

Thyrotoxic Periodic Paralysis: A Rare Case of Acute Lower Limb Weakness within the Western World

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Abstract

Thyrotoxic periodic paralysis (TPP) is characterised by weakness of skeletal muscles (predominantly of lower limbs) and is most common amongst the Asian population with the majority of cases reported in males and is triggered by exercise, high-carbohydrate meals or alcohol.

Here we present a 20 year old caucasian male who attended A&E with bilateral generalised lower limb weakness and an inability to mobilise, on a background of similar, milder episodes. There were no overt hyperthyroid symptoms and examination revealed a thyroid goitre and fine tremor. He was diagnosed and treated for TPP secondary to Graves' Disease, with resolution of his symptoms occurring once IV Potassium and Propranolol was given. He was discharged, however due to poor compliance re-attended A&E with similar symptoms. He was treated with a total Thyroidectomy and, to date, hasn't re-attended A&E with bilateral weakness of the lower limbs.

Because TPP is still considered rare within the western world and the symptoms of hyperthyroidism are often subtle within this group of patients, we recommend a careful history, examination and routine thyroid function tests (TFTs) with all patients who present with limb weakness and hypokalemia.

Keywords: *Thyroid Function Tests (TFTs); Thyrotoxic Periodic Paralysis; Acute Lower Limb Weakness*

Introduction

Periodic paralysis is predominantly an autosomal dominant disease relating to hypokalaemia. However, acquired hypokalemic periodic paralysis exacerbated by hyperthyroidism is termed Thyrotoxic Periodic Paralysis (TPP) [1]. TPP is generally characterised as weakness of the lower limbs with corresponding hypokalaemia and hyperthyroxinemia.

It is most common amongst the Asian population, predominantly those of chinese and japanese descent [2,3]. Because there is more propensity for the oriental population for TPP and is rarely found in caucasians, there seems to be a gap in knowledge amongst clinicians of the western world even though they know about the condition. 91% of TPP cases are reported in males [4], although the cause as to why remains unclear. Triggers include exercise, high-carbohydrate meals, stress, exposure to cold, menstruation or alcohol [4-6] and can be induced by a high glucose load, insulin or vigorous exercise [2,5,7].

Symptoms range from weakness, usually symmetrically of the lower limbs to isolated weakness within specific muscle groups; and from myalgia or stiffness to full paralysis of these muscles. Weakness of the respiratory muscles remain rare and strength recovers in reverse order of appearance with treatment [2,8,9]. Acute attacks usually last up to 96 hours [10]. Interestingly symptoms of hyperthyroidism are usually subtle within this group and therefore TPP can be under-diagnosed, leading to recurrent attacks [11].

Weakness is based on severity of potassium depletion [2,6], however paralysis has been recorded with normal potassium levels [12,13]. Additionally, TPP is often associated with hypophosphatemia and hypomagnesemia therefore a full electrolyte screen is advised on admission [8,14].

Case Report

A 20 year old caucasian male, with no known drug allergies or regular medications and a past medical history of Attention Deficit Hyperactivity Disorder (ADHD) and hypermobility presented to A&E with 6 episodes of ‘collapse’ over the past 12 hours, starting from 2pm on the same day, after eating a heavy lunch of spaghetti bolognese. He complained of multiple episodes of self-limiting, bilateral lower leg generalised weakness and painful thighs, leaving him unable to mobilise. He had several similar episodes previously, however, those were less severe and he remained mobile and therefore did not seek any medical attention.

Overall he was asymptomatic with no coryzal symptoms, fevers, pain, dyspnoea, vomiting, diarrhoea, urinary incontinence, bowel disturbance or constitutional symptoms. Additionally, he did not report any symptoms of hyperthyroidism including heat intolerance, palpitations, sweating or tremors. His family history included a sibling with Ehler Danlos Syndrome. However, no family members reported any hyperthyroid symptoms or periodic lower leg weakness. He denied smoking, illicit drug use or regular alcohol intake.

He was systemically well with examination revealing a heart rate of 101 beats/min regular, blood pressure of 99/52 mmHg, respiratory rate of 17 breaths per minute, oxygen saturation of 96% on air and a temperature of 36.7°C. BMI was 24. Neurological examination: cranial nerves normal: no abnormality of sensation, co-ordination or higher cortical functions. Power in upper limb was 5/5 whilst lower limb indicated hip and knee flexion of 3/5 bilaterally and hip and knee extension 4/5. Deep tendon reflexes were diminished. A fine tremor and mild goitre with no overt nodules were noted. There were no orbital features of thyroid eye disease or a thyroid bruit. The rest of the systemic examination was within normal limits.

Investigations included an initial venous blood gas which indicated normal pH. Laboratory bloods revealed serum potassium of 1.9 mmol/L (3.5 - 5.3 mmol/L). Other routine bloods were unremarkable including liver and renal function, sodium, magnesium and phosphate. Thyroid function tests were done in view of tachycardia with mild goitre and fine tremors which revealed TSH of 0.01 mUL/L (0.3 - 5.0 mUL/L), free T4: 43.7 pmol/L (7.9 - 16.0 pmol/L), free T3: 23.2 pmol/L (3.8 - 6.0 pmol/L) (Table 1). Anti-Thyroid Peroxidase antibodies: 539 IU/ml (< 9 IU/mL). The ECG on admission showed a sinus tachycardia with right bundle branch block, tachycardia-induced ST depression in V2 + V3. No Q waves were seen on the ECG. Thyroid Ultrasound indicated an ‘enlarged thyroid with increased vascularity and U2 nodules in both the right and left lobes’.

Date	Thyroid Stimulating Hormone (TSH) (0.3 - 5.0 mUL/L)	Free T4 (7.9 - 16.0 pmol/L)	Free T3 (3.8 - 6.0 pmol/L)	Potassium (3.5 - 5.3 mmol/L)
8/4/17	0.01	43.7	23.2	1.9
9/4/17	-	-	-	5.0
11/4/17	-	-	-	4.4
9/5/17	0.01	32.3	14.8	4.3
19/6/17	0.01	62.8	41.7	2.4
20/6/17	-	-	-	4.4
23/6/17	-	-	-	4.9
26/7/17	0.01	6.4	6	4.7
18/9/17	0.01	6.4	6	4.1
13/11/17	15.5	4.9	4.5	-
3/1/18	2	8.9	-	4.5
14/5/18	0.01	23.9	10.6	4.1
17/5/18	0.01	24.5	8.1	-
13/6/18	0.01	13.4	4.2	-
4/9/18	5.94	8.7	-	-
3/10/18	26.06	8.3	-	4.2
29/12/18	84.5	7.6	-	4.1
12/04/19	1.87	16.3	-	4.1

Table 1: Blood tests indicating TFTs and Potassium levels. TSH was initially low but rises post-thyroidectomy due to poor compliance with medications, before returning to within normal range. T4 and T3 indicates a negative correlation to TSH, initially being very high, before settling within normal range. Potassium was low on 2 occasions, requiring admission to hospital.

Due to the clinical history, thyroid goitre, sinus tachycardia and biochemical markers he was diagnosed with TPP secondary to Graves' disease. He was treated with intravenous potassium replacement, specifically 2 litres sodium chloride with 80 mmol potassium chloride (KCL) over 12 hours, at which point the weakness resolved and he was able to mobilise well. Carbimazole was initiated at 20 mg twice daily and propranolol at 80mg twice daily. He was discharged on oral potassium supplementation for 48 hours with aforementioned doses of carbimazole and propranolol along with blood tests in ambulatory clinic and outpatient endocrine clinic.

Due to poor compliance with medications, a second admission 2 months later was needed with further episodes of self-limiting, bilateral lower limb weakness and an inability to walk. Bloods confirmed hypokalemia with markedly raised free T4 and suppressed TSH (Table 1) and he was again treated with intravenous potassium replacement with good effect on his lower limb weakness. The importance of religiously complying with carbimazole was stressed and was once again prescribed at 20mg twice daily with propranolol 80 mg twice daily.

He received definitive treatment in the form of total thyroidectomy with subsequent maintenance Levothyroxine. He was initially prescribed Levothyroxine 100 mcg once a day, which was later up titrated to 150 mcg daily. He has, to date, not presented again with hypokalaemia and paraparesis following his surgery. At his final outpatient appointment, he was clinically euthyroid with TSH and T4 within normal ranges. He was therefore discharged from endocrinology outpatients.

Discussion

Even though Thyrotoxic periodic paralysis (TPP) itself is rare, it is most commonly seen in association with Graves disease. Women are commonly affected by Graves but TPP is mainly seen in men in their 2nd to 4th decade of life [8]. There is generally no family history of TPP, but the presence of certain HLA subtypes (for e.g. A2, B17, B5, DRw8) in some ethnic populations, especially Asian and Latino men, make them more susceptible to this condition [11]. The closest differential to TPP is Familial Periodic Paralysis (FPP) which is an autosomal dominant condition affecting both sexes equally and more common in caucasians with history of family members presenting with episodic lower limb weakness.

Clinical presentation

TPP is characterised by episodic weakness of muscles, more commonly of the lower limbs and proximal more than distal group. The weakness may be associated with some degree of muscle pain. The duration of each episode lasts from hours to days and varies greatly in terms of frequency. The bowel and bladder involvement has not been described during the episode however ocular muscle weakness may be seen. It is not clear whether the weakness of eye muscles is related thyrotoxicosis or TPP. Deep tendon reflexes are reduced or absent while sensation and higher cortical functions are spared [2,15]. Thyrotoxic signs of fever, tachycardia, moist skin, tremors, exophthalmos and goitre may be subtle. Blood investigations would show hypokalemia with thyroid functions suggestive of primary hyperthyroidism which predisposes the patient to serious dysrhythmias. Patients generally regain the muscle strength with treatment but they may end up with persistent muscle weakness overtime with repeated attacks [1].

Pathophysiology and triggers

The exact pathophysiology of TPP remains unclear as only approximately 2% of patients with hyperthyroidism go on to develop acute hypokalemic paralysis. However the severity of hypokalemia correlates with the level of paralysis and normalisation of potassium alleviates symptoms [16].

Shift of potassium into the cells is thought to be responsible for the muscle weakness seen during the episode of TPP. Any defect in any one of the many ion channels on the skeletal muscle could result in the muscle weakness and hence paralysis. TPP patients have been seen to have a higher activity of Na/K ATPase pump as compared to normal subjects. Catecholamine release increases the Na/K

ATPase activity potentially explaining the higher rates of attacks after exercise and during early mornings [7]. Exercise causes release of potassium from the intracellular space but during the rest period post exercise, there is an intracellular shift of potassium and this in addition to the catecholamine effect, results in TPP episode during the recovery phase of exercise. Foods high in carbohydrate content is also known to precipitate the attack of TPP. Insulin causes intracellular shift of potassium and when this is coupled with a defect in an ion channel, this would result in exaggerated shift of potassium into the cells, resulting in muscle weakness [7]. Androgens are also thought to be responsible for TPP as this condition is mostly found in men. Compared to women, men have more muscle to body mass ratio and this results in higher Na/K ATPase quantity in men making them more prone to attacks [7,17]. There are studies which showed elevated levels of testosterone in patients with TPP as well as case reports of patients with TPP noted to have adrenal adenomas with high levels of dehydroepiandrosterone and 17-hydroxyprogesterone [18,19]. Potassium channel Kir2.6 is expressed on the skeletal muscle and plays a vital role in stability of the membrane potential. This channel is unregulated by the thyroid hormone. Mutations in Kir2.6 gene would result in reduced outward potassium flow causing an impaired membrane depolarisation eventually resulting in muscle weakness [20].

Treatment: Despite a lack of national guidelines, traditional treatment of TPP has always been the rapid IV replacement of potassium due to the risk of arrhythmias, in addition to initiation of carbimazole and propranolol respectively for controlling hyperthyroid state. However there is growing concern regarding the risk of rebound hyperkalemia especially if more than 90 mmol of potassium is prescribed within a 24 hour period, with over 40% of patients experiencing this potentially fatal side-effect [8,21]. As a result there is a growing trend for minimal potassium replacement, with research indicating KCL supplementation should be less than 10 mmol/hr, unless cardiac arrhythmias require rapid replacement [22]. Additionally, the use of non-selective beta blockers e.g. propranolol as a first line treatment are being increasingly considered, with studies indicating successful treatment of TPP using either intravenous propranolol or oral (3 mg/kg) [14,22-24]. This had led to the resolution of all electrolyte abnormalities and symptoms, with no rebound hyperkalemia reported, within the space of several hours [8,14,24]. Prophylactic potassium supplementation has been found not to prevent acute attacks of limb weakness and therefore isn't used as a treatment option [25].

Differentials

The closest differential to TPP is Familial Periodic Paralysis (FPP) which is an autosomal dominant condition affecting both sexes equally and more common in caucasians with history of family members presenting with episodic lower limb weakness with hypokalemia. Other causes of hypokalemic periodic paralysis which are sporadic and not familial include barium poisoning [26], renal disorders which result in depletion of total body potassium secondary to renal potassium loss, endocrine disorders like primary hyperaldosteronism [27] causing potassium loss in urine and gastrointestinal loss of potassium due to gastroenteritis [28], tropical sprue [29] and malabsorption due to short bowel syndrome [30].

We believe there are certain clinical implications of TPP. First is that clinicians should not be biased by the fact that TPP is more commonly found in oriental ethnicity and should check for thyroid functions in all patients presenting with hypokalemic paralysis, even in non-oriental ethnicity. Second is that a definitive treatment should be undertaken in such cases sooner than later as they remain prone to develop severe hypokalemic paralysis in presence of hyperthyroxinemia. Our patient had compliance problems with the medications resulting in thyrotoxicosis and eventually symptomatic hypokalemic paralysis requiring a repeat admission to the hospital. And the final implication we believe is the patients' risk of hypokalemic paralysis remains higher than the general population if they develop hypokalemia due to any cause, given their previous predisposition for muscle weakness secondary to hypokalemia. Our index case remained non compliant even to thyroxine maintenance therapy post thyroidectomy (Table 1) but did not present with any limb weakness once his hyperthyroxinemia was cured. But does that mean he is not at risk of further episodes of hypokalemic periodic paralysis? A 10 year study of 135 TPP patients done by Sung et al^[6] did not report any recurrence of muscle weakness in patients who had curative treatment for hyperthyroidism but it did not mention if any of the 135 patients had hypokalemia and not develop any paralysis after receiving definitive treatment for their hyperthyroidism. We did not come across any case of recurrence of muscle weakness in TPP post thyroidectomy/ra-

dioiodine therapy within the literature search. However, we believe this requires further studies to quantify the actual risk of hypokalemic paralysis post treatment for hyperthyroidism.

Conclusion

Overall, paralytic attacks and generalised muscle weakness can occur due to hypokalemia, with triggers including heavy carbohydrate meals and strenuous activity. Although the weakness can vary, often the hyperthyroid symptoms are subtle, leading to a delay in diagnosis and management. As a result, TFTs are recommended to be checked in patients attending A&E with generalised weakness and hypokalemia, along with other electrolytes. Additionally, extra efforts must be made to explain the importance of compliance with medications and maintenance of euthyroidism to ensure resolution of symptoms. We recommend offering definitive treatment with thyroidectomy or radioiodine ablation early in the course of thyrotoxicosis especially if the control of hyperthyroid state is not achieved quickly.

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