Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Episodic Ataxia Type 1 (K-channelopathy) Manifesting as Paroxysmal Nonkinesogenic Dyskinesia: Expanding the Phenotype

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Ion channels are transmembrane proteins that facilitate ionic flow according to their electrochemical gradients. They play a key role in generating membrane potential and function in diverse cellular activities, such as signal transduction, neurotransmitter release, muscle contraction, hormone secretion, volume regulation, growth, motility, and apoptosis. More than 400 ion channel genes have been identified.[1] Channelopathies are a genetic or acquired heterogeneous group of disorders that involve ion channels' dysfunction. Ion channels are responsible for various nervous system disorders, such as generalized epilepsy with febrile seizures, familial hemiplegic migraine, episodic ataxia (EA), hyperkalemic or hypokalemic periodic paralysis, and myotonic or paramyotonic disorders. Encoded by more than 70 genes, potassium channels make up the largest group of ion channels found in virtually all cells of the human body.[2] Mutations in the potassium voltage-gated channel subfamily A (*KCNA1*) gene have been identified that cause a range of signs and symptoms affecting the nervous system, such as episodic ataxia type 1 (EA1) with or without myokymia, isolated myokymia, and epilepsy.[3]

We present an interesting child with a *KCNA1* gene mutation who presented with episodes of prolonged stiffness of both lower limbs, mimicking paroxysmal nonkinesogenic dyskinesia (PNKD).

Case Report

The study was approved by the Institutional Review Board of Wayne State University. Written informed consent from the legal guardian was obtained for all aspects of the study, the including videos (Video S1, Video S2). A 5-year old boy presented with intermittent stiffness of the legs bilaterally associated with pain. The first episode occurred at 3 years of age in the evening while he was sitting on the couch. The episode started with vomiting followed by painful, bilateral stiffening of the lower extremities without any jerking. He remained alert during the episode. However, he was not able to walk due to muscle stiffness and pain. He was taken to the emergency department. Metabolic workup was normal. He was discharged home, and he slept with continuing leg stiffness. On waking up in the morning, his symptoms resolved. He had multiple such episodes of 2 to 12 hours' duration occurring every few weeks to every few months preceded and/or followed by headache/vomiting and usually triggered by stress and fatigue (Video S1, Video S2). In between episodes, he was completely normal. Birth and developmental history was unremarkable. There was no family history of migraine, seizure, or episodic muscle stiffness. He had normal physical and neurological examinations in between spells.

Blood count, electrolytes, creatine kinase, and thyroid profile were normal. Serum amino acid, acylcarnitine profile, lactate, pyruvate, and urine organic acid levels taken in between and during the episodes were within normal limits. Paraneoplastic panel was negative. Prolonged video electroencephalographic (EEG) monitoring during the spell was normal as well as the interictal EEG. Brain and spine magnetic resonance imaging (MRI) was unremarkable. An extensive nerve-conduction study was normal, and a needle electrode examination was limited due to pain, but no myotonic or myokymic discharges were noted. Considering the prolonged episodes of forceful, involuntary muscle contraction involving both lower limbs, the episode resembled dystonia. Considering the possibility of PNKD, an empiric trial of clonazepam was tried without improvement of symptoms. After proper genetic counseling, whole-exome

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sequencing was undertaken through GeneDx whole-exome analysis (GeneDx, Gaithersburg, MD) using genomic DNA isolated from whole blood of the patient and both parents. The Agilent Clinical Research Exome kit (Agilent Technologies, Santa Clara, CA) was used to target the exonic regions and flanking splice junctions of the genome. These targeted regions were sequenced simultaneously by massive parallel sequencing on a sequencing system with 100-base-pair paired-end reads. The bidirectional sequence was assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg 19 (University of California Santa Cruz [UCSC] Genomics Informatics Group, UCSC Genomics Institute, Santa Cruz, CA), and analyzed for sequence variants using a custom-developed analysis tool. A capillary sequencing method was used to confirm all potentially pathogenic variants identified in samples from the patient and relatives. This sequencing identified the presence of a heterozygous R86Q variant (an arginine [R] to glutamine [Q] substitution at position 86), coding variant c.257 G>A (a guanine [G] to alanine [A] substitution at position 257) in the *KCNA1* gene, which is implicated in EA1. In addition, the patient was heterozygous for the de novo N404K variant (an asparagine [N] to lysine [K] substitution at position 404) of uncertain significance in the period circadian clock 2 (*PER2*) gene, which is involved in circadian rhythm. Both parents have been tested, and the mother is heterozygous for the *KCNA1* R86Q variant, but she has no symptoms. With the diagnosis of K-channelopathy, the patient was started on acetazolamide at 15 mg/kg daily, which provided dramatic relief of the symptoms without any recurrence for more than 10 months.

Discussion

EA is a genetically heterogeneous disorder. There are at least 7 different types of EA, and 2 are common: EA1 and EA2.[3] Whereas EA2 is caused by mutation in the calcium voltage-gated channel subunit α1 A (*CACNA1A*) gene on chromosome 19p13, EA1 is a K-channelopathy caused by heterozygous mutation in the potassium channel gene *KCNA1* on chromosome 12p13.[3] EA1 may have a broad spectrum of symptoms like ataxia and myokymia. During attacks, additional symptoms may be reported, including vertigo, blurred vision, diplopia, nausea, headache, diaphoresis, body stiffening, and difficulty breathing.[4]

Since the first description of EA1, the phenotypic spectrum of the disease has widened considerably. Some affected individuals may also display delayed motor development, choreoathetosis, carpal spasm, cognitive dysfunctions, expressive language delay, and inability to learn a motor task. A short-sleep phenotype and cataplexy have also recently been reported.[4]

PNKD is an autosomal-dominant disorder of early childhood with a frequency of attacks that varies from 3 per day to 2 per year. The attack may start with focal or generalized, dystonic or choreoathetotic movements, usually triggered by fatigue, alcohol, caffeine, and emotional excitement, and may last for minutes to hours. During the attack, the patient remains conscious and continues to breathe normally. The acute attack is typically relieved by sleep. Clonazepam is the treatment of choice, and almost 80% of patients show an excellent response.[5] In our patient, the infrequent episodes of hour-long stiffening of legs, provoked by stress and fatigue and relieved after sleep, pointed to the initial possibility of PNKD. Muscle stiffness, in a more episodic manner, has been well described in K-channelopathies as defective function of the K-channel in the muscle membrane that may delay the repolarization phase of action potential formation. The muscle membrane, thus, may remain depolarized for a longer duration, producing muscle stiffness. Muscle stiffness lasting for minutes to hours can be a close mimicker of dystonia, and even more so in the episodic dystonia observed in patents with PNKD.

In our patient, the clinical manifestations, characterized by severe pain, muscle cramps, and leg stiffness preceded or followed by headache and vomiting, pointed to the possibility of a channelopathy, which later was confirmed by whole-exome sequencing.[6] The R86Q variant in the *KCNA1* gene has not been reported previously as a pathogenic or benign variant. Because incomplete penetrance has been reported for *KCNA1* gene mutations in EA, the presence of an R86Q variant in an asymptomatic mother is quite plausible. R86Q appears to be extremely rare in the population and, to our knowledge, has not been reported previously in any existing database. Although not all rare variants are pathogenic, the very low frequency of this variant in the population supports the hypothesis that the R86Q variant is pathogenic. R86Q is a semiconservative substitution that may affect secondary protein structure. The R86Q amino acid is evolutionally conserved throughout vertebrates. In silico analyses have predicted that it is probably damaging. This change is not observed in known healthy cohorts from the National Heart, Lung, and Blood Institute Exome Sequencing Project and the Database of Single Nucleotide Polymorphisms. These findings suggest a pathogenic role for the mutation. To our knowledge, this is the first description of a *KCNA1* gene mutation without ataxia or myokymia but with prolonged stiffness of the legs.[3] We propose expanding the phenotypic expression of *KCNA1* gene mutations to include a prolonged period of stiffness in the limbs, mimicking PNKD.

Conclusion

PNKD-like symptoms consisting of prolonged episodes of leg stiffness without ataxia or myokymia can be a manifestation of EA type 1. Severe pain in the limbs affected by episodic dystonic posturing that persists during sleep points to channelopathy as the etiology.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

K.K.S.: 1A, 3A, 3B

A.F.L.: 1A, 1B, 1C, 3A, 3B

D.G.: 1C, 3A, 3B

A.H.M.H.: 3B

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Supporting Information

Videos accompanying this article are available in the supporting information here.

Video S1. A video obtained during a typical spell shows involuntary muscle contraction of muscles in the lower limbs, leading to stiff posturing without any associated chorea, athetosis, or tremor. Of note, the child was distressed due to pain and was unable to use both lower limbs during the spell.

Video S2. A second video shows persistent, painful, stiff posturing of the lower limbs with lack of movement.

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