Hypokalemic periodic paralysis: an underestimated autosomal-dominant disease with variable phenotypic presentations

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Abstract

Periodic paralysis (PP) diseases are autosomal dominant disorders due to gene-mutations that manifests with episodic muscle weakness and/or paralysis. Their mutations result in faulty ion-leaks that result in sustained muscle depolarization and inexcitability. The group include; hyperkalemic PP, hypokalemic PP (HypoPP type I & II), normokalemic PP, thyrotoxic PP, Paramyotonia congenita and Andersen-Tawil syndrome. The hypoPP is the most common disorder yet is underestimated in prevalence due to missed diagnosis mimicking hysterical disorders and neurological diseases as well as the hypokalemic syndromes (Bartter, Gitelman and renal tubular acidosis). Moreover, and due to their considerable gene-penetrance, their phenotypic spectrum ranges from infrequent attacks to progressive muscular failure. In this case report we present a patient with missed diagnosis for years and describe the algorithm of his diagnosis and management.

Keywords: channelopathies, diagnosis, hypokalemia, periodic paralysis, treatment.

INTRODUCTION

Channelopathies are hereditary muscle diseases characterized by pathological ion channels of muscle cells. Skeletal muscle cell is usually affected except for Andersen-Tawil syndrome (ATS) in which the cardiac muscle cell is also affected. Typical hereditary muscle channelopathies are congenital myasthenic syndromes, non-dystrophic myotonias, periodic paralyses, malignant hyperthermia, and central core disease. Periodic paralysis (PP) disorders are heterogeneous group characterized by episodic muscle weakness and/or paralysis. The episodes are precipitated by excessive exercise, surgery, anesthesia. PP include; hyperkalemic PP (HyperPP), hypokalemic PP (HypoPP type I & II), normokalemic PP (NormoPP), thyrotoxic PP, Paramyotonia congenita and ATS. These diseases are autosomal dominant conditions with considerable penetrance that result from gain-gene mutations except for thyrotoxic PP and ATS which are gene-loss. Their mutations result in faulty ion-leaks that result in sustained muscle depolarization and inexcitability. In general; channelopathies are rare disorders with unknown prevalence due to misdiagnosis associated with their considerable gene penetrance resulting in different disease-severity and episodic-frequency. In this case report we present a patient with severe yet infrequent attacks of HypoPP and highlight its diagnostic algorithm and its management.

THE CASE:

A 37-year-old man presented with 4-days severe muscle weakness associated with hypokalemia (K: 3 mmol/L) and 4-kg weight gain following surgery for nasal polypectomy. The patient describes 3 previous attacks in 2007, 2009 and 2011 which lasted for 1 week and followed by complete recovery. The first attack followed bacterial gastroenteritis and the second followed surgery for appendicitis while the third followed cruise tripe where he consumed heavy meals. At presentation; he denied fever, shortness of breath, oedema, vomiting, diarrhea, abdominal pain, skin rash and joint pains. He denied recent or chronic intake of medications. On physical examination; he was conscious, oriented X3 and afebrile with a body weight of 80 kg. He did not have signs of cerebellar disease or oedema. Systemic examination did not show abnormality except for flaccid muscle weakness 2/4 that included proximal more than distal muscles. There was no fasciculation’s. He did not have signs of cerebellar disease and sensory sensations to vibration and pin pricks were intact. Laboratory investigations; showed normal peripheral leucocytic and platelets counts. Hemoglobin was normal with normal MCV. ESR and CRP were normal. Serum sugar, urea, creatinine and liver functions were normal. Serum electrolytes were normal including magnesium as well as...
serum bicarbonate except for potassium (K) at 2.9 mmol/L. Serum creatinine phosphokinase was normal. Thyroid function tests were normal. Urine routine and microscopy were normal. Spot urine K was 10 mmol/L and urine pH was 6. Serum complements (C3 & C4) and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, RA, hepatitis B surface antigen and anti-HCV antibodies were negative. Chest x-ray was normal. ECG showed inverted T-wave with ST-depression and visible U-wave. Ultrasound as well as CT scan of the abdomen and pelvis did not show any tumors. MRI of cervical spines and nerve conduction studies did not show abnormality except for low amplitude of compound muscle action potential (CMAP). Hence; diagnosis of HypoPP and more likely type 2 was established. His serum K was corrected initially with intravenous KCl, in Manitol solution, then was kept on Slow K 600 mg X3 with Spironolactone 50 mg daily for 4 more days. As expected; the attack self-aborited within 1 week and medications were discontinued. Repeat of nerve conduction studies confirmed normal CMAP subsequently. Since he had infrequent attacks; he was instructed to avoid excessive high intake of carbohydrates and excessive exercise. The patient was informed and given a clear statement that future accidents, surgery and anesthesia are likely to precipitate similar attacks and should be dealt with as hypoPP.

DISCUSSION

The periodic nature of the “attacks” with normal serum potassium in between in addition of low urinary potassium during such attacks rule out the possibility of Bartter’s or Gitelman’s syndrome 5. Moreover, the patient did not have vomiting and/or diarrhea or drugs such as laxative or licorice root suppletuations. The associated muscle weakness prior, during and after the attacks, and despite correction of serum K, indicated that hypoK is a secondary phenomenon and the muscle weakness was the primary insult. Normal serum creatinine phosphokinase excluded rhabdomyolysis and myopathy 6. Normal MRI of cervical spines ruled out any cervical cord or root lesion/s. Physical examination and normal nerve conduction studies that confirmed lack of sensory defect and confirms low amplitude of CMAP further supported the motor defect diagnosis 7. The periodic attacks, with normal health in between, were against progressive neurological diseases such as motor neuron disease and myotonias. Moreover; a characteristic weight gain and decrease urine output due to shift of electrolytes into the cells is common in these patients. Based on the previous findings; diagnosis of hypoPP was established in this patient. Moreover, normal autoimmune work up, thyroid function tests and CT scan of the abdomen for retroperitoneal tumor confirm the diagnosis of primary etiology rather than a secondary defect. The prevalence of such rare disease is unknown. Failure to diagnose infrequent and non-life threatening cases may underestimates its true prevalence. In the hypokalemic form, 70% of affected people have a mutation in the alpha-subunit of the voltage-sensitive muscle calcium channel gene on chromosome 1q (HypoPP type I). In others, the mutation is in the alpha-subunit of the sodium channel gene on chromosome 17 (HypoPP type II). HypoPP1 differs from HypoPP2 by: (a) earlier age of onset (10 y), the longer duration of manifestations (20 h), and more tendency to have progressive disease with fixed proximal weakness (about 70%), compared with HypoPP2 patients (16 y, 1 h, none and even may disappear by age of 50 years) 8. Moreover; (a) muscle biopsy shows vacuolar myopathy in hypoPP1 compared to tubular aggregates in hypoPP2, and (b) acetazolamide in decrease frequency of attacks in hypoPP1. 9 In long-term management patients should be aware that; (a) attacks usually begin in the morning, often with strenuous exercise or a high carbohydrate meal on the preceding day, (b) sometimes, the time between premonitory symptoms to full-blown attack is in order of minutes, (c) attacks may also be provoked by stress, including infections, menstruation, lack of sleep, and certain medications (e.g., beta-agonists, insulin, corticosteroids), (d) weakness is usually symmetrical with truncal involvement, and (e) K-supplementation with Spironolactone should be just to keep K level > 3.5 mmol/L and only for few days to avoid hyperkalemia at the end of an attack with shift of potassium from intracellular compartment into the blood especially in patients with pre-existing kidney disease, (f) for IV KCl infusion; Mannitol should be used as solvent, as both sodium and dextrose worsen the attack, and (j) drug prophylaxis with carbolic anhydrase inhibitors Dichlorphenamide and Acetazolamide are only useful in 50% contrary to hyperPP 9. In conclusion; hypoPP is an underestimated autosomal dominant hereditary disorder that can start in families after gene-mutation. Missed diagnosis is not uncommon with manifestations simulating hysterical disorders and neurological diseases as well as Bartter’s, Gitelman’s and renal tubular acidosis for its hypokalemia.

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