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A Novel Phenotype in a Previously Described Epilepsy—Aphasia Disorder

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The clinical presentation of patients with epileptic encephalopathies can be heterogenous. When attempting to classify a patient's epilepsy syndrome, challenges can arise due to the phenotypic overlap of various epilepsies as well as the different presentations of mutations within the same gene. Genetic testing can be most helpful in evaluation of children with features spanning several epilepsy phenotypes. In this case, we report on a boy with an epileptic encephalopathy found to have a previously unreported mutation in a recently described gene.
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Introduction

Availability and use of targeted gene testing, epilepsy gene panels, and whole-exome sequencing (WES) have identified causative genes for epilepsy syndromes without previous genetic association, bridging the divide between syndromic diagnosis, and underlying genetic etiology. Such advances have been particularly notable in the epileptic encephalopathies. Genes previously identified as the cause of age-limited "benign" or familial epilepsies are being discovered in children with epileptic encephalopathies of unknown etiology and are thought to be pathogenic mutations.

Many children can be diagnosed clinically as having a specific epilepsy syndrome. Although some epilepsy syndromes are highly correlated with a specific genetic mutation (eg, the SCN1A gene mutation in Dravet syndrome), there is genetic heterogeneity such that pathogenic mutations in different genes can produce similar or overlapping clinical pictures, as is often the case in the epileptic encephalopathies.

Here we present the case of a boy with an epileptic encephalopathy who was found to have a de novo mutation in the GRIN2A gene, illustrating the potential for genetic evaluation and further expanding the GRIN2A epilepsy phenotype.

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Patient Case

The patient presented to our center at age 3 years 3 months for evaluation of multiple generalized seizure types. He was the product of an uncomplicated term pregnancy and had been developmentally appropriate and previously healthy until seizure onset at age 20 months. At that time, he developed generalized tonic-clonic (GTC) seizures lasting 2-3 minutes, which occurred weekly. With initiation of levetiracetam, frequency of GTCs dropped to monthly; however, atonic and absence seizures then began occurring multiple times daily.

Electroencephalogram (EEG) at evaluation demonstrated generalized polyspike and wave discharges with occasional right parietal and midline discharges in the setting of a normal background rhythm. There were recorded myoclonic seizures. Given the patient's history of normal development with GTC seizures, myoclonic, and myoclonic-atonic seizures, the potential diagnosis of myoclonic-astatic epilepsy was discussed. However, with focal right parietal and midline discharges, the possibility of an alternative diagnosis was raised. Neuroimaging with 3-Tesla MRI was unremarkable. Karyotype and chromosomal microarray were normal. Metabolic tests (urine amino acids, urine organic acids, urine acylglycines, urine purines and pyrimidines, serum acylcarnitine profile, serum amino acids, cerebrospinal fluid amino acids, and cerebrospinal fluid neurotransmitter metabolites) were within respective reference ranges.

The ketogenic diet was initiated with minor improvement in seizure frequency. However, 6 months later, while still on combination therapy with the ketogenic diet and levetiracetam,

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he developed a 2-week span of increased seizure frequency with almost daily GTC, atonic, myoclonic, and absence seizures, and was admitted in nonconvulsive status epilepticus. Seizures were refractory to IV midazolam, levetiracetam, ethosuximide and valproic acid, and he ultimately received intravenous immunoglobulin (IVIG) at a dose of 1 g/kg divided over 5 days. The patient responded electrographically and clinically with increasing periods of alertness with each subsequent day of therapy.

Seizure frequency slowly improved over the next several months and he regained verbal skills, was able to count to 25, and could ride a 2-wheeled bike. However, nonconvulsive status epilepticus recurred at age 5 years and was treated with intravenous methylprednisolone 30 mg/kg daily for 5 days, followed by addition of rufinamide. A repeat brain MRI was unchanged, and ophthalmologic examination was normal without evidence of retinopathy. An epilepsy gene panel demonstrated a pathogenic de novo heterozygous mutation in c.3813 G > A (p.W1271X) in the GRIN2A gene, not previously reported.

At the most recent follow-up at age 6 years, after a period of seizure freedom for nearly 1 year, the patient began having brief absence seizures with and without accompanying myoclonus occurring several times per week as well as nocturnal tonic seizures (Fig.). Ambulatory EEG demonstrated multifocal spike and sharp waves and generalized spike and sharp wakes with a spike-wave index of 20%-30% in slow wave sleep. He continues on ketogenic diet and rufinamide. Developmentally, he is progressing but is exhibiting mild intellectual disability and is working at a preschool level. Speech pathology evaluation showed skills in the low-average range on standardized testing (39% in oral expression and 21% in listening comprehension). Articulation in connected speech was felt to be generally consistent with single word testing but developmental speech sound errors were noted.

Discussion

There are various available testing options for epilepsy genetics. The choice of test may depend on several factors including patient presentation, epilepsy phenotype, acuity and severity of the clinical situation, and cost. As part of an initial screening evaluation, chromosomal microarray, including array comparative genomic hybridization and single nucleotide polymorphism analyses, may be ordered to test for disease-causing copy number variants (CNVs). CNVs are a source of genetic variation, however, some deletions or duplications may be pathogenic and CNVs may contribute to the cause of epilepsy in up to 10% of children.[1] When further evaluation is pursued, then either more targeted gene testing, epilepsy gene panel, or whole-exome sequencing are options. Next-generation sequencing (NGS) allows for the testing of millions of fragments of DNA at a time compared to the single fragment at a time testing of traditional Sanger sequencing. NGS technologies are used most often in gene panels and in WES, while in single-gene testing, Sanger sequencing may be used. Single-gene testing can be less cost effective, as the process can be more time consuming, however, in the right clinical context may be the test of choice. Targeted epilepsy gene panels are designed with genes of interest and multiple options are available depending on the laboratory. Some gene panels are offered with very few genes whereas others contain several hundred genes. Additionally, panels may be separated by clinical features such as myoclonic epilepsy, neonatal-onset epilepsy, or epileptic encephalopathy. A gene panel may be preferred when there is phenotypic overlap of the suspected diagnosis and other potential etiologies and the yield of single-gene testing may be low. Whole-exome sequencing is being used more frequently in clinical practice and may be the test of choice when there is no known etiology for the patient's epilepsy or encephalopathy. The use of NGS technology in WES is used to screen approximately 95% of the coding region of the genome.[2] An advantage of WES is the ability to perform "trio" testing of the affected child and unaffected parents to aid in the diagnosis of de novo mutations, which increased the diagnostic yield up to 31% in one study, compared to 25% in a singleton study.[3,4] In a study of three epileptic encephalopathy cohorts, WES trio testing was used to find a probable causative de novo mutation in up to 12% of probands.[5]

Depending on the specific mutation within a known gene, the clinical phenotype (ie, age of onset, severity, and associated findings) may be quite varied. One such example is in the potassium channel mutation KCNQ2, which is known to cause benign familial neonatal seizures. In this autosomal dominant inherited epilepsy syndrome, seizure onset is within the first 3-6 days of life with brief and frequent medication-responsive seizures. Following a course of normal development, infants are often seizure free within the first year of life.[6,7] Further being recognized is the KCNQ2 encephalopathy characterized by early onset pharmacoresistant neonatal epilepsy with tonic seizures, focal motor seizures and epileptic spasms, multifocal discharges on EEG with burst-suppression pattern, and severe developmental delay.[7-9]

GRIN2A encodes for the NR2A subunit of the NMDA glutamate receptor and is located on chromosome 16p13.2.[10] NR2A subunits are expressed in multiple cortical and subcortical locations and are necessary for brain development and synaptic plasticity.[11] Mutations in GRIN2A alter function of the tetrameric ligand-gated ion channel NMDA receptor, impairing ligand binding, channel opening state, and downstream signaling pathways.[12,13] Mutations in GRIN2A are inherited in an autosomal dominant manner; however, there is phenotypic variability and incomplete penetrance, which explains the clinical spectrum.[12,14,15]

In 2010, Reutlinger et al. reported on three children with varying dysmorphic features, intellectual disability, and epilepsy with mutations in 16p13, implicating GRIN2A. A feature shared by these children was discharges from the centrotemporal or rolandic region on EEG.[10] In 2013, the reporting of GRIN2A mutations in up to 20% of patients with the epileptic encephalopathies of Landau-Kleffner syndrome (LKS) and continuous spike and wave in slow wave sleep (CSWS), as well as atypical rolandic epilepsy with speech impairment, demonstrated that GRIN2A mutations are a potential monogenic cause of epilepsy-aphasia spectrum disorders.[16]