Clinical and Electroencephalographic Characteristics of Infantile-Onset Epilepsies Caused by Genetic Mutations

Yun Jung Hur, MD[1,2], Sookyong Koh, MD, PhD[1,3,*], John Millichap, MD[1], Srishti Nangia, MD[1], Lawrence J. Jennings, PhD[1], and Douglas R. Nordli, Jr, MD[1,4,*]

Objectives To determine whether certain characteristic electroencephalography (EEG) features are indicative of a genetic cause in early-life epilepsy.

Study design We enrolled a total of 100 patients with infantile-onset (<3 years) epilepsy due to known genetic cause (n = 50) and nongenetic cause (acquired, structural, or unknown, n = 50). The genetic group was classified into synaptopathies, channelopathies, mTOR (mammalian target of rapamycin)-opathies, and chromosomal abnormalities. The nongenetic group included epilepsy of unknown cause and structural abnormalities such as brain tumor, focal cortical dysplasia and encephalomalacia. The clinical features, magnetic resonance imaging, and video EEG obtained before 3 years of age and again at follow-up were reviewed. Specifically, the background rhythms and patterns of interictal epileptiform discharges were analyzed to define the EEG characteristics.

Results The genetic group was more likely to have seizure recurrence beyond infancy and significant developmental delay ($P < .01$). The genetic and nongenetic groups showed different EEG patterns in the initial EEGs that persisted in follow-up EEGs. Diffuse slowing with pleomorphic focal/multifocal epileptiform discharges were present more often in the genetic (86%) compared with the nongenetic group (20%) in the initial EEGs ($P < .01$). The last available follow-up EEG features were similar (81% in genetic versus 17% in nongenetic) to the EEG performed prior to 3 years of age.

Conclusions Our findings suggest a simple guide for genetic screening in children with early-onset epilepsy. Genetic testing may be indicated and useful in infants with delayed development, no obvious cause, and significant EEG background slowing with pleomorphic focal or multifocal epileptiform discharges. *(J Pediatr 2017;184:172-7).*

Early-life epilepsies often are devastating conditions, resulting in uncontrolled seizure and lifelong disability, which create an enormous burden on families. Genetic causes have emerged as important and frequent causes of early-onset epilepsy.[1,2] The phenotype only sometimes correlates with genotype and varies from self-limited conditions to epileptic encephalopathies defined as unremitting epileptic activities contributing to cognitive and behavioral deterioration.[3,4] Infants with unexplained epileptic encephalopathies, in particular, require a thorough diagnostic evaluation for treatable inborn errors of metabolism and a search for de novo genetic mutations. Screening strategies for candidates can be useful because the cost of genetic testing can be prohibitive, especially when many insurance companies still deny coverage.[2] The clinical presentation combined with characteristics on electroencephalography (EEG) may help identify certain features of epilepsy with a genetic cause and raise the diagnostic suspicion for genetic disease in others with delayed development and intractable seizures.

Recent studies have identified mutations in genes relating to synaptic function as well as ionic channels in infantile epileptic encephalopathy.[5-8] In addition, epilepsy with associated cortical malformations have been linked to mutations in mammalian target of rapamycin (mTOR) pathways[9,10] Previous studies have failed to delineate conclusively which specific EEG features correlate with genetic mutations.[11-14] In contrast, more general characteristics of the initial EEG have been found to predict seizure outcome.[11,15] We hypothesized that certain broad categories of EEG abnormalities are associated with genetic epilepsies and allow specific diagnosis by targeted molecular genetic testing. We sought to define and characterize the EEG features that can predict epilepsy with genetic cause by retrospectively analyzing interictal epileptiform discharges (IEDs) and background activity in infants diagnosed with specific genetic mutations.

BGR	Background rhythm
EEG	Electroencephalography
IED	Interictal epileptiform discharge
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
PDR	Posterior dominant rhythm
PFA	Paroxysmal fast activity
TSC	Tuberous Sclerosis Complex

From the [1]Epilepsy Center, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Department of Pediatrics, Haeundae Paik Hospital, Inje University College of Medicine, Pusan, Republic of Korea; [3]Department of Pediatrics, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; and [4]Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA

*Contributed equally.

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Methods

Our study was approved by the institutional review board of Ann & Robert H. Lurie Children's Hospital of Chicago, and data analyses were performed without patient identifiers. A total of 50 patients aged 3 months to 17 years old with genetically determined cause of epilepsy and 50 age-matched controls without genetic diagnosis were studied. All patients had a video-EEG performed between 2 months and 3 years of age at Lurie Children's. We identified patients with early-onset epilepsy and specific genetic conditions by searching video EEG reports databases. We also identified patients with nongenetic disease with the same methods, matching with age and underlying causes. Patients with genetic cause of epilepsy were divided into 4 groups. (1) Synaptopathies (diseases relating to dysfunction of synapses) from defects in *PCDH19* (n = 5), *CDKL5* (n = 4), or *GRIN2A* or *GRIN2B* (n = 2). *PCDH19* is involved in synaptic connection and transmission as it functions in calcium-dependent cell adhesion. *CDKL5* encodes a large protein containing serine-threonine kinase domain that is related to regulation of its catalytic activity.[7,16] *GRIN2A* and *GRIN2B* play important roles in synaptogenesis and synaptic plasticity.[17] (2) Channelopathies (disease relating to abnormal function of ion channel subunits or proteins that regulates ion channel) from defects in *ATP1A2*, *ATP1A3*, *KCNQ2*, *SCN2A*, or *SCN8A*. (3) mTOR (mammalian target of rapamycin)-opathies (diseases relating to a regulator of mammalian metabolism and physiology) from defects in *TSC1* or *TSC2*. (4) Chromosomal abnormalities including trisomy, microdeletion, or Angelman or Prader-Willi syndrome (maternal or paternal uniparental disomy on chromosome 15). In nongenetic groups, patients with structural abnormalities or epilepsy of unknown cause were enrolled to compare their EEG pattern with the genetic group. They consisted of encephalomalacia in 16, tumor or focal cortical dysplasia in 7, stroke or intracerebral hemorrhage in 10, and unknown etiology of epilepsy in 17 patients.

The clinical features, magnetic resonance imaging (MRI), and video EEG studies were reviewed. Clinical features included age, sex, age at seizure onset, age at diagnosis of genetic disease and epilepsy, seizure characteristics, age of video EEG, and a use of rapamycin as mTOR inhibitor. The treatment for epilepsy consisted of anticonvulsant medications as well as therapies other than drug therapy. These alternative therapies are used when epilepsy becomes drug-resistant and include ketogenic diet, vagus nerve stimulation, and resective surgery. Development was evaluated by parental report of milestones and by neurologic examination. Seizure outcome was reviewed for seizure frequency and seizure freedom recorded at the last visit. Three patients in the genetic group and 5 patients in nongenetic group were excluded because of a nonepilepsy diagnosis (febrile seizures) or loss to follow-up.

Chromosome tests were performed via peripheral blood lymphocyte cultures with GTG-banding. Whole-genome chromosome microarray was performed to detect copy number variant in the genomic DNA extracted from the peripheral blood leukocytes. The assay was use to compare the patient DNA with normal controls, via the Affymetrix Genome-Wide Human CytoScan HD SNP array (Thermo Fisher Scientific, Waltham, Massachusetts). For an epilepsy panel test of 70 genes (not including *ATP1A3*), sequence analysis and exon-level deletion/duplication analysis were performed. With the use of genomic DNA from the specimen, the coding exons and the flanking splice junctions were amplified with polymerase chain reaction and sequenced simultaneously by massively parallel (next-generation) sequencing on an Illumina HiSeq instrument (Illumina, San Diego, California). Bidirectional sequencing was compared with the reference sequence of the coding exons and splice junctions. For the suspected diagnosis of alternating hemiplegia of childhood, *ATP1A3* mutational analysis was performed. It was done from genomic DNA by polymerase chain reaction amplification of the 23 coding exons in *ATP1A3* gene.

The 24-hour long-term video EEG studies obtained before the child reached 3 years of age were examined by 2 independent reviewers blinded to the diagnosis. The last video EEG studies after 3 years of age also were reviewed in 46 children. In 4 children in the nongenetic group, no follow-up video EEG was performed, ie, only routine EEG done; thus, routine EEGs were reviewed instead. The interval between EEGs was at least 12 months. EEGs were performed with a digital acquisition system (Nihon-Kohden America, Inc, Irvine, California) and video EEGs were performed with Natus (Natus Medical Inc, Pleasanton, California) with 19 electrodes placed on the patient's scalp via the international 10-20 system with a sampling rate of 200 Hz and a band pass width from 0.5 Hz to 70 Hz.

Background rhythms (BGRs) were classified as normal, diffuse slowing, or focal slowing. For the assessment of background, posterior dominant rhythms (PDRs), unexpected rhythms such as excessive alpha or beta rhythms, and loss of normal expected rhythms or paroxysmal fast activities (PFAs) were specified. If there was consistent slowing but restricted to one location or in one hemisphere, this was classified as focal slowing. The region of focal slowing was identified and evaluated together with the location of the epileptiform discharges. IEDs were evaluated as generalized sharp and wave discharges, stereotyped focal spikes or sharp waves, polymorphic focal spikes or sharp waves, and multifocal or polymorphic spikes or sharp waves. According to the assessment for BGRs and IEDs, electrographic patterns were classified as following 5 patterns[18]: I, normal BGRs and no IEDs; II, normal BGRs and stereotyped generalized IEDs; III, normal BGRs and stereotyped focal or multifocal IEDs; IV, diffuse slowing and pleomorphic focal or multifocal IEDs (**Figure**, A; available at www.jpeds.com); and V, focal slowing and pleomorphic focal or multifocal IEDs (**Figure**, B).

The association between each assessed electrographic pattern and specific genetic and nongenetic diagnosis was analyzed statistically with t or χ^2 tests and the Fisher exact tests in MedCalc Statistical Software version 16.1 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). $P < .05$ was considered as significant.