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Caso Clínico

Hypokalemic Periodic Paralysis: Extreme Muscle Weakness Secondary to Hyperthyroidism

Mariana Fernandes Ornelas [a,*]; Eduarda Resende [a]; Pedro Gouveia [a]; Maritza Sá [a]; Margarida Ferreira [a]

[a] *Serviço de Endocrinologia / Hospital Central do Funchal, Funchal, Madeira, Portugal*

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A B S T R A C T

Acute muscle weakness may be a challenging diagnosis in the clinical setting. At the emergency department, recurrent paralysis associated with low potassium levels should raise the clinical suspicion of hypokalemic periodic paralysis. A 33-year-old Caucasian male with history of uncontrolled Grave's disease was admitted to the Emergency Department early in the morning with acute onset of symmetrical weakness and myalgias of the lower limbs that progressed to the upper limbs after intense physical exercise. The patient had no family history of hypokalemic paralysis. Admission laboratorial results demonstrated a severe hypokalemia (K+ 1.9 mEq/L) and hyperthyroidism, leading to clinical suspicion of thyrotoxic periodic paralysis. He was treated with intravenous potassium supplementation. This rare condition is underrecognized in the western countries and demands a high index suspicion.

Palavras-chave:
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Paralisia Periódica Hipocaliémica: Fraqueza Muscular Excessiva Secundária ao Hipertiroidismo

R E S U M O

A paralisia muscular aguda pode constituir-se como um diagnóstico clínico desafiante. Esta patologia deverá levantar a suspeita de paralisia periódica hipocalémica quando recorrente e associada a hipocalémia. O presente caso refere-se a um doente caucasiano com 33 anos e antecedentes pessoais de doença de Graves não controlada. Recorreu ao serviço de urgência por início súbito de paralisia simétrica e mialgias dos membros inferiores que progrediu para os membros superiores após realização de exercício físico intenso. Negava antecedentes familiares de paralisia hipocalémica. O estudo analítico à admissão revelou hipocalémia grave (K+ 1,9 mEq/L) e hipertiroidismo levantando a hipótese diagnóstica de paralisia periódica tireotóxica. Iniciou imediatamente suplementação endovenosa com cloreto de potássio, registando-se posteriormente normalização dos níveis de potássio. Esta condição é rara, subdiagnosticada em países ocidentais e requer um alto índice de suspeição.

* Autor Correspondente / Corresponding Author.
E-Mail: mariana_f_ornelas@hotmail.com (Mariana Ornelas)
Hospital dos Marmeleiros, Estrada dos Marmeleiros, 9050-495 Monte, Portugal

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Introduction

Muscle weakness is a nonspecific symptom that comprises an extensive differential diagnosis since any level of the neuromuscular pathway might be affected. Several etiologies as neurologic, myopathic, infections, genetic, drugs, toxins and electrolyte disturbances, are pointed as possible etiologies.[1] Periodic paralyses (PP) encompass a group of rare neuromuscular disorders characterized by sudden and severe episodes of muscle weakness associated with serum potassium levels variations (hyperkalemia and hypokalemia).[2] As the designation suggests, hypokalemic paralysis (HP) occurs secondary to low serum potassium levels. Most of these conditions are hereditary, usually with an autosomal dominant inheritance pattern. Nevertheless, there are other rarer acquired etiologies described such as thyrotoxic periodic paralysis (TPP) and paralyses secondary to permanent serum potassium levels changes. Graves' disease (GD) is the most common TPP etiology although essentially any cause of thyrotoxicosis may originate TPP. Some iatrogenic cases with levothyroxine therapy have been reported.[3-6] GD is an autoimmune thyroid disorder characterized by the presence of stimulatory circulating antibodies targeted to thyroid-stimulating hormone receptors (TSHR-Ab), causing thyroid hyperplasia and unregulated thyroid hormone synthesis with hyperthyroidism. TSHR-AB measurement is useful to confirm this diagnosis. Treatment involves symptoms amelioration with beta-adrenergic blockade and correction of thyrotoxic state with the use of antithyroid drugs (ATD) or definitive therapies (DT) - radioactive iodine (RAI) or surgery. Newly diagnosed GD patients are usually treated for 12–18 months with ATD and methimazole is the preferred drug. After an ATD course, DT may be considered if there is drug intolerance or noncompliance, maintenance of positive TSHR-AB or documented hyperthyroidism relapse.[7] Ultimately, PP may present as a medical emergency and prompt recognition of GD as a possible etiology is crucial for its effective management.[1,2]

Case Report

A 33-year-old Caucasian male with past medical history of asthma was followed in Endocrinology department for GD for 19 years. In the first years of medical therapy, he was treated with propylthiouracil (PTU), which was then GD first line agent. Due to his personal history of uncontrolled asthma, a beta-blocker was not prescribed. After two years of treatment, he had reached euthyroidism and negative TSHR-Ab levels and PTU was discontinued. Nevertheless, a GD relapse was documented soon after treatment discontinuation and PTU was reintroduced. After euthyroidism achievement, the patient was proposed for DT (RAI ablation/thyroidectomy) which he had refused. Thus, he was maintained on PTU therapy; nonetheless, he developed a secondary ANCA-associated small vessel vasculitis and medical therapy has been switched to methimazole. Despite being advised to take the medication continuously, he took it irregularly and so, his thyroid function fluctuated between euthyroidism and thyrotoxicosis along clinical follow-up. Some years later, the patient presented to the Emergency Department (ED) early in the morning with sudden onset of muscular weakness and intense myalgias of proximal muscles of lower and upper limbs. The symptoms started 2 days before, following strenuous physical exercise. He reported symmetrical lower limb weakness with posterior progression to upper limbs, denied other neurologic, ocular or pain symptoms and maintained the ability to urinate. The patient also referred similar complaints three years before. It should be underlined that methimazole dose had been adjusted to 30mg/day due to hyperthyroidism persistence in the previous week (TSH 0.06 uUI/mL [0.5 – 4.7], free T4 1.8 ng/dL [0.6 – 1.7]). Physical examination at admission revealed apyrexia, normal blood pressure (128/74 mmHg) and tachycardia (heart rate of 106 bpm). He also presented with discrete orbitopathy (clinical activity score < 3), large diffuse goiter, discrete temblor of the hands, moist and warm skin. He had flaccid weakness of lower and upper limbs and deep tendon hyporeflexia with preserved sensation. Blood analysis are listed in Table 1 and were compatible with thyrotoxicosis (supressed TSH level and high free T4 level) despite the antithyroid drug use, and severe hypokalemia (1.9 mEq/L) without history of vomiting, diarrhoea, laxative or diuretic use. The renal function and urinary potassium excretion were normal. Electrocardiogram revealed sinus tachycardia. The patient initiated immediately intravenous potassium reposition. However, the next day he presented with rebound hyperkalemia (5.6 mEq/L) and the potassium perfusion was stopped with posterior normalization of potassium levels. He also started a low carbohydrate/salt diet to prevent further crisis. The muscular weakness resolved completely within a few hours. The diagnosis of thyrotoxic periodic paralysis was suspected considering the clinical signs of abrupt myalgias, proximal muscle weakness of the limbs, hypokalemia, and thyrotoxicosis, in the absence of familiar history of hypokalemic paralysis. After clinical and biochemical stability, he was discharged with methimazole 30 mg/day. The patient's clinical file review revealed a previous episode of transient flaccid quadriplegia and low potassium levels (2.9 mEq/L) that rapidly normalized with potassium supplementation. By that time, he had been assessed by the Neurology department that excluded other neurologic diseases, namely Guillain-Barré syndrome. Later, in the same month of this occurrence, his blood analysis revealed hyperthyroidism, but TPP was not suspected then. During follow-up, it was again discussed with the patient a DT, and he finally agreed with a total thyroidectomy. There were no further muscular symptoms after surgery.

Discussion

This clinical case emphasizes recurrent muscle weakness associated with severe hypokalemia and thyrotoxicosis in a Caucasian male patient without PP familiar history. The hypokalemia differential diagnosis should begin with the type of potassium imbalance distinction, that mainly occurs secondary to potassium intracellular shift or renal/gastrointestinal losses. Particularly in this case, the absence of objective potassium losses and the fast hypokalemia correction associated with rebound hyperkalemia pointed to intracellular potassium shift. There are multiple causes underlying this

Table 1. Admission blood analysis.

Analyte	Value	Laboratorial reference range
TSH (uUI/mL)	0.07	0.5 – 4.7
Free T4 (ng/dL)	3.2	0.6 – 1.7
Potassium (mEq/L)	1.9	3.5-5.1

The admission blood analyses were compatible with thyrotoxicosis (supressed TSH level and high free T4 level) despite the antithyroid drug and also presented a severe hypokalemia.

hypokalemia mechanism including presence of alkalemia, insulin use and beta-adrenergic stimulation that were all excluded.[8] Thyrotoxicosis is a potentially reversible cause of PP predominantly reported in males aged between 20-40 years, albeit hyperthyroidism is commonly seen in female gender.[9] TPP is mostly described among Asian individuals with reported incidence of 2%, and it is ten times more frequent comparing to western populations (with reported incidence of 0.2% in North American males). Therefore, it may be difficult to recognize this condition in the latter population where it is often misdiagnosed.[3,10] Nevertheless, the incidence seems to be rising in the West due to globalization and immigration. TPP pathogenesis is not fully understood and the prevailing theories include sodium-potassium adenosine triphosphates (Na-K ATPase) pump hyperactivity and mutations in genes encoding Kir channels primarily expressed in the skeletal muscle.[4] Relatively to Na^+ K^+ ATPase, it has been reported a significantly higher pump number and activity in these patients presumably potentiated by thyroid hormones excess, compared to healthy subjects or thyrotoxic patients without PP.[10] On the other hand, 25%-33% of unrelated TPP patients had loss-of-function mutations in an inwardly rectifying potassium channel - Kir 2.611; this channel allows potassium to move more easily into rather than out of the cell and its transcription appears to be upregulated by thyroid hormone.[4,11,12] The dual hits of increased intracellular potassium influx from activated Na^+ K^+ ATPase and decreased potassium efflux from defective Kir channels potentiates the serum hypokalemia with subsequent muscular weakness, paralysis and myalgias.[4,10,13,14] There are several important triggering factors that exacerbate potassium intracellular shift. Alongside thyroid hormone excess, the hyperadrenergic state induced by hyperthyroidism, hyperinsulinism and androgens may enhance Na^+ K^+ ATPase activity; this supports the male gender preponderance of the disease.[7;9] Other precipitating factors described are salt intake excess, stress (trauma, surgery, emotional, rest after strenuous exercise, infections, cold exposure) and drugs (alcohol, ecstasy, diuretics, estrogens, epinephrine, laxatives, corticosteroids, non-steroidal anti-inflammatory drugs, antiretroviral therapy, interferon-alpha, licorice, fluoroquinolones, aminoglycosides and amphotericin B).[4,10,13,15] Thus, the resultant episodic hypokalemia is explained by the association of an acute stimulus with the underlying hyperthyroidism.[10] Attacks typically occur early in the morning due to the increased sympathetic tone, after strenuous exercise or hyperinsulinism due to high carbohydrate intake.[9,15] Muscular weakness may range from minor weakness to quadriplegia/total flaccid paralysis and rarely with respiratory musculature involvement. TPP initially involves the lower limbs and tendentially progresses to girdle and upper limbs, with more severe proximal muscular involvement rather than distal.[4,13] Bulbar, respiratory, and ocular muscles are usually preserved as well as bowel and bladder function, consistent with patient's findings. The patient presented with absent deep tendon reflexes, a typical TPP feature.[10,15] Acute symptoms are usually temporary and may spontaneously resolve within a few hours to two days, even without potassium chloride supplementation.[15] This resolution is explained by potassium cellular efflux that restores potassium serum levels, rather than a total body potassium depletion.[10] However, TPP may present with life-threatening complications namely respiratory insufficiency, cardiac arrhythmias and death if not promptly diagnosed and treated.[3-5] Hyperthyroidism symptoms are often mild or clinically undetectable[3] and nearly half of thyrotoxic patients have no obvious symptomology. The thyroid gland may be enlarged but Graves ophthalmopathy is not usually present.[15]

Important laboratorial findings for TPP diagnosis during the acute episode comprise both hypokalemia (potassium levels generally below 3 mEq/L) and hyperthyroidism (elevated free T3 and T4 levels and low thyrotropin).[9] Between the attacks, potassium serum levels are normal, which distinguishes periodic paralysis from other causes of hypokalemic paralysis.[10] Importantly, the clinical or biochemical hyperthyroidism severity does not correlate with hypokalemia degree or episodes of paralysis.[3,10] Other ionic disturbs such as hypophosphatemia and mild hypomagnesemia may associate with this condition and contribute to the muscular paralysis.[6] The ECG presented sinus tachycardia that is attributable to the hyperadrenergic state. Other possible findings are ST depression and U waves secondary to hypokalemia, and a paradoxically prolonged PR interval due to the thyrotoxicosis.[10] TPP is often confused with familial hypokalemic periodic paralysis (FHPP) due to its clinical similarity. However, they are differentiated by absence of familiar history, later onset of presentation (FHPP usually presents before 20 years old) and thyrotoxic clinical and biochemical findings in TPP.[4,10,15] Other muscular disorders like myasthenia gravis, Guillain Barre syndrome, transverse myelitis, botulism, tick paralysis should also be ruled out when patients present with acute muscle weakness.[4] TPP acute phase treatment includes immediate potassium chloride supplementation and non-selective beta-blockers administration.[5,13] Potassium chloride supplementation may be given orally and/or intravenously to normalize the plasma potassium concentration instead of repairing a potassium deficit with the aim to prevent cardiac arrhythmia and respiratory arrest.[15] The dose varies according to the hypokalemia severity and can be titrated according to renal function and cardiovascular status.[9,13] Nevertheless, it cannot prevent acute paralysis if given between attacks.[9] Overly aggressive treatment with potassium can result in rebound hyperkalemia since it shifts to the extracellular space as the acute attack ceases. Manoukian *et al* reported rebound hyperkalemia in approximately 40% of patients with TPP, especially if more than 90 mEq of potassium chloride was given within 24 hours.[6] It is recommended serial potassium levels monitoring during management to prevent this hazard.[9;6] In turn, non-selective beta-blockade prevents intracellular potassium shift and may ameliorate and prevent subsequent paralytic attacks.[13] Specifically in this case, a beta-blocker was not administered given the patient's medical history of unmedicated asthma and its potential to worsening this condition. Other preventive measures that may be effective are low-carbohydrate diet implementation, potassium-sparing diuretics use and avoiding precipitating factors.[9,10] The key in TPP management is to achieve euthyroidism[3] and it can be accomplished by antithyroid drugs, RAI or thyroidectomy, depending on the etiology and patient's functional status. Once euthyroidism is reestablished, periodic paralysis recurrence ceases.[15] Attending to the chronic history of GD complicated with a pANCA vasculitis secondary to PTU, a definitive therapy as surgery or RAI were the most suitable definitive options to achieve euthyroidism.

Conclusion

TPP is frequently dismissed in the hospital setting since its rarity in western populations and absence of obvious hyperthyroidism symptoms in many thyrotoxic patients. Unrecognition of this condition may lead to improper management and fatal neuromuscular and cardiovascular events that would be easily preventable. The manifestation of an acute hypokalemic paralysis should raise the clinical suspicion of TPP as a cause and promptly evaluate

thyroid function. This case also highlights the importance of serial potassium levels monitoring to prevent rebound hyperkalemia, a potential hazard of aggressive potassium administration.

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MO and ER: Conceptualization, data collection, writing original draft.
PG, MS and MF: Supervision and review.
All authors approved the final version.

MO e ER: Conceptualização, recolha de dados, redação do projeto original.
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