Case Report

Hyperkalaemia in a tetraplegic adolescent due to de novo sodium channel mutation

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Introduction

Maintenance of potassium homeostasis is crucial for the survival of humans and other mammals. In general, potassium levels result from the relationship between potassium intake, urinary potassium excretion and the distribution of potassium between the intracellular and extracellular space. In healthy subjects, potassium excesses are primarily buffered by rapid cell uptake. In a second step, excessive serum potassium is then largely balanced via potassium excretion in the urine, mediated by the renal cortical collecting tubules. These cellular and urinary adaptations normally prevent significant potassium accumulation in the extracellular fluid.

Hyperkalaemia is defined as a condition in which serum potassium levels exceed concentrations of 5.0–5.5 mmol/l. Nephrologists usually have to deal with hyperkalaemia on a daily basis and the causes thereof are indeed numerous. However, they can be assigned to four major categories: (i) excessive K⁺-intake and tissue necrosis, (ii) reduced renal K⁺-excretion, (iii) redistribution of internal K⁺ via K⁺-shift and (iv) pseudohyperkalaemia. Hyperkalaemia primarily affects skeletal muscles and the heart, resulting in typical clinical symptoms such as weakness, paralysis and palpitations [1]. Depending on interindividual susceptibility and the extent of hyperkalaemia, classical ECG changes such as ‘peaked T waves’ or ‘broadened QRS’ can develop, and in extreme cases even culminate in sudden cardiac arrest and death [2]. Renal specialists are often consulted for help in managing hyperkalaemic patients, but in some cases, the ‘renal trace’ can be misleading in unravelling the true root cause of the problem.

Here we report on an extremely rare cause of hyperkalaemia in a young patient who presented to the emergency room with sudden onset of rapidly progressing muscle weakness. Interdisciplinary efforts were pivotal in determining the underlying disease, which turned out to originate from a de novo sodium channel mutation.

Case report

A 14-year-old male adolescent was rushed into the emergency room on a stretcher after he had broken down on a tennis court. The patient was conscious and three times orientated but unable to move his arms or legs. He reported with slurred speech that he had suddenly sensed a rapidly increasing weakness in his extremities shortly after the exercise. Pain or loss of sensibility were denied, so was the intake of any drugs prior to the incident.

Physical examination found an uncomfortable-appearing adolescent, without apparent respiratory distress. Vital signs were stable with a pulse of 86 beats/min, blood pressure of 129/92 mmHg and a breathing rate of 17 breaths/min. Cranial nerves were intact. Motor examination revealed a nearly complete flaccid paralysis of both the upper and lower limbs. Strength was 0–1/5 in all major muscle groups with a slight predominance of the upper limbs. Neck extensors and flexors as well as bulb muscles were spared. No fasciculations, myoedema, myotonia or other abnormalities were noted. A sensory examination was normal. Muscle stretch reflexes were bilaterally hyporeactive with no Babinski signs. Neuroimaging of the brain and spinal cord, as well as an ECG, showed no abnormalities. Serum potassium and creatinine kinase (CK) were considerably increased to 6.3 mmol/l and 1024 U/l, respectively. Blood count, serum creatinine and the rest of the metabolic panel were within normal range. Further serological and immunological testing including cardiac enzymes and thyroid studies were non-contributory. Urine sediment analysis and toxicology screening, as well as renal ultrasonography, were unrevealing.

In summary, we saw a tetraplegic adolescent with significantly elevated serum potassium of unclear origin and elevated serum CK following exertion. As hyperkalaemia is a potential cause for muscle weakness and
flaccid paralysis, we decided to commence $K^+$-lowering measures. However, the patient surprisingly showed spontaneous improvement of muscle strength before any $K^+$-lowering therapy was initiated. Moreover, serum $K^+$ had spontaneously fallen to 5.7 mmol/l. In the course of 2 h, the patient regained full strength, the speech cleared up and serum potassium normalized.

Focussing on his past medical history, the patient reported several precedent incidents of intermittent mild-to-moderate weakness subsequent to physical exercise. Interestingly, the patient’s parents had sporadically noticed ‘temporary states of fatigue’ in their son since pre-school age. Hereditary diseases or other chronic illnesses and disabilities were denied. Notably, neither the patient’s parents nor the older brother suffered from these or similar symptoms.

After consulting our neurologists, a preliminary diagnosis was established. In view of the subject’s history of recurrent paralytic symptoms and concomitantly elevated potassium levels as recorded on admission, it seemed likely that our patient suffered from hyperkalaemic periodic paralysis (HyperPP). However, since HyperPP is an autosomal dominantly inherited disease and our patient had no first-degree relatives affected by symptoms of HyperPP, we decided to perform provocative testing and genetic analysis to corroborate our assumption.

Under clinical surveillance, we let the patient exercise on a bicycle ergometer for 30 min to increase heart rate to 120–160 beats/min, followed by a phase of absolute rest. Blood samples were taken every 20 min to monitor serum potassium levels (Figure 1). Shortly after the exercise the patient demonstrated an incremental physical weakness mainly affecting the legs. At 45 min after exercise, the weakness reached a maximum of ~60% strength reduction before starting to ameliorate spontaneously, and at 2 h after exercise complete recovery was evident. Notably, cardiorespiratory functions were stable at all times during and after the test. Moreover, an oral potassium challenge could trigger a similar attack. Molecular genetic testing for the seven currently known, HyperPP-causing $SCN4A$ gene mutations is available on a clinical basis and detects a mutation in ~55% of individuals affected by HyperPP as defined by clinical diagnostic criteria [3]. Since three mutations, namely I693T, T704M and M1592V, account for the vast majority of mutations detected, we decided in a first step to amplify and sequence only exon 13 and 24. The sequence analysis revealed a heterozygous C to T transition at coding sequence 2188 in exon 13 predicting a substitution of methionine for threonine at amino acid 704 (T704M). It is noteworthy that neither the patient’s parents, whose biological parenthood had been verified, nor his sibling showed this mutation (Figure 2). In a second step, we then analysed the remaining 22 exons including the intron/exon boundaries of the $SCN4A$ gene and were able to exclude other potential mutations respectively. Despite the fact that most patients with HyperPP have an affected parent from whom they inherited the disorder, we concluded that in this particular case, the disease had been caused by a de novo mutation of the $SCN4A$ gene.

Before the patient was discharged, we started a combination therapy with low-dose acetazolamide (2 × 125 mg/day) and salbutamol inhalation if required. Moreover, patient and parents were briefed on expedient modifications of behaviour to avoid or ameliorate future attacks. All laboratory findings on discharge were normal, only serum CK remained moderately elevated at 647 U/l. On a follow-up exam 1 year later, the patient reported that frequency of attacks had noticeably decreased from 3 to 5 to about once a month. Physical examination and laboratory testing were unremarkable, except for a persistently elevated serum CK (530 U/l).

Discussion

Hyperkalaemia describes a condition in which a patient’s serum potassium level is elevated. The extent of hyperkalaemia and individual susceptibility dictate neuromuscular symptoms, which can manifest as pronounced muscle weakness or even complete flaccid paralysis. When encountering a hyperkalaemic subject with freshly developed non-traumatic paralysis, it seems reasonable to consider hyperkalaemia aetiological to the muscular problem. However, in rare cases hyperkalaemia is not the paralysing cause, but rather a feature of another underlying pathological entity, comprising muscle weakness and paralysis as cardinal symptoms. As illustrated here,
HyperPP should be taken into consideration as a possible candidate disease, especially when dealing with young and otherwise healthy patients.

HyperPP is a rare inherited channelopathy which manifests as abnormal muscle membrane excitability leading to episodic flaccid paralysis. It belongs to a group of inherited sodium channel disorders of the muscle with an estimated prevalence of ~1 : 200 000 [4] and is caused by point mutations in the SCN4A gene (chromosomal locus 17q23-q25) encoding the voltage-gated skeletal muscle sodium channel [5,6]. To date, seven mutations have been reported, all characterized by an autosomal dominant mode of inheritance [5]. Functionally, the aberrant Na+-channels fail to inactivate upon muscle cell depolarization. Operationally, this defect in mutant channel gating generates a gain-of-function, and the increased Na+-current will excessively depolarize affected muscle and inactivate normal sodium channels, thus leading to inexcitability of muscle fibres, which dictates weakness and even paralytic phases [7]. It is assumed that the prolonged Na+-influx entails an increased compensational K+-efflux, which results in temporarily elevated serum potassium levels. Hyperkalaemia in HyperPP can therefore best be categorized as a redistributitional disorder of internal K+ via K+-shift. Clinical diagnosis of HyperPP and distinction from other periodic weakness disorders as hypokalaemic periodic paralysis or paramyotonia congenita [8] can be obtained by taking a number of criteria into consideration. It requires a history of transient episodes of weakness, determination of ictal serum potassium levels and exclusion of other hereditary or acquired forms of hyperkalaemia [3]. In HyperPP, ictal K+ levels are often increased to >5.0 mmol/l but can remain within the normal range in up to 50% of cases [9]. Therefore, the term ‘K+-sensitive’ periodic paralysis is suggested to be more appropriate, since weakness is typically provoked by K+ administration. The diagnosis is strongly supported by persistently elevated serum CK concentrations. In case of diagnostic uncertainty, provocative testing (exercise or K+-intake) under clinical surveillance should be employed. A muscle biopsy is generally not recommended because it detects weakness and even paralytic phases [7]. It is assumed that the prolonged Na+-influx entails an increased compensational K+-efflux, which results in temporarily elevated serum potassium levels. Hyperkalaemia in HyperPP can therefore best be categorized as a redistributitional disorder of internal K+ via K+-shift. Clinical diagnosis of HyperPP and distinction from other periodic weakness disorders as hypokalaemic periodic paralysis or paramyotonia congenita [8] can be obtained by taking a number of criteria into consideration. It requires a history of transient episodes of weakness, determination of ictal serum potassium levels and exclusion of other hereditary or acquired forms of hyperkalaemia [3]. In HyperPP, ictal K+ levels are often increased to >5.0 mmol/l but can remain within the normal range in up to 50% of cases [9]. Therefore, the term ‘K+-sensitive’ periodic paralysis is suggested to be more appropriate, since weakness is typically provoked by K+ administration. The diagnosis is strongly supported by persistently elevated serum CK concentrations. In case of diagnostic uncertainty, provocative testing (exercise or K+-intake) under clinical surveillance should be employed. A muscle biopsy is generally not recommended because it provides no specific findings and has no influence on therapeutic strategies or prognosis. However, in order to reliably confirm HyperPP, additional direct DNA testing of the SCN4A gene is necessary. Molecular genetic testing is available on a clinical basis for the seven currently known mutations and detects a mutation in more than half of individuals with suspected HyperPP. Considering the huge variability of mutation detection rates, it may be prudent to first focus on exon segments with the most common SCN4A mutations instead of sequencing the whole gene in the first place.

Most HyperPP patients have inherited the disease from an affected parent, but sporadic cases from de novo mutations have been documented [3,7], suggesting mutational hot spots in the SCN4A gene. HyperPP has high penetrance and symptoms usually manifest at a very early age. In our patient, however, the first massive paralytic attack emerged at the rather late age of 14. To our knowledge, this is the first reported case of an emergently hospitalized, hyperkalaemic and tetraplegic adolescent with first diagnosed HyperPP due to a de novo mutation in the SCN4A gene.

Management of HyperPP is symptomatic and behavioural, not curative. Affected individuals should learn to avoid precipitating triggers through lifestyle and dietary modifications, especially by avoiding potassium-rich food, drugs that increase serum K+ (e.g. amiloride, spironolactone) and fasting [7]. For acute treatment of paralytic attacks, patients should continue with mild activity or ingest sweets in order to prevent or shorten attacks. Use of β-agonist inhalers (e.g. salbutamol, albuterol) has been shown to attenuate hyperkalaemic attacks [10]. Calcium gluconate given intravenously may terminate attacks in some patients. Interestingly, the regular use of carbonic anhydrase inhibitors (acetazolamide, dichlorphenamide) was reported to reduce attack frequency, although the mechanism of action is still unclear [11,12].

Overall, HyperPP has a good prognosis and some treatment is indeed available. Moreover, HyperPP does not affect intellect. However, the attacks produce disability and many affected individuals develop persistent, interattack weakness. Genetic counselling is therefore strongly recommended once the diagnosis has been firmly established.

In summary, we presented a case of a young patient with substantial hyperkalaemia, sudden onset of paralysis and no family history of congenital diseases. Although HyperPP was suspected by means of clinical features and provocative testing, it was sequential genetic analysis that corroborated the diagnosis and identified a de novo mutation in the SCN4A gene.

Conflict of interest statement. None declared.


References


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