nerve tissue included H&E, eriochrome for myelin and markers of inflammatory cells.

Results: All control mice developed neurological signs of transverse myelitis with an average EAE score of 2.5. Mice treated with 10 M AQP4(135-155) stratified equally into three groups: those who responded well with no evidence of

disease or weight loss, those who developed disease but to a less severe degree with an average EAE score of 1.0, and those who did not respond to treatment and developed disease to a degree similar to controls. Mice treated with higher doses of AQP4(135-155) at 10x and 100x died of anaphylaxis. Pathological examination showed inflammation in the spinal cord and optic nerve tissue in control mice; in mice treated effectively with 10 M AQP4(135-155), the inflammation was markedly reduced.

Conclusions: In this animal model of NMO, tolerization therapy with subcutaneously injected AQP4(135-155) reduced the frequency and severity of NMO disease. Further studies are necessary to translate this approach to human NMO patients.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Michael Levy receives research support from NIH, Guthy Jackson Charitable Foundation, Shire, Alexion, Acorda, Sanofi/Genzyme, Alnylam, NeuralStem and Genentech, and serves as a consultant for Chugai Pharmaceuticals, Shire, GlaxoSmithKline, Quest Diagnostics and Alexion Pharmaceuticals.

Dementia and Aging

M114. Characterization of Molecular Mechanism(s) Underlying ApoE4-Induced Brain Phospholipid Dysregulation in Alzheimer's Disease

Dongming Cai, Farida El Gaamouch, Li Zhu, Michael Ohlmeyer, Gregory Elder, Christopher Cardozo and Vahram Haroutunian. New York, NY and Bronx, NY

Background: The apolipoprotein E4 (ApoE4) allele is the strongest genetic risk factor for sporadic Alzheimer's Disease (SAD). However, the mechanisms that underlie pathogenic nature of ApoE4 in SAD are not well understood. Our recent findings suggest that ApoE proteins are critical determinants of brain phospholipid homeostasis and that the ApoE4 isoform is dysfunctional in this process. We have found that the levels of phosphoinositol biphosphate (PIP2) are reduced in human and mouse brain tissues of ApoE4 carriers. These changes are secondary to increased expression of the phosphoinositol phosphatase synaptojanin 1 (synj1) in ApoE4 carriers.

Aims: (1) Investigate the molecular mechanism(s) underlying ApoE4-induced PIP2 dysregulation; and (2) Search for pharmacological strategies targeted at synj1 expression.

Methods: Using ApoE4 knock-in (KI) mouse models and postmortem human brain tissues derived from parietal cortex of ApoE4 carriers, we performed miRNA-sequencing and qPCR analysis to determine miRNA expression profiles. For drug discovery studies, we used cultured cortical neurons and AD mouse models (APP/PS1 transgenic mice and ApoE4 KI mice) to screen selected compounds from a library and assess new analogs.

Results: Like ApoE null conditions, ApoE4 fails to stimulate efficient degradation of synj1 mRNA, in contrast to ApoE3. mRNA stability is often regulated by microRNA binding to 3'-UTR regions. We identified changes in two

microRNAs (miR195 and miR374) in ApoE4 mouse brain tissues, as well as in human brain samples of ApoE4 carriers (with diagnosis of MCI/early AD), as compared to non-ApoE4 counterparts. Over-expression in ApoE4 neurons of miR195 but not miR374 reduced synj1 protein levels. In parallel, we screened a library of compounds with the potential to reduce synj1 protein levels and found that the FDA-approved drug nimodipine had synj1/A β -lowering effects in neuronal cultures. Administration of nimodipine for one month reduced brain content of synj1/A β and improved cognitive function in AD mouse models. The synj1-reducing effects of nimodipine were independent of its calcium channel inhibitory activities. We designed and synthesized a batch of structural analogs of nimodipine and found that one analog (Synatocpd #9) had increased potency at lowering A β and synj1 levels with attenuated calcium channel blockade effects, when compared to nimodipine.

Conclusions: miR195 is involved in ApoE4-induced phospholipid dyshomeostasis in AD. Novel therapeutic directions for AD include nimodipine and its analogs that affect brain PIP2 dyshomeostasis independent of previously known activities against calcium channels.

Health Services Research

M115. Hospital Tax Status and Carotid Artery Stent Utilization in US Hospitals Performing Carotid Revascularization

Justin V. Chandler, Benjamin P. George, Adam G. Kelly and Robert G. Holloway. Rochester, NY

Objective: The Faculty Advocating Collaborative and Thoughtful Carotid Artery Treatments have suggested carotid artery stenting (CAS) is less effective and more expensive than carotid endarterectomy (CEA). We sought to identify the association of hospital tax status (non-profit vs. for-profit) on CAS vs. CEA utilization for patients admitted to US hospitals for carotid revascularization.

Methods: Using the Nationwide Inpatient Sample admissions for carotid artery occlusive disease from 2008-2011, we identified all private, non-federated US hospitals that performed at least 20 carotid revascularization procedures annually; including carotid artery stenting (ICD-9 00.63) or carotid endarterectomy (ICD-9 38.12) as defined by the International Classification of Disease codes. We selected hospitals that performed a minimum of 20 revascularization procedures to minimize variability. Only hospitals performing at least one carotid artery stent were included in the analysis (Medicare certified hospitals). We then used a multilevel multivariable logistic regression; controlling for patient demographics, comorbidities and other hospital characteristics, to assess the effect of hospital tax status on CAS use.

Results: Across 723 hospitals (600 non-profit, 123 for-profit), 66,731 carotid revascularization admissions were identified. Approximately one of five (18.7%) revascularization admissions included in the analysis received a CAS. The hospital charge (adjusted in 2014 US dollars) per hospitalization for CAS was \$52,177 vs. \$29,078 for CEA

($p < 0.01$). The average annual rate of stenting among hospitals performing revascularization was 17.7 per 100 procedures (Median 12.5, Interquartile Range 5.4-26.7 per 100 procedures). The average carotid artery stenting rate among non-profit hospitals was 17.5 per 100 procedures (95% CI 16.2-18.9) vs. 24.2 per 100 procedures (95% CI 20.2-18.2) in for-profit hospitals. Adjusting for patient age, sex, insurance payer, Charlson comorbidity index, hospital carotid revascularization volume, region, urban/rural location, and teaching status; for-profit hospital designation was associated with a greater odds (Adjusted Odds Ratio 1.55, 95% CI 1.14-2.11) of CAS for patients undergoing carotid revascularization.

Interpretation: For-profit hospital tax status is associated with a higher rate of CAS compared to non-profit hospitals in those receiving carotid revascularization. Further research is needed to understand the individual and system level factors driving this difference.

Neuromuscular Disease

M116. Intrathecal Autologous Adipose-Derived MSC Treatment for ALS: Results of Phase I and Design of Phase II Clinical Trials

Nathan P. Staff, Nicolas N. Madigan, Eric J. Sorenson, Mark E. Jentoft, Jonathan M. Morris, Allan B. Dietz, Dennis A. Gastineau and Anthony J. Windebank. Rochester, MN

Mesenchymal stromal cells (MSC) have been proposed as an ALS therapy by virtue of their secretion of neurotrophic factors and alteration of the immune system. We have now completed a Phase I, dose-escalation clinical trial of intrathecal autologous adipose-derived MSC therapy for ALS. 27 patients with El Escorial clinically-definite ALS were enrolled and treated intrathecally at escalating doses (10 million x 1 dose, 50 million x 1 dose, 50 million x 2 doses monthly, 100 million x 1 dose, and 100 million x 2 doses monthly). The median age was 57 (range 36-75) and 15 were male. The median follow-up was 289 days (range 27-759) and there have been 12 deaths, none of which were attributed to MSC therapy (median death 334 days following injection (range 27-755)). The safety profile was positive, with the most common side-effects reported being temporary low back and leg pain at the highest dose level. Although the study was not designed for efficacy, ALSFRS-R was performed throughout the study and showed progression in all patients that did not appear, and was not reported by any patients, to be more rapid than prior to MSC therapy. Despite overall progression, 17 patients reported specific temporary clinical improvements following treatment. MSC therapy at the 50-100 million doses were associated with elevated CSF protein, nucleated cells and MRI imaging of thickened lumbosacral nerve roots. Preliminary autopsy data did not reveal any tumor formation, and may suggest implantation of MSCs in the lumbosacral nerve roots. Biomarker studies of peripheral blood immune status and CSF miRNA are ongoing. In conclusion, intrathecal treatment of autologous adipose-derived MSCs appears safe at the tested doses in ALS. These results warrant further

exploration in a multi-treatment Phase II trial, and our design for this will be presented.

M117. Fibronectin Connecting Segment-1 Peptide Modulates Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)-Patient Leukocyte Trafficking at the Blood-Nerve Barrier In Vitro and Chronic Demyelinating Neuritis in a Spontaneous Severe Murine Model of CIDP

Eroboghene Ubogu, Kelsey Greathouse, Steven Palladino, Rebecca Beacham, Chaoling Dong and Eric Scott Helton. Birmingham, AL

The pathogenesis of hematogenous leukocyte trafficking across the blood-nerve barrier (BNB) in Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is being elucidated. Fibronectin connecting segment-1 (FNCS1) is an alternatively spliced variant of fibronectin expressed by microvascular endothelial cells at sites of inflammation in vitro and in situ. FNCS1 is a counterligand for leukocyte α -4 integrin implicated in pathogenic leukocyte trafficking. We sought to determine the role of FNCS1 in CIDP patient mononuclear leukocyte trafficking across the BNB in vitro and in chronic demyelinating neuritis using representative spontaneous murine CIDP model in female CD86-deficient non-obese diabetic mice.

Mononuclear leukocytes from 7 untreated CIDP patients were independently infused into a flow chamber attached to confluent BNB endothelial cell dishes with a FNCS1 peptide containing the critical binding sequence for α -4 integrin, with appropriate controls including an irrelevant (FNCS1C) peptide. Real-time video microscopy was performed to quantify trafficking. The adhesion/migration index (AMI) was calculated by dividing the numbers of adherent/migrated cells for each patient following physiological BNB cytokine treatment by basal numbers obtained using the untreated BNB. 24-week old female mice with equivalent mean neuromuscular severity scores (NMSS = 2.75) were treated with 2 mg/kg FNCS1 or FNCS1C peptide once a day for 5 days with appropriate controls. NMSS were recorded 3 times a week for 30 days after treatment initiation, with bilateral dorsal caudal tail nerve (DCTN) and sciatic nerve motor nerve electrophysiology performed at day 30 prior to sciatic nerve harvesting for quantification of inflammation and morphometric assessment of demyelination.

25 μ M FNCS1 peptide maximally inhibited CIDP leukocyte trafficking in vitro, with a mean AMI of 0.77 (range 0.41-1.39), compared to FNCS1 peptide (AMI 2.09, range 0.81-3.67). FNCS1 peptide treatment resulted in statistically significant differences in mean NMSS compared to control peptide from day 8, with mean NMSS 1.41 vs. 3.63 on day 15 and 2.02 vs. 4.21 on day 30. This was associated with improved mean motor conduction velocities and distal waveform durations in the DCTN and sciatic nerves at day 30. The numbers of CD45+ leukocytes and % demyelinated area per section were also significantly reduced following FNCS1 peptide treatment. These results imply an important role for FNCS1- α 4 integrin-mediated leukocyte

trafficking in CIPD, providing a potential target for therapeutic modulation.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Eroboghene Ubogu: Royalty for marketing SV40 large T antigen immortalized human endoneurial endothelial cells from Baylor Licensing Group. Royalty from Springer Science + Business Media for a book titled “Chemokines: Methods and Protocols” that describes the BNB leukocyte trafficking assay.

M118. NK and NKT Cells Are Increased in the Peripheral Blood of ALS Patients

Benjamin J. Murdock, Carey Backus, Stephen A. Goutman and Eva L. Feldman. Ann Arbor, MI

Amyotrophic lateral sclerosis (ALS) is a devastating illness which results in progressive degeneration of the motor neurons. There is currently no cure and treatment options are incredibly limited. Previous studies have demonstrated that the immune system plays a dual role in ALS pathogenesis: it can protect against or exacerbate neuronal damage. It is therefore critically important to determine the role of specific immune cell populations during the course of disease. Immune cells from the peripheral blood are capable of altering disease pathogenesis; however, despite strong evidence that the immune system plays a significant role in ALS pathogenesis, clinical studies have yet to identify an upregulated cell population in the peripheral blood of ALS patients. Cells known as natural killer (NK) and natural killer T (NKT) cells play a key role in killing cancerous or infected cells in the body and are also capable of skewing the immune system towards a more destructive response. Our data show that NK cells and a subpopulation of NKT cells – CD3+ CD4+ CD8+ cells – are significantly increased in the blood of ALS patients and that the number of these cells increases over time. Moreover, we find that the number of CD3+ CD4+ CD8+ cells is increased in the peripheral blood of SOD1G93A ALS mice as the disease progresses. Unlike anti-inflammatory cell types that are currently being studied for use in ALS therapeutics, such as regulatory T cells, NK and NKT cells are purely pro-inflammatory and can be targeted in the blood using methods of depletion. Thus, these cell populations are an incredibly attractive target for future clinical trials.

Autoimmune Neurology

M119. Cellularity: A Novel Neuroimaging Approach to Detecting Inflammation in HIV

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Introduction: Diffusion based spectral imaging (DBSI)¹ is a variant of diffusion tensor imaging (DTI) that specializes in disseminating between different biological entities at the voxel level. DBSI assesses various diffusion patterns to isolate signals derived from axons, cellularity, extracellular space, and myelin inflammation. This technique is of particular interest in HIV research, where conventional DTI

findings are prominently reported, and the persistence of undetectable viral reservoirs that can trigger abnormal immune responses across the aging spectrum, even in medicated patients.

Methods: Forty-two HIV+ patients currently on medication with suppressed viral load and fifty-five HIV- controls were recruited for this study. The DTI sequence was acquired with two runs of 23 directions with multiple b-values and one b0. Initial processing was done through the FSL toolbox including eddy current correction, brain extraction and tensor calculation. Subjects that exceeded a 3.5 mm movement threshold were removed and post-processing was performed on homemade software in matlab to generate DBSI metrics. Fractional anisotropy maps were subjected to the TBSS pipeline with a 0.25 threshold for skeletonization and the same parameters were applied to each DBSI map. A voxel-wise analysis was conducted using randomize for each of the four DBSI measurements and correlations were performed between the skeletal average for each metric and years on medication.

Results: The voxel-wise analysis revealed increased cellularity in HIV+ compared to HIV- across the entire skeleton, with age and gender treated as covariates ($p < 0.05$ corrected for multiple comparisons). Cellularity was the only metric that showed a significant difference between the groups. Additionally, a negative relationship was seen between cellularity and years on medication independent of age.

Conclusions: Even in treated HIV patients, viral eradication is unlikely, due to the reengagement of an inflammatory immune response from undetectable viral reservoirs. Increase in cellularity has been linked to inflammation and gliosis² and therefore, may reflect an active immune response that is still present in these subjects. Therefore, the drop in cellularity that associates with prolonged medication may represent a reduction in the resurgence of viral antigen from these reservoirs.

M120. Anti-LGI1 Encephalitis Is Associated with Unique HLA Class II Subtypes

Tae-Joon Kim, Soon-Tae Lee, Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Jin Sun Jun, Byoungsu Park, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seongnam, Republic of Korea and Seoul, Republic of Korea

Based on recent discoveries of neuronal autoantibodies, the clinical significance and spectrum of autoimmune encephalitis is rapidly expanding. While immunotherapies improves symptoms in those with synaptic antibodies, such as anti-leucine-rich glioma-inactivated 1 (anti-LGI1) and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, the underlying immunopathogenesis is not fully understood except some paraneoplastic cases. Among the possible pathogenesis of autoimmune encephalitis, genetic susceptibility has not been evaluated previously. In consideration of the fact that HLA is the most relevant and important group of genes susceptible to autoimmune diseases, we investigated

whether the human leukocyte antigen (HLA) subtypes is associated with the diseases.

We prospectively enrolled total 11 patients with anti-LGI1 and 17 with anti-NMDAR encephalitis during June 2015 and December 2015 in a single institution, and sequenced the HLA subtypes including HLA-A, -B, -C, -DRB1, and -DQB1. The results were compared to the reported data set of 210 epilepsy patients and 485 healthy Korean controls. The association was confirmed using the HLA-peptide binding prediction algorithm servers, i.e. ProPred and NetMHCII. Then we performed the computational docking of the predicted protein segment into the associated HLA.

In anti-LGI1 encephalitis, 10 among 11 patients (90.9%) had DRB1*07:01-DQB1*02:02 haplotype, which is significantly higher than epilepsy controls (8.6%, odds ratio = 106.7, $P < 0.01$) and healthy controls (12.0%, odds ratio = 73.6, $P < 0.01$). While B*44:03 and Cw*07:06 alleles showed the statistical differences, the multivariate analysis showed that these alleles are linked to the DRB1*07:01 and DQB1*02:02 and therefore the results of linkage disequilibrium. On the other hand, there was no association between HLA and anti-NMDAR encephalitis. Additional analysis using HLA-peptide binding prediction algorithms identified the highest affinity between DRB1*07:01 and LGI1 protein sequence and computational docking underpinned the close relationship.

In conclusion, most of the anti-LGI1 encephalitis develops in population with the specific HLA subtypes, i.e. HLA-DRB1*07:01-DQB1*02:02, whereas anti-NMDAR encephalitis showed no HLA association. We proved the association by making full use of both methods including classic linkage disequilibrium and modern bioinformatics techniques. This result provides an insight for novel disease mechanisms in anti-LGI1 encephalitis.

M121. A Costly Condition: Assessing the Burden of Autoimmune Encephalitis at a Tertiary Institution from 2006-2015

Jesse Cohen, Javier Sotoca, John C. Probasco and Arun Venkatesan. Baltimore and Barcelona, Spain

Background AND Purpose: Recent epidemiologic work on autoimmune encephalitis (AE) has focused on clinical presentation and patient outcomes. However, patient- and system-level costs of AE are underrecognized. Here, we assess the disease burden of AE at a tertiary care center.

Methods: We reviewed medical records of 244 admissions between July 1, 2006 and June 30, 2015 with discharge diagnoses of encephalitis at the Johns Hopkins Medical Institutions. Patients that met consensus diagnostic criteria for definite or probable AE were included. Only data from the index admission were included. Demographic and clinical variables were obtained for definite and probable AE groups and the groups were pooled for further analysis. Length of stay (LOS) and hospital charges were compared with those of contemporaneous multiple sclerosis (MS) index admissions at our institution.

Results: Seventy-three patients met criteria for AE. Mean age on admission was 45.9 years (range 18-77); 39 (53.4%) were women. Twenty-seven patients (36.0%) tested positive for an AE-associated antibody in CSF or serum. Of 67 patients treated with immunotherapy, 56 (83.6%) were responsive. Eighteen (24.7%) were admitted to the ICU (median ICU LOS 24.5 days, IQR 55 days). There were no significant differences between definite and probable AE groups. Follow-up was available for 54 (74.0%) patients (median 13.5 months, IQR 25.8 months). For patients with follow-up, mean modified Rankin Score on admission, discharge, and last follow-up was $3.2 \pm .17$, $2.74 \pm .15$ and $2.24 \pm .21$ respectively. Overall AE median LOS was 15 days (IQR 19 days) (ICU-admitted patient median 37.5 days; non-ICU median 12 days; $p < 0.0001$). Overall AE median charges were \$59,950 (IQR \$88,880) (ICU-admitted patient median \$177,982; non-ICU median \$47,545; $p < 0.0001$). MS patients had median LOS of 4 days (IQR 3 days, $p < 0.0001$ compared to all AE) and charges of \$13,080 (IQR \$9,670, $p < 0.0001$ compared to all AE). Aggregate charges for AE (\$7.59 million) exceeded those of MS (\$6.08 million), despite nearly 5 times more admissions for patients with MS ($n=349$) than AE ($n=73$).

Conclusions: Patients with AE are hospitalized for long durations and have high rates of ICU admission, leading to increased hospital charges. Overall, AE represents a significant source of costs to the health care system, and its economic burden in the inpatient setting at our institution exceeds that of MS.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Arun Venkatesan served as a paid scientific advisory board member for Medimmune, Inc.

John Probasco, Javier Sotoca, and Jesse Cohen have no relevant disclosures.

Dementia and Aging

M122. Cardiac Vagal Tone Is Altered in Pre-Clinical Alzheimer's Disease

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Purpose: There is an extensive pathological overlap between Alzheimer's disease (AD), cardiovascular diseases (CVD) and cerebrovascular diseases (CBVD). Those diseases not only affect the same at-risk population, but they also share many common risk factors (Santos et al., 2016). In order to explore this relationship in pre-clinical AD, we have evaluated changes in vagal tone (respiratory sinus arrhythmia [RSA] and heart rate variability [HRV]) in a subjects with elevated cortical amyloid burden ($A\beta+$) compared to a matched cohort of healthy older adults with normal amyloid burden ($A\beta-$).

Methods: Participants: Sixty-three adults (ages 55-75 years) with a self-reported first degree family history of AD, and who identified themselves as having memory difficulties.

Neuroimaging: PET scan was performed at baseline, 370MBq (10 mCi $\pm$ 10%) bolus injection of 18F-florbetapir was administered intravenously. PET standardized uptake value (SUV) data were summed and normalized to the whole cerebellum SUV, resulting in a region-to-cerebellum ratio termed SUV ratio (SUVr). We defined A β + as individuals with anterior cingulate (ACC) SUVr $\geq$ 1.1.

Cardiac measures: ECG measures of RSA and HRV were recorded at the 18 month follow-up visits for each participant at rest, sitting quietly in a semi-supine position (120 seconds), then during their performance on a computer-administered hidden maze learning test (GMLT; to induce mild cognitive stress for approx. 190 seconds), and then once again while relaxing quietly in a semi-supine position (120 seconds).

Results: Increased HRV was observed in A β - subjects during cognitive stress ($p=0.0061$; adj. $p=0.0304$), and subsequently decreased at rest ($p<.0001$; adj. $p=0.0007$). By contrast, A β + subjects did not consistently show alteration in HRV in response to cognitive stress. This same pattern, and group differences, were observed for RSA, with A β - subjects showing an increase during cognitive stress, relative to both pre- and post-stress conditions ($p<.0001$). A β + subjects showed no change in RSA at any point during testing.

Conclusion: We have previously shown inefficient myocardial oxygen use in pre-clinical AD, as evidenced by increased rate pressure product (RPP) for participants who are A β +. These results suggest that a decrease in autonomic arousal is observable in pre-clinical AD. Specifically, we found reduced HRV and RSA, during mild cognitive stress, in individuals with substantial cortical amyloid aggregation. These results suggest that modest cardiovascular changes are observable in the very earliest stages of AD.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? The Scope Study is supported by an unrestricted grant from Pfizer Inc. Contact the co-author P.J. Snyder: psnyder@lifespan.org for enquiries.

M123. Electrostimulation Effects in lvPPA and nvfPPA

Kimberly T. Webster, Tushar Chakravarty, Bronte Ficek, Chiadikaobi Onyike, Constantine F. Frangakis, Argye E. Hillis and Kyrana Tsapkini. Baltimore, MD

Primary progressive aphasia (PPA), a neurodegenerative syndrome marked by progressive language impairment and subsequent dementia, has three variants: semantic (sv), logopenic (lv), and non-fluent (nvf), each associated with its own symptoms. The underlying pathology varies from corticobasal degeneration to Alzheimer's disease. Language therapy studies (mainly in single-subject designs) have shown improvements but with little evidence of sustainability or generalization of therapy gains. Anodal tDCS over the frontal and prefrontal cortex combined with language therapy has recently been shown to improve spelling and naming in individuals with PPA (Cotelli et al., 2014; Tsapkini, et al.,

2014). However, characteristics that predict a differential response to treatment have not been identified. We hypothesized that the PPA variant may be such a characteristic.

We investigated whether individuals with lvPPA respond differently than those with nvfPPA to anodal tDCS in the left inferior frontal gyrus (L IFG) during written language (spelling) intervention.

Fourteen participants (7 nvfPPA; 7 lvPPA) received anodal tDCS and sham treatments with therapy for 10-15 sessions in a within-subjects crossover design. We targeted the L IFG for stimulation as a written language production area. Participants were evaluated before, immediately after, 2 weeks post- and 2 months post-intervention for each treatment period.

In the lvPPA participants, tDCS over the L IFG was more beneficial than sham for trained items, even at the 2-month follow-up period. Additionally there was generalization of treatment gains to untrained items. Conversely, in the nvfPPA participants, tDCS over the L IFG was not more beneficial than sham for sustaining therapy effects up to 2 months and generalizing them to untrained items.

The present study showed that intervention gains of tDCS over the L IFG coupled with written language treatment were better sustained and generalized in the lvPPA than the nvfPPA variant. Results have implications with regard to atrophy distribution in the two variants and for specifying tDCS intervention for each PPA variant.

References:

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M124. Novel Role of the Neurospecific SCF^{Fbx2}-E3-Ligase in Mechanisms Associated with the Promotion of Synaptic Plasticity Through Rescue of cAMP-CREB Signaling Pathway in a Model of Alzheimer's Disease

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The neuronal specific SCF^{Fbx2}-E3-ligase (Fbx2), has been found to specifically recognize neurospecific N-glycoproteins including beta-secretase1(BACE1), through its Fbox associated (FBA) domain, thus promoting BACE1 ubiquitination and degradation in the subcellular compartments of the secretory pathway. Inhibition of BACE1 in the Alzheimer's disease (AD) brain has been shown to significantly reduce the accumulation of beta amyloid (A β) and improve cognitive function. Exogenous delivery of Fbx2 into mouse brains using AD (Tg2576) mice, a transgenic mouse model, has shown improvement in synaptic plasticity and decrease in accumulation of A β . To further investigate the potential therapeutic role of Fbx2 in AD, we generated transgenic mice overexpressing human Fbx2 in brain tissue (TgFbx2).

By crossing the TgFbx2 mice with Tg2576 AD mice, a new AD mouse model (TgFbx2/Tg2576 mice) was produced. We assessed long-term potentiation (LTP) in the hippocampal formation and short-term memory by the fear conditioning freeze test. We found that 18-24 month old TgFbx2/Tg2576 mice showed a significant improvement with regards to LTP in hippocampal formation and short-term memory, compared to their Tg2576 littermates. These improvements are associated with a reduction in BACE1 levels and A β accumulation in the brain. We further investigated the underlying mechanism by which the NMDAR-CaMKII-MAPK-CREB signaling pathway, which is downregulated in Tg2576 AD brain, was rescued by the overexpression of Fbx2 in double transgenic mice Tg2576/TgFbx2. Our study demonstrated that Fbx2 promotes BACE1 ubiquitination and degradation, which reduces A β toxicity and rescues the cAMP-CREB synaptic signaling pathway. This suggests that Fbx2 could be a novel therapeutic target for AD treatment.

M125. Increased microRNA-206 Levels in the Brain of Alzheimer's Disease Can Be Detected from Early Stage via Intranasal Biopsy of Olfactory Epithelium

Jangsup Moon, Soon-Tae Lee, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Korea

Early diagnosis of Alzheimer's disease (AD) is important; however, none of the current biomarkers can differentiate patients with mild cognitive impairment from cognitively healthy controls. Brain-derived neurotrophic factor (BDNF) is the core molecule involved in the regulation of synaptic plasticity and memory. MiRNA-206 (miR-206), which suppresses the expression of BDNF, is known to be elevated in the brain of AD patients. Here, we reproduced the elevation of miR-206 levels in autopsied brain of AD patients, and assessed the probability of olfactory mucosal miR-206 level as a potential biomarker in early dementia patients.

We obtained the lateral temporal cortex tissues of autopsied AD patients (n=6) and age-matched controls (n=6) from the Boston Brain Bank and performed real-time PCR. The relative miR-206 level exhibited a 1.5-fold increase ($P<0.001$) in the AD group. Next, we performed intranasal biopsy of the olfactory epithelia of early dementia patients (n=24) and cognitively healthy controls (n=9). Patients with significant depression (n=8) were analyzed separately, as their cognitive impairments were thought to be caused by their depression. Real-time PCR was performed on the biopsied tissues. The relative miR-206 level exhibited a 7.8-fold increase ($P=0.004$) in the mild cognitive impairment group (CDR 0.5; n=13) and a 41.5-fold increase ($P<0.001$) in the CDR 1 group (n=11). However, this level was not increased in the depression group, even in those with cognitive decline. Using the optimal cutoff value, the sensitivity/specificity for diagnosing CDR 0.5 and CDR 1 dementia were 87.5%/94.1% and 90.9%/93.3%, respectively. In ROC analysis, the AUCs were 0.942 and 0.976 in the CDR 0.5 and CDR 1 groups, respectively. The olfactory

mucosal miR-206 level and cognitive assessment scores were significantly correlated in the non-depressed subjects with cognitive impairment.

In conclusion, the olfactory mucosal microRNA-206 level can be easily measured, and it can be utilized as an excellent biomarker for the diagnosis of early AD, including mild cognitive impairment.

M126. Fewer Neurofibrillary Tangles and Slower Conversion to AD in MCI Patients Taking RAS Acting Antihypertensives

Whitney Wharton, Liping Zhao, Kyle Steenland, Marla Gearing and Felicia Goldstein. Atlanta, Ga

With the projected increase in Alzheimer's disease (AD) prevalence, repurposing existing drugs generally recognized as safe, and that show promise in AD studies, shortens the time to provide urgently needed treatment options.

The renin angiotensin system (RAS) regulates blood pressure and research suggests that antihypertensives that act via the RAS, may decrease the risk of Alzheimer's disease (AD) possibly via A β and/or tau.

We previously reported that individuals taking RAS acting medications (ACE-Is or A2RBs), particularly those that are centrally acting, show slower cognitive decline and are less likely to progress from mild cognitive impairment (MCI) to AD over three years. However, the potential mechanism was unclear, due to the absence of neuropathological findings on these individuals.

Here we present data from the RUSH ADRC, obtained during the 2015 Friday Harbor Psychometrics Conference to test the hypothesis that individuals taking RAS acting antihypertensives may exhibit slower clinical disease progression and less AD related neuropathology than individuals taking non-RAS acting antihypertensives.

Participants included 83 individuals with MCI at Baseline who were taking an antihypertensive medication at Baseline and during at least two consecutive follow up visits (RAS medication N=38; non-RAS medication N=45). Postmortem neuropathological data were available for all participants. There were no group differences on demographic variables. Participants were older (M=83.1 yrs), 32% male, well educated (M=15.7 yrs) and 9.2% self-identified as Black. Groups did not differ in percent of individuals who were ApoE4 positive (28%) or Baseline MMSE score (M=26). While there were no group differences in blood pressure (M=138/72 mmHg), HDL (M=59mg/dL) or LDL (M=101 mg/dL), RAS users were more likely to be diabetic than non-RAS users ($p=.01$).

In line with our previous reports, participants with MCI at Baseline who were taking a RAS medication were less likely to progress to AD than non-RAS users ($p=.02$). There were no significant group differences in brain weight or NIA Reagan or Braak scores. However, individuals taking RAS acting medications exhibited significantly fewer neurofibrillary tangles (NFT) than non-RAS users in 5 brain regions including the midfrontal cortex, midtemporal cortex, inferior parietal cortex, entorhinal cortex, and hippocampal CA1 region ($p=.03$).

Results suggest that prevention of NFTs via abnormal tau hyperphosphorylation represents a plausible mechanism by which RAS acting medications aid in slowing the progression from MCI to AD.

M127. Relationship Between Orthographic and Phonological Treatments with Brain Atrophy in PPA

Andreia V. Faria, Aaron Meyer, Rhonda Friedman, Donna Tippet and Argye B. Hillis. Baltimore, MD and Washington, DC

Anomia is a common deficit in neurodegenerative disorders such primary progressive aphasia (PPA)¹. To evaluate which patients are benefited by different kinds of therapeutics in this heterogeneous group is challenging. Clinical performance is the straightforward measure; however, clinical tests can be too broad, or lack reliability, or they may be better if complemented by other methods. We evaluated relationships between regional atrophy in brain MRI and treatment effects in 21 PPA patients under an orthographic treatment condition (OTC) and a phonological treatment condition (PTC), with Prophylaxis items (named correctly at baseline) and Remediation items (named incorrectly at baseline). Left temporal regions had significantly lower volume in the PPA patients at baseline, compared to 11 controls. We then examined the relationships between baseline volume within each of the left temporal regions and the treatment effects for Exemplar 1 (a set of pictures that was tested at baseline, utilized during treatment, and tested at one month post-treatment) in PPA. We found negative correlations between the treatment effect for Remediation items in OTC and volume of left inferior temporal gyrus and pole, regions that have been associated with semantic processing^{2,3}. These findings suggest that individuals with greater semantic deficits should be more likely to respond to orthographic treatment for remediation items.

We also examined the relationships between the treatment effects for Exemplar 1 and the changes in brain volume between baseline and one month post-treatment. For Prophylaxis items in PTC, a larger treatment post effect occurred for participants with a larger increase in atrophy in the left inferior frontal gyrus (IFG) and left temporal regions; and right hemisphere areas that are a subset of the areas that are homologous to those left hemisphere regions. The left IFG has been associated with speech production^{2,4}, and the left temporal regions with semantic processing^{2,3}. In contrast, for Prophylaxis items in OTC, participants with a larger increase in atrophy in bilateral temporal regions, but not frontal areas, demonstrated a larger treatment effect.

These results indicate that the effects of PTC and OTC are both correlated with atrophy in left temporal areas that deteriorate in svPPA^{2,3}, while the effect of PTC is also correlated with atrophy in the left IFG, which deteriorates in nfvPPA^{2,4}. Therefore, nonfluent individuals may be more likely to benefit from phonological treatment, while individuals with semantic impairment may benefit from orthographic or phonological treatment.

M128. A Genetic Study of a Large Pedigree with Late-Onset Alzheimer's Disease

Thomas S. Wingo, David J. Cutler, James J. Lah and Allan I. Levey. Decatur, GA and Atlanta, GA

Alzheimer's Disease (AD) is known to have a strong genetic basis that is incompletely understood. Prior work with families that inherit AD as an autosomal dominant trait focused on large pedigrees, primarily, with early-onset AD (EOAD; AD onset before 60-65 years). That work led to discoveries of AD-causing mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) and helped establish the role of beta-amyloid in AD pathogenesis. By comparison, there have been relatively few investigations of families with late-onset AD that appear to transmit the disease in a dominant manner, which is likely due to difficulties with ascertainment. Here, we present a unique extended pedigree that has been systematically recruited since 2001 at the Emory Alzheimer's Disease Research Center with apparent autosomal dominant transmission of late-onset AD. This pedigree is remarkable in a number of ways: (1) the parent-offspring concordance for AD is 44.3%, suggesting AD is dominantly inherited in this pedigree ($\chi^2=0.2056$, $df=1$, $p=0.65$); (2) detailed genealogy data are available on 2710 members spanning 3 main branches with between 7 and 11 generations from the original founders; (3) biologic material is available on 175 individuals, including 24 with AD, 5 who have mild cognitive impairment and 27 who are cognitively normal but at-risk for AD (i.e., older than 60 years); (4) 11 autopsies have confirmed AD as the primary neuropathologic diagnosis among affected individuals; and, (5) sequencing of all coding exons of APP, PSEN1, and PSEN2 revealed no coding mutations in 15 affected individuals. To identify causal mutations, we performed whole-exome sequencing on 6 of the most distantly related affected individuals. No unique or rare variant (MAF <5%) was shared among all individuals. There were 153 variants unique to the pedigree shared by >2 individuals. We found a single deleterious variant shared by 3 individuals when filtering by candidate regions that show significant or nominal association with AD in genome-wide association studies (GWAS). The gene, RAB31, has markers with p-values of ~10⁻⁶ in GWAS and has been previously implicated in age-dependent effects on blood pressure. Validation of all variants by 2-point linkage within the pedigree described herein is ongoing.

M129. Alzheimer Disease Associated Presenilin 2 N141I Mutation Leads to Loss of Gamma-Secretase Function and Enhanced Pro-Inflammatory Behavior in Microglia

Susan Fung, Amanda Case, Carole L. Smith, Pete J. Amos, Bryce Sopher, Gwenn A. Garden and Suman Jayadev. Seattle, WA

Mutations in Presenilin 1 or Presenilin 2 (PSEN2) cause autosomal dominant Alzheimer disease (AD), establishing a pathogenic role for these genes in AD associated neurodegeneration. Presenilins form the catalytic subunit of the gamma-secretase complex which cleaves, in addition to APP, numerous substrates mediating diverse cell functions across

multiple CNS cell types including immune cell regulation. While dysregulation of innate immunity is emerging as a relevant contributor to neurodegenerative disease, the molecular pathogenesis of neuroimmune dysfunction in AD is not clear. Recent genetic and hypothesis driven studies have established that microglia, the resident innate immune cells of the CNS are primary mediators of neuroinflammatory mechanisms in AD.

We have previously shown that Psen2 serves as the primary γ -secretase in murine microglia and that Psen2 KO microglia demonstrate a pro-inflammatory phenotype as measured by increased pro-inflammatory cytokine release and NFkB activity. We hypothesize that the familial AD associated PSEN2 N141 mutation impairs gamma-secretase function, resulting in microglial dysfunction and pro-inflammatory phenotype ultimately leading to neurodegeneration.

To study the impact of PSEN2 N141 in microglia as well as in in vivo neuroinflammation paradigms, we created a transgenic mouse model with one human PSEN2 N141 mutant allele and one normal mouse Psen2 allele. Adult microglia were isolated ex vivo from transgenic mice and controls and assessed for baseline immune gene expression. Neonatal microglia were isolated and cultured from mutant and control animals, then assessed for response to TLR4 stimulation, amyloid-beta phagocytosis and immune gene, microRNA and protein expression.

Microglia expressing PSEN2 N141 show decreased gamma-secretase activity, similar to what was observed in PSEN2 KO microglia, suggesting a dominant negative function for the N141 mutations. Further, PSEN2 N141 mutant microglia demonstrate increased NFkB activity and dysregulated immune gene expression. Our results indicate that familial AD PSEN2 mutation impairs microglial function causing chronic inflammatory activation that could promote neuronal injury. Further studies are underway in our laboratory to interrogate these PSEN2 pathways in human microglia differentiated from PSEN2 N141 patient derived induced pluripotent stem cells. Together these murine and human studies will explore the impact of AD mutation associated microglia dysfunction on neurons and AD pathogenesis.

Headache and Pain

M130. Ziprasidone as a Potential Abortive Treatment for Status Migrainosus

Eric C. Landsness, Leo H. Wang and Robert C. Bucelli. Saint Louis, MO and Seattle, WA

Background and Purpose: Migraine headache is among the most prevalent neurological disorders. Status migrainosus often leads to hospitalization and multiple medications are sometimes required for symptomatic relief. In 2008 neurologists at our institution started using the atypical antipsychotic ziprasidone as an abortive medication for status migrainosus.

Methods: The Clinical Investigation Data Exploration Repository (CIDER) was used to search for patients

admitted to the Barnes-Jewish Hospital inpatient neurology service with diagnoses of headache or migraine. Patients were identified as status migrainosus if they met the International Headache Society criteria for a migraine lasting greater than 72 hours. Clinical records of identified patients were then entered into a secure online database (REDCap).

Results: Thirty-four patients between 2008 and 2015 received 10 to 40 mg of ziprasidone for the treatment of status migrainosus. Among patients that received ziprasidone, headache severity decreased 5.7 $\pm$ 3.0 points on a 10-point scale from admission to discharge. Ziprasidone was the last abortive medication added prior to discharge in 65% of cases. The thirty-day readmission rate for migraine headache in patients that received ziprasidone was 12%. Ziprasidone was well tolerated with side effects limited to a mild dystonic reaction (n=1), rhinorrhea (n=1) and a prolonged QTc of 495 milliseconds (n=1).

Conclusions: This observational study suggests that ziprasidone may be a safe, effective abortive medication for the treatment of status migrainosus. Further studies comparing ziprasidone to standard of care are warranted.

M131. Peripheral Neuropathic Changes in Pachyonychia Congenita

Baohan Pan, Kelly Byrnes, Mary Schwartz, C. David Hansen, Michael Caterina and Michael Polydefkis. Baltimore, MD and Salt Lake City, UT

Background: Paronychia Congenita (PC) is a rare genodermatosis due to mutations in keratin genes (6A, 6B, 6C, 16 or 17), and is characterized by dystrophic, thickened and painful palmoplantar keratoderma. Foot pain frequently limits patients' mobility. Little is known regarding the origin, nature or underlying mechanisms of pain in these patients. In the present study, we investigated the histopathology and distribution of cutaneous nerve fibers, subsets of epidermal nerve fibers, mechanoreceptors, myelinated nerves, and blood vessels in patients with PC. Skin samples were obtained from affected thickened plantar skin and from an unaffected nearby area in PC subjects and from the corresponding areas in healthy control subjects.

Subjects and methods: Three mm punch biopsy skin samples were obtained from the feet of 10 patients genetically confirmed with PC (with a mutation in KRT6A). Skin samples from similar locations were also obtained from 10 healthy control subjects of similar age and sex distribution. Tissue was processed to visualize intraepidermal nerve fibers (IENF) (PGP9.5), subsets of IENF (CGRP, SP, tyrosine hydroxylase), myelinated nerve fiber (Neurofilament H), blood vessels (CD31), Meissner's corpuscles and Merkel cells (cytokeratin 20). Structures were quantified using stereology or validated quantification methods.

Results: Histologically, the PC affected skin showed a dramatically thickened stratum corneum compared to PC-unaffected or anatomically matched sites in control subjects. The PC affected skin had a disorganized histological appearance with dermal papilla and stratum corneum/callus often being intermingled. In the affected skin of PC patients, when compared to unaffected sites and normal control

subjects, there are significant increases in the number of Merkel cells located primarily at the base of epidermis, and increased number of blood vessels in the dermal papilla. In contrast, Meissner's corpuscles were significantly reduced in PC-affected skin compared to both PC-unaffected skin and anatomically matched control biopsies. Moreover, there are trends for PC-affected plantar skin to have lower IENF densities (PGP9.5) and sweat gland innervation compared to PC-unaffected skin or anatomically matched control skin. There were no differences in myelinated nerve fiber densities, SP or CGRP between the groups.

Conclusions: These findings suggest that alterations in PC in several sensory structures including Merkel cell sensory complex and thin nerve fibers extend beyond keratinocytes and may provide strategies to study and treat neuropathic pain in PC.

M132. A Randomized Controlled Study Evaluating the Impact of Gabapentin, Gastroretentive Gabapentin, and Pregabalin on Daytime Function in Healthy Volunteers *Peter Schmidt, Christine Rocha and Srinivas Rao. Newark, CA*

Introduction: Dizziness and somnolence are among the most commonly observed adverse effects of pregabalin and gabapentin in clinical trials in patients with post-herpetic neuralgia (PHN). These adverse effects have the potential to negatively impact daytime function.

Objectives: The primary objective of this study was to determine the relative impact of gastroretentive gabapentin (G-GR), gabapentin (G), and pregabalin (P) on daytime function, as assessed by driving simulator performance and measures of sedation and cognition, and to correlate with subjective impairments. Here we report the results of the driving simulator test.

Methods: In this double-blind, placebo-controlled, crossover study, healthy volunteers were randomly assigned 1:1:1:1 to a 4 period dosing sequence with a 7-day washout between periods. Dosing consisted of G-GR, or G, or P, or placebo (PBO) at PHN labeled doses, in the evening on day 1, and ending in the morning on day 3, all under fed conditions. A 60 minute driving simulator test was administered at screening, baseline and 2 hours post-treatment on day 3. The primary outcome measure was the change from baseline in standard deviation of lateral position (SDLP) on the driving simulator. SDLP is a stable measure of driving performance with high reproducibility. A larger SDLP reflects greater weaving during simulated driving.

Results: Thirty-two participants were dosed, 28 completed all 4 dosing periods. The median age was 47.5 years, 75% were male, 38% were white, and 59% were black/African American. The least squared mean difference in SDLP change (feet) from baseline for G-GR (n=28) was 0.255. Corresponding values for G (n=31), P (n=30), and PBO (n=30) were 0.395 (P=.0275), 0.356 (P=.1103), and 0.135 (P=.0611). The least squared mean difference in Standard Deviation of Vehicle Speed change (miles/hour) from baseline for G-GR (n=28) was 0.831. Values for G, P,

and PBO were 0.947 (P=.8293), 1.319 (P=.3666), 0.851 (P=.9705), respectively.

Conclusion: In this exploratory study in healthy volunteers initiating gabapentinoids at PHN labeled doses, SDLP increases were numerically greater for G and P than G-GR, reaching statistical significance for G. SDLP change for G-GR was not statistically different from PBO. Though not necessarily reflective of clinical practice, these results may inform larger trials, which may further elucidate the relative impact on driving of different PHN treatments.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Employee of Depomed, Inc.

M133. Chemogenic Silencing of Nav 1.8 Nociceptors Reverses Neuropathic Pain and Small Fiber Degeneration in Painful Diabetic Neuropathy (PDN)

Nirupa D. Jayaraj, Bula Bhattacharyya, Ren Dongjun, Abdelhak A. Belmadani, Richard J. Miller and Daniela M. Menichella. Chicago, IL

Painful Diabetic Neuropathy (PDN) is a debilitating affliction present in 26% of diabetic patients with substantial impact on their quality of life. Despite this significant prevalence and impact, current therapies for PDN are only partially effective. Moreover, the electrophysiological mechanisms underlying PDN are not well understood.

Pain is a physiological response to potentially dangerous noxious stimuli. However, pathological or "neuropathic pain" is associated with sustained excitability of sensory neurons within pain pathways including Dorsal Root Ganglia (DRG) neurons, so that pain is produced in the absence of appropriate stimuli. In recent years, extensive characterization of DRG neurons has revealed molecularly defined subpopulations of DRG neurons including Nav 1.8 nociceptors. The specific role of Nav1.8 nociceptors in PDN is unknown.

In order to understand the role of the Nav 1.8 neurons in PDN we first studied the electrophysiological properties of these nociceptors in normal and diabetic mice. In DRG neurons from diabetic Nav1.8::Cre, Ai9 mice, we found increased action potentials compared to DRG neurons derived from non-diabetic mice, indicative of diabetes induced hyper-excitability. Therefore in order to investigate if Nav 1.8 nociceptors hyper-excitability contributes to neuropathic pain and progression of small fiber neuropathy in PDN, we generated mice in which hM4D receptors (Designer Receptor Activated by a Designer Drug, DREADD) were expressed exclusively in these DRG neurons. We demonstrate that DREADD receptors can be selectively activated by the drug clozapine-N-oxide (CNO) allowing Nav 1.8 nociceptors silencing (AP blocking), reduced calcium influx and reversal of neuropathic pain in diabetes. Furthermore, we observed significant improvement of skin innervation in diabetic mice with chronic activation of DREADD receptors and chronic silencing of Nav 1.8 nociceptors.

This study reveals for the first time a critical role of Nav 1.8 nociceptors hyper-excitability in the pathogenesis of neuropathic pain and small fiber neuropathy in diabetes. Furthermore, these observations will add to our understanding of how changes in the excitability and calcium influx of sensory neurons contribute to the progression of small fiber neuropathy in PDN, which is a critical barrier to progression for effective and disease modifying treatment of this currently intractable and widespread affliction.

Health Services Research

M134. Successful Reduction in Falls Among Neurology Outpatients After Initiation of a Fall Screening Program

William G. Buxton, Robin Clarke and Andrew Hackbarth.
Los Angeles, CA

Objective: To determine if a fall screening initiative in a high-volume neurology practice results in fewer falls.

Background: Falls are a very common in patients with neurological disorders, are associated with significant morbidity and mortality, and are costly. This risk extends beyond older patients. Prior falls, especially with injury, indicate a significant risk for future falls. Additionally, physical therapy (PT) for strengthening and gait and balance training is the most proven fall-prevention intervention. After demonstrating that an in-office fall screener can lead to an increase in therapy referrals, we have sought to determine whether this results in fewer falls.

Methods: Since July, 2013, all patients seen in our university-based general neurology practice and selected subspecialty clinics have received a paper screener asking if they have experienced a single fall, two or more falls, or any fall with injury in the last 12 months. The provider was encouraged to refer any patients with serious (i.e. multiple or injurious) falls to PT. We completed a retrospective search of the electronic medical record for referrals for PT after serious falls, screens positive for falls, and emergency department (ED) visits or admissions from the ED related to falls.

Results: Comparing the fall rate before and after January 1, 2014, the fall rate declined from 20.6% (124 out of 601 cases) in the first six months of our program to 17.0% in the subsequent 24 months (720 out of 4224 cases). ($p=0.030$ by Chi squared test). Additionally, using an ordinary least square best-fit model, the rate of admissions from the ED related to falls has trended downward among all ages in the thirty months since the program was initiated. Among those younger than 65 years old, the rate of ED visits related to falls has also trended downward.

Conclusions: In a high-volume neurology outpatient practice, screening all patients for falls has resulted in a significant reduction in falls. Additionally, the intervention has been associated with a trend toward fewer admissions from the ED related to falls in all age groups, and among younger patients, fewer ED visits related to falls. With time this may lead to a statistically significant reduction in ED visits and admissions related to falls.

Interventional Neurology

M135. Amelioration of Peripheral Neuropathy in HFD-STZ Mice Through Dietary Reversal

Phillippe D. O'Brien, Lucy M. Hinder, John M. Hayes, Carey Backus, Elizabeth S. Bruno and Eva L. Feldman. Ann Arbor, MI

Peripheral neuropathy (PN) is a common complication of type 2 diabetes (T2D) for which there is no effective treatment. We have evidence demonstrating that PN which manifests in mice fed a high fat diet (HFD) can be completely corrected through a paradigm of dietary reversal (DR). As HFD-fed mice more closely represent a model of impaired glucose tolerance/prediabetes than T2D, it is unclear whether DR can similarly benefit patients with frank T2D. To address this, we first characterized PN in HFD-fed mice injected with streptozotocin (STZ) to more accurately model a T2D phenotype. We then investigated the effects of DR on PN in HFD-fed STZ mice to determine if DR could similarly reverse PN.

From 5 wk of age, male C57BL6/J mice were fed either a standard diet (10% kcal fat; CTRL) or a HFD (60% kcal fat; HF). At 12 wk, a subset of HF mice were administered with low dose STZ (1×75 mg/kg, 1×50 mg/kg; HF-STZ). HF-STZ mice underwent longitudinal metabolic and PN phenotyping until 36 wk. For the DR component of our study, a subset of CTRL, HF, and HF-STZ mice were sacrificed at 16 wk for baseline metabolic and PN phenotyping, and additional subsets of HF and HF-STZ mice were placed on a 10% kcal fat diet for 8 wk (HF-DR and HF-STZ-DR, respectively) until study conclusion at 24 wk when terminal PN phenotyping was performed.

As a consequence of STZ administration, HF-STZ mice developed severe hyperglycemia compared to HF mice. Surprisingly, despite this extreme hyperglycemia, the presentation of PN was similar to that seen in HF mice, suggesting that the added hyperglycemia did not accelerate neuropathy. In our DR study, HF mice displayed signs of impaired glucose tolerance and a robust PN that was completely corrected by DR. Interestingly, similar to HF-DR mice, HF-STZ-DR mice displayed an improved metabolic profile and an absence of peripheral nerve deficits after 8 wk of DR.

In conclusion, using HF-STZ mice we demonstrate two important findings. First, our data show that PN remains unchanged despite hyperglycemia in HF-STZ mice, suggesting that factors other than glucose may drive PN progression. Second, we demonstrate that DR of HF-STZ mice results in restoration of peripheral nerve function. These data support the idea that dietary intervention is a feasible strategy to improve peripheral nerve health in patients with both pre-diabetes and T2D.

Neuromuscular Disease

M136. Direct Motor Neuron Transplantation Maintains the Regenerative Capacity of Chronically Denervated Peripheral Nerves

Christopher R. Cashman, Ruifa Mi and Ahmet Hoke.
Baltimore, MD

While the peripheral nervous system can regenerate more efficiently than the central nervous system, it is severely limited by the slow rate of regeneration and long distance in large animals like humans; distal areas of the nerve become chronically denervated and unable to support extending axons, even as the proximal aspect of the injury may be appropriately supportive of regeneration. To reduce chronic denervation in nerves, we propose the transplantation of motor neurons to effectively reduce the time and distance necessary for regeneration by creating a relay to the muscle. Additionally, the transplanted neurons may widen the window to effective regeneration by supporting host cells that are responsible for guiding and facilitating regeneration until the nerve is fully recovered.

Transplantation of motor neurons derived from mouse embryonic stem cells into the one-week denervated tibial nerve of a rat was found to increase recovery after both a two and three-month delay to repair. In vitro co-culture systems were developed to test primary rat motor neuron to derived mouse motor neuron synaptogenesis, where calcium imaging during electrical depolarization suggested the two populations can form functional glutamatergic synapses.

Following transplantation, the relay hypothesis was tested by immunofluorescent staining, electromyography, and electron microscopy of the transplanted nerves, showing successful engraftment of transplanted cells, integration into local circuitry, and emergence of a possible relay between spinal cord and muscle. Analysis of Schwann cell activation capacity by electron microscopy and expression analysis of three markers of active Schwann cells (c-Jun, p75, ErbB3) showed they were more capable of activation in animals transplanted with motor neurons than those treated with negative controls. Thus, motor neuron transplants into the peripheral nerve was able to maintain the regenerative capacity of two- and three-month denervated nerves by serving as post-synaptic targets to regenerating fibers as well as supporting pro-regenerative host cells during the denervated state. These findings suggest novel uses of stem cells and nerve guides to improve recovery after peripheral nerve injury.

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M137. Response to IVIG in Patients with CIDP: The INSIGHTS Quality Improvement Project

Todd Levine, Jonathan Katz, Richard Barohn, David Saperstein, Gil Wolfe, Lara Katzin, Tahseen Mozaffar, Mazen Dimachkie, Gary Badger, Leslie Vaughan, Elissa Ritt and Michelle Greer. Phoenix, AZ; San Francisco, CA; Kansas City, KS; Buffalo, NY; Tampa, FL; Irvine, CA; Burlington, VT and Temecula, CA

Objective: Over the last four years, we have undertaken a quality improvement project to determine the clinical, laboratory, and electrophysiologic criteria most predictive of a positive response to treatment in neuromuscular disease patients prescribed IVIG.

Background: IVIG is prescribed for a wide variety of neuromuscular diseases. Despite established criteria for

diagnosing diseases such as CIDP, myasthenia gravis, and myositis, there is a large amount of variability in the types of patients who are prescribed IVIG.

Methods: We collected clinical, laboratory, and electrophysiologic data on 585 patients who were prescribed IVIG. A panel of blinded, independent neuromuscular neurologists reviewed the clinical, electrophysiologic, and laboratory data. Positive outcomes were determined based on quality-of-life measures, Patient Global Impression of Change, and clinical documentation. Data was entered into the REDCap system housed at the University of Kansas.

Results: The largest group of patients who began IVIG therapy were patients diagnosed with neuropathy (N=166). 40% of these patients were judged appropriate candidates for IVIG. This mirrored the overall response rate of 48%. Meeting AAN or EFNS criteria for a demyelinating neuropathy was a positive predictor of response (63% vs 33%). Among patients who met criteria for CIDP, the response rate was 58% and was 63% for MMN. This was compared to a 25% response rate for patients with axonal neuropathies. There was no association with age, distribution of symptoms, dose or brand of IVIG, or chronicity of disease.

Conclusions: Overall response rate to IVIG in patients diagnosed with demyelinating neuropathies is 48%. Adhering to AAN or EFNS criteria improved this response rate to 58% for CIDP and 63% for MMN. This represents the longest and largest collection of outcomes in patients receiving IVIG for neuromuscular diseases and suggests more specific recognition of diseases can improve outcomes and limit over-utilization.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Employed by NuFACTOR Specialty Pharmacy

M138. Cellular and Molecular Analysis of Corticospinal Motor Neuron Vulnerability in hTDP-43A315T Mice

Mukesh Gautam, Javier H. Jara, Ki Dong Kim and Hande Ozdinler. Chicago, IL

Corticospinal motor neurons (CSMN) play central role in the initiation and modulation of voluntary movement due to their unique ability to receive and integrate inputs from different regions of the cerebral cortex, and to transmit this information to distinct segments of the spinal cord with distinct precision. CSMN degeneration is thus an important aspect of motor neuron diseases. We recently generated and characterized a novel reporter line for CSMN, the UCHL1-eGFP mice, in which CSMN are genetically labelled with eGFP expression that is stable and long lasting, allowing their visualization and detailed cellular analysis. Since TAR DNA binding protein (TDP-43) is an evolutionarily conserved DNA/RNA binding nucleoprotein involved in various functions, and that TDP43 pathology is one of the most common pathologies observed in ALS patients, we generated a CSMN reporter line with TDP43 pathology by crossing UCHL1-eGFP with hTDP-43A315T mice, which recapitulate most ALS pathology and offer a great tool to study cellular basis vulnerability.

Our ongoing studies begin to reveal the cellular aspects of progressive CSMN degeneration in the presence of TDP43 pathology. Loss of CSMN is accompanied by compromised motor behaviour in terms of their poor performance on a rotating rod and weak hind limb strength. Prominent increase in astrogliosis and microgliosis shows an evoked immune response in the motor cortex. Immunocytochemistry coupled with electron microscopy reveals vacuolated apical dendrites and mitochondrial aggregation in diseased CSMN. Here we not only display the use of UCHL1-eGFP mice to mark CSMN with eGFP expression in different mouse models of disease, but also reveal the role of TDP-43A315T mutation on CSMN vulnerability and progressive degeneration.

M139. Motor Neuron Disease with HIV infection: Activation of HERV-K and Response to Anti-Retroviral Therapy

Lauren N. Bowen, Richa Tyagi, Wenxue Li, Tariq Alfahad, Bryan Smith, Mary Wright, Elyse J. Singer and Avindra Nath. Bethesda, MD and Los Angeles, CA

Objective: To evaluate whether patients with HIV infection and motor neuron disease (HIV-MND) have activation of and humoral response to human endogenous retrovirus-K (HERV-K) and monitor their response to antiretroviral therapy.

Background: Amyotrophic Lateral Sclerosis (ALS) or MND is a rare complication of HIV infection. Previous studies have shown that HIV protein Tat can activate an endogenous retrovirus HERV-K. Further HERV-K is activated in the brains of patients with ALS and is implicated with its pathophysiology. We present five patients with HIV-MND.

Design/Methods: Real-time PCR: DNA free plasma from four HIV-MND patients, 41 ALS patients, and controls were tested by real-time PCR for levels of HERV-K env and/or gag RNA. Western Blot: The recombinant HERV-K(HML2) extracellular domain envelope protein was run against patient serum at 1:500 dilution in four HIV-MND, twelve clinically-definite ALS patients, and five controls. Disease progression was graded according to ALSFRS-R.

Results: Cases 1-3 showed recovery in motor symptoms. Case 1 had weakness of upper and lower limbs and was treated with indinavir/ritonavir/emtricitabine/tenofovir (CPE=9). Case 2 had weakness of upper limbs only and was treated with abacavir/lamivudine/dolutegravir (CPE=9). HERV-K viral load was 1,539 copies/ml. Case 3 had upper and lower extremity weakness with dyspnea and became compliant with lopinavir/ritonavir/abacavir/lamivudine (CPE=9). HERV-K viral load was 500 copies/ml and became undetectable after treatment. Cases 4 and 5 had progressive decline despite treatment with combined antiretroviral therapy but are long term survivors. Case 4 was treated with dolutegravir/emtricitabine/tenofovir (CPE=8). HERV-K viral load was undetectable, but HERV-K env protein antibody response was positive. Case 5 had dyspnea and orthopnea with limb involvement at time of onset and

was treated with raltegravir/emtricitabine/tenofovir (CPE=7) initially but HERV-K viral load despite treatment was 215,790 copies/ml in plasma. Antibody response to HERV-K env protein was not detected. He was switched to abacavir/lamivudine/darunavir/ritonavir/raltegravir (CPE=12). The HERV-K viral load became undetectable. HERV-K env protein antibody response was present. HERV-K viral sequence showed 100% homology to HERV-K on chromosome 22 at locus q11.21

Discussion: HIV-MND was associated with activation of HERV-K in blood from a locus on chromosome 22. There was also an immune response to HERV-K. Elevated HERV-K levels responded to optimization of antiretroviral therapy for CNS penetration. All HIV-MND patients showed improved or slowed disease course with increased ARV CPE.

M140. Microglial, pTDP43, and Neuronal Pathologies in the Brainstem and Spinal Cord of ALS Patients: Relationship to Site of Symptom Onset and Disease Duration

Matthew Cykowski, Suzanne Powell, Hidehiro Takei, Andreana Rivera, Joan Appel, Ellen Chang and Stanley Appel. Houston, TX

Neuroinflammation is a prominent pathological feature of amyotrophic lateral sclerosis with neuronal injury and cell death associated with phosphorylated TDP-43 (pTDP-43) and activated microglia. To determine their relative contributions to disease progression, we examined autopsy tissue specimens of 30 ALS patients (16 with lower extremity onset, 14 with bulbar onset), and evaluated the interrelationships of pTDP43 pathology, microglial density, and neuronal loss to clinically determined sites of onset and disease duration. We hypothesized that microglial activation would be driven by neuronal injury and enhanced pTDP43, and that clinical onset would dictate neuropathology - e.g. clinical lower extremity onset would be associated with increased TDP-43 and activated microglia in the lumbar region, and bulbar onset would be associated with increased TDP-43 and activated microglia in the dorsomedial medulla. Microglial density was quantitated using a color based segmentation algorithm of Iba1 immunofluorescence preparations in lumbar and cervical ventral horns, medullary pyramidal and olive, dorsomedial medulla, and cerebellar white matter. Neuronal loss was assessed using Nissl-stained sections of medulla, cervical spinal cord, and lumbar spinal cord. pTDP43 density was examined using immunofluorescence preparations through hypoglossal nuclei, reticular formation of medulla, inferior olive, and lumbar horn of the spinal cord. Surprisingly, a dissociation of pathologies by clinical onset site was not seen, as lower extremity patients had greater microglial densities in both medulla and cord (dorsomedial medulla, $p = 0.03$ and lumbar cord, $p = 0.06$) and greater neuronal loss in cervical cord ($p = 0.03$) and lumbar cord ($p = 0.03$). Further, microglial density across all regions-of-interest was strongly associated with decreased patient survival ($p = 0.008$). A similar trend was seen between greater pTDP-43 density and reduced survival,

particularly in lumbar cord ($p = 0.06$), although pTDP-43 did not differ between groups by site of onset, did not differ between c9orf72 expanded and wild-type groups, and was not associated with neuronal loss. These findings are not in accord with a hierarchical progression of pathologies and some patients have more diffuse pathology than clinical onset alone would suggest. This interpretation is tempered by the cross-sectional view inherent in autopsy material but suggests opportunities for further translational studies. Moreover, these results suggest that microglial density, independent of symptom onset site, is strongly associated with decreased survival in ALS.

M141. CAT-1004, an Oral Agent Targeting NF- κ B: MoveDMD Trial Results in Duchenne Muscular Dystrophy (DMD)

Erika Finanger, Krista Vandenborne, Richard Finkel, H. Lee Sweeney, Gihan Tennekoon, Sabrina Yum, Maria Mancini, Jeff Danis, Pradeep Bista, Andrew Nichols and Joanne Donovan. Portland, OR; Gainesville, FL; Orlando, FL; Philadelphia, PA and Cambridge, MA

In DMD, NF- κ B in muscle is activated from infancy, driving inflammation, muscle degeneration and inhibiting muscle regeneration. CAT-1004 is an oral small molecule that inhibits NF- κ B and improves muscle degeneration, regeneration, and function preclinically. In Phase 1 trials in adults, CAT-1004 was generally well tolerated without safety signals and evidence of NF- κ B inhibition was seen after single and multiple doses. The MoveDMD trial is evaluating CAT-1004 in boys aged 4-7 with genetically confirmed DMD not on glucocorticoids for at least 6 months. As previously reported, Part A evaluated safety, tolerability and pharmacokinetics over 7 days at three doses of 33, 67 and 100 mg/kg/day ($N=17$), with exploratory measures of NF- κ B activity. CAT-1004 was generally well tolerated, without serious adverse events or drug discontinuations. AUC and C_{max} were consistent with previously observed levels in adults at which inhibition of NF- κ B was seen. Genes enriched for NF- κ B targets were assessed in whole blood by mRNA sequencing. Compared with baseline, two independently curated NF- κ B gene sets were significantly down-regulated (Wilcoxon rank-sum test p -values of 3.4×10^{-2} , and 1.2×10^{-7} for the two gene sets in the high dose cohort). Several gene transcripts in the TLR and Fc receptor pathways, including TLR4 and FCGR2A were reduced after a week on CAT-1004 (ANOVA $p < 0.05$ and FDR < 0.05 in pooled analysis compared to baseline). These results support a 12-week, double-blind, placebo-controlled trial in ~30 boys aged 4-7 with DMD, with T2 MRI of leg muscles as the primary endpoint and functional measures as secondary endpoints. By reducing inflammation and muscle degeneration with potentially positive longer-term effects on muscle regeneration and function, CAT-1004 may have potential to be disease-modifying in DMD patients, regardless of mutation type.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Salary, Stock

Sleep Disorders and Circadian Rhythm

M142. JZP-110, a Dopamine Norepinephrine Reuptake Inhibitor (DNRI), with Robust Wake-Promoting Effects and Low Abuse Potential

Michelle Baladi, Jed Black and Lawrence P. Carter. Palo Alto, CA; Redwood City, CA and Little Rock, AR

Introduction: Excessive sleepiness (ES) is a clinical hallmark of narcolepsy, present in all patients and often the first presenting symptom. There are several FDA-approved medications to treat narcolepsy symptoms; however, current treatments for ES, such as traditional stimulants, have limitations. JZP-110, a dopamine norepinephrine reuptake inhibitor (DNRI), is a second-generation wake-promoting agent that reduced ES and increased wakefulness in patients with narcolepsy in a phase 2a clinical trial. The aim of these studies was to compare the pharmacological effects of JZP-110 with traditional stimulants and to further evaluate the clinical effects in patients with narcolepsy.

Methods: Radioligand binding and dopamine (DA), norepinephrine (NE), and serotonin (5-HT) reuptake and release assays were conducted in HEK293 cells and rat synaptosomes. Nonclinical studies of conditioned place preference and drug self-administration were conducted in Sprague-Dawley rats and recovery of sleep was evaluated in mice. A phase 2b, double-blind, placebo-controlled, parallel-group clinical trial investigated the safety and efficacy of JZP-110 over 12 weeks in adults with narcolepsy.

Results: In contrast to other drugs that have robust wake-promoting effects, such as *d*-amphetamine, JZP-110 was more selective and less potent in inhibiting reuptake at DA ($IC_{50}=2.9 \mu M$) and NE ($IC_{50}=4.4 \mu M$) transporters. In addition and in contrast to *d*-amphetamine, JZP-110 did not promote NE release in rat brain synaptosomes, produce significant conditioned place preference in rats, or produce rebound hypersomnia in mice. In contrast to cocaine (0.8 mg/kg/infusion), JZP-110 did not maintain self-administration (<5 infusions/session) at doses of 0.25, 0.5, and 1.0 mg/kg/infusion. Lastly, the phase 2b clinical trial showed that once-daily treatment with JZP-110 significantly increased the ability of patients to stay awake on each of the 5 trials of the Maintenance of Wakefulness Test across 9 hours throughout the day with 93% of patients reporting improvement ($P < 0.0001$ compared with placebo). The most common adverse events versus placebo were insomnia (22.7% vs 8.2%), headache (15.9% vs 10.2%), nausea (13.6% vs 6.1%), decreased appetite (13.6% vs 0%), diarrhea (11.4% vs 6.1%), and anxiety (11.4% vs 0%).

Conclusions: Taken together, these data suggest that JZP-110 is a DNRI with a distinct mechanism of action and low abuse potential, compared with traditional stimulants. Phase 2b data indicate that once-daily dosing with JZP-110 might have therapeutic potential for the treatment of ES and impaired wakefulness in patients with narcolepsy.

Support: Study sponsored by Jazz Pharmaceuticals.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Drs Baladi and

Carter are employees of Jazz Pharmaceuticals, who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc. Dr Black is a part-time employee of Jazz Pharmaceuticals and stock holder of Jazz Pharmaceuticals plc.

M143. Novel Application of Brain-Targeting Polyphenol Compounds in Promoting Resilience Against Sleep Deprivation-Induced Cognitive Dysfunction

Wei Zhao, Simoni Tiano and Giulio M. Pasinetti. New York

Sleep deprivation produces deficits in hippocampal synaptic plasticity and hippocampal-dependent memory storage. Recent evidence suggests that SD disrupts memory consolidation through multiple mechanisms, including the down-regulation of the cAMP-response element-binding protein (CREB) and of mammalian target of rapamycin (mTOR) signaling. In this study, we tested the effects of brain bioavailable bioactive polyphenol precursors on the attenuation of sleep deprivation-induced cognitive deficiency. We found sleep deprivation leads to significantly impaired contextual memory compared to the vehicle group (% of freezing: 31.66 ± 2.001 vs. 56.66 ± 3.248 , respectively, $p < 0.001$). Combination treatment with two polyphenol precursors currently identified in our laboratory, quercetin and malvidin-3-O-glucoside, restored the sleep deprivation-induced contextual memory (% of freezing: 41.87 ± 3.780 vs. 31.66 ± 2.001 , $p < 0.05$). To further explore mechanistically, we explored in vitro potential signal transduction pathways that may be responsible for beneficial effects of these brain bioavailable bioactive polyphenol precursors. Excitingly, we found that treatment with 250 nM of malvidin-3-O-glucoside and quercetin-3-O-glucuronide significantly increases CREB phosphorylation in primary hippocampal-cortico neurons. Interestingly, we also found that malvidin-glucoside also significantly increases the level of phospho-p70S6K on Thr412. Western blot analysis revealed that treatment with malvidin-glucoside in primary neurons increases the phosphorylation of p70S6K and its upstream kinase, mTOR, and the activation of mTOR and p70S6K can be blocked by rapamycin, an mTOR signaling-specific inhibitor. Collectively, our study provides new information that the polyphenol precursors quercetin and malvidin-glucoside may significantly attenuate sleep deprivation-induced cognitive impairment in mouse model of acute sleep deprivation through mechanisms associated with activation of mTOR pathways. Our data suggests the feasibility of using select brain-targeting polyphenol compounds derived from a complex polyphenol mixture as potential therapeutic agents in promoting resilience against sleep deprivation-induced cognitive dysfunction.

Autoimmune Neurology

M144. Optimizing Immunoglobulin Dosing in Chronic Inflammatory Demyelinating Polyneuropathy

Lesley D'Albini, Lori Paulsen and Jill Nellis. St Louis, MO

Background: There is wide variability in dosing regimens of IVIG for chronic inflammatory demyelinating

polyneuropathy (CIDP). In the absence of a specific and validated biomarker to direct optimal dosing, the application of a Clinical Care Management program at the specialty pharmacy (SP) can drive evidence based pharmacist recommendations to prescribers.

Methods: Data was retrospectively reviewed to evaluate the IVIG dose, INCAT (Inflammatory Neuropathy Cause and Treatment) score, and appropriate application of an evidence based program to drive pharmacist recommendation to dose adjust IVIG in CIDP. Patients were included if: they had a valid prescription for IVIG, a prescriber adjudicated diagnosis of CIDP, at least 2 INCAT scores a minimum of 12 weeks apart, and uninterrupted admission to the SP through the review period.

Results: 123 patients (median age 60; range 15-90) met the inclusion criteria and were reviewed. All IVIG doses (mg/kg) were converted to an every 3 week (Q3W) equivalent for the purposes of direct comparison. The average dose was 945 mg/kg (range 102-3195) Q3W. Regimens were stratified as low (≤ 408), medium (424-987), or high (≥ 988) dose. A total of 300 INCAT scores were reviewed and matched to a dose. A threshold of ≥ 4 on INCAT was considered a marker for uncontrolled disease and warranted further evaluation of the regimen. 62% of low dose, 52% of medium dose, and 38% of high dose regimens were associated with an INCAT ≥ 4 . Results were even more striking on review of a cohort of patients with comorbid diabetes mellitus: 78% of low dose, 88% of medium dose, and 47% of high dose regimens were associated with an INCAT ≥ 4 . 34 (28%) patients qualified for 37 pharmacist recommendations to adjust the IVIG Q3W equivalent dose: 27 (77%) were accepted by the prescriber (16 to increase the Q3W dose equivalent; 11 to decrease). Follow-up a minimum of 12 weeks later revealed that 67% of patients for whom the prescriber accepted the recommendation had an improved or stable [with dose reduction] INCAT. Zero patients for whom the prescriber declined the pharmacist recommendation had an improved or stable INCAT.

Conclusions: Application of an evidence based program directing regimen adjustment guided by dose stratification and an objective measure such as INCAT can successfully optimize therapy outcomes while decreasing waste and overall cost of IVIG in CIDP.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Salary and Stock in Accredo, Inc

M145. Treatment of Progressive Multifocal Leukoencephalopathy with Pembrolizumab, a PD-1 Inhibitor

Irene Cortese, Bryan Smith, Matthew Schindler, Joan Ohayon, Maria Chiara Monaco, Caroline Ryschkeewitsch, Yoshimi Akahata, Steve Jacobson, Daniel Reich, Eugene Major and Avindra Nath. Bethesda

Background: PML is a devastating brain infection caused by JC virus in the setting of underlying

immunosuppression. In many cases, no effective therapy to reverse immunosuppression is available and long-term disability and mortality rates remain high. T-cells from patients with PML show increased expression of the programmed cell death-1 (PD-1) receptor, and PD-1 expression is more frequent on JC-specific CD8 cells. Pembrolizumab, a PD-1 inhibitor, is an FDA-approved treatment for specific cancers and, along with other checkpoint inhibitors, has gained attention for the safety, tolerability, and effectiveness in refractory cancers. It is hypothesized that in the setting of chronic viral infection, checkpoint inhibitors may be beneficial by reinvigorating specific anti-viral activity.

Objective: To pilot the use of pembrolizumab in patients with Progressive Multifocal Leukoencephalopathy (PML), collect initial data on safety and tolerability and explore clinical, radiologic, and viral outcomes.

Design/Methods: Pembrolizumab at 2mg/kg was given to four patients enrolled in the NIH Natural History Study of PML with persistent JC viral titers in CSF and evidence of an ongoing immunosuppressed state. Underlying predisposing conditions were lymphoproliferative disease treated with immunosuppressants, idiopathic lymphocytopenia, and HIV infection with low CD4 despite prolonged antiretroviral therapy. Up to three doses were given at 3-4 week intervals. Safety and tolerability were assessed at each clinic visit along with detailed clinical and radiological evaluations. Quantitative JC virus levels were measured by PCR in CSF, plasma, and urine before and after pembrolizumab.

Results: No significant adverse reactions were observed in the four treated patients. Viral copy numbers declined or remained stable in CSF and peripheral blood. Detailed immunophenotyping showed persistent down-regulation of PD-1 expression on CD4 and CD8 populations in both CSF and peripheral blood following treatment, while effector, memory and naïve T cell subpopulation proportions remained stable. PML lesion burden remained stable on MRI; treatment with pembrolizumab did not induce imaging evidence of IRIS. Clinical evaluations to assess PML-related disability outcomes are ongoing.

Discussion: Pembrolizumab was safe and well tolerated in four patients with PML. Inhibition of PD-1 expression may be a valid strategy to prevent inactivation of JC virus-specific T-cells in the setting of chronic infection and warrants further investigation.

Dementia and Aging

M146. Differential Effects of IL-12, IL-23 and Their p40 Subunit on Alzheimer's Disease Pathogenesis, Cognitive Performance, and Brain Atrophy

Dimitrios Kapogiannis, Emmette Hutchison, Erez Eitan, Maja Mustapic, Mark P. Mattson and Edward J. Goetzl. Baltimore, MD

Background: Microglia-derived interleukins (IL) 12p70 and 23, which share a p40 subunit, have been implicated in Alzheimer's disease (AD) pathogenesis, but the differential roles of cytokine dimers and of p40 have remained unclear.

Methods: In 45 subjects with cognitive impairment due to AD (from Mild Cognitive Impairment to moderate dementia), we examined associations of cognitive performance (MMSE, ADAS-cog), clinical dementia rating (Global CDR, CDR-sob), and gray matter volume (MRI), with a comprehensive panel of CSF cytokines (including IL-2, IL-12, IL-23, and p40), A β 1-42, total-tau, and p181-tau. To examine the pathophysiological effects of cytokines on neurons, we treated mouse cortical neuron cultures with IL-12p70, p40 and IL-23 followed by RNA extraction for gene array analysis and survival assays (treatment with 5mg/mL A β and 100mM glutamate). We also performed immunoblot and ELISA assays for Clusterin, which emerged from the gene array analysis.

Results: As expected, higher total-tau predicted lower cognitive performance and functional status, and greater temporoparietal atrophy. IL-23 and p40 predicted lower cognitive performance and IL-2 worse clinical dementia rating. Higher IL-12p70 uniquely predicted higher cognitive performance and less posterior cingulate, orbitofrontal and lateral temporal atrophy. We found that treatment of neurons with IL-12p70 had a protective effect against A β and glutamate challenge whereas IL-23 treatment enhanced cell death. Furthermore, IL-12p70 treatment increased Clusterin (Clu or ApoJ) at both the transcript and the protein level (secreted high molecular weight form).

Conclusions: These findings suggest that CSF IL-12p70, IL-23, p40, and IL-2 may be useful as AD biomarkers reflecting beneficial, as well as deleterious, roles of neuroinflammation in disease pathogenesis that need to be carefully considered in evolving therapeutic interventions that target specific cytokines (such as monoclonal antibodies against p40). Importantly, CNS IL-12p70 may have beneficial effects on cognition and brain atrophy in AD, as opposed to IL-23 and p40. The beneficial role of IL-12p70 was further corroborated by the findings that it protects neurons against A β and glutamate toxicity and increases the anti-apoptotic secreted form of Clusterin.

M147. Predicting Brain Amyloidosis Using Peripheral Blood-Based Gene Expression Measures

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Background: With over 20 AD risk genes discovered and replicated in large-scale genome-wide association studies, we still cannot fully explain the genetic heritability of AD. The missing heritability may be explained by mechanisms that result in aberrant transcription of these genes.

Methods: Peripheral blood mRNA, neuropsychological testing, and ApoE4 genotype were obtained from 108 mild cognitive impairment (MCI) and 52 cognitively normal controls (NC) from ImaGene. 70 subjects underwent F18-Flutemetamol PET scans. Baseline log2-transformed mRNA levels were correlated with hippocampal volume and ranked by the absolute value of their association. We explored the 3D association between the top 100 ranked mRNA transcripts with hippocampal radial distance and global cortical

thickness. The top 25 transcripts that showed an AD-like pattern of association with hippocampal and/or cortical atrophy were used to develop a multimodal biomarker classifier for predicting brain amyloidosis (defined as global PET standard uptake value ratio (SUVR) >1.27 after normalization to whole cerebellum). We used a support vector machine (SVM) algorithm to build classifiers with leave-one-out cross validation. Selected features from the ImaGene classifier were validated in 572 Alzheimer's Disease Neuroimaging Initiative (ADNI) subjects with available F18-Florbetapir PET (global PET SUVR >1.17 after normalization to whole cerebellum) and overlapping mRNA transcript data.

Results: The ImaGene classifier achieved an accuracy of 84.7% and an AUC=0.87 using 4 mRNA transcripts, APOE4 genotype, age and sex. Our replication classifier model in the ADNI dataset achieved an accuracy of 75.3% and an AUC=0.96.

Conclusions: To our knowledge this is the first report of predicting brain amyloidosis using peripheral blood transcript levels. Abnormal gene expression in peripheral blood shows promise as a noninvasive test that can be helpful in detecting AD pathology in both the symptomatic and pre-symptomatic AD stages.

M148. Blood Pressure Trends in Mid-To-Late Life and Risk of Dementia

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Background: Elevated blood pressure in mid-life (40-64y) and low blood pressure in late-life ($\geq 65y$) have been associated with an increased risk of cognitive decline. However, the association between mid-life hypertension and blood pressure trends over mid-late life and clinically confirmed dementia is less clear. In this study, we determined the association between mid-life hypertension and trends in blood pressure from mid-to-late life and subsequent risk of dementia in a community based prospective cohort.

Methods: We included participants in the Framingham Offspring Cohort who attended 5 sequential examinations at 4 yearly intervals starting at mid-life (1983-1987, mean age 55y) and continuing into late-life (1998-2001, mean age 69y, N=1440) who were dementia free at the fifth examination. Blood pressure measurements were recorded at each visit during the 20-year exposure period. Participants were subsequently followed for a mean of 8y for a diagnosis of dementia. We used Cox proportional hazards models to examine the association between blood pressure parameters [mid-life hypertension ($\geq 140/90$ mmHg), late-life hypertension, persistent hypertension during mid-to-late life and slope of change in blood pressure from mid-to-late life] and risk of dementia, adjusting for age and sex.

Results: 107 participants were diagnosed with dementia; 50% utilized antihypertensive medication during the exposure period. Both mid-life systolic hypertension (HR 1.70, 95% CI 1.14-2.53) and late-life systolic hypertension (HR 1.48, 95% CI 1.01-2.19) were associated with an increased risk of dementia. Persistent systolic hypertension (HR 2.15,

95% CI 1.37-3.35) and a rapid decline in systolic blood pressure from mid-to-late life (HR 1.62, 95% CI 1.08-2.44 for slope of change <-0.5 vs. >-0.5) were strongly associated with risk of dementia. Results did not vary according to antihypertensive use.

Conclusion: Mid-life systolic hypertension is associated with an increased risk of dementia. Persistence of hypertension and a rapid decline in blood pressure during mid-to-late life are both strongly associated with increased dementia risk. This is the first study to reliably report an association between mid-life systolic hypertension (≥ 140 mmHg) and clinically confirmed dementia in late-life.

M149. Carotid Intima-Media Thickness, Plaque, and Cognition: The Northern Manhattan Study

Michelle R. Caunca, Hannah Gardener, Chuanhui Dong, Palma Gervasi-Franklin, Ying Kuen Cheung, Mitchell S.V. Elkind, Ralph L. Sacco, Tatjana Rundek and Clinton B. Wright. Miami, FL and New York, NY

Carotid artery intima media thickness (cIMT) and non-stenotic carotid plaque are suggested markers of carotid atherosclerosis and may be related to cognition in the elderly. We hypothesized that individuals with greater cIMT or with carotid plaques would exhibit worse cognition at baseline and have greater cognitive decline. Stroke-free Northern Manhattan Study (NOMAS) participants had carotid ultrasound and repeated neuropsychological (NP) testing. Carotid IMT and plaques were imaged with standardized B-mode ultrasound protocols and analyzed by a certified sonographer. We used multivariable linear regression to examine cIMT, plaque presence, and plaque area as correlates of domain-specific NP Z-scores cross-sectionally and after six years follow-up. We also investigated effect modification by APOE $\epsilon 4$ allele status. Neuropsychological testing was performed among 1166 participants at baseline and among 826 participants at follow-up (mean=6.2 years). The mean cIMT was 0.93 ± 0.09 mm (mean age= 71 $\pm$ 9 years; 60% women; 15% white; 18% black; 67% Hispanic white). Participants with greater cIMT had worse episodic memory at baseline after adjustment for demographics and vascular risk factors ($\beta = -0.60$, $P = 0.04$). APOE $\epsilon 4$ carriers with greater cIMT exhibited worse episodic memory ($\beta = -1.26$, $P = 0.04$), semantic memory ($\beta = -1.35$, $P = 0.01$), and processing speed ($\beta = -1.22$, $P = 0.02$) at baseline. Participants with greater cIMT at baseline did not exhibit cognitive decline in episodic or semantic memory, but did exhibit decline in executive function and processing speed, though these associations did not reach significance. The APOE $\epsilon 4$ allele was a significant effect modifier: participants without an APOE $\epsilon 4$ allele who had greater cIMT at baseline exhibited more decline in executive function ($\beta = -1.03$, $P = 0.05$). Neither plaque presence nor area was significantly associated with cognitive performance in any domain in cross-sectional or longitudinal analyses. Results remained similar after restricting the analysis to those who were categorized as cognitively unimpaired at baseline based on their Mini-Mental Status Examination score. Our cross-sectional findings in this race/ethnically diverse community-based urban sample suggest that being at elevated

genetic risk of Alzheimer disease as well as having a greater vascular disease burden may have cognitive consequences. A greater burden of vascular disease may have domain-specific cognitive consequences in the absence of genetic Alzheimer disease risk. Atherosclerotic lesions may be less important in the pathology of vascular cognitive changes, but larger studies are needed. Arterial wall thickening due to compensatory and inflammatory arterial remodeling are mechanisms that should be explored in future studies.

Headache and Pain

M150. Migraine and Complex Regional Pain Syndrome: A Case-Referent Clinical Study

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Aim: The aim of this study was to evaluate clinical phenotype differences among migraineurs who developed CRPS and those who did not.

Methods: Cases of migraine with CRPS (Mig+CRPS) and referents of migraine without CRPS (Mig-CRPS) aged ≥ 18 years were continuously enrolled from a case-referent cohort study performed on electronic chart review from January 1, 2014 to January 1, 2016 at the Stanford Headache and Pain Clinic. Diagnosis was in accordance to the International Classification of Headache Disorders-3 beta for migraine and International Association for the Study of Pain for CRPS. Both migraine with and without aura were included. Data was abstracted by two investigators for interrater reliability (IRR) testing.

Results: A total of 70 Mig+CRPS cases (13% males, mean age of 48 years) and 80 Mig-CRPS referents (17% males; mean age of 51 years) were included. IRR revealed a Cohen's of 0.85. Sex differences amongst the two cohorts was not associated with CRPS occurrence (Odds Ratio or OR=1.30, 95% CI 0.33, 5.11). Thirty-three % of the Mig+CRPS cohort exhibited Episodic Migraine while the remaining 66% had Chronic Migraine. Similarly, 38% of the Mig-CRPS cohort exhibited Episodic Migraine (EM) while the remaining 62% suffered from Chronic Migraine (CM); this revealed that migraine frequency was not associated with CRPS occurrence (Odds Ratio of 0.98, 95% CI 0.36, 2.67). Age at first migraine attack was mostly around early school years and was found to be comparable between the two cohorts of Mig+CRPS and Mig-CRPS. Migraine onset preceded CRPS onset among all cases of Mig+CRPS with a median of 18.5 years (IQR 10-25). Median duration of CRPS was 3 years (IQR 3-5) among the EM+CRPS (Episodic Migraineurs with CRPS) cohort and 6 years (IQR 4-12) among the CM+CRPS (Chronic Migraineurs with CRPS) cohort (Mann-Whitney test, $p < 0.02$). Mig+CRPS (57%) cohort carried higher burden of psychological problems compared to the Mig-CRPS cohort (6%) (OR 16.7, 95% CI 10.2, 23.6).

Conclusion: Migraine frequency was not associated with CRPS occurrence; however, higher migraine frequency was associated with longer CRPS duration. Migraine-to-CRPS progression occurred in about 2 decades. Migraineurs who develop CRPS had higher prevalence of psychological and

medical disorders. Managing migraine by reducing its frequency can lessen CRPS duration and may have important implications for future treatment options. Alleviating migraineurs' psychological and medical comorbidities can help lower CRPS occurrence.

M151. Initial Diagnostic Criteria to Warrant Early Therapeutic Intervention in Complex Regional Pain Syndrome, Type 1, Reflex Sympathetic Dystrophy (CRPS/RSD)

Robert L. Knobler. Fort Washington, PA

Objective: The Budapest Criteria are now embraced as guidelines to diagnose CRPS: (1) Continuous pain disproportionate to any inciting event; (2) One symptom in 3 of 4 of sensory, vasomotor, sudomotor/edema, motor trophic categories; (3) One sign at time of evaluation in two or more of these categories; (4) No other diagnosis that better explains signs and symptoms. These criteria inherently impose a restriction upon the diagnosis, which can impede the onset of early therapy. Consistent early features of these diagnostic criteria were sought to overcome possible diagnostic delay of treatment which can impede recovery.

Methods: Evaluate earliest consistent clinical features of suspected CRPS/RSD utilizing established criteria in order to initiate treatment goals of reducing pain and encouraging movement sooner.

Results: Fifty two consecutive individuals referred with suspected CRPS/RSD within one month of onset were evaluated to determine the most reliable diagnostic characteristics following established guidelines detailed above. Early presenting features were variable among individuals, but two characteristics were consistently present; burning pain/allodynia and hyperpigmented hair follicles. Early burning/allodynia often responded best to mixed medication therapy and repetitive movement/desensitization. Hyperpigmented hair follicles were slower to respond.

Conclusions: Features of early CRPS/RSD can be effective in identifying patients for encouraging early treatment. The best responses were obtained with mixed medication therapy and vigorous repetitive movement/desensitization. Chronic intractable pain can occur following limited movement. Burning pain/allodynia and hyperpigmented hair follicles have emerged as reliable early indicators of CRPS/RSD, even when all other presently accepted criteria have not been met. Further investigation regarding the merit of early diagnosis/early treatment is being explored.

Since early intervention is most effective in treating CRPS/RSD, the goal was to identify the primary diagnostic features of this disorder to facilitate initiation of early treatment and enhance recovery.

Neuromuscular Disease

M152. Age-Dependent Painful Neuropathy in Metabolic Syndrome

Joseph F. Ward, Can Zhang, Jacqueline R. Dauch, Liam Cheng, Rudolph E. Tanzi and Hsinlin T. Cheng. Boston, MA and Ann Arbor, MI

Metabolic syndrome is a prevalent condition that associates with painful polyneuropathy especially in the elderly population. However, little is known about how the aging process increases the peripheral pain sensitivity in metabolic syndrome. In the current study, we used high-fat-diet (HFD) to induce painful polyneuropathy in young (5 wk-old), mature (36 wk-old), and aged (72 wk-old) mice to study the age-related molecular mechanisms that lead to the development of painful polyneuropathy in metabolic syndrome. In HFD-treated mice, symptoms of metabolic syndrome, including increased body weight, fasting blood glucose, and plasma cholesterol levels were detected. In addition, increased sensitivity to mechanical (mechanical allodynia) and thermal (thermal hyperalgesia) stimuli were detected in hind paws of HFD-treated mice after 5 wk, 3 wk, and 1 wk of HFD treatment in young, mature, and aged mice respectively. In addition, increased proinflammatory tumor necrosis factor (TNF)- α and reduced anti-inflammatory interleukin (IL)-10 expressions in lumbar dorsal root ganglia (LDRG) were detected in mature and aged HFD-treated mice. Fenofibrate (0.1% in diet) treatment reduced plasma cholesterol and improved impaired fasting blood glucose levels in HFD-treated mice. However, fenofibrate treatment had no effect on the pain behaviors in HFD-treated mice. In contrast, exogenous IL-10 (1 g/kg, ip) treatment significantly improved HFD-induced mechanical allodynia and thermal hyperalgesia and, in parallel, inhibited the upregulation of TNF- α in LDRG of HFD-treated mice. In addition, IL-10 treatment reduced the activation of epidermal inflammatory langerhans cells and macrophages in the hind paw skin of HFD-treated mice. These results suggest that there is age-dependent cytokine-mediated neurogenic inflammation that contributes to the development of painful polyneuropathy in metabolic syndrome. This mechanism is independent of glycemia status and dyslipidemia. Targeting cytokine-mediated inflammation could be an effective approach for treating painful polyneuropathy in elderly patients with metabolic syndrome.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Cheng receives salary support as a medical monitor through a contract between Massachusetts General Hospital and Pfizer for a clinical trial.

M153. Is C9orf72 ALS Different from Sporadic Disease? A Comparative Study in an ALS Clinic Population

Mfon Umoh, Christina Fournier, Yingji Li, Meraida Polak, Latoya Shaw, William Hu, Marla Gearing and Jonathan Glass. Atlanta, GA

Objectives: The C9orf72 hexanucleotide repeat expansion is the most common genetic cause of amyotrophic lateral sclerosis (ALS). Previous studies suggest patients carrying this mutation are clinically distinct from those without the expansion. We investigated whether the C9orf72 expansion mutation is associated with unique demographic and clinical features.

Methods: Between 2001 and 2015 DNA was collected from 50% of ALS patients seen at the Emory ALS Clinic. DNA from this unselected sample of 781 patients was screened for the C9orf72 expansion, and demographic and clinical data were compared between those with and without the C9orf72 mutation. For mutation carriers without a family history of ALS, we sought further family history of dementia and other non-ALS neurodegenerative diseases in first degree relatives.

Results: The C9orf72 expansion was identified in 7.8% of patients. Compared to those without the expansion mutation these patients did not differ in race or age and site of onset. As expected, C9orf72 patients were more likely to have a family history of ALS (59% vs 7.9%), and to present with comorbid frontotemporal dementia (FTD) (14.8% vs. 1.7%). Survival was shorter in patients with the expansion (log-rank $\chi^2(1) = 45.323$, $p < 0.001$). Further investigation in 28 patients initially categorized as having no known family history of ALS identified family history of dementia in 16 cases, six of these had characteristics suggestive of FTD.

Conclusion: In this large cohort, patients carrying the C9orf72 mutation were clinically similar to the general ALS population. Additionally, we found that assessing family history for dementia may identify other family members likely to be carrying the C9orf72 expansion, reduce the number of sporadic cases, and thus increase our understanding of disease penetrance.

M154. Closed Loop Intracortical Brain Computer Interface Control in a Person with ALS Using a Filtered Gaussian Process Decoder

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Background: Brain Computer Interfaces (BCIs) are being designed to allow individuals with tetraplegia and locked-in syndrome to control assistive communication and environmental control devices. A core component of BCI technology is a decoder: an algorithm that translates neural information into command signals for external devices. Recent studies have used linear regression to map kinematic variables to firing rates, with subsequent smoothing using linear averaging or Kalman filtering. However, the relationship between firing rates and motor commands may be highly nonlinear. To address this limitation, we developed a non-parametric decoding algorithm that we call the Gaussian-process discriminative Kalman filter (GPDFKF). The innovation of this approach is that we are able to learn the relationship between neural firing behavior and motor commands, rather than having to define an explicit parametric model. Importantly, the method yields an analytic solution with interpretable parameters, and provides a principled approach to dealing with signal noise. We validated this decoding approach during closed-loop intracortical BCI use by a person with tetraplegia.

Methods: A research participant (T9) with amyotrophic lateral sclerosis (ALSFRS-R score = 7) was implanted with two 96-channel multielectrode arrays in the dominant precentral gyrus as part of the BrainGate2 pilot clinical trial. The participant performed standard BCI-enabled closed-loop computer cursor tasks with the GPDF decoder.

Results: T9 achieved unassisted closed-loop control at the first attempted session. On the third session, T9 used the GPDF to select letters on a QWERTY keyboard to communicate. Standard Fitts regression parameters had slope 0.9 (+/- 0.1 SEM) and intercept 0.8 (+/- 0.1 SEM), comparable to previously published results. Offline analyses suggested the GPDF was more robust to non-stationary signal behavior than a Kalman filter.

Conclusions: The GPDF decoder is a novel approach to neural decoding that learns the nonlinear relationship between neural behavior and kinematic variables. It provides principled methods for addressing signal non-stationarities in BCIs, and preliminary results suggest neural control quality is at least comparable to previously published approaches.

M155. Canine Degenerative Myelopathy-An Emerging Disease Model for ALS

Raghav Govindarajan and Joan Coates. Columbia

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive muscle weakness. Patients typically die within 3-5 years from onset of symptoms secondary to respiratory failure. Elucidation of the mechanisms underlying ALS and its treatment remain elusive to date with one of the reasons being lack of suitable disease models. The discovery of mutations in SOD1 in canine degenerative myelopathy (DM) has provided naturally-occurring disease model as a 'tool' for study of ALS

Objective: To share the natural history, clinical staging and histopathology of canine DM

Results: Canine DM is a naturally-occurring, adult-onset, progressive disease that, like ALS, leads to paralysis and death. The earliest clinical signs begin when the dog is 9 years or older. Asymmetric spastic weakness and general proprioceptive ataxia in the pelvic limbs (stage 1) progresses to paraplegia (stage 2) within 1 year from onset of signs. At disease onset, spinal reflexes are consistent with upper motor neuron (UMN) loss. Dog owners often elect euthanasia when their dog becomes paraplegic. When euthanasia is delayed, weakness spreads to the thoracic limbs (stage 3) and LMN signs emerge as flaccid quadriplegia (stage 4), widespread muscle atrophy, dysphagia and loss of bark. The pattern of clinical progression of canine DM is relatively uniform within breeds and between breeds. Histopathologic changes include gliosis and neuronal fiber degeneration and loss of sensory and motor pathways that are most severe in the mid- to caudal thoracic spinal cord.

Conclusion: DM is a spontaneous disease with homogeneity at onset of clinical signs and disease progression that provides an unique opportunity to study the pathophysiology of SOD1 related mutation, do biomarker research that can be paralleled in human subjects and provide a large

vertebrate model to do more rigorous pharmacokinetic and pharmacodynamic trials.

M156. Genetic Deletion of Sarm1 Attenuates Vincristine-Induced Neuropathy in a Mouse Model

Stefanie Geisler, Ryan A. Doan, Amy Strickland, Jeffrey Milbrandt and Aaron DiAntonio. Saint Louis, MO

Peripheral polyneuropathy is a very common, potentially dose-limiting side effect of many chemotherapeutic agents despite manifold disparate mechanisms of action. Most neuropathies are characterized by early axonal degeneration suggesting that the various insults of chemotherapies converge in a common axonal degeneration program. Unfortunately, therapies that inhibit this axonal destruction process do not currently exist. Recently, others and we discovered that genetic deletion of Sarm1 dramatically protects axons from degeneration after axotomy in mice. This finding fuels hope that inhibition of Sarm1 or its downstream components can be used therapeutically in patients threatened by axonal loss. However, axon loss in most neuropathies, including chemotherapy induced neuropathy, is the result of subacute/chronic processes that may be regulated differently than the acute, one time insult seen in axotomy. Here we evaluate if genetic deletion of Sarm1 decreases axonal degeneration in a mouse model of neuropathy induced by the commonly used chemotherapeutic agent vincristine. In wild-type mice, four weeks of twice-weekly intraperitoneal injections of 1.5mg/kg vincristine caused a significant decrease in tail compound nerve action potential (CNAP) amplitude, pronounced loss of intra-epidermal nerve fibers and significant degeneration of myelinated axons in the distal sural nerve. The predominantly motor tibial nerve assessed at the same proximal-distal level as the distal sural nerve and the proximal sural nerve did not have axon loss. These findings are consistent with the development of a length-dependent, sensory predominant axonal polyneuropathy that closely mimics vincristine induced polyneuropathy (VIPN) in humans. Using the same regimen of vincristine treatment in Sarm1 KO mice, the loss in tail CNAP amplitude was prevented. In addition, Sarm1 KO mice did not have significant loss of unmyelinated fibers in the skin or myelinated axons in the sural nerve after vincristine. These findings indicate that genetic deletion of Sarm1 improved functional outcome following vincristine as shown by rescued nerve conduction and reduced degeneration of myelinated and unmyelinated axons. Our results reveal for the first time that subacute/chronic axon loss induced by vincristine occurs via a Sarm1 mediated axonal destruction pathway. This further establishes Sarm1 as the central determinant of a fundamental axonal degeneration pathway that is activated by diverse insults. We suggest that targeting Sarm1 or its downstream effectors may be a viable therapeutic option to prevent VIPN and possibly other peripheral polyneuropathies.

M157. Longitudinal Natural History of Orofacial Muscle Strength Changes in Amyotrophic Lateral Sclerosis Patients

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Langford, Nicole M. Lucas, Tamara L. Sanders, Tiffany Williamson and Melissa Johnson. Charlotte, NC

Background: There is next to nothing in the literature on the longitudinal natural history of orofacial [facial, lingual-oro-pharyngeal] muscle strength measurements by clinical scales compared with the ALS Functional Rating Scale – Revised Bulbar subscale [Speech, Salivation, Swallowing] in patients with Amyotrophic Lateral Sclerosis (ALS) or Bulbar-Spinal Muscular Atrophy. Other groups have proposed clinical strength rating scales validated by quantitative strength measurements [Solomon NP et al Assessment of Orofacial Strength in Patients with Dysarthria J Med Speech Lang Pathol. 2008 Dec 1;16(4):251-258]

Objective: Present natural history of 75 patients with ALS followed prospectively over 12 months from entry into a clinical trial.

Methods: Forehead wrinkling, eye closure, pursing lips, puffing out cheeks, platysma contraction, clinically assessed tongue strength was rated [0- no movement 1- minimal movement, 2, full movement gravity-eliminated, 3- full movement against gravity, 4- full movement but not full resistance, 5- full resistance], tongue click was rated [0-absent, 1-minimal, 2-more than minimal, 3- moderate, 4- hard click, 5-maximal click], presence of gag reflex were assessed Functional Rating Scale –Revised was completed at 3 month intervals in 75 patients [21 bulbar onset; 54 limb onset]

Results: Median ALSFRS-R Bulbar subscore declines 4.5 [-5.8 to -1.3 (95% CI)] units in bulbar onset patients and 0.5 (-2.1 to 0.0) units in limb onset patients over 12 months [$p=0.0068$]. Tongue click which is actually higher in limb onset patients declines faster by 1.5 [-2.0 to -0.9 (95%CI)] units compared with bulbar onset patients -0.3 [-1.6 to 0.0 (95%CI)] units in 12 months. Change in tongue click correlated significantly with change in tongue strength [$r=0.8324$; $p=0.005$] over 12 months. Change in ALS FRS Bulbar subscore correlated significantly with change in platysma strength [$r=0.5933$; $p=0.006$].

Conclusions: The natural history of orofacial muscle strength measured clinically correlates with ALS FRS-R Bulbar subscale and other measurements offering a novel set of new clinimetrics to assess new treatment regimens in the bulbar domain.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Clinical Trials Medicinova Cytokinetics Neuraltus,

Autoimmune Neurology

M158. Fc γ RI (CD64) Fc Receptors Are Expressed on CNS Neurons: A Potential Mechanism for Neuronal Immunoglobulin Uptake and Antibody-Mediated Neuronal Injury]

Suzanne C. Liu, Kenneth E. Hill, Susan A. Clawson, Blair Wood, Stacey L. Clardy, Noel G. Carlson and John E. Greenlee. Salt Lake City, UT

Paraneoplastic and related autoimmune neurological syndromes are frequently accompanied by an immunoglobulin G (IgG) antibody response directed against intracellular neuronal proteins. Such antibodies include anti-Yo, found in patients with gynecological and breast cancers and cerebellar degeneration; anti-Hu, associated with encephalomyelitis in the setting of lung cancer; and anti-Ri, found in patients with ataxia and opsoclonus in the setting of breast or lung cancers. Neurons have traditionally been assumed to exclude IgG, and for this reason it has been considered unlikely that these antibodies could play a role in disease causation. However, it has never been established that neurons are impermeable to IgG; and our previous studies, using organotypic (slice) cultures of rodent brains, have demonstrated that antineuronal antibodies such as anti-Yo, anti-Hu, and anti-Ri are readily taken up by neurons and can directly cause cell death. More recently, we have shown that neuronal IgG uptake does not depend on the immunoreactive Fab portion of the IgG molecule but rather is dependent upon the Fc portion. We have also shown that neuronal uptake of paraneoplastic antibodies can be inhibited by preincubation of cultures with normal IgG. Although these observations suggest that neurons might possess Fc receptors, little work has been done to determine the nature and distribution of Fc receptor expression on CNS neurons. In this study, we probed paraformaldehyde-fixed mouse and rat brain sections with antibodies for the three major types of Fc receptors: Fc γ RI (CD64), Fc γ RII, (CD32) and Fc γ RIII (CD16). Expression of Fc γ RI receptors, but not Fc γ RII and Fc γ RIII receptors, was identified on multiple populations of neurons throughout cerebrum, cerebellum, and brainstem. Our work demonstrates that neurons possess previously unidentified Fc receptors capable of binding IgG. Although the biological function of these neuronal receptors is unknown, their presence suggests a mechanism through which antibodies reactive with intracellular neuronal proteins could be taken up, bind to their target antigens, and cause neuronal injury and death.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Associate Editor for Medlink

Chapter author for The Merck Manual

Dementia and Aging

M159. Levels of Hemostatic Factors in Middle Age and 20-Year Cognitive Change: The Atherosclerosis Risk in Communities (ARIC) Study

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Background: Levels of several hemostatic factors are associated with venous thrombosis and to a lesser degree with atherothrombosis. Hemostatic factors may, however, contribute to vascular related cognitive impairment, which is associated with arteriolar, or possibly even capillary, insufficiency.

Whether hemostatic factors assessed in middle age, are associated with cognitive decline remains largely unknown in a community-dwelling population.

Methods: Using longitudinal data from 1987 to 2013 in 14,233 ARIC participants, we assessed the associations of hemostatic factors with 20-year change in cognitive performance. A global Z- score was constructed based on 3 cognition tests: Delayed Word Recall Test, Digit Symbol Substitution Test, and the Word Fluency Test, assessed three times between 1990 and 2013. Hemostatic factors were measured during 1987-89, except for d-dimer, which was measured during 1993-95. Exposures were categorized as quintiles. Mixed-effects models with random intercept/slopes and a time-spline were employed to assess the change in cognitive performance, adjusted for demographic covariates, common cardiovascular disease risk factors and use of medications affecting hemostasis. We hypothesized that higher levels of coagulation factors but lower level of APTT are associated with faster cognitive decline.

Results: Participants were aged from 44 to 66 years at baseline, 55.4% were female and 24.7% were African American. We tested the association of cognitive function with exposures: fibrinogen, von Willebrand factor, factor VIII, factor VII, antithrombin III, d-dimer and activated partial thromboplastin time (APTT), using the lowest quintile as a reference. Significantly lower baseline cognitive performance scores were observed in the highest quintiles of fibrinogen (Difference in z: -0.06 [95%CI: -0.11 to -0.01]) and von Willebrand factor (-0.07 [95%CI: -0.12 to -0.02]), but not for other hemostatic factors. The highest quintile of factor VII was associated with faster cognitive decline (Difference in 20-year cognition score change: -0.17 [95%CI: -0.31 to -0.02]). Significantly slower cognitive decline was observed in the highest quintile of APTT (0.17 [95%CI: 0.04 to 0.31]). Higher levels of other hemostatic factors were not associated with greater change in cognitive performance.

Conclusions: Overall, our study found few significant associations between mid-life hemostatic factors and 20-year cognitive decline, except for factor VII and APTT, in a community-living sample. Future research should examine whether hemostasis status abnormalities are associated with cognitive decline in younger and older populations.

Education

M160. Network for Excellence in Neuroscience Clinical Trials, NeuroNEXT: Increasing Efficiency in Clinical Trials

Marianne K. Chase, Dixie Ecklund, Michael Bosch, Brenda Thornell, Christopher Coffey and Merit Cudkowicz. Boston, MA and Iowa City, IA

Objective: The NeuroNEXT Network was designed to expand NINDS' capability to test promising new therapies, increase efficiency of clinical trials, and respond quickly as new opportunities arise to test promising treatments for people with neurological disorders.

Background: In Oct 2011, NINDS awarded the Clinical Coordinating Center (CCC) grant to MGH, the Data Coordinating Center (DCC) grant to the University of Iowa, and Clinical Study Sites (CSS) grants to 25 academic institutions, with a goal of conducting 5 to 7 phase 2 studies in neurological disorders over 7 years. Each CSS executed a Reliance Agreement with a Central IRB (CIRB) and a Master Clinical Trial Agreement (MCTA) with the CCC. The CCC and DCC work with investigators to develop study design and prepare grant applications. Grants undergo peer review at NINDS. Once funded, CCC and DCC work to operationalize the study: select sites, train investigators, distribute drug and supplies, regulatory compliance, create study database, and implement statistical analyses.

Methods: As of March 2016, 5 studies received funding and 2 studies have been approved for funding but are awaiting their Notice of Grant Award (NOGA). We assess timing for each study from receipt of NOGA to key metrics.

Results: The first study in infants with Spinal Muscular Atrophy began in Dec 2012, completed enrollment on time and is in the data analysis phase. The second study in Progressive Multiple Sclerosis began in Nov 2013 and completed enrollment in Jan 2015; the third study in Myasthenia Gravis began in Sept 2014 and is on track to complete enrollment in Spring 2016; and the fourth study in Acute Stroke began in Jan 2015 and is expected to complete enrollment by the end of 2016. The fifth study in Huntington's Disease will begin enrollment in April 2016. For the first four studies, the median time for CIRB approval of the study protocol was 50 days; from NOGA to first site activated was 4 months; from NOGA to first subject enrolled was 5.5 months, and from NOGA to database ready was 3.5 months.

Conclusions: The NeuroNEXT Network has successfully established infrastructure and continues to efficiently execute clinical trials. The Network sites have demonstrated their capacity to effectively enroll subjects in trials conducted for a variety of neurologic diseases, both in pediatric and adult populations.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? No conflicts to report for Marianne Chase, Merit, Cudkowicz, Dixie Ecklund, Michael Bosch and Brenda Thornell. Conflicts are listed on attached forms for Christopher Coffey.

Interventional Neurology

M161. Reasons for Failed Mechanical Thrombectomy: Initial Data from Two Tertiary Care Centers

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Background: Failure to achieve successful recanalization in patients with ischemic strokes results in poor radiological and clinical outcomes.

Objective: We aimed to evaluate factors resulting in failed thrombectomy (FT) defined as a recanalization grade

TICI 2a or less in patients undergoing cerebral thrombectomy.

Methods: With institutional review board approval, we retrospectively reviewed data of patients who were taken for stroke thrombectomy between July 2012 and October 2015. The following data were collected: demographics, risk factors, intravenous tPA, treatment times, TICI recanalization grade, complications, and 90-day modified rankin scores (mRS).

Results: A total of 215 patients were included in the study, with a mean age of 68.7 (26-94), and 103 (47.9%) men. Baseline demographics were comparable in both groups. Successful recanalization (SR), defined as TICI grade 2b or higher was achieved in 161 (74.9%) patients and unsuccessful recanalization (FT) occurred in 54 (25.1%) patients. The most common cause for FT was chronic occlusion (n=25), identified as inadequate recanalization despite appropriate access and use of stent retrievers and aspiration. Multiple occlusions characterized by two or more distinct sites of occlusion in the ICA, MCA M1, MCA M2, or ACA resulted in FT in eleven patients. Failed access due to vessel tortuosity (n=7), repeated vessel reocclusion (n=5), iatrogenic arterial dissection (n=4), and proximal vessel stenosis or calcification preventing catheter access (n=2) were other factors resulting in FT. Patients who failed thrombectomy (FT) were more likely to have a lower ASPECT score, a longer procedure time and a higher mean number of passes. Overall, there was a significantly poorer outcome, defined as a mRS score of 3 or greater in the FT group as compared to the SR group.

Conclusion: The most common causes for failed cerebral thrombectomy are chronic or multiple occlusions. A low ASPECT score is consistent with a lower likelihood of an adequate recanalization grade. TICI grade 2b or higher recanalization resulted in favourable clinical outcome (mRS ≤ 2) at three months compared to patients who had recanalization grades of TICI grade 2a or less.

Sleep Disorders and Circadian Rhythm

M162. Sleep Disturbances Induced by Gastroesophageal Reflux Disease (GERD) in the US General Population

Maurice M. Ohayon and Cristina Milesi. Palo Alto, CA

Introduction: GERD is a digestive disease originating from the spilling of gastric acid from the stomach into the esophagus. The objective of this study was to assess the prevalence of GERD in the US general population and analyze its association with sleep, medical and psychiatric conditions. The survey is longitudinal and allowed to follow the evolution of sleep disorders associated with GERD.

Methods: representative sample of the US general adult population. 12,218 subjects were interviewed at wave 1 (W1) and 10,830 subjects were interviewed at wave 2 (W2). The analyses were carried on the subjects who participated in both interviews (N=10,930). In average, three years separated the two interviews. All the interviews were using the SleepEVAL system.

Results: we found that 10.6% of the sample reported having seen a physician for GERD and/or were taking a medication for GERD at W1. At W2, this prevalence increased to 12.4%. GERD was chronic for 3.9% of the sample interviewed. The prevalence of GERD increased with age until 55 y.o. GERD chronicity increased with age, with individuals between 45 and 64 being at greater risk. Subjects affected by GERD reported significantly higher nocturnal awakenings and were significantly more often diagnosed with obstructive sleep apnea and restless leg syndrome, while insomnia disorders were significantly higher only among subjects with chronic GERD. Subjects affected by GERD were more likely to report other medical conditions, such as hypercholesterolemia, diseases of the musculoskeletal system and connective tissue and hypertension, than people that never experienced GERD. Individuals with chronic GERD were also significantly more likely to be affected by a major depressive disorder.

Conclusion: Sleep disorder symptoms such as nocturnal awakening are highly prevalent among GERD patients and can often lead into a sleep disorder diagnosis when they are not treated.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Educational grant from Takeda Pharmaceuticals.

M163. Outdoor Artificial Lights at Night Relate to Sleep Quality/Quantity and Circadian Rhythms Disorders

Maurice M. Ohayon and Cristina Milesi. Palo Alto, CA

Introduction: With electric lights human populations have modified the spectrum, the intensity and timing of their light exposure. In our study we examined the consequences of exposure to artificial outdoor nighttime lights (ONL) on the sleep quality/quantity, sleep habits and sleep disorders of the American general population.

Methods: A representative sample of 15,863 individuals was interviewed by telephone using the Sleep-EVAL expert system geolocated by latitude and longitude. Data collected: sleep habits, sleep, medical and psychiatric disorders. ONL radiance for the locations of the interviews from the Defense Meteorological Satellite Program's Operational Linescan System (DMSP/OLS) nighttime imagery.

Results: The intensity of nighttime lights strongly influences sleep duration, bedtime and wake up time. The analysis excluded night workers and shift workers. Individuals sleeping less than 6 hours per night were living in areas with greater ONL than those sleeping 6 hours or more ($t = -5.445$; $P < 0.0001$). After adjusting for age, gender, population density and other environmental factors, ONL was significantly associated with excessive sleepiness (OR: 1.20 [1.12-1.29]; $P < 0.0001$). We show that sex, population density and sleeping in a bright bedroom were unrelated to shorter sleep duration. Conversely, being a shift worker, unemployed or homemaker, watching TV in bed, sleeping with a light on, sleeping in a noisy place at night and sleeping on the sofa or on the floor were associated with a greater likelihood of sleeping less than 6 hours per

night. Bed time hour also increased linearly with the intensity of ONL. Wake up time became later as ONL increased. The risk of being dissatisfied with sleep quality and or quantity increased with the intensity of ONL. **Global sleep dissatisfaction with difficulty initiating sleep, nocturnal awakenings, early morning awakenings were not significantly associated with ONL.** Individuals living in areas with greater ONL were more likely to have a diagnosis profile congruent with a circadian rhythm disorder. **DSM-V insomnia disorder, sleep-related breathing disorder, restless leg syndrome disorder were unrelated to ONL.** Confusional arousals were significantly related with an increase in ONL.

Conclusion: The result of this study shows that individuals living in areas with greater ONL were at greater risk of reporting symptoms consistent with circadian rhythm disorders. They present also more frequently sleep symptoms affecting quality and quantity of sleep and presenting a daytime excessive sleepiness as a consequence.

Autoimmune Neurology

M164. Bowman Birk Protease Inhibitor Suppresses GM-CSF, Th17 Cells and CNS Autoimmune Inflammatory Demyelination

Farinaz Safavi, Zichen Li, Bogoljub Ciric, Javad Rasouli, Limei Wang, Guang-Xian Zhang and Abdolmohamad Rostami. Philadelphia and Towson

Serine proteases play numerous roles in immune system and their inhibition modulates immune and autoimmune responses. Bowman Birk inhibitor (BBI), a soybean-derived serine protease inhibitor potently suppresses experimental autoimmune encephalitis (EAE) after oral administration. In this study, we show that BBI inhibits development of Th17 cells and reduces Th17 cell encephalitogenicity by suppressing their GM-CSF production and decreasing their numbers in the CNS of EAE mice. We also demonstrate that BBI induces IFN- γ production in Th17 cell culture, and that lack of IFN- γ or IFN- γ R abrogates Th17 suppressive effect of BBI. In addition, BBI requires IL-27R, Stat-1, T-bet, and IL-10 to inhibit Th17 development.

Taken together, our data demonstrate that BBI suppresses pathogenic Th17 cells through IFN- γ dependent pathway and ameliorates EAE. This suggests a novel immunomodulatory effect for serine protease inhibitors in immunity. In addition, BBI has potential to be safe oral therapy for autoimmune diseases, such as multiple sclerosis.

M165. Central Canal Enhancement and the Trident Sign in Spinal Cord Sarcoidosis

Nicholas L. Zalewski, Karl N. Krecke, Brian G. Weinshenker, Allen J. Aksamit, Brittani L. Conway, Andrew McKeon and Eoin P. Flanagan. Rochester, MN

Myelopathy is a common neurological manifestation of sarcoidosis, and when present often represents the initial and only clinical feature despite common concurrent subclinical pulmonary involvement. Thus, identification of radiologic clues to distinguish spinal cord sarcoidosis (SCS) from other

myelopathies is important. We have observed a unique pattern of central canal gadolinium enhancement in SCS which, when combined with dorsal subpial enhancement, (a recently described characteristic feature of SCS) forms a distinctive “trident” appearance. Nine patients (78% women) were included of which eight were Caucasian and one was African-American. The median onset age was 43 years (range, 33-63). MRIs showed central canal enhancement alone (11%) or in combination with dorsal subpial enhancement (89%) forming the hallmark axial “trident-like pattern”. Serum angiotensin converting enzyme was normal in all. Cerebrospinal fluid abnormalities included: elevated white blood cell count, 9 (median 55/mcL; range, 23-248), elevated protein, 9 (median, 98 mg/dL; range, 49-242) and CSF hypoglycorrhachia, 2. Lung biopsies in seven patients revealed non-caseating granulomas consistent with sarcoidosis, and two patients without pathological confirmation had hilar adenopathy. We have not encountered this radiologic pattern with myelopathies of other etiologies. Identification of central canal enhancement and the trident sign in subacute myelopathy strongly suggests SCS.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Nicholas Zalewski has no disclosures

Dr. Krecke has no disclosures

Dr. Weinshenker receives royalties from RSR and Oxford University for technology license for aquaporin-4 autoantibodies used for diagnosis of neuromyelitis optica. He serves on data safety monitoring committees for Novartis, Biogen-Idex and Mitsubishi pharmaceutical companies, and serves on an adjudication panel for Medimmune Pharmaceuticals. He served as a consultant for GlaxoSmithKline, Elan, Ono, Chugai and Alexion and Novartis pharmaceutical companies. He serves on editorial boards for Neurology, the Canadian Journal of Neurological Sciences, and Turkish Journal of Neurology.

Dr. Aksamit has no disclosures

Dr. Conway has no disclosures

Dr. McKeon has received research support from Medimmune and has served as a consultant for Medimmune (without personal compensation)

Dr. Flanagan has no disclosures

M166. Functional Analysis of Cx30 in Experimental Autoimmune Encephalomyelitis

Ryo Yamasaki, Mei Fang, Hiroo Yamaguchi and Jun-ichi Kira. Fukuoka, Japan

Objective: Connexins are known to compose gap junctions by a pair of hemichannels connected in a head to head configuration. Each hemichannel is composed by hexameric cluster of connexins. There are 20 members of connexins known as connexin family in mice, and are expressed on each cell surface in different fashion. Connexin 30 (Cx30) is mainly expressed on the surface of oligodendroglia and astrocyte in central nervous system (CNS), but little is known about the functional relevance in neuroinflammatory diseases. To elucidate the role of Cx30 in the pathogenesis

of neuroinflammatory disease, we induced experimental autoimmune encephalomyelitis (EAE) on Cx30 knock-out (Cx30-KO) mice and analyzed the clinical and neuropathological findings with wild-type control.

Methods: C57BL/6J and Cx30-KO mice > 12 weeks of age were used in this study (N > 3 in each group). EAE was induced by immunization of mice with MOG35-55 peptide emulsified in CFA at a dose of 200 µg per mouse, followed by the administration of pertussis toxin (500 ng per mouse) on days 0 and 2. Mice were sacrificed and brain, spinal cord, spleen, and optic nerve were harvested for immunohistochemical analyses at the acute and chronic phases of EAE. Mice with EAE were scored as follows: 0, no disease; 1, limp tail; 2, abnormal gait and hind limb weakness (shaking); 2.5, paralysis of one hind limb; 3, paralysis of two hind limb; 3.5, ascending paralysis (able to move around); 4, tetraplegia; and 5, moribund (death). At the onset and chronic stage of EAE, mononuclear cells were isolated and analyzed by flow cytometry to check the distinct characteristics of cellular populations in inflamed CNS lesions.

Results: Initial screening of immunohistological difference revealed basic activation of microglial cells in naïve Cx30-KO mice without any behavioral phenotype. Clinical signs of EAE were ameliorated in the Cx30-KO mice than in the control group mainly during the chronic phase of disease course. Immunohistochemical analyses of the fourth lumbar segment, brain and optic nerve revealed increased number of microglia in the Cx30-KO mice. Flow cytometric analysis also confirmed the findings. In contrast, there were no significant change in astroglial or oligodendroglial phenotype.

Conclusion: Microglial activation appears to be the key factor in the Cx30-KO mice EAE with alleviation of chronic disease scores. Unexpectedly, microglia were already activated in naïve CNS, indicating protective phenotypic change of microglia in Cx30-KO mice.

M167. Abnormal Brain Metabolism on FDG-PET/CT Is a Common Early Finding in Autoimmune Encephalitis

John C. Probasco, Abhinav Nalluri, Krystyna M. Jones, Mehrbod S. Javadi, Lilja Solnes and Arun Venkatesan. Baltimore, MD

Background and Purpose: Descriptions of brain metabolism by dedicated FDG-PET/CT in comparison to other paraclinical findings in patients with autoimmune encephalitis (AE) are limited. Here we compare rate of abnormal cerebral metabolism by quantitative FDG-PET/CT to other paraclinical study findings in inpatients with AE.

Methods: Retrospective review of clinical data and initial dedicated brain FDG-PET/CT studies for neurology inpatients with AE, per published consensus guidelines, treated at a single academic medical center over a ten year period. Z-score maps of FDG-PET/CT scans were made using three-dimensional stereotactic surface projections with comparison to data from age group matched control subjects. Z-scores with magnitudes > 2.0 were interpreted as significant. Comparisons were made to rates of abnormal initial brain MRI (T2/FLAIR hyperintensity, enhancement or

diffusion restriction), abnormal initial EEG (temporal lobe slowing, epileptiform discharges or seizures) and presence of intrathecal inflammation (CSF WBC > 5/mm³, IgG index > 0.8, or unique oligoclonal bands in the CSF).

Results: Brain FDG-PET/CT was performed for 49 AE patients (25 seropositive, 24 seronegative) at a median of 4 weeks of symptoms (IQR 11 weeks) and within a median of 4 days of MRI (IQR 6 days). FDG-PET/CT was abnormal in 43 (88%) of patients, with 42 (86%) demonstrating significant hypometabolism, most commonly in the parietal lobes (61 patients). Significant hypermetabolism was demonstrated in 8 (16%) patients, most commonly in the caudate nuclei (5 patients). Areas of both hypometabolism and hypermetabolism were noted in 7 (14.3%) of patients. CSF inflammation was evident in 26/43 patients (61%), while initial EEG was consistent with AE in 14/45 patients (31%) and MRI was abnormal in 23/46 patients (50%). There were no differences in proportions of abnormal diagnostic results between seropositive and seronegative AE patients.

Conclusions: FDG-PET/CT was more often abnormal than initial EEG, MRI and CSF studies in neurology inpatients with AE, with significant cerebral hypometabolism most frequently observed.

M168. Phase 1b, Open Label Study of Ublituximab in Acute Relapses of Neuromyelitis Optica Spectrum Disorder

Maureen A. Mealy and Michael Levy. Baltimore, MD

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disease targeting the spinal cord and optic nerve leading to paralysis and blindness. The pathology of acute NMOSD lesions demonstrates a robust humoral response with significant perivascular antibody (IgG and IgM) deposition. The standard of care for acute NMOSD lesions is geared towards suppressing the immune response with steroids and/or plasmapheresis as quickly as possible. In order to minimize inflammatory-mediated damage, we tested a CD20 B-cell depleting monoclonal drug, ublituximab, added to current standard of care.

Methods: We conducted an open-label phase 1b safety and proof-of-concept trial in 5 subjects with NMO-IgG seropositive NMOSD who presented with acute transverse myelitis and/or optic neuritis. In addition to treating acutely for 5 days with 1 gram of daily intravenous methylprednisolone, we infused 450 mg intravenous ublituximab. The primary outcome measure was safety, and the secondary efficacy measures are change in Expanded Disability Scale Scores (EDSS) and timed 25-foot walk.

Results: Three NMOSD subjects have been enrolled thus far, all of whom presented with acute transverse myelitis. Ublituximab proved safe in all 3 subjects with no serious adverse events. Two subjects had an infusion-related body pain amenable to acetaminophen. One subject had an acute lymphopenia following the infusion that resolved over the next few days. EDSS scores dropped from a mean of 7.1 on admission to 6.8 on day +5. Two of the three subjects required escalated therapy with plasma exchange due to persistent significant deficits on day +5.

Conclusions: Ublituximab is a safe add-on therapy for NMOSD patients presenting with acute relapses. Preliminary evidence suggests a promising benefit with ublituximab in reducing damage and improving outcomes. A placebo-controlled trial is necessary to confirm these findings.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Michael Levy receives research support from NIH, Guthy Jackson Charitable Foundation, Shire, Alexion, Acorda, Sanofi/Genzyme, Alnylam, NeuralStem and Genentech, and serves as a consultant for Chugai Pharmaceuticals, Shire, GlaxoSmithKline, Quest Diagnostics and Alexion Pharmaceuticals.

M169. Improving Detection of Neuronal Membrane or Synaptic Antibodies

Maxwell Greene, Lindsey Bandini, Junxian Zhang, Joyce Gonzalez, Elisabeth Burnor, Anne Crivaro, Malek Kamoun and Eric Lancaster. Philadelphia, PA

Objective: To examine the prevalence of autoantibodies to neuronal membrane or synaptic antigens in patients' samples referred for testing for suspected autoimmune encephalitis.

Background: Over 12 different autoantibodies associated with autoimmune encephalitis have been reported. Testing procedures differ substantially among institutions and it is uncertain which methods are most sensitive or specific. In addition, the yield of some assays is unclear. We have examined CSF and serum samples from patients referred to the University of Pennsylvania clinical laboratory over a 15 month period.

Design/Methods: 482 samples (188 CSF, 144 serum, and an additional 75 CSF/serum pairs) were examined in the clinical laboratory and in the research laboratory at the University of Pennsylvania over the course of 15 months. The clinical laboratory performed cell-based assays using fixed cells on slides for a panel of autoantibodies: N-methyl-D-aspartate receptor (NMDAR), GluR2 subunit of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), γ -aminobutyric acid-B receptor (GABABR), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), and glutamic acid decarboxylase 65 (GAD65). In the research laboratory all samples were screened for reactivity to brain sections and for anti-NMDAR using live and fixed cell assays, with additional tests done on patients with brain reactivity.

Results: In the clinical laboratory there were 64 samples that were positive for NMDAR antibodies (32 CSF, 32 serum, 8 CSF/serum pairs), and the remaining positive results were 6 GAD65, 2 LGI1, 1 CASPR2, and 2 GABABR. 73 samples, mostly sera, had one or more indeterminate results in the clinical laboratory. In the research laboratory, all positive clinical lab results were confirmed. The research lab detected an additional 3 cases with antibodies to NMDAR, 1 to AMPAR, and 2 to LGI1, that were not detected in the clinical laboratory. All indeterminate samples were resolved as positive or negative in the research lab, except for 8 sera with excessive Background.

Conclusions: Autoantibodies to CNS cell surface/membrane antigens were detected in 74 of 482 samples (15.4%), with NMDAR antibodies being most common in our population. Additional testing in the research lab may be useful for detecting some additional cases of autoimmune encephalitis (1.2%), and for resolving indeterminate results that accounted for 73 out of 482 samples (15.1%). CSF is a more accurate biofluid than serum to analyze for autoimmune encephalitis, yielding results that are less susceptible to Background and yield indeterminate results less often.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? EL has taught courses for Grifols Inc., consulted for Medimmune Inc., and reviewed cases for the Vaccine Injury Compensation Program

M170. Cerebrospinal Fluid Findings in Ebola Survivors with Neurological Sequelae

Bridgette Jeanne Billioux, Bryan Smith, Eric Stavale, Deborah Wentworth, Joseph Dorbor, Helen Tarfeh-Burnette, Elizabeth Higgs, Michael Sneller, Clifford Lane, Mosoka Fallah and Avindra Nath. Bethesda, MD; Ft Detrick, MD; Minneapolis, MN and Monrovia, Liberia

Background: Neurological findings are a common feature of acute infection with Ebola virus and have been reported in Ebola virus disease (EVD) survivors. Reports of a Scottish nurse who developed recurrent meningoencephalitis months after recovery from EVD emphasize the need of monitoring for neurological complications. The persistence of virus long after EVD recovery suggests that the nervous system may harbor the virus.

Methods: We selected a subset of Ebola survivors with neurologic sequelae for lumbar punctures (LP) to evaluate for Ebola virus persistence. EVD survivors enrolled in the Prevail III EVD natural history study were examined by a team of neurologists. Participants with neurological symptoms both during EVD (coma, delirium, or meningitis symptoms) and during recovery (headache or memory loss), and abnormal neurological exams were identified as potential candidates for LP (n= 22). These participants were informed about the procedure; those who decided to proceed were screened to determine eligibility for LP (n=18). Participants were 18-60 years, antibody positive to Ebola virus, had no new neurologic findings on exam at the time of LP, were HIV antibody negative, had no recent seizure or head trauma or NSAID, no papilledema and PT, aPTT, and platelet results within normal limits prior to LP. For patients who met these criteria and signed informed consent (n=14), LPs were performed in the standard fashion, with operators in full personal protective equipment (PPE). 15-20 cc of CSF was collected with each LP. The fluid was evaluated for Ebola viral RNA by two different Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assays at the Liberian Institute for Biomedical Research (LIBR) lab. CSF cell count, glucose, and protein were also measured. Evaluation of inflammatory markers is ongoing.

Results: In total, 8 participants underwent LP, with 7 successful LPs performed. The median time from Ebola Treatment Unit discharge was 407 days. CSF from the 7 patients were all negative for Ebola by PCR. All 7 samples had normal cell count, glucose, and protein.

Conclusions: In this study, seven EVD survivors with neurologic sequelae underwent LP. No evidence of Ebola persistence or overt inflammation was detected in CSF. This study is the first systematic evaluation of CSF in Ebola survivors.

M171. Peripheral Nerve Autoantibodies in Acute and Chronic Autoimmune Neuropathies

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Background: Peripheral nerve proteins may be target antigens in autoimmune neuropathies. Antibodies against the NF155 and NF186 isoforms of Neurofascin, and against Gliomedin, have been reported in some patients with Guillain-Barre syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP). We have tested the prevalence and persistence of IgG and IgM responses to these antigens in an international cohort.

Methods: We tested sera and CSF of 65 patients with autoimmune neuropathies collected from Hunan, China, and 51 patient sera and CSF collected from Philadelphia, Pennsylvania; patients had GBS (46), CIDP (45), Miller-Fisher syndrome (10), AMAN (2), Bickerstaff's encephalitis (6), POEMS syndrome (5), and multifocal-motor neuropathy (2). Live cell-based assays were used to test for IgG and IgM reactivity to NF155, NF186, and Gliomedin. 29 patients with genetic or idiopathic (non-autoimmune) neuropathies were used as controls.

Results: 11 of 116 autoimmune neuropathy patients, but 0 of 29 controls, had autoantibodies to Neurofascin. 7 patients had autoantibodies to only NF155 (3 CIDP, 4 GBS). Two patients samples reacted only with Neurofascin 186 (both CIDP). 2 patients reacted with both NF155 and NF186 (both CIDP). One patient with very strong IgG reactivity to both NF155 and NF186 had extremely severe CIDP refractory to IVIG treatment. Responses were IgG only (2 patients), IgM only (4 patients), and both IgG and IgM (5 patients). None of the 115 samples had IgG or IgM antibodies to Gliomedin. No (0 of 29) controls had Neurofascins or Gliomedin responses. Follow-up samples were collected for five of the Neurofascin positive patients. Two GBS patients had no reactivity to Neurofascin in samples collected 10-13 months after their initial samples. Three CIDP patients demonstrated ongoing reactivity to neurofascin two months to three years following the initial samples.

Conclusions: 9% of patients with CIDP, GBS, and AIDP exhibit IgG and/or IgM autoantibodies to Neurofascin. Symptom severity and responses to treatment were highly variable. A mixture of IgG and IgM responses to two main isoforms (NF155 and NF186) was observed. Neurofascin antibodies may be transient in GBS and persistent in CIDP. Gliomedin antibodies were not detected in our cohort, bringing into question their utility in diagnosing autoimmune neuropathy.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Eric Lancaster consulted for Medimmune Inc., consulted and testified for the Vaccine Injury Compensation Program, and taught courses for Grifols Inc. Steven S. Scherer taught courses for Grifols, Inc.

M172. A Neuroinflammatory Precision Medicine Board: Leveraging Metagenomics and Proteomics to Advance Diagnosis of Meningitis and Encephalitis

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Objective: We created an interdisciplinary Neuroinflammation Precision Medicine Board to advance care for patients with challenging autoimmune and neuroinfectious diseases. The board is designed to integrate clinical and research-based findings to develop consensus diagnostic and management recommendations.

Background: Metagenomic next-generation sequencing (mNGS) and multiple proteomics-based approaches have the potential to revolutionize neuroinflammatory diagnostics. Precision medicine, an approach to disease management that incorporates individual variability and leverages genomic or other biologic data, is an emerging paradigm in medicine. Although currently used in oncology and genetics, it has not been applied to suspected neuroinflammatory disease.

Design/Methods: A multidisciplinary board with specialists in autoimmune neurology, infectious disease, laboratory medicine, microbiology, laboratory medicine, behavioral neurology, inpatient neurology, neuropathology, genomics, proteomics, neuroscience and bioinformatics met monthly to review cases and research techniques.

Results: Utilizing the resources of the UCSF Center for Next-Gen Precision Medicine Diagnostics under established research protocols, patient samples were analyzed with various genomic and proteomic techniques to identify pathogens, antibodies and characterize host gene expression. In the neuroinflammation board, clinical assessment was integrated with research-based findings. Consensus opinions were achieved and communicated to treating clinicians. The board also serves as an educational forum.

Conclusions: A multidisciplinary neuroinflammation precision medicine board is an innovative and efficient way to achieve consensus about complex interpretation and potential clinical application of rapidly advancing and evolving genomic and proteomic technologies in neurological diagnosis.

Dementia and Aging

M173. Lipopolysaccharide (LPS) – Ischemia – Hypoxia Produces Amyloid-Like Plaques in Rat Brain and LPS Co-Localizes with Amyloid Plaques and Peri-Vascular Amyloid in Human Alzheimer's Disease Brain

Xinhua Zhan, Boryana S. Stamova, Bradley P. Ander, DaZhi Liu, Glen C. Jickling and Frank R. Sharp. Sacramento, CA

We have shown that systemic Lipopolysaccharide followed one day later by brief focal cerebral ischemia and brief systemic hypoxia produces myelin and axonal injury in cortex and hippocampus of adult rats (Zhan et al., *J Alzheimers Dis.* 2015;46(2):507-23). The myelin injury is associated with formation of aggregates of myelin basic protein and other myelin proteins which form the nidus for deposition of APP and abeta. These myelin-abeta aggregates have the shape and distribution of amyloid plaques seen in mouse Alzheimer's Disease models (AD) and in human AD brain. We proposed that the myelin aggregates formed amyloid-like plaques in this model. To determine if this model is relevant to human AD brain pathology we performed two subsequent studies. We examined human AD brain for evidence of myelin injury and aggregates. Evidence of myelin injury in AD cortex included increased degraded Myelin Basic Protein (dMBP) in AD gray matter compared to control ($p < 0.001$) and dMBP in AD neurons. Evidence of interaction of A β PP/A β 1-42 with myelin or axonal components included greater binding of dMBP with A β PP in AD brain; MBP at the margins of amyloid plaques; dMBP colocalized with A β 1-42 in the core of amyloid plaques in AD brains; and interactions between A β 1-42 and MBP/dMBP by co-immunoprecipitation and mass spectrometry. We concluded dMBP and MBP associate with amyloid plaques and dMBP associates with A β PP and A β 1-42 (Zhan et al., *J Alzheimers Dis.* 2015;44(4):1213-29). In the present study we determined if LPS and other molecules from gram negative bacteria were present in AD brain. *E. coli* K99 pili protein and Lipopolysaccharide (LPS) were detected immunocytochemically in brain parenchyma and vessels in all AD and control brains. DNA sequencing confirmed that *E. coli* DNA was found in human control and AD brains. *E. coli* K99 protein levels by Western blots were greater in AD compared to control brains and K99 was localized to neurons in AD but not control brains. LPS colocalized with A β 1-40/42 in amyloid plaques and with A β 1-40/42 around vessels in AD brains. We conclude that LPS is co-localized with amyloid in plaques and around vessels in AD brain, and combined with the rat model, suggest LPS could play a role in producing myelin injury and forming plaques in human AD brain.

M174. Cortical Amyloid-beta and Slow Gait in Older Adults without Dementia: Influence of Cognition and APOE4 Genotype

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Aim: We studied the cross-sectional association between global and regional amyloid-beta (A β) deposition and gait speed in dementia free older adults and examined the influence of cognition and APOE4 on this relationship.

Methods: In 183 older adults without dementia (mean age 86 years) enrolled in the Pittsburgh site of the Ginkgo Evaluation of Memory (GEM) study, we estimated cortical A β on Pittsburgh B (PiB) PET and gait speed over a 15-foot

walk. We compared gait speed in high-A β [PiB(+)] and low-A β [PiB(-)] groups defined on standard cutoffs of global PiB uptake averaged across six cortical regions. We examined the association between gait speed and global PiB binding in the whole group and in the cognitively normal subsample adjusting for cardiac risk and cerebral small-vessel disease. We then included MMSE score and APOE4 status separately in the analyses. We also assessed the adjusted association between regional PiB uptake and gait speed and examined the regional influence of APOE4 on these relationships.

Results: PiB(+) and PiB(-) were similar on demographic, cardiovascular risk, body weight, general cognitive and physical performance measures, parkinsonism, number of falls, and key brain measures. However, PiB(+) group walked slower (0.85 vs 0.92 m/sec, $p=0.012$) and had a higher proportion of APOE4 carriers (32% vs 6%, $p<0.001$) than PiB(-) group. In the whole sample ($n=183$), the association between global PiB retention and slower gait ($p=0.026$) withstood statistical adjustments but was attenuated by MMSE ($p=0.056$) and APOE4 status ($p=0.095$). In the cognitively normal subsample ($n=144$), the adjusted association between global PiB retention and slow gait ($p=0.042$) was no longer significant after adjustment for MMSE or APOE4 (both $p>0.1$). Gait speed was associated with regional PiB uptake in several regions in the whole group but was limited to PiB binding in the temporo-occipital ($p=0.02$ to 0.03) and subcortical white matter ($p=0.02$) after further adjustment for APOE4. In the cognitively normal subsample, gait speed was associated with PiB retention in the striatum ($p=0.04$) and precuneus, supplementary motor and lateral temporal cortices (all $p=0.02$) but further adjustment for APOE4 rendered these regional associations statistically non-significant.

Conclusion: The association between A β and gait speed is modest in dementia free older adults and weaker in cognitively normal elders. The relationship between global cortical A β and gait speed is modified by APOE4 genotype. APOE4 predominantly influences regional A β in an anterior-posterior gradient and particularly in cognitively normal older adults. A β is likely not the main driver of gait slowing in preclinical AD.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? GE Healthcare holds a license agreement with the University of Pittsburgh. Drs. Klunk and Mathis are co-inventors of PiB and, as such, have a financial interest in this license agreement. GE Healthcare provided no grant support for this study and had no role in the design or interpretation of results or preparation of this manuscript. All other authors have no conflicts of interest with this work.

M175. An Interferon-Alpha Binding Protein Reverses Behavioral Impairments in a Mouse Model of HIV Associated Neurocognitive Disorders

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Infection with HIV commonly causes HIV associated neurocognitive disorders (HAND) despite life-prolonging combined antiretroviral therapy (cART). There is substantial evidence that interferon-alpha plays a role in cognitive impairment in HAND. We have previously shown that a decoy protein that sequesters type I interferons, B18R, ameliorates HIV induced histopathology. We tested if co-administration of B18R with cART provides enhanced protection from HIV encephalitis in comparison to B18R or cART treatments alone in a mouse model of HAND. After 10 days of treatment mice were sacrificed and brains extracted and frozen for tissue sectioning. Five micron coronal sections were immunostained for a neuronal marker (MAP2), astrocytes (GFAP), HIV (p24) and mononuclear phagocytes (CD45). The data suggests that B18R simultaneously administered with cART reduced encephalitis markers more than either of the two treatments administered alone. In a separate set of experiments, B18R was tested for its ability to reverse behavioral abnormalities of HAND mice using an Object Recognition Test (ORT). The ORT was administered to HAND mice and controls before and after treatment with B18R. ORT showed a strong trend in the reversal of behavioral impairment in HAND mice treated with B18R. Because of its ability to act in concert with cART as well as reverse behavioral abnormalities in HAND mice, B18R is a potential therapeutic agent for a Phase I trial in HAND patients.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Maroun developed the molecule, B18R, used in this study and his company, Meiogen, holds the patent. Dr. Maroun (Meiogen) provides this molecule to the Tyor lab for testing. These studies are also part of a Specific Aim of a VA Merit award (1I01BX001506-01A2; Tyor PI). Dr. Maroun has received funding through Dr. Tyor's Merit award for contracted services (B18R production).

M176. Does tDCS Affect Non-Treated Language and Cognitive Functions in Primary Progressive Aphasia?

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Primary progressive aphasia (PPA) is a neurodegenerative syndrome in which language abilities gradually deteriorate (Gorno-Tempini et al. 2011). There is currently no treatment. Given the helpful but limited effects of language therapy, the neuromodulation technique transcranial direct current stimulation (tDCS) has recently been used to supplement language therapy. In a previous study we showed that tDCS over the left IFG coupled with language therapy was significantly more beneficial than language therapy alone: therapy gains were longer sustained and generalized to untrained items (Tsapkini et al. 2014). In the present study, we aimed to assess the effects of anodal tDCS combined with language therapy (mostly spelling intervention)

on language and cognitive functions not introduced in therapy. We hypothesized that if left-IFG-associated tasks trained in therapy improve, then other language and cognitive functions that involve the same neural substrate will improve, despite not being explicitly treated.

Sixteen individuals with PPA participated in a within-subjects crossover design with two experimental conditions: speech-language therapy plus anodal left-IFG tDCS and speech-language therapy plus sham tDCS. They were evaluated before, immediately after, 2 weeks after, and 2 months after each therapy phase. We performed McNemar's test for correlated responses to assess each person's scores individually.

We stratified participants into two categories: those recruited early in the disease progression (2-3 years since symptom onset) and late in the disease progression (3-10 years since symptom onset). For IFG-associated tasks, such as letter (FAS) and semantic verbal fluency tasks, most early participants showed more improvement in the tDCS than sham condition, sustained up to two months. For late participants, however, improvement was scarce; in verbal fluency tasks, only one or two individuals significantly improved in any condition, and that improvement was not sustained. Other IFG-associated cognitive tasks, such as the digits forward and backward task, did not improve.

These results indicate that tDCS combined with language therapy may not improve cognition or language in general, but specific language tasks that are either trained or subserved by the stimulated area. Effects may be more beneficial for individuals early in the disease progression, as scores significantly increased with tDCS, but did not for those late in the disease progression.

Gorno-Tempini, M.L. (2011). *Neurology*.

Tsapkini, K.C. (2014). *Aphasiology*.

M177. Proton Pump Inhibitor Use Is Associated with Initial Diagnosis of MCI or AD in the www.Alzcenter.com Neurology Clinic

Heenaben Patel, Malini Nair and Anil K. Nair. Quincy, MA

Background: Proton pump inhibitor (PPI) use relates to dementia diagnosis, may accelerate amyloid deposition, and are candidate biomarkers for binding tau. We analyzed PPI use and MCI or AD diagnosis in www.alzcenter.com neurology clinic.

Methodology: Cross sectional data on age, gender, race, initial diagnosis (Normal/MCI/AD) and PPI use among www.AlzCenter.com outpatients from 01/01/2010 to 12/31/2015 were analyzed. Univariate and multivariate models analyzed PPI use and dose to MCI/AD and AD diagnosis.

Results: 348 patients with initial diagnosis of normal, MCI or AD gave consent for medication review. 92 (26.44%) had no cognitive complaints, 113 (32.47%) had MCI, 143 (41.09%) had AD. Data were non-normal; mean age 73.47 ± 11.54 , (Normal 72.01 ± 12.23 , MCI 69.34 ± 12.84 , AD 77.67 ± 8.15 , $p < 0.01$); 199 (57.18%) females and 324 (93.10%) caucasians. PPI users were 106 (30.46%) in MCI/AD and 82 (34.89%) in AD analysis groups. Kruskal Wallis testing showed PPI use in MCI/AD

($\chi^2=20.67$, $p<0.001$) and AD ($\chi^2=13.02$, $p<0.001$) were significantly different from normal subjects. Multivariate analysis confirmed the association of PPI use to MCI/AD diagnosis. (F statistic 3.875 on 4 and 339 DF, p -value=0.0043). Visual analysis of residuals suggested nonlinear residual error distribution in the MCI/AD subjects. PPI use is also associated to AD diagnosis, with normal distribution of residual error on Q—Q plots. (F-statistic: 5.213 on 4 and 228 DF, p -value<0.001). Multivariate dose models analyzed available doses of omeprazole 10, 20, 40, 80 mg; pantoprazole 20, 40, 80 mg; esomeprazole 10, 20, 40 mg, lansoprazole 30 mg; dexlansoprazole 60 mg doses as individual factors affecting diagnosis. Omeprazole 20 mg, 40 mg and pantoprazole 20 mg doses were significantly associated with diagnosis in the MCI/AD (F-statistic: 3.642 on 15 and 328 DF, p -value<0.001) and AD groups (F-statistic: 3.921 on 14 and 218 DF, p -value<0.001). Other doses or agents were not associated with diagnosis. However, stepwise regression could not eliminate other doses and agents as factors from the overall regression model.

Conclusion: PPI use is significantly associated with MCI/AD or AD diagnosis. Lower doses of omeprazole 20 and 40 mg and pantoprazole 20 mg doses are significantly related to diagnosis. Confounding from PPI use duration, non-linear dose responses in MCI/AD subjects needs further study.

M178. 90 Year Olds Are Less Likely to Fall If They Were Physically Active Two Decades Earlier: The 90+ Study

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Objective: To determine if physical activity reported 24 years earlier is associated with the risk of falling and to examine factors related to falls in the oldest-old.

Background: The risk of falls and injuries sustained from falls increase with age. Although risk factors for falls in the elderly have been well characterized, only limited information is available about the oldest-old, people 90 years and older.

Methods: The study included 1536 participants from The 90+ Study, a longitudinal investigation of aging and dementia in the oldest-old. Participants were originally members of the Leisure World Cohort Study (LWCS), an epidemiological study of life style practices. Falls (yes/no) were reported by a participant or informant at the baseline examination of The 90+ Study. Other factors also reported at the baseline examination and known to be related to falls in younger elderly were also examined. Physical activity information was collected in the LWCS 24 years earlier (range:16-34) and was reported as 15 minutes, 30-45 minutes, or 1+ hour/day. Using logistic regression we examined the relationship between physical activity reported 24 years earlier and falls.

Results: At The 90+ baseline visit, participants were on average 94 years (range=90-107), most were women (78%), and had at least a college degree (52%). Falls were reported by 52% (N= 799) of participants and were associated with

a higher number of prescription medications, history of TIA or stroke, depression, arthritis, vision disease, heart disease, presence of dementia, and use of assistive devices. After adjusting for potential confounders, and compared to people who reported no physical activity, activity of 30+ minutes/day was associated with approximately a 30% lower likelihood of falling. The falls odds ratios were 0.63 ($p=0.03$) for 30-45 minutes/day and 0.66 ($p=0.03$) for 1+ hour/day.

Conclusions: People over 90 have an especially high risk of falling for a variety of reasons such as overall deterioration of health and increased functional impairment and disabilities due to neurodegenerative diseases. Previous physical activity was related to lower risk of falling even in the presence of comorbidities or needing assistive devices. Regular physical activity may be a good strategy to reduce falls in the oldest-old and could provide an intervention to prevent falls in this rapidly growing age group.

M179. The Hippocampal Network Model: A Neuroimaging Approach to Identifying Dementia Biomarkers

Eithan Kotkowski and Peter T. Fox. San Antonio, TX

Metabolic syndrome or systemic metabolic dysfunction (SMD) is one of the most common disease states disproportionately afflicting the Hispanic population in the United States. Evidence suggests that effects of SMD and neurocognitive dysfunction are bidirectional and complex, with genetic, environmental, and behavioral causes (Biessels et al., 2014). It has been recently shown that the underlying pathology does not resemble that of AD (Abner et al., 2016). Studies using contrast-enhanced MRI show age-dependent blood-brain barrier (BBB) breakdown in the hippocampus, worsening with mild cognitive impairment and correlating with injuries to the BBB pericytes (Montagne et al., 2015). Rodent models have also implicated the hippocampus in cognitive deficits resulting from T2DM (Stranahan et al., 2008). Consequently, we propose to create a hippocampal network model (HNM), using meta-analytic co-activation modeling (MACM) and structural equation modeling (SEM), to detect and quantify network abnormalities associated with neurocognitive decline in SMD. Our immediate research goal is to create functional and structural meta-analytic connectivity maps (FMACM and SMACM) of the hippocampi in order to develop the HNM that can be used to assess cognitive impairments in individuals with metabolic syndrome. Our preliminary data has found 13 key nodes of functional connectivity with each individual hippocampus (right and left) all of which address highly significant behavioral paradigms known to be affected in individuals with dementia (i.e. working and explicit memory, cognition, etc.) We hypothesize that SMACM and FMACM will jointly identify an extended hippocampal connectivity network with different components being associated with different behavioral domains and neuropsychiatric disorders.

M180. Preclinical Studies Targeting Toxic Tau Oligomers by Immunotherapy

Diana Castillo-Carranza, Julia Gerson, Urmi Sengupta, Kelly Dineley, Alan Barrett and Rakez Kaye. Galveston, TX

A number of neurodegenerative disorders associated with dementia and motor dysfunction, including Alzheimer's disease and Parkinson's disease with dementia are characterized by the accumulation of aggregated tau protein. However, while neurofibrillary tangles comprised of tau filaments are the classical hallmark of these diseases, our lab and others have shown that intermediate aggregates—tau oligomers—are in fact the most toxic form of tau. Therefore, we created a tau oligomer-specific monoclonal antibody (TOMA) in order to specifically study the toxic oligomeric tau, as well as for use as a therapeutic agent. We characterized tau pathology in three different animal models: P301L mutated tau mice, non-mutated human tau mice and Tg2576 mutated amyloid precursor protein mice. We then evaluated the preventative and reversal efficacy of targeting tau oligomers in each mouse model by passive immunotherapy with TOMA. Following treatment, we evaluated the cognitive and motor function of P301L mice and memory in human tau and Tg2576 mice. We found that targeting tau oligomers in both the tauopathy mouse models and the Alzheimer's disease mouse model attenuated memory loss, as well as reduced motor dysfunction in P301L mice. Following behavioral analysis, we collected brain tissue for biochemical and immunohistological analysis for levels of pathological tau and markers of neuronal dysfunction. We found that in both tauopathy mouse models, TOMA treatment significantly lowered levels of tau oligomers without affecting tau monomer or neurofibrillary tangles. Additionally, in the Tg2576 mouse model we found that pathological amyloid- β was lowered with treatment as well as tau oligomers. Additionally, dendritic spines in mice treated with TOMA were significantly larger than spines in control transgenic mice, suggesting that synaptic transmission may be improved with treatment, underlying cognitive benefits. We have previously demonstrated that tau oligomers likely mediate the toxicity and spread of pathology in disease. Collectively, the findings reported here support the idea that eliminating tau oligomers by passive immunotherapy may be an effective therapeutic strategy for Alzheimer's disease and a number of other tauopathies.

M181. Polygenic Risk Scores in Familial Alzheimer's Disease

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Background: Large genome-wide association studies of non-Hispanic Whites with late-onset Alzheimer's disease (LOAD) have identified over 20 common single-nucleotide polymorphisms (SNPs) albeit with weak effects. Polygenic risk scores represent an alternative strategy to summarize sparse genetic information and identify profile risks. LOAD

has been shown to have a significant polygenic component in case-control studies but this has never been investigated in families multiply affected by LOAD.

Methods: Using data from the National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease (NIA-LOAD) families study, we conducted mixed regression models testing the association between LOAD and genetic risk score (GRS), based on SNPs previously associated with LOAD. We modeled associations using unweighted and weighted scores based on estimates derived from the literature. In secondary models, we adjusted GRS models for presence of APOE- ϵ 4 allele and investigated their interaction.

Results: The unweighted GRS was not associated with LOAD. On the contrary, weighted GRS was significantly associated with LOAD (OR=2.05 $p<0.001$). Results did not change after adjusting for APOE- ϵ 4. Significant interaction between APOE- ϵ 4 allele and weighted GRS was also found (OR=1.14, $p=0.02$).

Conclusion: Higher polygenic scores are associated with familial LOAD. Risk associated with GRS accounts for about half the risk derived from APOE- ϵ 4 allele. Higher polygenic scores in the presence of APOE- ϵ 4 allele further increases this risk.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr Boeve was an investigator for clinical trials sponsored by Cephalon, Inc, Allon Pharmaceuticals, and GE Healthcare; receives royalties from the publication of a book titled Behavioral Neurology of Dementia (Cambridge Medicine; 2009); has received honoraria from the American Academy of Neurology; serves on the Scientific Advisory Board of the Tau Consortium; and receives research support from the National Institute on Aging (NIA) (P50 AG016574, U01 AG006786, RO1 AG032306, RO1 AG041797) and the Mangurian Foundation. Dr Rosenberg has received clinical trial grants from Janssen and Pfizer Inc; holds a US patent for "Amyloid β Gene Vaccines"; and serves on the editorial board of the Journal of the Neurological Sciences. Dr Farlow has received grant and research support from Accera, Biogen, Eisai Med Res, Eli Lilly & Company, Genentech, MedAvante/AstraZeneca, and Navidea; serves on the speaker's bureau at Eisai Med Res, Pfizer Inc, Forest, Novartis, and Eli Lilly & Company; serves on the consultant/advisory boards at Accera, Alltech, Avanir, Eisai Med Res, Inc, Helicon, Medavante, Medivation, Inc, Merck and Co, Inc, Novartis, Pfizer Inc, Prana Biotech, QR Pharma, Roche, Sanofi-Aventis, Schering-Plough, Toyama Pharm, Eli Lilly & Company, UCB Pharma and Elan. Dr Sweet is a consultant for Eli Lilly & Company. No other disclosures were reported.

Education

M182. Diagnosing Bias in Physicians: The Influence of Language on Diagnostic Judgment

Megan Richie and Scott A. Josephson. San Francisco, CA

Purpose: Heuristics are cognitive shortcuts that may introduce bias and contribute to error. The authors examined

whether medical students and physicians untrained in decision-making are subject to bias from heuristic use, and how this bias may be related medical training level.

Method: Subjects completed surveys containing medical and non-medical scenarios that required assignment of probabilities to various potential outcomes. Surveys randomly presented scenarios in one of two versions: Version A, which encouraged use of a heuristic, and Version B, worded more neutrally. The primary outcome measure was the difference in probability judgments for Version A versus Version B scenario options.

Results: Of 167 participants recruited, 139 were enrolled. Participants assigned significantly higher mean probability values to Version A scenario options than Version B (9.6 versus 9.0, $p < 0.01$). This result remained significant when analyzing medical scenarios alone (9.4 versus 8.9, $p = 0.02$). Analyzing medical scenarios by heuristic revealed a significant difference between Version A and Version B for the availability (6.5 versus 5.5, $p < 0.01$) and representativeness (11.5 versus 10.7, $p = 0.02$) heuristics. When stratified by training level, only the availability heuristic maintained significance, specifically for students (7.3 versus 5.8, $p < 0.01$) and residents (7.2 versus 5.6, $p = 0.02$).

Conclusions: The way information is presented may influence physician diagnostic impressions, subjecting them to bias due to the use of heuristics. Higher levels of training may decrease availability bias. The methods used in this study closely approximate the way physicians evaluate patients in academic institutions where trainees often act as first-responders before formally presenting to an attending. These results support the importance of formal training about sources of bias in clinical decision-making for students and physicians.

M183. The Neurology Clinic as a Training Model for Multiple Health Care Professions

Elena Shanina, Robert G. Smith, Karen Aranha, Jill Seale and Judith Rowen. Galveston, TX

Objectives: To develop clinic-based interprofessional learning activities, evaluating collaboration between students of Medicine and Allied Health Programs.

Background: There is growing recognition that effective interprofessional communication and collaboration leads to optimal delivery of health care, improving patient satisfaction, safety, and outcomes. Students of different healthcare professions are routinely involved in learning about neurological disorders, but each specialty has different learning objectives and patient assessment methodologies. We introduced an interprofessional learning activity, providing opportunity for these students to learn about each other's roles in patient care delivery, and training in coordinated therapy planning.

Design/Methods: A Grant-sponsored Neurology Clinic was the site for a pilot interprofessional collaborative clinical experience. 62 students participated in this activity (15 Medical, 5 Nurse Practitioner, 24 Occupational Therapy, and 18 Physical Therapy students). Initial individual student clinical evaluations were followed by an interdisciplinary

collaborative meeting, therapy session, and post-therapy discussion. Participants completed surveys before and after this clinical experience.

Results: Pre-activity surveys revealed that while 53% students knew about interprofessional teams, only 35% were familiar with interprofessional team training. Students commented that they had limited knowledge about responsibilities and educational requirements of other healthcare professionals. In post-activity surveys, all students agreed that Neurology patients benefitted from coordinated interprofessional therapy, and that shared learning increased students' understanding of Neurology patient clinical problems. 98% of students strongly agreed/agreed that interprofessional education sessions provided valuable opportunities to work with students of other professions, and 87% strongly agreed/agreed that the session provided team approach training in overcoming clinical challenges. Self-assessment of interprofessional communication competency was significantly lower than peer assessment (two tailed Wilcoxon $p = 0.0002$), demonstrating lack of confidence or low comfort level in interprofessional communication.

Conclusion: Effective interprofessional collaboration is expected from all healthcare professionals in clinical practice. This pilot project showed the feasibility of interprofessional learning in actual clinical settings using practical approaches. Because neurological cases routinely require multidisciplinary therapeutic approaches, Neurology clinics can be effective learning environments applicable to many different interprofessional groups.

M184. Observing the Effect of Online Educational Modules on Student Satisfaction with the Flipped Classroom

Chanel Wood, Krishan Chandar and Maureen McEnery. Cleveland, OH

Objectives: The Case Western Reserve University School of Medicine second year medical school curriculum features flipped-classroom-style sessions, Medium-Sized-Groups (MSGs), on the topics of Neurology and Neuroscience. We hypothesized that redesign of the videos assigned as preparatory materials for these sessions could improve student satisfaction with the MSGs. Our aim was to design online educational modules using existing lecture materials and, in the process, outline a template for creation of future modules.

Methods: In the second year Block 6 curriculum, we designed and launched three preparatory modules for use as preparation for existing MSGs. Prior to any intervention, a voluntary End-of-Year Survey was distributed to the exiting second year class (C2016). In this survey, students rated MSGs, overall, on twelve quality parameters and commented on the effect of different learning modalities on their learning. The modules were launched the following year to C2017, to whom the End-of-Year Survey was also distributed at the conclusion of the course. Both C2017 and their successors, C2018, also completed the Mid-year Survey, in which they were asked to evaluate MSGs individually on eleven parameters.

Results: End-of-Year Survey: C2017 (n=20) rated MSGs significantly higher than C2016 (n=50) on ten of twelve parameters ($p<0.05$ unpaired t-test). Mid-Year Survey: Mean ratings by C2017 (n=33) of modules were significantly higher than unaltered videos (redesigned vs. unaltered comparisons, $p<0.05$, paired t-test). In general, C2018 (n=33) rated redesigned videos significantly better than pre-existing videos. Finally, there were statistically significant improvements in the degree to which C2017 and C2018 reported that MSG videos contributed to learning Block 6 content as compared to C2016 ($p<0.05$, unpaired t-test).

Conclusions: It has been suggested that content delivery by short, variable speed, interactive videos is a viable and effective strategy to complement in-class delivery methods. Based on longitudinal data, our educational modules demonstrably increased students' satisfaction with MSGs. There is a difference in the degree to which each class is affected, the cause of which has yet to be identified; an obstacle to our drawing conclusions is the low level of survey completion. The authors look forward to observing the impact of these and future modules on measurable student outcomes in our curriculum.

Headache and Pain

M185. Headaches Among HIV+ Persons in Rural Rakai, Uganda

Deanna Saylor, Gertrude Nakigozi, Noeline Nakasujja, Kevin Robertson, Ronald H. Gray, Maria J. Wawer and Ned Sacktor. Baltimore, MD; Rakai, Uganda; Kampala, Uganda and Chapel Hill, NC

Objective: To determine the prevalence and severity of headaches among a sample of HIV+ persons in rural Uganda.

Background: Headache is one of the most prevalent disorders worldwide and the most common cause of years lost to disability among neurologic diseases, but little is known about its prevalence in Sub-Saharan Africa.

Methods: 205 HIV+ participants in the Rakai Community Cohort Study completed the ID Migraine Screen and Headache Impact Test 6 (HIT-6). Prevalence of headache was defined as a "yes" answer to the question, "Do you have headaches?" Migraine diagnosis was based on the ID Migraine Screen (affirmative answers to 2/3 questions), and severity of headaches was based on HIT-6 scores (<49-little to no impact; 50-55-some impact; 56-59-substantial impact; >60-severe impact). Headache risk factors were determined using t-tests for continuous variables and chi-square tests for categorical variables. Overweight/obese was defined as body mass index > 25. Depression was defined as a score of > 16 on the Center for Epidemiologic Studies Depression Scale (CESD).

Results: Participants were 49% male, mean age 38 (SD 9), median CD4 425 cells/ μ L (IQR 295-546), 90% on antiretroviral therapy. Headaches were reported in 35% (n=72) of participants, and 14 participants (6%) met criteria for migraine. Compared to those without headaches, participants with headaches were more likely to be women

(71% vs. 41%; $p<0.001$) and overweight/obese (31% vs. 18%, $p=0.04$). 54% of participants with headaches reported a negative impact on their daily life: 25% - some impact; 13% - substantial impact; 15% - severe impact. Participants with headaches were more likely to report functional impairment (Patient Assessment of Own Functioning Inventory (PAOFI) total score: 148 vs. 155, $p=0.004$; Karnofsky score: 94 vs. 97, $p=0.02$) and score higher on the CESD (7 vs. 4, $p=0.01$). Compared to those with no or little impairment, participants reporting substantial or severe impairment due to headaches were more likely to meet criteria for depression (30% vs. 8%, $p=0.001$) and report fatigue (25% vs. 10%, $p=0.04$) and functional impairment (PAOFI 144 vs. 154, $p=0.008$).

Conclusion: Headaches were common among HIV+ participants in rural Uganda and commonly associated with fatigue, functional limitations, and depression. Effective headache treatment is needed to improve quality of life in this population.

M186. Clinical Manifestations of Parvovirus B19 Encephalitis in Immunocompetent Patients

Jin Sun Jun, Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Byoungsu Park, Seon-Jae Ahn, Hye Rim Shin, Yoon Hyuk Jang, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu Chu. Seoul, Republic of Korea

Parvovirus B19 (PVB19) is associated with erythema infectiosum, transient aplastic crisis, non-immune hydrops fetalis, and arthritis. To date, few reports have described PVB19 infection of immunocompetent adults in association with neurological manifestations. The role of PVB19 in neurological diseases remains obscured and incompletely described. Here we report various clinical characteristics and responses to treatments.

The first patient experienced sudden onset of high fever, headache, and tremor. The second patient had headache, fever, nausea, and vomiting followed by generalized tonic-clonic seizure. His neurologic exam was unremarkable and neck was not stiff. The third patient discovered unconscious at home and was brought to the emergency department. His body temperature was high and he was in confusion and was unresponsive to stimuli. After administration of intravenous diazepam and other antiepileptic drugs, he could make eye contacts, but was still drowsy. The fourth patient had recurrent meningitis, dizziness, binocular diplopia. The fifth patient showed altered mentality and fever. His mentality was aggravated after admission.

Routine analysis, bacteriological examination, PCR and serology of blood and cerebrospinal fluid (CSF) were performed in all the five patients. Also, brain imaging and EEG were done. All patients were previously healthy. The CSF results revealed leukocytosis (lympho-dominant), elevated level of protein, and normal glucose level. PVB19 DNA PCR was positive in the serum of all five patients and was positive in the CSF of the third patient. Other PCR, serological tests, and culture of blood and CSF were negative. Every patient had no previously reported skin

manifestations or blood lab abnormalities, suspecting the clinical suspicions of systemic parvovirus infections. MRI of three patients was normal, but two of them showed abnormal findings. EEG finding of all patients showed no epileptiform discharges. Three patients received antiviral and antibacterial therapy. IVIG plus IV steroid pulse therapy was done in patient 4, and only IVIG was performed in patient 5. Two patients with seizures received antiepileptic drugs. All patients were discharged with complete recovery.

PVB19 should be considered as one of the possible etiology of meningoencephalitis in immunocompetent adults. Since PVB19 encephalitis can present with various nonspecific symptoms, PVB19 PCR should be considered in suspected patients. Also, we can try immunotherapy in Parvovirus B19 encephalitis patients when symptoms are not improved after antiviral therapy.

Health Services Research

M187. Post-Hospitalization Outcomes of Neurologic Inpatients Before and After Mandatory Follow-Up Appointment Scheduling

Alexandra Kvernlund, Steven Bondi, Andre Son, Marissa Lanoff, Natali Baner, Peter Benedict, G. Kyle Harrold, Laura Balcer and Jori Fleisher. New York, NY

Objective: To examine the rate of outpatient follow-up among patients discharged from the inpatient general neurology and stroke services at an urban, academic medical center before and after an intervention to enhance continuity of care.

Background: Hospital readmission rates are increasingly used as a measure of the efficacy of healthcare systems and a surrogate marker of care coordination. Studies in elderly populations estimate 90-day readmission rates to be 34%. One key strategy promoted to address this is scheduling timely outpatient follow-up prior to discharge, as early follow-up has been associated with lower readmission rates in some studies. To our knowledge this has never been studied in patients with neurologic disease, who may be particularly susceptible to barriers to accessing care in the setting of neurologic deficits.

Methods: Retrospective pre- and post-intervention study of 958 patients discharged from the inpatient neurology services at New York University. The intervention entailed follow-up appointment scheduling prior to discharge via an order set in the electronic medical record routed to dedicated call center staff. The primary outcome measure was follow-up with a neurologist, primary care physician, or other specialist within 90 days of discharge. Secondary outcome measures included hospital readmission or emergency department (ED) visit within 90 days.

Results: There were no significant differences in the demographics of the pre- and post-intervention groups, except for a significant increase in Medicaid patients (5.7 vs. 11.1%). Pre-intervention (n= 401), 3.7% had an appointment scheduled prior to discharge, while post-intervention (n = 557), 25% had an appointment scheduled. In the pre-intervention group, 65% saw a clinician within 90 days vs.

72% in the post-intervention group ($p = 0.03$). Older age and discharge to acute rehabilitation were associated with increased odds of having a follow-up appointment scheduled, while Medicaid insurance was associated with lower odds of scheduled follow-up ($p < 0.01$). No significant change in readmission or ED visit rates was detected.

Conclusion: Facilitated outpatient appointment scheduling significantly increased follow-up care, without a change in readmissions. Of interest, there was an increase in the Medicaid population in the post-intervention group, likely reflecting the effects of the Affordable Care Act. Medicaid also had a detrimental effect on the likelihood of having scheduled outpatient care. These findings highlight existing health disparities as well as the need to further characterize factors associated with readmission among neurology inpatients.

M188. Screening of Respiratory Virus PCR Panel in Adults with CNS Infection: Seoul Neuroinfection Registry

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Respiratory viruses including adenovirus, respiratory syncytial virus (RSV) A, B, rhinovirus A/B, coronavirus, Influenza A, B, parainfluenza 1, 2, 3 and metapneumovirus are well known causes of upper respiratory infection in infants and young children. There are a few reports on meningitis or encephalitis associated with respiratory viruses but most of them are pediatric cases. We now demonstrate some cases of central nervous system (CNS) infection with respiratory virus in adults which are diagnosed by respiratory virus (RV) PCR panel.

We reviewed the registry for central nervous system infection between 2000 and 2015 at the Seoul National University Hospital, and identified patients with positive for RV PCR panel in sputum or CSF. We analyzed the clinical presentations, laboratory findings, and outcome.

Out of total 681 patients in registry, 253 (37.1%) were viral infection. Among them, 15 patients (5.9%) showed positive results for RV PCR panel consisting of 3 Influenza A, 3 rhinovirus A/B, 2 adenovirus, 2 parainfluenza virus, 2 corona virus, 2 RSV A, 1 RSV B, 1 influenza B, 1 metapneumovirus. Four were positive in CSF, ten were positive in sputum and one was positive in both though specific viruses were different in each specimen. Median age was 37 (range from 21-72).

Eight (53%) presented with meningitis and seven (47%) with encephalitis. Seven (47%) complained URI symptoms prior to neurologic manifestations. Magnetic resonance imaging (MRI) of ten (66%) patients revealed abnormality. Leptomeningeal enhancement was the most common abnormal pattern (53%). Two patients with each adenovirus and RSV B in CSF showed parenchymal T2 signal hyperintensity in MRI. Lympho-dominant pattern pleocytosis was the majority (73%) of the CSF findings.

Most of the patients (93.3%) had good prognosis even with encephalitis. One encephalitis patient with positive influenza A in CSF was clinically deteriorated despite of multi antiviral therapy.

We identified that CNS infection related to respiratory viruses is rare, however does exist not only in children but also in adult. Even though most patients showed good response to antiviral therapy, some patients would have higher chance of bad outcome especially with positive PCR in CSF. Screening of CSF and sputum RV PCR panel in adults with CNS infection would be helpful for proper etiological diagnosis.

M189. Physician Satisfaction with Teleneurology Service Provided via Tablet Technology

Kelly Harper, Maxim Turchan, Derek Riebau, Amber Humphrey, Heather Meyers, Eli Zimmerman, Mark Baker and David Charles. Nashville, TN

Background: A 2013 American Academy of Neurology Study found that the US would need to increase the current number of neurologists by 11% to meet patient needs and that number is expected to increase to 19% within the next decade¹. In order to address this shortage of neurologists in our state, Vanderbilt University Medical Center (VUMC) initiated a teleneurology consult service utilizing low-cost tablet technology for nine community-based hospitals.

Methods: Vanderbilt's teleneurology service is provided via iPads linked through a HIPPA compliant secure network to allow real-time video examinations at community hospitals. Images from the community are viewed on the iPad using Jenesis, an application developed at Vanderbilt University. Physician satisfaction surveys are administered to community-based hospital physicians via REDCap, a secure web application for building and managing online surveys developed at Vanderbilt University. Community physicians rate the timeliness of connecting with the neurologist, timeliness of receiving clinical documentation at the conclusion of a consult, whether they found the neurologist helpful in managing the care of patients, and their overall satisfaction with the consultation.

Results: Over the 24 months beginning February 2014, 1,980 emergent teleneurology consults were completed. Fifteen physicians at nine community hospitals completed 68 physician surveys. 90% reported the speed at which they were connected with a neurologist to be faster than or as expected, 93% reported the timeliness in receiving clinical documentation to be faster than or as expected, 96% reported the neurologists to be better than or as expected at managing patient care, and 92% reported the overall experience to be excellent or satisfactory. Community physicians, supported by consulting teleneurologists, successfully evaluated and treated 87% of patients. The percent of patients requiring transfer to a higher level of care was 13%. Patient diagnoses included 29% stroke, 9% seizure, 5% headache/migraine, and 5% altered mental status.

Conclusions: Teleneurology provided via low-cost tablet technology is highly effective for elevating the level of specialty neurologic care provided in community hospitals and

it also enables the majority of patients to remain closer to their homes and family. Community physician are highly satisfied with the timeliness of consultations and clinical documentation, patient management, and overall service provided.

1. Dall TM, Storm MV, Chakrabarti R, et al. Supply and demand analysis of the current and future US neurology workforce. *Neurology* Epub 2013 Apr 17.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Vanderbilt University receives income from grants and contracts with Allergan, Ipsen, Merz, and Medtronic for research led by Dr. Charles. Dr. Charles receives income from Allergan, Ipsen, Concert, and Medtronic for consulting and education services. There are no conflicts of interest for Kelly Harper, Maxim Turchan, Derek Riebau, Amber Humphrey, Heather Meyers, Eli Zimmerman, or Mark Baker.

Neuromuscular Disease

M191. Comprehensive Characterization of Muscle Disease in *Col6a2* Null Mice, a Novel Mouse Model of Collagen VI-Related Disorders

Payam Mohassel, Jachinta Rooney, Apurva Sarathy, Yaqun Zou and Carsten G. Bonnemann. Bethesda, MD

Mutations in collagen VI cause a spectrum of muscle disease ranging from severe Ullrich congenital muscular dystrophy to the milder Bethlem myopathy. The three protein components of collagen VI encoded by *Col6a1*, *Col6a2*, and *Col6a3*, undergo extensive assembly after translation before being excreted and incorporated into the extracellular matrix (ECM). Collagen VI is an integral component of the ECM, making collagen VI-related dystrophies (COL6-RD) prototypical disorders of the muscle ECM. However, the pathophysiologic mechanisms of how collagen VI absence from the ECM results in muscle weakness, atrophy, degeneration, and fibrosis remain unknown. In this study, we introduce a new mouse model of COL6-RDs, characterized by homozygous inactivation of the *Col6a2* alleles (*Col6a2*^{-/-}) and characterize the histologic and functional changes associated with this genotype in skeletal muscle fibers. *Col6a2*^{-/-} mice show histologic abnormalities including myofiber atrophy, degenerating and regenerating myofibers, increased internalized nuclei, and increased fibrosis that worsen over time, consistent with a dystrophic myopathy. These findings correlate with decreased performance on functional assessments (e.g. grip strength) and *ex-vivo* physiologic measures (e.g. tetanic force) compared to wild-type and heterozygous controls. Similar to patients, they exhibit typical, albeit milder, histologic and functional changes. Dysregulation of growth factor signaling, which is closely regulated by the ECM, may play a significant role in pathogenesis of this disease. *Col6a2* knockout mice serve as a novel animal model for COL6-RDs and can be used to study these mechanisms and test efficacy of potential therapeutic interventions in preclinical studies.

M192. Post-Exposure Vaccination of *M.leprae*-Infected Armadillos Does Not Exacerbate Peripheral and Cutaneous Sensory Nerve Involvement

Gigi J. Ebenezer, Richard W. Truman, Maria T. Pena, Kelly Cunningham, Michael Polydefkis and Malcolm S. Duthrie.
Baltimore, MD; Baton Rouge, LA and Seattle, WA

Armadillos were tested for the safety of a LEP-F1/GLA-SE vaccine in the early subclinical stages of *M.leprae* infection particularly for immune-mediated nerve damage. Nine armadillos had experimental vaccination (VC) at 1, 2 and 3 months after *M. leprae* inoculation. *M. leprae*-infected (ML) and naïve animals served as controls. 3mm skin punches and tibial nerve biopsies were taken at the distal leg 16 and 28 months after inoculation and intraepidermal nerve fiber density (IENFD, fibers/mm) Schwann cell density (SCD, cells/mm³) estimated and expressed as mean $\pm$ SEM.

Results: The *M. leprae*-infected Remak axons were dilated without degeneration and the diameter was lower in the vaccinated group (in nm, ML: 697.5 $\pm$ 8.2, VC: 678.5 $\pm$ 10.3, $p=0.002$). The ML group had a lower IENFD (22.5 $\pm$ 4.7) than naïve animals (24.8 $\pm$ 4.3), and trended higher among vaccinated group (32.1 $\pm$ 3, $p=0.23$). SCD significantly increased in the infected group (naïve: 3172 $\pm$ 403, ML: 5089 $\pm$ 675, $p=0.02$, VC: 4624 $\pm$ 417, $p=0.7$).

Conclusion: *M. leprae*-infected Schwann cells undergo proliferation for a long period without sensory fiber degeneration and this depicts an early preclinical model of peripheral neuropathy in armadillos. LEP-F1/GLA-SE immunization appears to be safe on small sensory fibers with no evidence of early nerve fiber injury.

M193. Effect of Amyloidosis on Small Sensory Nerve Fibers and Peripheral Nerve Function in Distal Leg of Patients with Transthyretin Familial Amyloid Polyneuropathy

Gigi J. Ebenezer, Ying Liu, Kelly Cunningham, Noel Carter, Blessan Sebastian, Kelly Byrnes and Michael Polydefkis.
Baltimore, MD

Methods: To assess the role of skin biopsies to demonstrate amyloid infiltration, twenty-four V30M TTR-FAP patients and age/gender-matched healthy controls underwent neurological examination and 3 mm skin biopsies at the distal leg and stained with anti-PGP9.5 antibody and Congo red. Amyloid burden was measured (Image J), intraepidermal nerve fiber density (IENF, fibers/mm), autonomic nerve fiber subsets including sweat gland nerves (SGNF, m/mm³) and pilomotor nerves (PMNF/mm) were determined by stereology and correlated with Neuropathy Impairment Score-LL (NIS-LL).

Results: The Congo red sections revealed brilliant red amyloid deposits with an apple-green birefringence infiltrating collagen (93%), piloerector muscles (73%) and neurovascular bundles (67%). Congo red staining in skin biopsies had a diagnostic sensitivity of 63% and specificity 100%. IENF, SGNF, and PMNF densities were all significantly reduced ($p<0.05$) in TTR-FAP patients vs. controls and

were associated with more severe NIS-LL (IENF: $p=0.003$, $r=-0.68$, SGNF: $p=0.02$, $r=-0.58$). Amyloid burden inversely correlated with IENFD ($p=0.004$, $r=-0.56$), SGNF ($p=0.01$, $r=-0.71$), PMNF ($p=0.02$, $r=-0.49$).

Conclusion: Skin biopsies from stage 1 TTR-FAP patients exhibit prominent endoneurial infiltration with amyloid and degeneration of sensory nerves. Skin biopsies are a well-tolerated tool to establish tissue diagnosis for FAP, demonstrate sensory neuropathies and well as a biomarker marker in therapeutic clinical trials.

M194. Inhibitory Synapses Formed by Human Spinal Cord Stem Cells: Reversing Excitotoxicity in ALS

Kevin S. Chen, Lisa M. McGinley, Osama N. Kashlan, Carey Backus, Crystal M. Pacut, Elizabeth S. Bruno, Josh S. Chang, Faye E. Mendelson, Maegan A. Tabbey, Samy R. Kashlan and Eva L. Feldman. Ann Arbor, MI

Background: Amyotrophic lateral sclerosis (ALS) is a devastating neuromuscular disease characterized by progressive loss of upper and lower motor neurons (MNs). Although the mechanisms underlying ALS pathology remain largely unknown, damage to inhibitory interneurons and subsequent MN excitotoxicity plays a major role in disease pathogenesis. Human spinal stem cells (hSSCs) could restore inhibitory tone to motor neurons by forming new inhibitory synapses. We recently completed Phase 1 and 2a clinical trials examining safety and dosing of hSSC in ALS patients and our supporting preclinical data showed that these cells form a small percentage (about 2%) of inhibitory synapses onto host MNs. The present study aims to test our hypothesis that increased inhibitory tone rescues MNs from excitotoxicity, and that enriching inhibitory synapse formation in hSSCs will more efficiently reverse MN pathology in ALS models.

Methods: The hSSC cell line NSI-566RSC was provided by Neuralstem Inc., and was co-cultured with primary rat motor neurons, and electrical activity recorded using a multi-electrode array. Subsequently, hSSCs were modified using a lentiviral vector to allow inducible expression of developing brain homeobox-2 (hSSC-Dbx2), a transcription factor that drives differentiation of neural progenitors to inhibitory interneurons during normal development. For in vivo testing, a T13-L1 laminectomy was performed in 60d SOD1G93A ALS mice, and injections of hSSC, hSSC-Dbx2, or vehicle control were targeted to the ventral gray matter of the spinal cord. Motor function was evaluated every other week and survival endpoint was defined by a loss of righting reflex.

Results/Conclusions: Electrophysiological analysis indicated that primary rat MNs exhibited diminished firing when co-cultured with differentiated hSSCs capable of forming synapses but not with undifferentiated hSSCs. This demonstrates that in ALS, hSSC may provide increased inhibitory tone by the formation of new inhibitory synapses. We next established hSSC-Dbx2, a novel cell line with robust inducible Dbx2 expression. Intraspinal injection of hSSC and hSSC-Dbx2 successfully targeted the ventral horn in the SOD1G93A mouse. Although no differences were

observed in motor performance to date, studies are still ongoing. Quantification of inhibitory synapses and MN survival at the study end will confirm the role of hSSC-mediated inhibitory synapse formation in ALS. In conclusion, our findings suggest that reversal of excitotoxicity in ALS via restoration of inhibitory tone is a potential therapeutic mechanism of hSSCs and support further development of enhanced stem cell therapies to translate to patients.

M195. Predicting Respiratory Insufficiency in Guillain-Barré Syndrome Using Clinical Presentation Characteristics and Electrophysiological Findings

K.H. Vincent Lau, Irene Yang, Amanda Lakraj, Daniel DiCapua and Richard Nowak. New Haven, CT

Background: Accurately assessing the risk of respiratory insufficiency in Guillain-Barré syndrome (GBS) has important implications for triage and determining frequency of respiratory monitoring. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) predicts the need for mechanical ventilation (MV) based on symptom duration prior to presentation, overall weakness severity, and facial or bulbar involvement. Previous models to predict respiratory insufficiency also evaluated electrophysiological, respiratory monitoring and cerebrospinal fluid (CSF) data, finding the former two relevant.

Objective: We aimed to validate prior predictive models for MV in the acute setting using clinical characteristics upon presentation at our institution. In addition, we aimed to develop an improved model that includes neurophysiological data and CSF findings.

Methods: All GBS cases at a major academic center with hospital admissions from 2000 to 2016 were retrospectively reviewed. Inclusion criteria were GBS diagnosis by NINDS criteria and availability of either CSF protein or electrophysiology data during initial admission; cases of GBS variants were excluded. Thirty-six possible factors were recorded (3 for demographics, 17 for clinical presentation, 2 for initial respiratory monitoring, 11 for infection and serology, 1 for CSF protein, 2 for neurophysiology findings). Binary logistic regression analysis was used to identify predictors of mechanical ventilation.

Results: We identified 240 possible GBS cases. As of this writing, ninety-one were analyzed with forty-three meeting inclusion criteria. Our dataset was validated against total EGRIS ($p = 0.004$). Based on preliminary data, exploratory factor analysis using a null model identified the following characteristics as predictive of MV: Medical Research Council (MRC) sum score ($p = 0.000$), disability score ($p = 0.001$), preceding symptom of diarrhea ($p = 0.001$), ophthalmoplegia ($p = 0.005$) and a history of respiratory disease ($p = 0.043$). There was also a trend for non-demyelinating nerve conduction studies being protective. Elevated CSF protein was not predictive based on the current dataset.

Discussion: We validated total EGRIS score as predictive of MV using our dataset. This supports its potential use as a clinical tool broadly. In addition, our exploratory factor

analysis suggests that a model including additional clinical features and electrophysiological data for prediction of MV is possible. Our next steps are to complete data collection to improve power and to complete binary logistic regression analysis with confirmatory factor analysis.

M196. An Assessment of Treatment Guidelines, Clinical Practices, Demographics, and Progression of Disease Among Individuals with Amyotrophic Lateral Sclerosis in Japan and the United States

Koji Takei, Manabu Hirai, Fumihiko Takahashi, Kikumi Tsuda and Joseph M. Palumbo. Jersey City, NJ and Tokyo, Japan

Background: There continues to be a need for new therapies to treat amyotrophic lateral sclerosis (ALS). Edaravone (MCI-186) has been investigated in Japanese patients with ALS using the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R).

Objective: Assess clinical practice and treatment guidelines, and compare the progression of disease among patients with ALS in Japan and the US.

Methods: To assess relative similarities and differences that might exist between Japanese and US medical practice for ALS, we reviewed country-specific practice guidelines. We also performed a literature review to compare the demographics and baseline characteristics of ALS for Japanese and US populations. Using reference studies of ALS in the US and edaravone studies in Japan, progression of ALS disease was assessed in patients receiving placebo using a random coefficient model, with an assumption that ALSFRS-R score declines in a linear fashion within each patient. The changes per month in ALSFRS-R score were calculated and compared between the studies. These results were also compared with published longitudinal data from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database.

Results: Overall, diagnostic criteria, recognition of ALS symptoms, comorbidities, use of riluzole as the first-line therapy, nutrition, and respiratory support were similar between the Japanese and US guidelines. Regarding demographic and baseline characteristics of the published literature, there were similarities in the incidence of sporadic ALS (93% vs 94%-96%) and bulbar onset (25%-30% vs 32%-33%), time from onset to diagnosis (11 months vs 11-12 months), and use of percutaneous endoscopic gastrostomy (29%-33% vs 9%-27%) among the Japan and US populations, respectively. However, use of tracheostomy-based invasive respiratory support was higher in Japan (29-34%) than the US (4%). Progression of disease, as assessed by ALSFRS-R score in patients receiving placebo, was similar between the reference studies including the US population (range across 6 studies, -0.89 to -1.28 points/month) and edaravone studies in the Japanese population (range across 3 studies, -0.98 to -1.21 points/month). These results parallel with published data from the PRO-ACT database (-1.02 ± 2.3 points/month) (Atassi et al. *Neurol* 2014;83:1719-25).

Conclusion: Clinical practice and treatment guidelines for ALS between Japan and the US are similar, with the

exception of tracheostomy use. Progression of disease, as assessed by ALSFRS-R, appears similar between Japanese and US patients with ALS.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? KT, KT, and JP are employees of Mitsubishi Tanabe Pharma Development America, Inc. MH and FT are employees of Mitsubishi Tanabe Pharma Corporation.

Autoimmune Neurology

M197. Neuromyelitis Optica and Neoplasia

Leticia Tornes, Nida Usmani, Luis Tornes, Silvia Delgado, Alexis Lizarraga, Kottil Rammohan and William Sheremata. Miami, FL

Rationale: An increased risk of neoplasia in neuromyelitis optica (NMO) has been regarded as likely to be a paraneoplastic phenomenon. In a prior review we found malignancies amongst cases meeting the 2006 Wingerchuck NMO Criteria. However, more recently, we have been impressed by the absence of malignancies NMO and neuromyelitis spectrum disorder (NMOSD) and sought to relate this to changes in treatment modalities.

Methods: Data from an IRB approved NMO/NMOSD study was reviewed to identify cases of malignancy and their relationship to drug management.

Results: A total of 75 cases meeting NMO or NMOSD diagnostic criteria on treatment were identified (80% female; mean age of onset = 34 years). Malignancies were identified in 6 of the 75 cases. Treatment duration varied; 12 had been on treatment for more than 10 years, 41 for 5 – 10 years, and 22 for less than 5 years. In the last 10 years, rituximab supplanted the use of azathioprine and steroids. Two (2) others had used mycophenolate mofetil for brief periods. Use of azathioprine treatment (1 – 20 years) was associated with all of the malignancies [seminoma (1), breast (2), uterus (1), lymphoma, (1) parotid (1)]. In 2 of the 6 cases with malignancies, the patient had received less than 5 years of treatment (putatively a paraneoplastic event) and in 2 others diagnosis was shortly after initiation of rituximab therapy. No cases of malignancy were observed in patients treated with rituximab alone.

Conclusions: Use of azathioprine appears to be an important risk factor for neoplasia in NMO. This risk is not shared by patients treated with rituximab, even for extended periods of time. Further follow-up will be needed. The risk for use of other immunosuppressant drugs cannot be ascertained from the available data.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Tornes, Usmani, Tornes, Delgado, Lizarraga, Sheremata have no disclosures.

Rammohan -

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Interventional Neurology

M198. CT Angiography Delays Groin Puncture in Mechanical Thrombectomy for Large Vessel Occlusion in Stroke

Kunakorn Atchaneeysakul, Anita Tipirneni, Priyank Khandelwal, Vasu Saini, Richard Ronca, Steven Lord, Luis Guada, Kevin Ramdas and Dileep Yavagal. Miami, FL

Introduction: Thrombectomy in proximal anterior circulation occlusions has shown significant improvement in functional outcome over tPA alone. Recent trials have utilized CT angiography(CTA) for vascular imaging immediately following non-contrast CT(NCCT). Thin section NCCT with automated MIP reconstructions has high accuracy in showing occluding thrombus. However,multiple imaging modalities may delay time to groin puncture(GP).We hypothesized that CTA after NCCT increases time to GP compared to thin section NCCT alone.

Method: This is a retrospective cohort study of consecutive patients receiving thrombectomy for anterior circulation occlusions at our tertiary-care academic medical center. All stroke NCCTs are thin section(0.625mm) with software automated maximal intensity projection(MIP) reconstructions available within 2 minutes of CT images. When “hyperdense sign” was seen on thin section MIPs in anterior circulation, physician may forgo CTA and bring patient directly to angiography suite. We excluded all transfer patients,in-hospital stroke,and receiving stroke imaging other than NCCT or CTA prior to thrombectomy. NCCT-CTA and NCCT groups were compared for time from initiation of NCCT to GP(tNCCT-GP) and total imaging time prior to GP(tIMAGING). Time from imaging completion to GP was included in multivariate analysis as potential confounder increasing tNCCT-GP.

Results: From March 2008 through August 2015,289 patients underwent thrombectomy with 56 patients meeting inclusion/exclusion criteria(24 NCCT,32 NCCT-CTA group). tIMAGING was significantly lower in the NCCT group compared to NCCT-CTA group, 3.2 ± 1.4 vs 56.9 ± 14.1 min ($p<0.001$). Multivariate analysis showed significantly lower tNCCT-GP in NCCT only group, 100 ± 22.1 vs 124.8 ± 16.1 min ($p<0.001$).

Conclusion: Performing CTA after NCCT prior to thrombectomy does significantly delay time to groin puncture. Selecting LVO patients with thin section NCCT with MIPs showing hyperdense sign may significantly save time, brain,and further improve outcomes.

M199. The Role of Intestinal Microbiota in the Characterization of Novel Natural Drug Compounds in the Treatment of Major Depressive Disorder

Jun Wang, Jeremiah Faith, Lap Ho, Simoni Tiano and Giulio Pasinetti. New York

A number of recent human studies indicate that psychosocial stressors increase peripheral cytokine production and may be an important factor in the development of major depressive disorders (MDD). Subsets of patients with MDD

have higher levels of multiple inflammatory markers, including the cytokine Interleukin 6 (IL-6). The nucleus accumbens (NAc) plays a central role in brain reward circuits, and synaptic plasticity of the NAc is critical for resilience to stress-induced depression/anxiety. Using a model of repeated social defeat stress (RSDS), we demonstrated that stress-mediated long-term disruptions in NAc medium spiny neuron (MSN) synaptic plasticity and induction of IL-6 in the periphery are key factors contributing to depression/anxiety phenotypes. We found that dietary supplementation with a novel polyphenol rich preparation (PRP) undergoes significant gastrointestinal microbiota metabolism leading to generation of selective bioactive PRP metabolites in the circulation to promote resilience to depression/anxiety phenotypes in the RSDS model. We found that treatment significantly promotes resilience to RSDS-induced depression/anxiety phenotypes, compared to vehicle-treated control mice. In particular, we found that the treatment significantly improved social interaction ratio compared to vehicle-treated control mice (1.8 ± 0.8 vs. 1.1 ± 0.4 , $p < 0.05$) associated with significant reduction in inflammatory IL-6 circulatory levels. These changes coincided with an improvement of anhedonia, as assessed by sucrose preference test following chronic social stress ($74.3 \pm 14.4\%$ vs. $31.9 \pm 24.8\%$, $p < 0.01$). Our studies strongly support the role of the intestinal microbiome in contributing to the benefits of a novel PRP in promoting resilience to stress-induced depression/anxiety through generation of select PRP metabolites. Gnotobiotic mice are currently being developed through fecal transplantation of select commensal microbes characterized by enhanced generation of PRP metabolites in vitro to allow further investigation in vivo for the contribution of select microbiota in attenuating RSDS-induced depression and anxiety.

M200. Development of a Cerebral Angiography Calibration Model Based off of Relative Arterial Diameters

Maximilian J. Bazil, Christopher P. Kellner, J. D. Mocco and Johanna T. Fifi. New York, NY

This study attempts to derive a calibration model for the measurement of cerebral angiographic details on de-identified images lacking a scale. The retrospective measurement of anatomical details on cerebral angiography (CA) such as vessel diameter for stent placement and aneurysm size is complicated by the loss of the calibration scale during the transfer of data from interventional angiography systems to a picture and communications system (PACS). This is a three part study including a systematic literature review, development of a calibration model, and validation of the model on a separate set of images. A systematic literature review of the mean diameters of the anterior cerebral artery (ACA), the middle cerebral artery (MCA), and the internal carotid artery (ICA) was performed, analyzing data from approximately 7,000 patients to quantify vessel diameter variability. This review was followed with a retrospective analysis of 107 CA images, establishment of a set range of

diameters, the determination of the most commonly used scales for neuroimaging analysis in CA, prioritization of these scales, and the overall creation of a model for the conversion of Pixel Diameter to Actual Diameter. It was determined that the models created were, on average, correct within 0.1177 mm and 5.3% ($p < 0.0001$), 0.1387 mm and 5.0% ($p < 0.005$), and 0.1357 mm and 3.8% ($p < 0.05$) for the ACA, MCA, and ICA respectively. This model forms the basis for a computer program that can be used to automate the measurement of CA imaging for use by clinical trials and patient care.

Neuromuscular Disease

M201. INSIGHTS: Analysis of IVIG Responsiveness in Patients with Myasthenia Gravis

Todd Levine, Leslie Vaughan, Gary Badger, Gil Wolfe, Lara Katzin, David Saperstein, Tahseen Mozaffar, Richard Bahron, Jonathan Katz, Mazen Dimachkie, Michelle Greer and Elissa Ritt. Phoenix, AZ; Temecula, CA; Burlington, VT; Buffalo, NY; Tampa, FL; Irvine, CA; Kansas City, KS and San Francisco, CA

Objectives: Over the last four years we have conducted a quality improvement project, INSIGHTS, to examine the clinical, laboratory, and electrophysiologic criteria of neuromuscular patients prescribed IVIG across the US

Background: IVIG is commonly used off-label for treatment of exacerbations and for maintenance therapy of myasthenia gravis (MG). Due to a lack of positive controlled trials, there is tremendous variability in the types of patients who are prescribed IVIG for MG in clinical practice.

Methods: We collected clinical, laboratory, and electrophysiologic data on 585 neuromuscular patients who were prescribed IVIG from across the country. A panel of independent expert neuromuscular neurologists reviewed the information. Positive outcomes were independently determined based on quality-of-life measures, Patient Global Impression of Change, and clinical documentation. Data was entered electronically in the REDCap system at the University of Kansas.

Results: We present the data from 89 MG patients who received IVIG. 44 of these patients were naïve to IVIG, and 68% of these patients had a positive response. 45 patients had received IVIG previously, and 73% of these patients had a positive outcome. The average dose of IVIG was 1.73 gm/kg/month with a range of 0.4 gm/kg/month to 4gm/kg/month. 59 patients (66%) were receiving ongoing maintenance therapy, while 30 patients (34%) received treatment only for an exacerbation. Positive response was most strongly associated with the independent reviewers' determination that the patient was appropriate for IVIG (92% vs 50%, $p = .06$) based on progressive generalized weakness. Patient's age, sex, distribution of weakness, disease time course, and antibody status had no significant association with response.

Conclusions: Overall response rates of patients with MG to IVIG was 70%. This suggests that larger controlled trials of IVIG in MG should be performed with the potential to

receive an indication for therapy both for exacerbations and maintenance.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? T. Levine: Baxalta (Speaking), Nufactor(Consulting), Questcor (Consulting). Dr Levine also has a financial interest in Corinthian Reference Labs, Mallinkrodt. L. Vaughn: None. G. Badger: Received financial support from Nufactor. G. Wolfe: Grifols speakers bureau, advisory board

Baxter, advisory board. L. Katzin: Grifols (speakers bureau), NuFactor (consultant). D. Saperstein: Baxalta (Speaking) NuFactor (consultant), Corinthian reference lab (partial owner),. T. Mozaffar: Dr. Mozaffar received personal compensation from Genzyme Corporation and Grifols for speaking engagements. He has served as an advisory board member for Amicus, Biogen idec, Biomarin, Genzyme, Idera, Pharmaceuticals and Ultragenyx., Dr. Mozaffar received clinical research support to conduct clinical trials by cytokinetics, alexion, biomarin, grifols, GSK, ultragenyx, and novartis. R. Barohn; Dr Barohn received honoraria from Grifols & Genzyme, Speakers Bureau

NuFactor (consultant), Covered Editor Neurology Clinics of North America, Served as an investigator in clinical trials sponsored by Cytokenetics. J. Katz: Blue Cross, Grifols, Clinical trials PI: Teva, Synapse. M. Dimachkie: Dr. Dimachkie has received personal compensation for activities with Pfizer, Depomed, Merck, CSL-Behring, Nufactor, Biomarin, Baxter and Catalyst as a consultant, speaker, advisory board member, or. M. Greer: Michelle Greer is employed by NuFACTOR Specialty Pharmacy. E. Ritt: Elissa Ritt is employed by NuFACTOR Specialty Pharmacy.

Sleep Disorders and Circadian Rhythm

M202. Hyperglycemia Is Associated with Autonomic Dysfunction During Sleep in Patients with Obstructive Sleep Apnea (OSA)

Amanda C. Peltier, Kanika Bagai, Rene Harder, Farhad Iqbal, Emily Garland, Beth Malow, David Robertson and Andre Diedrich. Nashville, TN

OSA is hypothesized to cause a hypersympathetic state, a mechanism for increased incidence of cardiovascular disease in OSA. However, the high prevalence of hyperglycemia in OSA may be a confounding cause of autonomic dysfunction. Previously, we have shown that daytime heart rate variability (HRV), an indicator of autonomic function, demonstrated greater association with hyperglycemia than with measures of OSA. It is unknown if these associations persist for nighttime HRV. We hypothesized that autonomic dysfunction, captured by nighttime HRV, will have more dominant associations with hyperglycemia than with OSA.

Thirty-five patients with OSA and eleven controls underwent polysomnography, glucose tolerance testing, autonomic function tests, baseline ECG and continuous blood pressure measurements for spectral analysis. Of these, 28 OSA patients and eight controls had adequate ECG tracings without artifact for HRV assessment for each sleep stage. Sixteen

OSA patients and two controls had hyperglycemia. There was no difference between OSA patients and controls in gender, age, body-mass index, glucose, or standard autonomic function tests. Average apnea-hypopnea index (AHI) in OSA patients was 18 ± 15 .

We compared HRV from polysomnography during different sleep stages throughout the night in addition to daytime parameters collected during autonomic function testing. Polysomnography data were classified for stages Wake, non-rapid eye movement sleep N1, N2, N3, and rapid eye movement sleep (REM) following standard AASM guidelines. Linear regression models were used to study the effect of age, diagnosis, and hyperglycemia on each sleep stage.

OSA patients had higher resting heart rates overnight, and higher ratio of low frequency (LF) to high frequency (HF) power, an indicator of increased sympathetic activity, during NREM sleep. OSA and autonomic indices had only one positive partial correlation between AHI and LF component of HRV during N1 ($r=0.38$, $P<0.05$). In contrast, we found multiple associations with parameters of hyperglycemia. Insulin resistance index (HOMAIR) had negative partial correlation with HF power, an indicator of parasympathetic tone, during Wake ($r=-0.33$, $p=0.01$) and during REM ($r=-0.36$, $p<0.001$). A positive partial correlation with LF/HF during N3 was found for HOMAIR ($r=-0.36$, $p<0.05$) and baseline glucose level ($r=0.33$, $p<0.05$).

These results suggest hyperglycemia has an important role in autonomic dysfunction leading to a reduction of vagal modulation and increase of sympathetic dominance during sleep.

Autoimmune Neurology

M203. Quantitatively Decreased Visual Cortex Metabolism by FDG-PET/CT: An Early Biomarker of Acute Anti-NMDA Receptor Encephalitis

John C. Probasco, Abinav Nalluri, Krystyna M. Jones, Mehrbod S. Javadi, Lilja Solnes and Arun Venkatesan. Baltimore, MD

Background AND Purpose: Various patterns of FDG-PET/CT metabolism have been reported in patients with anti-NMDA receptor encephalitis (anti-NMDAR). Descriptions of FDG-PET/CT in anti-NMDAR relative to other autoimmune encephalitides (AE) are limited. Here we describe quantitative FDG-PET/CT in inpatients with anti-NMDAR in comparison to other AE.

Methods: We performed a retrospective review of clinical data and FDG-PET/CT studies from neurology inpatients meeting criteria for AE, per published consensus guidelines, treated at a single academic medical center over a ten year period. Z-scores and 3D stereotactic surface projection maps of brain metabolism on FDG-PET/CT were generated for all patients by comparison with age-matched normal controls. Z-scores for respective brain areas were compared between AE groups as well as with control patients without AE.

Results: 49 inpatients with possible AE who underwent FDG-PET/CT were identified (4 anti-NMDAR, 21 seropositive for other antibodies, 24 seronegative). FDG-PET/CT was performed a median of 4 weeks after symptom onset with no variation across AE groups. FDG-PET/CT demonstrated hypometabolism in the bilateral visual cortices of anti-NMDAR patients (median right visual cortex $Z = -3.9$, left $Z = -4.1$), diminished relative to all other AE (right $Z = -2.3$, $P < 0.01$; left $Z = -2.3$, $P = 0.01$) with no significant differences noted for other cortical areas. When compared to only other seropositive AE patients, anti-NMDAR patient metabolism was diminished in the bilateral visual cortices (seropositive AE right $Z = -2.2$, $P < 0.01$; left $Z = -2.1$, $P < 0.01$) as well as the occipital cortices (right anti-NMDAR $Z = -3.3$, seropositive AE $Z = -1.9$, $P = 0.02$; left anti-NMDAR $Z = -3.5$, seropositive AE $Z = -2.0$, $P = 0.07$). When comparing anti-NMDAR patients to the sample of control patients, the right frontal (anti-NMDAR $Z = -2.6$, control $Z = -0.7$, $P = 0.02$) and the bilateral visual cortices and occipital lobes were hypometabolic (control right visual $Z = -0.2$, $P = 0.02$; left visual $Z = -0.4$, $P = 0.02$; right occipital $Z = 0.0$, $P = 0.02$; left occipital $Z = 0.3$, $P = 0.02$). One anti-NMDAR patient underwent subsequent FDG-PET/CT three and six months after the initial scan, with normalization of visual cortex metabolism correlating with clinical recovery.

Conclusions: Marked visual cortex hypometabolism by FDG-PET/CT may serve as an early biomarker for discriminating anti-NMDAR encephalitis from other causes of AE. Resolution of visual cortex hypometabolism may correlate with clinical improvement in anti-NMDAR encephalitis.

M204. Depletion of Abundant Sequences by Hybridization (DASH): Using Cas9 to Remove Unwanted High-Abundance Species to Enhance Microbial Detection via Next-Generation Sequencing (NGS)

Brian D. O'Donovan, Wei Gu, Emily D. Crawford, Michael R. Wilson, Eric D. Chow, Hanna Retallack and Joseph L. DeRisi. San Francisco

Objective: Development of a novel molecular technique leveraging the CRISPR-Cas9 system to selectively deplete unwanted sequences from metagenomic NGS libraries and enhance microbial detection.

Background: The presence of unwanted, high-abundance, human RNA species increases the cost and worsens the limit of microbial detection in clinical metagenomic analyses. Further, the ultralow RNA quantities in samples such as cerebrospinal fluid (CSF) prohibit the use of commercially available depletion strategies requiring nanogram-scale amounts of starting material. To address this challenge, we developed a novel and programmable depletion technique (DASH) that can be employed subsequent to the generation and amplification of complementary DNA.

Design/Methods: DASH was applied to RNAseq libraries generated from HeLa cell cultures and the CSF of three patients with infectious meningoencephalitis. Fifty-four single guide RNAs were designed, targeting a 2.5 kilobase

region of the human mitochondrial chromosome encoding the two most abundant rRNA genes. Depletion of targeted genes and enrichment of clinically relevant species was quantified by comparing coverage and complexity of DASHed libraries to those prepared with standard workflows.

Results: DASH effectively depleted targeted genes by up to 99% and increased library complexity and representation of pathogen sequences by an average of 6-fold in clinical CSF samples.

Conclusions: DASH is a novel, targeted, customizable technique that can be adapted to enrich for microbial sequences in NGS libraries constructed from any amount or type of input nucleic acid and can be adapted for a wide range of neurogenetics applications.

M205. Clinical Miller Fisher Syndrome in a Patient Who Received Botulinum Toxin A Injections

Daniel A. Graf, Rahul Shah and Todd Masel. Galveston, TX

Background: Miller Fisher Syndrome (MFS), a variant of Guillain-Barré syndrome¹⁻² is characterized by cranial nerve involvement, presenting as a triad of ophthalmoplegia, ataxia and areflexia³. The majority of individuals with MFS have antiganglioside anti-GQ1b antibodies⁴⁻⁵. MFS is typically a self-limited disease with good prognosis, with clinical improvement beginning a few weeks after symptom onset, and complete recovery by 6 months⁶⁻⁷. Immunomodulatory therapies including intravenous immunoglobulin or plasmapheresis may be used to hasten recovery time⁸⁻¹⁰.

Objective: To discuss an unusual case clinically suggestive of MFS.

Methods: Case report.

Results: A 51-year old female fitness instructor with a history of hypothyroidism secondary to Hashimoto's Thyroiditis received cosmetic botulinum toxin injections (Onabotulinum A) to multiple areas of her face. Two days later, she began to experience itching and tingling in her right cheek. Over the next 2 weeks, she developed blurred vision, right facial droop, and unsteady gait. On presentation, she was found to have areflexia and gait ataxia, as well as impaired heel-to-shin testing bilaterally. She was given a clinical diagnosis of MFS. Initial CSF findings showed an elevated protein of 144 mg/dL, unremarkable glucose, and 38 white blood cells per microliter, with lymphocyte predominance. MRI of the brain and cervical spine were unremarkable. Sarcoidosis, syphilis, and paraneoplastic etiologies were excluded by CSF studies. She received 3 sessions of plasma exchange without clinical improvement. A repeat lumbar puncture showed the CSF protein to have risen to 161 mg/dL, with elevated CSF albumin at 107 mg/dL, and 84 white blood cells with lymphocyte predominance. Nerve conduction (NCV) studies were normal, including F-wave responses. She was subsequently started on 5-day course of IV methylprednisolone, with rapid improvement in her symptoms. At 3 months follow up, she had some mild residual paresthesias and easy fatigability and by 6 months, she was back to her pre hospitalization baseline.

Discussion: Clostridium botulinum toxin type A binds to the gangliosides GQ1b and GT1a and can produce a pattern of weakness similar to MFS⁶. Other features commonly seen with botulinum toxin exposure are mydriasis, ptosis, bulbar weakness, descending paralysis and autonomic symptoms which were absent in our patient. Although our patient clinically showed all the features of a MFS, CSF showing substantial leucorrhachia, normal NCV and F-waves¹¹ and poor response to PLEX but positive response to steroids were unusual. We postulate this was likely an atypical case of MFS.

Dementia and Aging

M206. CD4: CD8 Ratio Is Associated with Brain Subcortical Volume in Women with HIV Infection

Howard A. Crystal, Susan Holman, Diana Marcela Rojas-Soto, Deborah Gustafson, Yvonne W. Lui and Glenn T. Stebbins. Brooklyn, NY; NY, NY and Chicago, IL

Objective: To test the association of a marker of immunological senescence with MRI volumes and measures of white matter integrity in women with HIV

Background: CD4:CD8 ratio may be a marker of immunological senescence and chronic inflammation. It is associated with death from non-HIV causes, worse vascular structure and function, and worse and kidney function in patients with HIV. Because chronic inflammation may be a cause for cognitive impairment in HIV, we asked whether CD4:CD8 ratio might be associated with brain structure.

Design/Methods: Women were recruited from the Brooklyn site of the Women's Interagency HIV Study (WIHS) as part of a study of vascular health and cognition in HIV. MRIs were obtained on a 3 Tesla machine and quantified by the Stebbins lab using FreeSurfer software. CD4 and CD8 counts were measured within 6 months of the time of the MRI. The relationship between CD4:CD8 ratio and MRI measures was assessed using partial correlations

Results: 48 women were included in the study (mean age 46.8, SD = 7.4 years), 27% had a history of AIDS, 77% were African-American). After controlling for age, intracranial volume, race/ethnicity, and hypertension, CD4:CD8 was marginally associated with subcortical volume ($\rho = 0.29$, $p = 0.05$), but not with cortical, total white matter, or abnormal white matter volume. The partial correlation of CD4 with subcortical volume was not significant ($\rho = 0.19$, $p = 0.21$) and the partial association of CD8 number with subcortical volume was marginal ($\rho = -.27$, $p = 0.08$). Among subcortical structure, significant associations were found for the putamen, globus pallidus, and hippocampus, but not for the caudate or thalamus.

Conclusion: CD4:CD8 ratio may be associated with subcortical volume.

M207. Protective Roles of Intestinal Microbiota in Alzheimer's Disease Through Mechanisms Involving Short Chain Fatty Acids and Phenolic Acids

Lap Ho, Jeremiah Faith, Kenjiro Ono, Simoni Tiano and Giulio M. Pasinetti. New York and Tokyo, Japan

There is increasing evidence supporting a protective role of intestinal microbiota against diverse medical conditions, including neurological disorders such as Alzheimer's disease (AD) by modulation, in part, of metabolic and immune responses. For example, gut bacteria metabolize soluble dietary fiber into biologically available short chain fatty acids (SCFAs) that may help modulate immune responses in the periphery and in the brain. Gut bacteria are also known for their role in converting dietary polyphenols into biologically available phenolic acids with anti-oxidant activities. However, there is little information on the potential role of SCFAs and phenolic acids in AD. The present study is designed to investigate effects of these SCFAs and phenolic acids in beta-amyloid (A β)-mediated pathologic processes that play key roles in AD pathogenesis. We conducted in vitro studies using multiple complementary assays to investigate individual SCFAs and phenolic acids that are generated by gastrointestinal (GI) microbial metabolism of dietary fiber and polyphenols for their dose-responsive effects in interfering with the assembly of A β peptides into neurotoxic soluble A β aggregates. We also conducted in vitro studies investigating effects of isolated human GI bacteria in converting dietary fibers and select polyphenol products into biologically available SCFAs and phenolic acids that are effective in inhibiting A β aggregation. We found several phenolic acids that potently inhibited A β aggregation. We also found significant differences among GI microbiota from different healthy human donors in converting dietary polyphenols into these bioactive phenolic acids and in further metabolic degradation of these phenolic acids. Ongoing studies are investigating effects of individual SCFAs in A β aggregation and the efficacy of GI microbiota from different human donors in the generation (and degradation) of these SCFAs. Intestinal microbiota may help protect AD, in part, by supporting the generation of phenolic acids and SCFAs that interferes with the formation of toxic soluble A β aggregates. Presence of interpersonal differences in the human gut microbiota may lead to interpersonal variation to benefit from the protective effects of dietary fiber and polyphenols in AD. Outcomes provide critical information for developing probiotics to help prevent and/or treat AD.

M208. Cerebrovascular Disease Risk Factors, Arteriolar Sclerosis, and Cognitive Decline in the Kentucky Appalachian "Stroke-Belt"

Omar M. Al-Janabi, Ahmed A. Bahrani, Erin L. Abner, Charles D. Smith, Peter T. Nelson, Debra Moser and Gregory A. Jicha. Lexington, KY

Background: The relationship between cerebrovascular disease (CVD) risk factors and cognitive impairment or dementia has been widely studied with significant variability in findings between groups. We hypothesized that chronic small vessel injury in the form of arteriolar sclerosis, measured quantitatively (using MRI T2 volumetric analysis of white matter hyperintensity (WMH) volumes), would identify specific CVD risk factors and patterns of cognitive decline, associated with mild cognitive impairment of the cerebrovascular type (MCI-CVD), that represent the core

features of vascular cognitive impairment in our Kentucky “stroke-belt” population, at risk for cognitive decline and the future development of dementia.

Methods: A Cross-sectional analysis of clinical and quantitative MRI data on 114 subjects with normal cognitive function (n=52) and mild cognitive impairment (MCI; n=62) was performed. Quantitative total WMH volumes were examined in relation to potentially causative CVD risk factors and resultant test scores across cognitive domains using linear regression models adjusted for age, gender, and education.

Results: Among CVD risk factors analyzed, age ($p < 0.001$), education ($p = 0.003$), hypertension ($p = 0.012$), and hyperlipidemia ($p = 0.008$) demonstrated the strongest associations with WMH volumes. Conversely, CVD risk factors such as diabetes, smoking, history of heart attacks, atrial fibrillation, and history of stroke that have shown associations with CVD pathology on imaging in other studies were not statistically associated with increased WMH in this cohort. Unexpectedly, Framingham risk scores (FRS) and modified (short version) Hachinski Ischemic Scale (HIS) measures were not statistically associated with quantitative WMH volumes in this study. WMH volumes were associated with decrease performance on the Trial Making Test type A & B and long delayed free recall on the California Verbal Learning Test.

Conclusion: Our findings suggest similarities and yet differences in comparison to other studies, regarding the impact of CVD risks and associations with cognitive performance with the development of CVD pathology measured by WMH on MRI. Hypertension and hyperlipidemia appear to represent common shared risks across geographically disparate groups. Our findings, like others, suggest CVD pathology impact processing speed and executive function and provide further evidence for CVD effects on short-term memory in those at risk for cognitive decline and the future development of dementia in our Kentucky “stroke-belt” population.

Key words: Arteriolar Sclerosis, Hypertension, Hyperlipidemia, vascular cognitive impairment, dementia.

M209. Clinical Characterization of Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia

Takuya Konno, Kunihiko Yoshida, Toshiki Mizuno, Toshitaka Kawarai, Masayoshi Tada, Hiroaki Nozaki, Shu-ichi Ikeda, Masatoyo Nishizawa, Osamu Onodera, Zbigniew K. Wszolek and Takeshi Ikeuchi. Jacksonville, FL; Niigata, Japan; Matsuyama, Japan; Kyoto, Japan and Tokushima, Japan

Background: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare hereditary leukoencephalopathy caused by mutations in the *colony stimulating factor 1 receptor (CSF1R)* gene. While over a hundred cases with *CSF1R* mutations have been reported since the gene's discovery, the clinical characteristics of ALSP have not been fully investigated.

Methods: To clarify the characteristics of ALSP, we reviewed the available clinical data from *CSF1R* mutation carriers who were evaluated at our institutions or who were

previously reported. We summarized demographic data and initial symptoms and extracted detailed clinical findings using an investigation sheet that was created to collect further information.

Results: We identified 122 patients with *CSF1R* mutations from the US, Europe, and Asia. Fifty-eight different mutations were found. Thirty-six cases were sporadic. The mean age of onset was 43 years (range: 18-78 years), the mean age at death was 53 years (range: 23-84 years), and the mean disease duration was 7 years (range: 1-29 years). The age of onset was significantly younger in women than men (40 vs. 47 years, $P = 0.0006$, 95% confidence interval [CI] 3.158-11.177). An age-dependent disease penetrance was observed with a significant difference between sexes ($P = 0.0013$). The cumulative incidence was 95% by age 60 years ($n = 117$, a median of 43 years, 95% CI: 41-45). Initial symptoms were recorded for 106 cases; cognitive dysfunction ($n = 63$, 59%) was most frequently the first symptom followed by psychiatric symptoms ($n = 47$, 44%), motor symptoms ($n = 40$, 38%), and speech problems ($n = 20$, 19%). While cognitive dysfunction was the most frequent symptom overall, motor dysfunction was the most frequent initial symptom in young women whose symptoms presented when they in their twenties. Besides signal changes in the white matter, enlargement of the lateral ventricles, cortical atrophy, thinning of the corpus callosum, abnormal signaling in the pyramidal tracts, and diffusion-restricted white matter lesions were characteristic on brain MRI. In addition, some cases showed small calcified lesions in the white matter on brain CT.

Conclusions: We elucidated the characteristics of ALSP with *CSF1R* mutation. The presentation of ALSP phenotypes is different between the sexes.

M210. The Relationship Between Mutations in the glucocerebrosidase1 (GBA1) Gene and Cognition in Non-Manifesting GBA1 Carriers

Eileen Moran, Mindy Katz, Laurie Ozelius, Robert Ortega, Alison Schwartz, Richard Lipton, Molly Zimmerman and Rachel Saunders-Pullman. Bronx, NY; Boston, MA and New York, NY

Background: Mutations in the glucocerebrosidase1 (*GBA1*) gene are the most frequently observed genetic contributor to Parkinson's disease (PD) worldwide. *GBA1* related PD is characterized by more prominent cognitive decline than idiopathic PD, and *GBA1* mutations are the genetic factor most commonly associated with dementia with Lewy bodies (DLB). Thus, it is possible that *GBA1* mutations could be associated with cognitive decline independent of PD, or that a cognitive prodrome might be present in a subset of at-risk gene carriers. On the other hand, elderly mutation carriers might have genetic modifiers or other factors that mitigate disease and are responsible for the markedly reduced penetrance of this gene. The goal of this study was to examine cognitive function in at-risk *GBA1* gene carriers without PD or DLB.

Method: We evaluated neuropsychological function in 26 carriers of *GBA1* mutations (25 N370S, 1 IV2 + 1) and

130 age (± 5 years), gender, and education (± 3 years) matched mutation negative controls (5:1 matching) who were enrolled in the community-based Einstein Aging Study (Age mean = 78.7(4.8) years, 65% female). Controls were enrolled in the study within ± 1 year from enrollment of the matched case. Association between cognition at enrollment and gene mutation status was compared using paired samples t-tests.

Results: There were no differences between groups on tests of global cognition (BIMC), executive functioning (verbal fluency, Trail Making Test part B, WAIS-III Digit Symbol), attention (WAIS-III digit span), psychomotor speed (Trail Making Test part A), and visuospatial functioning (RBANS Complex Figure Copy, WAIS-III Block Design). There was a trend towards significance indicating that mutation carriers performed worse on a test of verbal memory (FCSRT) than controls (carriers mean=32.4, controls mean=34.1, $t(25)=-1.81$, $p=0.08$).

Conclusion: In this study of 26 *GBA1* mutation carriers, we did not demonstrate a clear association with cognition and mutation status with the exception of a trend towards significance on a test of memory. However, our study was limited by power from the relatively small sample size, and most of the carriers were N370S carriers. Previous research has demonstrated variable expression of GBA mutations, therefore it possible that an effect may have been observed with a larger proportion of severe mutation carriers. Further longitudinal study with a larger sample that includes individuals with a range of mutation types is warranted.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? R Saunders-Pullman: NIH U01094148, K02 NS073836, Genzyme Sanofi, RB Lipton: NIH [PO1 AG03949 (Program Director, Project and Core Leader), RO1AG025119 (Investigator), RO1AG022374-06A2 (Investigator), RO1AG034119 (Investigator), RO1AG12101 (Investigator), K23AG030857 (Mentor), K23NS05140901A1 (Mentor), and K23NS47256 (Mentor), the National Headache Foundation, and the Migraine Research Fund; serves on the editorial board of Neurology, has reviewed for the NIA and NINDS, holds stock options in eNeuraTherapeutics; serves as consultant, advisory board member, or has received honoraria from: Allergan, American Headache Society, Autonomic Technologies, Boehringer-Ingelheim Pharmaceuticals, Boston Scientific, Bristol Myers Squibb, Cognimed, Colucid, Eli Lilly, ENDO, eNeuraTherapeutics, GlaxoSmithKline, Merck, Novartis, NuPathe, Pfizer and Vedanta.

M211. NADPH Dehydrogenase Quinone 1 (NQO1) Demonstrates Increased Expression and Pathologic Aggregation in Glial Cells in Chronic Traumatic Encephalopathy

Chadwick Hales, Ahmad Zeineddin, James Webster, Jon Giuliano, Duc Duong, Nicholas Seyfried, Eric Dammer, Ann McKee, Allan Levey and James Lah. Atlanta, GA and Boston, MA

We previously utilized proteomic sequencing of postmortem human brain to identify novel proteins that may contribute to disease pathogenesis of Alzheimer's disease and other neurodegenerative disorders. We hypothesized that important disease associated proteins could also be identified in cases of chronic traumatic encephalopathy. We therefore performed dual mass spectrometry followed by quantitative proteomic analysis to characterize the CTE insoluble brain proteome. We identified many significantly enriched targets, including NADPH dehydrogenase quinone 1 (NQO1), a protein involved in the reduction of reactive oxygen species. Protein blotting confirmed NQO1 enrichment in the insoluble brain fraction and also identified a more global increase in NQO1 in total brain homogenates and soluble brain fractions. Enrichment of NQO1 in the insoluble proteome suggested that there could be pathologic aggregates of NQO1 in CTE brain. We therefore performed immunohistochemical analysis of CTE frontal cortex and identified multiple large NQO1 positive cells, including astrocytes and oligodendrocyte precursor cells as determined by dual immunofluorescence labeling. The number of NQO1 positive cells increased with higher stages of CTE pathology. These cells did not colocalize with beta-amyloid plaques, however, some NQO1 positive cells demonstrated colocalizing hyperphosphorylated tau immunoreactivity. We also assessed for the NQO1 C609T polymorphism as seen in previous Alzheimer's disease (AD) studies; however, the polymorphism was not enriched in the CTE group. Mechanistically, a global elevation in NQO1 may occur in response to increasing oxidative stress in neurodegeneration, however increasing insoluble and therefore dysfunctional or aggregated NQO1 may directly contribute to additional cellular injury. Since elevated NQO1 expression was previously reported in AD, future studies will be needed to further clarify how NQO1 contributes to disease pathogenesis in CTE, AD and other neurodegenerative disorders.

M212. RNA Destabilization in Amyotrophic Lateral Sclerosis and Frontotemporal Lobar Dementia

Sami Barmada, Hilary Archbold, Elizabeth Tank, Xingli Li, Michelle Paulsen and Mats Ljungmann. Ann Arbor, MI

RNA decay is a crucial aspect of RNA metabolism that is regulated by a series of highly conserved physiological pathways. Our work directly implicates abnormalities in RNA decay as a primary mechanism of disease in the neurodegenerative disorders amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Both ALS and the most common subtype of FTLD (FTLD-TDP) share key molecular pathologic features, including cytoplasmic deposition of the RNA binding protein TDP43. TDP43 binds to and regulates thousands of RNA transcripts, and as a result, TDP43 deposition dramatically perturbs RNA metabolism. In healthy cells, TDP43 regulates itself by binding its own mRNA and triggering RNA decay through a pathway that requires the RNA helicase UPF1 (up frame-shift 1). We previously demonstrated that UPF1 expression extends neuronal survival in models of ALS and FTLD-TDP. Rescue by UPF1 requires RNA decay, and expression

of other RNA decay components also suppresses toxicity. We have now identified a set of transcripts that are destabilized by TDP43 using Bru-seq, a powerful RNA labeling and sequencing technique. TDP43 deposition consistently destabilized ribosome protein-encoding transcripts and those involved in mitochondrial function. Importantly, we detected a similar destabilization of these transcripts in cells from patients with familial ALS and FTLTDP43 due to C9orf72 mutations, the most prevalent mutation responsible for both conditions. Our data therefore suggest that TDP43 is a fundamental regulator of RNA stability. In addition, the accumulation of TDP43 in ALS and FTLTDP may trigger widespread transcript destabilization and consequent interruption of basic processes such as protein translation and energy metabolism, as evident in patient-derived cells. Ongoing work seeks to determine if cell type-specific differences in RNA stability underlie the selective vulnerability of motor neurons or forebrain projection neurons in ALS and FTLTDP, and whether the expression of RNA helicases such as UPF1 can rescue RNA destabilization and neurodegeneration.

M213. Neurodegeneration-Like Pathological and Behavioral Changes in a AAV9-Mediated p25 Overexpression Mouse Model

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Background: The transgenic mice models overexpressing human p25 contribute greatly to the in-vivo neurotoxic mechanism of p25 in neurodegenerative diseases. However, it is time-consuming to manipulate existing transgenic mice models.

Objective: Here, we aim to establish a novel mouse model of neurodegeneration by overexpressing p25 mediated by recombinant adeno-associated virus serotype 9 (rAAV9).

Methods: AAV9-GFP-p25 encoding GFP-fused p25 driven by synapsin promoter, and the control, AAV9-GFP, were delivered in mice by tail-vein injection. Assessments of p25 expression, neurodegenerative pathology, and behavioral disorders in the model were performed and compared with APP/PS1-Tg mouse model and control group.

Results: GFP expression was detected by in-vivo imaging as early as one week after virus injection. Notably, widespread overexpression of p25 was obviously found in cortex, hippocampus and cerebellum in the model. Moreover, decreased hippocampus volumes in AAV9-GFP-p25 mice were detected by 7T MRI examination about one month after injection. Further, these AAV9-GFP-p25 mice exhibited progressive memory impairment from three-month to six-month after virus injection. At last, hyperphosphorylated tau, neurofibrillary tangles, activated astrocytes and microglia cells were elevated in p25 mice at about six months after virus delivery. However, amyloid- β (A β) plaque, overt neuronal loss and apoptosis in the hippocampus and cortex were not significantly induced by AAV9-mediated p25 overexpression.

Conclusion: The AAV9-mediated p25 overexpression mouse model, which is a practical model with

neurodegenerative pathology and behavior, provides an easier and time-saving method to explore the functions of p25 in vivo, as well as an alternative tool for development of drugs against neurotoxic of p25.

M214. Simple Test of Manual Dexterity Can Identify Persons at High Risk for Neurodegenerative Diseases in the Community

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Background Early identification of individuals at high risk of developing neurodegenerative diseases is essential for timely preventive intervention. However, simple methods that can be used for risk assessment in general practice are lacking.

Methods Within the population-based Rotterdam Study, we used the Purdue Pegboard Test (PPT) to assess manual dexterity in 4856 persons (median age 70 years, 58% women) free of parkinsonism and dementia between 2000 and 2004. We followed these persons until 1 January 2012 for the onset of neurodegenerative diseases (defined as first diagnosis of parkinsonism or dementia). We determined the association of PPT scores with incident neurodegenerative disease, adjusting for age, sex, study cohort, level of education, smoking, preferred hand, parental history, memory complaints and Mini-Mental State Examination. Furthermore, we determined the incremental predictive value of PPT, expressed as change in risk classification and discrimination.

Results During follow-up (median 9.2 years), 277 participants were diagnosed with a neurodegenerative disease (227 with dementia, 50 with parkinsonism). Lower PPT scores were associated with higher risk of incident neurodegenerative diseases (hazard ratio HR=1.28, 95% confidence interval [1.18; 1.41]) and improved discrimination of incident neurodegenerative diseases. We also observed significant associations of PPT scores separately with Parkinson's disease (HR=1.35 [1.11; 1.67]), secondary parkinsonism (HR=1.49 [1.12; 1.96]), Alzheimer's disease (HR=1.22 [1.06; 1.39]) and any other type of dementia (HR=1.33 [1.14; 1.54]).

Conclusions A rapid, non-laboratory test of manual dexterity improves prediction of neurodegenerative diseases. This highlights the importance of motor function in the preclinical phase of both dementia and parkinsonism, and may aid in selecting individuals for refined screening and neuroprotective trials.

Education

M215. Clinician-Defined Case Mix on an Academic Inpatient Neurology Service

Robert C. Bucelli, Arun Varadhachary, Gabriela de Bruin and Amar Dhand. St. Louis, MO

Introduction: Understanding the range of pathologies on an inpatient neurology service is important for providing optimal clinical service, monitoring exposure for trainees,

and identifying research opportunities. Case mix on modern inpatient services has changed due to an emphasis on shorter lengths of stay and higher acuity care. Usual methods of determining case mix rely on billing codes, which lack clinician-specified diagnoses that may better define, organize, and highlight cases of teaching value.

Methods: Four neurohospitalists, covering approximately 80% of the service time for an inpatient “general” (non-vascular) neurology service at a single tertiary-care academic medical center, kept record of consecutive cases for 9.5 months of service. Data were collected on patient characteristics, inpatient stay, localization, etiology, diagnostic category, diagnostic process, and teaching cases. Multiple localizations, diagnostic categories, and/or etiologies could be selected, if appropriate. All data were entered at or soon after patient discharge.

Results: 741 cases were documented, of which 348 (47%) were new diagnoses. Patients’ mean age was 52. 58% of patients were female. The race breakdown was 67% white, 29% black, and 4% other. The most common localizations of the primary disease process were cortical (323), non-localizing (171), and brainstem/cranial nerves (90). The predominant etiologies were inflammatory (285), idiopathic (266), vascular (113), and metabolic (109). Primary diagnostic categories were seizure disorders (147), neuromuscular disorders (99), headache (72), and encephalitis/meningitis (66). 109 cases were designated as teaching cases.

Conclusions: This study characterizes the patient composition of an academic inpatient neurology service. The findings parallel those of prior studies that highlight seizure disorders, neuromuscular disorders, headache, and encephalitis/meningitis as the most common non-vascular diagnoses on an inpatient academic neurology service. Our finding of “inflammatory/immune-mediated” as the most common etiologic category emphasizes the importance of ensuring trainee and faculty comfort in managing inflammatory conditions of the central and peripheral nervous systems. This information helps identify areas where neurologists should be well-prepared, strengths and limitations of the primary learning environment for trainees, and resource allocation. The high prevalence of teaching cases (15%) emphasizes the value of this database as a library for trainee education and as a resource for residents interested in projects for publication.

M216. Structured Preparation of Neurology PGY3 Residents for Participation in Medical Education Benefits Them as Teachers and Learners

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Objectives: To determine if Neurology PGY3 residents (NPGY3R) participating as facilitators in medium-sized groups (MSG) of second-year medical students (M2) increased their content knowledge and comfort level as teachers.

Methods: NPGY3R participated in a neurotransmission MSG alongside basic science faculty (BSF). All facilitators were provided with access to pre-class foundational materials

. An online survey assessed self-reported facilitator knowledge in each of 13 subject areas before and following the MSG activity and if participation in the MSG increased their comfort level in teaching the content.

Results: We compared self-reported facilitator knowledge before and after the MSG using the Student paired t-test. NPGY3R reported that the exposure to the material significantly “improved understanding” relative to their prior knowledge in eight of thirteen subject areas. BSF reported improved knowledge in one area. For each group, we also evaluated the correlation between their content knowledge following the activity and their “comfort in teaching” (NPGY3R, $r^2=0.66$; faculty, $r^2=0.84$).

Conclusions: Structured preparation for M2 MSG teaching serves both to educate and improve the comfort level among NPGY3R in teaching the basic science neurology content described in this study. The added value that NPGY3R bring to medical education is an under-developed resource in our curriculum.

Headache and Pain

M217. Post Partum Bilateral Abducens Nerve Palsy

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Introduction: The acute onset of horizontal diplopia, headache, and cranial nerve (CN) deficits mandates careful consideration of the underlying pathology. Differential diagnosis includes venous sinus thrombosis, multiple sclerosis, sarcoidosis, lupus, hypothyroidism, and meningitis. In patients presenting after recent epidural anaesthesia, incidental dural puncture should be included in the differential. CN palsy after such procedures is thought to result from CSF leak leading to intracranial hypotension causing traction on structures^{1,2}. Dural puncture following epidural anaesthesia is described in 0.19% - 4.4% of cases³. Of these, approximately half will experience post dural puncture headache believed to be caused by the same underlying mechanism as CN palsy described above².

Patient Presentation: A 35-year old young woman presented with headache, blurry vision, and diplopia 10 days after vaginal delivery during which she received an L4-L5 epidural. Approximately 8 hours post delivery, patient began to have severe, throbbing frontal headache associated with blurry vision, neck pain, numbness and tingling in her arms which was aggravated by movement. She refused epidural blood patch. Three days after delivery patient noticed diplopia upon central and lateral gaze bilaterally. Her diplopia persisted so she returned to the ED one week later. On physical exam, the patient was noted to have bilateral abducens nerve paralysis. The remainder of her neurologic exam was benign. Magnetic Resonance Imaging (MRI) showed pachymeningeal dural thickening and enhancement consistent with dural puncture during epidural anaesthesia⁴. Magnetic Resonance angiogram (MRA) and venogram (MRV) were normal.

Conclusion: We present a rare complication of bilateral abducens nerve palsy after epidural anesthesia. Diagnosis

requires a high degree of suspicion. Patients presenting within three weeks after an epidural with bilateral lateral rectus paralysis and severe headache should be evaluated for the diagnosis¹. MRI, MRA and MRV findings help to finalize the diagnosis.

References:

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- 2 Sabharwal, *Continuing Education in Anaesthesia, Critical Care & Pain*. 2011.
- 3 Kuczkowski, *Archives of Gynecology and Obstetrics*, 2007.
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- 5 Nishio, *Anesthesiology*. 2004.

M218. The Effect of Propofol on the Pain and Frequency of Chronic Headaches

Robert T. Knipe, Matthew Wicklund, David Giampetro, Amy Welch, Joseph Nguyen and Ashlee Pruett. Hershey, PA

Objective: In a real world setting, to learn the relationship of propofol on chronic headaches, whether there is a decrease in headache frequency and intensity following propofol sedation for endoscopies at two and thirty days.

Background: Migraine headaches can be debilitating with detrimental impact on work productivity, physical functioning, lifestyle, psychological well-being, and leisure activities. Of many studies on chronic headache treatment, few have evaluated the role of propofol. Krusz et al., reported dramatic abolition of ongoing migraine in patients treated with propofol in preparation for epidural and other nerve blocks.

Design/Methods: This is a prospective observational study with 25 patients. Patients, ages 18-75 years with chronic headaches, who were scheduled to undergo endoscopy with propofol sedation, were recruited from an outpatient endoscopy center. Patients were administered the Headache Impact Test (HIT-6) with baseline scores from 36-78. The HIT-6 is a validated measure that includes social-role functioning, pain severity, emotional distress and well-being, cognitive functioning, and vitality. The HIT-6 was completed before endoscopy and at 30 days post procedure. Additionally, patients were contacted two days post endoscopy with questions about their headaches using a verbal Likert rating scale from 0-10.

Results: At 2 days post endoscopy, 20/25 patients had a decrease in their headache pain score, and only 2/25 had an increase. The average pain reduction was 2.96 points on the Likert scale. At day 30, 18/25 had a reduction of the HIT-6 score, and only 6/25 had an increase. The average change was a reduction of 6.68 points, the largest decrease being 63. 7/18 patients had a decrease of at least 10 points with an average propofol dose of 310mg (versus 276.8mg for the entire cohort).

Conclusions: Propofol infusions may be helpful for multiple headache types, not just refractory migraine headaches. Propofol infusion may have lasting beneficial effect in some patients with chronic headaches.

M219. Diplopia in Children's Headache Drawings Differentiates Pseudotumor Cerebri from Migraine

Erica B. Lee and Carl E. Stafstrom. Baltimore, MD

Background: The features of headaches associated with pseudotumor cerebri (idiopathic intracranial hypertension) are nonspecific and difficult to distinguish clinically from migraines. Children's headache drawings have a high predictive value for migraine versus nonmigraine headaches (Stafstrom CE et al, *Pediatrics* 109:460-472, 2002). We hypothesized that drawings could help to differentiate pediatric headaches associated with pseudotumor cerebri from migraines.

Methods: Children aged 5-18 years attending a tertiary care pediatric headache clinic were asked to draw a picture of what their headache feels like. From our database of over 1200 headache drawings, those drawn by children with clinically diagnosed pseudotumor cerebri were compared to age-matched non-pseudotumor (migraine) drawings.

Results: 21 children with pseudotumor were identified (15 females), ranging in age from 6-18 years (mean $\pm$ SD, 13.9 $\pm$ 3.0). Pseudotumor drawings depicted: pounding pain (n=8), exploding pain (3), photophobia (7), dizziness (2), recumbency (1). Severe pain indicators included: hammers, bombs, a falling anvil, vise grip. Positive visual phenomena included scintillations, scotomata, or blurring (5). Most drawings by children with pseudotumor were similar to those drawn by children with migraines. However, 4 of the 21 (19%) pseudotumor drawings depicted diplopia (crossed eyes, double images), whereas none of 100 migraine comparison pictures depicted diplopia ($p < 0.001$).

Conclusions: Headache drawings by children with pseudotumor cerebri were similar to those drawn by children with migraine but diplopia was depicted only in pseudotumor cases. Diplopia is considered to be characteristic of pseudotumor, due to increased intracranial pressure affecting cranial nerve VI.

Health Services Research

M220. Cultural and Contextual Appropriateness of the NIHSS Naming List Test Among Stroke-Free Urban Blacks

Madeleine Gordillo. New York, NY

Background: The Naming List test in the best language subdomain of the National Institutes of Health Stroke Scale (NIHSS) card is a clinical assessment tool widely used to assess aphasia in stroke patients when performing an NIHSS assessment or a general neurological examination. While the NIHSS as a whole instrument has demonstrated good reliability and validity for assessing stroke severity, the Naming List component, which uses standardized figures, is vulnerable to cultural influence and has not undergone cross-cultural validation among urban Blacks.

Methods: We conducted in-person surveys on a random sample of urban Black residents to assess the cultural and contextual appropriateness of the 6-item NIHSS Naming List. All participants were English-speaking and at least 18 years old, with no history of stroke or cognitive dysfunction.

Participants completed a 22-item self-report questionnaire that included demographic information and the NIHSS Naming List test. Data were analyzed using univariate descriptive and chi-square statistics.

Results: A total of 190 urban Blacks were surveyed. Approximately 63% were female and more than 80% had completed at least a high school education. Overall, respondents correctly identified the majority of the NIHSS Naming List objects, although, the hammock (31.1%) and cactus (22.6%) were the most often misidentified. There was a significant association between education and incorrectly identifying the hammock ($X^2=11.19$, $p=.001$) and cactus ($X^2=8.23$, $p=.004$). Participants with a high school education or less were more likely to incorrectly identify these two items. In addition, the glove and feather were commonly interpreted with ambiguity. Specifically, 12.1% misidentified the glove, and of these 91% called the glove a hand. Similarly, 25.3% misidentified the feather, and of these 68.8% called the feather a leaf.

Conclusion: In this modest sample of stroke-free Urban Blacks, we found that the inclusion of a hammock and cactus on the NIHSS Naming list test may lead to false positive results and potential diagnostic error. The ambiguity regarding the interpretation of the glove and feather may also lower the sensitivity of this test. Our results suggest a need for psychometric analysis of this subdomain, including cultural and contextual adaptation of items.

Neuromuscular Disease

M221. De Novo PMP2 Mutations in Families with Type 1 Charcot-Marie-Tooth Disease

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Charcot-Marie-Tooth disease (CMT; also known as Hereditary Motor and Sensory Neuropathy; HMSN) is the name for inherited peripheral neuropathies that are not part of more complex syndromes. With an estimated prevalence of 1 in 2500 persons, CMT/HMSN is one of the most common neurogenetic diseases, and is subdivided according to clinical, electrophysiological, histological, and genetic features. CMT1/HMSN-I is a dominantly inherited demyelinating neuropathy, and is characterized by age of onset in first or second decade of life, nerve conduction velocities less than 38 m/s in upper limb nerves, and segmental demyelination and re-myelination with onion bulb formations in nerve biopsies. We performed whole exome sequencing on a patient with Charcot-Marie-Tooth disease type 1 (CMT1) and identified a de novo mutation in PMP2, the gene that encodes the myelin P2 protein. This mutation (p.Ile52Thr) was passed from the proband to his one affected son, and segregates with clinical and electrophysiological evidence of demyelinating neuropathy. We then screened a cohort of

136 European probands with uncharacterized genetic cause of CMT and identified another family with CMT1 that has a mutation affecting an adjacent amino acid (p.Thr51Pro) that segregates with disease. Our genetic and clinical findings in these kindred demonstrate that dominant PMP2 mutations are a new cause of CMT1.

M222. Understanding Molecular Basis of the Interplay Between Vulnerable Upper Motor Neurons and Innate Immunity

Hande Ozdinler. Chicago, IL

Amyotrophic lateral sclerosis (ALS) emerge as one of the most complex neurodegenerative diseases with the involvement of both upper and lower motor neurons as well as non-neuronal cells, each playing an important role for disease pathology. Even though the relationship and the communication between motor neurons and the non-neuronal cells are beginning to emerge, the cellular and molecular basis of the perturbed balance that leads to enhanced motor neuron death is not well understood. Astrocytes and microglia are important for maintenance and proper health of motor neuron circuitry, but in cases of diseases the interaction between the non-neuronal cells and the motor neurons are perturbed either leading to neuronal vulnerability or enhancing the ongoing degeneration. Corticospinal motor neurons (CSMN) are the key component of cortical component of the motor neuron circuitry that degenerate in ALS. We have evidence to show that their degeneration is an early event in ALS and that occur both due to intrinsic and extrinsic factors. The intrinsic factors are mediated via cellular events that are perturbed inside motor neurons that become vulnerable, and the extrinsic factors are mediated via non-neuronal cells that modulate innate immunity. One of the earliest events in vulnerable CSMN is the perturbation of ion influx and membrane potential, leading to an early hyperexcitation, and initiation of cascade of events that trigger many pathways that lead to neuronal vulnerability. At this time, the communication between CSMN and non-neuronal cells are also impaired and innate immunity is initiated much earlier than motor neuron death. As the neuron is trying to maintain its homeostasis, the non-neuronal cells already trigger "death" command and the relationship between the motor neuron and the non-neuronal cell is changed forever. Since motor neuron fails to maintain homeostasis and the non-neuronal cells become more aggressive and less supportive, the neuronal degeneration is accelerated at a cellular level. Understanding the basis of this communication and interaction is key for building effective treatment strategies for ALS and other motor neuron diseases.

M223. Targeting Safe Harbor Genomic Loci with Transcription Activator-Like Effector Nuclease (TALEN) Technologies to Produce Clinical-Grade Autologous Mesenchymal Stem Cell Therapies for Amyotrophic Lateral Sclerosis

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In human trials for the treatment of amyotrophic lateral sclerosis (ALS), penetrance of systemically delivered neurotrophic factors (NTFs) into the central nervous system (CNS) is limited by the blood-brain barrier. A cell-based system for the delivery of molecular therapies from within the CNS could improve efficacy through locally-directed and sustained bioavailability. We have recently completed a Phase I, dose-escalation safety trial using autologous, adipose-derived mesenchymal stem cells (adMSCs), injected into the intrathecal space by lumbar puncture in 27 patients with ALS. There was an excellent safety profile across a broad range of single and multiple doses. Our collaborative team is now using gene-editing technology to develop clinical-grade, genetically-modified autologous MSCs for use in ALS trials. The study objective is to modify human adMSCs by means of targeted gene-insertion into pre-defined 'safe-harbor' regions of the human genome using transcription activator-like effector nuclease (TALEN) reagents. TALEN technology is readily adaptable to current Good Manufacturing Practices (cGMP). Two candidate TALEN pair binding sites were identified for each of two safe harbor genomic loci, the AAVS1 (PPP1R12C) site on Chromosome 19 and the CLYBL site on Chromosome 9. Four pairs of TALEN plasmids were cloned. Human adMSCs were isolated from two normal control and two ALS patients. As adMSCs were resistant to chemical transformation, an electroporation protocol to efficiently deliver plasmid DNA to adMSCs was optimized. Cell viability, transformation efficiency, and TALEN pair cutting efficiency were measured 48 hours after electroporation. One TALEN pair at the AAVS1 locus was then selected on the basis of superior cutting efficiency, and was carried forward for detailed analysis of gene targeting and donor integration using a Red Fluorescent Protein (RFP) reporter fusion construct. Ongoing analyses include determining the efficiencies of on-target gene insertion versus off-target genomic modification, long-term rates of cell survival/apoptosis, and cell cycle disruption. Future directions will include developing cGMP protocols to establish the safety and reproducibility of high-throughput modified cell production. We anticipate that this technology will have broad applicability in a diverse range of neurologic conditions where direct delivery of agents into the CNS may improve the potential for therapeutic benefit.

M224. Identification of a Post-Translational Modification with Ribitol-Phosphate and Its Defect in Muscular Dystrophy

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Glycosylation is an essential post-translational modification that underlies many biological processes and diseases. α -dystroglycan (α -DG) is a receptor for matrix and synaptic proteins that causes muscular dystrophy and lissencephaly upon its abnormal glycosylation (α -dystroglycanopathies). Here we identify the glycan unit ribitol 5-phosphate (Rbo5P), a

phosphoric ester of pentose alcohol, in α -DG. Rbo5P forms a tandem repeat and functions as a scaffold for the formation of the ligand-binding moiety. We show that enzyme activities of three major α -dystroglycanopathy-causing proteins are involved in the synthesis of tandem Rbo5P. Isoprenoid synthase domain-containing (ISPD) is cytidine diphosphate ribitol (CDP-Rbo) synthase. Fukutin and fukutin-related protein are sequentially acting Rbo5P transferases that use CDP-Rbo. Consequently, Rbo5P glycosylation is defective in α -dystroglycanopathy models. Supplementation of CDP-Rbo to ISPD-deficient cells restored α -DG glycosylation. These findings establish the molecular basis of mammalian Rbo5P glycosylation and provide insight into pathogenesis and therapeutic strategies in α -DG-associated diseases.

M225. Spectrum of Non-Dystrophic Pediatric Muscle Channelopathies

Partha S. Ghosh and Fouad A. Alghamdi. Boston, MA

Introduction: The skeletal muscle channelopathies are a heterogeneous group of disorders whose clinical manifestations range from flaccid paralysis to myotonia.

Objective: To describe the spectrum of non-dystrophic muscle channelopathies in children.

Methods: Retrospective review of children with channelopathies diagnosed in a pediatric neuromuscular clinic. The diagnosis was established by clinical features, EMG findings and/or genetic testing.

Results: Thirty-one patients were identified in this cohort. Fifteen children had periodic paralysis (PP). Twelve of them had hypokalemic PP [CACNA1S-5, unknown genetic cause (3), Andersen-Tawil syndrome (KCNJ-3, not confirmed-1)]; EKG abnormalities were detected in 7; preventive treatment included acetazolamide (7) and spironolactone (1). Three children had hyperkalemic PP (SCN4A-3); clinical myotonia detected in 1 and preventive treatment included acetazolamide (1). Sixteen children had non-dystrophic myotonia. Six of them had chloride channelopathy [CLCN1, Thomsen disease (5), Becker disease (1)]; 5 had clinical myotonia and all had electrophysiological myotonia. Ten had sodium channelopathy [SCN4A, autosomal dominant myotonia congenita (8), paramyotonia (2)]; 8 had clinical myotonia and 7 had electrophysiological myotonia (EMG not performed-3). One presented with neonatal hypotonia, feeding and respiratory difficulties. Out of 16 children with non-dystrophic myotonia, 11 received treatment (Mexiletine-10, acetazolamide-1).

Conclusion: Non-dystrophic muscle channelopathies are a rare but distinct group of neuromuscular disorders in children with diverse clinical manifestations (PP, proximal weakness, myotonia, muscle hypertrophy, neonatal feeding and respiratory difficulties). Cardiac arrhythmias can be life-threatening in hypokalemic PP. Acetazolamide and Mexiletine are mainstays of therapy in PP and myotonia respectively.

M226. Diverse Etiologies of Hyperckemia in Children

Fouad A. Alghamdi and Partha S. Ghosh. Boston, MA

Introduction: Creatine kinase (CK) is a sensitive marker of muscle diseases.

Objective: To identify various etiologies of hyperCKemia in children.

Methods: Retrospective chart review of children with elevated CK evaluated in Neurology clinic over a 10 year-period. Elevated CK was defined as values >150 U/L (4-150) or >175 U/L (4-175) based on our laboratory controls.

Results: 1948 children with hyperCKemia were identified. Out of them 468 (24%) had various neuromuscular disorders: genetic myopathies (muscular dystrophies, congenital myopathies) either confirmed by genetic testing or suspected based on clinical features, EMG or muscle biopsy: 243 (52%); inflammatory myopathies (dermatomyositis, polymyositis/associated with other connective tissue disorders): 21 (4.5%); metabolic myopathies (glycogen/lipid metabolism disorders, mitochondrial myopathies, unspecified rhabdomyolysis): 115 (24.5%); muscle channelopathies (periodic paralysis, myotonic disorders): 24 (5%); infectious/drug induced myositis: 12 (2.5%); and neurogenic causes (spinal muscular atrophy, neuropathy): 53 (11.5%). These patients presented with one or more symptoms suggestive of muscle disorders (weakness, myalgia, cramps/stiffness, rhabdomyolysis). In addition, a significant proportion (1480, 76%) had miscellaneous causes (genetic/metabolic disorders, neurodevelopmental disorders, brain malformations/epilepsy, developmental delays/hypotonia, movement disorders, CNS infections, hypoxic/ischemic events, arthrogryposis) where symptoms for muscle disorders were nonspecific.

Conclusion: CK is an inexpensive screening tool to diagnose muscle disorders. HyperCKemia along with symptoms suggestive of muscle disorders increases final diagnostic yield of myopathies. Neurogenic disorders particularly spinal muscular atrophy can have high CK and mimic myopathies which should always be considered in the differential diagnosis.

M227. Hematopoietic Stem Cell Transplantation for Adolescent/Adult Cerebral and Olivo-Ponto-Cerebellar Adrenoleukodystrophy

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Background & Purpose: There have been accumulating evidences supporting the efficacy of hematopoietic stem cell transplantation (HSCT) for childhood cerebral adrenoleukodystrophy (ALD) when performed at an early stage of the disease. To date, there have been only two reported cases of adult cerebral ALD (ACALD) treated with HSCT and the clinical efficacy remains to be established. The purpose of this study is to evaluate the clinical efficacy of HSCT for adolescent/adult cerebral and olivo-ponto-cerebellar ALD.

Methods: To determine the optimum timing for HSCT, we have been following 31 ALD patients [adolescent cerebral ALD (n = 1), ACALD (1), adrenomyeloneuropathy (AMN) (12), AMN with later development of cerebral ALD (AMN-Cer) (9), olivo-ponto-cerebellar ALD (OPC)

(3), OPC-Cer (2), Addison only (2) and presymptomatic male (1)] in a prospective manner. The average observation period was 5.8 years. The patient has been observed at the interval of 3-6 months to detect appearance of the early cerebral symptoms. Indications for HSCT include an early stage of the disease and the presence of enlarging white matter lesions. Conditioning regime included intravenous busulphan and cyclophosphamide, or fludarabine and melphalan with total body irradiation with brain shielding, or total lymphoid irradiation. We performed chimerism analysis of peripheral blood leukocytes after HSCT. PCR products of *ABCD1*, the causative gene of ALD, were subjected to deep sequencing employing MiSeq

Result: We performed HSCT for 5 patients who developed cerebral form and a patient who develop OPC at an early stage. 4 patients received HSCT from 8/8 HLA-matched unrelated donor, and 2 patients from one HLA-DR-mismatched unrelated donor. Observation periods after HSCT for each patient are 8, 4, 2.5, 2 and 0.5 years with stable clinical courses. The other with OPC is 1.5 months after HSCT with stable clinical course. Enhancement on brain MRI remains disappeared after HSCT with no enlargement of white matter lesions. White matter lesions reduced after HSCT in 3 patients. The ratios of wild type to mutant type *ABCD1* sequences were less than 1% in cases 1, 2, 3 and 4 after HSCT in chimerism analyses of peripheral blood leukocytes. Cases 5 and 6 are just after HSCT.

Conclusion: The present study suggests the efficacy of HSCT for adolescent/adult cerebral ALD. It is important to determine the optimum timing of HSCT for cerebral ALD to accomplish a good outcome from HSCT.

M228. Familial Inclusion Body Myositis Associated with Digenic Inheritance of Mutations in Valosin-Containing Protein and Filamin C

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Sporadic inclusion body myositis (sIBM) is the most common acquired myopathy in Caucasians over age 50 and is typically distinguished from hereditary inclusion body myositis (hIBM) by later age of onset, lack of family history, characteristic pattern of weakness involving the quadriceps and finger flexors, and presence of autoinvasive endomysial inflammation on muscle biopsy. While the cause of sIBM is unknown, genetic susceptibility is thought to play a role based on the association of specific major histocompatibility complex haplotypes with sIBM. In addition, rare families with multiple members displaying an sIBM phenotype have also been described (termed familial IBM), although causative genes have not been determined. Here, we describe a large family with multiple members who developed an sIBM-like pattern of weakness in their 50's and who meet ENMC 2013 diagnostic criteria for sIBM. Multiple family members were found to have a pathogenic variant of

valosin-containing protein (VCP) (R159C), however this did not fully segregate with disease. Whole exome sequencing revealed an additional novel variant in filamin C (FLNC) (F2616S) in multiple family members, and the combination of these two variants co-segregated with the sIBM phenotype. Mutations in VCP cause “multisystem proteinopathy” with IBM, Paget’s disease of bone and frontotemporal dementia as common presenting features. The R159C mutation in particular has been associated with the broadest phenotypic spectrum, also including amyotrophic lateral sclerosis, Parkinson’s disease and hereditary spastic paraparesis, although no members of this family developed evidence of cognitive dysfunction, motor neuron disease or movement disorder. FLNC mutations have been described in myofibrillar myopathy with clinical and pathological overlap with hIBM. We propose a digenic mode of inheritance in this family, wherein VCP R159C is necessary but not sufficient for weakness, and disease penetrance is increased by the additional presence of the FLNC F2616S variant.

M229. Quantification of Proximal Nerve Pathology in Charcot-Marie-Tooth Diseases via Magnetization Transfer MRI

Richard D. Dortch, Lauren Brooks and Jun Li. Nashville, TN

Introduction: The overall goal of this work was to evaluate a novel quantitative magnetization transfer (qMT) MRI protocol of the human sciatic nerve (SN) as a potential biomaterial in Charcot-Marie-Tooth (CMT) diseases. Current tools for assessing CMT diseases target distal nerves, which are often severely degenerated and, therefore, unavailable for evaluation. We previously developed a magnetization transfer ratio (MTR) MRI protocol for detecting myelin content changes (from de/dysmyelination and/or axonal loss) in proximal nerves, which are partially preserved in CMT due to its length dependent nature. Although MTR values related to impairment, they were also sensitive to hardware/experimental parameters, making multi-site longitudinal studies difficult. Quantitative MT (qMT) methods offer objective measures of myelin content with reduced sensitivity to these experimental factors at the cost of increased scan times and complexity. In this work, i) the feasibility of performing qMT in human SN was evaluated and ii) preliminary data were acquired in a cohort of patients with CMT.

Methods: qMT data were collected at 3.0T (Philips Achieva) in nine healthy volunteers (23-35 y.o.) and five CMT1A patients (19-60 y.o., clinical portion of CMT neuropathy score, or CMTNS=2-21) from mid-thigh to the knee. In all subjects, fat-suppressed volumes with 17 different MT-weightings were acquired (resolution=1x1x6 mm³, scan time=9 min). Independent measures of T₁, B₁, and B₀ are required for the qMT model and were, therefore, collected in the same volume. Mean SN signal intensities for the qMT and T₁ data were then fit to a two-pool model of MT (with B₁ and B₀ corrections) to determine the macromolecular/water pool-size-ratio (PSR), which is sensitive to myelin content changes from dysmyelination or axonal loss.

Results: Mean SN PSR values were reduced in the CMT1A patients ($5.8 \pm 1.4\%$) relative to controls ($10.4 \pm 1.6\%$). In addition, a trend of correlation between PSR and the CMTNS was observed in patients with CMT1A (PSR= $5.2 \pm 0.9\%$ for patients with CMTNS ≥ 10 , PSR= $6.2 \pm 1.8\%$ for patients with CMTNS < 10).

Conclusions: These results demonstrate the feasibility of performing high-resolution qMT in the SN of patients with CMT1A within clinically feasible scan times. This technique is being applied to a larger cohort to determine if PSR is significantly related to CMTNS. In addition, novel optimization methods are being evaluated to reduce scan times. If successful, PSR may be a viable biomarker of proximal nerve pathology for future multi-site longitudinal studies of CMT.

Study Supported by: NIH/NIBIB K25-EB13659 and NIH R01-NS066927.

M230. Clinical and Electrodiagnostic Correlations of Paraproteineic Neuropathies

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Background: Paraproteineic neuropathies show varied clinical and electrophysiological presentation. Early diagnosis is required for specific treatment of underlying disease.

Objective: To perform an institutional based retrospective chart review to correlate the clinical presentation and electrodiagnostic features of neuropathies in patients diagnosed with monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), Waldenstrom’s macroglobulinemia (WM), and Polyneuropathy, organomegaly, endocrinopathy, M protein and Skin changes (POEMS).

Methods: Retrospective chart review of patients seen at an academic neurology practice for monoclonal gammopathies (MGUS, MM, WM and POEMS) and neuropathy over 10 year period (2005 to 2015). Patients were grouped into malignant (MM, WM, POEMS) and non-malignant paraproteinemia (MGUS) determined by immune diagnosis (immunofixation, electrophoresis) and associated clinical features. Neuropathy diagnosis was based on clinical and electrodiagnostic characterization and exclusion of potential other etiologies. Study was approved by the Institutional Review Board.

Results: Twenty nine of 45 subjects were included in the analysis, 20 (69%) presented with MGUS, 4 (14%) with MM, 4 (14%) with WM and 1 (3%) with POEMS. Age range 32- 85 (mean 65) with female predominance (16/29). Initial symptoms were distal numbness and paresthesia. IgG heavy chain/IgG kappa was associated primarily with length dependent axonal sensory peripheral neuropathy while a demyelinating sensorimotor polyneuropathy was seen with IgGHC/IgG lambda MGUS. Patients with elevated IgM levels had demyelinating sensorimotor neuropathy and small fiber neuropathy. Three patients with MGUS (IgM-Kappa) had positive anti MAG antibodies. All MM had clinical evidence of large fiber sensorimotor neuropathy. Four patients with WM showed symptoms of severe small fiber neuropathy. The patient with POEMS had severe distal paresthesia

and was found to have a median and ulnar mononeuropathy as well.

Two patients with anti-MAG IgM paraproteinemia were not treated and one with symptoms suggestive of small fiber neuropathy treated with rituximab, steroids and intravenous immunoglobulin with no clinical response. MM, WM and POEMS were treated with chemotherapy per protocol and symptomatically for the neuropathy.

Conclusion: Paraproteinemic neuropathies are rare but when suspected, need to be carefully characterized to facilitate timely treatment. Almost all patients identified in our cohort had first presented with neuropathy symptoms and etiological work up revealed the hematological diagnosis leading to treatment as needed. Our cohort analysis is comparable to data presented in the literature. Future studies are planned to evaluate neuropathy as early sign of paraproteinemic disorders and correlation with disease progression in individual patients.

Autoimmune Neurology

M231. Transverse Myelitis in Veterans

Verena C. Samara, Michael Sweeney, Haley Carlson, M. Mateo Paz Soldan, John E. Greenlee, Noel G. Carlson, John W. Rose and Stacey L. Clardy. Salt Lake City, UT

Background: Transverse myelitis is a neurological condition that is caused by inflammation throughout a segment of the spinal cord that causes demyelination as well as axonal and neuronal injury. Resulting symptoms include pain, weakness, and abnormal sensation, incontinence and paralysis. TM may arise from many etiologies including immune-mediated, vascular, paraneoplastic, infectious and post-infectious disorders.

Objectives: To describe demographics and clinical data in a cohort of patients with transverse myelitis (TM) in the VHA population. The Veterans Health Administration (VHA) population represents America's largest integrated health care system with 1700 sites, serving 8.76 million Veterans annually.

Methods: Retrospective review of patient's charts with at least one of several ICD-9 codes queried to designate TM evaluated at VHA Clinics and Hospitals. To capture as many true TM cases as possible, we identified over 4,000 unique patients with ICD-9 codes consistent with possible TM within the VHA System, and retrospectively reviewed each case and characterized it as TM or other neurologic disease.

Results: The TM cases are described in detail in terms of relevant demographic and clinical data. The large majority of patients were male, in keeping with the demographics of the VA population. Etiologies identified included multiple sclerosis, neuromyelitis optica, Sjogren's syndrome, systemic lupus erythematosus, sarcoidosis, infectious and post-infectious, radiation-induced, post-vaccination, paraneoplastic, and idiopathic.

Conclusions: This is the first comprehensive characterization of TM in the VHA Veteran population. Patients with TM within the VHA system provide a population for long-term evaluation of disease characteristics and response to treatment.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? -Verena C. Samara - nothing to disclose

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M232. The Burden of Neuromyelitis Optica Spectrum Disorder on Patients' Quality of Life

Maureen A. Mealy, Alexandra Simpson, Dorlan J. Kimbrough and Michael Levy. Baltimore, MD and Boston, MA

Background: Neuromyelitis optica spectrum disorder (NMOSD) is an immune-mediated disorder of the central nervous system (CNS) that preferentially affects the spinal cord and optic nerves and is distinct from multiple sclerosis (MS). Historically, brain lesions were thought to be uncharacteristic of NMOSD, but the discovery of the highly-specific antibody against aquaporin-4 associated with NMOSD has enabled clinicians and researchers to better characterize the disease, allowing for a broader spectrum that includes brain disease. Compared to MS and transverse myelitis (TM), the impacts of fatigue and depression on quality of life in NMOSD patients have been inadequately investigated and have yielded equivocal results. This study aims to better elucidate our understanding of the relationship that pain, disability, depression and fatigue have on quality of life in NMOSD patients compared to TM and MS.

Design/Methods: We contacted 81 patients who were seen at the Johns Hopkins Hospital for the diagnoses of NMOSD (n=36), TM (n=16) and MS (n=29). Data were collected via online surveys. Pain, depression, fatigue, and disability were assessed using the Brief Pain Inventory (BPI) short form, Beck Depression Inventory-II (BDI-II), Fatigue Severity Scale (FSS), and patient-administered Expanded Disability Status Scale (pEDSS).

Results: We did not find a significant differences between disease groups on any psychological outcome measure in this limited sample size, we did observe several trends. First, NMO and TM patients had higher levels of disability and pain severity than MS patients, yet MS and TM patients displayed more fatigue and depressive symptomatology than NMO patients. Relationships between disability scores and the psychological outcome variables (BDI, FSS, and BPI scores) were assessed by correlational analysis. We found that disability correlated with measures of depression ($r = +0.56$), fatigue ($r = +0.42$), pain severity ($r = +0.50$) and pain interference ($r = +0.42$) in the MS group.

Conclusions: NMOSD patients were more disabled and had greater pain severity, but they were less depressed than MS and TM. Further studies are needed to understand the relationships among these quality of life factors.

M233. The Etiology of Acute Encephalitis in Korean Population

Tae-Joon Kim, Jangsup Moon, Jun-Sang Sunwoo, Jung-Ick Byun, Jung-Ah Lim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea and Seongnam, Republic of Korea

Recently the spectrum of acute encephalitis is widened including autoimmune and paraneoplastic encephalopathy as well as new emerging infectious etiologies. Herein, we comprehensively investigated the etiology of acute encephalitis in Asian patients.

We prospectively enrolled patients in two prospective observational registries in a tertiary single center; one is autoimmune synaptic and paraneoplastic encephalitis registry and the other is infection registry. Consecutive patients with possible autoimmune/paraneoplastic neurological syndromes infectious encephalitis who visited the Seoul National University Hospital between June 2012 and May 2015 were included in the registries, respectively. The antibodies including neuronal surface (NMDAR, LGI1, CASPR2, AMPA1, AMPA2, and GABAB-R) and onconeural (anti-Hu, -Yo, -Ri, -Ma2, -CV2/CRMP5, and -amphiphysin) antibodies were tested for suspicious autoimmune/paraneoplastic patients.

Total 59 patients were identified; mean age was 49.0 ± 21.1 and 61.0% were male. Etiologies comprises infectious (n = 18, 30.5%), autoimmune (n = 14, 23.7%) and unknown/others (n = 27, 45.8%). There was no patient with acute encephalitis of paraneoplastic origin. Patients with autoimmune syndromes (mean age 47.6 ± 22.7) were younger than infectious encephalitis patients (mean age 52.5 ± 19.9). In addition, autoimmune encephalitis had female predominance (71.4% versus 44.4% in infectious origin). Epidemiology of unknown origin was similar to autoimmune syndromes, but the presenting symptoms of unknown origin were closer to infectious origin. Autoimmune syndromes included 6 anti-NMDAR, 4 anti-LGI1 and 4 anti-GABAB-R encephalitis patients. Infectious etiologies were 12 viral, 2 bacterial, 2 fungal, 1 rickettsia and 1 parasite.

In this study, the autoimmune encephalitis comprised nearly one fourth of the total acute encephalitis patients in Korean population visiting a tertiary center. These results indicate that the autoimmune etiology has to be significantly considered in managing acute encephalitis. The clinical manifestations and prognostic factors were to be investigated and added to the results.

M234. Recurrent Asystole in Paraneoplastic anti-N-methyl-D-aspartate Receptor Encephalitis Necessitating Permanent Pacemaker Placement

Prachi Parikh and Jinny Tavee. Cleveland, OH

Objective: We report a case of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis with persistent episodes of cardiac conduction block and asystole despite teratoma removal and immunotherapy.

Methods: Case report and review of the literature

Case: A 22-year-old woman was transferred from an outside hospital for bizarre behavior, hallucinations and agitation that evolved to episodes of obtundation and seizures requiring intubation. On examination the patient grimaced to pain, but did not follow commands or make eye contact. The patient also demonstrated intermittent rotatory nystagmus, diffuse hypertonia and hyperreflexia with ankle clonus. Continuous telemetry revealed multiple episodes of sinus bradycardia (34 beats-per-minute [bpm]) and second-degree atrioventricular block followed by sinus tachycardia (131bpm). Diagnostic evaluation revealed an elevated anti-NMDA antibody titer of 1:64 in the CSF and an ovarian teratoma on CT, which was surgically excised. On post-operative day one, the patient had recurrent episodes of asystole, the longest lasting 60 seconds requiring CPR and temporary pacemaker placement. She was treated with pulse dose intravenous corticosteroids and plasmapheresis with minimal improvement. Intravenous immunoglobulin (2gm/kg) was then given followed by rituximab. As the cardiac parameters appeared to have stabilized, the temporary pacemaker was removed. Within hours, the patient had a two-minute episode of asystole that required resuscitation. She subsequently underwent permanent pacemaker placement. The patient slowly improved after her second dose of rituximab and by discharge one month later was able to follow minimal commands and was seizure free on anti-epileptic medications.

Discussion: The etiology of cardiac arrhythmias in anti-NMDAR encephalitis is unclear and may be related to autonomic dysregulation. One hypothesis is that the NMDA receptors found in the nodose ganglion (which contains the cell bodies of vagal afferents) and the solitary nucleus (which contain their target neurons) may serve as targets for anti-NMDAR antibodies. NMDA receptors are also present in the insular cortex where they have been shown to modulate the baroreflex in unanesthetized rats. As NMDA antagonists have been shown to cause reflex bradycardia in these rats, it is possible that immune-mediated damage of these receptors via anti-NMDAR antibodies may have a similar effect.

Conclusion: This is the first case of anti-NMDAR encephalitis requiring permanent pacemaker placement due to recurrent episodes of prolonged asystole despite teratoma removal and aggressive immunotherapy. As clinical recovery in these patients is often prolonged and unpredictable, careful ongoing cardiac monitoring is warranted even after optimal surgical and medical management.

Dementia and Aging

M235. Cognitive Impairment in Spinal Cord Injury: Impact on Quality of Life and Activity Limitation

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Background: Most of the cognitive test batteries require adequate hand control. This restricts their use in people with Spinal Cord Injury (SCI) who often have poor hand functions. The impact of cognitive impairment on quality of life (QoL) in this population is also not known.

Aim: The aim of this study was to test the cognitive ability of people with SCI patients using the Edinburgh Cognitive and Behavior Screen (ECAS), designed for individuals with motor neuron disease with limited hand motor functioning. The impact of cognitive dysfunction on QoL and activity limitation was also assessed.

Participants and Methods: Forty one consecutive patients with SCI were assessed using ECAS, the brief version of World Health Organisation Quality of Life questionnaire (WHOQOL-BREF) and the Spinal Cord Independence Measure (SCIM), respectively.

Results: All participants could complete ECAS. 28 of the 41 participants scored below the cut off threshold for cognitive impairment in ECAS. The domains affected were language-63%, memory-51%, executive function-44%, verbal fluency-44% and visuospatial skills-24%. On multiple regression analysis ECAS Total and SCIM Total could moderate-strongly explain the variance in the WHOQOL-BREF Psychological domain. Age and ECAS Total score had a significant influence on the WHOQOL-BREF Environmental domain. Multiple regression analysis did not find any effect on the WHOQOL-BREF social domain or physical domain. The cognitive impairment did not have significant impact on SCIM.

Conclusion: It was feasible to use ECAS for testing cognition in individuals with SCI. The cognitive ability influenced the QoL of people with SCI.

M236. Hypoxia Inducible Factor 1 α Mediates Neuroprotective Role in Rat Model of Chronic Cerebral Hypoperfusion

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Background And Objective: We have previously shown that chronic global cerebral hypoperfusion triggered long-lasting accumulation of HIF-1 α protein in rat hippocampus. However, the exact role of the stabilized HIF-1 α in Chronic Cerebral Hypoperfusion (CCH) is unknown. The aim of our study was to ascertain the role of endogenous HIF-1 α stabilization during chronic cerebral hypoperfusion in rats.

Methods: Lentivirus expressing HIF-1 α small hairpin RNA was injected into bilateral hippocampus and bilateral ventricles to knock down HIF-1 α gene express in hippocampus and some other brain areas. One week following the injection, permanent bilateral common carotid artery occlusions (2-vessel occlusions (2VOs)) were performed to induce CCH in male adult Wistar rats. Four weeks later, we assessed the effect of HIF-1 α knockdown on cerebral capillary density, oxidative stress, histopathological changes of the brain, and cognitive function.

Results: After 2VO, rats with lentivirus-mediated HIF-1 α knockdown showed significantly reduced cerebral capillary density, increased oxidative damage, and increased density of

astrocytes and microglia in cortex and some subregion of hippocampus. Furthermore, HIF-1 α knockdown also aggravated consequential spatial learning and memory impairment induced by 2VO.

Conclusion: Our findings suggest that HIF-mediated pro-survival responses are dominant in rats with CCH. The accumulated HIF-1 α after CCH mediates endogenous adaptive process to defend against more severe hypoperfusion injury of brain.

Key words: Chronic Cerebral Hypoperfusion, Hypoxia Inducible factor 1 α (HIF-1 α), neuroprotective, cognition

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M237. Clip Test: Manipulospacial and Language Correlates

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Background: In a previous study we demonstrated that the "Clip Test", a simple test evaluating complex motor behavior, could be useful in helping to distinguish normal cognitive aging, mild cognitive impairment, and Alzheimer's disease. The current report presents results of a finer-grained analysis of cognitive features of this test, specifically with regard to manipulospacial behavior, memory, and auditory comprehension.

Participants: 276 consecutive adults aged 43-94 years (mean age 79.7 ± 7.5) who presented themselves to a Neurology Clinic with a complaint of memory disorder were included. Sample comprised 105 men (78.6 ± 7.3), 171 women (80.4 ± 7.2).

Methods: All participants were administered the following tests: clip test, MMSE, ADAS-cog, and Kohs' Block design test. Time required to complete the clip test was used to divide the subjects into 3 groups: A, below 200 seconds; B, 201-400 seconds; C, greater than 400 seconds. Mean scores of performance for each of the cognitive tests of each group were computed. Correlations of performance for each test with performance on the clip test were determined by means of polytomous logistic regression analysis.

Results: In all groups, statistically significant correlations were found for slowness of clip test performance and poor performance on Kohs' blocks and on the test of auditory comprehension. No other significant correlations were found.

Conclusions: These findings confirm the clinical relevance of the clip test as a useful simple clinical test of manipulospacial and linguistic behavior. Additionally, they provide further support for the recently proposed theory of "neural multifunctionality", wherein language functions and non-linguistic cognitive functions are mutually dependent. (The REF to the multifunctionality paper is Cahana-Amitay and Albert, 2014. It is available online.)

M238. Proximal Middle Cerebral Artery Velocity Is Associated with Mean Diffusivity on Brain MRI in Women with HIV

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Cognitive impairment is prevalent in HIV even among patients well treated with combined antiretroviral therapy (cART) who have had sustained viral suppression. Brain vascular disease, possibly exacerbated by the HIV virus, chronic inflammation, and/or toxicity from cART, may contribute to cognitive impairment. Previous studies have focused on carotid disease and shown that carotid lesions accounted for as much variance in cognitive score as AIDs. However, data on the relationship between intracranial large vessel function as assessed by middle cerebral artery velocity (MCA-V) and brain structure in HIV are lacking. To obtain these data, women were recruited from the Brooklyn site of the Women's Interagency HIV study (WIHS) as part of a study of vascular disease and cognition. Measures of white matter integrity, mean diffusivity (MD), and fractional anisotropy [FA] were obtained from 3T MRIs and brain volumes were determined. MCA-V was measured with transcranial Doppler. The relationships between MCA-V and outcomes (quantitative MRI measures) were analyzed with partial correlation analyses controlling for intracranial volume, age, and history or presence of hypertension. A complete dataset was available on 40 age-matched women (26 HIV-infected and 16 HIV-uninfected). The mean age of the participants was 44.5 (SD = 7.3) years. MCA-V was 64.6 (15.7) cm/sec and not associated with HIV-infection, hypertension, or age. MCA-V was associated with mean diffusivity ($R = -.54$, $p = 0.001$), fractional anisotropy ($R = 0.33$, $p = 0.04$), and white matter hyperintensities ($R = -.31$, $p = 0.05$). MCA-V was also associated with cortical volume ($R = 0.32$, $p = .04$), subcortical volume ($R = 0.49$, $p = 0.001$), total gray volume ($R = 0.32$, $p = .03$), but not the hippocampus ($R = 0.18$, $p = .28$) or caudate ($R = 0.06$, $p = 0.73$). This study showed that MCA-V was associated with measures of white matter integrity and brain volume in women with HIV. However, it is not clear if these associations are simply due to neurovascular coupling or whether decreased MCA-V may have a causative role in brain degeneration. Longitudinal studies are needed to answer this question.

M239. White Matter Differences Between Dementia with Lewy Bodies and Parkinson's Disease: A Diffusion Tensor Image Study

Jingping Shi, Dayong Sun, Donglin Zhu and Chaoyong Xiao. Nanjing, Jiangsu, China

Background: Accurate clinical diagnosis of dementia with Lewy bodies (DLB) is important due to the differences in prognosis and management compared with Parkinson's disease (PD). However, because of considerable clinicopathologic overlap, the differential diagnosis between DLB and

PD based on established clinical criteria is often difficult at early stages.

Objective: To investigate micro-structural white matter differences between DLB and PD.

Methods: Diffusion tensor imaging (DTI) was performed on 10 patients with DLB, 16 patients with PD and 16 controls. A whole-brain automated analysis of DTI data was performed by tract-based spatial statistics (TBSS) to compare differences in fractional anisotropy (FA) and mean diffusivity (MD) between the three groups. Clusters showing diffusivity abnormalities were used as region of interests for correlation analysis.

Results: FA/MD values in left inferior longitudinal fasciculus (ILF) and left inferior fronto-occipital fasciculus (IFO) in DLB were significantly different from PD or controls, but these significant differences were not found between PD and controls. For DLB group, FA values in left ILF and IFOF were significantly correlated negatively with disease duration (all $r = -0.708$; $P < 0.05$), and MD values in the left ILF correlated positively with the motor part of the Unified Parkinson's Disease Rating Scale ($r = 0.682$; $P < 0.05$).

Conclusions: These findings indicated that the abnormalities of left ILF and IFOF were specific for DLB relative to PD or controls, and seemed to be promising for differential diagnosis.

M240. Alabama Brief Cognitive Screener Demonstrates a Factor Structure Similar to the MMSE and Shows High Levels of Internal Consistency at Multiple Levels

Marissa C. Natelson Love, Giovanna Pilonieta and David S. Geldmacher. Birmingham, AL

Background: The Alabama Brief Cognitive Screener (ABCs) was developed as an alternative to the Mini Mental State Exam (MMSE) for use in an electronic health record. It is based on a 30 point scale and intended to closely replicate the scoring distribution of the MMSE. Preliminary results indicate that ABCs scores correlate with scores on the Functional Activities Questionnaire at a level commensurate with other comparisons of cognitive and functional measures in mild cognitive impairment and dementia. We next wished to understand the factor structure and internal consistency of the ABCs instrument.

Methods: ABCs data were analyzed from 1047 individuals receiving care at the University of Alabama at Birmingham Memory Disorders Clinics with diagnosis of mild cognitive impairment (MCI), Alzheimer dementia (AD), dementia, and cerebral degeneration.

Results: Mean ABCs score was 20.3 (SD 6.4). Mild decrements (ABCs=24-29) were observed in 413 patients, moderate decrements (scores 15-23) in 419, and severe decrements (scores 0-14) in 215. Factor analysis identified three factors that explained approximately 63.04% of the total variance. These factors represent 1) orientation and delayed recall (42.2%), 2) immediate memory and naming (12.3%), and 3) attention and working memory (8.4%). Reliability/internal consistency analysis demonstrated standardized Cronbach's $\alpha = 0.841$. Standardized alpha values for

each of the 10 cognitive domains evaluated by the ABCs range from 0.82-0.834.

Conclusions: The ABCs demonstrates a factor structure similar to the MMSE and shows high levels of internal consistency at multiple levels including 1) whole test, 2) by cognitive domain, and 3) dementia diagnoses. It appears less reliable in MCI. This is likely due to heterogeneity in causes of MCI in the Memory Disorders Clinics, and that the ABCs was not designed around detection or classification of MCI. Other tests such as the Montreal Cognitive Assessment and the St Louis University Mental State test may be superior for MCI.

M241. The Robotic Assistant for MCI Patients (RAMCIP) with Proactive Functions

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Introduction: Robotic Assistant for MCI Patients at home (RAMCIP) is a three-year research project within the HORIZON2020 programme funded by the European Commission, (started in January 2015) with the aim of develop a novel robot that can provide assistance to elderly people with MCI and early AD. at their homes, allowing them to maintain an independent living and quality of life. Technical solutions are built based on the specific user requirements. However, due to different attitudes towards new technology among them, conservative realization of user requirements should be replaced by proactive robot behaviour. The aim of our study was to indicate which user requirements for MCI and early AD population depend on the patients attitudes.

Methods: Based on workshops performed in two centers (Poland and Spain) we created surveys for the patients. The main themes of the surveys were: functional requirements; human-robot interaction and user acceptance aspects. Simultaneously, different technology attitudes and questions were addressed. Based on received data, user requirements were prioritized and compared with positive and negative users attitudes.

Results: We gathered 83 completed surveys from the mild cognitive impairment and early Alzheimer disease patients. Users with positive attitudes compared to the rest of the group gave higher level of priority to user requirements connected with direct physical interaction and entertainment provided by the robot. Additionally, they more frequently indicated that these function should be provided autonomously than only on demand.

Conclusion: User attitudes towards new technology influence some aspects of human-robot interaction and connected with them user requirements. Results highlight a value of proactive function of the social assistive robots and can contribute to an increased rate of users acceptance.

On behalf of RAMCIP Group.

Education

M242. U.S. China Neurology Exchange Program to Improve Clinical Practice, Research, and Global Relationships

Antonio Moya, Richard Isaacson and Dexter Sun. New York, NY

Background: Global neurology, which transcends national borders and prioritizes health equity for people worldwide, is a growing sub-specialty in neurology. This burgeoning field has been integrated into neurology programs nationwide, attracting physicians who want to understand the inner workings and challenges of low and middle income country health systems. The Weill Cornell Neurology Program has developed a new neurology exchange program with Zhejiang University in Hangzhou, China that can be used as a template for other programs seeking to integrate global neurology into its training curriculum.

Methods: Over a three week period, a Cornell neurology resident or fellow travels to Zhejiang University, Hangzhou, China and participates in neurology rounds, clinic, as well as teaching of medical students at the university. This physician also spends one week learning in one of the rural hospitals in Jiangshan. The physician is required to give three presentations during the exchange, one of which is a clinical case presentation, the other of which is a research presentation, and a third on lessons learned from the elective. In exchange, a Zhejiang University resident or fellow travels to New York City to present analogous presentations and be engaged in neurologic clinical discussion and research at Weill Cornell. Two residents or fellows each year from each program are involved in this exchange.

Results: The program highlights three main objectives specific to U.S.-China neurology practice 1) improve clinical care through exchange of the most up-to-date, evidence-based medical information from each country 2) foster cultural and language enrichment 3) underscore lessons learned from each respective medical system (e.g. cost-effective care strategies used in China and U.S. medical education standardization) taking into account different patient-care models, namely the more individualized U.S. patient care model versus the more community-driven health care model in China. A report of this experience is distributed amongst faculty for critique, further discussion, and publication.

Conclusion: By establishing this neurology exchange program between these two universities, a template of a successful global neurology program has been created for other medical universities in the U.S. and China. The aforementioned objectives must be consciously revisited during and after the rotation and addressed in an end-of-the-rotation report. Through such exchange programs, neurology residency programs can equip neurologists with the experience to improve clinical practice, research, and collaboration worldwide.

Headache and Pain

M243. Bilateral Cisternal Abducens Nerve Involvement with Ophthalmoplegic Migraine

Richa Tripathi and Evanthis Bernitsas. Detroit, MI

Objective: To report rare imaging finding in patient with Ophthalmoplegic migraine.

Background: Ophthalmoplegic migraine is a rare condition which presents as headaches and ophthalmoplegia. It affects more commonly the oculomotor nerve, followed by the abducens and the trochlear nerve. There has been one case report of enhancement of cisternal portion of the abducens nerve. Here we present another such case with bilateral abducens nerve enhancement on magnetic resonance imaging.

Design/Methods: A 36 year old right handed woman presented with left-sided pounding headaches associated with nausea. She complained of subjective diplopia since several weeks. She denied floaters, focal weakness, paresthesias, speech or swallowing problems. She did not have recent illness, travels or immunizations. Examination revealed restricted left eye abduction and right eye adduction on horizontal gaze. A spinal tap was performed to rule out other causes of ophthalmoplegia and headache. Cerebrospinal fluid was sent for inflammatory markers and infectious causes. Blood work for ANA, ENA, paraneoplastic panel, GBS and variants was sent. Imaging of her brain was also performed.

Results: CSF study revealed normal cell count, glucose, protein level and absent inflammatory markers. Antinuclear antibody, ANCA, dsDNA, IgG index, VZV, HSV, co GM1 triad, Lyme screen and western blot, TSH, vitamin B1, hemoglobin A1c, paraneoplastic panel were all within normal range. Magnetic resonance imaging (MRI) scan of the brain showed presence of bilateral abducens nerve enhancement in the cisternal portion of the nerves.

Conclusion: We present rare involvement of cisternal portion of the abducens nerve in the ophthalmoplegic migraine.

M244. Trigeminal Neuralgia with TS-HDS Antibodies

Syeda Alqadri and Raghav Govindarajan. Columbia

Background: Trisulfated heparin disaccharide (TS-HDS) IgM antibodies are associated with painful sensory neuropathies and in some cases more generalized pain symptoms. Here we report two cases who presented with clinical features of trigeminal neuralgia and had highly elevated TS-HDS IgM antibodies and responded to immune therapy.

Cases:

Case 1: A 42-year-old lady with a history of Hashimoto's thyroiditis presented with a 4-month history of sudden sharp pain lasting few seconds on the right side of the face. Initially the attacks were once a day but in the last month she has had multiple attacks almost to the point that even speaking loudly could trigger the pain. She had been diagnosed with trigeminal neuralgia and started on carbamazepine currently on 600mg BID, gabapentin 1200mg BID, baclofen 20mg BID with no relief of pain. MRI brain was normal. Given her history of autoimmune disease she was tested for TS-HDS which was elevated (1:10000, Washington University in St. Louis lab). She was treated with weekly IV steroid infusions for 2 months followed by every other week for two months and currently on monthly infusion. The attack frequency reduced to once a month and she is currently only on gabapentin 1200mg BID.

Case 2: A 48-year-old lady with a history of celiac disease (antibody positive, biopsy proven, on diet control) presented with a 16-month history of sudden sharp pain lasting few seconds on the right side of the face. Initially the attacks were once or twice a day but in the last 6 months she has had multiple attacks almost to the point that even chewing soft food could trigger the pain. She had been diagnosed with trigeminal neuralgia and started on carbamazepine currently on 800mg BID, gabapentin 1200mg TID, baclofen 20mg BID, oxycodone 15mg q4hrs as needed with no relief of pain. MRI brain was normal. Given her history of autoimmune disease she was tested for TS-HDS which was elevated (1:20000, Washington University in St. Louis lab). She was treated with weekly IV steroid infusions for 4 months followed by every other week for 4 months and currently on monthly infusion. The attacks happen once a week and she is currently only on gabapentin 1200mg TID and carbamazepine 800mg BID.

Conclusion: Trigeminal neuralgias can be associated with TS-HDS antibodies and should be tested in those patients with a known history of autoimmune disorder as they may be amenable to immunotherapy.

M245. Acceptability of Placebo in Cluster Headache Clinical Trials: A Patient Survey and Literature Review

Melissa L. Rayhill, Brian E. McGeeney and Elizabeth W. Loder. Buffalo, NY; Boston, MA and Jamaica Plain, MA

Background: Cluster headache is a severe and disabling form of primary headache. Particularly in chronic cluster headache, depressive symptoms and suicidal tendencies are common. High quality clinical trials are sorely needed to identify more effective treatments for these patients. However, performing placebo-controlled trials can be somewhat controversial in this population, given the condition severity. Studies of placebo acceptability have been performed in primary care and in higher risk clinical scenarios such as placebo surgery, but not in cluster headache. Having representative data about patient opinion on use of placebo in a variety of possible research scenarios will enable internal review boards and researchers to ensure that patient views inform the design and approval of research.

Methods: We intend to evaluate patient perspectives regarding the acceptability of placebo in cluster headache clinical trials using vignettes and an acceptability rating scale (Not at all acceptable; Somewhat unacceptable; Uncertain; Somewhat acceptable; Definitely acceptable). We hypothesize that acceptability of placebo use will differ among trials studying preventive drugs, abortive drugs, and medical devices. We also hypothesize that some participants would accept placebo under some circumstances to ensure a high quality trial, while some participants would find some placebo use unacceptable. Patient perspectives on the use of placebo in cluster headache clinical trials will be assessed using a paper-based survey. Participants will be recruited during a national conference held for patients with cluster headaches ("Clusterbusters" Annual Meeting in September 2016). We plan to set up an informational booth at the conference with access to the survey and will invite participants to a

small compensation. Eligible patients would include attendees who are 18 years of age and older, of any gender, who identify themselves as having either episodic or chronic cluster headache.

Results: We will approach patients with cluster headache at the Clusterbusters Annual Meeting, present them with vignettes and ask them to rate the acceptability of placebo in a variety of situations including tests of abortive treatment, preventive treatment, non-pharmacologic and device treatments.

Conclusions: At present we lack a firm evidence base to inform decisions about the use of placebo in cluster headache treatment studies. We intend to evaluate patient perspectives on the acceptability of placebo in cluster headache clinical trials in order to help establish ethical guidelines for investigators.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Melissa Rayhill, MD: No disclosures.

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Elizabeth Loder, MD, MPH: No disclosures.

Health Services Research

M246. Using Telemedicine to Improve Access to Specialty Care for Underserved Patients with Neurodevelopmental Disorders

Deepa U. Menon, Vini Singh and Lana Warren. Baltimore, MD

Telemedicine was used as a modality to improve access to specialty care for Children & Youth with Special health Care Needs (CYSHCN) in our state, where there is a regional disparity in access to care due to poverty & transportation issues. In Dec 201, a collaboration using live audiovisual consultation was developed between Kennedy Krieger Institute in central MD to a community based Atlantic General Hospital on the Eastern Shore of MD. The twice monthly telemedicine clinic assessed children between the ages of 18 months to 21 years with issues with school difficulties, developmental delays and behavioral issues.

Aim: 1. To improve access for CYSHCN in a rural community to neurodevelopmental specialists at the tertiary hospital 2. Identify and mitigate the barriers to access to tertiary services and improve quality of care in the medical home.

Results:

Since Nov 2013 the twice monthly clinic has evaluated 100 patients (new 80; followup 27)

Age:52%-5-12 yo;24%- 3to 5 yo; 15%-over age 12; 8% below 3 yo.

Diagnoses: ADHD; Autism; Language delay; Learning Disability; Disruptive behavior, Anxiety;seizure disorder; sleep disorder; feeding issues

Show rate: 90%

Parent Satisfaction:: 80%

Mileage saved: 280 miles round trip; money saved 50-300\$; Time saved: 6 hr round trip

Local Provider uptake has improved and more networking between community providers and specialists for case conferences and community education events.Has improved dialogue between services at the local hospitals and schools.

Innovation: 1. It is possible to conduct quality standardized neurodevelopmental evaluations using live audiovisual techniques

2. Telemedicine is a useful and relevant tool to address the manpower shortage, improve access to care and improve quality of life and creating a more family centered approach to providing care for developmentally disabled children within the medical home.

M247. Should There Be Public Reporting of Acute Stroke Outcome Data?

Nirav Bhatt, Amer Malik, Negar Asdaghi, Jose Romano, Dileep Yavagal, Seemant Chaturvedi and Ralph Sacco. Miami, FL

Background: Intravenous (IV) tissue plasminogen activator (t-PA) for acute ischemic stroke has been approved for close to 20 years. However, regional variation persists regarding t-PA use. Endovascular thrombectomy has also been demonstrated to improve patient outcomes. Some states mandate the public reporting of surgical complications. For patients at risk for stroke, it is unclear how much information is publicly available in order to select the hospital with the most experience with thrombolysis and acute stroke intervention.

Objectives: To assess the quality of publicly available information for acute stroke outcomes in the State of Florida.

Methods: Publicly available data was used to generate a list of all state designated comprehensive stroke centers and primary stroke centers with the highest number of yearly stroke in-patient admissions for the state of Florida between 10/1/2013 to 9/30/2014. Medicare Hospital Compare website was used to compare these centers on the basis of their performances in various aspects of acute stroke care.

Results: A total of 65 stroke centers were analyzed out of which 32 were comprehensive stroke centers and 33 primary stroke centers. 47 hospitals (72.3%) reported data on IV t-PA administration. Of the 47 hospitals, 35 (74.5%) centers reported that the rate of IV t-PA administration for patients seen within three hours of stroke onset was >80% (range 19-100%). 63 centers (96.9%) provided data on use of antiplatelet medications within 48 hours of stroke onset. Only nine centers (13.8%) reported data on acute brain imaging within 45 minutes of arrival to the Emergency Department. No information was provided on hospital IV t-PA volumes or complications. No information was available regarding which hospitals provided endovascular stroke therapy or endovascular volumes or outcomes.

Conclusions: For patients at risk for stroke, the quality of publicly available information regarding acute stroke

treatment results for an individual hospital is quite limited. The reported rates of IV t-PA administration seem high compared to other studies. Despite the emergence of endovascular therapy, no information was available pertaining to acute stroke intervention. Patient advocacy groups and professional organizations should evaluate whether greater transparency in hospital acute stroke volumes and outcomes is desirable.

M248. Does Headache Neuroimaging Reduce Time to Glioma Diagnosis? A Cohort Study Using a Comprehensive Claims-Based Database

James F. Burke, Kevin A. Kerber, Leslie E. Skolarus and Brian C. Callaghan. Ann Arbor, MI

Introduction: Headache neuroimaging is common and costly, yet the diagnostic yield is low. Determining which patients benefit from headache neuroimaging requires careful quantification of the risks and benefits. We sought to quantify one of the potential benefits of headache neuroimaging—more timely identification of malignant gliomas.

Methods: We determined the proportion of headache patients receiving malignant glioma diagnoses and time from headache visit to glioma diagnosis in subjects with and without initial headache neuroimaging. Analyses were performed in the Optum Database from 2001 to 2014. Optum is a comprehensive claims-based database for all United Healthcare enrollees across all clinical settings that also includes sociodemographics, test results and mortality data. All adult outpatient headache visits were identified using validated ICD-9 codes. Subjects were included if they had an incident headache presenting in an outpatient setting (no prior headache claim in the prior 3 years) without other neurologic diagnoses meriting neuroimaging (e.g. epilepsy, stroke, dementia, multiple sclerosis), no structural brain lesion within the prior 3 years and continuous enrollment for either three years after headache visit or any subsequent malignant glioma diagnosis. Early neuroimaging was defined as MRI or CT (using CPT codes) within 30 days of the headache visit. Malignant glioma was identified with ICD-9 codes 191.xx and 192.xx.

Results: 154,291 incident headache patients were included, 23% of which received an early neuroimaging study (11% CT, 12% MRI). A subsequent malignant glioma code was identified in 0.8% of subjects undergoing early imaging and 0.2% of subjects who did not undergo early neuroimaging. The mean time to a glioma diagnosis in the early imaging group was 220 days vs. 485 days in subjects without early imaging. A minority of glioma diagnoses were made close to the time of the index headache visit (20% at 30 days and 28% at 100 days).

Conclusions: In this large cohort study, headache patients that received early neuroimaging were more likely to receive a glioma diagnosis and had a shorter time to diagnosis. Two non-exclusive interpretations may explain the shorter time to malignant glioma diagnosis in headache patients with early imaging: initial imaging strategies result in earlier glioma detection and/or clinical features not

captured in claims data lead to initial neuroimaging and early glioma diagnosis. Further work to differentiate the relative contribution of these interpretations is needed to inform headache neuroimaging decisions.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr. Burke has received payments from Astra Zeneca and UCSF for case adjudication in the SOCRATES clinical trial.

M249. Validation of a Cognitive Testing Battery Using a Mobile, Tablet-Based Software Package: Defense Automated Neurobehavioral Assessment (DANA)

Kristen R. Hollinger, Alexis Adams-Clark, Dominique Tosi, Steven Woods and Adam I. Kaplin. Baltimore, MD

The ability to do informative, sensitive and accurate cognitive assessment in the clinical setting is important for a range of neurological diseases that have direct and indirect effects on the brain. Conventionally this has been limited by the time required, the cost involved and the need to send patients to remote locations for comprehensive neuropsychological testing. The present study was designed to measure cognitive function in individuals undergoing electroconvulsive therapy (ECT) for major depressive disorder (MDD) using the Mini Mental State Examination (MMSE) and Defense Automated Neurobehavioral Assessment (DANA). The selection of ECT was chosen because of the known cognitive impairment associated with this treatment, and the availability of patients on whom longitudinal assessments could be performed. The MMSE has routinely been used to assess cognition for over 4 decades, while the DANA is a more recently developed battery of cognitive tests delivered on an electronic tablet. The 5 subtests of DANA included were the reaction time (RT), procedural reaction time (PRT), code substitution (CS), special processing (SP), and memory search (MS) tests. 17 subjects receiving inpatient ECT were tested using the MMSE and DANA an average of 7.5 times throughout their course of treatment (average length of stay = 56 days). Correlations were observed between MMSE and performance on 3 of the 5 DANA subtests ($P < 0.05$). The MMSE only factors accuracy into the test score and has a ceiling of 30 possible points. The DANA factors both accuracy and time into performance analysis, eliminating a clear ceiling and allowing for improvements in cognition to be measured in individuals that would achieve the maximum score in the MMSE. Therefore, a second set of analyses were performed in which MMSE scores of 30 were removed to eliminate the ceiling effect. Correlations were observed between MMSE score and performance on all 5 DANA subtests ($P < 0.05$), indicating that the ceiling effect of the MMSE is a clear impediment to accurately measure cognition. DANA MS, PRT, and SRT test performance correlated to all MMSE scores and MMSE scores < 30 , but significance levels improved in all cases when 30s were omitted. Taken together, these data suggest that the DANA is a more sensitive method of measuring cognition as compared to the MMSE.

Interventional Neurology

M250. Hypothyroidism is Associated with Cerebral Aneurysms in Women

Kunakorn Atchaneeysakul, Anita Tipirneni, Tony Zhang, Priyank Khandelwal, Brian Snelling, Sushrut Dharmadhikari, Sudheer Ambekar, Kevin Ramdas, Luis Guada and Dileep Yavagal. Miami, FL

Background: Endocrine dysfunction, including thyroid function, has been known to cause cerebral vascular dysfunction. Hypothyroidism has been shown to cause mucopolysaccharide deposition which has been associated with the weakening of blood vessel walls and aneurysm formation in some case reports. However, the connection between hypothyroidism and cerebral aneurysm has not been well studied. We hypothesized that hypothyroidism may be associated with occurrence of cerebral aneurysms.

Methods: We performed a retrospective case-control study of consecutive patients receiving cerebral angiography at our tertiary-care academic medical center. Inclusion criteria included undergoing 3-vessel angiography. Exclusion criteria included any ruptured aneurysm or previous intracranial hemorrhage. Medical history of hypothyroidism was noted along with all other risk factors. The control group of patients did not have any intra-cranial abnormality on angiography. Patients with cerebral aneurysm were matched with controls for known risk factors of cerebral aneurysm, including: age, hypertension, and smoking history. Cases were further subdivided base on gender given females are known to have higher incidence of hypothyroidism.

Results: From 2008 through 2013, 82 female and 59 male patients with aneurysms were identified for this study and were matched with equal numbers of controls. Among women, hypothyroidism was present in 20.7% (17/82) among patients with cerebral aneurysms vs. in only 6.1% (5/82) among matched controls: odds ratio (OR) 4.03 (95% CI 1.41-11.51, $p=0.01$). Among men, 8.5% (5/59) cases and 0/59 controls had hypothyroidism, showing no significant association, with an odds ratio of 12.01 (95% CI 0.65-222.3, $p=0.095$).

Conclusion: We found a significant association of history of hypothyroidism with cerebral aneurysm in women in our patient cohort. Given the potential pathophysiologic connection between hypothyroidism and vascular wall dysfunction, this should be explored further.

M251. Effect of Hypothyroidism on Unruptured Cerebral Aneurysm Dimensions and Endovascular Coiling Outcome

Kunakorn Atchaneeysakul, Anita Tipirneni, Tony Zhang, Priyank Khandelwal, Luis Guada, Kevin Ramdas, Sushrut Dharmadhikari, Sudheer Ambekar, Brian Snelling and Dileep Yavagal. Miami, FL

Background: In a previous case-control study, we found significant association of history of hypothyroidism with occurrence of unruptured cerebral aneurysm in women within our patient cohort. Hypothyroidism has been shown to

cause mucopolysaccharide deposition with association to blood vessel wall weakening and aneurysm formation in some case reports. We hypothesized that women with hypothyroidism may also have larger aneurysm size.

Methods: We performed a retrospective cohort study of consecutive female patients with cerebral aneurysm receiving 3-vessel cerebral angiography at our tertiary-care academic medical center. Exclusion criteria included any ruptured aneurysm. We compared aneurysm dimensions measured from digital subtraction angiography between the group with hypothyroidism and without. multivariate analysis between the groups to control for age, hypertension, diabetes, hyperlipidemia, smoking, alcohol or drug abuse, and family history of aneurysm. Endovascular coiling outcome was recorded as Raymond-Roy Occlusion Classification (RROC) and recanalization on follow-up angiography

Results: From 2008 through 2013, 178 female patients with cerebral aneurysms were identified. 34 patients had hypothyroidism. Aneurysms dimension in the hypothyroidism group and control group shows significant different in neck sizes 5.4 ± 0.5 vs 4.2 ± 0.2 mm ($p=0.01$). The mean of other dimensions were, height 10.4 ± 1.2 vs 8.3 ± 0.4 mm ($p=0.059$), maximal dimension 10.6 ± 1.1 vs 9.3 ± 0.5 mm ($p=0.2$), and aspect ratio 2 ± 0.1 vs 2 ± 0.2 . No significant difference was noted in RROC and subsequent recanalization.

Conclusion: Hypothyroidism has a significant association with cerebral aneurysm neck size in women and trend to higher aneurysm height and maximal dimension which may link to higher risk of rupture. There was no significant difference in endovascular coiling outcome.

M252. Safety Outcome of Carotid Artery Stenting in Long Carotid Lesion with Proximal versus Distal Embolic Protection Devices

Vasu Saini, Kunakorn Atchaneeysakul, Sudheer Ambekar, Kevin Ramdas, Luis Guada and Dileep R. Yavagal. Miami, FL

Objectives: To compare safety outcome in patients with long carotid lesion (>10 mm) undergoing carotid artery stenting (CAS) with either proximal embolic protection devices (PPD) or distal filter embolic protection devices (DPD)

Background: Embolic Protection Devices can prevent the atherosclerotic emboli during carotid artery stenting (CAS) and reduce the risk of stroke. Long carotid lesion >10 mm have been reported with increased stroke and cardiovascular events. Theoretically, there is a higher risk of embolism during deployment of DPD in patients with long lesions. Newer PPD reverses the flow of blood in the internal carotid artery and may reduce that risk. Our study aims to analyze the difference in safety outcome between DPD and PPD in carotid lesion >10 mm.

Methods: We conducted a retrospective review of consecutive patients undergoing CAS with either PPD or DPD respectively at an academic tertiary care center. Long carotid lesions >10 mm were identified. Peri-procedural outcomes

including minor/major stroke and myocardial infarction (MI) were recorded.

Results: From January 2010 to December 2014, we included 43 consecutive patients with long carotid lesion undergoing CAS, 20 in the PPD group and 23 in the DPD group. There was a technical success rate of 100% in stent placement with either protection device. Mean lesion length was $14.9 \pm 1.3\text{mm}$ vs. $17.3 \pm 2.94\text{mm}$ for PPD and DPD respectively. In PPD group, none of the patients developed coronary or stroke event, whereas 2/23 patient in DPD group developed a minor (NIHSS ≤ 4) and a major stroke (NIHSS >4) respectively ($p=0.345$).

Conclusion: Patients with carotid lesion length $>10\text{mm}$ undergoing CAS with PPD shows a trend to better safety outcomes including perioperative stroke than patients with DPD. A larger prospective study is needed to confirm this finding.

Neuromuscular Disease

M253. Castleman's Disease Neuropathies

Michelle L. Mauermann, Elie Naddaf, Jay Mandrekar and Angela Dispenzieri. Rochester

Introduction: Castleman's disease (CD) is a rare lymphoproliferative disorder characterized by lymphoid follicle proliferation with involution of germinal centers and endothelial hyperplasia. CD has a broad spectrum of clinical manifestations and can be associated with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes). There is little known about the peripheral neuropathy phenotypes seen with CD.

Methods: With Mayo clinic Investigational Review Board approval, we conducted a retrospective chart review for patients with biopsy-proven CD evaluated between January 2003 and December 2014. Patients with associated peripheral neuropathy (PN) were identified and divided into two groups: CD without POEMS (CD-PN) and CD with POEMS (CD-POEMS). A cohort of POEMS patients was used as controls. Clinical, electrophysiologic, and laboratory characteristics were collected and compared among patient subgroups.

Results: There were 7 patients with CD-PN, 20 with CD-POEMS and 122 with POEMS. Patients with CD-PN had the mildest neuropathy characterized by predominant sensory symptoms with no pain, and mild distal sensory deficits [median Neuropathy Impairment Score (NIS) of 7 points]. Although both CD-POEMS and POEMS patients had a severe sensory and motor neuropathy, CD-POEMS patients were less affected (median NIS of 33 and 66 points respectively). The degree of severity was also reflected on electrodiagnostic testing where CD-PN patients demonstrated a mild degree of axonal loss, followed by CD-POEMS and then POEMS. Demyelinating features, defined by the EFNS/PNS criteria, were present in 43% of CD-PN group, 78% of CD-POEMS and 86% of POEMS group.

Conclusion: There is a spectrum of demyelinating peripheral neuropathies associated with Castleman's disease.

CD-PN is sensory predominant and is the mildest phenotype, whereas CD-POEMS is a more severe, often painful, sensory and motor neuropathy. Compared to POEMS cohort, CD-POEMS neuropathy has a similar but less severe phenotype. Whether these patients respond differently to treatment deserves further study.

M254. Co-Morbid Pain Syndromes in HIV-Associated Peripheral Neuropathy

Jessica Robinson-Papp, Jocelyn Jiao, Eric So, Jebakaran Jebakumar, Mary Catherine George and David M. Simpson. New York, NY

Objective: Peripheral neuropathy (PN) is a common complication of HIV, often causing chronic neuropathic pain. There is increasing awareness that some forms of PN, particularly small fiber neuropathies, can be associated with chronic widespread pain syndromes in addition to the more classic symptoms of distal dysesthesias, paresthesias, and numbness. Given the high prevalence of both PN and chronic pain in HIV, we sought to determine whether patients with a diagnosis of HIV-PN were more likely to experience other chronic pain syndromes.

Methods: Data were obtained from the Clinical Data Warehouse maintained by our institution, which contains comprehensive de-identified clinical data on over 3 million patients extracted from the electronic health record on a nightly basis. All HIV-infected patients receiving standard of care antiretroviral therapy ($n=638$) in our institution's primary care HIV clinic were included. Diagnoses of HIV-PN and other chronic pain disorders were established based on ICD-9/10 codes.

Results: Patients were 57% men, and were predominantly minority (93%), with a mean age of 48 years. HIV was well-controlled (73% with HIV-1 viral load <50 ; median CD4 count 564 cells/mm³). Sixty-eight patients (11%) had a diagnosis of HIV-PN. Patients with HIV-PN were more than twice as likely to have other chronic pain disorders (66% versus 32%; $\chi^2=30.3$, $p<0.001$). Co-morbid pain disorders experienced by patients with HIV-PN included: spinal degenerative disorders (38%), other joint pain (22%), headache disorders (10%), muscular pain (6%), and unspecified disorders (16%). Patients with HIV-PN were older (53 versus 47; $t(636)=-3.8$; $p<0.001$), however the association of PN with other chronic pain disorders persisted after adjusting for age $\chi^2(2)=34.3$, $p<0.001$. Patients with PN and a co-morbid chronic pain disorder experienced higher average pain intensities, and were more likely to be treated with multiple pain medications, compared to patients with HIV-PN alone. Overall patients with HIV-PN were commonly treated with opioids (32%), regardless of a presence of a co-morbid pain disorder.

Interpretation: Patients with HIV-PN commonly experience other chronic pain disorders, suggesting that for some patients HIV-PN may be part of a chronic widespread pain syndrome. Clinicians managing HIV-PN, should seek a broad understanding of patients' pain experience since this may alter management strategies. Further research is needed to determine the mechanism underlying this association,

and its potential implications for therapeutic trial design in HIV-PN.

M255. Changes in Clinical Outcome Measures in a Longitudinal Prospective Natural History Study of C9orf72 Mutation Carriers

Mary Kay Floeter, Jennifer Farren, Laura E. Braun, Bryan J. Traynor, Zachary Gala, Devin Bageac, Michael Tierney and Edythe Wiggs. Bethesda, MD

Background: In order to select appropriate outcome measures for clinical trials of persons carrying the C9orf72 mutation, the untreated rate of change should be established.

Objectives: 1) To determine the magnitude of change in clinical measures in

25 unrelated C9orf72 mutation carriers followed for 6 months or longer in natural history study 1NCT01925196. 2) To explore differences in progression among clinical phenotypes of C9orf72.

Methods: Clinical diagnoses at each visit according to revised El Escorial and Rasovsky criteria (possible or higher). Outcome measures: Survival, ALSFRS-R, MMT, Dementia Rating Scale (DRS-2), Frontobehavioral Inventory score (FBI), Frontal assessment battery (FAB).

Results: Clinical diagnoses: Baseline diagnoses: 9 ALS only, 2 ALS with incomplete cognitive testing, 6 ALS-FTD, 3 FTD only, 5 asymptomatic (3 of similar age to affected family members). At 6-month follow-up one ALS patient met criteria for FTD. No change in diagnosis among asymptomatic carriers. Initial symptom (by history): 7 bulbar onset, 7 limb onset, 6 cognitive change. In ALS-FTD patients, 3 with initial cognitive/behavioral symptoms developed motor symptoms 3-63 months later; 4 with initial motor symptoms developed cognitive/behavioral symptoms 2-39 months later. Survival: Four patients died in Year1 following enrollment; three died in Year2, of whom one was TIV 1 year prior to death. Baseline clinical diagnoses were ALS (2) or ALS-FTD (5). ALSFRS-R: In 17 patients with motor symptoms, bimodal distribution of ALSFRS-R and initial ALSFRS-R progression rates (PR1). All 3 patients with PR1 > 1.0 died. No correlation between PR1 and PR at 6- and 12-month intervals. MMT: MRC scale was totaled for 7 muscles/limb plus hand muscles. 6-month scores declined only in ALS and ALS-FTD patients. PR1 was correlated with baseline scores ($r = -0.76$, $p < 0.001$) and changes in limb MRC score at 6-mo in those patients ($r = 0.86$, $p = 0.004$). DRS-2, FBI: Differed at baseline between patients with and without cognitive impairment, but no clear trend of change at 6-mo. FAB: lower at baseline and trend for decline at 6- and 12-mo in ALS-FTD patients. Not correlated with survival.

Conclusion: With the caveat for a small sample size: mixed cognitive/behavioral and motor symptoms are common in C9orf72 carriers, regardless of initial presenting symptom. In symptomatic carriers, ALSFRS-R and MMT demonstrated progression of motor dysfunction over 6-months. Onset and progression of cognitive/behavioral

symptoms were more difficult to quantify. Validated longitudinal cognitive/behavioral scales will be needed.

M256. Guillain-Barre Like Syndrome: A Manifestation of Nelarabine Therapy

Bushra Javed, Prachi Kale, Anila Thomas and Brij Singh Ahluwalia. Valhalla, NY

Objective: We present a case of Nelarabine induced neurotoxicity which appears clinically and electrophysiologically similar to Guillain-Barre Syndrome.

Background: Nelarabine is an FDA approved antineoplastic purine analog used for the treatment of refractory or relapsed T cell lymphoblastic leukemia or lymphoma. The side effects include peripheral neuropathy (Guillain-Barre like syndrome), myelopathy, dysautonomia, somnolence and seizures usually within 10 to 12 days of therapy.

Design/Case Presentation: This is a case report of a 54 year old man with a history of T cell acute lymphoblastic lymphoma who presented with a relapse of lymphoma. He was treated with nelarabine, cytarabine, mercaptopurine and cyclophosphamide. The patient developed sudden onset of ascending weakness of the bilateral lower extremities, mild upper extremity weakness and areflexia in all extremities at nine days post Nelarabine therapy.

Results: Spinal imaging did not show evidence of cord compression or signal change. Cerebrospinal fluid (CSF) results were significant for an elevated protein of 70 mg/dl and white blood cell count of 0 cells/mm³. Electromyography (EMG) of the lower extremities showed conduction block, prolonged distal motor latency and absent F waves on nerve conduction with reduced recruitment of normal appearing motor units on EMG, consistent with an acute demyelinating polyneuropathy. He was treated with intravenous immunoglobulin followed by plasmapheresis with only minimal improvement in symptoms over time.

Conclusion: We present a patient with a clinical and electrophysiologic presentation similar to Guillain Barre Syndrome following treatment with Nelarabine. Due to the severity of symptoms, treatment for an immune-mediated process was initiated with only minimal improvement over time. Whether Nelarabine toxicity is an aberrant immune response against myelin or chemo toxicity remains unknown. Awareness and early identification of this medication side effect could be utilized in screening and preventative strategies during treatment.

M257. Obesity Attenuates Epidermal Nerve Fibers in the Distal Limb

Gigi J. Ebenezer, Shaun Truelove and Michael Polydefkis. Baltimore, MD

We investigated the status of small sensory nerve fibers among 45 healthy-weight subjects (BMI < 25kg/m²) and 72 overweight/obese subjects (BMI ≥ 25kg/m²), aged 20-69 years. Subjects underwent neurological examinations and had 3 mm skin punches taken from distal leg (DL), thigh (DT), and proximal thigh (PT) sites, from which 50 μm sections were stained with anti-PGP9.5 antibody for quantifying epidermal nerve fiber density (ENFD; fibers/mm).

Results: We used multivariable linear regression models to control for multiple variables. After controlling for height, age, and obesity, females were found to have lower distal leg ENFD (-2.6 ; $P=0.02$). Increasing age and height were significantly associated with decreasing DL ENFD, with decreases of -1.6 fibers/mm per 10 years ($P<0.001$) and -2.55 fibers/mm per 10cm ($P<0.001$), respectively. Even after controlling for height, being overweight/obese was associated with reduced DL ENFD, with 2.5 fibers/mm lower DL ENFD than healthy-weight individuals ($P=.01$). These findings remained consistent across distal thigh and proximal thigh ENFD, though not all associations remained significant.

Conclusion: Distal sensory fiber density is influenced by age and height of individuals. Obesity further accelerates attenuation of fibers across the lower limb even after controlling for other associated factors.

M259. Systematic Approach of the Clinical, Serological and Histological Findings in a Cohort of Inclusion Body Myositis

Rey N. Bello, Tulio Bertorini, Lehong Shen and Olivia Yambem. Memphis, TN

Introduction: To evaluate a series of Inclusion body myositis patients seen in our clinic.

Methods: This is a retrospective study of a series of 35 cases with biopsy-confirmed diagnosis of inclusion body myositis.

Results: A total of 35 cases, 10 (28.6%) females, and 25 (71.4%) males, with ages from 38 years to 79 years; age distribution: 1(3%) each for 30-40 years and 41-50 years, 5 (14%) 51-60 years, 20 (57%) for 61-70 years, and 8 (23%) for 71-80 years. The weakness in the upper extremities mainly involved the finger flexors in 31.4%, wrist flexors and extensors in 17%, and shoulder girdle in 8%. In the lower extremities, the muscle weakness mainly involved the thigh muscles 51.4%, anterior legs 31.4%, hamstring 14%, plantar flexors 5.7%. Two (5.7%) had no significant weakness. Twelve patients had serologic assay for Anti-cN-1A antibody; 3 (25%) was positive, and 9 (75%) were negative. Sixteen (45.7%) patients had associated neuropathy of which 8(22.8%) were secondary to diabetes mellitus and other medical conditions, 2 (5.7%) had HIV, and 2 (5.6%) had hepatitis C. Five (14.2%) patients with neuropathy had no identifiable causes. Fourteen (40%) had supportive care, of which 13 (92.8%) continued to have progressive weakness and 1(7%) with stabilization of symptoms; 10(28.6%) received steroid with 9 (90%) had progressive weakness and 1(10%) stabilized; 3 (8.5%) received immunosuppressant other than steroid with 2(66.6%) had progressive weakness and 1(33.3%) stabilized; 2(5.7%) received intravenous immunoglobulin with improvement of the weakness in 1 patient who was HIV positive after about 6 months of treatment. Six (17%) of the patients did not have enough data for the course of treatment received.

Conclusion: Sporadic inclusion body myositis appears in individuals after the sixth decade of life and, as previously reported, is more common in men. The distribution of

weakness mainly involved the finger flexors, thigh, and anterior leg muscles. Of the patients tested for anti-cN-1A antibody, 25% had positive results which is different from what was previously reported. Peripheral neuropathy was found in 16 (45.7%) of patients, with no identifiable causes in 14.2%. The presence of Hepatitis C and HIV suggest that viral infection may predispose to inclusion body myositis. Immunotherapy did not appear to be beneficial except for 1 patient.

M260. Neurolymphomatosis: A Review of 82 Cases

Jose David Avila and Carolina Vivar. St. Louis, MO and Danville, PA

Introduction: Neuropathy may occur in up to 5% of patients with lymphoma. There are multiple potential causes, including infections, adverse effects of chemotherapeutic drugs, immune mechanisms, and infiltration of neoplastic cells into the nerves. The latter is known as neurolymphomatosis (NL) and has an estimated prevalence of 0.2% in non-Hodgkin lymphoma (NHL).

Methods: We searched PubMed for cases of NL published from 2013 to 2015.

Results: Eighty two cases were identified in 37 articles. There were 46 men (57%) and 35 women (43%). The median age at presentation was 60 years (27-85). Thirty patients (37%) had primary NL and 52 (63%) had secondary NL. Diffuse large B cell lymphoma was the most common type in both groups (76%). Clinical presentations included painful radiculopathy or neuropathy (38%), mononeuropathy (24%), cranial neuropathy (23%), mononeuropathy multiplex (10%) and painless neuropathy (5%). Cerebrospinal fluid analysis (CSF) was performed in 45 patients showed malignant cells only in 18 (40%). Magnetic resonance imaging (MRI) showed enlarged nerves, usually with contrast enhancement in 48 of 58 patients (83%). Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) was performed in 60 patients and in 55 (91%) showed abnormal root, plexus or nerve uptake. Biopsies, performed in different nerves and roots, yielded diagnostic results in 39 of 43 patients (91%).

Conclusions: NL is a rare cause of neuropathy. It is extremely important for clinicians to recognize NL, as this may be the initial presentation of lymphoma or may be a manifestation of relapse of spread of a known malignancy. In both scenarios early detection has implications on treatment. The clinical presentations vary but the use of MRI and FDG-PET may help in diagnosis and selecting targets for biopsy. CSF analysis has limited utility.

M261. Tracking Nerve Health Following Implantation of Bilateral Femoral Nerve Cuff Electrodes (NCEs)

Max J. Freeberg, Gilles C. Pinault, Ronald J. Triolo and Rabila Ansari. Cleveland, OH

Objective: Case report tracking the health of the femoral nerves in a spinal cord injury (SCI) patient implanted with bilateral Compliant Flat Interface Nerve Electrodes (C-FINE).

Background: Functional electrical stimulation can restore function in individuals with CNS lesions, such as SCI. NCEs offer potentially stable and selective methods for activating paralyzed muscles. Studies have assessed chronic stimulation through NCEs. However, no study has evaluated how NCEs chronically affect clinical measures of nerve health and cuff stability in human subjects.

Methods: Patient is a 25-year-old man with SCI - C6 ASIA C, with bilateral lower extremity paralysis. In restoring his ability to stand, he received C-FINEs around bilateral femoral nerves. The C-FINE is comprised of a pliable insulating polymer with multiple embedded electrical contacts for selective fascicular stimulation. This is the first human trial to report on the short and long-term safety and health of the nerve stimulated with such an electrode. Nerve conduction studies and needle EMG quantified nerve health pre-operatively, intra-operatively, and post-operatively at 2 days, 1 week, and 3 weeks. Femoral motor nerve conduction velocity (NCV), femoral motor (CMAP) and saphenous sensory (SNAP) nerve conduction studies, and insertional activity were measured.

Results: Motor NCV, with C-FINE stimulation, has remained above normal levels ($NCV > 41$ m/s, $p < 0.05$). Surface measurements of the saphenous SNAP and the femoral CMAP (rectus femoris) have shown consistent and normal responses at all time-points. Furthermore, at post-operative time-points, the CMAP amplitudes, areas, and duration are unchanged with hip flexion (zero versus 90 degrees). The only significant change is increased pulse duration was required at both 1 week and 3 weeks postoperatively to reach supramaximal stimulation. This is expected following implantation and consistent with literature. Needle EMG was performed, at each time-point, on muscles innervated by the femoral nerves bilaterally: sartorius, rectus femoris, vastus medialis, and vastus lateralis. Normal insertional activity was noted preoperatively and 2 days postoperatively in every tested muscle. One week postoperatively, borderline active denervation was only seen in the right sartorius and in the left rectus femoris. Three weeks postoperatively, borderline active denervation was only seen in the left sartorius and in the left vastus lateralis. This suggests minor nerve irritation, likely occurring during implantation.

Conclusion: Chronic C-FINE placement around proximal femoral nerves have not caused clinically significant nerve damage up to 3 weeks post-implantation.

Sleep Disorders and Circadian Rhythm

M262. Results from a Clinician Survey Rating the Use and Utility of the Swiss Narcolepsy Scale

Markus Schmidt, Christian Sturzenegger, Ulf Kallweit and Ann Kim. Bern, Switzerland; Dublin, OH; Zurich, Switzerland and Palo Alto, CA

Introduction: The Swiss Narcolepsy Scale (SNS) is a short and easy-to-complete 5-question patient-response questionnaire designed to enhance physician screening in clinical practice for narcolepsy type 1 (with cataplexy), with 3

questions on excessive daytime sleepiness and 2 on cataplexy. Surveys were conducted to assess SNS awareness, use, and perception among physicians treating patients with sleep disorders.

Methods: Online market research surveys were conducted among physicians (sleep specialists, pulmonologists, primary care physicians, neurologists, psychiatrists) at two time points, April-May 2015 (Group one) and Oct-Nov 2015 (Group two). Inclusion criteria included spending $\geq 75\%$ of time in patient care, and treating ≥ 30 patients with sleep disorders/month and ≥ 2 patients with narcolepsy/month. Survey questions covered knowledge and use of SNS and the impact of results on clinical diagnosis.

Results: 202 physicians were in Group one, 200 in Group two, and 48 physicians participated in both surveys; with an overall mean of 15.5 years in clinical practice and $\geq 95\%$ of their time seeing patients. Overall awareness of the SNS was 22% for Group one and 34% for Group two and use of SNS was 16% and 23%, respectively. Among physicians who were aware of the SNS and took both surveys, SNS use was 15% (Group one) and 27% (Group two). Physicians who use the SNS reported that narcolepsy was diagnosed in 60% of patients with a suspected sleep disorder screened with the SNS, with 29% diagnosed with narcolepsy type 1. Once made aware of the SNS, most physicians surveyed in both groups considered using the SNS for patients with suspected narcolepsy (86% and 94%, Groups one and two, respectively). More than half of Group two SNS users confirmed its reliability (51%) and 60% rated "agree/strongly agree" for its value in screening for narcolepsy type 1.

Conclusions: Although awareness and use of the SNS to screen patients for narcolepsy type 1 (with cataplexy) was higher over the survey period among clinicians who treat sleep disorders and the consideration for use is high among clinicians who are aware of the SNS, its current awareness and use remains relatively low. Clinicians using this screening tool have reported high utility for identifying patients who should be evaluated for narcolepsy. The SNS is specifically designed for narcolepsy type 1 (with cataplexy) and may help facilitate its diagnosis and recognition.

Support: This market research was conducted by Jazz Pharmaceuticals.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Dr Schmidt has consulted for XenoPort, served on the speakers' bureau for XenoPort and UCB, and contributed to a physician educational training video for Narcolepsy Link. Dr Sturzenegger is the Medical Director and Executive Board Member of the Klinik Lengg AG. Dr Kallweit has received honoraria from UCB Pharma, Biogen Idec, and Heinen + Löwenstein Medizintechnik; and has received a senior investigator grant from the European Narcolepsy Network. Ms Kim is an employee of Jazz Pharmaceuticals who, in the course of this employment, has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc.

M263. Case Report: Beneficial Effect of Treatment of Obstructive Sleep Apnea on Neuropathy Symptoms in a Patient with CMT-Type 1A- A Case Report

Pinar Polat, Huong Pham, Jun Li and Kanika Bagai. Nashville, TN

A 53 year-old female with Charcot-Marie-Tooth disease, type 1A (CMT1A) presented to sleep clinic with a several year history of difficulty with sleep-onset and sleep-maintenance as well as numbness and cramps in her hands and legs that were worse at night.

She experienced numbness in her hands every night for the past 6 years that was worse during the night and in the early mornings -resulting in night-awakenings. The numbness and cramps in her legs were intermittent, and only occurred at night causing her to awaken, especially in the early morning hours. She used hand splints with intermittent benefit and the numbness in her hands and legs occasionally improved with activity. In addition, she had symptoms of sharp pains in her feet, for which she was taking Pregabalin 150mg daily for the last 3 years with some relief of pain, but no improvement of numbness. A recent nerve conduction study (NCS) to evaluate for carpal tunnel syndrome was inconclusive.

Additionally, she reported restlessness in her legs that was worse at night, and improved with movement. Her husband reported occasional snoring when sleeping supine. She reported symptoms of non-restorative sleep and excessive daytime sleepiness.

A portable sleep study revealed obstructive sleep apnea (OSA) with an Apnea-Hypopnea Index (AHI) of 16.5 with oxygen desaturation to 63%. On repeat sleep study for CPAP titration, she had a residual AHI of 1.6 with improvement in her OSA with CPAP pressure of 8cm H2O.

Shortly after initiating treatment of her OSA with CPAP, she had near complete resolution of the numbness and cramps in her legs and she no longer had awakenings related to these symptoms. The nighttime numbness in her hands also improved significantly. Additionally, she reported decreased numbness in her hands during the day as well. Approximately 1.5 years after initiating CPAP treatment, she remained adherent with CPAP, and continued to have improvement in symptoms of numbness or cramps in her legs, and minimal numbness in her hands.

There is a higher prevalence of sleep disorders, including OSA and RLS, in patients with CMT. The presence of these sleep related disorders affects the quality of life of patients with CMT. Our case report adds to the possible options for treatment of sleep related symptoms in patients with concomitant CMT and OSA. Treatment with CPAP in patients with OSA and CMT may also be a viable treatment for other sleep related disturbances.

M264. Comorbidity and Mortality in a Longitudinal Study of Narcoleptics' Family Members

Maurice Ohayon and Cristina Milesi. Palo Alto, CA

Introduction: Narcolepsy is a rare disabling sleep disorder. The genetic etiology of the disease is shown by its higher prevalence among close relatives of narcoleptics. The

objective of this study is to estimate the incidence of Narcolepsy among family members, the prediction value of the major symptoms for Narcolepsy, the comorbidity and mortality among narcoleptic family members.

Methods: 4,045 family members of 362 individuals with narcolepsy were interviewed between 2011 and 2015; 3,313 family members and 300 narcoleptic individuals were interviewed on two occasions 5 years apart. Target population: first (1,194), second (1,410) and third-degree (531) relatives; 178 spouses/roommates as control group. Interviews were conducted using the Sleep-EVAL system.

Results: At follow-up, 192 family members were deceased and 54 couldn't be interviewed due to debilitating or terminal disease. The incidence of narcolepsy among family members was two to three times higher than in the control group. Half of the family members reported moderate to severe sleepiness at follow-up, and, among these, 34.2% reported an increase in their sleepiness. Incidence of excessive sleepiness was highest among third-degree relatives. Incidence of sleep paralysis was highest among second-degree relatives. At follow-up, the frequency of sleep paralysis increased in 57% and decreased in 19% of cases. The predictors of developing narcolepsy at follow-up were presence of sleep paralysis at the first interview (AOR: 4.73) and presence of excessive sleepiness (AOR: 4.95). Cataplexy-like symptoms were reported only among family members. The symptoms were chronic (present at W1 and W2) for 12.3% of the members. Among the factors at W1 predicting sleep paralysis at W2, there were: 1) Presence of hypnagogic hallucinations (AOR: 3.6); 2) Presence of hypnopompic hallucinations (AOR: 3.6) and 3) Presence of cataplexy-like symptoms (AOR: 2.2).

Conclusion: New cases of narcolepsy were found in 1.2% of the family members. Sleep paralysis and Excessive Sleepiness at W1 are giving 5 times more chance to have Narcolepsy at W2. Cataplexy is high in the first-degree family members. Excessive sleepiness is more often chronic and increases in severity with time. Hypnagogic and hypnopompic hallucinations are good predictors of Sleep Paralysis at W2. Finally, between the first and second interview, 192 family members died and 54 developed a debilitating or terminal disease showing that Narcolepsy has the same severity for family members as for probands.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Educational grant from Jazz Pharmaceuticals.

Autoimmune Neurology

M265. Recurrent Guillain Barre Syndrome Associated with Herpes-Zoster Attack-A Case Report

Syed W. Abbas and Robert N. Schwendimann. Shreveport, LA

Objective: To report a unique case of recurrent GBS preceded by recurrent Herpes-Zoster attacks.

Background: Guillain Barre Syndrome (GBS) is an autoimmune polyradiculoneuropathy that presents with ascending paralysis and areflexia. GBS can recur in only 5% of the

cases following infectious illness and can be defined as 2 or more episodes at least 2 months apart with identifiable recovery after each attack. Recurrent GBS (RGS) occurs more frequently in patients under 30 years, with milder symptoms and in those with Miller Fischer syndrome and responds favorably to treatment with plasmapheresis or IVIG. There are only few case reports of GBS following Herpes Zoster(H-Z) attacks. We are reporting the very first case of recurrent GBS following recurrent H-Z attacks.

Case presentation: We report a 68-years old female with history of GBS at the age of 37 following Herpes-Zoster attack and responded well to plasma exchange with complete recovery over next 6 weeks. This time she presented again with progressive weakness and numbness in both legs and inability to walk for last 2 days. Two weeks earlier she had a painful herpetic abdominal rash. Her pan spinal MRI was unremarkable. Over next 2 days she rapidly developed ascending flaccid paralysis, areflexia, droopy eyes and respiratory failure requiring mechanical ventilation. She met the Brighton's criteria for diagnosing GBS. Her spinal fluid study showed cell count 28 mostly lymphocytes, proteins 51 and unremarkable for viral cultures and VDRL. Anti GM1 Ab, HIV and hepatitis serology was also negative. She was started on plasma exchange therapy. Neurophysiologic examination at 2 weeks showed demyelinating predominantly motor pattern of polyneuropathy. Over the next one week her motor strength improved from scale 1 to 3 in all extremities and her deep tendon reflexes came back. Later she was discharged to long term acute care facility with tracheostomy and G-tube in place.

Discussion and Conclusion: Recurrent GBS is very rare and life threatening condition with long lasting residual neurological deficits. Few case reports of acute flaccid paralysis following H-Z attack has been reported requiring close follow up. Our patient is the only in literature presenting with recurrent GBS following recurrent H-Z attacks. There is only one case control study showing 0.03% of patients with HZ attack developed GBS in next 1-8 weeks. We propose that further studies are required to establish any causal association between H-Z attacks leading to recurrent GBS.

Dementia and Aging

M266. A Case of Alice in Wonderland Syndrome Due to Heidenhain Variant of CJD

Emer R. McGrath, Ayush Batra, Alice D. Lam, Joseph F. Rizzo and Andrew J. Cole. Boston, MA

Introduction: We describe a case of the Heidenhain variant of Creutzfeldt-Jacob Disease (CJD)

Case report: A 64 year-old man presented with a four-week history of bilateral distorted vision. He reported that objects in his central visual field appeared to change shape and were disproportionately large or small. He also noted altered color perception. His family noted intermittent confusion and difficulties recognizing family members. Examination revealed intact mental status, equal and reactive pupils, visual acuity of 20/30 OD and 20/40 OS, severe impairment of color vision, binocular central distortion of

vertical lines on Amsler grid testing, left incongruous homonymous hemianopia, normal fundoscopic exam and otherwise normal neurological exam. Work-up revealed a negative toxicology screen, EEG with continuous 1-2 Hz generalized periodic discharges with occipital predominance and MRI brain with a cortical ribboning pattern of restricted diffusion involving the right occipital-parietal lobe. CSF analysis revealed normal protein and glucose, absent cells, negative paraneoplastic panel and cytology, positive 14-3-3 protein and elevated t-tau protein. He was diagnosed with 'probable' Heidenhain variant of sporadic CJD. He developed rapid cognitive decline and died shortly thereafter. An autopsy was performed which confirmed abnormal prion protein (PrP). Sequencing of the PrP gene did not reveal a pathogenic mutation.

Discussion: Alice in Wonderland syndrome is a perceptual disorder involving somesthetic and visual misperceptions of the patient's own self, or the external environment. Reported causes include Epstein Barr virus, varicella zoster virus, influenza, migraine, seizure, stroke and toxic encephalopathy. The symptoms are thought to localize to the non-dominant posterior parietal and anterior occipital lobes. The Heidenhain variant of CJD is characterized by predominant visual symptoms, with mild to no cognitive symptoms early in the disease course, followed by a rapidly progressive course.

M267. Whole Exome Sequencing in an Early Onset ADRC Dementia Cohort

Suman Jayadev, Malia Rumbaugh, Christopher Hale, David S. Hanna, Elaine Peskind, Debby Tsuang and Tom D. Bird. Seattle, WA

Alzheimer disease (AD) is the most common cause of cognitive impairment in the elderly. Identification of Mendelian genes associated with familial early onset AD have driven extensive and useful studies elucidating the mechanisms of those forms of AD. However, the majority of AD, even in patients with affected family members, is not explained by the presence of an autosomal dominantly inherited gene. We and others have reported an increased prevalence of late onset AD in those with affected first degree relatives underscoring the genetic contribution to AD incidence in the general population. Now, with next-generation sequencing and evolving bioinformatics tools, the complex genetic underpinnings of AD and related dementias can be systematically evaluated to identify frequency of known AD risk genes, novel candidate genes and candidate gene-gene interactions contributing to disease.

We identified more than 150 individuals in our University of Washington Alzheimer Disease Research Center (ADRC) with a clinical diagnosis of early onset AD/dementia (age of onset <55 years) or with strong family history, and detailed clinical evaluation by ADRC investigators. Neuropathological studies, imaging data and DNA samples from family members is available for a subset of this cohort. Whole exome sequencing is performed with the IDT Exome v1.0 enrichment system and Illumina Sequencing. Results will be available at the time of this meeting.

We hypothesize that in an AD cohort enriched for early onset disease or significant family history there is higher likelihood of identifying risk variants driving pathogenesis in distinction from surveying a heterogeneous older population with a concomitant array of comorbidities contributing to dementing illness. Through correlation between genetic variation in this well phenotyped population and neuropathological/clinical features, we hope to further define the molecular pathways contributing to particular disease phenotype. Exome sequencing in a well-designed cohort can be leveraged to highlight specific candidate pathogenic drivers which then serve as platforms for hypothesis based mechanistic studies. Further, screening for genetic risk variants may be included in future clinical and research evaluation as part of a multi-modal biomarker assessment including CSF, imaging and other measures to determine high risk for AD or risk for specific subtypes of AD.

Education

M268. Ezio Sciamanna, Early Progenitor of Cortical Mapping

Anthony L. Ritaccio and Sara Casciato. Albany, NY and Rome, Italy

Electrical cortical stimulation mapping (CSM), remains a preferred method for identification of functional areas prior to neurosurgery to minimize or prevent functional loss. Influenced by Ferrier's initial CSM experience across several species published in 1873, 19th century experiments applying electric current to exposed human brain followed. Bartholow is commonly credited with the first report of CSM in a conscious human in 1874. What is not well established is that prominent Italian neurologist, Ezio Sciamanna, localized sensorimotor function in a human demonstration of CSM shortly thereafter in 1882.

Ezio Sciamanna (1850-1905) was a founder of The School of Medicine at Sapienza University of Rome. After obtaining his degree at the Rome University in 1876, Sciamanna's continuing studies included apprenticeship with Charcot in Paris. He was a member of the Accademia dei Lincei ("Academy of the Lynx"), an elite Italian scientific society founded in 1603, whose membership over centuries has included Galileo Galilei and Albert Einstein. His case was published in Academy annals in 1882.

Sciamanna performed CSM on a trauma victim who underwent trepanation and repair of parietal region skull fracture. Extradural and subdural stimulation using both Faradic and Galvanic currents produced reliable contralateral motor responses in face, head/neck, and forearm. Testing was terminated after four days, due to death. Bartholow's patient had a malignancy and infection that eroded skull and exposed cortex. Electrical stimulation performed with penetrating needles may actually have represented white matter tract stimulation, giving further importance to Sciamanna's clearer extradural and subdural explorations.

Sciamanna represents a vital historical link between 19th century investigators like Ferrier and 20th century icons of CSM such as Cushing and Penfield. He was the vanguard

of functional localization of brain function through direct stimulation of human gray matter. Unlike Bartholow, who has been canonized in the annals of CSM, Sciamanna has remained obscure, despite the fact that his case may represent a better example of true subdural CSM than his better known contemporary.

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Headache and Pain

M269. Burning Mouth Syndrome with Subjective Hyposmia, Hyposmia, Hypogeusia

Sumit Kanwar, Manisha R. Chand, Malinda Walford and Alan R. Hirsch. Weston, FL; Willemstad-Curacao, Netherlands Antilles and Chicago

Objective: Hyposmia has been described in a myriad conditions including multiple chemical sensitivity, pregnancy, odor-induced limbic dysregulation, migraines, cluster headaches, benzodiazepine withdrawal, Addison's disease and cystic fibrosis. While hyposmia has been described with burning mouth syndrome (BMS), subjective hyposmia has not heretofore been described.

Methods: Case study: A 45 year old female, six weeks after beginning treatment with duloxetine, quetiapine and alprazolam, noted a gradual onset of burning and metallic taste, which increased in the anterior tongue and palate. Concurrent with this odors intensified to 200% of normal, particularly with aromas of foods, chemicals, perfume and canine excrement.

Results: Olfactory testing: Anosmia: Brief Smell Identification: 3, Quick Smell Identification: 1, Alcohol Sniff: 3, Sniff Magnitude: 1.49, SNAP phenylethanol olfactory threshold: Left(L) > -2.0, Right(R) > -2.0, Sniffin' Sticks: Threshold: L <1, R <1, Bilateral(B) <1. Normosmia: Pocket Smell: 3, Suprathreshold amylacetate odor intensity, Retronasal smell: Retronasal Smell Index: 6. Hyposmia: Odor Memory: 0 - 10 seconds(s), 4 - 30s, 2 - 60s. Total 6, Olfactometer Identification: L 18 (normosmia), R 14, Sniffin' Sticks: B Discrimination: 8, B Identification: 10. Suprathreshold amylacetate odor hedonic: Crossed pattern. Gustatory: Propylthiouracil disk: 2 (abnormal). Taste: Normogeusia to urea and phenylthiocarbamol. Hypogeusia to NaCl, sucrose, HCl. Taste quadrant: Sucrose impaired throughout the tongue and palate. Front to back difference with reduced ability to taste anteriorly to all modalities. Alcohol and carbonated water: Normal. Fungiform papillae count: R 24, L 18. Piezometry: Tongue normal. Saxon: 3 (normal). Electrogustometry: L palate >34, R palate >34, Tongue: L anterior = 22, R anterior = 24, L posterior = 14, R posterior = 14.

Discussion: This is the first reported case of complaints of hyperosmia with burning mouth syndrome. Subjective hyperosmia with hyposmia and hypogeusia occurring coincident with burning mouth syndrome suggests a common pathology. It is possible that a single pathogenic agent (quetiapine) may have simultaneously damaged the olfactory, gustatory and somesthetic systems causing her cluster of symptoms. Quetiapine has been reported to cause BMS, and may act to induce hyposmia and hypogeusia due to blockade of D2 receptors and serotonin receptors. Moreover, her complaints of hyperosmia in the presence of hyposmia suggests a disinhibition phenomena similar to recruitment in sensorineural hearing loss. Further investigation into hyposmic hyperosmia is warranted.

Health Services Research

M270. Association Between Counseling and Patient-Reported Treatment Adherence in Epilepsy

Lidia M.V.R. Moura, Emily L. Thorn, Thiago S. Carneiro, Michael P. Seitz, Andrew J. Cole, Barbara G. Vickrey and Daniel B. Hoch. Boston, MA and New York City, NY

Introduction: Epilepsy in adults is treated primarily through persistent use of anti-epileptic drugs (AEDs). Regardless of demographic and clinical characteristics of the patients, the most recent national practice guidelines recommend physicians to query about treatment side-effects on every visit (2014 AAN Epilepsy Quality Measures). This study examines whether evidence of treatment counseling is associated with increased patient-reported adherence to treatment.

Methods: We identified 243 adults with epilepsy who were seen at two major academic medical centers in an outpatient neurology setting and had at least two visits over a three year period. We abstracted demographic and clinical characteristics and offered them a phone interview. Counseling by physicians with respect to anti-seizure prophylactic treatment, according to the national guideline, was measured through a) phone interview (patient-reported treatment counseling) and b) medical records abstraction relevant to the study time-frame (physician-documented treatment counseling). Medication adherence was assessed using the validated Morisky's Medication Adherence Scale (MMAS-4). Complete adherence was defined as patient answer "no" to all questions. We used a Chi-square test to assess the association between treatment counseling (yes vs. no) and complete medication adherence (yes vs. no).

Results: There were 62 (25%) patients who completed the interviews. Participants and non-participants were comparable with respect to demographic and clinical characteristics; however, a smaller proportion of participants had a history of drug-resistant epilepsy than non-participants (17.7% vs. 30.9%, $p=0.04$). Among the participants, evidence of treatment counseling was present in 48 (77%) medical records (physician-documented treatment counseling) and reported by 51 (82%) patients. Participants reported a mean seizure frequency in 6 months of 7.6 ± 27.7 and the minority had treatment side effects

($n=12$; 20%). 28 (45%) patients reported complete adherence to treatment. The most common reason for incomplete adherence was missing dose due to forgetfulness ($n=31$, 91%). There was no association between treatment counseling (neither physician-documented nor patient-reported) and complete medication adherence ($p=0.22$ and 0.20).

Conclusion: Among patients with epilepsy, evidence of treatment counseling was not associated with patient-generated reports of treatment adherence.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Lidia Moura – Is the recipient of a 2015 Clinical Research Fellowship sponsored by the American Brain Foundation (salary) and reports no other disclosures.

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Barbara Vickrey – Receives funding from NINDS, California Community Foundation, and UniHealth Foundation (salary); Consultant – Genentech and reports no other disclosures

M271. Role of Pre-Stroke Major Depressive Disorder in the High Prevalence of DNR (Do Not Resuscitate) Utilization in Acute Hemorrhagic Stroke

Zeeshan Mansuri, Achint Patel, Tapan Mehta, Girish Nadkarni, Uvesh Mansuri, Sarah Noble, Zabeen Mahuwalla, Ashutosh Lodhi, Ruchir Goswami and Sanjeeva Reddy Onteddu. Philadelphia, PA and Fayetteville, AR

Objective: We sought to determine the association of pre-stroke major depressive disorder (MDD) on the high prevalence of DNR utilization in patients with acute hemorrhagic stroke (AHS).

Background: There is a significantly high prevalence of DNR utilization in patients of AHS with estimates ranging from 15-20%. Studies examining the relationship between pre-stroke MDD and DNR utilization are largely lacking.

Methods: We used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) from years 2011-2012. We identified AHS and MDD as a primary and secondary diagnosis respectively using validated International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM) codes. We defined DNR status with ICD code V49.86 entered during the same admission as a secondary diagnosis and estimated severity of illness by the 3MTM All Patient Refined DRG (APR DRG) Classification System. A hierarchical two level multivariate regression model was generated to estimate odds ratios (aOR) to estimate the independent effect of MDD on DNR utilization.

Results: We analyzed 142,519 patients with ICH out of which 12,523 (8.8%) had MDD. Proportion of DNR utilization was 15.5% vs. 16.9% ($p<0.01$) among MDD patients from 2002 to 2012. The median age of patients who had DNR utilization were similar in MDD and without MDD (80 vs 79, $p=0.10$). However hospitalizations

with DNR utilization and having MDD had higher proportion of female (67.9% vs. 56.4%, $p < 0.01$) and whites (84.3% vs. 74.1%, $p < 0.01$). In multivariable regression analysis, after adjusting for demographics, hospital level characteristics, APR DRG severity scale, DNR utilization was similar among those patients with or without MDD (aOR 0.9; 95%CI 0.8-1.1, $p = 0.31$).

Conclusion: Our study indicates that DNR utilization is more in females and whites. Also, as the results we obtained indicate, MDD does not have a major role to play in the high DNR utilization by AHS patients. This finding is significant given the complex relationship between competence, MDD and AHS. Other factors, which could play a role in the high prevalence of DNR utilization in whites and females needs to be explored in greater detail.

Neuromuscular Disease

M272. Ambulatory Blood Pressure Monitoring in Orthostatic Hypotension and Postural Orthostatic Tachycardia Syndrome

Jun-Sang Sunwoo, Do-Yong Kim, Jangsup Moon, Jung-Ick Byun, Jung-Ah Lim, Tae-Joon Kim, Jin Sun Jun, Byoungsu Park, Soon-Tae Lee, Keun-Hwa Jung, Kyung-Il Park, Sang Kun Lee and Kon Chu. Seoul, Republic of Korea

Blood pressure (BP) variability is associated with the risk of cardiovascular events and target organ damages. However, there has been little information concerning BP variability in orthostatic hypotension (OH) and postural orthostatic tachycardia syndrome (POTS). Herein, we measured 24h ambulatory BP and heart rates (HR) in patients with OH and POTS and normal controls (NC). A total of 71 patients were included: 21 OH; 17 POTS; 33 NC. The mean age of the patients was 48.6 years (standard deviation [SD], 18.2) and 62% were female. On an average, patients with POTS were younger than other groups ($p < 0.001$). Orthostatic intolerance symptom scores measured by questionnaires were 10.2 (SD, 6.0), which were not different among groups. Patients with OH had a higher awake SBP than patients with POTS ($p = 0.033$), but there was no difference in the mean DBP. Regarding BP variability, the SD and coefficient of variation (CV) of sleep SBP were significantly higher in OH patients compared with POTS patients ($p = 0.014$ and 0.035). BP variability of DBP did not differ between groups. In addition, the extent of morning BP surge, BP dipping during sleep as well as the difference between awake and sleep BP were not different significantly. Regarding HR variability, there was a marginal trend toward the higher CV of 24-h and awake HR in patients with OH ($p = 0.054$ and 0.051). Among BP variability parameters, only the SD of 24-h DBP were significantly correlated with subjective symptom scores ($\rho = 0.234$, $p = 0.05$). Our findings indicated that patients with OH had increased BP variability especially during sleep compared to patients with POTS. Further study with larger populations is warranted.

M273. Winged Scapula Secondary to Neuroborreliosis

Anna M. Bank, Matt T. Bianchi and Shibani S. Mukerji. Boston, MA

Background: Neuroborreliosis is a known complication of Lyme disease, occurring in 15% of cases. CSF tests for the spirochete *Borrelia burgdorferi* include PCR and enzyme immunoassay (EIA). We present a case of painful Lyme meningoradiculoneuritis, including brachial neuritis and involvement of the long thoracic nerve, with negative Lyme PCR and positive Lyme EIA, illustrating the clinical value of EIA versus PCR for neuroborreliosis.

Methods: Case report.

Results: A 76-year-old woman presented in September with 10 days of band-like, intractable pain extending from the waist to the shoulders and neck and accompanied by a raised erythematous rash. She was treated with analgesics and antivirals for possible shingles. She lived in a tick-infested region. Her neurological exam showed a right pronator drift and weakness of right shoulder abduction and elbow extension. MRI of the brain and spine demonstrated T1 post-contrast enhancement of the left facial nerve and geniculate ganglion, and both oculomotor nerves, as well as diffuse leptomeningeal enhancement of the spinal cord, cauda equina nerve roots, and dorsal and ventral nerve roots of the lower thoracic levels. CSF studies showed 453 WBC/mm³ (92% lymphocytes), normal glucose, and total protein 109 mg/dL. Lyme IgG serologies were present in serum. CSF PCR was negative for Lyme, enterovirus, CMV, HHV6, HSV 1 and 2, VZV, EEE, WNV, and arbovirus. CSF cytology was negative on three independent samples. She was presumptively treated for neuroborreliosis with intravenous ceftriaxone for four weeks. MRI of the spine at two month follow up showed near resolution of enhancement. At that time, frozen pre-treatment CSF samples were reanalyzed for antibodies to *B. burgdorferi* using antibody capture EIA, demonstrating CSF:serum ratio of IgM = 2.2, IgG >42 and IgA = 19.4, confirming the diagnosis. Examination at two and six months showed prominent medial winging of the right scapula on arm flexion, and weakness of intrinsic hand muscles, suggestive of C5 through C8 involvement including long thoracic nerve impairment. Her neuropathic pain resolved by six months.

Conclusion: Brachial neuritis and scapular winging due to Lyme disease have been rarely been reported. We suspect that this patient's symptoms were secondary to direct nerve invasion by *B. burgdorferi*. Despite extensive neurological infection, she had a negative CSF Lyme PCR, reinforcing the insensitivity of this test and the importance of EIA to confirm the diagnosis.

M274. Sensory and Autonomic Neuropathy in the db/db Mouse

Blessan Sebastian, Ben Liu, Baohan Pan, Yiyue Zhang, John Fissel, Ying Liu and Michael Polydefkis. Baltimore, MD

We sought to characterize large and small sensory and autonomic nerve fiber structure and function in the DM II mouse model. 45 db/db mice and 36 db/+ mice were studied. Large myelinated fiber function was assessed by standardized electrophysiology, small fiber sensory function by

thermal threshold, and autonomic function by sweat droplet quantification. Small unmyelinated nerve fiber structure was defined by intraepidermal nerve fiber density (IENFD) and sweat gland nerve fiber density (SGNFD) derived from hind limb footpads. All measures were performed at 6wk and 24wk.

There were no differences in NCV, CMAP, or SNAP at 6wk in db/db vs. db/+ animals. In contrast, footpad withdrawal to heat was delayed at 6wk in db/db vs. db/+ animals ($P < 0.05$). IENFD and SGNFD were both reduced at 6wk in db/db vs. db/+ animals ($P < 0.05$). Comparing %reduction in db/db vs. db/+ animals, SGNFD was more severely reduced than IENFD, suggesting that autonomic unmyelinated nerve fibers are affected more severely than sensory unmyelinated nerve fibers (reduction of SGNFD vs. IENFD was 50.7% vs. 33%).

Sweat droplet formation was reduced at 12 min in db/db vs. db/+ animals ($P < 0.001$). Furthermore, we compared the correlation in denervation with function tests. We observed that %denervation in both autonomic and somatic systems are consistent: for autonomic, %reduction of SGNFD vs. %reduction of sweating spots at 12 min was 50.7% vs. 49.8%; for somatic, %reduction of IENFD vs. %delayed thermal latency was 33% vs. 26.32%.

By 24wk, abnormalities in large myelinated nerve fiber function was observed in db/db vs db/+ animals. NCV, CMAP, and SNAP were reduced in db/db animals ($P < 0.05$). Abnormalities in small fiber structure and function test were more severe compared to 6wk data (IENFD in db/db animals at 24 weeks vs. 6 weeks: $P < 0.001$; SGNFD in db/db animals at 24wk vs. 6wk: $P < 0.05$). No significant difference for IENFD or SGNFD between control animals at 24 and 6 weeks.

The data indicate that structure and function of large myelinated and small unmyelinated nerve fibers are affected in db/db animals. Small unmyelinated fibers were affected earlier than large myelinated fibers. Autonomic fiber structure and function were affected to a greater degree than unmyelinated sensory nerve fibers.

M275. “Tachycardia, Twitches and the Thymus: What’s the Link?”

Ali Sheharyar, Anusha Edara, Aparna M. Prabhu, Sumeet S. Multani, Yongwoo J. Kim and Rabia Choudry. Philadelphia, PA

Introduction: Morvan’s syndrome is a rare, potentially fatal condition of peripheral nerve hyperexcitability with CNS manifestations and dysautonomia. Strong association with underlying thymoma and with auto-antibodies against voltage-gated potassium channel complex proteins (anti-VGKC) including contactin-associated protein-like 2 (Caspr2) and leucine-rich glioma inactivated protein 1 (LGI1-Ab) suggests an autoimmune etiology. Hallmark features are encephalopathy with hallucinations, dysautonomia, and clinical or electrophysiological evidence of myokymia/neuromyotonia.

Case: A previously healthy 49-year-old male presented with 3 weeks of fatigue, progressive muscle weakness and muscle twitching. Review of systems was positive for

insomnia, hyperphagia and severe constipation. Physical examination revealed hypertension, resting tachycardia and diaphoresis. Neurological exam reflected generalized, irregular muscle contractions primarily in proximal musculature, weakness and diminished reflexes in the legs. No sensory deficits were appreciated. Initial labs were significant for elevated Creatine Kinase with the rest of the labs including thyroid function tests essentially normal. Contrast-enhanced MRI brain was unremarkable. EMG studies revealed fasciculation potentials only. CSF showed mildly elevated proteins with no other abnormalities. During the hospital stay, the patient was noted to have marked spatial/temporal disorientation, hallucinations with compulsive behavior and hypersexuality. EEG was normal. A presumptive diagnosis of Morvan’s syndrome was entertained and therapy with plasma exchange and corticosteroids initiated with improvement in symptoms. Contrast-enhanced CT Chest revealed an anterior mediastinal mass suggestive of thymic tumor. Serum tested positive for Anti-AchR and Anti-VGKC antibodies. Unfortunately, patient eloped from the facility while awaiting a thymectomy and suffered a fatal PEA arrest.

Conclusion: The clinical features of Morvan’s syndrome are diverse; however diagnosis can be made in the presence of encephalopathy with hallucinations, autonomic instability and myokymia and/or neuromyotonia. Electromyographic evidence of neuromyotonia supports the diagnosis but its absence does not completely exclude Morvan’s syndrome, especially in patients with a typical clinical picture. Thymic tumors are the most commonly associated neoplasms and should be suspected even in the presence of another apparent etiology.

M276. Neurological Abnormalities in Cerebrotendinous Xanthomatosis: Case Series and Literature Review

Janice C. Wong, Kailey Walsh and Florian S. Eichler. Boston, MA

Objective: To determine the most commonly reported neurological abnormalities and their temporal onset in cerebrotendinous xanthomatosis (CTX) using a case series and a comprehensive literature review.

Methods: In the case series, 4 patients with confirmed CTX diagnoses were evaluated longitudinally over 3 to 14 years by a neurologist at Massachusetts General Hospital. In the literature review, we comprehensively reviewed published case series or cohorts of CTX patients. A search performed using PubMed for “cerebrotendinous xanthomatosis” yielded 590 publications. Exclusion of papers not published in English, papers not about human patients, review papers or case reports with fewer than 2 CTX patients resulted in 63 publications that were included in the study. In analysis of these publications, the presence and age of onset (if available) of neurological abnormalities in CTX patients were documented. To determine the proportion of publications reporting a specific neurological abnormality, the presence of a reported neurological abnormality was counted only once for each publication, even if multiple patients were reported to have the abnormality.

Results: In the case series of 4 patients (1 female; age at diagnosis ranged from 27 to 41 years old), who all received chenodeoxycholic acid therapy, neurological symptoms included speech changes (4), gait abnormality (4), ataxia (3), tremor (3), cognitive difficulty (2), psychiatric changes (2) and sensory loss (2). In the literature review of 63 publications, the most commonly reported neurological symptoms were cognitive difficulty (84.1% of publications), ataxia (81.0%), corticospinal tract abnormality (81.0%), sensory loss (46.0%), seizure (46.0%), speech changes (33.3%), gait abnormality (28.6%), psychiatric changes (23.8%), hyperreflexia (23.8%) and parkinsonism (19.0%). A timeline of onset of neurological abnormalities in CTX patients was illustrated to understand the temporal sequence of these abnormalities during CTX disease progression.

Conclusions: Identifying the most commonly reported neurological abnormalities and understanding their temporal onset in CTX are important for diagnosis in clinical practice and evaluation of therapeutic efficacy in clinical trials.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Janice Wong: Nothing to disclose.

Kailey Walsh: Nothing to disclose.

Florian Eichler: There is an industry-sponsored research contract (Retrophin) with MGH. No personal compensation to disclose.

M277. Neurologic Involvement in V122i Familial Amyloidosis

Sami Khella, Brian Drachman, Patricia DiVito, Thomas Brannigan III and Michael Polydefkis. Philadelphia, PA

Objective: Describe new phenotype in V122i familial amyloid cardiomyopathy.

Introduction: Late onset cardiomyopathy with heart failure is the phenotype of familial amyloidosis, which occurs in African Americans (AA) in the United States at a rate 4 times that of whites after the age of 60 years. 3.9% of AA are heterozygous for the amyloidogenic allele where isoleucine substitutes for valine at position 122 (Val-122-Ile) of the serum carrier protein transthyretin (TTR). We report on the observed neurologic changes in addition to the cardiomyopathy. Setting: Academic, tertiary care referral centers

Methods: case series, retrospective review

Results: Seven patients with the ATTR V122i gene mutation had amyloid staining on myocardial biopsies and one patient with amyloid staining on a flexor retinaculum biopsy. All had symptoms of peripheral neuropathy. Causes of a peripheral neuropathy other than amyloid were excluded. All seven patients had axonal predominant progressive peripheral neuropathy, confirmed by NCV and EMG. One patient had a superimposed painful (narcotic requiring), lumbar radiculopathy, by EMG, without corresponding structural MRI abnormalities. One patient had multiple entrapment neuropathies (bilateral wrists and elbows), as well as, a prominent small fiber neuropathy documented by reduced intraepidermal nerve fiber density and autonomic nerve abnormalities with reduced sweat gland nerve fiber density.

Conclusion: Seven ATTR V122i patients who are known to have amyloid cardiomyopathy also have a peripheral neuropathy probably due to amyloid deposition in the nerve. We also describe a patient with the carpal tunnel syndrome and a progressive peripheral neuropathy without a cardiomyopathy with this mutation. In one patient, the symptoms of radiculopathy, confirmed by EMG, may be explained by dural amyloid infiltration. Further studies of this phenotype are warranted to confirm these findings and to determine incidence and prevalence of this potentially treatable and likely under recognized neuropathy. This case series expands our previous report of 6 patients¹ and amplifies a recent description of a single patient.²

1. Khella S et al: Neurologic Involvement in V122i Familial Amyloidosis International Symposium on Familial Amyloid Polyneuropathy. 2011

2. Carr AS et al: Neuromuscul Disord. 2015.

M278. Clinical and Electrophysiological Response to a Factor Xa Inhibitor in Distal Acquired Demyelinating Sensory Motor Neuropathy (DADS)

Alexis A. Lizarraga, Thomas I. Cochrane and Aaron L. Berkowitz. Miami, FL and Boston, MA

Objective: To report a novel case of clinical and electrophysiologically confirmed improvement of an inflammatory neuropathy with rivaroxaban.

Background: Distal acquired demyelinating sensory motor neuropathy (DADS) neuropathy is a subtype of chronic inflammatory demyelinating polyneuropathy (CIDP). The pathogenesis of the DADS variant of CIDP remains poorly understood, with both cellular immunity, involving CD8+ T-cell activation, and humoral factors implicated. Rivaroxaban is an oral anticoagulant that works as a direct factor Xa inhibitor, which has been shown to interfere with the pro-inflammatory actions of coagulant and fibrinolytic processes, leading to activation of proteinase-activated receptors and downregulation of interleukin-6, tumor necrosis factor- α , and monocyte chemoattractant protein. There is therefore interest in the role of Xa inhibitors as anti-inflammatory agents.

Methods: Case report

Results: An 87-year-old man presented with tingling in the extremities and gait imbalance. Examination demonstrated decreased vibratory sensation to the knees, trace right biceps and patellar reflexes but areflexia elsewhere, and a wide based gait with walker dependence. Nerve conduction studies (NCSs) revealed prolonged distal latencies and distal-predominant borderline demyelinating range conduction velocities, suggestive of DADS neuropathy. The patient deferred immunomodulatory treatment. The patient was subsequently placed on rivaroxaban for a lower extremity DVT, and noted marked improvement of dexterity and sensation. Examination revealed emergence of normal reflexes at the biceps, brachioradialis, and patellae bilaterally, improvement of vibration sense and walker independence. Repeat NCS demonstrated emergence of the previously-absent median and radial sensory responses and median motor responses.

Conclusions: Elevated pro-inflammatory cytokine levels have been demonstrated in the CIDP population, and

thusly rivaroxaban may modulate inflammation in DADS. This case report identifies a possible role for factor Xa inhibitors in the treatment of DADS neuropathy, potentially via anti-inflammatory mechanisms. Further studies with a larger patient population are needed.

M279. Vasculitic Neuropathy in the Setting of Nivolumab Therapy for Metastatic Mesothelioma

Bing Liao, Wei Wang, Julie Hammack and Michelle Mauermann. Rochester, MN

Introduction: Nivolumab is a novel monoclonal antibody developed to inhibit the immune checkpoint programmed death 1 (PD-1) receptor. It has been used for treatment of metastatic or unresectable melanoma, non-small cell lung cancer, renal cell carcinoma and mesothelioma. It restores the patient's antitumor immune response that has been suppressed by cancer. PD-1 checkpoint inhibitors are associated with a spectrum of immune-related adverse events; however vasculitic neuropathy caused by nivolumab has not been reported. Most immune-related adverse events are clinically well-manageable by discontinuing the offending medication, and by using systemic corticosteroids.

Objective: To describe a patient who developed pathologically confirmed peripheral nerve vasculitis after being treated with nivolumab for metastatic mesothelioma.

Case report: A 31 year-old man experienced tingling in his left foot 3 months following treatment with nivolumab intravenous infusion at 3 mg/Kg daily on day 1 of 14-day cycle for metastatic mesothelioma. Two weeks later, similar symptoms involved the right foot and both hands. One month later, he noted weakness which started in his left foot, followed by the right one. Neurological examination demonstrated asymmetric sensorimotor neuropathy with bilateral foot drop and hand weakness. Electromyogram and nerve conduction studies on his showed evidences for a severe axonal sensorimotor peripheral neuropathy. A left sural nerve biopsy revealed a fulminant vasculitic neuropathy characterized by a severely decreased density of myelinated fibers, active axonal degeneration and fibrinoid necrosis of large nerve vessels. Nivolumab was discontinued after the diagnosis of peripheral nerve vasculitis. He also received methylprednisolone intravenous infusion at 1 g per day for five consecutive days. The patient reported improvements of his strength.

Summary/Conclusions: This case highlights the possible association of nivolumab with peripheral nerve vasculitis. Early recognition and discontinuation of treatment is paramount.

Interventional Neurology

M280. Treatment of Complex Regional Pain Syndrome type II (CRPS-II) with Simultaneous Multi-Target Spinal Cord and Motor Cortex Stimulation: A Case Report

Faddi G. Saleh Velez, Juanita Duran, Erich T. Fonoff and William O. Contreras. Charlestown, MA; Sao Paulo, Brazil and Bucaramanga, Santander, Colombia

Background: Deafferentation pain (DP) secondary to brachial plexus avulsion (BPA) is present in approximately 90% of patients (preganglionic lesions) and frequently

complicates as complex regional pain syndrome type II (CRPS-II). CRPS-II is usually refractory to most pharmacologic treatments. Positive results have been reported after invasive stimulation; however long-lasting relief of symptoms has not yet been achieved.

Objective: We present a case of long-lasting pain relief of CRPS-II after combined multi-target spinal cord stimulation (SCS) and motor cortex stimulation (MCS).

Method: Case Report

Case Description: A 30 year-old woman was diagnosed with DP syndrome secondary to right BPA by firearm wound. She was treated with a combination of opioids, tricyclic antidepressants and physical rehabilitation with no relief of pain (Visual Analogous Scale (VAS):10); consequently diagnose with CRPS-II. SCS was indicated to the patient. Pulses of electrical stimulation were delivered to the dorsal aspect of the spinal cord through an implanted 16-channel, multi-program stimulation system. A 40% pain relieve was observed post-SCS treatment. However, pain levels increased after a traumatic event over the patient's right arm and scapula; therefore, an increase in medication doses and pulse intensity was needed. A year after, the patient was admitted to the emergency room with signs of opiates overdose secondary to recurrent pain crisis. These events were correlated to depletion of the SCS pulse generator battery, managed with surgical implantation of a rechargeable one. Further assessment of pain reported VAS of 7 with combined SCS and maximum doses of Methadone, Tramadol, and Venlafaxine. Due to the presence of secondary effects from the medications, MCS was indicated. Two quadripolar epidural electrodes were implanted over left primary motor cortex (M1), showing immediate intra-operative pain relief. During a year follow-up, pain remained controlled (VAS:3) during the on vs. off stimulation condition of the MCS device. Additionally, important improvement in right upper limb skin color, muscular mass volume, and sensitivity was observed.

Conclusion: Combined treatment (SCS+MCS) may be a suitable option for patients with CRPS-II. Although the pathophysiologic process underlying CRPS-II remains unclear, existing evidence suggests complex reorganization of the nervous system. Treatment of maladaptive changes with SCS and MCS can functionally modulate these abnormal neuroplastic changes, and ameliorate pain. Further studies are needed to completely understand the mechanisms underlying these multi-target pain treatments.

Autoimmune Neurology

M281. A Rare Case of Autoimmune Polyendocrine Syndrome Type 2 Associated with Anti-GAD Positive Ataxia and Seizure

Shri K. Mishra, Nastaran Rafiei, Hadi Mohammad Khanli and Parastou Tizro. Los Angeles, CA

Background: Autoantibodies to glutamic acid decarboxylase (GAD Ab) have been described in patients with autoimmune polyglandular failure. In addition, high titres of GAD

Ab were seen in a few patients with progressive cerebellar ataxia, suggesting an autoimmune origin.

Objective: This is a report of a patient presenting with cerebellar ataxia associated to autoimmune polyendocrine syndrome type 2.

Case report: We report a 48 years old right handed Hispanic female with a past medical history of Addison's disease, premature ovarian failure and Hashimoto's hypothyroidism presented with vertigo, nystagmus, slowly progressive ataxia and one episode of generalized tonic clonic seizure. Based on the history of Addison's disease, premature ovarian failure and hypothyroidism this patient was diagnosed with autoimmune polyendocrine syndrome type 2 or Schmidt's syndrome. For 8 years, she had complained of slowly progressive gait imbalance, and vertigo. Positive findings in neurological physical exam included rotational nystagmus noted on horizontal gaze and impaired tandem gait. Muscle strength were 5/5 in all extremities with down going plantar reflexes and deep tendon reflexes were symmetric and 1+. Cranial nerves exam were intact. The medication included hydrocortisone, levothyroxine and keppra.

Methods: Brain imaging, routine biological and detailed immunological screening as well as a genetic study for spinocerebellar ataxia type 10 were performed.

Results: Brain magnetic resonance imaging revealed mild cerebellar atrophy. Routine biological screening showed low aldosterone and high renin which is confirmative for Addison's disease. Immunological screening was positivity for high titers of GAD Ab and negative for Purkinje Cell Cytoplasmic antibody. Serum FSH was high in post-menopausal range. Genetic test result was negative for spinocerebellar ataxia type 10.

Conclusion: Cerebellar ataxia associated with high titers of GAD antibody is a rare condition affects patients specially females with stiff person syndrome, late onset diabetes mellitus and other autoimmune disorders such as autoimmune polyendocrine syndrome type 2 or Schmidt's syndrome.

Dementia and Aging

M282. Visual Hallucinations as the Initial and Predominant Presenting Symptom in an 83-Year-Old Patient with Posterior Cortical Atrophy

Erin L. Sadler and Hamid R. Okhravi. Norfolk, VA

Posterior Cortical Atrophy (PCA) is a nonamnestic presentation of dementia most commonly due to underlying Alzheimer's disease. Progressive visuospatial and visuoperceptual defects, including features of Balint syndrome (simultanagnosia and oculomotor apraxia), are prominent. Criteria compiled by Tang-Wai (Neurology, 2004) are widely used throughout the literature to guide diagnosis. A minority of patients with posterior cortical atrophy develop visual hallucinations (VH) during their progressive clinical course. There is unclear evidence for visual hallucinations intrinsic to PCA: previous reports describe such hallucinations as precedent to the development of Lewy Body Dementia (DLB). In these patients, VH emerge years after dementia

presentation, and patients exhibit parkinsonian features. We describe an unusual case of posterior cortical atrophy in which visual hallucinations are the initial and predominant presenting symptom, predating the development of dementia by several years, and which notably lacks motor features of DLB.

The patient is an 83-year-old female who at age 73 began experiencing frequent VH of intruders in the home and mild impairment in distance vision. She continued having progressive visual and memory problems and decline in her functional status. At 78 years of age, she was diagnosed with dementia of unknown etiology. Her cortical blindness, which is her main clinical feature, has progressed to the point that, at age 83, she is dependent in almost all activities of daily living. Comprehensive eye examination by her ophthalmologist ruled out other causes of blindness, such as cataract, glaucoma, and macular degeneration.

The diagnosis is supported by MRI demonstrating occipital, parietal, and hippocampal volume loss. Additionally, 18F-fluorodeoxyglucose (FDG) PET results are consistent with prior series of PCA, demonstrating symmetric hypometabolism of the parietal and occipital lobes with preservation of frontal lobar and basal ganglial activity. Presentation of VH several years prior to significant cognitive and visual impairment in a patient without prominent motor deficits suggests that VH may be intrinsic to PCA.

Education

M283. The Curse of the Goddess

Sanam Anwer, Apoorv Prasad and Mihai Cornelia. Syracuse, NY

Introduction: Ondine's curse is a rare syndrome which signifies failure of automatic respiration. Although rare in adults, it is seen in children as congenital hypoventilation syndrome. Acquired causes have been implicated in adults due to multiple sclerosis, brainstem infarction, posterior fossa surgery etc. {1}. Here we discuss a case of acquired central hypoventilation secondary to brainstem astrocytoma.

Case report: 34 year old female with past medical history significant for brain stem astrocytoma grade 2, (1p/19q deletion negative), s/p radiation therapy followed by radiation necrosis, resulting in quadriplegia, neurogenic bladder and orthostatic hypotension who was admitted under hematology oncology service for further evaluation of new 1.3 cm non-enhancing mass along the posterior aspect of the medulla oblongata. It was postulated that this new mass could be due to residual or recurrent tumor vs post-surgical lobulated tissue. During her hospital stay code blue was activated. Neurology was consulted immediately as the patient was suspected to have seizure like activity. As per the description by the nursing staff, the patient was awake and was being turned, when she was witnessed to have apneic spells by the nursing staff. The spells were described as "patient turning cyanotic with unresponsiveness" There was no postictal state witnessed. On examination the patient was alert and oriented. She was quadriplegic with symmetric hyper reflexia. The patient was immediately transferred to

Medical Intensive Care Unit (MICU). During the next few days several episodes of hypoapnea and apnea were witnessed when the patient was asleep. She eventually was put on positive pressure ventilation which prevented further attacks.

Conclusion: Ondine's curse is a catastrophic breathing pattern which is a result of the failure of automatic breathing center in the descending anterolateral medullocervical pathway.

[2] During sleep when the patient is not aware of breathing, the respiratory drive does not work and patient goes into episodes of hypoventilation and apnea. Patients generally require tracheostomies and lifetime mechanical ventilation in order to survive. However, it has now been shown that Biphase Cuirass Ventilation can effectively be used without the need for a tracheotomy.[3] In severe cases apnea has also been reported when the patient is not asleep[4]. Our case is unique in this way as apneic spells were also witnessed while the patient was awake.

Headache and Pain

M284. Delayed Exacerbation of Burning Mouth Syndrome

Laila E. Ahmed and Alan R. Hirsch. Cane, Saint Vincent and the Grenadines and Chicago, IL

Introduction: Spicy foods have been noted to worsen Burning Mouth Syndrome (BMS). In these instances, the burning occurs coincident, or immediately after, ingestion. Exacerbation of BMS following a prolonged delay after consumption of a food has not heretofore been described.

Methods: Case Study: A 47-Year old right handed female presented with a four-year history of BMS, of sudden onset, initially on top of the tongue and over time spreading to the gums, top of her mouth, palate and lips. Her pain is constant, with intensity levels ranging from 2/10-8/10, worsening in the evening. She could eat some foods without problem, other foods would immediately exacerbate her BMS, others would, one hour to several hours after ingestion, worsen the burning, which would last several hours to a whole day in duration. For instance, some foods, such as rice, cheese, eggs, and crackers cause no pain at all. On the other hand, eating sugar, raw onion, coffee, mint, or cinnamon immediately causes the burning pain to worsen from baseline of 2/10 to become 5/10 which lasts for several hours. Bread, potatoes, French fries and potato chips cause the pain to exacerbate one to two hours after eating from 2/10 to 4/10 and the pain would last for several hours. Eating the foods that do not cause a problem for her, after eating the inciting foods does not prevent the delayed burning from occurring.

Results: Abnormalities in Neurologic Examination: Motor Examination: Drift Testing: mild left pronator drift with bilateral abductor digiti minimi signs. Reflexes: 3+ throughout. Bilateral Hoffman reflexes. Chemosensory Testing: Olfaction: Brief Smell Identification Test: 11 (normosmia). Alcohol Sniff Test: 9 (hyposmia). Pocket Smell Test: 3 (normosmia). Retronasal Smell Testing: Retronasal Smell

Index: 9 (normal) Gustatory Testing: Propylthiouracil Disk Taste Test: 9 (normogeusia). Taste Quadrant Test: patchy loss over tongue and palate to sodium chloride, sucrose, citric acid. Decreased anterior tongue to sodium chloride, sucrose, citric acid and alcohol. Taste weakness to quinine throughout tongue and palate. Other: Sjoren Antibodies: negative. Fungal culture: positive for *Candida albicans*.

Discussion: Possibly the delay is related to food particles associated with remnants of mastication persisting on the tongue, acting as prolonged irritants. *Candida albicans* may have acted on these food remnants creating irritating byproducts. In those with BMS, query should be made about temporal patterns of pain in relation to eating specific foods.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Alan R. Hirsch MD has ownership in the Smell & Taste Treatment and Research Foundation and consults with multiple companies and health care facilities.

M285. Burning Mouth Syndrome; Induction by Quetiapine

Sumit Kanwar, Manisha R. Chand and Alan R. Hirsch. Weston, FL and Chicago, IL

Objective: Burning mouth syndrome (BMS) while usually idiopathic, has been demonstrated to be caused by myriad conditions, including a number of different medications. While quetiapine, a widely used antipsychotic can cause glossodynia, BMS has not been reported.

Methods: Case 1: A 35 year old female with life-long depression and multiple suicide attempts. She was started on escitalopram and later quetiapine. Within five weeks after beginning quetiapine, she developed persistent burning pain in the anterior tongue, continuous, all day, level of 7/10 in severity. Concurrent with the burning is a distorted ability to taste so that chocolate tastes sour. She denies any change in her ability to smell. Her BMS has continued despite tapering off quetiapine. Case 2: A 45 year old right handed female, six weeks after beginning treatment with duloxetine, quetiapine and alprazolam, noted a gradual onset of oral irritation while eating spicy foods. This increased over time to a burning sensation with all foods and ultimately became a burning in the anterior tongue and anterior palate independent of eating. Initially mild, this became more severe, 10/10 (especially at night) and is constant. It is aggravated with spicy foods, citrus, coffee, wine, beer, and foods with high texture. Coincidentally, she also developed a metallic taste, which occurs twice a week in the anterior tongue and palate, 4/10 in severity and is made better with food and sleeping.

Discussion: There exists multiple possible mechanisms to describe the pain associated with quetiapine induced BMS. Quetiapine may act to inhibit the taste, and taste inhibited pain, this induces disinhibition of pain. It may cause inhibition of large vibratory A fibers causing C-fiber (pain) disinhibition. The patient may be suffering from misattribution syndrome: the pain existed before but is inappropriately

ascribed to quetiapine. The BMS may have existed prior to the quetiapine but underlying depression may have lessened, so they may now be energized and have enough self-confidence to complain about the pain, as opposed to suffering silently with it. Quetiapine's anticholinergic properties may cause mouth dryness and this can secondarily predispose them to BMS. These cases suggest it is warranted to query those on quetiapine for symptoms of burning mouth syndrome.

Neuromuscular Disease

M286. Atypical Presentations of Vitamin B12 Deficiency in a Population of Northern Manhattan Clinic Patients

Elina Zakin and Susan Shin. New York, NY

Background: The water-soluble B vitamins, including cyanocobalamin, thiamine, and pyridoxine, are essential for optimal nervous system function. Pernicious anemia, celiac disease, bariatric surgery, and vegan diet are all implicated in B12 deficiency. A vitamin B12 level is often ordered when a patient presents with symptoms suggestive of neuropathy or memory loss. With the socioeconomic heterogeneity among the Northern Manhattan population of neurology clinic patients, vitamin B12 deficiency is not uncommon, and may be due to malnutrition. We have observed that vitamin B12 deficiency in this population is often not recognized due to its atypical presentation.

Methods: Retrospective chart review of vitamin B12 levels in the uninsured/under-insured population of Northern Manhattan neurology clinic patients over four years (2012-2016).

Results: Of the 160 patients who had low vitamin B12 levels (<300 pg/mL), 57 (36%) individuals had chief complaints of non-classical symptoms, including headache, dizziness and diffuse body aches, 51 (31%) individuals had a chief complaint of extremity paresthesias, and 52 (32%) individuals had a chief complaint of cognitive impairment. Of those individuals with non-classical complaints, 26 (46%) had B12 deficiency (<211 pg/mL); while 18 (35%) individuals with extremity paresthesias and 20 (38%) individuals with memory impairment had B12 <211 pg/mL. Within the group of 57 individuals with non-classical symptoms, 20 (35%) individuals reported the complaint of dizziness; 15 (26%) individuals reported the complaint of headache; 13 (22%) individuals reported the complaint of diffuse body aches; 5 (9%) individuals reported the complaint of diffuse fatigue. Only one individual had pernicious anemia, and six individuals underwent bariatric surgery. No individual reported specific dietary restrictions. Co-morbid thiamine (<70 nmol/L) deficiency was present in 15 (9%) individuals. 51 (32%) individuals reported improvement of their symptoms post-repletion, 15 (9%) reported no change, and 94 (59%) were lost to follow up.

Conclusion: Vitamin B12 deficiency is most commonly associated with neurologic symptoms of extremity paresthesias and cognitive impairment, though more atypical presentations can occur. Non-classical chief complaints of dizziness, headache, diffuse body aches and fatigue were

seen in our patient population who had vitamin B12 deficiency without dietary restrictions or typical risk factors for malabsorption, suggesting underlying malnutrition. We postulate that this uninsured and under-insured patient population would benefit from evaluation of vitamin B12 deficiency as a cause of their constellation of symptoms as they may not present with the typical symptoms of vitamin B12 deficiency.

M287. Novel NPC1 Gene Variant in Adult-Onset Niemann-Pick Disease Type C

Shri K. Mishra, Maren Schuner, Nasheed Jamal, Hadi Mohammad Khanli and Parastou Tizro. Los Angeles

Background: Niemann-Pick disease type C (NPC) is a rare autosomal recessive lysosomal storage disease that has an extremely heterogeneous clinical presentation. The adult form of NPC typically manifests as neurological and psychiatric symptoms with or without hepatosplenomegaly. This disorder is associated with mutations in either the NPC1 or NPC2 gene.

Objective: To report the clinical course of a patient presenting with progressive neurocognitive decline who was found to have biochemical testing consistent with NPC and whole exome sequencing with two NPC1 gene variants, one of which has not been previously described to be pathogenic in NPC.

Case report: We report a 36 year-old Hispanic man, with history of depression, hyperlipidemia and obesity but no family history for any neurologic disorders, who presented at age 31 years with slowly progressive neurocognitive decline. At age 8 years, he began having slowed fine motor movements and mild forgetfulness. In his early twenties, he began having difficulty driving, walking, and finding words. In his late twenties, he developed gradually progressive aphasia, impaired memory, delayed reaction time, dysphagia, resting tremor, paresthesias, and gait instability. At age 31 years, he was referred to the Neurology Clinic after several falls. On exam, he was found to have short-term memory loss, impaired attention, frontal release signs, and restricted extraocular eye movements. Exam also showed increased tone, brisk deep tendon reflexes, bilateral upgoing toes, wide-based gait with dystonic feature in upper extremities. The patient was later referred to multiple subspecialty clinics for in-depth examinations and an extensive diagnostic workup.

Methods: Brain imaging, routine biological and screening tests for secondary causes of ataxia and dementia as well as a genetic study including genome sequencing were performed.

Results: Routine lab screening revealed normal TSH, anti-TPO/TG, ANA, HIV, Ceruloplasmin, urine Cu, homocysteine, MMA, Vitamin E, urine heavy metals, and anti-GAD/gliadin. Enzymatic assay for arylsulfatase A and genetic study for Huntington disease and spinocerebellar ataxia type 17 were all negative. Brain MRI showed mild posterior periventricular white matter changes with mild cerebral atrophy. Whole exome sequencing revealed two heterozygous variants in the NPC1 gene — one known

pathogenic variant (c.1554-1009G>A, p.?) and one variant of unknown significance (c.2524T>C, p.Phe842Leu). Oxysterol testing was consistent with NPC.

Conclusion: Given the oxysterol test results and the patient's clinical course, the patient has NPC due to one known pathogenic variant and one novel variant of the NPC1 gene.

M288. Familial Amyloid Polyneuropathy (FAP) Accompanied with Severe Post-Micturitional Abdominal Pain and Orthostatic Hypotension with Novel Transthyretin (TTR) Mutation (TTR, Lys80Arg)

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Hereditary transthyretin (TTR) amyloidosis is characterized by TTR amyloid deposits in various tissue sites and organs such as peripheral nerves, heart, gastrointestinal tract, kidneys, eyes, and leptomeningeal tissues of the brain. So far, more than 130 mutations in the TTR gene have been found. Here, we report a Japanese late onset case with familial amyloid polyneuropathy (FAP), caused by a novel TTR mutation TTR (Lys80Arg), who shows orthostatic hypotension, electric shock like pain and allodynia in the trunk and severe pre/post micturitional pain with mild neuropathy and cardiopathy without vitreous opacity. Immunohistochemistry and serum-mass spectrometry showed that the amyloid fibrils were composed of TTR, in conjunction with a typical FAP phenotype. His younger brother developed mild polyneuropathy without micturitional pain, who had a novel compound heterozygous TTR Val30Met/Lys80Arg mutation. These results indicate that the novel TTR mutation (Lys80Arg) is the cause of amyloidosis and symptoms of micturitional abdominal pain. However, a novel compound heterozygous TTR Val30Met/Lys80Arg mutation may cause mild and late-onset of systemic amyloidosis.

M289. Genetic Analyses and Counselling of Sporadic Amyotrophic Lateral Sclerosis in Japan

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Amyotrophic lateral sclerosis (ALS) seemed unrelated with genetic factors, except for 5-10% of familial cases. However, recent reports demonstrate that 11% of patients with sporadic ALS (SALS) have genetic mutations. Genetic counseling is complicated for patients and families to accept unwilling genetic results in sporadic cases. It is especially difficult, when the mutations are novel because their pathogenicity remains unclear. In this study, we analyzed genes known to be causative for ALS in 94 Japanese patients with SALS. We report representative cases of genetic counseling for mutation-positive families. We found nine mutations including four novel mutations (SOD1, VCP [p.R487H], p62 [p.A53T and p.P439L]). In contrast to the results in

the Western countries, no mutations were identified in the C9ORF72 gene. We tested the pathogenicity of the identified novel mutations using fibroblasts of the patients and neuronal cells expressing mutants. The patients' cells or cells expressing mutant proteins were susceptible to oxidative stress generated by hydrogen peroxide or l-buthionine sulfoximine, which inhibits synthesis of glutathione, a free-radical scavenger. Genetic counseling was requested by four families but was declined by one, and others were not followed up. Even though cellular toxicity of the mutants was observed, we provided highly inconclusive information on counseling, where patients and families only partly understood the situations. In conclusion, we should perform genetic analyses on SALS to clarify its pathomechanism, but consider and overcome many difficulties on counseling.

M290. Reversible Cerebral Vasoconstriction and Posterior Reversible Encephalopathy in Guillain-Barre Syndrome

Armin Maghsoudlou, SeyedAli Hejazi, Avani Shah and Eufrosina Young. Syracuse, NY

Introduction: Reversible cerebral vasoconstriction syndrome (RCVS) is a group of syndromes characterized by reversible segmental constriction of cerebral arteries. Posterior reversible encephalopathy syndrome (PRES) is another clinical-radiologic syndrome characterized by reversible, posterior-predominant brain edema. There are recent reports of PRES and one case report of RCVS associated with Guillain-Barre syndrome (GBS). We report such a case in a woman who was diagnosed with GBS and manifested both clinical and radiological findings of RCVS and PRES.

Case description: The patient is a 52-year-old Caucasian female who initially presented with acute onset of paresthesia and weakness in bilateral lower extremities. She then developed headache, blurred vision and encephalopathy along with two episodes of tonic colonic seizures. Brain MRI showed vasogenic edema in bilateral occipital regions and MRA brain and Cerebral Angiogram revealed beaded appearance in the middle and posterior cerebral arteries. Cerebrospinal fluid analysis demonstrated albuminocytological dissociation and nerve conduction studies showed an axonal demyelinating polyradiculoneuropathy, which confirmed the diagnosis of GBS. She received a five-day treatment course with plasmapheresis, which resulted in modest improvement of the lower extremities weakness. A repeat MRI showed marked improvement in vasogenic edema compared to the previous study and MRA revealed resolution of previously visualized vasculopathy. It has been postulated that the autonomic dysregulation in GBS may have been the cause of a breach in the blood-brain barrier leading to RCVS/PRES, which can completely remit with an adequate management.

Discussion: Autonomic dysfunction is a well-known complication of Guillain-Barre syndrome (GBS) and may manifest as hemodynamic fluctuations. RCVS is characterized by reversible multiple segmental narrowing of large and medium-sized arteries. Patients with RCVS may present with hemorrhage, infarctions, or PRES. PRES and RCVS

have, in rare cases, been reported as initial manifestation and complication of GBS likely related to endothelial dysfunction and cerebral auto regulation dysfunction. In RCVS however, the angiographic appearance can resembles vasculitis, except that the abnormalities resolve during the course of several months. Because the treatment of RCVS differs from that for vasculitis, therefore high index of suspicion for PCRS and accurate diagnosis based on the repeated imaging studies is crucial.

Conclusion: Patients with GBS may initially develop symptoms of RCVS/PRES likely secondary to autonomic dysregulation. While RCVS can mimic angiographic findings of vasculitis, the presence of PRES and evidence of improvement in follow up imaging can help to distinguish the two entities.

M291. Temporal Trends in Guillain-Barre Syndrome at Assaf Harofeh Medical Center 2010-2015

Gilad Kenan, Mark Kushnir and Carmel Armon. Tel Aviv, Israel and Zerifin, Israel

Background: Guillain Barre syndrome (GBS) is a seasonal autoimmune disorder with a range of clinical presentations and courses. There has been a shift in the treatment approach for this disorder, favoring early treatment even of patients with mild disease.

Objectives: To determine if there have been changes in (1) the frequency and severity of presentation of patients with GBS at Assaf Harofeh Medical Center (AHMC) over the past six years; (2) treatments administered and times from onset and hospital presentation to treatment initiation; (3) patient outcomes, in terms of disposition (home or other).

Methods: Records of patients with a discharge code corresponding to GBS were reviewed, and those aged 18 years or older, with an initial occurrence, in whom the diagnosis was confirmed, were abstracted. The data were reviewed in three two-year periods to look for trends.

Results: A total of 54 patients were identified, 15, 21, and 18 in the three time periods, respectively. 43% were male. The average age was 50 years (SD=16 years) and ranged from 18-74 years. Median time from onset to admission was 4 days, ranged 0-31 days. Treatment was initiated within 24 hours of admission in 96% of patients. 92% of patients were treated with IVIg alone, and 4% received IVIg and plasmapheresis. One patient developed asystole and could not be resuscitated, and 9 patients (17%) required ICU care (6 ventilated, 11%). Serious treatment-related events necessitated stopping IVIg treatment in 2 patients (1-confusion, 1-chest discomfort). Milder side effects (head-aches, fevers, shivering) were treated symptomatically and by slowing the infusion rate, or resolved spontaneously. Thirty five patients (65%) could not walk at all or without support on admission: 6 (17%) were discharged home and 28 (80%) required inpatient rehabilitation. Nineteen patients (35%) were able to walk independently on admission: 11 (57%) were discharged home and 7 (37%) needed inpatient rehabilitation. There was a greater proportion of independently-walking patients in the latter two periods.

Conclusions: Frequency of GBS fluctuated slightly, possibly upward. The representation of males in our population was lower than that reported in the literature. The percentage of patients discharged home correlated inversely with walking impairment on admission. A significant percentage of those walking independently on admission deteriorated and required inpatient rehabilitation, supporting early treatment of mildly affected patients, who would otherwise attribute their deterioration to withholding or delay of treatment.

M292. Focal Bioimpedance (BIA) and Its Superiority Over Total Body BIA

William H. Mays and Tulio E. Bertorini. Memphis, TN

Bioimpedance as a marker for neuromuscular disease is a rapidly growing field of interest which has been shown to have a beneficial predictive value concerning long-term prognoses of many disorders.¹ Previously, many disease processes which have shown to benefit from this relatively new modality had unpredictable courses which were difficult to quantify. As such, bioimpedance has shown promising utility in a field where other more traditional objective parameters have failed to demonstrate significant usefulness.² For these reasons, the specifics of the testing itself as well as the reliability of the data it generates are of substantial import and are thus the target of increasingly closer inspection. Of chief significance in this regard is the difference between focal muscle testing and total bioimpedance.

Bioimpedance involves the placing of two electrodes on the skin to evaluate the difference in potential; this difference is reflective of the tissue's density and thus its specific composition (primarily the percentage of muscle, fat, and bone).³ Some investigators have employed a process of total body impedance: this method is comprised of placing electrodes on the right hand (e.g.) and the right foot thus theoretically measuring the average of the total body's tissues' resistance and reactance. This estimation has been hypothesized by many to be reliable.⁴

Other methods have used focal bioimpedance. This process focuses on a specific muscle (i.e., quadriceps femoris) and the tissues' overall resistance and reactance across this isolated muscle group.⁵

These two modalities require completely different equipment and techniques. We attempt to show the dangers of some of the assumptions required to employ total body bioimpedance, and we consequently demonstrate and advocate for the superiority of focal muscle testing.

Dementia and Aging

M293. Imaging and EEG Findings of the Heidenhain Variant of Creutzfeldt-Jakob Disease

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Background: Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare neurodegenerative spongiform encephalopathy. Diagnostic and clinical findings are consistent with basal ganglia and frontal destruction but in certain variants these can

differ. This case illustrates the occipital findings of the rare Heidenhain variant of CJD (HsCJD).

Case Description: A 65yo male began developing vision problems three months prior to seeking medical attention. On exam, pertinent findings included indifferent affect, slight weakness in left upper limb, decreased visual acuity bilaterally, and myoclonic jerks. MRI & EEG were consistent with HsCJD. CSF analysis showed 36 nucleated cells, glucose of 80 and elevated protein of 393. Neuron specific enolase and 14-3-3 were both elevated.

Discussion: The patient's clinical presentation along with characteristic EEG, MRI, and CSF findings of enolase and 14-3-3 protein is consistent with the HsCJD. Definitive diagnosis is based on brain biopsy; however the diagnosis of probable CJD requires a rapidly progressive dementia with at least two out of four clinical signs of myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs, seizures, and ultimately akinetic mutism as well as positive EEG, MRI or 14-3-3 CSF protein. Unique to his presentation, all of his findings were occipital, including the characteristic periodic sharp wave complexes of 0.5-2 Hz frequency and a DWI hyperintensity more than FLAIR and ADC cortical ribboning.

Conclusions: In patients presenting with clinical symptoms of visual disorders of unclear origin presenting with or shortly after psychosis or dementia, the HsCJD must be considered in the differential diagnosis.

Interventional Neurology

M294. Circadian Timing of Emergent Large Vessel Occlusion and Its Association with Efficacy of Mechanical Thrombectomy and Patient Outcomes

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Introduction: Mechanical thrombectomy is currently standard of care for the treatment of emergent large vessel occlusion (ELVO). However, data regarding the effect of the circadian timing of vessel occlusion in relationship to the efficacy of thrombectomy and patient outcomes is lacking. Our study aims to describe the relationship of the circadian timing of ELVO with endovascular therapy and patient outcomes.

Methods: We conducted a retrospective review of patients presenting with large vessel ischemic stroke that underwent endovascular therapy at Upstate Medical Center from January 2010 to February 2015. Patients were divided according to their time of arrival in to 2 groups 0700-1700 and 1700-0700. We analyzed data including baseline patient characteristics, endovascular procedural times and outcome variables. Outcome variables included TICI reperfusion grade, rate of symptomatic intracranial hemorrhage, discharge NIHSS, 90-day - mortality and modified Rankin scale.

Results: Charts of 177 patients were analyzed (0700-1700 n=86 vs. 1700-0700 n=91). Baseline characteristics included age (mean 68.31 vs 67.07 yrs), gender distribution (female 54.65% vs 38.46%), presence of co-morbidities -

DM (25.58% vs 31.46%), HTN (93.02% vs 92.22%), Dyslipidemia (77.91% vs 78.89%), Sleep apnea (5.81% vs 4.44%), Afib(43.02% vs 36.67%), CHF(15.11% vs 12.22%), CAD(25.58% vs 27.78%), admission NIHSS (median 14 each), SBP(mean 146.48 vs 145.91), DBP(mean 77.68 vs 78.29), and did not show any statistically significant difference between the two groups. Time parameters included door-to-CT(mean 26 min vs 48.16 min), door-to-groin puncture (155.37 min vs 162.35 min), door-to-first pass (220.79 min vs 207.82 min), door to recanalization (247.02 min vs 239.32 min) and onset to recanalization (364.24 min vs 392.16 min), TICI 2b/3 reperfusion grade (58% vs. 65%) and did not show any statistically significant difference between the two groups. Outcome parameters included immediate (30.59% vs 28.09%) and 3-months mortality (4% vs 0%), discharge NIHSS (median 5 vs 5), discharge (median 4 vs 4) and 3-month mRS (median 1 vs 1), and did not show any statistically significant difference.

Conclusion: In our study, endovascular therapy times, angiographic and patient outcomes were similar irrespective of the circadian timing of ELVO. This suggests that an emphasis on rapid triage and prompt communication, rather than the in-house availability of the endovascular team on call, can result in timely therapy regardless of the time of hospital presentation.

Dementia and Aging

M295. "Serum MCI Screening Test" Is Correlated with CSF A β 40/A β 42 and Valuable for the Enrollment of MCI Patient to Clinical Trial

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Objective: To evaluate whether "serum MCI screening test" efficiently select candidate patients in mild cognitive impairment (MCI) clinical trial.

Background: It is challenging to diagnose MCI since patients' cognitive deficits are mild, cerebral atrophic changes are subtle and there are not efficient biomarkers. In the clinical trial of MCI such as anti-amyloid therapies, the screen failure rate is high because there are strict inclusion/exclusion criteria and some patients reveal having no accumulation of amyloid beta in the PET study or lumbar puncture. Recently "serum MCI screening test" are commercially available in Japan (not covered by health insurance) (MCBI inc. Japan). This test evaluate the risk to develop MCI which measure serum transthyretin (TTR), apolipoprotein A1 (apoA1) and complement 3(C3), then add the score of MMSE, and statistically calculate the cut-off and categorize the risk: A (healthy), B (low risk), C (moderate risk), D (high risk) (http://mcbi.jp/news/info/2015/pdf/20150626_02.pdf).

Design/Methods: In addition to MRI and 99m Tc-ECD SPECT, ten consequent patients who were candidate of clinical trial had "serum MCI screening test".

Results: Seven patients were scored as D. Finally three of them diagnosed as MCI and three of them diagnosed as AD and one patients revealed having no accumulation of amyloid beta. One patient scored as C who failed to enroll one clinical trial because cognitive function was not declined but finally enrolled in another MCI trial. One patient was scored as B and another patient was scored as A. Both of them seemed to be pre-MCI whose cognitive functions were intact.

Conclusions: The score of “serum MCI screening test” seems to correlate with the staging of the disease, and it is not fully exclude the non-AD dementia. Combination of spectrography and “serum MCI screening test” may be useful to efficiently select the patients who are candidate of MCI clinical trial.

M296. Modeling the Impact of Neurogenesis and Cell Death on the Function and Structure of Neuronal Tissue

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This work evaluates an in silico model taking into consideration simultaneous neurogenesis and cell-death processes in neuronal structures, and their effects on cognitive and memory capabilities. This model considers parameters such as probabilistic distribution of the number of synapses, probabilistic distribution of the length of synapses, rate of neurogenesis, rate of cell death. The neuronal structure is subject to periodic stimulus retraining to evaluate its capability to learn and store previously acquired knowledge. We evaluate when neurogenesis can be excessive and compromise the capability of the neuronal structure to learn and store knowledge.

Research on these models is relevant to dementia and aging, as it may give a better understanding of what can be expected in new therapies favoring neurogenesis. Questions to be answered include what level of neurogenesis is needed to compensate for both normal and abnormal cell death rates, what is the effect of different rates of synapses formation on the capability of new cells to integrate themselves in the neuronal structure, how much new synapses formation can compensate for cell death.

Our methodology uses both classical neuronal models with enhancements to better mimic biological neural structures. Random effects are considered, e.g. different distributions of number of synapses per neuronal cell and synapses lengths, full and partial connectivity among cells. The model addresses a neuronal structure subject to periodic or continuous stimulus retraining, which corresponds to brain regions associated to sensorial processing. The model assumes constraints in the availability of nutrients and growth factors in the neuronal tissue, restricted to represent changes due to aging or other chronic health problems found in different types of dementia. The model allows to modulate the rate of neurogenesis and cell-death as a function of constraints of nutrients throughout the tissue.

The results of the model demonstrate what could be expected in a biological neuronal structure. Because of the flexibility in setting multiple input parameters and constraints, the model allows to visualize effects and correlations

not easily available through a in vitro or animal models. This model can help researchers in neurology of aging and dementia to better forecast the effect of different pharmaceutical interventions and treatment protocols. The model is an interactive tool to educate patients, their families and the public at large in dynamics of normal versus accelerated aging processes in the brain.

Education

M297. Charles Bonnet Syndrome Associated with Reversible Posterior Leukencephalopathy Syndrome

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Background: We present a case of acute cortical blindness, psychosis, complex visual hallucinations with occipital epileptiform discharges secondary to Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Prior case studies have reported psychiatric manifestations, however Charles Bonnet syndrome with epileptiform discharges in setting of RPLS is rare.

Objective: To postulate the neuroanatomical localization and connections of complex visual hallucinations in RPLS

Case report: A fifty-nine years old lady, with history of adrenal insufficiency, hypertension, hypothyroidism, depression, on Citalopram, thyroid hormonal therapy and Infliximab, presented with three-day history of sudden bilateral blindness, with only notable exam finding of hypertension and mild optic ataxia. MRI brain revealed bilateral occipital T2 hyper-intensities, without restricted diffusion, suggesting vasogenic edema. Routine laboratory studies (including cerebrospinal fluid) were normal, except for hypomagnesemia. Urine drug screen revealed benzodiazepine exposure. She was diagnosed and treated as possible RPLS. 2 days later, she developed acute psychosis with well-formed visual hallucinations (of deceased relatives) with severe agitation and combativeness, refractory to lorazepam and haloperidol. Prolonged QT interval limited aggressive antipsychotic medication use. Patient was transferred to the Neuro-Critical care unit with dexmedetomidine and nicardipine infusions for optimal blood pressure control. Despite absence of clinical seizures, her electroencephalogram demonstrated frequent epileptiform discharges in bilateral occipital areas that attenuated with phenytoin, along with clinical improvement in mental state, and slow and almost complete recovery in her vision. Repeat MRI, on day 10, showed resolving occipital hyper-intensities.

Discussion: Visual hallucinations can occur with visual sensory deprivation, or with direct stimulation of visual cortex or its de-afferentiation. Less commonly, they may be associated with dysfunction of the ascending brainstem cholinergic pathway. Charles Bonnet syndrome (CBS), with complex visual hallucinations and ocular blindness, is well described. Its association with cortical blindness has also been reported, but such patients usually retain normal cognition and insight. Our case report highlights the complex interaction of different neurobiological factors, such as, cortical blindness, structural brain lesion and epileptiform brain

activity in the pathophysiology of this unique syndrome. Occipital lesions, are typically associated with unformed visual symptoms. In our patient, occipital epileptiform discharges, bilateral occipital vasogenic edema, with symptom resolution after phenytoin use along with resolution of vasogenic edema over time strongly corroborates our case of RPLS with its unusual presentation as CBS. This is suggestive of non-convulsive non-striate occipital cortex seizures as another possible pathophysiological mechanism for generation of complex visual hallucinations.

Headache and Pain

M298. Allieaceous Burning Mouth Syndrome

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Objective: Allieaceous food induced Burning Mouth Syndrome (BMS) has not specifically been described.

Methods: Case #1: A 60 year old female presented with a six month history of burning in the tongue and palate, level 5/10 in severity, with diurnal variation, which worsened with eating raw onions. Neither the scent of onions, nor eating cooked onions had this effect. Thus, she scrupulously avoided eating any raw onions.

Results: All Chemosensory Tests normal: Brief Smell Identification: 10. Retronasal Smell Index: 7. Propylthiouracil Disc: 6.

Methods: Case #2: 47 year old female presented with four years of burning of the tongue, lips, gums, and palate, level 8/10 in severity, all day, everyday, aggravated with eating raw onions.

Results: Normal Chemosensory Tests: Brief Smell Identification: 11. Pocket Smell Test: 3. Retronasal Smell Index: 9. Propylthiouracil Disc: 9. Abnormalities included: Alcohol Sniff Test: 6 cm. Fungiform papillae: right: 32, left: 34. Taste Quadrant Testing: impairment anteriorly to all modalities and to quinine hydrochloride throughout the tongue and palate.

Discussion: The mechanism whereby the allieaceous foods amplify the pain in BMS is unclear. Manducating allieaceous foods creates olfactory and trigeminal stimulation through retronasal pathways. The sulfhydryl groups in these compounds are trigeminally activating, stimulating TRPA1 receptors in the trigeminal nerve (Bautista 2005, Bautista 2006). This functions to provoke calcitonin gene-related peptide and substance P release (Bautista 2005, Kunkler 2011). This causes parasympathetic nervous system discharge in the semilunar ganglion, with associated neurogenic inflammation and nociceptive discharge. The odorant component may induce change in emotion which then induces enhanced pain (Ehrlichman 1988). Moreover, it may act to evoke olfactory or gustatory nostalgia, thereby inducing negative mood changes which would further predispose to exacerbation of pain. Alternatively, the allieaceous compounds may have functioned on the tongue itself, with the sulfhydryl groups causing discharge of the small C nociceptor in a manner similar to irritant compounds, analogous to capsaicin, thus directly inducing pain. Moreover, these

compounds may have acted immunologically to cause local tongue allergenic response (histamine-mediated via degranulation of mast cells) causing a positive neuroinflammatory feedback loop and allodynia, with associated exacerbation of any underlying stomatitis and pain. Query as to allieaceous precipitants of BMS is warranted.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? COI: Alan R. Hirsch MD has ownership in the Smell & Taste Treatment and Research Foundation and consults with multiple companies and health care facilities.

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Neuromuscular Disease

M299. Chemosensation in Charcot Marie Tooth Disease

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Introduction: Chemosensory dysfunction has not been described in Charcot Marie Tooth (CMT). Three such cases are reported.

Methods: Case Report

Case 1: A 58-year-old right-handed female with CMT 1A presented with eight years of gradual reduced ability to smell and taste, and two years of intermittent metallic, garbage phantasias.

Results: Abnormalities in Neurologic Examination: bilateral hammertoes. Drift Testing: bilateral abductor digiti minimi signs. Unstable heel, toe and tandem gait. Bilateral finger to nose dysmetria. Bilateral positive Holmes rebound phenomenon. Decreased light touch, pinprick and temperature distally in both lower extremities Areflexic. Chemosensory Testing: University of Pennsylvania Smell Identification Test: 26 (hyposmia). Brief Smell Identification Test (BSIT): 10 (normosmia). Retronasal Smell Index (RST): 5 (normal). Propylthiouracil Disc Taste Testing (PTU): 1 (ageusia). EEG normal. MRI with and without infusion: normal.

Case 2: A 76-year-old right-handed female with CMT type 4 presented with a one-year history of gradual reduction of smell and taste, phantasmia of frying bacon, and dysgeusia, wherein yogurt tastes like chemicals.

Results: Abnormalities in Neurologic Examination: Bilateral thenar and hypothenar atrophy, 4/5 left abductor pollicis brevis. Left pronator drift. Decreased light touch and vibration distally in both lower extremities. Reflexes: 1+ throughout except absent ankle jerks. Chemosensory Testing. Dirhinus Quick Smell Identification Test: 2 (hyposmia). BSIT: 9 (normosmia). Pocket Smell Test (PST): 2 (hyposmia). Alcohol Sniff Test (AST): 1 (anosmia). RSI: 1 (abnormal). Taste Threshold Testing: normal to sodium chloride and phenylthiocarbamoyl. Mild hypogeusia of 10-30% to urea and ageusia to sucrose and hydrochloric acid. MRI of brain with and without infusion: normal.

Case 3: 53-year-old right-handed male with CMT presents with 20 years of gradual reduction to smell and

taste and a constant phantosmia for one year of foul breath or feces. .

Results: Abnormalities in Neurological Examination: bilateral hammertoes. Left pronator drift. Absent reflexes. Chemosensory Testing: BSIT: 11 (normosmia). AST: 10 (hyposmia). PST: 3 (normosmia). RSI: 1 (absent). Gustatory Testing: PTU: 9 (normogeusia). Taste Threshold: normogeusia to sodium chloride, sucrose, hydrochloric acid, urea, and phenylthiocarbamoyl.

Discussion: The genomic defect in CMT on short arm of chromosome 17 (17p12) is adjacent to 17p13, the gene coding for olfactory reception. Such close proximity suggests that they both may be influenced by a co-mutation. The above cases highlight the importance of assessing chemosensation in those with CMT as well as assessing for CMT in those who present with chemosensory complaints.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? **Source of Funding:** Smell and Taste Treatment and Research Foundation, Chicago, IL

COI: Alan R Hirsch MD has ownership in the Smell and Taste Treatment and Research Foundation and consults with multiple companies and health care facilities.

M300. Case Report of Giant Pseudomeningocele Masquerading as Monomelic Amyotrophy

William K. Jens, Rae Bacharach, Sandip Savaliya and Divpreet Kaur. Hershey, PA

Introduction: This case illustrates an atypical presentation of pseudomeningocele (PM) that appeared to mimic monomelic amyotrophy (MMA). PM is a known cause of myelopathy; however, it is typically associated with bilateral symptoms as a surgical complication. Spinal PMs are rare extradural collections of cerebral spinal fluid, with a giant PM defined as being greater than 8 cm in length. It is formed by a breach in the dural-arachnoid layers, typically either traumatic or iatrogenic. This case is the first reported instance of unilateral myelopathy.

Methods: We describe the clinical course, electromyogram, and radiologic findings of an Indian male diagnosed with giant PM.

Case Review: A 28 year-old right-handed Indian presented to the clinic for evaluation of right arm weakness and atrophy. He previously suffered a traumatic right humerus fracture in 2005, with mild residual atrophy and weakness that had mostly resolved. In the last two years, he noted the right upper extremity (RUE) atrophy and weakness had progressively worsened, with no other systemic symptoms. Physical exam confirmed weakness and atrophy with normal sensation and slightly reduced reflexes. Given the clinical history and ethnicity, MMA was the initial diagnosis. EMG showed normal conductance with extensive chronic focal disorder of motor neurons with some ongoing denervation. A cervical spine MRI showed a giant PM from C2-L4. The patient underwent surgical correction and in 2 months reported improvement in RUE strength.

Discussion: This case illustrates the unique findings of PM. PM is a rare cause of myelopathy and should be included in the differential of unilateral myelopathy.

M301. Treatment Related Effects of Anti-GAA Antibodies in Late Onset Pompe Disease

Marie A. Wencel, Claudia Shambaugh, Namita A. Goyal, Virginia E. Kimonis and Tahseen Mozaffar. Orange, CA

Late onset Pompe disease (LOPD), a lysosomal storage disorder characterized by deficiency of the enzyme acid alpha-glucosidase (GAA), presents with diaphragm and skeletal muscle weakness with little or no cardiac involvement. The disease is progressive, and if left untreated, may result in significant motor disability and respiratory failure. Pompe disease is now considered treatable, with FDA-approved enzyme replacement therapy (ERT) Lumizyme®. Initial published data in LOPD showed improvement in forced vital capacity (FVC) and endurance, measured by 6-minute walk. However, subsequent publications have shown plateauing of this benefit and worsening of FVC may occur with time. In infantile cases of Pompe disease, development of IgG antibodies against GAA results in reduced treatment efficacy, especially in cross-reactive immunologic material negative (CRIM-) individuals. The role of these antibodies in neutralizing effects of treatment in LOPD is not clear since most individuals at this stage are CRIM+. We plan to present a retrospective analysis of our 9 patients who regularly follow with us, have been on uninterrupted enzyme replacement therapy and have been checked for these antibodies on a routine basis. We intend to correlate their treatment related adverse events, their treatment response, as measured by muscle function tests (manual muscle strength, 6-minute walk test), respiratory function trends (serial FVC, maximal inspiratory pressures (MIP) and sniff nasal inspiratory pressures (SNIP)), and quality of life data with the antibody titers. Furthermore we will correlate these data with their genotype results, and when available, pretreatment GAA enzyme levels and urinary Hex4 results. Our hypothesis is that development of anti-GAA antibody titers has no effects on treatment efficacy in LOPD.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Ms. Wencel had travel paid for to attend investigator meetings by Amicus, aTyr and Amicus.

M302. Pharmacokinetic Profile of Edaravone: A Comparison Between Japanese and Caucasian Populations

Yoshinobu Nakamaru, Atsuhiko Kawaguchi, Shuji Kinoshita, Koji Takei and Joseph M. Palumbo. Tokyo, Japan and Jersey City, NJ

Background: Amyotrophic lateral sclerosis (ALS) affects persons of all races, and there continues to be a need for effective therapies to treat the disease.

Objective: We performed a population pharmacokinetic analysis (PPK) to compare the pharmacokinetics of edaravone in Japanese and Caucasian populations.

Methods: A total of 5 pharmacokinetic (PK) studies in healthy volunteers among Japanese (3 studies) and Caucasian (2 studies) populations were evaluated. The PPK model was constructed using non-linear mixed effect modeling. Initially, 2-compartment and 3-compartment models were assessed, and other models with linear elimination were evaluated for appropriateness in describing the PK data. Covariate effects by race, gender, weight, and age were investigated to explain variability in the PK parameters, including maximum plasma concentration (C_{max}), terminal plasma concentration (C_{tau}), and area under the plasma-concentration time curve (AUC). Simulations of the final PPK model, using a virtual population based on published literature of ALS clinical trials in Europe and the United States, were used to support dose extrapolation.

Results: The PPK analysis included 86 subjects. There was a near-equal distribution of Japanese and Caucasian subjects, 54.7% vs 45.3%. The mean age (SD) of subjects was 45.8 (17.4) years, and approximately three-quarters of subjects were male (76.7%). A 3-compartment model with Michaelis-Menten plus linear elimination was selected as the best fit model. Race was statistically detected as a covariate for the second peripheral volume of distribution (V_2), indicating a 26% increase for Caucasian subjects compared to Japanese subjects. Based on PPK modeling using a virtual ALS population, the small difference of V_2 was associated with a difference of C_{tau} around 1 ng/mL after infusion. This difference was minimal compared to C_{max} (approximately 1000 ng/mL), and did not result in the accumulation of drug concentration after multiple dosing. No significant differences were observed for C_{max} or AUC between the populations. Gender, age, or weight did not affect any PK parameters.

Conclusion: The PPK analysis of edaravone, best fit with a 3-compartment model with Michaelis-Menten plus linear elimination, demonstrated a 26% increase of V_2 for Caucasian subjects compared to Japanese subjects, but the difference of V_2 was minimal compared to C_{max} and it did not result in the accumulation of drug concentration. There were no significant differences in C_{max} or AUC of edaravone between the populations. The PK parameters for edaravone were not affected by gender, weight, or age.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? YN, AK, and SK are employees of Mitsubishi Tanabe Pharma Corporation. KT and JP are employees of Mitsubishi Tanabe Pharma Development America, Inc.

Traumatic Brain Injury

M303. Differential Expression of Cerebral Autonomic Function in Special Forces and Non-Special Forces Exposed to TBI

Thomas J. DeGraba, Kathy Williams, Melissa Rampino, Chloe LaRochelle and Geoffrey Grammer. Bethesda, MD; Olney, MD and Silver Spring, MD

Objective: To characterize the differential response of cerebral autonomic function following traumatic brain injury

(TBI) between Special Forces (SF) and Non-Special Forces (nSF) military personnel.

Background: Combat and training exposure to blast and blunt forces resulting in TBI is the “signature” injury of the conflict in Iraqi and Afghanistan for both SF and nSF personnel. The Institute of Medicine report highlights disruption of cerebral autonomic function as a significant consequence following head trauma. Transcranial Doppler (TCD) provides a reliable and reproducible method for measuring cerebral blood flow (CBF) and cerebral vasomotor reactivity (CVR) to CO₂ challenge. Based on previous observations in our TCD lab, we hypothesize that a greater percentage of SF personnel preserve CVR, as measured by TCD breath hold index (BHI) following head injury compared with nSF military personnel.

Methods: Service members (SM) (n= 438) returning from combat operations with persistent deficits from TBI were referred to the National Intrepid Center of Excellence, Walter Reed National Military Medical Center for a four-week intensive outpatient program. Neurological deficits were represented by the Neurobehavioral Symptom Inventory (NSI). TCD measured autonomic control of cerebral blood flow by using the BHI which measures the change in CBFV in the middle cerebral arteries (MCAs) in response to 30 seconds of breath holding. Arteriole dilation resulting from CO₂ elevation causes increased CBFVs. Normal BHI scores are reported as >1.2%/second change in CBFV. Abnormal BHI scores are reported as <1.0%/second change.

Results: Comparison between SFs (n=279) and nSFs (n=159) revealed a significantly smaller percentage of SF with abnormal BHIs. Cramer's V= .338, p<.001 (8.96% of SFs, n=25 vs 35.84% of nSFs, n=57). These findings are despite a significantly higher incidence of total reported TBIs in SFs (M= 5.5, SD=10.0) vs nSFs (M= 2.8 SD= 2.8), t=-3.46, p=.001. Further analysis indicated that nSFs had significantly higher post-concussive symptoms as indicated by their NSI scores, t=8.16, p<.001.

Conclusion: SFs demonstrate greater preservation or recovery of CVR following head injury than nSFs despite a greater number of TBI events. These findings suggest that SF personnel possess either an innate predisposition to resistance cerebral vascular injury following TBI or an acquired resilience based on selection and training. Further study of this phenomenon may provide clues for future resilience training and treatment of combat related head injury.

M304. Parieto-Occipital delta alpha Spectral Power in Electroencephalogram Indexes Post-Traumatic Confusion and Predicts Recovery After Traumatic Brain Injury

Maliheh Mohamadpour, Sudhin A. Shah, Gulce Askin, Risa Nakase-Richardson, Dobrivoje S. Stokic, Mark Sherer, Stuart A. Yablon and Nicholas D. Schiff. New York, NY; Tampa, FL; Jackson, MS and Houston, TX

Objectives: To determine electrophysiological correlates of post-traumatic confusional state soon after injury and their utility in predicting long-term outcome.

Methods: Standard resting electroencephalographic (EEG) data were recorded during eyes closed in 49 patients diagnosed with post-traumatic confusional state. The delta-to-alpha frequency band ratios (DARs) from different areas were evaluated as predictors for a) Confusion Assessment Protocol (CAP) score total and subscores assessed on the same day (n=35) using linear and logistic regression analyses, and b) Functional Independence Measure total score (FIM) at 1 (n=45), 2 (n=42), and 5 (n=34) year(s) post-injury using linear regression analysis.

Results: Higher occipital and parietal DARs were significantly associated with higher CAP symptom count ($\beta=1.88$, $p<0.01$; $\beta=1.62$, $p<0.05$), on the same day, after controlling for injury severity. Also, occipital DARs predicted the same day CAP subscore 2 (i.e., GOAT error score, OR=2.01, $p<0.05$), and CAP subscore 4 (fluctuation of symptoms, OR= 2.33, $p<0.05$) after controlling for injury severity. Parietal and occipital DARs were significant predictors of FIM at 1, 2, and 5 years post-injury, but this disappeared after controlling for injury severity.

Conclusions: DAR is a marker of severity of post-traumatic confusional state and a predictor of functional recovery up to 5 years post-injury. EEG slowing in parieto-occipital areas likely reflects functional de-afferentation of the posterior medial complex (PMC). This suggests that altered function of the PMC may be a unifying physiological mechanism underlying acute and chronic confusional states.

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M305. Initial GCS and Laboratory Findings of Patients with TBI Are Associated with the GOSE and Mortality Rate at One Year, a Prospective Study

Elabe Bordbar, Shahram Paydar, Mehdi Taghipour, Hosseinali Khalili and Mehran Jafari. Baltimore, MD and Shiraz, Islamic Republic of Iran

Introduction: Traumatic brain injury (TBI) is the main cause of mortality and morbidity in people under 45 years

old in developing countries. A large number of patients with TBI are admitted to intensive care units; however, outcomes after one year are difficult to anticipate during the acute period. The aim of this study is to evaluate the relationship between presenting Glasgow Coma Scale (GCS) or laboratory data of patients with TBI and Extended Glasgow Outcome Scale (GOSE) and final outcome (deceased, survived) at one year.

Methods: In this prospective study, 74 (59 males and 15 females) patients who presented with TBI were entered into the study. Mean age $\pm$ SD of the included patients was 40 ± 19 years. The patients were examined by an expert neurosurgeon and a general surgeon. Injury severity score (ISS) and GCS at the first, second, fourth and sixth day of hospital admission were evaluated and GCS and laboratory data were recorded. The patients received routine treatment and management as indicated in the course of hospitalization. After one year, GOSE level and final outcome were evaluated with 11 yes/no questions obtained from the patients or their first degree relatives.

Results: After one year, 27 (36.4%) patients had died and 47 (63.5%) patients had survived. In terms of GOSE categorization, half of the patients were in the extreme ranges. For instance, one quarter had died (27/74, 25.6%); whereas, the other quarter were in good condition (lower good recovery and upper good recovery; 27/74, 25.6%). The patients with lower GCS on admission or day six, significantly had lower GOSE. Moreover, the lower the GCS in the first week of admission, the poorer the final outcome. Among laboratory data, the base deficit (BD) level of -6 or worse on admission was an indicator of mortality at one year. Hyponatremia was the only laboratory factor which predicted poor GOSE after a year. Furthermore, patients with serum hyponatremia, hyperkalemia and high PTT levels on the first week of admission had poor final outcome.

Conclusions: Presenting GCS and metabolic derangements are reliable indicators of long-term outcome and GOSE at one year.

M306. Screening for Novel Calpain-2 Selective Inhibitors

Shayan Torabi Moghaddam, Yubin Wang and Michel Baudry. Pomona, CA

Calpains are calcium-dependent cysteine proteases playing key physiological and pathological roles in the central nervous system (CNS). Two major calpain isoforms in the CNS are calpain-1 and calpain-2. Recent studies in our laboratory have indicated that calpain-1 is neuroprotective while calpain-2 is neurodegenerative. Furthermore, calpain-1 activation is required for the induction of long term potentiation (LTP), while calpain-2 activation during the consolidation period restricts the amplitude of LTP. This study was therefore directed at identifying cysteine protease inhibitors, which would be selective for calpain-2. Because the phosphatase PTEN is a selective calpain-2 substrate, we generated peptides based on the sequences surrounding two putative calpain-cleavage sites to provide a template for a calpain-2 selective inhibitor. We first co-expressed calpain-2

large subunit and calpain-4, the small calpain subunit common to both calpain-1 and calpain-2, in E-coli and used NI-NTA column to purify the calpain-2/calpain-4 complex. Calpain-2 activity was measured using an in vitro calpain activity assay. We tested 14 potential calpain-2 selective inhibitors, which are peptides with the sequence of the spectrin cleavage site or putative PTEN cleavage sites and compared their inhibitory activity to that of a known calpain-2 inhibitor. We further tested the inhibitors in a PTEN cleavage assay using mouse brain homogenates. Our results indicate that the peptide sequence of the spectrin cleavage site has a higher inhibitory activity for calpain-2 than for calpain-1, an effect which was further confirmed by the PTEN cleavage assay. Further studies are needed to generate an even more selective calpain-2 inhibitor, which would have potential therapeutic applications in disorders associated with neurodegeneration such as Traumatic Brain Injury (TBI).

M307. Pupillary Dysfunction in Post Traumatic Headache

Natalie A. Rea, Christopher E. Sciarretta, K.C. Brennan and Melissa Cortez. Salt Lake City, UT

Post-traumatic headache (PTH) is a common, often treatment refractory consequence of traumatic brain injury (TBI). While differences in autonomic physiology have recently been reported in acute concussion, it is not clear whether these changes are also contributory to the chronic manifestations of TBI, including PTH. The objective of this study was to measure discrete autonomic parameters, beginning with pupil function in subjects experiencing post-traumatic headache (PTH) compared to normal controls.

Twenty-six subjects, 12 PTH and 14 non-headache controls (NH) were recruited. Post-traumatic headache diagnoses were made using the International Classification of Headache Disorders III-beta. Pupil cycle time (PCT), a measure of pupillary oscillations in response to a sustained light stimulus is used as a screen of autonomic pupillary dysfunction. Pupillary light reflex (PLR), a measure of pupil size changes in response to a brief pulse of light allows for the assessment of parasympathetically and sympathetically dominated functions (e.g. constriction parameters, dilation parameters). PLR was assessed in a subset of individuals (8 PTH and 14 NH). Groups were compared using the Mann-Whitney test and Student t- test, as appropriate.

PCT was significantly prolonged in PTH subjects compared with NH ($p=0.01$). PLR assessment demonstrated significantly slower constriction velocities (CV) among PTH subjects (a parasympathetic parameter) compared to NH controls ($p=0.03$).

In summary, our findings suggest that PTH subjects differ significantly from NH on autonomically mediated pupillary measures. The findings suggest a possible parasympathetic lesion in pupillary function versus persistently over-riding sympathetic drive. Future studies are needed to ascertain whether this finding is limited to pupillary control, or if it represents a more widespread autonomic disturbance. Our findings serve as preliminary support

for further investigation of pupillary dysfunction as a physiological and clinical biomarker in PTH.

M308. Etiologies of Concussion in Pediatric Population *Megan Edwards, Amanda Witt and Sara Dawson. Jackson, MS*

Objective: To explore the etiologies of concussion in pediatric population.

Methods: The study was a retrospective analysis using our pediatric concussion clinic database spanning over 1.5 years of patients ranging from ages 3- 17 years. A total of 78 patients were analyzed to assess the cause of their concussion. Etiologies were separated into six categories: motor vehicle collisions (MVCs), falls, sports, all-terrain vehicle (ATV) accidents, multiple events, and unknown. For calculations, unknown and multiple event patients were removed from the total. Sports related events were then broken down into various sports: football, basketball, soccer, biking, and tetherball.

Results: Out of the 73 patients included in the calculations- 11 patients had concussions secondary to ATV accidents (0.15), 13 from falls (0.18), 33 due to MVCs (0.45), and 16 related to sports (0.22). There was 1 patient with unknown cause and 4 patients with multiple events. Multiple event patients included a patient with an ATV accident and MVC, a patient with multiple falls, a patient with fall and ATV accident, and a patient with 2 sports related events (Hoverboard and basketball). Sports associated concussions included 2 basketball (0.125), 2 biking (0.125), 8 football (0.5), 3 soccer (0.19), and 1 tetherball (0.06).

Conclusions: In our population, MVCs are the leading cause of concussion in pediatrics. Sporting related concussions are ranked second and among sports recorded, football is the leading sport in concussion related injuries.

M309. Efficacy of an Interdisciplinary Intensive Outpatient Program in Treating Combat-Related TBI and Psychological Health Conditions

Thomas J. DeGraba, Geoffrey Grammer, Kathy Williams and James P. Kelly. Bethesda, MD; Silver Spring, MD and Aurora, CO

Background: Service members (SMs) with combat-related traumatic brain injury (TBI) from the conflicts in Iraq and Afghanistan screen positive for the psychological health (PH) conditions at a prevalence of greater than 40% with many SMs failing to achieve improved quality of life and return to duty. Limited information exists to guide treatment for SMs with complex brain injury.

Our goal is to develop and evaluate the immediate and long term efficacy of an interdisciplinary intensive outpatient program (IOP) combining conventional therapy with integrative medicine to reduce morbidity, improve function, and enhance readiness of SMs with the invisible wounds of war deemed "unfixable" by conventional therapies.

Methods: Service members ($n=650$) greater than 6 months from TBI with comorbid PH conditions were enrolled in the National Intrepid Center of Excellence's 4-week IOP, which utilizes a patient-centric holistic model to optimize healing and patient-provider rapport. Emphasis is

placed on attaining self-efficacy techniques through integration of mind-body training with conventional medicine to enhance sustainable recovery. Interdisciplinary teams of providers encompassing 17 disciplines consolidate evaluation to expedite diagnostic workup of multiple cerebral domain dysfunction and treatment implementation. In order to adequately assess program efficacy, the post-concussive syndrome response to treatment, was measured with Neurobehavioral Symptom Inventory (NSI), PTSD Checklist-Military Version (PCL-M), Satisfaction with Life Scale (SWLS), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder-7 (GAD-7) which were given on admission (adm) and at discharge (d/c) (week 4). Cross sectional follow-up was obtained at 1, 3 and 6 months post-discharge to measure durability of the effect(s).

Results: All outcome measures significantly improved following the 4 week program treatment, $p < .01$. Within subjects, Cohen's d show that the largest changes were seen with the GAD-7 ($d=1.58$) followed by the PHQ-8 ($d=1.16$), PCL-M ($d=1.05$), SWLS ($d=1.00$), NSI ($d=0.99$). Cross sectional follow-up showed sustained improvement at 1,3 and 6 months for all scales ($p \leq .01$).

Conclusion: This study is the first to demonstrate that an interdisciplinary IOP results in significant and sustainable recovery in SMs suffering from combat-related TBI and psychological health conditions. These findings underscore the value of coordinated care.

M310. Post-Traumatic Dueling Synesthesias- Pathologic Gustatory vs Physiologic Retronasal Olfactory

Al-Mounawara Yaya and Alan R. Hirsch. Willemstad, Curacao, Netherlands Antilles and Chicago, IL

Introduction: Rapid conversion from normal taste to dysgeusic taste has not heretofore been described.

Method:

Case report: A 60 year old right handed female, 6 months prior to presentation, fell striking her head, with loss of consciousness for one minute. Within a few days, she noted reduced taste to 20% of normal and dysgeusia wherein food tastes salty or like nothing. The salty taste is temporally related to ingestion of food, such that lemonade initially tastes like lemon and within a few seconds transforms into the taste of salt. Similarly, Oreos, chocolate chips cookies, lemon pancakes, meatloaf, and spaghetti, for the first and second bites taste as they should, but after the third bite, they rapidly acquire a salty taste. Once the food has acquired the salty taste, eating other foods between exposures does not change of the original foods' salty taste upon re-exposure.

Results: Abnormalities in Neurologic Examination: Mental Status Examination: Memory Testing: Immediate recall: 4 digit forwards and backwards. Recent recall: 2 or 4 objects in 3 minutes without improvement with reinforcement. Motor Examination: left pronator drift, left cerebellar spooning, left abductor digiti minimi sign. Gait examination: heel walking with decreased right arm swing. Chemosensory Testing: Olfaction: Brief Smell Identification Test: 11 (normosmia). Retronasal Smell Testing: Alcohol Sniff Test: 19 (normosmia). Pocket Smell Test: 2 (hyposmia).

Quick Smell Identification Test: 2 (hyposmia). Retronasal Smell Index: 2 (abnormal). Gustatory Testing: Propylthiouracil Disk Taste Test: 9 (normogeusia). Taste Threshold: normogeusia to sucrose, hydrochloric acid, urea and phenylthiocarbamide. Mild hypogeusia to sodium chloride. Taste Quadrant Test: impaired posteriorly to citric acid. Taste weakness to sodium chloride and sucrose.

Discussion: Primary olfactory loss might cause rapid olfactory adaptation which leads to a decrease in olfactory input with associated reduction in retronasal smell (loss of physiologic synesthesia) combined with food-whereby food texture induces salty taste (pathologic gustatory synesthesia). In this model, the physiologic synesthesia of retronasal smell was initially predominant and inhibited the pathological synesthesia. As smell adapted, the salty dysgeusia prevailed. This may represent a dual diagnosis of 1- olfactory dysfunction with rapid adaptation and 2- taste distortion. Thus, this could be the chemosensory analogue to the double crush phenomenon in peripheral nerve disease, wherein two lesions are needed for symptoms to occur. Given the above, it would be worthwhile to evaluate those with complaints of taste abnormality for concurrent olfactory defects.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? **Source of Funding:** Smell and Taste Treatment and Research Foundation, Chicago, IL

COI: Alan R Hirsch MD has ownership in the Smell and Taste Treatment and Research Foundation and consults with multiple companies and health care facilities.

Autoimmune Neurology

M311WIP. Stiff-Person Syndrome in Association with Cerebellar Ataxia: Overlapping Syndrome: A Case Report

Varun H. Chauhan and Abbas A. Jowkar. Detroit, MI

SPS (Stiff-person Syndrome) is a rare autoimmune condition; part of stiff person spectrum disorder (SPSD), that also includes overlapping syndromes: SPS or stiff limb syndrome (SLS) in association with cerebellar ataxia, epilepsy, or limbic encephalitis. Here, we report one such uncommon case of SPS in association with cerebellar ataxia: overlapping syndrome. Our patient has classical features of SPS with cerebellar ataxia, positive serological antibodies (anti-GAD65), and demonstrated significant improvement in his symptoms with appropriate treatment.

M312WIP. ARA 290 for Sarcoidosis and Painful Small Fiber Neuropathy

Daniel A. Culver, Jinny Tavee, Albert Dahan, Daiva Bajorunas, Maria Jeziorska, Monique Van Velzen, Leon Aarts, Martijn Tannemaat, Ann Dunne, Rita Kirk, Ioannis Petropoulos, Anthony Cerami, Rayaz Malik and Michael Brines. Cleveland, OH; Leiden, Netherlands; Tarrytown; Manchester, United Kingdom and Doha, Qatar

Small fiber neuropathy (SFN) frequently complicates sarcoidosis. In prior studies, the innate repair receptor agonist

ARA 290 demonstrated nerve fiber regrowth, suggesting disease-modifying potential. This phase 2b, double-blind, randomized, placebo-controlled trial assessed efficacy of daily subcutaneous 1, 4, 8mg ARA 290 versus placebo for 28 days in 64 subjects with sarcoidosis SFN.

Primary endpoint was corneal nerve fiber area (CNFA) with objective, symptomatic, functional and biomarker endpoints obtained. Consistency of results in a larger population of sarcoidosis SFN subjects was evaluated in post-hoc analyses of key endpoints.

Placebo-corrected least square mean changes from baseline in CNFA (μm^2) at Day 28 were 234.8 (95% CI: -355.14, 824.78), 632.7 (44.92, 1220.43), and 482.2 (-128.46, 1092.85) in the ARA 290 1, 4, 8mg groups, respectively. The ARA 290 4mg group demonstrated an 18% increase from baseline ($p=0.035$). Growth-associated protein-43 immunoreactivity in skin biopsies increased by 23% for ARA 290 4mg ($p=0.035$), significantly correlating with CNFA change ($\rho=0.575$; $p=0.025$) and 6-minute walk distance ($\rho=0.645$; $p=0.009$). Pooled analyses showed similar results.

ARA 290 increased small nerve fibers with improvements in functional and biomarker parameters, supporting continued evaluation as a disease-modifying treatment in SFN.

Disclosure: Have you received funding or in-kind support/will your presentation be supported/sponsored (in any way whatsoever, including grants) by a commercial interest? Co authors/investigators are key members of Araim pharmaceutical company, which provided funding for the study

M313WIP. GABA-B Receptor Antibodies Inhibit GABA-B Receptor Signaling

Eric Lancaster, Elisabeth Burnor, Maxwell Greene, Ankit Jain and Sheena Baraton. Philadelphia, PA

Objective: To develop a novel assay for γ -aminobutyric acid-B receptor (GABA-B-R) activation and use it to determine whether GABA-B-R autoantibodies block receptor signaling.

Background: GABA-B-R is a metabotropic inhibitory receptor that has a presynaptic (GABA-B1a/GABA-B2) and post-synaptic (GABA-B1b/GABA-B2) isoforms. GABA-B antibodies associate with autoimmune encephalitis. GABA-B-R antibodies decrease the responses of neuronal cultures to the GABA-B agonist baclofen, but a direct measure of receptor function is needed.

Design/Methods: We created a luminescent assay for GABA-B-R signaling. HEK cells were transfected to express GABA-B subunits, Gq15 G-protein, a luciferase activated by the G-protein, and a control luciferase. Cells were treated with case or control heat-inactivated sera, purified IgG or CSF. The effects of these samples on baclofen-induced signals were quantified.

Results: Our assay produced dose-dependent luminescent signals in response to baclofen. 7 of 7 heat-inactivated GABA-B-R antibody-positive sera produced concentration-dependent inhibition of GABA-B-R signals compared to 7 control sera. Purified case IgG and CSF had similar effects.

Patient sera showed similar effects on the presynaptic and post-synaptic isoforms.

Conclusions: Autoantibodies the GABA-B receptor inhibit signaling by both isoforms of GABA-B-R. Our assay will allow us to determine whether autoantibodies to other metabotropic receptors function analogously.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? 1. Fees for teaching courses for Grifols, Inc.

2. Consulting for Medimmune Inc.

3. Consulting for Janssen Inc.

4. Consulting for the Vaccine Injury Compensation Program

Have you received funding or in-kind support/will your presentation be supported/sponsored (in any way whatsoever, including grants) by a commercial interest? **Grant support:** NIH K08-NS-075142-01A1 and DANA foundation Neuroimmunology Award.

M314WIP. CASE REPORT: A Case of Area Postrema Syndrome as a Debut of Neuromyelitis Optica Spectrum Disorder

Jimmy Palacios-Garcia and Brian J. Villafuerte-Trisolini. Lima, Peru

We report a 18-year-old peruvian right-handed woman, with no past medical history, who present to neurology service with lower limbs weakness and gait disturbance. She refers two months ago nausea, vomiting and persistent hiccups, severe itching, urinary retention and constipation, then mild weakness with paresthesia in lower limbs that progressed over time. At physical examination we found paraparesia, tonics spasms, increased deep tendon reflexes, bilateral babinski, sensory loss and no Lhermitte sign. Regarding to MRI, multiple T2 weighted and gadolinium-enhancing lesions were found at dorsal spinal cord and brainstem in the periphery of the 4th ventricle. The initial diagnosis was longitudinally extensive transverse myelitis, however the description of area postrema syndrome and neuroimaging raised the diagnosis of Neuromyelitis Optica Spectrum Disorder (NMOSD) with unknown status Anti AQP4 IgG. She received methylprednisolone, plasma exchange and azathioprine with complete remission of symptoms. NMOSD is a rare systemic autoimmune disease and there are few reports in latinamerica and it is important to remember in case like similar presentation.

M315WIP. Spectrum of Zika Virus Associated Neurological Disease in Colombia

Paula Barreras, Laura Munoz, Beatriz Parra, Jairo Lizarazo, Jorge A. Jiménez-Arango, Andres F. Zea-Vera, Guillermo González-Manrique, José Vargas, Jorge A. Angarita, Gonzalo Zuñiga, Reydmir Lopez-Gonzalez, Cindy L. Beltran, Karen H. Rizcala, Maria T. Morales, Anupama Kumar, David R. Cornblath, Lyda Osorio and Carlos A. Pardo. Baltimore, MD; Cali, Colombia; Cucuta, Colombia; Medellin, Colombia; Neiva, Colombia and Barranquilla, Colombia

In parallel with the Zika virus (ZIKV) outbreak in the Americas, increased cases of neuroimmunological disorders

have been observed. The Neurovirus Emerging in the Americas Study (NEAS) evaluated neurological disorders during the ZIKV outbreak in Colombia. 43 GBS, 9 encephalitis, 2 myelitis and 2 optic neuritis patients were evaluated in 6 Colombian hospitals between January-May, 2016. Patients underwent neurological and virological studies. RT-PCR for ZIKV in blood, cerebrospinal fluid (CSF) and urine, and anti-flavivirus antibody assays were performed. ZIKV infection was confirmed by RT-PCR in 18 GBS patients. Most of the positive RT-PCR tests were in urine (16/18) although 4 CSF samples were also positive. In 18 GBS patients with negative RT-PCR, recent ZIKV infection was supported by anti-flavivirus antibodies. Infection was confirmed by RT-PCR in 3 encephalitis cases (2 in CSF and 1 in Urine), 2 cases of myelitis (1 in CSF and 1 in Urine) and in 1 case of Optic neuritis in urine.

The demonstration of ZIKV infection in patients with neuroimmunological disease during the ZIKV outbreak in Colombia lends support to the role of such infection as pathogenic factor in the development of neurological disorders.

M316WIP. An iPSC Derived Human Minibrain to Study Zika Virus Associated Neurological Disease

Paula Barreras, David Pamies, Anupama Kumar, Laura S. Munoz, Beatriz Parra, Celina Abreu, Lucio Gamma, Helena Hogberg, Thomas Hartung and Carlos A. Pardo. Baltimore, MD; Cali, Colombia and Baltimore

As the Zika virus (ZIKV) epidemic spreads in the Americas, understanding the mechanisms underlying the link between ZIKV and neurological diseases becomes an urgent public health concern, with need for in-vitro models which recapitulate the mechanisms of disease in the human nervous system. We developed an iPSC-derived 3D mini-brain model that consist of human neuronal and glial cell populations including GABAergic, glutaminergic and dopaminergic neurons, astrocytes and oligodendrocytes. We have shown efficient maturation of the iPSC and characterized the cell phenotype by using immunocytochemistry, RT-PCR, and flow cytometry. These minibrains have spontaneous electrical activity and exhibit myelination of axons. Here, we show that Guillian-Barre syndrome and microcephaly derived ZIKV strains are able to produce infection in the iPSC-3D minibrain model. The infection was confirmed by RT-PCR and electron microscopy. Infected minibrains released infectious ZIKV particles after ZIKV was washed out. Immunofluorescence identified ZIKV particles in the cytoplasm of astrocytes and neurons in the model with increased cell death noted as compared with the controls. Our findings establish an experimental model to study the mechanisms of ZIKV associated neurological disease and explore therapeutic compounds.

Dementia and Aging

M317WIP. Relationship Between Obesity and Stroke vs Obesity and Cardiovascular Disease

Gargya Malla and Colin T. Farrell. Bowling Green, KY

The effect of obesity on different vascular territories of the body is varied. The aim of the study was to evaluate obesity as an independent predictor of stroke and cardiovascular

disease (CVD). Data collected by 2013 Behavioral Risk factor Surveillance System was analyzed through multivariate binary logistic regression (n=348,027). 11.34% of the obese suffered from CVD and 4.97% suffered from stroke. Age, ethnicity, smoking status, hypertension, hypercholesterolemia, alcohol intake, physical activity, diabetes mellitus and weight status were found to be strong predictors of both CVD and stroke. With increasing age, the likelihood of stroke and CVD increased. While females had higher odds of stroke, males had CVD. Race and ethnicity had varying effects. Behaviorally, individuals who smoke currently or were former smokers experienced greater risk of CVD and stroke. Alcohol and physical activity were protective. Hypertension, diabetes, and hypercholesterolemia increased the odds of CVD and stroke. Obesity was directly related to stroke (OR=1.671) and CVD (OR=1.736). The current study suggests that risk of both CVD and stroke is high and comparable in the obese. Hence, it is important to educate adults about stroke as a complication of obesity.

M318WIP. Periodontal Disease as the Contributing as Well as Independent Risk Factor of Stroke and Cerebrovascular Diseases

Navdeep S. Lail, Gurleen K. Sohi, Ashkan Mowla, Robert N. Sawyer and Robert J. Genco. Buffalo, NY

Introduction: Stroke is the 4th leading cause of death in the US. It is a polyetiological disease with its risk factors including hypertension, diabetes mellitus, atrial fibrillation, alcohol, and past history of stroke. Periodontal disease and cerebrovascular disease share common risk factors. Periodontal inflammation can modulate systemic changes like inflammation, bacteremia, and platelet activation, increasing in coagulation factors and elevation of C - reactive protein and fibrinogen and alveolar bone loss. Thus, there may be a possible role of the periodontal disease in atherosclerosis and stroke.

Methods: A systematic review of the literature and analysis of the relevant papers including cohort study, longitudinal study, cross-sectional study and case reports was undertaken to advocate the recommendation.

Conclusion: After analyzing the mechanisms, we propose that periodontitis not only acts as a contributing factor in cerebrovascular diseases, but is, in fact an independent risk factor. We suggest that periodic dental check-ups and oral hygiene maintenance is a pre-requisite to prevent the occurrence of atherosclerosis and stroke. Furthermore, we recommend substantial investigations and research need to be done in order to evaluate the veritable effect of treating periodontitis on the occurrence of stroke.

M319WIP. Feasibility of a Tablet-Based System for Prehospital Neurological Assessment: The Improving Treatment with Rapid Evaluation of Acute Stroke via Mobile Telemedicine (iTREAT) Study

William M. Clark, Jason M. Lippman, Jack Cote, Brett J. Schneider, Timothy L. McMurry, Brian S. Gunnell, David C. Cattell-Gordon, Debra G. Perina, Nina J. Solenski, Sherita N. Chapman Smith, Bradford B. Worrall and Andrew M. Southerland. Charlottesville, VA

Background: Recent advances in acute stroke treatment emphasize the importance of accurate and efficient prehospital care, particularly the diagnosis and triage of patients with large vessel occlusion. We designed the iTREAT study to test the feasibility of a low-cost, tablet-based system for prehospital neurological assessment during ambulance transport.

Innovation: The iTREAT system comprises low-cost, utilitarian components that are portable and adaptable for ambulance deployment, and able to generate reliable, two-way video consultation using local cellular networks. We have previously shown the technical feasibility of our system using simulated stroke scenarios. During ambulance trials in both urban and rural EMS settings, we achieved correlation of 0.96 on the NIH Stroke Scale between ambulance and hospital assessments.

Approach: We are currently enrolling in a prospective, phase II feasibility trial to determine correlation of the NIHSS during prehospital stroke assessments. Eligibility criteria include (1) dispatch for acute neurological symptoms, or (2) positive Cincinnati Prehospital Stroke Scale from participating rural-based ambulance agencies. We have currently enrolled 21/50 patients and anticipate initial results by 2017.

Disclosure: Have you received funding or in-kind support/will your presentation be supported/sponsored (in any way whatsoever, including grants) by a commercial interest? U.S. Provisional Patent Application Serial No. 61/867,477

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Education

M320WIP. Self-Administered Gerocognitive Examination (SAGE) Correlates to Montreal Cognitive Assessment (MOCA) in a Suburban Neurology Clinic

Ansh Bhammar, Heena Patel, Malini Nair and Anil Nair. Quincy, MA

Background: Self-Administered Gerocognitive Examination (SAGE) and Montreal Cognitive Assessment (MOCA) are commonly used evaluation tools in geriatrics. We compared the scores on SAGE to MOCA scores corrected for education among patients attending the www.alzcenter.com clinic.

Method: We collected SAGE, education corrected MOCA scores, education, age, gender and race from patients attending a suburban neurology clinic from 2010-2016. As data were not normally distributed, spearman correlation tests were used. Linear models were used for multivariate analyses.

Results: SAGE score were significantly correlated to corrected MOCA scores ($\rho=0.63$, $p<0.0001$). After adjusting for age, gender and race effects, the association persisted ($p<0.0001$).

Conclusion: SAGE scores correlated to education-corrected MOCA scores among patients attending a suburban neurology clinic.

M321WIP. Dementia Cost by Diagnosis and Geographic Location

Leslie Wilson, Yingjia Chen, Tracy Lin, Sutep Laohavanich, Kathrine Possin, Michael Schaffer, Paulina Ong, Winston Chiong, Stephen Bonasera and Bruce Miller. San Francisco, CA and Omaha, NE

The Dementia Care Ecosystem funded by a CMS innovation grant has delivered care to over 300 patient/caregivers in three states. To assess its economic consequences we need to understand current costs drivers. We determined Medicare dementia cost-of-illness by cost types, dementia diagnosis and geographic regions. We analyzed costs using 2014 Medicare claims for ≥ 45 in California, Nebraska, or Iowa. We determined means, SD; used chi-square and Welch T-tests and multivariate Poisson regression adjusted costs. There were 230,957 dementia and 3,035,975 non-dementia patients. Total annual cost/person for dementia was \$24,965 and \$6,913 for non-dementia ($p<0.001$) and costs for hospice and skilled nursing were 10 times greater for dementia. Hospitalization costs/LOS were higher for dementia (\$9,425/4.5 vs 2,514/0.9; $p<0.0001$). Total costs varied from \$18,376 for frontotemporal dementia to \$36,561 for Lewy body dementia. Also high was vascular dementia (\$34,763), while Alzheimer's cost \$24,301. Lewy body dementia had highest SNF costs (\$8,691). Adjusted dementia costs in California were double Iowa, and only 40% higher for non-dementia, despite metropolitan preponderance for both. Dementia costs are high and vary greatly by dementia type. Medicare program cost comparisons must account for dementia type and location.

Headache and Pain

M322WIP. Quality of Epilepsy Care of Native Americans Is at a Crisis Stage!

Miguel E. Fiol and Kirk Allison. Minneapolis, MN

Native Americans (NA) with epilepsy have had little research on: clinical aspects, quality, availability of care, and psycho-social impact.

Methods: 65 Minnesotans NA, 29 with epilepsy, 36 w/o; 241 non-NA 127 with, 114 w/o had 38 items survey: knowledge, barriers to care, stigma, religiosity, driving, education, income, and clinical care. Fishers exact test, chi square and t test was done.

Results:

Mean age 43.2 ± 14.3 .

Urban 72- 94%, females 54%-83%.

NA #drugs 1.21, Non-NA 1.69 $p \leq .05$

Non NA w/o ever married 78%, other groups 48-57% $p \leq .010$

Education higher levels non-NA, lowest NA with $p \leq .010$.

Employment NA with epilepsy had no FT job $p \leq .001$

Income: all NA lower, worst in epilepsy group $p \leq .001$

Driving with epilepsy: NA 21%, Non-NA 52% $p \leq .01$

Health Care: NA view barriers higher, providers trust worse ($p \leq .001$).

NA/Non-NA with: highest stigma in school ($p \leq .05$)/ $p \leq .10$.

NA with:viewed lack of community knowledge more as barrier than NA w/o ($p \leq .001$)

Insurance:NA higher coverage ($p \leq .001$).

NA viewed epilepsy having more of a spirituality than Non NA $p[ite].05$

Conclusions:

This study shows mayor psycho-social and medical barriers to good epilepsy care for NA.

The findings are supportive of an urgent need for health policy changes.

Study support: Sioux Mdewakenton tribe.

M323WIP. Progressive Cardiac Dysautonomia Preceded Asystole with Sequential Electrographic Stages of Focal Status Epilepticus

Adeel A. Memon, Raima A. Memon, Sandipan B Pati and Chetan Nayak. Birmingham, AL and Bangalore, India

Disturbances in autonomic nervous system (ANS) with marked sympathetic overdrive is a proposed mechanism underlying the acute cardiopulmonary complications of convulsive status epilepticus (SE). Previously, studies have reported patterns of dysautonomia with a seizure but not with SE. We analyzed heart rate variability (HRV) in time and frequency domain during SE. We report a 26-year-old male with a four-year history of partial epilepsy following a significant traumatic brain injury from a motorbike accident. During the video-EEG evaluation, he had five sequential stages of status epilepticus that lasted 67 minutes and terminated with hypoventilation and asystole. Conventional scalp EEG recording and lead I-EKG were analyzed using Kubios HRV software version 2.1. We found that with the onset of SE and early stages (Stage I and II), there was marked activation of both systems of the ANS with sympathetic overdrive. In the late stages of SE (Stage IV and V), there was a progressive increase in parasympathetic activity leading to hypoventilation and ictal asystole. The case highlights the dynamic changes in sympathovagal imbalances with sympathetic predominance in the early stages and parasympathetic predominance in the late stages of SE.

M324WIP. Characterizing Peri-Ictal Mood Changes in Psychogenic Nonepileptic Seizures

Katarina Vasiljevic, Erin Lanzo, Scott Thompson, Mark Kvarita and Jennifer Hopp. Baltimore, MD

Psychogenic nonepileptic seizures (PNES) are relatively common but their etiology is not yet well established. While PNES patients are known to have psychological dysfunction, little is known about their mood and anxiety symptoms immediately post-ictally. We hypothesize that if the seizures in PNES patients are a physical manifestation of their coping mechanisms, they should show an improvement in their mood and anxiety in the hours following a seizure. Patients completed the Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventories (BAI) in the Epilepsy Monitoring Unit at baseline and after seizures. Seizures were characterized as epileptic or psychogenic nonepileptic. The preliminary data show that there is a change from baseline toward improvement of mood in the 24-hour post-ictal period and

that there is a tendency to return to baseline 2 weeks following the seizure. BDI-II showed a decrease in depression scores compared to baseline after 1-4 hours ($-1.1, -3.3$), 12 hours ($-3.1, -6.3$), and 24 hours ($-1.8, -5.2$). Average anxiety scores on the BAI decreased at 1-4 hours (-3.6), 12 hours (-6.9), 24 hours (-5), and 2 weeks (-1.3) after seizure. A repeated measures ANOVA showed no statistical significance in the average changes from baseline (p greater than 0.05).

Health Services Research

M325WIP. Neurological Complication Rates Associated with Epidural Injections

Byungkwan Hwang, Joongyub Lee and Byung-Joo Park. Lubbock, TX and Seoul, Republic of Korea

The purpose of this study is to estimate the incidence of neurological complications and deaths associated with epidural injection and compared incidence between steroid and non-steroid injections. We used the Health Insurance Record Review & Assessment Service database from 2009 to 2013 to make a retrospective cohort. We excluded patients who were treated under ICD-10 codes of neurological complications or who had spine operation before 2010. We estimated incidence and hazard ratios in propensity score matched cohort using Charlson comorbidity index, age and gender. We identified complications in patients who were admitted to the hospital within 24 hours after an epidural injection at outpatient clinics and were treated under ICD-10 codes of neurological complications during admission or death at discharge. Incidence rate per 100,000 person-days for epidural steroid injection (1.38, 95% CI 1.14-1.70) was higher than one for epidural injection without steroid (0.75, 95% CI 0.36-0.94). Incidence of particulate steroid injection (1.52, 95% CI 1.20-1.81) was higher than one for non-particulate steroid injection (0.84, 95% CI 0.38-0.95). In conclusion, epidural steroid injection is dangerous than epidural injection without steroid, mainly due to particulate steroid.

M326WIP. Abnormal Amygdala Volumes Predicted by Behavioral Measures in Patients with Chronic Daily Headache

Danielle D. DeSouza, Yohannes W. Woldammanuel, Meabh O'Hare, Bharati Sanjanwala and Robert P. Cowan. Palo Alto, CA

Neuroimaging abnormalities in the amygdala have previously been described in headache patients. However, it remains unclear how these abnormalities relate to behavior. This study aimed to assess amygdala volume in chronic daily headache (CDH) patients and determine behavioral variables predictive of these abnormalities.

68 participants (34 patients and 34 sex- and age cohort-matched healthy controls) were included. MRI (3T GE system) scans included high-resolution T1-weighted scans. Behavioral questionnaires included Patient Health Questionnaires 9 and 15, Generalized Anxiety Disorder-7, Pain Catastrophizing Scale, Pittsburgh Sleep Quality Inventory, Primary-Care Post-Traumatic Stress Screen, and Pain Self-Efficacy Questionnaire. A region of interest based voxel-

based morphometry analysis examined amygdala volume and step-wise multiple regression analyses assessed predictive values of behavioral data on amygdala volume.

To date, the results indicate that CDH patients have regions of larger amygdala volumes bilaterally ($p < 0.05$, corrected). The variables most predictive of left amygdala volume include right amygdala volume, sleep quality, anxiety, and pain catastrophization ($p < 0.05$). Only left amygdala volume predicted right amygdala volume ($p < 0.05$).

Amygdala abnormalities in CDH are predicted by multiple behavioral measures. These findings have potential diagnostic and therapeutic implications for CDH patients.

M327WIP. The Human Visual Cortex Responds to Isolated Melanopsin Stimulation

Geoffrey K. Aguirre, David H. Brainard and Manuel Spitschan. Philadelphia, PA

Melanopsin is a light sensitive, retinal photopigment known to mediate non-image forming responses to light, (pupil response, photophobia, circadian entrainment). It is unknown if melanopsin contributes to conscious visual perception.

A tailored modulation of the spectral content of light can selectively stimulate the cones (which mediate perception of color and luminance) or melanopsin (Spitschan et al., 2014 PNAS). In a series of studies we have obtained functional MRI data from four human subjects while they viewed pulses of spectral change that target either the cones or melanopsin. Concurrent pupillometry confirm that our stimuli evoke distinct, differential pupil responses.

We find that melanopsin stimulation produces responses in the visual cortex. Differential contrast response functions are found for the melanopsin and cone pathways. Maximal melanopsin stimulation produces a temporally extended response, consistent with the known physiological properties of the melanopsin containing retinal ganglion cells.

In ongoing measurements we are formally characterizing the perceptual experience of isolated melanopsin stimulation. That is, what does it “look like” to see with melanopsin alone, a circumstance not previously encountered by humans. These measurements may be extended to patients with photosensitivity from migraine or circadian dysfunction.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? G.K.A., D.H.B., and M.S. are listed as inventors on a patent application filed by the Trustees of the University of Pennsylvania on September 11, 2015 (U.S. Patent Application No. 14/852,001, “Robust Targeting Of Photosensitive Molecules”). The authors declare no other competing financial interests.

Interventional Neurology

M328WIP. A Rare but Costly Disease: The Case of Myasthenia Gravis

Jacklyn Omorodion, Jesse M. Pines and Henry J. Kaminski. Washington, DC

Myasthenia gravis (MG) is a rare and chronic autoimmune neuromuscular disorder for which disease management is

primarily outpatient, but disease exacerbations leading to hospital admission occur in 1 in 3 patients. We explore trends in U.S. inpatient costs of care for MG over a 10-year period in comparison to multiple sclerosis (MS) and to overall hospital discharges. Total costs of MG inpatient care rose 13-fold from 2003 to 2013, however, MS and all inpatient costs doubled. Increases in MG costs were accounted for by an over 6-fold increase in the number of discharges and a 2-fold increase in cost per discharge. In contrast, MS discharges remained stable and total discharges dropped, while cost per discharge demonstrated similar increases. For MG, the under 17 and over 85 age groups experienced the greatest increase in discharges. Use of private insurance decreased while Medicare and Medicaid use increased. Regional variations in cost for MG were also apparent with greater rises in costs in the Midwestern and Southern U.S., disproportionate to MS and all hospital discharges. These findings most likely reflect changes in practice patterns.

Traumatic Brain Injury

M329WIP. Loss of MUNC13-1 Function Causes Microcephaly, Cortical Hyperexcitability and Fatal Myasthenia

Andrew G. Engel, Duygu Selcen, Xinming Shen, Margherita Milone and Charles M. Harper. Rochester, MN

Objective: To identify the molecular basis of a fatal syndrome of microcephaly, cortical hyperexcitability, and myasthenia.

Methods: We performed clinical and in vitro microelectrode studies of neuromuscular transmission, examined neuromuscular junctions cytochemically and by EM, and searched for mutations by Sanger and exome sequencing.

Results: Neuromuscular transmission was severely compromised by marked depletion of the readily releasable pool of quanta but the probability of quantal release was normal. Cytochemical and EM studies revealed normal endplate architecture. Exome sequencing identified a homozygous nonsense mutation in the N-terminal domain of MUNC13-1 (UNC13A) truncating the protein after 101 residues.

Conclusions: Loss of Munc13-1 function predicts that syntaxin 1B is consigned to a nonfunctional closed state; this inhibits cholinergic transmission at the neuromuscular junction and glutamatergic transmission in the brain. The closed conformation of syntaxin accounts for the cortical hyperexcitability because low-expressor or null mutations of syntaxin 1B cause epilepsy. We hypothesize that normal Munc13-1 activity is essential for normal development and electrical activity of the brain.

Disclosure: Have you received funding or in-kind support/will your presentation be supported/sponsored (in any way whatsoever, including grants) by a commercial interest? NIH

M330WIP. A Critical Period for Motor Skill Development in Rats: A Microgravity Study

Neeraj Singh, Kerry Walton and Shannon Harding. Albany, NY; New York, NY and Fairfield, CT

Neonatal rats experiencing low-earth orbit (LEO) microgravity starting on postnatal day (P) 14 have previously

been shown to have impaired swimming and surface righting after returning to normal gravity, with changes persisting into adulthood. We report here on surface righting and swimming for rats experiencing microgravity starting at a younger age: P7 or P8. Neonatal rats were flown on two space shuttle missions: STS-72 (9 days) and STS-90 (16 days). Both groups were tested after landing, and were compared with pre-flight rats, as well as age-matched control rats in standard vivariums or flight-like cages. Surface righting timing and tactics, swimming speed and posture, and pre-swimming behavior were measured. After landing, flight rats from both missions had significantly fewer mature righting tactics, but also started swimming sooner, than control rats. While the effects on righting persisted, the differences in swimming speed and posture resolved by ten days after landing. These findings support the existence of, and define a window for, a critical period for mammalian motor skill development, particularly with swimming.

M331WIP. Retrospective Analysis of Effects of Edaravone on Functional Decline in Amyotrophic Lateral Sclerosis (ALS) Using ALS Milano-Torino Functional Staging System

Charlotte (Charley) Merrill, Ellen M. Dukes, Rebecca K. Bornheimer, Wendy Agnese, Pingping Ni, Marc Rivière and Gerry Oster. Jersey City, NJ; Brookline, MA; London, United Kingdom and Montreal, QC, Canada

Edaravone delayed functional decline, based on Revised ALS Functional Rating Score (ALSFRS-R), in Protocol MCI186 J19, which randomized patients to edaravone 60 mg/d (n=69) or placebo (n=68) for six 4-week cycles, followed by 6 more cycles of open-label edaravone (both groups). ALSFRS-R was retrospectively mapped to ALS Milano-Torino Functional Staging System (MITOS) using patient-level data from this Phase III trial. By 24 weeks, 46.4% (95% confidence interval: 34.8%, 58.0%) and 47.1% (35.3%, 58.8%) of edaravone and placebo patients, respectively, experienced ≥ 1 -stage decline in MITOS; corresponding figures for ≥ 2 -stage declines at 24 weeks were 2.9% (0.0%, 7.2%) and 5.9% (1.5%, 11.8%), respectively. By 48 weeks, 66.7% (55.1%, 76.8%) of edaravone-to-edaravone patients, and 73.5% (63.2%, 83.8%) of placebo-to-edaravone patients, experienced a ≥ 1 -stage decline in MITOS, and 10.1% (4.3%, 17.4%) and 23.5% (13.2%, 33.8%) of these patients experienced a ≥ 2 -stage decline in this measure. This retrospective analysis of data from the Phase III trial, MCI186 J19, suggests that edaravone might delay loss of function in ALS, based on the MITOS staging system.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? CM is an employee of Mitsubishi Tanabe Pharma America, Inc.

Have you received funding or in-kind support/will your presentation be supported/sponsored (in any way whatsoever, including grants) by a commercial interest? Abstract development was supported by Mitsubishi Tanabe Pharma America, Inc.

M332WIP. Guillain-Barre Syndrome and Zika Virus: Epidemiological Surveillance in Puerto Rico

Carlos A. Luciano, Jose E. Arias-Berrios, Brenda Deliz, José R. Carlo, Gishlaine Alfonso and Brenda Rivera-García. San Juan, Puerto Rico and Houston, TX

Zika virus (ZIKV) infection is spreading through the Americas and is a public health emergency of international concern. Countries affected by ZIKV have reported increased frequency of cases of Guillain-Barre Syndrome (GBS). In February 2016, the Puerto Rico Department of Health (PRDH) reported the first case of GBS with ZIKV infection, and ZIKV-associated GBS is expected to increase given ongoing local transmission. To address this, the PRDH, in collaboration with the Centers for Disease Control and Prevention (CDC) and the University of Puerto Rico, has implemented a prospective epidemiologic and surveillance study to monitor the frequency of cases of GBS, and to identify and characterize cases associated with ZIKV. From January through June 2016, 36 confirmed or suspected cases of GBS have been identified. ZIKV infection was identified in 19 (53%) of the 36 cases. Patients with ZIKV-associated GBS were 21 to 82 years old (median, 55 years) and 13 (68%) were female. Electrodiagnostic studies showed axonal and demyelinating subtypes of GBS. Our findings support the notion that ZIKV infection can be associated with GBS and these can be of different subtypes.

M333WIP. Retrospective Analysis of Effects of Edaravone on Clinical Anatomic Progression in Amyotrophic Lateral Sclerosis (ALS) Using King's ALS Clinical Staging System

Wendy Agnese, Rebecca K. Bornheimer, Ellen M. Dukes, Charlotte (Charley) Merrill, Pingping Ni, Marc Rivière and Gerry Oster. Jersey City; Brookline; London, United Kingdom and Montreal, QC, Canada

Edaravone delayed functional decline, based on Revised ALS Functional Rating Score (ALSFRS-R), in Protocol MCI186 J19, which randomized patients to edaravone 60 mg/d (n=69) or placebo (n=68) for six 4-week cycles, followed by 6 more cycles of open-label edaravone (both groups). ALSFRS-R was retrospectively mapped to King's Clinical Staging System (King's) using patient-level data from this Phase III trial. We examined clinical progression at weeks 24 and 48 based on any decline in King's stage. By week 24, 42.0% (95% confidence interval: 30.4%, 53.6%) of edaravone patients and 55.9% (44.1%, 67.6%) of placebo patients had experienced clinical progression. At week 48, corresponding estimates were 72.5% (62.3%, 82.6%) and 79.4% (69.1%, 88.2%) for edaravone-to-edaravone patients and placebo-to-edaravone patients, respectively. This retrospective analysis of data from the Phase III trial, MCI186 J19, suggests that edaravone might delay clinical anatomic progression in ALS according to the King's staging system.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past

12 months) with any commercial interests? WA is an employee of Mitsubishi Tanabe Pharma America, Inc.

Have you received funding or in-kind support/will your presentation be supported/sponsored (in any way whatsoever, including grants) by a commercial interest? Abstract development was supported by Mitsubishi Tanabe Pharma America, Inc.

M334WIP. A Randomized, Double-Blind, Placebo-Controlled Trial of L-Serine in Hereditary Sensory and Autonomic Neuropathy Type 1 (HSAN1)

Eichler Florian, Vera Fridman, William David, Peter Novak, Anne Louise Oaklander, Eric Macklin, Robert Brown and Hornemann Thorsten. Boston; Worcester and Zurich, Switzerland

HSAN1 is an autosomal dominant disorder caused by mutations to serine palmitoyl-CoA transferase. The mutations induce a permanent shift in the substrate preference from serine to alanine thereby forming a class of neurotoxic 1-deoxysphingolipids. We report on a two-year, delayed-start placebo-controlled clinical trial evaluating the safety and efficacy of oral L-serine (400 mg/kg/d) in HSAN1. Eighteen HSAN1 patients with prominent sensory loss, limb ulcers and neuropathic pain were enrolled. Subjects were equally randomized to L-serine or placebo for 1 year. At 48-weeks, participants remained on or crossed-over to L-serine for one additional year. Sixteen subjects completed their 96-week visit. No serious adverse events related to L-serine were reported. Over the first year plasma deoxy-sphinganine declined by 59% among participants randomized to L-serine vs. a 9% increase among placebo participants ($p < 0.001$). At 1 year, participants randomized to L-serine experienced a significant decline in CMT Neuropathy Scores relative to placebo (-1.8 units, 95% CI -3.3 to -0.3 , $p = 0.02$). Both groups improved in the second year. We conclude that L-serine is a safe and potentially efficacious treatment option for patients with HSAN1.

Disclosure: Do you (or your spouse/partner) have any relevant financial relationships (currently or within the past 12 months) with any commercial interests? Consultant to Retrophin on Cerebrotendinous Xanthomatosis

Consultant to Alexion Pharmaceuticals on molybdenum cofactor deficiency

Consultant to RegenxBio on Leukodystrophies

Consultant to Third Rock Ventures on rare neurological disorders

Spouse is employed as Editor at UpToDate

Have you received funding or in-kind support/will your presentation be supported/sponsored (in any way whatsoever, including grants) by a commercial interest? PI of ex vivo lentiviral gene therapy trial in cerebral adrenoleukodystrophy sponsored by bluebird bio

PI of L-serine trial in HSAN1 sponsored by FDA Orphan Disease Group, R01 FD004127

NINDS: R01 NS072446, R01 NS082331

M335WIP. Answer ALS: A Clinical and Comprehensive Multi-Omics Signature for ALS Employing Induced Pluripotent Stem Cell Derived Motor Neurons from 1000 Sporadic and Familial ALS Patients Nationwide

Jeffrey D. Rothstein, Clive N. Svendsen, Merit Cudkowicz, James Berry, Nicholas Maragakis, Alex Sherman, Dhruv Sareen, Steve Finkbeiner and Ernest Fraenkel. Baltimore, MD; Los Angeles, CA; Boston, MA and San Francisco, CA

ALS likely represents a collection of different subtypes of patient populations and molecular etiologies. Answer ALS is a comprehensive multi-omics approach to ALS to ascertain, at a population level, the various clinical-molecular-biochemical subtypes of ALS. ALS patients, nationwide are followed with deep clinical data collection. Patients wear a personal health monitoring device with an associated Android/iOS app collecting data on motor activity, voice and pulmonary function. iPS motor-neurons derived from each patient undergo whole genome sequencing, transcriptomics, epigenomics, proteomics, metabolomics, lipomics and high content imaging. Clinical and biological signatures are generated using bioinformatics and computational biology. The data is open source and online downloadable without IP restrictions. The goal of this effort will be to 1) identify true biological subsets of ALS which will inform future clinical trials, help develop therapies targeting the proper molecular pathway for the right patient subgroup, provide a platform of human patient derived authentic neurons for use in patient subgroup drug discovery and appropriate biomarker for use in clinical trials.

Sleep Disorders and Circadian Rhythm

M336WIP. Genetic-Encoded Calcium Indicators in Mice to Monitor Whole-Cortex Activity During Sleep

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The cellular and molecular mechanisms underlying slow oscillations during anesthesia and sleep remain poorly understood. We have utilized transgenic mice genetically encoded to express calcium indicators in cortical neurons (GCaMP) to monitor neuronal activity in living mice. We report the neural correlates of ketamine anesthesia sedation and compare them to wakefulness.

Transgenic mice selectively expressing a Thy1-GCaMP6 protein were implanted with chronic, through-bone windows and EEG screws. Optical intrinsic signal imaging (OIS) was utilized to detect calcium-induced fluorescence under waking and ketamine anesthesia.

There is a significant increase in the spectra content of the GCaMP signal in the 1-2 Hz range during anesthesia compared to wakefulness that are recapitulated in the EEG signal. We report a marked anterior to posterior propagation of GCaMP6 activity similar to previously described propagation of sleep slow waves.

OIS imaging of GCaMP mice provides high spatial and temporal resolution data enabling us to better understand the cortical slow oscillation. By combining this novel

imaging approach with powerful genetic and surgical manipulations, we will be able to study molecular mechanisms underlying sleep-related slow oscillations under neuro-pathological conditions and develop targeted sleep-related interventions.

Headache and Pain

M337WIP. Evaluating Peri-ictal Mood Changes in Patients with Epilepsy

Sharon R. Ong, Erin Lanzo, Mark D. Kvarta, Scott M. Thompson and Jennifer L. Hopp. Baltimore, MD

Depression and anxiety are among the most common comorbid conditions associated with epilepsy. While the occurrence of these conditions has been studied in the post-ictal and inter-ictal periods, little is understood about mood changes in the peri-ictal period. We hypothesize that patients with baseline depressive moods will show improvements in mood in the peri-ictal period. We also hypothesize that patients with focal onset seizures are more likely to have mood improvements in the peri-ictal period than those with generalized onset seizures.

We studied peri-ictal mood changes in the Epilepsy Monitoring Unit (EMU) at the University of Maryland Medical Center. We administer the Beck Depression Inventory and the Beck Anxiety Inventory to patients in the EMU to measure symptoms of depression and anxiety prior to a seizure and at 4 intervals post-ictally. Our data show that epileptic patients show improvement in both mood and anxiety post-ictally. There was significant difference in 4-hour average BDI scores from baseline ($p=0.0086$) and 12-hour BAI scores ($p=0.0152$). We also saw a significant average maximal change over 24 hours in focal and generalized onset epileptic patients ($p=0.02$), and significant anxiety improvement in focal onset patients ($p=0.04$).

Autoimmune Neurology

CD540. The Effect of Vitamin D on Markers of Oxidative Stress in X-linked Adrenoleukodystrophy

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Background: The demyelinating form of adrenoleukodystrophy affects 30% of affected boys, but lacks predictive biomarkers and preventive therapies. Vitamin D status has a predictive and therapeutic role in multiple sclerosis (MS) which shares features of adrenoleukodystrophy. Oxidative stress has been implicated in both disorders.

Hypothesis: Vitamin D status may offer predictive and therapeutic strategies for adrenoleukodystrophy. Vitamin D may confer anti-inflammatory and anti-oxidant effects.

Methods: We used LCMSMS to analyze plasma samples from 24 adrenoleukodystrophy boys. We used flow cytometry to study the effect of vitamin D supplementation on glutathione and disease scores in experimental autoimmune encephalitis (EAE). We used flow cytometry and MR

spectroscopy to measure glutathione status in blood and brain of adrenoleukodystrophy patients and controls.

Results: We found (1) vitamin D levels predicted later onset of demyelination in adrenoleukodystrophy boys (OR 0.24; 95% CI 0.06-0.94 for each 10ng/ml increase in vitamin D), (2) vitamin D supplementation improves disease scores and increases intracellular glutathione levels in immune cells of EAE mice, (3) adrenoleukodystrophy patients had lower glutathione levels than controls.

Interpretation: Our data support further investigation of vitamin D and glutathione in adrenoleukodystrophy.

Headache and Pain

CD542. Psychosocial and Family Risk in Pediatric Chronic Migraine and Tension-Type Headache

Emily F. Law and Tonya M. Palermo. Seattle, WA

Background: Chronic migraine and tension-type headache are common in childhood and can be associated with significant disability and distress. Although psychosocial treatments are effective for youth with headache, given scarce resources available, screening of families most in need of treatment is desirable. In other chronic conditions, the Psychosocial Assessment Tool (PAT; Kazak et al., 2012) has been well-validated and effectively implemented in clinical practice to identify family psychosocial risk. The purpose of this study is to apply this psychosocial screening approach to pediatric headache by validating a new headache version of the PAT (PAT-HA).

Methods: This is an ongoing validation study of the PAT-HA in 225 families of children ages 11-17 with chronic migraine and tension-type headache. Families complete a validation battery of psychosocial measures following their first visit in pediatric neurology, and again six months later. 17 families have been enrolled to date.

Planned Data Analysis: Psychometric validation analyses will be completed including assessment of construct validity, internal consistency, and predictive validity.

Future Directions: Future work will apply the PAT-HA as a psychosocial and family risk screener to target psychosocial treatments for this population.

Autoimmune Neurology

CD544. Cognitive Function and Structural Neuroimaging in Behaviorally Acquired HIV+ Youth

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Background: Behaviorally-acquired HIV infection during youth occurs during key brain developmental processes (frontal lobe pruning, network selection). 13-24 year-old youth now account for 26% of all new domestic HIV infections; incident cases among these youth are rising. However, we know little about the effects of acquired HIV at these ages on brain development. This pilot study: 1) describes cognitive deficits; and 2) is the first to measure the impact of HIV on brain volumes in behaviorally-acquired HIV+

youth compared to HIV- age/sex-matched historical controls.

Methods: Cross-sectional study of fourteen 18-22 year-old behaviorally-acquired HIV+ youth. Subjects completed a neurocognitive battery, behavioral health questionnaires, and phlebotomy. 7/14 youth underwent brain MRI.

Results: 43% demonstrated cognitive impairment. HIV+ youth had 14% lower striatal and 18% lower amygdala volumes than controls. Notably, these volume

differences are greater than those described in adult literature despite shorter infection durations and higher CD4+ T-cell nadirs.

Conclusions: We found prevalent cognitive impairment and significant deep gray volume loss in this small sample of HIV+ youth compared to controls. The reason for differences between these data and the adult literature remains to be determined. Further investigation into these findings and their effects on associated developing network function is warranted.

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