Journal of Endocrinology, Metabolism and Diabetes of South Africa 2023; 28(2):72–75
https://doi.org/10.1080/16089677.2023.2170955

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

CASE REPORT

Thyrotoxic periodic paralysis: a presentation of hyperthyroidism increasing in frequency around the world

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Thyrotoxic periodic paralysis (TPP) is a complication of hyperthyroidism commonly seen in Asian populations. It presents as sudden-onset muscle paralysis and hypokalaemia. Diagnosis is often delayed due to the rarity of the disease, the subtlety of the hyperthyroidism and the fleeting nature of the clinical presentation. With global expansion, physicians outside Asia should be aware of this disease for early recognition and treatment as severe cardiac arrhythmias, which may prove fatal, can occur. Several breakthroughs have been made in identifying the pathophysiological mechanism resulting in the severe hypokalaemia, including mutations in the Kir2.6 channel, an inwardly rectifying potassium channel, which results in a massive intracellular potassium shift. Treating the underlying hyperthyroidism is the definitive treatment; however, beta blockers and potassium supplementation are vital in acute management of this condition. This is a report of a case seen in Cape Town, South Africa with a review of the literature regarding the clinical features, pathophysiology and treatment.

Keywords: thyrotoxic periodic paralysis, hypokalaemia, thyrotoxicosis

Introduction/background

Hypokaleamic periodic paralysis is a rare, yet fascinating medical emergency typically affecting otherwise healthy young patients who present with painless, severe muscle weakness. Periodic paralysis should initially be divided into those caused by potassium shifts versus true potassium losses. Once true potassium gastrointestinal or renal losses have been excluded, two distinct forms of either hereditary or acquired periodic paralysis are described.[1]

To date in Western countries, autosomal dominant hypokalaemic periodic paralysis is the more common presentation of the disease, affecting approximately 1 in 100 000 patients.[2] Mutations in voltage-gated sodium, potassium and calcium channels in the skeletal muscle membrane result in the clinical presentation of periodic paralysis with initial clinical presentations typically occurring in the first and second decades of life.[3]

In Asia, the acquired form of periodic paralysis secondary to thyrotoxicosis is far more common, with an incidence of approximately 2%.[4] Thyrotoxic periodic paralysis is often the first clinical presentation of hyperthyroidism in Asian populations; however, sporadic cases have been documented in Caucasians, Hispanics and African Americans.[4,12] Typically, primary autoimmune hyperthyroidism affects females more than males (female-to-male ratio 9:1); however, for reasons not yet established, thyrotoxic periodic paralysis more commonly affects males than females, with a male-to-female ratio of 26:1.[5] The average age of onset of thyrotoxic periodic paralysis is 20–40 years; this also coincides with the average age of onset of Graves' disease.[6–8]

With the rarity of this disease, particularly in the Western world, it is often misdiagnosed or overlooked, resulting in poor outcomes, although the exact mortality rate is not known.[5] With global expansion on the rise, it is expected that this disease will increase in frequency, rendering it imperative for physicians to be aware of it.

Case presentation

We present a 25-year-old male of Asian descent. He was previously well and had no history of prior hospital admissions. He reported a one-day history of progressive muscle weakness, which began in his lower extremities in the morning and progressed to involve all four limbs by the evening. Bowel and bladder function remained intact with no difficulty in breathing or swallowing reported. He had no family history of paralysis and no history of illicit drug or medication use. He denied any recent episodes of vomiting or diarrhoea. The patient did report a caffeine binge on the night prior to the attack of weakness. He had had no similar previous episodes of sudden muscle weakness.

His general examination was not remarkable. There were no features of lymphadenopathy, dehydration, or abnormal skin or hair changes. He also did not display any typical clinical features of hyperthyroidism, such as goitre or exophthalmos (more commonly seen in Graves' disease). He did not describe any weight loss, heat intolerance or palpitations, symptoms often reported by patients with hyperthyroidism.

His neurological examination revealed global weakness in all four limbs with proximal muscle groups being more affected than distal. Tone was noted to be reduced in all four limbs. Power was 0/5 proximally and 1/5 distally. He was unable to lift his head off the bed. Reflexes were diminished globally. Plantar response was flexor in both lower limbs. Sensation and proprioception were intact and the cranial nerves were not affected. Respiratory muscles, swallowing and bladder and bowel function were not affected. Examination of other organ systems was unremarkable.

A point-of-care blood gas was performed, which revealed a severe hypokalaemia with a potassium of 1.4 mmol/l (3.5–5.5 mmol/l), a normal pH and no evidence of metabolic acidosis.

ECG showed a sinus arrythmia with premature atrial beats (Figure 1). There was also an impression of lateral ST depression of less than 1 mm.

First-line treatment

A potassium chloride infusion was initiated in the Emergency Centre at a rate of 15 mmol/hour while awaiting further workup for the acute paralysis and profound hypokalaemia.

Blood results later revealed that the patient had hyperthyroidism with a TSH of < 0.01 mIU/l (0.27–4.20 mIU/l), a T4 of 87.5 pmol/l (12.0–22.0 pmol/l) and a T3 of 21.7 pmol/l (3.1–6.8 pmol/l). His formal electrolytes were also found to be deranged and confirmed the point-of-care blood gas findings: sodium = 142 mmol/l (136–145 mmol/l); potassium = 1.7 mmol/l (3.5–5.1 mmol/l); calcium = 2.63 mmol/l (2.15–2.50 mmol/l); magnesium = 0.85 mmol/l (0.63–1.05 mmol/l) and phosphate = 0.62 mmol/l (0.78–1.42 mmol/l). Creatine kinase was only mildly elevated at 248 U/l (20–200 U/l). Further workup confirmed the presence of TSH receptor antibodies with a level of 5.82 U/l (< 1.8 U/l). The patient's final diagnosis was thyrotoxic periodic paralysis precipitated by newly diagnosed Graves' disease.

He was treated with potassium supplementation, carbimazole and propranolol. In total, he received 180 mmol of potassium chloride IVI over 18 hours; no oral potassium was given. Once the potassium had corrected, his fluids were changed to Ringer's lactate at 100 ml/hour. His potassium on discharge was 4.5 mmol/l. In addition, 6 g of magnesium sulphate was administered IVI over the initial 18-hour period. His tetraplegia resolved within 24 hours of treatment initiation and the patient was able to mobilise around the ward freely. He was discharged with follow-up at the endocrinology department for possible iodine treatment. His discharge doses of propranolol and carbimazole were 10 mg per os 8 hourly, and 20 mg per os daily, respectively.

The patient continues to follow up with the department of endocrinology. He declined radioactive iodine therapy and now receives 5 mg of carbimazole per os daily. His latest thyroid function tests have almost normalised with a TSH of 5.16, T4 of 14.5 and T3 of 5.0. To the authors' knowledge, he has had no further episodes of weakness since initiating treatment of his hyperthyroidism.

History

The combined presentation of muscle weakness and hyperthyroidism was first described in the literature in 1902.[5] It was later described by the Mayo Clinic in the English-language literature in 1931, where patients were noted to have resolution of their paralysis with treatment of the hyperthyroidism and relapse of the paralysis upon relapse of the hyperthyroidism.[9] Since then, evidence shows that the degree of hypokalaemia is proportional to the severity of the paralysis.[10]

Pathogenesis

The true pathogenesis of thyrotoxic periodic paralysis has largely remained uncertain. Severe acute hypokalaemia is the main laboratory finding with the severity of hypokalaemia being directly proportional to the severity of the paralysis. Normalisation of serum potassium levels leads to resolution of the muscle weakness. Skeletal muscle holds the largest proportion of total body potassium stores, thus playing a vital role in extracellular potassium homeostasis.[4] Hypokalaemia in the setting of thyrotoxicosis occurs due to a transcellular potassium shift, from the extracellular into the intracellular (mainly muscle) compartment. There is no true potassium deficit. The main access points for potassium movement in skeletal muscle include the Na/K ATPase and K^+ channels, as well as inward-rectifying potassium channels (Kir) and delayed rectifying potassium channels – all of which are stringent in maintaining extracellular potassium homeostasis.[11]

The importance of potassium myocyte efflux on extracellular potassium homeostasis is demonstrated by patients with barium poisoning developing severe hypokalaemia and muscle paralysis as barium inhibits skeletal muscle potassium channels.[4,11]

The significance of Na/K ATPase pumps in the pathogenesis of thyrotoxic periodic paralysis is established by the observation that activity of the pump is significantly increased. Thyroid hormone can stimulate Na/K ATPase pumps by binding to thyroid hormone response elements, thus upregulating the transcription of genes encoding Na/K ATPase. Thyroid hormone can also promote insertion of the pump into the membrane.[4]

Hyperinsulinaemia is also seen in patients with symptomatic thyrotoxic periodic paralysis. Insulin induces cellular potassium shifts by stimulating the membrane insertion of Na/K ATPase as well as increasing the intrinsic activity.[4] This effect lends explanation to the observation of a high carbohydrate meal precipitating an episode of acute paralysis. Rest after exercise has also been shown to precipitate hypokalaemia due to the promotion of potassium influx into skeletal cells.[14] Hyperthyroidism is also known to stimulate a B-adrenergic response, which increases cAMP production; this in turn stimulates Na/K ATPase pump activity in skeletal muscle. Sympathetic activity also stimulates insulin release from B cells in the pancreas, further exacerbating the hyperinsulinaemia. These combined effects help to describe the rationale of beta-blocker use in thyrotoxic periodic paralysis-induced hypokaleamia.[4,11,12]

This being said, Na/K ATPase activity cannot be the only mechanism resulting in thyrotoxic periodic paralysis as only approximately 2% of patients with hyperthyroidism develop periodic paralysis. The increased Na/K ATPase activity can also be compensated for by increased potassium efflux, thus maintaining extracellular potassium homeostasis and limiting the degree of hypokalaemia. This would imply that additional factors, such as diminished potassium efflux, would need to be affected for clinically significant hypokalaemia to occur.[4]

Several observations have been made which suggest a genetic predisposition, including the more frequent occurrence in those of Asian descent.[12] The clinical similarity between familial hypokalaemic periodic paralysis and thyrotoxic periodic paralysis resulted in the initial evaluation of candidate genes that were known to cause familial hypokalaemic periodic paralysis. These included the voltage gated calcium channel $Ca_v1.1$ ($CACNA_1S$), the skeletal sodium channel $Na_v1.4$ (SCN_4A) and the inward rectifier potassium channel Kir2.1 ($KCNJ_2$).[5,13,14] No mutations in the aforementioned genes have been found in patients with thyrotoxic periodic paralysis.[15,16]

Numerous studies have shown decreased Kir activity in patients with both familial and thyrotoxic periodic paralysis.[4] Mutations in the gene encoding Kir2.6 (a skeletal-muscle-specific Kir channel) were associated with thyrotoxic periodic paralysis

and predisposed patients to paralytic episodes. The prevalence of this has been shown to be as high as 33%.[17]

Thyroid hormone, through upstream thyroid hormone response elements in the promotor region of the gene, also upregulates transcription of Kir2.6. Further studies have found loss of function mutations in Kir2.6 channels in patients with both familial and thyrotoxic periodic paralysis.[18] It is thus suggested that loss of Kir2.6 function, combined with increased Na/K ATPase activity, may trigger a feed-forward cycle of hypokalaemia.

Decreased inward currents of potassium predispose the sarcolemma to paradoxical depolarisation, resulting in inactivation of sodium channels and thus muscle inexcitability.[4,17–19] The Kir2.6 mutation has been found in only approximately 30% of patients, none of whom were of Thai or Chinese descent. Thus, the majority of patients with thyrotoxic periodic paralysis have as yet unidentified disease-causing mutations.[17] Further genome-wide association studies have shown several genetic variants that affect Kir expression to be associated with thyrotoxic periodic paralysis, particularly in patients of Chinese and Korean descent, implying that inward-rectifier potassium channels play a vital role in the predisposition of this disease.[5,20]

Overall, there is compelling support for the genetic mutations in the Kir2.6 potassium channel resulting in loss of its function, combined with increased activity of Na/K ATPase to be the cause of a positive feed-forward cycle of hypokalaemia, leading to paradoxical depolarisation with resultant sodium channel inactivation and, hence, muscle inexcitability with eventual clinical paralysis.[4,19]

Clinical features

Thyrotoxic periodic paralysis only occurs during the state of thyrotoxicosis and resolves with resolution of the thyrotoxicosis. A prodrome of muscle cramping, stiffness and weakness has been reported with features occurring one hour to three days prior to paralysis.[21] Weakness usually begins in the proximal muscles of the lower extremities and may progress to all four limbs, in some cases resulting in complete flaccid paralysis.[12] The degree of weakness is proportional to the severity of the hypokalaemia.[5] There have been no correlations discovered between serum T3 and T4 levels and the degree of paralysis. Respiration, swallowing, bowel and bladder function and facial expression are usually not affected.[5,21] Deep tendon reflexes are diminished or absent while sensation and level of consciousness are preserved.[7] The episodes of weakness can last from a few hours to up to three days.[12] Episodes of weakness tend to recur with the recurrence of hyperthyroidism (most commonly due to cessation of treatment).[7]

A precipitating factor for the attack is often found; these include alcohol binges, high carbohydrate intake, infection, caffeine excess and B2-adrenergic bronchodilators. Glucose loading was noted to precipitate an attack in a minority of subjects. Episodes usually occur in the mornings of warmer seasons.[5,22,23]

The clinical features of thyrotoxicosis, such as tachycardia, exophthalmos, goitre, warm skin etc., can be very subtle and are often missed in the initial examination.[7]

Laboratory results include a very low serum potassium level without any acid-base disturbance.[21,22] Renal excretion of potassium is also low, thus excluding renal potassium wasting. A high urinary calcium-to-phosphate ratio has been proposed to distinguish thyrotoxic periodic paralysis patients from those with familial hypokalaemic periodic paralysis.[5] Suppressed thyroid stimulating hormone levels with raised T3 and T4 levels are pathognomonic of the disease. Unsurprisingly, Graves' disease is most commonly diagnosed in patients with thyrotoxic periodic paralysis; however, thyroiditis, toxic multinodular goitre and TSH-producing pituitary tumours have also been reported.[21,22,24] The ECG may show U-waves, prolonged PR interval and both supraventricular and ventricular ectopic beats. The risk for life-threatening ventricular tachycardias or fibrillation remains high until the hypokalaemia is corrected.[25,26]

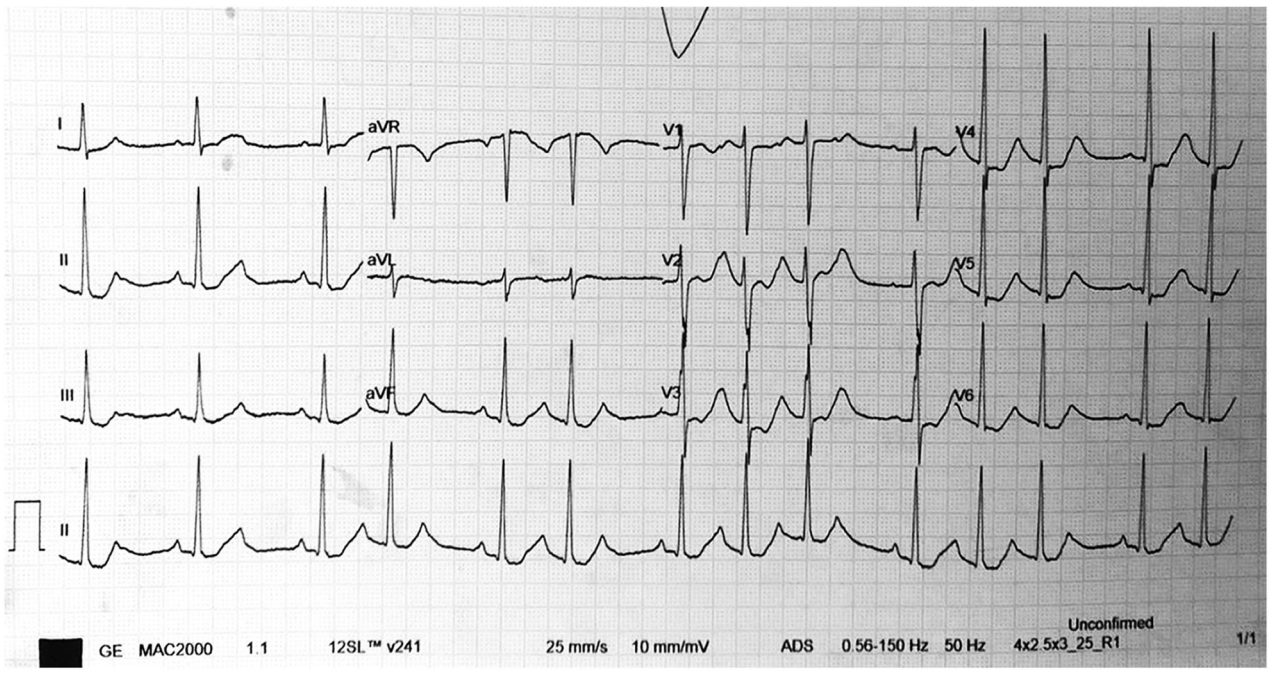

Figure 1: ECG showing a sinus arrythmia with premature atrial beats

Treatment/management

Initial treatment should be aimed at correction of the hypokalaemia to prevent life-threatening complications, such as cardiac arrythmias. Some studies have demonstrated that potassium supplementation shortens the recovery period of the paralysis.[27] However, it remains imperative to remember that potassium stores are in fact normal, and aggressive potassium supplementation can result in rebound hyperkalaemia. This has been shown to occur in 40–60% of cases.[20,25] Low-dose potassium supplementation of up to 20 mmol/hour is, therefore, recommended, unless there are serious life-threatening cardiac complications.[5]

Propranolol has been shown to normalise potassium levels within two hours without any rebound hyperkalaemia by reversing the adrenergic stimulation of Na/K ATPase activity. It has also been shown to decrease the conversion of T4 to T3 in the liver, thereby reducing circulating T3 levels.[5,7]

The definitive treatment, however, remains treatment of the hyperthyroidism. The use of radioactive ablation or surgery is preferred, as the use of medical therapy is more likely to be associated with a relapse, especially during withdrawal or tapering of medication.[5] Propranolol should be continued until a euthyroid state is achieved and precipitants should be avoided.[5,7]

Conclusion

Periodic paralysis should be considered in patients with sudden-onset paralysis and hypokalaemia. Thyrotoxicosis is a rare form of acquired periodic paralysis that is no longer confined to Asian populations due to global expansion. Clinicians should have a high index of suspicion for this diagnosis as the signs and symptoms of thyrotoxicosis are often subtle. If left untreated, hypokalaemia is likely to recur and may result in grave cardiac arrythmias. Treatment includes potassium supplementation and the use of non-selective beta blockers, such as propranolol. Definitive treatment remains the management of the underlying hyperthyroidism. Due to the potassium shift and no true potassium losses, regular serum potassium levels should be checked during supplementation to avoid rebound hyperkalaemia. Clinicians should also guard against aggressive potassium supplementation. With the expansion of globalisation, clinicians are more likely to encounter thyrotoxic periodic paralysis in all corners of the globe; awareness of this condition is thus imperative.

Disclosure statement – No potential conflict of interest was reported by the author(s).

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Received: 9-08-2022 Accepted: 18-01-2023