

2020 American Clinical Neurophysiology Society (ACNS) Annual Meeting

Poster Abstracts

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THERAPEUTIC OUTCOMES OF RNS POST FAILED MRI GUIDED LASER INTERSTITIAL THERMAL THERAPY—A CASE REPORT

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F2

A PATIENT WITH MEGACYSTIS MICROCOLON INTESTINAL HYPOPERISTALSIS SYNDROME WITH A NOVEL VARIANT IN ACTG2

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Introduction: Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is associated with inability to spontaneously void due to distended neurogenic bladder, difficulty feeding from intestinal hypoperistalsis and microcolon. Absent and immature intestinal ganglion cells with molecular defects in the nicotinic acid receptor subunits are demonstrated in the disease, however some cases report normal size and number of ganglion cells. MMIHS is categorized under the umbrella of ACTG2 gene related disorders. ACTG2 encodes for gamma-2-actin protein that is necessary for contractile function of smooth muscle in bladder and intestines. It is not known whether this disorder is a primary myopathy or a primary ganglionopathy that subsequently leads to neurodegeneration of visceral smooth muscle. We report a patient with MMIHS with a novel variant of uncertain significance in ACTG2. Intestinal histopathology demonstrated no abnormality in ganglion cells, but inflammatory cells and friable mucosa. We summarize the clinical and histopathological findings in the disease along with genetic mutations reported, in an attempt to better understand the etiopathology of this disorder. **Case Report/Case History:** An 18-year-old female is followed in our clinic for MMIHS. Prenatal ultrasound showed distended bladder and neurogenic bladder was diagnosed postnatally. Intestinal hypomotility was also noted after birth. She presented with bilious emesis and difficulty feeding, was unable to spontaneously urinate and required catheterization. There were no focal neurological deficits. Sequencing of ACTG2 gene revealed a novel variant of uncertain significance (VUS) c.811G>A, p.E271K. Due to the rare nature of the variant and its predicted impact on secondary protein structure, we believe that the variant is likely pathogenic. Intestinal biopsies were negative for ganglionic abnormalities, but with inflammatory cells in all layers. **Conclusion:** We present a patient with MMIHS with a novel VUS in ACTG2 and postulate that the variant is likely pathogenic, adding to the

genotype phenotype correlation for this condition. We summarize clinical and histopathological phenotype in MMIHS with genotype correlation to better understand the ganglionic and myopathic dysfunction in the disease.

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EXAMINING THE USE OF H/M RATIO AS A MEASURE OF SPASTICITY FOR STUDIES ON MOTOR NEURON DISEASE

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Introduction: The Hoffman reflex (H-reflex) is a mono-synaptic reflex that is analogous to the Achilles stretch reflex. Dysfunction of this reflex is linked to upper motor neuron dysfunction. The H/M ratio is a method of measuring spasticity in an objective way. It works best in collaboration with clinical measures of spasticity, such as the Modified Ashworth Scale.⁹ The Modified Ashworth Scale (MAS), regarded as the gold standard to examining spasticity, is a non-instrumented ordinal scale that measures response to passive movement which may not be considered objective because they are subject to the rater's interpretation. The MAS does not measure the neural component that contributes to passive resistance in particular. EMG measurements, such as H/M ratios may provide a more objective clinical tool for the measurement of spasticity. Only one study has examined the H/M ratio in patients with amyotrophic lateral sclerosis (ALS), and our literature review revealed no studies that looked at H/M ratio in patients with Primary Lateral Sclerosis. A previous study in ALS showed that the F/M amplitude ratio, vibrated-H/rest-H amplitude ratio and conditioned H/rest H amplitude ratio were significantly increased in patients with predominantly UMN, as well as in those with predominantly LMN signs, however no change in the H/M ratio. However, this has not been attempted to be replicated. Another study showed that H-mean is effective in assessing the clinical course of ALS and could be useful in monitoring clinical trials, but did not look at H/M ratio. Knowledge of the characteristics and limitations of spasticity measures for particular patient populations is necessary for accurate interpretation of findings and subsequent clinical trials and decision making. **Methods:** Adult patients with a diagnosis of PLS, who had an EMG were included. All patients included had spasticity, equal or above 1 in the MAS for spasticity in 2 or more muscle group of at least 3 months duration. If taking antispasmodics, a stable dose had been achieved. Patients were excluded if they had any concomitant disease or disorder that has spasticity-like symptoms or that may influence the subject's level of spasticity, received Botulinum Toxin during the preceding 6 months, have a Baclofen pump, are bedridden, with tracheostomy, have fixed-tendon contractures, or pregnant women. Four subjects with Primary Lateral Sclerosis

not associated with VPA. Clinical management of those on VPA was altered due to hyperammonemia in 11/17 (64.7%), including discontinuation or reduction of VPA and administration of levocarnitine or lactulose. Alteration in clinical management did not lead to a significant difference in length of stay. **Conclusion:** Ammonia is inconsistently checked in SE. Although receiving VPA was strongly associated with ammonia testing, hyperammonemia was not statistically associated with receiving VPA. Nonetheless, hyperammonemia in the setting of VPA resulted in a change in management in 64.7% without a reduction in length of stay. Further studies are necessary to understand the clinical utility of ammonia testing in patients with SE and VPA.

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INTRAVENOUS GANAXOLONE ACHIEVES RAPID AND DOSE-DEPENDENT SUSTAINED IMPROVEMENT IN EEG SEIZURE BURDEN IN PATIENTS WITH REFRACTORY STATUS EPILEPTICUS

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Introduction: The treatment objective for patients with refractory status epilepticus (RSE) is to achieve rapid and durable status cessation. Aggressive treatment with 3rd-line intravenous (IV) anesthetics for burst-suppression is associated with increased morbidity, mortality, and healthcare utilization. There remains a need for a new, safe, and effective antiseizure medication (ASM) that does not exacerbate medical complications. Ganaxolone (GNX) is a synthetic neurosteroid that acts as a positive allosteric modulator of synaptic and extrasynaptic GABAA receptors. **Methods:** RSE patients (n = 17) were enrolled in a Phase 2, open-label, dose-escalation study and treated with IV GNX. Of these patients, 15 were deemed evaluable for this analysis based on baseline seizure burden. Seizure burden, defined as time with electrographic seizure activity normalized per total unit time, was calculated for all patients one hour prior to and following initiation of GNX infusion. Evaluable patients were allocated to three dose cohorts: 500 mg/day GNX (Low, n = 4), 650 mg/day GNX (Medium, n = 4), or 713 mg/day GNX (Target, n = 7). EEG data were obtained in all patients and retrospectively analyzed by a central reader. **Results:** Evaluable patients enrolled in the Low, Medium, and Target dose groups had baseline SB's within the 60 minutes prior to GNX administration of 0.71, 0.97, and 0.51, respectively. In all dose groups, a rapid reduction in seizure burden of ~45% was seen within 0-5 minutes of GNX administration and further enhanced to at least an 80% reduction within 10-15 minutes post-GNX initiation. Only evaluable patients in the Target dose achieved at least an 80% sustained reduction in seizure burden for the entire analysis window (24 hrs) whereas seizure activity partially returned in the Low and Medium doses at times aligning with decreased GNX exposure. No patients required escalation to 3rd line IV anesthetics for RSE treatment within 24 hours after GNX initiation. **Conclusion:** IV GNX achieved a rapid and dose-

dependent sustained reduction in seizure burden in patients with RSE. Here EEG served as an objective diagnostic tool to support GNX's treatment effect. Together, these promising data warrant further clinical investigation of IV GNX for the treatment of RSE.

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GENOMICS, PATHOLOGY, NEUROIMAGING, AND ELECTROPHYSIOLOGY OF EPILEPSY-AFFECTED BRAIN TISSUE WITH SOMATIC MOSAICISM OF SLC35A2 MUTATION

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Introduction: While germline mutations are a known cause of many epilepsy phenotypes, several studies have identified somatic mosaicism associated with epilepsy in which genetic mutations are present only in a subset of brain cells. Still, the genetic etiology of many epileptic phenotypes associated with somatic mosaicism remains ill-defined. We have established a research program to identify brain somatic mosaicism in patients with treatment refractory epilepsy who have undergone surgical resection. **Case Report/Case History:** We present a 3-year-old male patient with West syndrome and intractable tonic seizures who underwent comprehensive pre-surgical epilepsy evaluation and intracranial EEG (iEEG). Twelve separately resected samples from different brain regions were obtained and studied using our comprehensive genetic analysis with targeted sequencing of somatic mosaic variants, along with neuroimaging, histopathology, and electrophysiology studies of epileptogenic tissue. We identified a pathogenic frameshift somatic variant in SLC35A2, present at a range of variant allele fractions (VAF) (4.2%-19.5%) in twelve different brain tissues. The proportion of the SLC35A2 mutation correlated with severity and location of neurophysiology and neuroimaging abnormalities for each tissue. iEEG was consistent with seizure onset from the hippocampus, which had the highest mutation VAF, but showed only occasional seizure onset from the occipital lobe/pole, one of the lowest VAFs. **Conclusion:** Our findings support the importance of tissue-based sequencing and highlight a correlation in our patient between SLC35A2 mutation fractions and the severity of epileptogenic phenotypes in different brain tissues. Tissues with low-level variant fractions appeared to be unaffected according to neuroimaging and onset of seizure activity, suggesting a potential threshold effect for epileptogenesis. Additional such combinatorial comparisons which include genetic, neurophysiological, radiographic, and histopathologic evaluations may enable for a better understanding of the pathogenesis of refractory epilepsies.