The importance of genetic testing in pediatric epilepsy

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Background and Objective: Epilepsy is a very common medical problem worldwide, affecting 0.5-1 percent of the population. Although there can be multiple etiologies for seizures, such as brain malformations or traumatic brain injury, it is increasingly recognized that genetics plays an important role in epilepsy. Testing options include chromosomal microarrays, epilepsy panels, and whole Exome sequencing. Genetic causes of epilepsy are many, but include mutations in ion transporters or channels, neurotransmitter receptors, metabolic disorders, and many others. The discovery of a genetic etiology can have profound impacts on treatment decisions, recurrence risk, and prognosis, and thus testing should be considered in all patients with an otherwise unexplained cause for their seizures.

Study Design: More than 100 patients with epilepsy were tested by a combination of chromosomal microarrays, epilepsy panels, and whole Exome sequencing as part of their evaluation for recurrent seizures. Additionally, MRI imaging and EEGs were done, to correlate with seizures and genetic test results. Some patients underwent Vagus Nerve Stimulation (VNS) placement for refractory seizures with demonstrated benefit above medical therapy alone.

Study Participants and Settings: All patients were between the ages of newborn to 30 years old and seen as inpatients or outpatients through Tulane University School of Medicine.

Materials and Methods: Samples were collected from > 100 patients with a variety of epilepsy types, and sent for chromosomal microarray, epilepsy panels, or whole Exome sequencing, depending on the clinical indications. Some patients with negative microarrays and epilepsy panels were reflexed to whole Exome, to determine if that increased the yield of detecting abnormalities.

Results: A variety of pathogenic mutations were found, some of which had tremendous impact on treatment decisions. Chromosomal duplications and deletions detected by chromosomal microarray can be rapidly tested for at low cost, but had a lower yield than epilepsy panels, where genes suspected to be involved with epilepsy are fully sequenced. Whole Exome sequencing or mitochondrial DNA testing rarely added additional information regarding etiology in patients without other neurological signs and symptoms such as autism or developmental delay. Additionally, VNS implantation demonstrated benefit even in young children and those with generalized seizures, with both reductions in seizures and improvements in behavior and development.

Conclusion: Epilepsy panels were very high yield, followed by chromosomal microarrays and whole Exome sequencing. Important examples include avoiding sodium channel blocking antiepileptic medications in patients with sodium channel mutations, treatment by Ketogenic diet in patients with CSF glucose transporter mutations, etc. Furthermore, the fact that some patients with genetic mutations associated with severe epilepsy phenotypes that were refractory to multidrug therapy were responsive to VNS suggests this should be an early consideration in patients with genetic epilepsies. Early genetic testing can have significant impacts on treatment decisions, and thus should be strongly considered in patients with epilepsy, especially those that are refractory to medications or who have comorbid conditions such as autism or developmental delay.