CASE REPORT

Persisting fatigue and myalgia as the presenting features in a case of hypokalaemic periodic paralysis

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SUMMARY

We report a case of a 9-year-old boy who developed hypokalaemic periodic paralysis (HypoPP) following a prodrome of persistent fatigue and muscle aches associated with mildly elevated creatine kinase (CK) levels.

HypoPP is usually associated with a sudden onset of weakness and hypokalaemia at presentation. A review of published cases failed to identify any other reports of individuals with a similar onset of symptoms and elevated CK levels prior to the development of frank HypoPP.

In the case described above, the association of these symptoms with elevated levels of CK may have been related to the underlying mutation in the skeletal muscle calcium channels that was subsequently identified.

In cases of persisting fatigue and myalgia associated with elevated CK levels it may be helpful to consider HypoPP in the differential diagnosis.

BACKGROUND

We report a case of a 9-year-old boy who developed hypokalaemic periodic paralysis (HypoPP) following a prodrome of persisting fatigue and muscle aches associated with mildly elevated creatine kinase (CK) levels.

HypoPP is usually associated with a sudden onset of weakness and hypokalaemia at presentation.^{1 2} In some patients, features of later disease have been described including myopathy, progressive muscle weakness and vacuolar myopathy on muscle biopsy.¹⁻³

A review of published cases failed to identify any other reports of individuals with a similar onset of symptoms that was associated with elevated CK levels prior to the development of frank HypoPP.

CASE PRESENTATION

A 9-year-old boy with no significant prior medical history presented to a paediatric outpatient department in March 2013 with a 4-month history of persistent fatigue, loss of appetite and generalised aches and pains following an episode of self-limiting 'flu-like' illness.

The fatigue was reported to increase following episodes of physical exertion but no other precipitating features were noted. The fatigue was significant enough to interrupt the child's usual activities and his school attendance was adversely affected. The pains were reported to affect the 'muscles and

bones' in his limbs and back and were most painful in the morning.

The family history was normal with no other family members affected by symptoms of fatigue, myalgia or weakness.

The examination at presentation was normal, with normal peripheral power, tone and reflexes.

Investigations at the time of presentation demonstrated normal renal function, thyroid function, inflammatory markers, haematological parameters and iron studies. Serum potassium at this stage was 3.8 mmol/L. He was managed for symptoms of persistent fatigue with referral for further assessment and investigation in the local chronic fatigue syndrome clinic.

As part of the assessment of persistent fatigue further investigations including CK were arranged. The CK level was mildly elevated at this stage (305 iU/L; upper reference limit of normal in local laboratory 175 iU/L for a 9-year-old child) but the other biochemical parameters were normal.

In August 2014 he presented with a sudden onset of weakness and was unable to move—he described feeling as though he was 'glued to the bed.' The examining clinicians described weakness in the legs (details of the peripheral tone, power and reflexes were not described using objective scoring methods at this time). Investigations at this stage demonstrated potassium of 2.0 mmol/L and CK 495 iU/L. After management with oral potassium supplements his symptoms resolved and his potassium level normalised. A diagnosis of possible HypoPP was made.

In November 2014 he presented with a second episode of limb weakness associated with reduced tone and reflexes (power 2/5 in legs, 4/5 arms). At this time serum potassium was 2.3 mmol/L. Again, the child's symptoms improved with oral potassium supplementation. The fluctuations in serum potassium and CK values over time are outlined in [table 1](#).

INVESTIGATIONS

Investigations were arranged to exclude secondary causes of hypokalaemia. These demonstrated normal thyroid function, normal calcium and magnesium levels, a normal aldosterone/renin ratio, normal urinary electrolytes and normal 17-hydroxyprogesterone levels.

Genetic testing was subsequently arranged and this highlighted a heterozygous pathogenic mutation affecting the calcium voltage-gated channel subunit alpha 1s (CACNA1S) gene. The CACNA1S

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Table 1 Changes in serum potassium and creatine kinase values over time

Date	Serum potassium (mmol/L)	Creatine kinase (iU/L)	Episodes of paralysis
6 March 2013	3.9	NA	
26 September 2013	4.0	NA	
23 December 2013	NA	306	
9 June 2014	3.7	305	
13 August 2014	2.0	495	Paralysis
17 August 2014	4.2	NA	
11 November 2014	2.3	NA	Paralysis
12 November 2014	3.8	NA	
30 November 2014	3.6	NA	
24 March 2015	3.5	308	
7 January 2016	3.8	204	
29 August 2016	2.3	195	Paralysis
30 August 2016	4.0	NA	
7 September 2016	2.6	NA	Paralysis
13 September 2016	3.1	265	
30 September 2016	3.4	260	
4 October 2016	3.5	242	
25 September 2016	3.9	292	
28 October 2016	3.9	321	

NA, not applicable.

gene is located on the long (q) arm of chromosome 1 at position 32.1. Mutations in the gene may result in alterations in the structure of the CACNA1S protein which forms part of the calcium channel in skeletal muscle. Affected calcium channels open more slowly which adversely affects muscle function. CACNA1S mutations are well described in cases of HypoPP.^{4 5}

The mutation affecting the CACNA1S protein is most commonly inherited in an autosomal dominant fashion; however, around one-third of cases are thought to result from de novo mutations. In this case, the asymptomatic family members have not been tested and the altered gene is presumed to represent a de novo mutation.

TREATMENT

Management is ongoing and includes treatment with oral potassium supplementation and acetazolamide. The affected child

has had two further admissions with episodes of paralysis (see figure 1). His symptoms of myalgia and fatigue are ongoing and largely unchanged from presentation. In between episodes of weakness the child continues to have normal peripheral power, tone and reflexes.

DISCUSSION

HypoPP is a rare condition characterised by periods of episodic weakness accompanied by low serum potassium levels. The condition is most commonly associated with genetic mutations affecting the calcium channel gene on chromosome 1.^{6–9}

Criteria for the diagnosis of HypoPP have previously been proposed and are summarised in a Cochrane review of the treatment of HypoPP.¹⁰ Important diagnostic features may include:

- ▶ recurrent episodes of muscle weakness associated with hypokalaemia;
- ▶ an episode of muscle weakness in a proband with a relative known to have episodic weakness associated with hypokalaemia;
- ▶ onset in the first or second decade;
- ▶ a genetic mutation associated with HypoPP;
- ▶ symptoms following known triggers for episodes of muscle weakness including high carbohydrate meals, stress, rest after periods of exertion;
- ▶ improvement of symptoms with oral potassium supplementation.

Other causes of hypokalaemia including renal, adrenal or thyroid disorders, renal tubular acidosis and diuretic and laxative use should also be excluded.¹⁰

The case of HypoPP we describe is unusual due to the preceding features of myalgia and persistent fatigue associated with mildly elevated CK levels. A literature review (see online supplementary appendix S1 for details) identified two previously reported cases of HypoPP where the presentation with weakness was preceded either by an isolated finding of a raised CK or by muscle pain.^{11 12} Although cases of HypoPP associated with elevated levels of CK have been described,¹³ no previous case reports identified an initial presentation with persisting fatigue, myalgia and elevated CK levels.

Persisting fatigue and myalgia are commonly encountered symptoms and may contribute to the diagnosis of chronic fatigue syndrome.^{14 15} In the case described above, we suggest that the association of these symptoms with elevated levels of CK may

Figure 1 Serum potassium and Creatine Kinase levels over time.

have been related to the underlying mutation in the skeletal muscle calcium channels that was subsequently identified in this patient.

In cases of chronic fatigue and myalgia, it may be helpful to consider HypoPP in the differential diagnosis even if these symptoms precede any episodes of weakness. Elevated CK levels may suggest an underlying myopathy and have also been described in association with HypoPP. Enquiry about family history and triggers for the exacerbation of symptoms (ie, factors associated with falling serum potassium levels such as the consumption of carbohydrate-rich meals, strenuous exercise or eating food with a high sodium content) may be helpful features of the history in similar cases.

In cases where there is a clinical suspicion of HypoPP genetic investigations are available and may confirm the diagnosis.

Learning points

- ▶ Hypokalaemic periodic paralysis (HypoPP) may not always present with sudden onset of weakness.
- ▶ Common symptoms such as myalgia and fatigue may be associated with underlying skeletal muscle calcium channel mutations known to cause HypoPP.
- ▶ Genetic investigations can confirm a diagnosis of suspected HypoPP in cases where this forms part of the differential diagnosis.
- ▶ Creatine kinase should be checked in any patient with suspected HypoPP.

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