Rare disease

A young man presenting with paralysis after vigorous exercise

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Summary

Thyrotoxic periodic paralysis (TPP) is a rare metabolic disorder characterised by muscular weakness and paralysis in predisposed thyrotoxic patients. Although patients with TPP are almost uniformly men of Asian descent, cases have been reported in Caucasian and other ethnic populations. The rapid increase in ethnic diversity in Western and European nations has led to increase in TPP reports, where it was once considered exceedingly rare. Correcting the hypokalaemic and hyperthyroid state tends to reverse the paralysis. However, failure to recognise the condition may lead to delay in diagnosis and serious consequences including respiratory failure and death. We describe a young man who was diagnosed with hyperthyroidism who presented with acute paralysis. The clinical characteristics, pathophysiology and management of TPP are reviewed.

BACKGROUND

Thyrotoxicosis is a common condition in the UK. Thyrotoxic periodic paralysis (TPP) is a commonly misdiagnosed syndrome in Western countries because of its similarities with familial periodic paralysis, which is an autosomal-dominant condition. Misdiagnosis or delayed diagnosis may have serious consequences with morbidities and mortalities. Although it has been reported in the literature, the case is a reminder of a rare but important condition that we may encounter in Asian patients living in, or visiting, the UK and much less commonly in the white Caucasian population.

CASE PRESENTATION

A 30-year-old South East Asian gentleman was admitted with sudden-onset weakness of all four limbs 14 h prior to presentation, rendering him unable to mobilise and hence seeking assistance.

The upper-limb weakness gradually improved and on presenting to accident and emergency department his main symptoms constituted bilateral lower-limb weakness and myalgia. He was also experiencing uncomfortable palpitations. Further questioning revealed a history of vigorous exercise, consisting of long-distance running 1 day prior to admission. The patient's past medical history included palpitations, for which he underwent radiofrequency ablation approximately 10 years before presentation. He had no other relevant medical history. On systematic enquiry, he reported weight loss of 5 kg over the past 3 months despite a good appetite. He had no symptoms of tremor, sweating, palpitation, chest pain, urinary or bowel dysfunction or visual disturbance. He complained of myalgia in both shoulder girdles and both legs proximally.

His observations were as follows: pulse 120 bpm, blood pressure 158/75 mm Hg, respiratory rate 28/min, blood

sugar 8.0 mmol/l, SaO₂ 100% on air. He was afebrile. Respiratory and abdominal examinations were normal. Heart sounds were normal with no murmurs audible. Neurological examination revealed normal tone in all limbs with a power of 5/5 in the upper limbs and 1/5 for both lower limbs. Reflexes were normal in all limbs and plantar responses were negative. There was no sensory deficit, with intact perineal sensation. The patient had a mildly enlarged, asymmetrical, non-tender goitre with no audible bruit and moderate exophthalmos of both eyes.

INVESTIGATIONS

His investigations revealed the following: Hb 15.6 gm/dl, mean corpuscular volume 83.0 fl, white cell count 10.5×10^9 /litre, platelets 274×10^9 /litre, low potassium at 2.6 mmol/l, urea 3.4 mmol/l, creatinine 50 µmol/l, C-reactive protein <5 mg/dl, magnesium 0.85 mmol/l, calcium 2.32 mmol/l, raised creatine kinase at 3499 IU/l, lactate dehydrogenase 273 IU/l, slightly raised alanine transaminase at 69 IU/l, all other liver function tests were normal. His thyroid function tests showed markedly raised free thyroxine (T4) >100 pmol/l and suppressed thyroid-stimulating hormone (TSH) at <0.01 mU/l. A series of 12-lead ECGs were performed on admission to the emergency department, which showed atrial flutter with right bundle branch block fluctuating rate 117–164 bpm (figure 1).

DIFFERENTIAL DIAGNOSIS

- ▶ Polyneuropathies such as Guillain-Barré syndrome.
- ▶ Spinal cord diseases such as transverse myelitis, primary and secondary tumours.
- ▶ Primary acute myopathies such as periodic paralysis, electrolyte abnormalities and polyomyositis.

Figure 1 ECG on Day 1.

- Neuromuscular junction diseases such as myasthenia gravis, Eaton Lambert syndrome and botulism.
- Psychiatric and functional disorders such as conversion disorder and Munchausen syndrome.

TREATMENT

The patient was infused with amiodarone 300 mg over 30 min (before the blood results were processed) and his heart rate dropped to around 90 bpm. Upon receipt of the

patient's blood results (low potassium), amiodarone infusion was stopped and he was commenced on intravenous fluids with potassium. He was started on carbimazole 40 mg once daily, beta-blockers and oral potassium supplementation. The following day the patient's potassium normalised at a value of 4.5 mmol/l and the leg weakness resolved. A diagnosis of TPP was made. His ECG the day after admission showed right bundle branch block with regular complexes at a rate of 84 bpm (figure 2).

Figure 2 ECG on Day 2.

OUTCOME AND FOLLOW-UP

The patient's weakness recovered completely. He was discharged and referred to an endocrinology clinic. He was unfortunately lost to follow-up and so the aetiology of his thyrotoxicosis was not elucidated.

DISCUSSION

TPP is an uncommon presentation of thyrotoxicosis in Western countries, mainly due to the fact that TPP is predominantly associated with people of East Asian origin. Unfamiliarity with this condition among physicians can lead to delayed or missed diagnosis.^{1 2} Interestingly, although thyrotoxicosis is more common in women, TPP is a condition that predominantly affects men, with a male-to-female ratio ranging between 17:1 and 70:1.³ The condition usually manifests in East Asian gentlemen aged between 20 and 40 years of age, with recurrent episodes of muscular weakness predominantly affecting the proximal musculature. These paroxysms of weakness can vary in severity from mild fatigue to complete flaccid paralysis and tetraplegia, very rarely involving the ocular, bulbar and respiratory muscles.^{3 4} Classically, the weakness begins in the lower limbs and ascends to involve the upper extremities. Attacks are usually precipitated by strenuous exercise (as in this case) or by high carbohydrate meals, alcohol, or experienced on waking from sleep.³ TPP is distinguished from other causes of leg weakness such as Guillain-Barré syndrome, cord compression and transverse myelitis by the history of previous events and precipitants, evidence of thyrotoxicosis, hypokalaemia during the attack and lack of sensory, bowel and bladder dysfunction.³ Deep tendon reflexes in TPP are usually diminished, but may occasionally be normal or brisk.³ The autosomal dominant, familial hypokalaemic periodic paralysis is differentiated from TPP by its earlier age of onset, positive family history, lack of predilection for men or Asians and absence of thyrotoxicosis.

In one study of 19 patients presenting with 24 episodes of periodic paralysis and thyrotoxicosis, hypokalaemia occurred in 100% of the cases.⁵ Hypokalaemia is thus central to the pathophysiology of TPP attacks and due to intracellular shifts of potassium, rather than bodily losses. Diagnostic difficulty may arise, however, if the patient presents in the recovery phase of an attack, where potassium levels may be normal. Creatine kinase levels may be elevated, especially where the precipitant was strenuous exercise and in severe cases rhabdomyolysis has been reported.⁵

Hypokalaemia in TPP results in myocyte membrane hyperpolarisation and resultant myopathic changes that are demonstrable on EMG.³ The vast majority of cases are sporadic and postulated to be due to increased $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump activity. Thyroid hormones directly stimulate, and indirectly enhance $\text{Na}^+\text{-K}^+\text{-ATPase}$ action via increased levels of circulating catecholamines and insulin. These indirect mechanisms explain the resolution of paralysis when non-selective beta-blockers are used, as well as the precipitation of events by high-carbohydrate-containing meals.³ A genetic predisposition for myocyte membrane hyperpolarisation has been suggested, with mutations in voltage-gated potassium⁶ and sodium⁷ channels being proposed. These electrolyte disturbances also affect the

myocardium, with resultant arrhythmogenic effects. Various ECG changes are seen in TPP patients, including tachyarrhythmias, conduction abnormalities and increased QRS voltages.⁸ Our patient presented with atrial flutter with right bundle branch block. In a study of 23 consecutive patients with hyperthyroidism caused by Graves' disease, 65% of patients had pulmonary hypertension. Almost all patients normalised the increased pulmonary artery pressure with definitive treatment of the Graves' disease.⁹ It may be that some component of the 'right heart failure' and peripheral oedema that can accompany hyperthyroidism is caused by this reversible change in pulmonary artery pressure.¹⁰

Definitive management of TPP involves correcting the thyrotoxic state.³ While this is achieved; potassium replacement and beta-blockade effectively terminate the attacks. Non-selective beta-blockers such as propranolol, but not cardioselective beta-blockade or potassium supplementation, have been shown to prevent attacks.³

Although corticosteroids have been used in treating hyperthyroidism, they may also produce detrimental effects, including the development of TPP. A literature review revealed at least two cases of TPP induced by methylprednisolone and two cases caused by a single dose of prednisolone.¹¹⁻¹³ Glucocorticoids inhibit insulin secretion from the B-cells of the pancreas and also have metabolic effects on carbohydrate, protein and fat metabolism, thereby affecting peripheral glucose uptake. After initiation of definitive therapy for hyperthyroidism, patients should avoid precipitating factors and continue propranolol until euthyroid state is achieved to prevent recurrence.^{14 15}

Learning points

- ▶ Diagnosis of thyrotoxic periodic paralysis (TPP) on initial presentation is often delayed and confused with more familiar causes of hypokalaemia and lower-limb paralysis because thyrotoxic signs may be subtle.
- ▶ Checking thyroid-stimulating hormone is imperative in patients presenting to the emergency department with no clear cause of acute weakness.
- ▶ Early recognition of TPP and potassium replacement will prevent morbidity and mortality.

Competing interests None.

Patient consent Obtained.

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