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Perspective

AES Poster Demonstrates the Increasing Relevance of a Genetic Diagnosis to the Treatment of Epileptic Children at a Center of Excellence

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ABOUT THE STUDY

Genetic analysis led to a change in treatment for almost half of the children with epilepsy who received a consultation at Boston Children's Hospital for whom a firm etiology was lacking, according to a poster presented on December 5 at the 2021 annual meeting of the American Epilepsy Society in Chicago. Treatment was impacted in 45% of individuals, including 36% with an impact on anti-seizure medication choice.

In light of developing knowledge of the disease and emerging therapies, providers should routinely use genetic testing to evaluate children with epilepsy, "Genetic Diagnosis in Pediatric Epilepsy Impacts Medical Management," which was said to be the first study to report on the impact of a genetic diagnosis on the medical management of pediatric epilepsy in a clinical setting. Pediatric epilepsy is unexplained in about two-thirds of cases, so a genetic diagnosis is especially important for children. Geneticists have determined that epilepsy is a highly variegated disease, with some studies reporting that up to 78% of patients with epilepsy of unknown cause having significant genetic variants [1].

"There are over 500 genetic variants implicated in epilepsy, and they're all very rare," said Heather Olson, MD, attending physician at Boston Children's Hospital, and assistant professor of neurology at Harvard Medical School, senior author on the poster. The poster found that in 10% of the patients, genetic testing had an influence on the discussion of participation in ongoing gene-specific clinical trials. In some forms, epilepsy is not only a severe, limiting condition, but can even be fatal. For example, some children with the BRAT-1 variant, which is thought to be related to mitochondrial homeostasis, die a few months after birth due to cardiopulmonary arrest. Nevertheless, genetic testing remains controversial among insurers, with an ICER of around $15,000 per diagnosis.

In the study, researchers examined course-of-treatment and other outcomes for 602 children with epilepsy who received next-generation genetic sequencing at Boston Children's Hospital between 2012 and 2019. About one-quarter of the children who were tested received a genetic diagnosis. "Patients with childhood epilepsy usually receive genetic testing at our hospital when no other cause has been identified," explained Isabel Haviland, MD, lead author and postdoctoral research fellow at Boston Children's. Of the children who received an epilepsy gene assay with or without exome, 152 received a clinical diagnosis of genetic epilepsy, which had an impact on medical management in 110 or 72% of those patients. Of those 110 patients, the choice of anti-seizure medication was impacted in 36% of patients, while 10% were eligible for gene-specific clinical trials or investigational new drug use. Another 3% of the 110 patients were treated off-label. The 152 patients who received a genetic diagnosis, care coordination were impacted in 48%, and vitamin treatment and/or metabolic treatment such as the ketogenic diet was ordered in 7%.

Additionally, genetic testing led to a change in diagnosis in some children. "For two children who initially had a diagnosis of primary mitochondrial disorder, it was found that their epilepsy was in fact due to a genetic cause," explained Haviland. One child was found to have a variant in gene PRRT2 and was switched to a different anti-seizure medication, eventually becoming seizure-free.

Diagnosis of genetic epilepsy frequently determines treatment

Due to the variegated nature of genetic epilepsy, genetic diagnoses in the children resulted in differential treatment in the form of vitamin supplements, dietary regimens, off-label treatment with already approved drugs, new or experimental treatment with small molecule drugs, or enrollment in gene therapy clinical trials. While outright cures are very rare, even something as simple as supplementing the child's diet with vitamins may partially correct the problem and treat the epilepsy. "For example, vitamin B6 is important for brain development, but some genetic disorders affect its pathway in the brain," said Haviland.

Another nutritional intervention sometimes used is the ketogenic diet. "This results in changes in not only ketones, but

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insulin, glucose, and free fatty acids; all of these metabolic changes may have a role in reducing seizure frequency," she added, noting that initiating the ketogenic diet in a child requires hospitalization.

Some drugs are already approved for the treatment of genetic epilepsy, such as fenfluramine, which was approved in June of 2020 to treat Dravet syndrome, one of the first established epilepsies. "We recently published a case report about an individual who had been having monthly seizures, who had to go into the intensive care unit each time [2]. Having now received an accurate genetic diagnosis of Dravet syndrome, the patient is now three years seizure free," said Olson [3].

Then there are the genetic epilepsies for which off-label treatments can be used, such as epilepsy with a variant in GRIN2A, a gene involved in brain cell communication, which has been treated with memantine, a drug approved only for Alzheimer's disease. There are also small molecule drugs under development for some genetic epilepsy. "But generally, the only way to cure genetic epilepsy is with a gene therapy that modifies and corrects the variant in the patient's gene, such as an antisense oligonucleotide. An ASO is designed just for one child, but these are very few and far between," explained Olson [3].

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