Unusual presentation of more common disease/injury

Pop-provoked paralysis: silent Graves' disease presenting as thyrotoxic periodic paralysis

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Summary

A 48-year-old Filipino man presented after several episodes of worsening limb paralysis that occurred after drinking cola beverages. In the emergency department he was found to be hypokalaemic, and although he exhibited no symptoms of thyrotoxicosis he was biochemically hyperthyroid. Thyroid stimulating hormone receptor antibody serology was positive indicating Graves' disease as the underlying cause of his hyperthyroidism. Intravenous potassium supplementation resulted in complete resolution of symptoms, and a diagnosis of thyrotoxic periodic paralysis was made. He was started on a regimen of propylthiouracil and propranolol and subsequently given radioiodine as the definitive treatment for Graves' disease. There were no recurrent attacks of paralysis once a stable euthyroid state was achieved, and the patient was able to resume cola consumption without issue.

BACKGROUND

Thyrotoxic periodic paralysis (TPP) is a rare disorder characterised by transient weakness or paralysis and hypokalaemia. It is usually associated with a broader thyrotoxic clinical picture. This case illustrates how it may also be the presenting feature of otherwise clinically silent hyperthyroidism. Our patient had also recently been diagnosed with type-2 diabetes mellitus, highlighting the link between hyperinsulinaemia and TPP.

CASE PRESENTATION

A 48-year-old Filipino man presented to the emergency department in the early morning with a 4-h history of complete limb paralysis. He had awoken in the middle of the night with a full bladder and found that he could not move. Before going to bed that night he had drunk a large bottle of cola. The patient had experienced three previous episodes of mild weakness over the previous few months. In two of them he was unable to get out of a chair, and in a third he could not climb a flight of stairs. Each episode lasted 2 h before completely resolving, and they also occurred shortly after drinking cola. Relevant history included his recent diagnosis of type-2 diabetes mellitus, and a sister with hyperthyroidism. The patient had no symptoms of thyrotoxicosis. Physical examination revealed severe weakness of the upper and lower limbs as well as absent lower limb deep tendon reflexes and muted plantar reflexes. The thyroid gland was diffusely enlarged and his eyes exhibited mild periorbital oedema and conjunctival erythema.

INVESTIGATIONS

Serum potassium on presentation was 2.3 mmol/l (normal range 3.5–5.2 mmol/l). Thyroid function tests were consistent with primary hyperthyroidism with thyroid stimulating hormone (TSH) <0.01 and Free T4 64.4 (normal range 10–21). ¹³¹Iodine thyroid uptake and scan studies supported Graves' disease as the underlying

aetiology of his hyperthyroidism (62% diffuse uptake at 24 h). Graves' disease was further confirmed by 4× elevated TSH receptor antibodies.

DIFFERENTIAL DIAGNOSIS

Hypokalaemia of any aetiology can cause weakness, and therefore common causes such as vomiting, diarrhoea and diuretic use should be ruled out in the history. TPP is, by definition, associated with hyperthyroidism and usually affects Asian males between the ages of 30 and 50. Hypokalaemic periodic paralysis, however, usually presents in Caucasian men before the age of 20 and is dominantly inherited with strong male penetrance. This latter clinical picture is therefore at times referred to as familial periodic paralysis. The presentation of the paralysis in either thyrotoxic or familial periodic paralysis is indistinguishable. They are precipitated by heavy carbohydrate loads, exercise or stress and may last from hours to days. Hyperkalaemic periodic paralysis, another autosomal-dominant channelopathy, has a similar clinical presentation; however attacks are triggered by fasting or potassium-rich food rather than carbohydrate. Potassium levels during an attack of hyperkalaemic periodic paralysis are high or normal.

TREATMENT

Emergent treatment with intravenous potassium in the emergency department resulted in complete resolution of symptoms. He was advised to temporarily avoid sweet snacks and carbohydrate-rich meals. Hyperthyroidism was treated initially with propranolol and propylthiouracil; once the patient achieved a stable euthyroid state he was offered radioiodine treatment for his Graves' disease.

OUTCOME AND FOLLOW-UP

There were no further episodes of paralysis after the initiation of medical therapy. Most importantly for the

patient, he was able to resume consumption of his favourite cola beverage.

DISCUSSION

TPP is a potentially lethal manifestation of hyperthyroidism resulting from a massive intracellular potassium shift. Its hallmarks are transient muscle weakness and hypokalaemia. TPP is relatively common in Asian men, affecting 13% of male thyrotoxic patients versus 0.17% female thyrotoxic patients in China.¹ The incidence in North America is much lower at 0.1–0.2% of thyrotoxic patients, with sporadic cases being reported in non-Asian populations.² Nearly half of all patients presenting with TPP do not have obvious symptoms related to hyperthyroidism.³

Aetiology

TPP can occur as a result of any cause of hyperthyroidism. Patients with TPP most frequently have Graves' disease as a cause of their hyperthyroidism although cases of TPP have also been reported in patients with toxic multinodular goitre, iodine-induced thyrotoxicosis, excessive thyroxine use, solitary toxic thyroid adenoma, lymphocytic thyroiditis, TSH-secreting pituitary adenoma and amiodarone-induced thyrotoxicosis.⁴

Pathophysiology

Muscle paralysis and serum hypokalaemia occur due to defective sodium and potassium transport across the myocyte cell membrane. In mammalian striated muscle cells, the Na⁺/K⁺-ATPase transporter is responsible for restoring the membrane resting potential after myocyte depolarisation. It accomplished this with the influx of 2 K⁺ in exchange for 3 Na⁺, resulting in net loss of positively charged intracellular ions. Thyroid hormones and catecholamines both increase the number and sensitivity of membrane Na⁺/K⁺-ATPase transporters.⁵ Hyperthyroidism and its associated sympathetic drive therefore increase Na⁺/K⁺-ATPase activity. In TPP this transporter activation is further increased to unusual levels and exceeds compensatory mechanisms resulting in significant serum potassium drops and clinical paralysis.⁶ Of particular relevance to our case, hyperinsulinaemia further augments Na⁺/K⁺-ATPase activity based on the observation that heavy carbohydrate loads trigger attacks of TPP.⁴ Accordingly, patients with TPP frequently have insulin resistance and thus exaggerated insulin release in response to carbohydrate loads compared with thyrotoxic patients without TPP.^{7 8}

It has been suggested that patients with TPP have a genetic predisposition towards Na⁺/K⁺-ATPase transporter dysregulation; however, studies have not yet revealed a compelling causative mutation in the Na⁺/K⁺-ATPase transporter sequence.^{3–5 9}

Clinical features

TPP usually occurs in patients between the ages of 20 and 40. Attacks most frequently occur in the evening and early hours of the morning.⁵ The most frequent triggers are heavy carbohydrate loads and rest after exercise. Other precipitating factors include alcohol, infection, trauma, menstruation and cold exposure. Weakness usually begins in the lower limbs with ascending progression, and proximal muscles are more affected than distal.

Although respiratory paralysis has been reported, it is rare.⁹ Ocular, bulbar, mental function and sensation are usually spared.^{3–5 9} If left untreated, attacks may last for up to 72 h.³

Biochemical features

The hallmark of TPP is serum hypokalaemia, which can be as low as 1.1 mmol/l.¹⁰ The severity of muscle weakness usually corresponds to the degree of hypokalaemia and resolves with its correction.⁴ Hypophosphataemia and hypomagnesaemia may be simultaneously present and are thought to be secondary to catecholamine-induced intracellular shifts of these ions as serum phosphate and magnesium levels correct without supplementation once paralysis has resolved.^{5 9}

Hypokalaemia may be severe enough to produce classic ECG changes such as prominent U waves. The distinct ECG features associated with TPP are sinus tachycardia (secondary to hyperthyroidism), high QRS voltages and Wenkebach anterioventricular block.³

Treatment

There are two stages in the treatment of TPP. In the acute stage, the goal of treatment is to relieve muscle paralysis and restore serum potassium levels. Potassium supplementation is controversial as rebound hyperkalaemia occurs frequently and has resulted in fatal dysrhythmia.^{3 11–13} Nonetheless, intravenous potassium replacement shortens the recovery time compared with patients who are not given supplementation.¹⁰ If given at all, the infusion rate of KCl should be less than 10 mmol/h and serum potassium levels should be checked frequently.¹² Propranolol, the non-selective β -blocker, has emerged as an alternative therapy in the acute setting. It acts to lower the β -adrenergic tone, thereby inhibiting the catecholamine-mediated potassium uptake into cells, overcoming an aspect of the underlying pathophysiology of TPP. Caution is again emphasised, as intravenous propranolol has been associated with rebound hyperkalaemia and resultant cardiac arrhythmias.³ In contrast, large oral doses of propranolol have been shown to ameliorate paralysis and normalise serum potassium without rebound hyperkalaemia in a study involving two cases.¹³ Despite the fact that propranolol has been used to treat TPP since the 1970's, no prospective case-control studies have been performed to evaluate its effectiveness or toxic effects.

The second component of management is aimed at the prevention of recurrent attacks and the treatment of hyperthyroidism. Paralysis does not occur in patients who have achieved a euthyroid state, regardless of the means.^{3 4 7} Therefore, potential triggers of paralytic episodes should be avoided until normal thyroid hormone levels are achieved. After the acute stage of management, a patient should be started on a regimen of propranolol and antithyroid medication in order to achieve rapid control of thyrotoxicosis.^{3 4} Depending on the underlying cause of hyperthyroidism radioiodine ablation or surgery may be considered as a definitive treatment.^{3 4 7} Acetazolamide, while being effective for the long-term treatment for familial periodic paralysis, should not be used in the management of TPP as it can precipitate attacks.^{3 9}

Learning points

- ▶ A history of preceding triggers, including a heavy carbohydrate load, exercise or stress, may be present prior to each paralytic event.
- ▶ Thyrotoxic patients who are also insulin resistant may have higher risk of developing thyrotoxic periodic paralysis (TPP).
- ▶ Over half of TPP cases do not have thyroid symptoms despite biochemical evidence of hyperthyroidism.
- ▶ Emergency potassium replacement during attacks should be slowly and cautiously administered to avoid harmful rebound hyperkalaemia.
- ▶ Correction of the underlying hyperthyroidism is curative for subsequent paralytic episodes.

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Competing interest None.

Patient consent Obtained.

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