

Neuromuscular tetanic hyperexcitability syndrome associated to a heterozygous *Kv1.1 N255D* mutation with normal serum magnesium levels

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Mutations of the main voltage-gated K channel members *Kv1.1* are linked to several clinical conditions, such as periodic ataxia type 1, myokymia and seizure disorders. Due to their role in active magnesium reabsorption through the renal distal convoluted tubule segment, mutations in the *KCNA1* gene encoding for *Kv1.1* has been associated with hypomagnesemia with myokymia and tetanic crises. Here we describe a case of a young female patient who came to our attention for a history of muscular spasms, tetanic episodes and muscle weakness, initially misdiagnosed for fibromyalgia. After a genetic screening she was found to be carrier of the c.736A > G (p.Asn255Asp) mutation in *KCNA1*, previously described in a family with autosomal dominant hypomagnesemia with muscular spasms, myokymia and tetanic episodes. However, our patient has always presented normal serum and urinary magnesium values, whereas she was affected by hypocalcemia. Calcium supplementation gave only partial clinical benefit, with an improvement on tetanic episodes yet without a clinical remission of her spasms, whereas magnesium supplementation worsened her muscular symptomatology.

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Conflict of interest

The Authors declare no conflict of interest

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Introduction

Voltage-gated K channels are a family of membrane proteins involved in determining the potential of the cellular membrane at rest, shaping action potentials and controlling neuronal excitability ¹. In these proteins, a central ion conduction channel is encircled by four subunits, each consisting of six transmembrane-spanning-helices (S1-S6) where segments S1-S4 form the voltage-sensing domain and segments S5-S6 form the pore domain ². Among voltage-gated K channels, the Shaker-related group *Kv1.1* is encoded by the *KCNA1* gene and is abundantly expressed in excitable and non-excitable cells. Its mutations may cause both a significant reduction in current amplitude and altered kinetic properties related to K⁺ balance ¹. So far, mutations in *Kv1.1* have been linked to several disorders such as periodic episodic ataxia type 1 (EA1), presumably caused by defective *Kv1.1* in the cerebellum ³, myokymia, caused by the alteration of Ca²⁺ homeostasis due to the dysfunction of juxtapanodal *Kv1.1* channels ⁴, and isolated neuromyotonia ⁵. The wide expression of *Kv1.1* in the nervous system explains the manifold clinical phenotypes of

its mutations⁶. The molecular genetic testing of *KCNA1* has further broadened the clinical spectrum of the disorders associated to mutations in the gene, *e.g.* delay in motor development, choreoathetosis, cognitive dysfunction, transient postural abnormalities in infancy, shortening of the Achilles tendon in children⁶, non-ataxic cataplexy⁷ and atypical episodic ataxia with migraine and hyperthermia⁸.

Finally, and interestingly, due to the *Kv1.1* localization in the renal distal convoluted tubule segments, mutations in *KCNA1* have also been related to hypomagnesemia leading to tetany and myokymia, as shown in a single family³. In kidney, the K⁺ secretion via *Kv1.1* provides an electrical gradient that drives Mg²⁺ reabsorption via the permeable transient receptor potential cation channel TRPM6. The amino acid substitution of a highly conserved asparagine for an aspartic acid in the third transmembrane segment of *Kv1.1* (p.Asn255Asp) results in a non-functional channel causing an autosomal dominant hypomagnesemia associated to muscle cramps, tetanic episodes, tremor, and muscle weakness³. The substitution of the asparagine with other hydrophobic, polar, or charged amino acids cause a nonfunctional channel, confirming *in vitro* the central role of asparagine in the right functioning of the channel¹. An additional *KCNA1* mutation resulting in a nonfunctional channel (p.Leu328Val) with hypomagnesemia has been reported in a young female patient affected by tetany who had an abnormal urinary Mg²⁺ excretion². This finding suggested a possible role of *KCNA1* mutations besides p.Asn255Asp in hypomagnesemia.

Notwithstanding the large variability of symptoms in EA1, the most common phenotype associated to *KCNA1* mutations, the penetrance of the hypomagnesemia phenotype has yet not been assessed, as it has rarely been reported in EA1⁵. Here we describe a case of muscular spasms and tetanic episodes in a female patient affected by *Kv1.1 N255D* mutation with normal serum magnesium levels.

Case report

A 31 years old female patient came to our attention in 2012 at the Neuromuscular Unit in Santa Chiara Hospital, Pisa- Italy, for a history of recurrent muscular spasms, tetanic episodes, diffuse and persistent muscle weakness and diarrhea. The muscular spasms were mainly localized at face and hands, lasted from several minutes to one hour, were often associated to tachycardia and worsened with carbohydrates ingestion and physical effort. These symptoms started in infancy with low frequency and low intensity but exacerbated after her first delivery and during breastfeeding, so that she required a medical consult.

The patient had no track record of neuromuscular diseases in her family, except for a history of occasional muscular spasms in her father and a juvenile cardiac disease with heart conductance alterations in her grandmother, not better investigated. After an initial misdiagnose of a rheumatological disorder (fibromyalgia), the patient was asked for a neurological evaluation and thus came to our attention. The neurological examination was normal, except for a mild and fluctuating weakness of iliopsoas muscles (MRC 4/5 bilaterally). She had no signs of myotonia or dyskinetic movement, neither she had ataxia. Objective clinical signs of cerebellar dysfunction, including nystagmus, multistep or overshoot saccades, dysmetria in the finger-nose test, and decomposition of movement of the legs on heel-to-shin test, were absent.

The patient underwent an electromyography (EMG) showing polyphasic motor unit potentials suggestive for myopathic changes; the EMG tetany test resulted positive in several occasions, as after 1'30" of physical effort, grouped motor unit discharges appeared and persisted for over 2 minutes. All biochemical values were normal, including blood count, renal function, hepatic function, thyroid function, estroprogestinic hormones, parathormone, glucose metabolism, autoimmune tests, GAD antibodies, and iron balance. The blood dosage of aldolases, creatine phosphokinase and the lactic dehydrogenase also resulted normal. Due to a reduced ammonium production in the ischaemic lactate-ammonia test, the patient underwent a DNA analysis for myoadenylate deaminase deficiency, resulting negative. Since the history of cardiac disease in her grandmother, DNA analyses for *LMNA* gene was also performed, resulting negative. Based on the muscular transient weakness, serum acetylcholine receptors antibodies (Ab) and muscle-specific tyrosine kinase Ab were tested, also resulting negative. Muscular spasms coupled with tetanic episodes suggested to dose blood electrolytes, discovering a mild hypocalcemia (ionized calcium 3.3 mg/dl with normal values of 4.4-4.9 mg/dl), while the magnesium dosage in the serum always resulted normal, although at lower limits.

The clinical picture therefore prompt us to perform genetic analysis for channelopathies. The NGS analysis showed a heterozygous mutation c.736A > G (p.Asn255Asp) in *KCNA1*, further confirmed with Sanger method, previously reported in association with autosomal dominant hypomagnesemia with sudden episodes of facial myokymia, tremor, muscle spasms with painful cramps, muscular weakness, and tetanic contraction episodes. A genetic test for mutations in exon 1 of *KCNA1* on both parents was conducted through PCR amplification and direct sequencing, but resulted negative. This at first instance suggests that the patient's *KCNA1* mutation appeared *de novo*². The patient completed the analysis

with urinary magnesium excretion that showed a normal magnesium excretion (81,5 mg/24h with normal values less than 120). Following literature reports, a magnesium integration was added to her treatment, but was later discontinued due to a subjective worsening of the muscular symptoms. The same adverse effects were reported for a potassium supplementation. Several myorelaxants (*e.g.* baclofen, benzodiazepines, cyclobenzaprine, and tizanidine) and neuromodulator drugs (*e.g.* trazodone, pregabalin, and amitriptyline) were tested, but only calcium integration had a slight clinical benefit on the tetanic episodes and on the muscular weakness, whilst muscular cramps and spasms persisted. Eventually, a cerebral MRI and a cardiological balance with electrocardiogram, echocardiogram and troponine dosage all resulted normal. The patient is currently monitored on a yearly basis and appears in a stable condition.

Discussion

Several genes are known to be involved in hereditary hypomagnesemia, including tight junction proteins claudin 16 and 19, the thiazide-sensitive sodium chloride cotransporter (NCC), the γ -subunit of the Na⁺/K⁺ ATPase (FXVD2), TRPM6, and the magnesiotropic hormone EGF¹⁰. The c.736A > G (p.Asn255Asp) mutation in *KCNA1* has been reported to cause an autosomal dominant hypomagnesemia with sudden episodes of facial myokymia, tremor, muscle spasms with painful cramps, muscular weakness, and tetanic contraction episodes³. This is to be put in relation with the localization of Kv1.1 in the apical membrane of distal convoluted tubule (DCT) cells, where TRPM6 controls Mg²⁺ entry driven by its electrochemical potential. Mutations in Kv1.1 protein, while having no direct effect on TRPM6, exhibit reduced K⁺ conductance, thus depolarizing the apical membrane of DCT cells reducing the electrical driving force, favoring Mg²⁺ entry and leading to renal Mg²⁺ loss⁹.

Puzzling, hypomagnesemia has rarely been reported in relation to *KCNA1* mutations. In the family described by Glaudemans et al.³, the severity of the phenotype varied among affected members, with some cases of severe tetanic crises (in one case leading to death in infancy) and other cases having a milder muscular involvement. Low serum Mg²⁺ levels were observed in variable amounts among family members, whereas urinary Mg²⁺ excretion levels were normal, suggesting an impaired tubular Mg²⁺ reabsorption. In the patients described, both serum K⁺ and Ca²⁺ levels and urinary Ca²⁺ excretion levels were normal, in contrast with other forms of inherited hypomagnesemia¹⁰. In these patients, magnesium integration led to partial clinical benefit, yet without a complete control on the muscular symptoms.

In the case here reported, the clinical phenotype concerning the muscular involvement was similar to that reported in previous literature. However, the patients' serum and urinary magnesium dosages resulted normal in repeated measures. Interestingly, low values of serum ionized calcium were consistently reported, and calcium supplementation was indeed the only treatment that resulted effective in treating the symptoms, while magnesium integration resulted ineffective and perhaps worsened the symptoms, in contrast to what described in Glaudemans et al.³. These findings are in accordance with a key role in DCT cells in ionic balance not only for Mg²⁺, but also for Na⁺, K⁺, and Ca²⁺. The presence of other channels co-expressed throughout the distal tubule, *e.g.* ROMK for K⁺ and ENaC for Na⁺, makes it so that Kv1.1 is not the only contributing to apical conductance, underlying the complexity of the ionic balance system *in vivo*⁹. Altogether, our findings suggest to further research efforts in the characterization of the role of *KCNA1* mutations hypomagnesemia and the related clinical treatment.

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