Reminder of important clinical lesson

A 20-year-old Chinese man with recurrent hypokalemic periodic paralysis and delayed diagnosis

Muniba Naqi,¹ Vijaya Raj Bhatt,¹ Shradha Pant,² Rajesh Shrestha,³ Michael Tadros,¹ Srujitha Murukutla,⁴ Jeffrey Rothman⁴

¹Department of Internal Medicine, Staten Island University Hospital, Staten Island, New York, USA;

²Department of Internal Medicine, University of Science and Technology, Chittagong, Bangladesh;

³Department of Medicine, Institute of Medicine, Kathmandu, Nepal;

⁴Department Of Medicine, Staten Island University Hospital, Staten Island, New York, USA

Correspondence to Dr Srujitha Murukutla, srujitha.murukutla@gmail.com

Summary

Periodic paralysis in the setting of hypokalemia can be the result of several underlying conditions, requiring systematic evaluation. Thyrotoxic periodic paralysis (TPP), a curable cause of hypokalemic periodic paralysis, can often be the first manifestation of thyrotoxicosis. Because the signs and symptoms of thyrotoxicosis can be subtle and clouded by the clinical distress of the patient, the diagnosis of the underlying metabolic disorder can be overlooked. The authors report a case of TPP in a young Chinese man in whom the diagnosis of thyrotoxicosis was initially missed. This case illustrates the lack of awareness of TPP among many physicians, delay in the diagnosis of TPP and the importance of performing thyroid function testing in all cases of periodic paralysis.

BACKGROUND

Periodic paralysis can be a result of several uncommon conditions including various skeletal muscle channelopathies.¹ The presence of hypokalemia narrows diagnostic consideration to two general categories. Hypokalemic periodic paralysis (HPP) includes thyrotoxic periodic paralysis (TPP), familial HPP and sporadic cases of periodic paralysis in the absence of either family history or provable thyrotoxicosis. Conditions that result in recurrent potassium deficit (non-HPP) can also cause periodic paralysis² including renal tubular acidosis, profuse diarrhoea, ureteral diversion, excessive vomiting, diuretic use, Bartter's or Gitelman's syndrome, primary aldosteronism, apparent mineralocorticoid syndromes including licorice ingestion, ectopic corticotropin syndrome and Liddle's syndrome.²⁻³ Rare conditions including Wilson's disease,⁴ and cocaine abuse⁵⁻⁶ have also been reported to cause periodic paralysis associated with hypokalemia. For both prognostic and therapeutic reasons it is important to search for and address the underlying cause of periodic paralysis.

CASE PRESENTATION

A 20-year-old Chinese man presented to the emergency department with a 3-h history of progressive weakness of all extremities that began on awakening in the morning. The patient gave a history of similar episodes of muscle weakness occurring after intake of carbohydrate-rich food. One of these episodes led to hospitalisation 2 weeks prior to the current one. In between the attacks, he did not have any muscle weakness or limitation of physical activity. He denied any other medical or surgical problem. There was a history of periodic muscle weakness in his paternal uncle and grandfather. The patient's prior paralytic attacks were therefore attributed to familial HPP and he was treated with oral potassium supplementation. In addition to generalised

muscle weakness, physical examination revealed tremor of outstretched hands and tachycardia. The thyroid was not palpably enlarged. The patient improved after replacement of potassium. Further questioning revealed a history of tremors, sweating, tremulousness and 5-pound weight loss over the past 5 weeks as well as a history of hyperthyroidism in the patient's maternal grandmother.

INVESTIGATIONS

Laboratory tests included serum sodium of 138 mmol/l, potassium of 3.1 mmol/l, chloride of 103 mmol/l, bicarbonate of 30 mmol/l, calcium of 9.0 mg/dl, magnesium of 2.3 mg/dl, glucose of 104 mg/dl, creatine kinase of 186 IU/L, renin of 8.43 ng/ml and aldosterone of 3 ng/dl. Serum thyroid stimulating hormone concentration (TSH) was 0.06 µIU/ml, with free T4 concentration of 2.6 ng/dl. Complete blood count, renal and liver function tests were all within normal limits.

DIFFERENTIAL DIAGNOSIS

- ▶ Familial HPP
- ▶ TPP
- ▶ Other causes of HPP and non-HPP

TREATMENT

The patient was initially treated with intravenous potassium chloride with improvement of symptoms and a return to normal muscle strength.

OUTCOME AND FOLLOW-UP

A diagnosis of TPP was established and the patient was started on oral propranolol and methimazole and discharged home. Three days later, he was re-admitted with lower extremity weakness. He was found to have a serum

potassium concentration of 2.0 mmol/l. Potassium was replaced and the doses of propranolol and methimazole were increased. Six days later, he returned to the emergency department with complaints of muscle pain. He was found to have potassium of 2.8 mmol/l, which was corrected with oral potassium supplementation.

About 3 weeks later, after discontinuing methimazole for a week, 24 h radioactive iodine was 77% and thyroid imaging revealed diffuse thyroïdal uptake consistent with Graves' disease. The patient was then treated with a therapeutic oral dose of ¹³¹I. The patient resumed methimazole therapy 1 week after the radioiodine therapy. Five months after the radioactive iodine therapy, the patient is doing well.

DISCUSSION

TPP is a well-known complication of thyrotoxicosis in Asians, including Chinese, Japanese, Vietnamese, Koreans and Filipinos. In Chinese and Japanese patients with thyrotoxicosis, the incidence of TPP is 1.8% and 1.9% respectively.⁷⁻⁹ TPP is much less common among non-Asian ethnic groups.¹⁰ The incidence rate among thyrotoxic individuals in North America is 0.1–0.2%.⁷ TPP predominantly affects males with the male: female incidence ratio in thyrotoxic Chinese individuals 13%: 0.17%.^{7 11 12}

Patients with TPP are typically young adult males between the ages of 20–40 years. Attacks occur intermittently and are characterised by transient episodes of muscle weakness that range from mild weakness to flaccid paralysis. Prodromal symptoms of muscles cramps, aches and stiffness may occur.¹¹⁻¹³ Proximal muscles are affected more than distal muscles and the attacks tend to involve the lower limbs first with progression to upper limbs. Bladder and bowel function are not affected and respiratory muscles are rarely involved. Episodes may last a few hours up to 72 h. Episodes classically occur on awakening and are often preceded by ingestion of sweets or a carbohydrate-rich meal or by heavy physical exertion.¹³ TPP only occurs when the patient is thyrotoxic and is abolished by a return to a euthyroid state.⁷ Cardiac arrhythmias and acute respiratory failure have been reported but are rare.¹⁴

TPP can be difficult to diagnose because the hyperthyroidism may be mild and clinically manifest itself with only subtle symptoms and signs.¹¹⁻¹³ As in our patient, TPP is sometimes the initial presenting symptom of thyrotoxicosis and the hyperthyroidism can be nearly clinically silent making the diagnosis even more difficult.¹³ This can result in a delay in aetiologic diagnosis. In a study of 31 cases of TPP, only seven patients were diagnosed with thyrotoxicosis during their first attack. Among the remaining 24 patients, the patients were diagnosed an average of 13.88 months after their first paralytic attack.¹³ Therefore, it is important to directly inquire about symptoms of thyrotoxicosis. The majority of cases of thyrotoxicosis are due to Graves' disease but other causes of thyroid over-activity may be responsible.⁷

Serum potassium at the time of presentation is usually less than 3.0 mmol/l and is sometimes more markedly decreased. Hypokalemia occurs due to a massive shift of potassium into cells rather than total body potassium depletion. The degree of hypokalemia correlates with the severity of paralysis. Serum magnesium and phosphate may be decreased and this is also related to a shift to the intracellular compartment.⁷

The pathogenesis incorporates genetic susceptibility (mutations in skeletal muscle ion channels), thyrotoxicosis of any cause and precipitating factors. Recent evidence links TPP in a significant number of patients to mutations of the inwardly rectifying potassium channel called Kir2.6 that is encoded by a newly characterised gene (KCNJ18).¹⁵ Several ion channels such as Kv1.5 and Kv4.2 as well as Kir2.6 are known to be transcriptionally regulated by T3 through thyroid response elements on the related genes. Increased or decreased ion channel transcription during thyrotoxicosis may lead to marked changes in resting membrane potential and potassium accumulation with resulting muscle weakness in patients who do not manifest problems when euthyroid.¹⁶

When assessing patients who present with episodic muscle weakness it is important for both prognostic and therapeutic reasons to distinguish between those patients who are total body potassium depleted and those who are not.

Hypokalemia and paralysis may result from a rapid and massive shift of potassium to the intracellular compartment without potassium depletion (HPP) or from a true potassium deficit (non-HPP).¹² In addition to TPP, causes of HPP include familial HPP and sporadic periodic paralysis that may occur in the absence of either a family history or thyrotoxicosis. Causes of non-HPP include those associated with hyperchloremic metabolic acidosis such as distal or proximal renal tubular acidosis, profuse diarrhoea or ureteral diversion and those associated with hyperchloremic metabolic alkalosis such as excessive vomiting, diuretic use or abuse, Bartter's or Gitelman's syndrome, primary aldosteronism, apparent mineralocorticoid syndromes including licorice ingestion, ectopic corticotropin syndrome and Liddle's syndrome. Patients with non-HPP have abnormal acid-base state, and high urine potassium excretion manifested by urinary potassium-creatinine ratio of >2.5 mmol/mmol and transtubular potassium concentration gradient of >3 in hyperosmolar urine. In patients with HPP, the acid-base state is normal and the urine potassium excretion is low.^{3 17}

Differentiating between HPP and non-HPP is important because in HPP excessive potassium replacement, especially when given intravenously, may result in rebound hyperkalemia during recovery from paralysis when potassium is shifted back into the intravascular compartment.² In a retrospective study of patients who were proven to have HPP, during recovery approximately 30% of patients had potassium levels >5 mmol/l and 10% had levels >6 mmol/l even though these patients were given less potassium supplementation than those with non-HPP.³

In summary, TPP should be suspected when a young Asian male presents with acute muscle weakness, although females as well as patients from non-Asian ethnic groups can also be affected. A family history of thyroid disease may be present. Subtle sign and symptoms of thyrotoxicosis may be present but difficult to ascertain in the setting of acute paralysis. TPP is typically associated with hypokalemia and hypophosphatemia during attacks, which normalise with recovery.¹¹⁻¹³ A normal potassium level does not exclude the diagnosis.¹³ Thyroid function tests (low serum TSH and elevated thyroid hormone concentrations) establish the diagnosis of hyperthyroidism.¹¹⁻¹³ Clearly, thyroid function tests should be done in all cases of periodic paralysis to rule out TPP.¹³ Differentiating TPP from other

causes of HPP is important because unlike other causes of periodic paralysis, the syndrome resolves with correction of thyrotoxicosis.^{11–13}

The total body potassium is normal in TPP and rebound hyperkalemia during recovery can be a problem. The goal of potassium supplementation is normalisation of the serum potassium level, which should be done using low dose supplementation of potassium.¹² Potassium supplementation is not useful for prophylaxis against further episodes of paralysis and should not be used between attacks.⁷ Propranolol prevents intracellular shift of potassium and can normalise serum potassium as well as rapidly reverse muscle weakness. When used alone, it does not cause rebound hyperkalemia, hence it has been suggested as a first-line therapy. The definitive therapy for TPP is control of thyrotoxicosis. The underlying aetiology of the thyrotoxicosis should be investigated and treated with antithyroid medications, radioactive iodine or, if indicated, thyroidectomy. Until patients become euthyroid, they should be advised to avoid precipitating factors such as carbohydrate-rich meals or strenuous exercises and continue the use of propranolol. TPP does not recur once the patient is euthyroid.^{11–13}

Learning points

- ▶ A systematic approach should be applied to determine the underlying aetiology when encountered with periodic paralysis in the setting of hypokalemia.
- ▶ TPP can be the first manifestation of thyrotoxicosis, hence it is often missed initially. A high index of suspicion should, therefore, be maintained and a diagnosis of TPP should be actively sought when evaluating periodic paralysis.
- ▶ Although TPP is typically present in young Asian men, females and non-Asian ethnic groups can also be affected. Therefore, thyroid function test should be done in all cases of periodic paralysis.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Platt D**, Griggs R. Skeletal muscle channelopathies: new insights into the periodic paralyses and nondystrophic myotonias. *Curr Opin Neurol* 2009;**22**:524–31.
2. **Lin SH**, Chiu JS, Hsu CW, *et al*. A simple and rapid approach to hypokalemic paralysis. *Am J Emerg Med* 2003;**21**:487–91.
3. **Lin SH**, Lin YF, Halperin ML. Hypokalaemia and paralysis. *QJM* 2001;**94**:133–9.
4. **Chu CC**, Huang CC, Chu NS. Recurrent hypokalemic muscle weakness as an initial manifestation of Wilson's disease. *Nephron* 1996;**73**:477–9.
5. **Lajara-Nanson WA**. Cocaine induced hypokalaemic periodic paralysis. *J Neurol Neurosurg Psychiatr* 2002;**73**:92.
6. **Nalluri P**, Venkatesh S, Rao A. Cocaine-induced hypokalemic paralysis. *Muscle Nerve* 2000;**23**:1773.
7. **Kung AW**. Clinical review: Thyrotoxic periodic paralysis: a diagnostic challenge. *J Clin Endocrinol Metab* 2006;**91**:2490–5.
8. **McFadzean AJ**, Yeung R. Periodic paralysis complicating thyrotoxicosis in Chinese. *Br Med J* 1967;**1**:451–5.
9. **Okinaka S**, Shizume K, Iino S, *et al*. The association of periodic paralysis and hyperthyroidism in Japan. *J Clin Endocrinol Metab* 1957;**17**:1454–9.
10. **Kelley DE**, Gharib H, Kennedy FP, *et al*. Thyrotoxic periodic paralysis. Report of 10 cases and review of electromyographic findings. *Arch Intern Med* 1989;**149**:2597–600.
11. **Lam L**, Nair RJ, Tingle L. Thyrotoxic periodic paralysis. *Proc (Bayl Univ Med Cent)* 2006;**19**:126–9.
12. **Lin SH**. Thyrotoxic periodic paralysis. *Mayo Clin Proc* 2005;**80**:99–105.
13. **Maciel RM**, Lindsey SC, Dias da Silva MR. Novel etiopathophysiological aspects of thyrotoxic periodic paralysis. *Nat Rev Endocrinol* 2011;**7**:657–67.
14. **Wu CZ**, Wu YK, Lin JD, *et al*. Thyrotoxic periodic paralysis complicated by acute hypercapnic respiratory failure and ventricular tachycardia. *Thyroid* 2008;**18**:1321–4.
15. **Ryan DP**, da Silva MR, Soong TW, *et al*. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. *Cell* 2010;**140**:88–98.
16. **Tricarico D**, Camerino DC. Recent advances in the pathogenesis and drug action in periodic paralyses and related channelopathies. *Front Pharmacol* 2011;**2**:8.
17. **Lin SH**, Lin YF, Chen DT, *et al*. Laboratory tests to determine the cause of hypokalemia and paralysis. *Arch Intern Med* 2004;**164**:1561–6.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Naqi M, Bhatt VR, Pant S, Shrestha R, Tadros M, Murukutla S, Rothman J. A 20-year-old Chinese man with recurrent hypokalemic periodic paralysis and delayed diagnosis. *BMJ Case Reports* 2012;10.1136/bcr.01.2012.5541, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow

Keep up to date with all published cases by signing up for an alert (all we need is your email address) <http://casereports.bmj.com/cgi/alerts/etoc>