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Case Reports and Series

KCNQ2-related peripheral nerve hyperexcitability without epilepsy: a rare presentation.

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Abstract

Variants in potassium voltage-gated channel subfamily Q type 2 (KCNQ2) gene are associated with various types of epilepsy, along with peripheral nerve hyperexcitability (PNH). We report on a 12-year-old boy with a *de novo* in frame deletion in *KCNQ2*, presenting with muscle cramps without a history of prior epilepsy. This *KCNQ2* variant has already been described in a patient with epilepsy but never associated with PNH. Our case highlights the fact that potassium channelopathies must be considered in the differential diagnostic considerations of peripheral nerve hyperexcitability, even in the absence of seizures.

Data search
We performed a Pubmed search using the MeSH terms KCNQ2, myokymia, peripheral nerve hyperexcitability and channelopathy. From these data, we selected relevant papers on title and abstract in the period between 1997 and 2017. After selecting the abstracts, we reviewed the

genotypes and phenotypes of the patients. We also used the references of clinically relevant papers for the identification of additional manuscripts.

Background

Peripheral nerve hyperexcitability (PNH) is a clinically and etiologically heterogeneous disorder with a range of motor presentations. Frequent terms to describe PNH are myokymia, neuromyotonia or cramp-fasciculation syndrome.[1] The clinical presentation is broad and includes not only motor phenomena, such as cramps, twitching, spasms, stiffness, or weakness, but also sensory manifestations, such as paraesthesia, numbness, or dysesthesia. PNH can be divided into two neurophysiological groups: one group with characteristic doublet or multiplet (myokymic) motor unit discharges on electromyogram (EMG); the second with atypical findings.[1] Etiologic classifications distinguish between immune and non-immune types of PNH. The latter group includes genetic, toxic and degenerated causes of PNH.[1] A strong association exists between PNH and voltage-gated potassium channels.[1-3] In the majority of the auto-immune types of PNH, antibodies target these channels. Moreover, genetic types of PNH can be caused by pathogenic variants in genes encoding potassium channel subunits. Besides PNH, patients harbouring pathogenic variants in these genes often present with other neurological features, mostly epilepsy and episodic ataxia.[3] Isolated PNH in the absence of other neurological features was only reported in two cases harbouring a *KCNQ2* missense variant.[2,3]

We report the third case of a *de novo KCNQ2* pathogenic variant, presenting with isolated PNH in the absence of seizures.

Case presentation

A 12-year-old boy presented with the intermittent inability to extend the fingers of both hands, for over a year. These cramping sensations occurred daily or even multiple times a day, and lasted for about ten minutes each time. They were more pronounced in the morning, in cold weather, and after intense use of the hands, i.e. during writing. He did not experience any pain, numbness or swelling. During cold weather, redness of the skin of the

hands and fingers was observed. Muscle strength was normal, however fine motoric tasks were difficult to perform during such an episode. Sometimes he experienced muscle cramps in the legs, leading to impaired movement, inability to exercise and coordination difficulties.

His medical history was uneventful. There was especially no history of neonatal seizures or psychomotor retardation. Family history was negative regarding neurological/myogenic or cardiovascular conditions. The parents were non-consanguineous and of Moroccan descent. His twin sister did not experience any symptoms.

The initial neurological examination showed rigidity of the fingers after repetitive closure of the hands, in the absence of fasciculations, myokymia or myotonia. There was a slight, symmetric hypertonia of the legs without hyperreflexia. Plantar reflexes were normal. Peripheral neuropathy, muscular dystrophy and metabolic myopathy were considered as a differential diagnosis. Because of the episodic character and reported coordination problems, episodic ataxia 1 and epilepsy were also considered. Creatine kinase was measured repeatedly, both random as well as during the reported attacks, and was mildly elevated. Blood cholesterol, liver enzymes and lactate were all normal, as well as metabolic screening, including organic acids, amino acids, sialotransferrin isoelectric focusing and very long chain fatty acids. Targeted *KCN1A* sequencing was normal, excluding episodic ataxia 1. In addition, a single nucleotide polymorphism (SNP)-array – to exclude chromosomal copy number variants – did not show any abnormalities. A brain MRI – to exclude central pathology related to the coordination problems and hypertonia of the legs – was normal. Electroencephalography during sleep showed no epileptic activity during the reported events. Electromyography (EMG) showed normal sensory conduction (n. plantaris medialis, n. medianus and n. suralis) and motor conduction (n. fibularis profundus). Needle examination showed a polyphasic interferential contraction pattern with regular, spontaneous (myokymic) multiplets at relative rest, and no myotonic discharges. Re-evaluation of the neurological examination showed a delayed relaxation of the fingers in both hands after shaking hands.

Differential diagnosis was redirected towards muscle channelopathies. In the absence of neuromyotonic discharges on EMG, Isaacs and Morvan syndrome were considered less likely. Nevertheless, a chest X-ray – performed to evaluate possible mediastinal and lung masses – was normal. Analysis of VGKC-complex antibodies was not performed. A panel of 150 genes involved in epilepsy, including several channelopathy genes and proline-rich transmembrane protein 2 *PRRT2*, was analysed and showed the presence of a heterozygous deletion in the *KCNQ2* gene (c.346_348del), resulting in a deletion of the amino acid lysine at position 116 (p.Lys116del). The deletion was not found in the parents, which suggested a *de novo* occurrence in our patient.

After a one-year follow-up, the clinical situation was stable. Only a moderate effect was seen after physiotherapy, focused on reducing stiffness by using stretching exercises. The frequency of the attacks remained unchanged. Valproic acid did not have any effect on his clinical symptoms. Subsequent treatment with lamotrigine and carbamazepine also had no effect on the symptoms. A treatment with mexiletine initially gave a slight improvement, but only for a short time. Currently, gabapentin is being tried.

Discussion and conclusions

KCNQ2 variants are mainly associated with various forms of epilepsy, the most important are early infantile epileptic encephalopathy 7 (OMIM 613720) and benign familial neonatal seizures-1 (OMIM 121200). To our best knowledge, we report the third case of a *de novo KCNQ2* variant in a patient with PNH without prior history of seizures or other neurological symptoms. The case reported by Wuttke *et al*., with a variant involving R207Q, showed a great clinical similarity with our case, with also a clinical presentation of isolated PNH.[2] Another missense *KCNQ2* variant (R207W) was associated with PNH in a German family. Four of them had benign familial neonatal convulsions and one suffered from PNH. Functional studies of both variants showed strong dominant negative effects on WT $K_V7.2$

channels.[3] The p.Lys116del variant in our case was previously described in patients with benign childhood epilepsy with centrotemporal spikes.[4] Functional analysis in *Xenopus laevis* oocytes showed a pronounced deleterious effect of this deletion on channel function.[4]

KCNQ2 is located at chromosome 20q13.33 and encodes K_V7.2, which is one of the principal subunits of the M-channel. It can form either homomeric M-channels, composed of solely K_V7.2 subunits, or associate with other K_V7 subunits forming heteromeric M-channels.[5-7] This M-channel, named after its inhibitor – muscarinic acetylcholine – is crucial in controlling neuron excitability. The current within this channel has a time and voltage dependence that controls the membrane action potential when it is exposed to an excitatory stimulus. As such, it can suppress repetitive action potential discharges. The question remains why some patients with *KCNQ2* variants present with a phenotype only comprising PNH, without epileptic activity. In addition, intrafamilial phenotypic variability in families harbouring *KCNQ2* variants is described.[3,8] This suggests that differences in genetic background, genetic modifiers and/or environmental factors may be modulators of the phenotype.[2,8] Besides *KCNQ2* variants, PNH can also be associated with pathogenic variants in other potassium channel-encoding genes, such as *KCNA1*, and in genes encoding sodium channels, such as *SCN4A*.[3,9,10]

The cornerstone of treatment for PNH is the use of membrane-stabilising agents. The choice for a specific agent depends upon the disease severity, tolerance and experience of the clinician with particular drugs, and can be guided by reviews previously published.[11,12] In our patient, Retigabine – a specific K_V7 channel activator – was considered, but unfortunately it was withdrawn from the Belgian market due to reduced use and safety issues. Other substances targeting K_V7 channels can become therapeutic options in the future.

Our case demonstrates that in patients with myokymic discharges on EMG suggestive of PNH, muscle channelopathies must be considered in the differential diagnosis. Furthermore, *KCNQ2* variants must be considered in patients presenting with PNH, even

without any seizures. Future studies are needed to explain the phenotypic variability in *KCNQ2* pathogenic variants with predominant central pathology in *KCNQ2*-related epilepsy syndromes, versus PNH, with mainly peripheral nerve involvement.[3]

Competing interests

Nothing to declare.

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