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EX1031

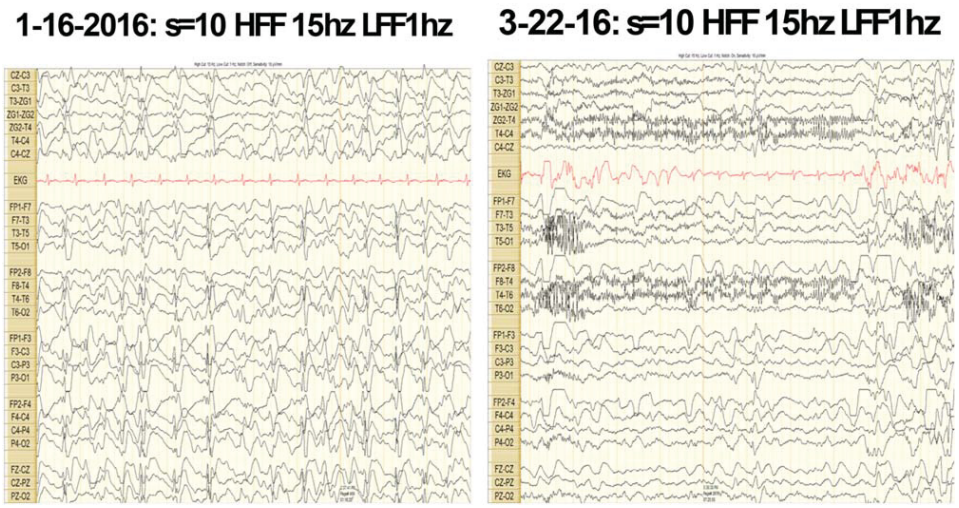

FIGURE 1: Abstract 55

55. Ganaxolone Therapy Improves Interictal EEG and Seizure Control in Lennox Gastaut Syndrome in Patients with PCDH19 and CDLK5

Chez M (Sacramento, CA)

Objective: Intractable childhood cases of Lennox Gastaut (LGS) show significantly abnormal Interictal EEG patterns that may affect developmental outcome. LGS can be caused by genetic epilepsy syndromes. We present 3 genetic syndromes cases with LGS presentation (2 PCDH19 and 1 CDKL5) showing Improved Interictal EEG patterns that correlate with improved seizure control. Ganaxolone (GNX) is a CNS-selective gamma-aminobutyric acid A (GABAA) positive allosteric modulator of the GABAA receptor with anticonvulsant and anxiolytic effects, and may improve EEG and function in LGS patients.

Methods: Patients with PCDH19(2) and CDKL5(1) with LGS were allowed to participate in an open label trial with ganaxolone (Marinus Pharmaceuticals). Dosages were up to 1800mg/day. EEG 24 hr baseline tracings were available with follow-up at 8-12 weeks. Seizure control and EEG changes in spike-wave percentage were quantified. Parental and Investigator CGI were done.

Results: Patients with PCDH19 showed a reduction in seizure frequency after 8 weeks treatment with 1200 and 1800mg/day of ganaxolone of 80% and 75%, respectively and EEG improvement in slow-spike and wave frequency of (> 90%, 80%) on awake and asleep EEG. The CDKL5 patient showed seizure reduction of (>67%) and EEG changes respectively as well (50% reduction in slow-spike wave discharges). CGI-I and CGI-parent were showing much improved for global function and seizure control.

Conclusions: This is a preliminary report of ganaxolone showing promise for refractive genetic cases of LGS with PCDH19 and CDKL5. More expanded study for other genetic, symptomatic, or idiopathic cases of LGS may be warranted.

Keywords: Epilepsy, Genetics, Translational/experimental therapeutics

56. Expanding the Phenotype of CACNA1H Mutations

Chourasia N (Houston, TX), Ossó-Rivera H, Von Allmen G, Koenig M

Objective: To expand the phenotypic spectrum of CACNA1H mutations and describe potential co-morbid conditions.

Methods: The phenotypic spectrum of five patients with de novo pathogenic CACNA1H mutations was explored. Included features were: age of seizure onset, seizure semiology, response to therapy, brain imaging findings, EEG characteristics, behavior, and co-morbid conditions.

Results: All patients had de novo pathogenic heterozygous mutations in CACNA1H. The mean age of seizure onset was 8 years. Seizure semiology varied with patients experiencing absence, complex-partial, myoclonic, atonic, and generalized tonic-clonic events. EEGs showed focal, multifocal or generalized discharges. One child had global developmental delay with autism and one had developmental regression following seizure onset. Two patients had failure to thrive and functional B-cell immunodeficiency.

Conclusions: CACNA1H encodes for the α_{1H} subunit of Cav3.2 channels, a subtype of T-type channels expressed at neuronal cell bodies and dendrites. CACNA1H mutations have previously been associated with susceptibility to idiopathic generalized epilepsy. Our series demonstrates that patients are also susceptible to focal onset epilepsy. Phenotype varied from mild to intractable with fifty percent of our patients responding to anti-epileptic medication. Two