Novel *CACNA1S* mutation in hypokalaemic periodic paralysis

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SUMMARY

A 15-year-old girl was admitted to emergency department with an acute flaccid tetraparesis with no other symptoms. A history of recurrent similar episodes with spontaneous recovery was reported and no family history was known. Laboratory tests revealed severe hypokalaemia and hypokaluria. Symptoms resolution occurred after potassium replacement. The diagnosis of hypokalaemic periodic paralysis (HPP) was confirmed by genetic testing, which revealed a not previously described mutation in *CACNA1S* gene (c.3715C>G p.Arg1239Gly). HPP is a rare neuromuscular disorder that causes episodic attacks of flaccid paralysis with concomitant hypokalaemia. Primary forms of the disease are skeletal muscle ion channelopathies. HPP occurs due to a problem in potassium distribution rather than a total body potassium deficiency. Therefore potassium replacement should be carefully performed because of the risk of rebound hyperkalaemia. Knowing this rare entity is important in order to avoid diagnostic delays and so that proper treatment can be initiated to reduce morbidity and mortality.

BACKGROUND

Acute flaccid paralysis (AFP) is usually an expression of neurological entities, such as peripheral neuropathies or myelopathies.[1] Hypokalaemic periodic paralysis (HPP) is a rare cause of AFP with typical onset in the second decade of life.[2] Its low prevalence along with its initial clinical expression at a distinctive time of life, during adolescence, may lead to a misdiagnosis or late diagnosis. We report a case of HPP in an adolescent diagnosed 9 months after the clinical onset.

CASE PRESENTATION

A previously healthy and fully vaccinated 15-year-old girl was admitted to emergency department with a 12-hour history of acute-onset flaccid tetraparesis preceded by lumbar pain and lower limb paresthesias. Fever, gastrointestinal, respiratory or urinary complaints were denied. There was no history of trauma, acute illness or any medication use. She travelled from Venezuela, where she was born, 6 months before. The days before symptoms onset the patient ingested a high amount of carbohydrates in several meals of typical Venezuelan cuisine and practised intense exercise. Neurological examination revealed a symmetrical bilateral weakness on upper (4/5) and lower limbs (3/5), according to the Medical Research Council (MRC) Scale for Muscle Strength, and symmetrical hyporeflexia of lower limbs. Cranial nerve function and sensory examination were normal and there were no dysautonomic symptoms.

The patient reported a 9-month history of recurrent similar episodes, the majority were mild and only affecting lower limbs, with spontaneous complete resolution in 24–36 hours. On the first episode she was admitted at a local hospital where an extensive investigation was performed (complete blood count, hepatic transaminases, renal function, lumbar puncture, brain and neuroaxis-MRI) and she was discharged after 36 hours with complete spontaneous symptoms' recovery. She was always asymptomatic between episodes. No family history of similar episodes was known.

INVESTIGATIONS

Regarding to the current episode, initial investigation revealed severe hypokalaemia (K^+ 2.3 mmol/L), increased creatine phosphokinase (CPK 478 U/L) and hypokaluria (single-sample urinary K^+ 7.13 mEq/L). Complete blood count, renal and liver function, glucose, other electrolytes, acid-basis balance and thyroid hormone levels were unremarkable. An ECG showed a sinus rhythm, normal corrected QT interval (0.35 s) and flattened T-waves.

TREATMENT

Intravenous potassium chloride (KCl) replacement (5 mEq/hour) was initiated with an increase in potassium serum level (4.2 mmol/L) and clinical improvement in 2 hours. A new decrease in potassium level (2.9 mmol/L) occurred 4 hours later and was slowly corrected with oral potassium replacement (5 mEq/hour). The ECG remained normal despite the fluctuation on potassium levels.

She was discharged after full symptom recovery, receiving nutritional counselling and guidance on changing her lifestyle to avoid episodes' triggers.

The diagnosis of HPP was confirmed by genetic testing, which revealed a pathogenic heterozygous mutation in *CACNA1S* gene (c.3715C>G p.Arg1239Gly), not previously described. Parents and brother of the patient were studied and none had the same variant.

OUTCOME AND FOLLOW-UP

During the follow-up, some episodes were triggered by high-carbohydrate intake, physical exercise, emotional stress and menstruation, so she started potassium supplementation (30 mEq/day of a sustained released formulation) followed by acetazolamide association till 500 mg/day. Currently attacks are prevented by lifestyle changes,

nutritional and psychological counselling and the previously described therapy. Potassium levels and neurological examination have been normal between episodes.

DISCUSSION

HPP is a rare neuromuscular disorder that presents with sudden and reversible episodes of flaccid paralysis in association with low serum potassium level.[3–6] Its estimated prevalence is 1 in 100 000.[2 7–9] HPP may be primary (familial or sporadic) or secondary to thyrotoxicosis, the latter being exceptional at paediatric age.[2 9 10] Primary forms are skeletal muscle ion channelopathies due to point mutations in *CACNA1S* or *SCN4A* genes, with a typical onset in the second decade of life.[2 4–6] Around 70% of the primary cases are caused by *CACNA1S* mutations (HPP type 1) and 10%–20% by *SCN4A* (HPP type 2).[2 5 9 11] Familial HPP, which accounts for the majority of the cases, has an autosomal dominant mode of inheritance with incomplete penetrance.[2 4 9 12 13] Sporadic mutations are responsible for approximately one-third of cases.[2 12 13]

Patients suffer intermittent attacks of focal or generalised weakness, predominantly affecting lower limbs, along with hyporeflexia or areflexia, without sensitive impairment or central nervous system affection.[2 4 5 9 12 13] Therefore, preservation of reflexes in a paralysed limb, prominent sensory or autonomic symptoms should evoke a different diagnosis.[9] However, a vague prodrome (paresthesias, fatigue, pain) may precede the attack, as occurred in this case.[12] Breathing, deglutition and ocular motility may be affected in severe episodes. Cardiac and smooth muscle are spared; therefore, possible arrhythmias can only occur due to severe hypokalaemia.[5 13 14] The frequency of the episodes is highly variable among patients, although it tends to be higher from the second to the fourth decades of life, and then usually decreases.[5 9 12 13 15] Episodes are usually triggered by high-carbohydrate and sodium meals, prolonged fasting, alcohol consumption, prolonged rest after intense exercise, cold exposure, acute emotional stress, infections, menstruation, lack of sleep or specific medications (beta-agonists, insulin or corticosteroids).[2–5 9 13] However, spontaneous attacks may occur.[12] Typically, the episodes occur during the night or in the early morning and can last from several hours to days, with gradual spontaneous recovery.[5 6 9 12]

It's important to distinguish whether the hypokalaemia is due to a decrease in total blood potassium levels or secondary to an intracellular shift, as occurs in HPP.[10 16] *CACNA1S* and *SCN4A* genes encode skeletal muscle voltage-gated calcium and sodium channels, respectively.[6 10] The reason why the calcium channel defect can lead to episodes of weakness is not yet identified. In patients with sodium channel defect, the paralysis results from an anomalous intracellular shift of this ion with aberrant depolarisation of muscle fibre, which eliminates the muscular excitability when extracellular potassium concentration is reduced.[2 9 11 12] This explains the potassium normal levels between episodes and the risk of rebound hyperkalaemia when an aggressive potassium correction is performed.[13 16]

Hypokalaemic paralysis may be also secondary to renal or gastrointestinal potassium loss, in which case the whole body levels of potassium are depleted and aggressive replacement is required.[7 13 14 16 17] In these contexts, there are clinical or laboratory evidences of the underlying systemic disease, hypokalaemia is persistent between attacks and muscle weakness fluctuates with the potassium levels, which leads to a non-periodic paralysis.[2 13] Failure to distinguish HPP from non-HPP may lead to overly aggressive treatment of an apparent potassium deficit, with rebound hyperkalaemia on recovery.[18]

In a first episode of tetraparesis, other diagnoses such as Guillain-Barre syndrome (GBS), acute myelopathy, myasthenic crisis, metabolic myopathies and botulism should be considered. A history of symmetrical muscle weakness with distal to proximal progression along with hyporeflexia or areflexia, mild sensitive changes and dysautonomic symptoms suggest a GBS, especially if symptoms are preceded by an infection. In this condition the cerebrospinal fluid usually shows an albuminocytological dissociation and definitive diagnosis may be confirmed by electromyography (EMG). Acute flaccid paraparesis, areflexia and sensitive impairment as well as sphincters compromise evoke an acute myelopathy that can be confirmed by neuroaxis-MRI. Myasthenic crisis, which can be confirmed by autoimmunity blood tests, usually include palpebral ptosis although it can progress to a generalised form with hypotonia and walking difficulties. Moreover, the presence of muscle weakness, hepatomegaly, increased liver enzymes, LDH and CK and a pattern of myopathy in EMG suggest a metabolic myopathy. Botulism is a rare entity, usually occurring in the first year of life in patients that live in the countryside or report honey ingestion; muscle weakness primarily affects muscles innervated by cranial nerves and then progresses downward; deep tendon reflexes are usually normal and constipation, urinary retention and dysautonomic symptoms are frequent; *Botulinum* toxin and *Clostridium botulinum* may be isolated in stool samples. Although all these conditions may cause AFP, the finding of ictal hypokalaemia suggests HPP, avoiding further investigation.[2] HPP diagnostic approach requires serum potassium measurement during an acute episode. Hyperthyroidism must be excluded and a blood gas analysis, blood urea nitrogen, creatinine and other electrolytes should be determined.[2 19] Urine analysis is also necessary to exclude kidney potassium losses.[18] An ECG should be performed to exclude cardiac complications.[2 19] CPK may be increased during the attacks.[4] Electrophysiological examinations, such as nerve conduction studies or EMG, might be helpful to rule out GBS and similar demyelinating neuropathies if diagnostic doubts persist. In HPP, if an EMG is performed, myopathy will be absent. Long exercise test may also help to establish the diagnosis when the neurological examination and serum potassium level have normalised or when the reported weakness may be difficult to distinguish from the one caused by other neuromuscular diseases. This examination involves measuring muscle fibre excitability during a period of rest after a strenuous isometric exercise of that muscle. However, if genetic testing is available we should prefer it over this neurophysiological technique.[20] Thus, recurrent transient episodes of flaccid paralysis, in the absence of clinical or electromyographic myotonia or other neurological findings, along with hypokalaemia only during the symptomatic phase establish the diagnosis, which can be confirmed by genetic testing.[2 12 15] Nevertheless, after an attack or between attacks, the diagnosis can be challenging as the serum potassium level usually remains normal in primary HPP. A positive family history may also be present.[2] Genetic testing of the patients' family members is important even if they are asymptomatic because those with HPP have a higher risk of anaesthetic complications, such as malignant hyperthermia (especially in *CACNA1S* mutation) and severe paralysis.[4 12] After the genetic study of this family, the mutation was assumed to be de novo and classified as pathogenic. There are some distinguishing phenotypic features between HPP types 1 and 2. When compared with *SCN4A* mutations-related phenotype, *CACNA1S* gene mutation is associated to a higher frequency of symptoms in men, an earlier onset and longer duration of episodes, high-carbohydrate meals

as a major trigger, the risk of malignant hyperthermia and a good response to acetazolamide.[4 12]

HPP management includes attacks prevention and treatment.[5] Acute episodes are managed with a gradual potassium replacement and close monitoring of the cardiac rhythm and serum potassium levels.[7] If hypokalaemia is severe (<2.5 mmol/L) or there is oral intolerance, intravenous potassium chloride solution should be infused at a maximum of 10 mEq/hour.[5 16] Milder attacks can be controlled only with oral potassium chloride, also with a slow rate administration (10 mEq/hour) and some of them can be aborted by low-level exercise.[2 4 9 13 18 19]

Prevention includes non-pharmacological and pharmacological strategies in order to decrease the frequency of the episodes. This is the only way to reduce morbidity and mortality associated with hospitalisation and acute treatment. A progressive strategy should be used beginning with non-pharmacological interventions that include avoiding triggers, through lifestyle and diet modification.[9 12 19] Adopting a high-potassium and low-carbohydrate and salt diet, avoidance of vigorous exercise, alcohol consumption and emotional stress may be effective in preventing episodes.[5 9] Pharmacological therapy may be initiated when the first measures are not sufficiently effective and is usually started with oral potassium replacement (30–60 mEq/day). Carbonic anhydrase inhibitors (CAI), such as acetazolamide (125–1000 mg/day), can be associated to potassium supplements and they are usually the most effective treatment in reducing attacks.[2 4 5 9 12] Dichlorphenamide (50–200 mg/day), another CAI, can be used in alternative, but is not currently available in our country. Patients with HPP due to *SCN4A* mutations are usually less responsive to acetazolamide or may even experience worsening of symptoms.[5 9 12 13] Patients who fail to respond to CAI may benefit from a potassium-sparing diuretic.[2 17 19]

Some patients with HPP may develop permanent muscle weakness during the fourth or fifth decade of life, although this situation is not related to frequency or severity of episodic weakness.[3 9 12 13] The myopathy affects mostly the muscles of the pelvic girdle and the proximal muscles of upper and lower limbs.[2 13] None of the mentioned treatments prevent progressive myopathic changes and there is no known therapy to delay the onset myopathy in HPP.[2 21]

Learning points

- This is a classic case of a rare entity due to a novel mutation. This case, in which symptoms were present for several months and there was no family history, highlights the diagnostic challenge hypokalaemic periodic paralysis may represent.
- Acute flaccid paralysis in adolescents should raise the suspicion of other possible diagnosis apart from neurological syndromes.
- It is important to value the patient's symptoms, even when they are mild, in order to establish the diagnosis and guarantee an early initiation of preventive strategies to reduce morbidity and mortality.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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