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"Video is part of ms."

Episodic Ataxia type 1 (K-channelopathy) manifesting as paroxysmal non-kinesogenic dyskinesia: expanding the phenotype

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Introduction

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 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). *KCNA1* gene mutations

have been found to 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 KCNA1 gene mutation presenting with episodes of prolonged stiffness of both lower limbs, mimicking paroxysmal non-kinesogenic dyskinesia.

Patient and Method

The study was approved by the Institutional Review board of Wayne State University. A written informed consent from the legal guardian has been obtained for all aspects of the study including video. A 5-year old boy presented with intermittent stiffness of the legs bilaterally associated with pain. The first episode occurred at three years of age in the evening while he was sitting on the couch. The episode started with vomiting followed by painful bilateral lower extremities' stiffening 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; slept with continuing leg stiffness. On waking up in the morning, symptoms resolved. He had multiple such episodes of 2-12 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 1, Video 2). 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 examination in between spells.

Blood count, electrolytes, creatine kinase and thyroid profile were normal. Serum amino acid, acylcarnitine profile, lactate and pyruvate and urine organic acid 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. Extensive nerve conduction study was normal; 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 paroxysmal non-kinesogenic dyskinesia, an empiric trial of Clonazepam was tried without improvement of symptoms. After proper genetic counseling, whole exome sequencing (WES) was undertaken through GeneDx's whole exome analysis using genomic DNA isolated from whole blood of the patient and both parents. The Agilent Clinical Research Exome kit was used to target the exonic regions and flanking splice junctions of the genome. These targeted regions were sequenced simultaneously by massive parallel (NextGen) sequencing on an Illumina Hiseq sequencing system with 100 bp paired -end reads. Bi-directional sequence was assembled, aligned to reference gene sequences based on human genomebuild GRCh37/UCSC hg 19, and analyzed for sequence variants using a custom -developed analysis tool (Xome Analyzer). Capillary sequencing method was used to confirm all potentially pathogenic variants identified in this patient and relative samples. This showed the presence of heterozygous R86Q variant, coding variant c.257 G>A in the KCNA1 gene, implicated in EA1. In addition, he was heterozygous for the de novo N404 K variant of uncertain significance in the PER2 gene, a gene involved in circadian rhythm. Both parents have been tested and mother is heterozygous for R86Q variant in the KCNA1 gene, but has no symptoms. With the diagnosis of K-channelopathy, the patient was started on acetazolamide at 15 mg/kg/day which provided dramatic relief of the symptoms without any recurrence for more than ten months.

Discussion

Episodic ataxia is a genetically heterogeneous disorder. There are at least seven different types of EA, however two common ones are EA1 and EA2(3). Whereas EA2 is caused by mutation in the calcium channel-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 in 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 been recently reported (4).

Paroxysmal non-kinesogenic dyskinesia (PNKD) is an autosomal dominant disorder of early childhood with the frequency of attacks varying from three per day to two 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, relief after sleep, pointed to the initial possibility of PNKD. Muscle stiffness, more so in an episodic manner has been well described in K-channelopathies as defective function of the K-channel in the muscle membrane may delay the repolarization phase of the action potential formation. The muscles 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, more so the episodic dystonia as seen in patents with paroxysmal nonkinesogenic dyskinesia (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, later confirmed by WES(6) **.** The R86Q variant in the KCNA1 gene has not been reported previously as a pathogenic or benign variant. As incomplete penetrance has been reported for KCNA1 gene mutations in episodic ataxia, presence of R86Q in asymptomatic mother is quite plausible. R86Q appears to be extremely rare in the population and it has not yet been reported 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 R86Q variant is pathogenic. R86Q is a semi-

conservative substitution which may affect secondary protein structure. The R86Q amino acid is evolutionally conserved throughout vertebrates. It is predicted to be probably damaging by in silico analyses. This change is not observed in known healthy cohorts in NHLBI Exome Sequencing Project, and Database of Single Nucleotide Polymorphisms. All these suggest a pathogenic role for the mutation. To our knowledge, this is the first description of KCNA1 gene mutation without ataxia or myokymia but with prolonged stiffness of legs(3). We propose expansion of phenotypic expression of KCNA1 gene mutation to include 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, persistence during sleep, are pointers to the channelopathy as the etiology.

Video 1. The video obtained during a typical spell shows involuntary muscle contraction of the muscles in 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 2. Second video showing persistent painful stiff posturing of lower limbs with lack of movement.

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Ethical Compliance Statement

Drs. Set, Ghosh, Huq and Luat confirm that the approval of an institutional review board was not required for this work.We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Author Contributions

KS conceived the study, contributed to manuscript preparation and revision. AFL conceived the study,contributed in patient care, manuscript preparation, critical manuscript revisions. DG contributed to the planning of patient care, critical manuscript revisions and writing. AHM contributed to critical manuscript revisions.

Disclosures

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