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A Case of Neonatal Seizures With an Unusual Electroclinical Pattern

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Abstract

Benign familial neonatal epilepsy is a syndrome characterized by recurrent seizures occurring in the neonatal period. Seizures commonly begin at day 3 of life and usually abate by 1 to 4 months of life. Seizures are usually described as tonic with an asymmetric component with associated autonomic features. The authors report a newborn presenting with an unusual electroclinical phenotype. The electroencephalogram demonstrated an unusual pattern of electrical attenuation at the onset of seizures. Identification of these features is important for early recognition of this neonatal syndrome, as well as initiation of proper therapy.

Keywords

neonatal seizures, familial, benign, electrodecrement, sodium channel blockers

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Genetic predisposition was thought to be a contributing factor in the development of epilepsy since the time of Hippocrates, yet neonatal familial seizures were first described in 1979.[1] "Benign familial neonatal seizures" or "benign familial neonatal epilepsy" is characterized by neonatal onset seizures typically presenting in the second or third day of life. Benign familial neonatal epilepsy has been reported to occur in approximately 14 per 100 000 live births and is characterized clinically by focal or multifocal clonic or tonic seizures. Development is usually normal, but febrile seizures have been noted to occur in approximately 15% of patients.[2] Benign familial neonatal epilepsy is caused by mutations in the gene that encodes voltage-gated K+ channel subunits (*KCNQ2*, *KCNQ3*) and is inherited in an autosomal dominant fashion.[3] Penetrance is estimated to be approximately 85%. A recent study demonstrated that *KCNQ2* was the most common gene identified in benign familial neonatal epilepsy.[4] *KCNQ2* mutations can result in a spectrum of phenotypes with benign familial neonatal epilepsy on the mild end and epileptic encephalopathy on the severe end.

The *KCNQ2* gene has been demonstrated to encode instructions for producing proteins that interact to form potassium channels. Potassium channels transport potassium in and out of cells and therefore play a key role in electrical signaling. These channels are found within the brain and are particularly important in creating an electrical signal called the M-current. The M-current is crucial for ensuring that the neuron is not constantly active. Thus, KCNQ2 mutations result in reduced M-current, increasing neuronal excitability, which can lead to seizures.[5] Reduction of protein product by approximately 25% in KCNQ2/KCNQ3 mutations is enough to increase neuronal excitability.[6]

It has been hypothesized that pathogenic variants that further downregulate the activity of the M-current may predispose patients to a worse prognosis. In a sample of families with benign familial neonatal epilepsy, patients with a more severe course tended to have mutations located in the S5 or S6 transmembrane domains. These domains provide the functionally important pore-forming region. Another patient with a severe course was reported to bear a mutation located in the accessory protein-binding domain within the large C-terminus of *KCNQ2*.[7] Therefore, the broad phenotypic spectrum of

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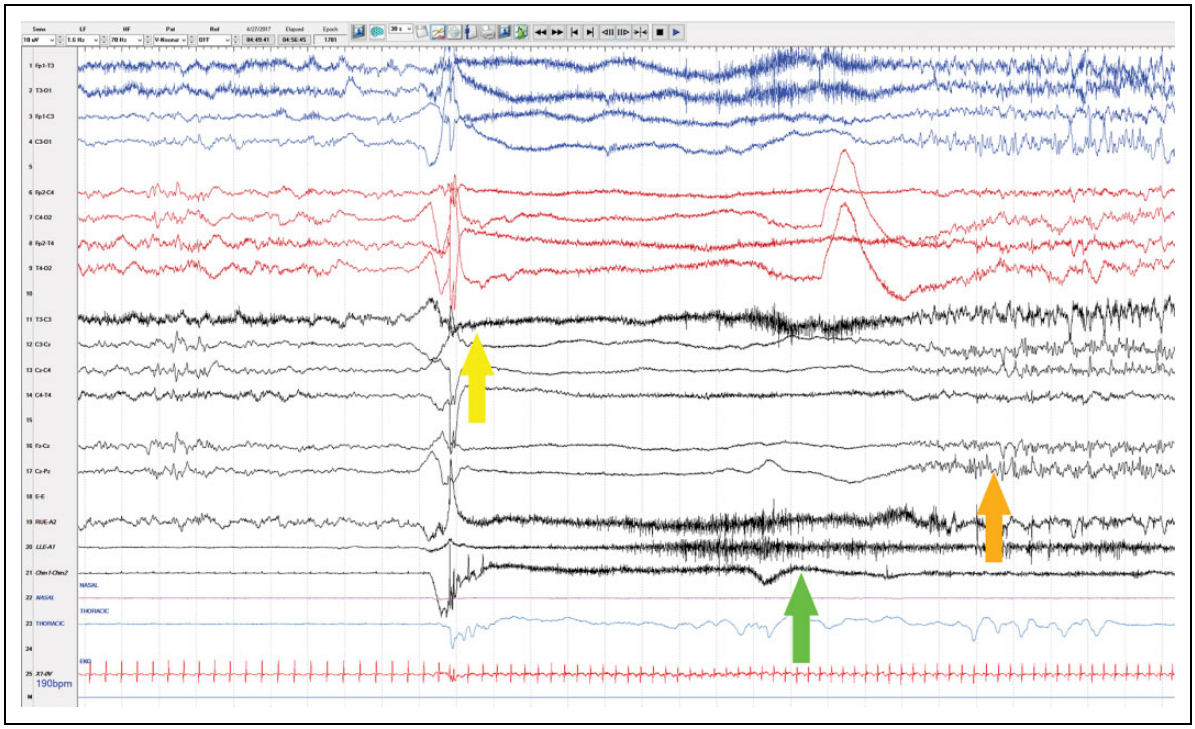

Figure 1. Electroencephalogram onset in patient with KCNQ2 mutation.

KCNQ2-related disorders could be driven by the location of the mutation. Mutations that occur "de novo" are also associated with a more severe phenotype.[8]

Patients with benign familial neonatal epilepsy can present with seizures showing a wide spectrum of features, including focal tonic or apneic episodes, focal clonic activity, or autonomic changes. Seizures are generally brief, lasting 1 to 2 minutes, but may occur frequently. Interictal electroencephalogram (EEG) may be normal or demonstrate focal discharges and rarely demonstrates a pattern described as "theta pointu alternant."

Patients with benign familial neonatal epilepsy show therapeutic response to sodium channel blockers, such as carbamazepine, oxcarbamazepine, and phenytoin. Potassium channel openers such as retigabine (which has been discontinued) and diclofenac have also been posited as possible treatments.

We present a case of a newborn with unusual electroclinical features, which lead to the appropriate diagnosis and prompted the institution of targeted therapy.

Case Description

Our patient was an ex 39 4/7-week baby boy born via cesarean section due to breech presentation. Appearance, pulse, grimace, activity, and respiration (APGAR) scores were 6, 8, and 9. There were no other complications during pregnancy or delivery. He presented to the neurology service with seizures on day 1 of life. Physical examination was unremarkable and no dysmorphic features were present. His father was noted to have febrile seizures and paternal grandfather had seizures in infancy associated with apnea.

His seizures were captured on video EEG monitoring. The clinical events consisted of asymmetric tonic posturing, with his head to the right and extension of arms to the left or head to the left and extension of arms to the right. Motor manifestations were accompanied by apnea and cyanosis, followed by a cry. Subsequently, asynchronous clonic movements of the extremities were observed (Supplemental Videos 1 and 2). The EEG showed a distinctive pattern consisting of "electrodecrement," which is a generalized attenuation of the electrical background activity (Figure 1). This pattern is rarely observed in patients affected by neonatal seizures. His seizures occurred in clusters and they were resistant to treatment with levetiracetam, phenobarbital, and topiramate. He was bolused with fosphenytoin with immediate control. He was then transitioned to oxcarbazepine after diagnosis was suspected and achieved complete seizure freedom.

Magnetic resonance imaging of the brain without contrast, sepsis workup, and metabolic panel were all normal. Chromosome microarray and fragile X analysis were normal. Genetic testing revealed a variant of unknown significance in *KCNQ2* c.704C>T (p.A235V), predicted to be benign by PolyPhen and deleterious by SIFT. This variant was absent from population controls, representing a missense variant. Parents tested negative for the alteration, suggesting the variant was inherited de novo or from a mosaic parent and assumed to be pathogenic as supported by the clinical picture. Currently, the patient is 2 years old and has since been diagnosed with autism with prominent speech delay that is improving with speech therapy. He

continues to remain seizure-free on oxcarbazepine but had a seizure when wean was obtained.

Discussion

Benign familial neonatal epilepsy is one of several epileptic disorders characterized as a channelopathy. Benign familial neonatal epilepsy is most commonly caused by *KCNQ2* mutations encoding potassium channel subunit KV7.2. Seizures are usually limited to the first year of life, but approximately 25% of patients develop epilepsy later in life. *KCNQ2* mutations have also been implicated in more severe phenotypes and early infantile epileptic encephalopathies.[9]

This case illustrates unusual electroclinical features observed in this syndrome, including a peculiar ictal pattern of "electrodecrement." Recognition of these features is important for the initiation of appropriate treatment. Institution of early therapy could potentially minimize developmental regression, especially in more severe phenotypes.[5]

Author Contributions

All authors contributed to contributed to conception and design, drafted the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee.

Supplemental Material

Supplemental material for this article is available online.

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