

Review Article

Hypokalemic Periodic Paralysis: Reports of Two Cases and Brief Review

Islam AKMM^a, Roy SS^a, Rahim MA^b, Zaman S^a, Ahmed F^a, Jesmin H^c

Abstract

Hypokalemic periodic paralysis (HPP) is a rare autosomal dominant channelopathy characterized by skeletal muscle weakness or paralysis when there is a fall in potassium levels in blood. Weakness may be mild and limited to certain muscle groups or more severe causing generalized paralysis. During an attack, reflexes may be diminished or absent. Attacks may last for a few hours or persist for several days, ultimately resulting in complete recovery. Some patients may develop chronic muscle weakness later in life. Recurrent muscle weakness accompanied by hypokalemia and exclusion of other causes help establish the diagnosis. Potassium supplementation is the mainstay of treatment of acute illness. Lifestyle modification with or without pharmacotherapy in the form of carbonic anhydrase inhibitors and/ or spironolactone can prevent future attacks. Here, we present two cases of HPP, the first one had no positive family history and responded to oral potassium and spironolactone, while the second case had family history suggestive of HPP and was managed with potassium and eplerenone.

Key words: Autosomal dominant, channelopathy, hypokalemic periodic paralysis.

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Introduction

Hypokalemic periodic paralysis (HPP) is a rare channelopathy affecting the skeletal muscles and is characterized by episodes of muscle weakness accompanied by hypokalemia. It constitutes one of the 3 types of primary periodic paralysis caused by mutations in the skeletal muscle sodium, calcium and potassium channels.¹⁻³ In HPP, weakness may be mild and limited to certain muscle groups or more severe causing generalized paralysis each time persisting for few hours to several days. HPP needs differentiation

from other causes of muscle weakness e.g., myasthenia gravis and also from other types of periodic paralysis like hyperkalemic periodic paralysis, Andersen-Tawil syndrome, thyrotoxic periodic paralysis and metabolic myopathies.⁴ Though incurable, the attacks may sometimes be prevented or aborted by simple lifestyle measures and treated by potassium supplementation or drugs. Physicians should have high degree of suspicion to think of HPP as a differential diagnosis while dealing with patients presenting with episodic skeletal muscle weakness. Timely diagnosis and judicious management can reduce morbidity and even mortality of these patients. Here, we present 2 cases of HPP who presented with recurrent muscle weakness and hypokalemia.

Case Reports

Case 1

A 35-year-old hypertensive lady who was on amlodipine 5 mg daily presented with sudden onset of weakness of both upper and lower limbs. The patient had gone to bed at night, woke up at late night and was unable to move her upper and lower limbs. She had no respiratory or swallowing difficulty and was able to move her neck and fascial muscles. She had no

Author Information

- AKM Monwarul Islam, Sharadindu Shekhar Roy, Shahana Zaman, Farhana Ahmed, Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.
- Muhammad Abdur Rahim, Department of Nephrology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh.
- Humayra Jesmin, Department of Nephrology, National Institute of Kidney Diseases & Urology (NIKDU), Dhaka, Bangladesh.

Address of Correspondence: AKM Monwarul Islam, Associate Professor, Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh. email: drmonwarbd@gmail.com

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pain or paresthesia. She denied any recent diarrhea, intake of new medications and consumption of alcohol. None of her family members had history of similar type of illness.

Physical examination revealed preserved consciousness and orientation with pulse 80 beats/min, blood pressure (BP) 150/100 mm of Hg, no jugular venous distension, goiter or lymphadenopathy. Cardiovascular system examination and examination of lungs and abdomen were unremarkable. Neurological examination revealed flaccid paralysis of all extremities involving the proximal muscles more severely than the distal ones, reflexes were diminished but sensory and cranial nerve functions were intact.

Investigations revealed normal hemogram, random blood glucose and serum creatinine. Serum electrolytes showed: Na^+ 139 mmol/L, K^+ 2.3 mmol/L, Cl^- 102 mmol/L and HCO_3^- 23 mmol/L. Serum calcium and magnesium levels were 2.4 mmol/L (normal 2.20-2.55 mmol/L) and 0.80 mmol/L (normal 0.7-0.95 mmol/L) respectively. Urine spot potassium was 11.3 mmol/L (normal 20-40 mmol/L). Arterial blood gas analysis revealed normal findings. Serum osmolality was 290 mosm/kg (normal 275-295 mosm/kg). Electrocardiogram revealed sinus tachycardia with widespread T wave inversion. Ultrasonogram of abdomen and computed tomography (CT) scan of brain showed normal findings.

She was given supportive treatment along with intravenous potassium chloride. Her conditions improved gradually, muscle power was regained and reflexes became normal. Blood pressure was controlled with losartan. She was discharged with stable condition. However, the patient had 4 episodes of similar flaccid paralysis accompanied by hypokalemia over the next 6 months. Her thyroid stimulating hormone (TSH), free triiodothyronine (FT_3), free thyroxine (FT_4), serum aldosterone and renin levels were found to be normal. A diagnosis of HPP was made. She was counselled about the nature of illness and was advised to avoid strenuous exercise and heavy carbohydrate meal. She was kept on spironolactone 100 mg daily. One further attack of paralysis was observed in the next 6 months.

Case 2

A 50-year-old hypertensive and diabetic gentleman, who was on atenolol, amlodipine, losartan, gliclazide and linagliptin, presented with sudden onset of weakness of limbs. The patient had taken a carbohydrate-rich diet forgetting his antidiabetic drugs and few hours later, he felt that he was unable to move his upper and lower limbs. He had no pain or paresthesia. His father suffered from same type of illness.

Physical examination revealed normal higher psychic function. His pulse was 70 beats/min, regular and BP was 140/90 mm of Hg. Neurological examination revealed flaccid paralysis involving all extremities but sensory and the cranial nerve functions were intact.

Investigations revealed: total leucocyte count 9000/ mm^3 ; neutrophil 65%, lymphocyte 28%, eosinophil 4%, monocyte 3%, basophil 0%; random blood glucose 13.6 mmol/L, serum creatinine 1.1 mg/dL. Serum electrolytes showed hypokalemia with potassium 1.7 mmol/L, serum calcium 2.5 mmol/L and magnesium 0.90 mmol/L (normal 0.70 to 0.95 mmol/L). Arterial blood gas analysis revealed normal findings and ketone body was absent in urine. Thyroid function tests were normal. Electrocardiogram revealed prolonged QT interval (514 ms) and left ventricular hypertrophy (Figure 1).

The patient was given supportive treatment along with intravenous potassium followed by oral potassium supplementation. Muscle weakness improved gradually without any residual neurological deficit. Follow up after 1 week was unremarkable. Over the next 3 months, he had 3 similar episodes of muscle weakness accompanied by hypokalemia, each time seriously compromising his well-being and responding to oral potassium chloride. Considering the positive family history, recurrent muscle weakness with hypokalemia and improvement with potassium supplementation, a diagnosis of HPP was made. He was advised to avoid heavy carbohydrate meal and strenuous exercise. Also, spironolactone 50 mg daily was prescribed; frequency of flaccid paralysis decreased but he developed bilateral, painful gynecomastia. Spironolactone was discontinued and substituted with eplerenone 50 mg daily. There was only 1 further, milder episode of illness in next 1 year.

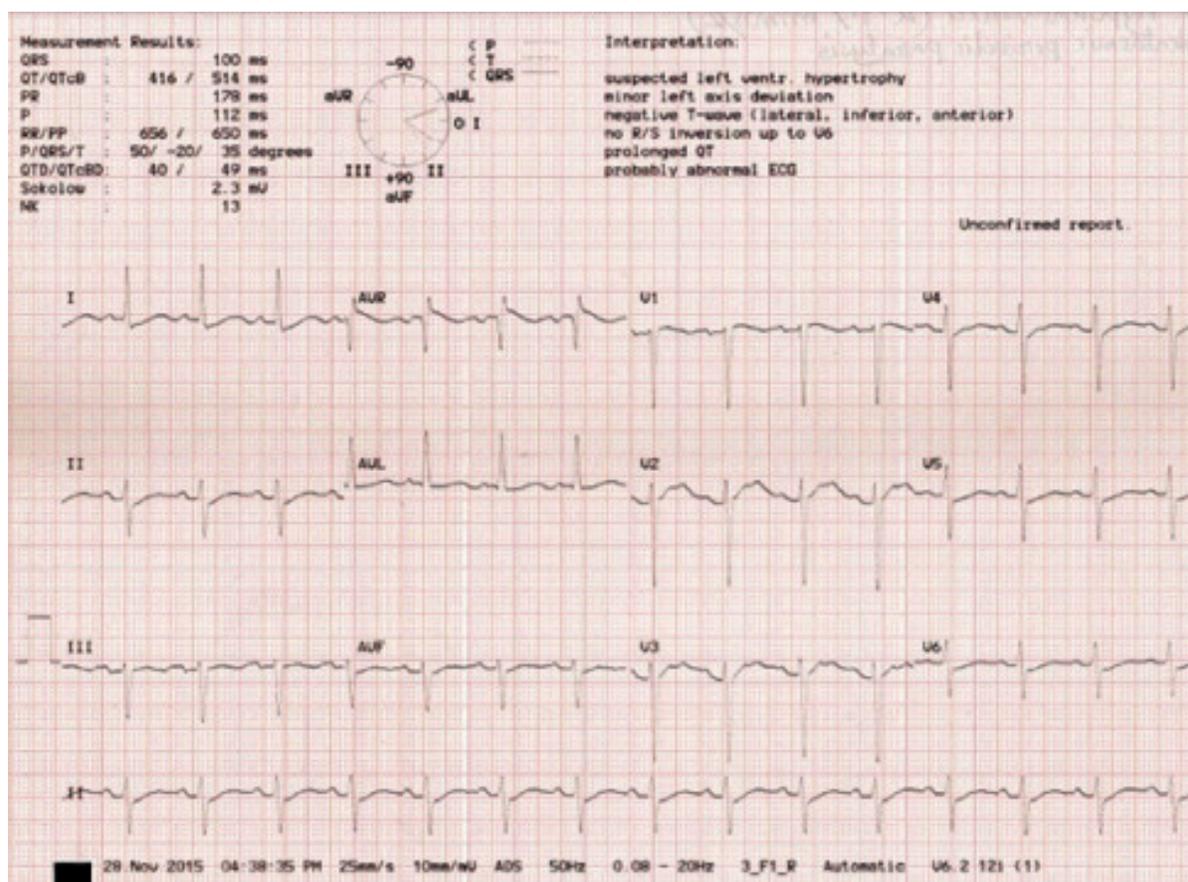


Figure 1 ECG of case 2 showing prolonged QT interval i.e., 514 ms and features of left ventricular hypertrophy

Review

HPP is usually an autosomal dominant disorder affecting the ion channels of skeletal muscle, first described by the Scottish physician Mary Walker in 1935 as familial periodic paralysis.⁵ Among the types of periodic paralysis associated with metabolic and electrolyte abnormalities, HPP is the most common with a prevalence of 1 in 100,000.⁶ HPP results from abnormal potassium regulation due to calcium or sodium channel abnormalities. Mutations of the CACNA1S gene is responsible for approximately 70% cases, while mutation affecting the SCN4A gene is responsible for rest of the cases of HPP.^{3,7-9} In patients with mutations in CACNA1S or SCN4A, the channels have a reduced excitability and signals from the central nervous system are unable to depolarize the muscle. As a result, the muscle cannot contract efficiently.

The first attack usually occurs between ages 5 and 35 years, but the frequency of attacks is highest between ages 15 and 35 years and subsequently decreases with age.^{1,10} The most striking presentation is sudden onset of mild to severe generalized weakness, usually sparing the bulbar and respiratory muscles. Individual attacks typically last for several hours; however, the duration may range from minutes to days. Weakness free intervals of weeks to months are common. Attacks may be triggered by rest after vigorous exercise, stress or a high-carbohydrate meal, often after a delay of several hours. Consciousness is always preserved. Neurologic examination during an attack demonstrates flaccid weakness, usually affecting proximal more than distal muscles and the legs more than the arms; tendon reflexes are diminished or absent. Between attacks, the neurologic findings are usually normal. Cardiac arrhythmias are not common. Late-onset proximal

myopathy may develop in some patients.² Both of our cases presented with recurrent episodes of flaccid paralysis without any lateralization and sparing the respiratory, pharyngeal and extraocular muscles, which are typical of HPP. For the first case, there was apparently no precipitating factor, however, the second case experienced paralytic attack after heavy carbohydrate meal in the background of omission of antidiabetic medication.

In case of hyperkalemic periodic paralysis, muscle weakness is accompanied by hypertonia. Andersen-Tawil syndrome is characterized by a triad of episodic flaccid muscle weakness, cardiac abnormalities (ventricular arrhythmias, prolonged QT interval and prominent U waves) and distinctive skeletal features (low-set ears, ocular hypertelorism, small mandible, 5th digit clinodactyly, syndactyly, short stature, scoliosis and a broad forehead).¹¹ Features of thyrotoxicosis may be present in thyrotoxic periodic paralysis. None of the 2 cases presented here had hypertonia or abnormal thyroid function.

Clinically, HPP needs to be differentiated from myasthenia gravis. In contrast to HPP, weakness in myasthenia gravis typically occurs predictably with mild exertion, does not occur in “attacks”, often involves bulbar and extraocular muscles and respiratory muscle involvement is common specially in myasthenic crisis.

The diagnosis is often straightforward in presence of established family history of HPP, as is the second case presented here whose father had similar episodic muscle weakness. Otherwise, the diagnosis is suggested by documentation of hypokalemia during a typical attack of weakness. Hypokalemia in HPP is usually not severe; in fact, serum potassium values <2.0 mmol/L often suggest secondary hypokalemia.¹² Other electrolytes are usually normal. Investigations are needed to rule out alternative diagnoses. Normal plasma potassium levels between attacks help distinguish primary HPP from other secondary causes of hypokalemic paralysis, such as distal renal tubular acidosis.¹³ Electrocardiographic changes are common and include depression of the ST segment, decrease in the amplitude of the T wave and an increase in the amplitude of U waves, but the changes do not correlate well with the measured serum potassium level.¹⁴ Thyroid function test should always be done to exclude thyrotoxic periodic paralysis.

Other available tests are genetic testing, provocative testing, electromyography and muscle biopsy. When available, genetic testing should always be carried out when there is an intermediate-to-high clinical suspicion.¹⁵ When genetic testing is negative, as in 30% cases of periodic paralysis, further testing with provocative tests and/or electromyography may help establish the diagnosis of HPP. Provocative testing includes an oral glucose load (2 gm/kg) and/or insulin administration (10 units subcutaneously), adrenocorticotrophic hormone (ACTH) administration and long exercise test; the last one is preferable. Long exercise test involves 30 minutes of running on the treadmill; a positive response is characterized by weakness with accompanying hypokalemia. During an attack, electromyography may show decreased amplitude of the compound muscle action potential, with reduced motor unit recruitment or electrical silence, depending on the severity of weakness.^{10,16,17} In our 2 cases, the presentation of illness was typical of HPP and secondary causes of hypokalemia were excluded clinically, as well as, by necessary investigations. Failure to make a distinction between HPP and non-HPP could lead to improper management. Use of spot urine for K⁺ excretion and evaluation of blood acid-base status could be clinically beneficial in the diagnosis and management.¹⁸ A low rate of K⁺ excretion coupled with the absence of a metabolic acid-base disorder suggests HPP, as are the cases presented here. Genetic testing is not readily available in Bangladesh. Provocative testing, electromyography and muscle biopsy were not done in our cases because these tests are not mandatory and the diagnosis could be made with reasonable certainty in both the cases.

Management of HPP involves treatment of acute attack and prevention of further attacks. For acute management of hypokalemia, potassium chloride is administered 30 mmol orally every 30 minutes until serum potassium normalizes.¹⁰ Simultaneous cardiac monitoring is needed. Slower rates of administration (10 mmol per hour), has also been recommended to minimize rebound hyperkalemia.¹⁹ Intravenous potassium should be avoided whenever possible; however, it is indicated for arrhythmia due to hypokalemia or airway compromise due to ictal dysphagia or accessory respiratory muscle paralysis.²⁰ Milder attacks can be aborted by low-level exercise.² Both of our patients responded well to

potassium supplementation during acute illness. Our second case was initially treated with intravenous potassium, because the hypokalemia was relatively severe, i.e., 1.7 mmol/L and there was QT prolongation.

For prevention, lifestyle measures and drug treatment are the available options. Low-carbohydrate diet and avoiding vigorous exercise may help prevent paralytic attacks. When these measures fail and the attacks continue to be disabling, prophylactic treatment is indicated to avoid morbidity and even mortality. While potassium can be taken chronically as maintenance, the favored approach is to add one of a variety of diuretics.²⁰ However, diuretics are not helpful for acute attacks; their role is to decrease the frequency and severity of attacks over time.²⁰ Potassium sparing diuretics e.g., spironolactone 25-100 mg/day, eplerenone 50-100 mg/day or triamterene 50-150 mg daily may be effective.²¹ Acetazolamide (125-1000 mg daily in divided dose)^{2,10,20,21} and dichlorphenamide (50 mg twice daily)^{22,23} are the available carbonic anhydrase inhibitors. Our first patient apparently responded to spironolactone 100 mg/day, as evidenced by reduction of number of recurrences. But, for the second case, spironolactone had to be substituted with eplerenone as there was painful gynecomastia. Dichlorphenamide (50 mg twice daily) was demonstrated to be more effective than placebo in reducing attack frequency.^{22,23} However, this drug is not available in Bangladesh. Topiramate^{24,25}, verapamil²⁶ and pinacidil^{22,27} have also been tried. There is no known treatment for the late-onset myopathy in HPP.

Conclusion

HPP is a rare genetic disease of skeletal muscles. High index of suspicion is necessary for diagnosing this otherwise rare entity, specially when encountering a patient with an acute attack of paralysis accompanied documented hypokalemia and no other explanation could be found. Failure to properly diagnose and treat HPP can be fatal, but rapid correction of potassium abnormalities can resolve the symptoms quickly and completely. Physicians should have appropriate preparedness to deal with this disease.

Conflict of interest: Nothing to declare.

References

- Cannon SC. Channelopathies of skeletal muscle excitability. *Compr Physiol* 2015;5:761-90.
- Fontaine B. Periodic paralysis. *Adv Genet* 2008;63:3-23.
- Matthews E, Labrum R, Sweeney MG, Sud R, Haworth A, Chinnery PF, et al. Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. *Neurology* 2009;72: 1544-47.
- Gutmann L, Conwit R, Shefner JM, Wilterdink JL. Hypokalemic periodic paralysis. Available at: www.uptodate.com, accessed 29 Aug 2018.
- Aitken RS, Allot EN, Gastelden LI, Walker MB. Observations on a case of familial periodic paralysis. *Clin Sci* 1937; 3: 47-57.
- Fontaine B, Vale-Santos J, Jurkat-Rott K, Reboul J, Plassart E, Rime CS, et al. Mapping of the hypokalaemic periodic paralysis (HypoPP) locus to chromosome 1q31-32 in three European families. *Nat Genet* 1994; 6:267-72.
- Wang W, Jiang L, Ye L, Zhu N, Su T, Guan L, et al. Mutation screening in Chinese hypokalemic periodic paralysis patients. *Mol Genet Metab* 2006;87:359-63.
- Wang Q, Liu M, Xu C, Tang Z, Liao Y, Du R, et al. Novel CACNA1S mutation causes autosomal dominant hypokalemic periodic paralysis in a Chinese family. *J Mol Med (Berl)* 2005;83:203-8.
- Sternberg D, Maissonobe T, Jurkat-Rott K, Nicole S, Launay E, Chauveau D, et al. Hypokalaemic periodic paralysis type 2 caused by mutations at codon 672 in the muscle sodium channel gene SCN4A. *Brain* 2001;124(Pt 6):1091-99.
- Venance SL, Cannon SC, Fialho D, Fontaine B, Hanna MG, Ptacek LJ, et al. CINCH investigators. The primary periodic paralyses: diagnosis, pathogenesis and treatment. *Brain* 2006;129(Pt 1):8-17.
- Plaster NM, Tawil R, Tristani-Firouzi M, Canún S, Bendahhou S, Tsunoda A, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* 2001;105:511-19.
- Miller TM, da Silva MRD, Miller HA. Correlating phenotype and genotype in the periodic paralyses. *Neurology* 2004; 63:1647-55.
- Ng HY, Lin SH, Hsu CY, Tsai YZ, Chen HC, Lee CT. Hypokalemic paralysis due to Gitelman syndrome: a family study. *Neurology* 2006;67:1080-2.
- Soule BR, Simone NL. Hypokalemic Periodic Paralysis: a case report and review of the literature. *Cases J* 2008; 1: 256.
- Fournier E, Arzel M, Sternberg D, Vicart S, Laforet P, Eymard B, et al. Electromyography guides toward subgroups of mutations in muscle channelopathies. *Ann Neurol* 2004;56:650-61.
- Sharma CM, Nath K, Parekh J. Reversible electrophysiological abnormalities in hypokalemic paralysis: Case report of two cases. *Ann Indian Acad Neurol* 2014;17:100-2.
- Cannon SC, George AL. Pathophysiology of myotonia and periodic paralysis. In: *Diseases of the Nervous System*, 3rd,

- Asbury AK, McKhann GM, McDonald WI, et al (Eds), Cambridge University Press, Cambridge 2002. p.1183.
18. Lin SH, Chiu JS, Hsu CW, Chau T. A simple and rapid approach to hypokalemic paralysis. *Am J Emerg Med* 2003;21:487-91.
 19. Lin SH, Lin YF, Chen DT, Chu P, Hsu CW, Halperin ML. Laboratory tests to determine the cause of hypokalemia and paralysis. *Arch Intern Med* 2004;164:1561-66.
 20. Levitt JO. Practical aspects in the management of hypokalemic periodic paralysis. *J Transl Med* 2008;6:18.
 21. Statland JM, Fontaine B, Hanna MG, Johnson NE, Kissel JT, Sansone VA, et al. Review of the Diagnosis and Treatment of Periodic Paralysis. *Muscle Nerve* 2018;57:522-30.
 22. Sansone V, Meola G, Links TP, Panzeri M, Rose MR. Treatment for periodic paralysis. *Cochrane Database Syst Rev* 2008;(1):CD005045.
 23. Tawil R, McDermott MP, Brown R Jr, Shapiro BC, Ptacek LJ, McManis PG, et al. Randomized trials of dichlorphenamide in the periodic paralyses. Working Group on Periodic Paralysis. *Ann Neurol* 2000;47:46-53.
 24. García-Sobrino T, Pardo J. Successful treatment of hypokalemic periodic paralysis with topiramate. *Eur J Neurol* 2014;21:e73-74.
 25. Fiore DM, Strober JB. Treatment of hypokalemic periodic paralysis with topiramate. *Muscle Nerve* 2011;43:127-29.
 26. Links TP, Arnoldus EP, Wintzen AR, van der Hoeven J, Gerritsen JJ, Brandenburg HC. The calcium channel blocker verapamil in hypokalemic periodic paralysis. *Muscle Nerve* 1998;21:1564-65.
 27. Ligtenberg JJ, Van Haefen TW, Van Der Kolk LE, Smit AJ, Sluiter WJ, Reitsma WD, et al. Normal insulin release during sustained hyperglycaemia in hypokalaemic periodic paralysis: role of the potassium channel opener pinacidil in impaired muscle strength. *Clin Sci (Lond)* 1996;91:583-89.