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Thyrotoxic periodic paralysis in new-onset hyperthyroidism – a case report and review of the literature

Paralisia periódica tireotóxica em hipertireoidismo recém-diagnosticado – um relato de caso e revisão da literatura

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Abstract
Background: *Thyrotoxic periodic paralysis (TPP) is a rare condition related to hyperthyroidism, with specific clinical and physiopathological features.* ***Objective:*** *Discussion of a case report of a patient that develops TPP with no previous history of thyroid illness.* ***Methodology:*** *Retrospective analysis of medical record of a patient that developed TPP.* ***Results:*** *The study of this case report highlights semiological characteristics that can help Emergency physicians to suspect of this condition. At the text, we also review the recent articles about TPP, with focus on the molecular basis of ion channelopathies and predisposing factors, and discuss the therapeutic approach at acute phase of TPP and prevention of crisis recurrence.* ***Conclusion:*** *The authors suggest that any patient that has a sudden muscle weakness associated with serum potassium abnormalities should be screened to hyperthyroidism.*
Keywords: *Hyperthyroidism, Thyrotoxic Crisis, Hypokalemic Periodic Paralysis*

Resumo
Introdução: A paralisia periódica tireotóxica (PPT) é uma condição rara relacionada com o hipertireoidismo, com características clínicas e fisiopatológicas peculiares. **Objetivo:** Apresentação do caso clínico de um paciente acometido com PPT, em contexto de ausência de histórico prévio de patologias tireoidianas. **Metodologia:** Revisão retrospectiva de prontuário de paciente acometido com PPT. **Resultados:** O estudo do caso ressalta aspectos semiológicos que podem ajudar na suspeita clínica para aqueles profissionais que atuam em serviços de Emergência. O texto também traz uma revisão sobre os principais artigos recentes sobre PPT, com foco nos aspectos moleculares relacionados às canalopatias iônicas e fatores predisponentes, bem como na adequada abordagem terapêutica nos quadros agudos e na prevenção da recorrência das crises. **Conclusão:** Os autores sugerem que todo paciente com fraqueza muscular aguda associada a distúrbios do potássio sérico deve ser rastreado para hipertireoidismo.
Palavras-chave: Hipertireoidismo, Crise Tireotóxica, Paralisia Periódica Hipopotassêmica

INTRODUCTION

Hyperthyroidism is defined by the excess of production and release of thyroid hormones by the thyroid gland[1]. The term "thyrotoxicosis" is used to describe the spectrum of signs and symptoms related to excessive circulating thyroid hormones, secondary to hyperthyroidism or due to other causes. The typical clinical features of thyrotoxicosis usually includes tachycardia, involuntary weight loss, anxiety and irritability, tremor (usually a fine trembling in hands and fingers), sweating, increased sensitivity to heat and, specifically in the autoimmune hyperthyroidism (Graves' disease), ocular proptosis (bulging of the eye anteriorly out of the orbit).

The thyrotoxic periodic paralysis (TPP) represents a rare complication of hyperthyroidism, regardless of etiologic origin of the disease that carries a high risk of severe complications, and sometimes death[2]. This disorder is characterized by an acute-onset muscular weakness related to markedly electrolyte disturbances. In this article, we report a case of thyrotoxic periodic paralysis in a male patient with no previous history of thyroid illness, discussing some clinical and molecular aspects that could help clinicians in the management of this syndrome.

CASE REPORT

A 48-years-old Caucasian man was admitted at the Emergency Care Unit of a General Hospital (Portuguese Hospital, Salvador, Brazil) reporting a sudden muscular weakness, more intense at limbs (arms and legs). Initially, he was assisted by a Home Care Team, that have transferred the patient to the Hospital. He reported no history of chronic illness or continuous use of medications; irregularly he have been taken some multivitamins (Centrum®). He has denied drug abuse or alcohols consume in the past days, no history of smoking, but have pointed regular intake of sugar drinks (about 3 liters of sugar-rich cola drinks per day). When asked about thyroid illness, he reported no personal history but his

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sister had hyperthyroidism secondary to Graves' disease some years ago, and was successfully treated with radioiodine.

At admission, he had normal blood pressure (110/70 mmHg), a normal-high resting pulse rate (95 beats per minute), and a respiratory rate of 22 incursions per minute. On physical examination, the main finding was a loss of muscular strength at legs (grade 1/5) and arms (grade 2/5). The laboratorial profile have showed an important hypokalemia (1.7 mmol/L, normal range 3.5-5.1 mmol/L), a discrete hypophosphatemia (1.6 mmol/L, normal range 2.5-4.5 mmol/L) and a normal-low magnesemia (1.6 mmol/L, normal range 1.6-2.3 mmol/L). The serum levels of sodium and calcium were at normal ranges. The arterial blood gasometry didn't show acid-base alteration. There was also an elevation of the total bilirubin (4.3 mg/dL, normal range 0.2-1.3 mg/dL) and the creatine phosphokinase (CPK) levels (566 U/L, normal range 55-170 U/L). The myocardial injury specific markers CK-MB (creatine kinase-myocardial band) and troponin were normal. The electrocardiogram presented a right bundle branch block, with a sinusal rhythm. The axial computed tomography of the brain was normal.

An intravenous drip with 20 mEq/L of potassium chloride diluted in saline (0.9% sodium chloride solution) was started, and the patient was transferred to the Intensive Care Unit of the Hospital. A normalization of serum potassium levels to 3.8 mmol/L was associated with an important improvement of the muscular weakness, allowing the patient to walk with the help of an assistant 12 hours after the start of the drip.

The Endocrinology team of was called to investigate the etiology of the electrolyte disturbance. At his first analysis, the Endocrinologist (J.C.S.Jr.) noted a normal heart-beat rhythm (72 beats per minute), and no alterations at blood pressure, or respiratory rate. The patient had a subtle ocular proptosis (not measured) and, at neck palpation, the thyroid gland was enlarged (twice the normal volume), but no pain and nodules were observed.

The thyroid function tests confirmed thyrotoxicosis, with a suppressed TSH level (TSH < 0.02 mUI/L), associated with elevated total T4 of 24.2 ng/dL (Table 1). A thyroid ultrasound revealed an augmented gland (20.8 cm^3 of volume, normal range until 15 cm3), with no nodules.

Thyrotoxicosis treatment was promptly started with propylthiouracil 300 mg per day (100 mg three times a day), prednisone 20 mg per day and propranolol 40 mg twice a day. The patient was followed for more five days at hospital, with a satisfactory clinical evolution. At discharge, he was oriented to maintain use of propylthiouracil 100 mg three times a day and propranolol 40 mg twice a day; the corticosteroid was stopped. He was advised to stop the regular consumption of sugar-rich diet.

Thirty days after the onset of the symptoms, the patient returned for consultation, with thyroid function tests showing a great response to anti-thyroid drugs (see Table 1). The TRAb (thyroid stimulating hormone receptor antibody) value was 4.5 UI/L (normal range: below 1.75 UI/L). Following the recommendation of most recent guidelines[3], we have changed the anti-thyroid drug to methimazole 10 mg once a day. Due to a slow heart beat (56 beats per minute), propranolol dose was reduced to 20 mg twice a day.

In the follow-up, 4 months after the diagnosis of hyperthyroidism, the patient referred absence of symptoms of thyrotoxicosis and no recurrence of muscle weakness (see Table 1 to view the laboratory profile). Patient refused treatment with radioiodine at this moment due concern about infertility. The methimazole dose was maintained with recommendation of return each 3 months (or before, if symptoms recurrency).

Table 1. *Laboratorial findings.*

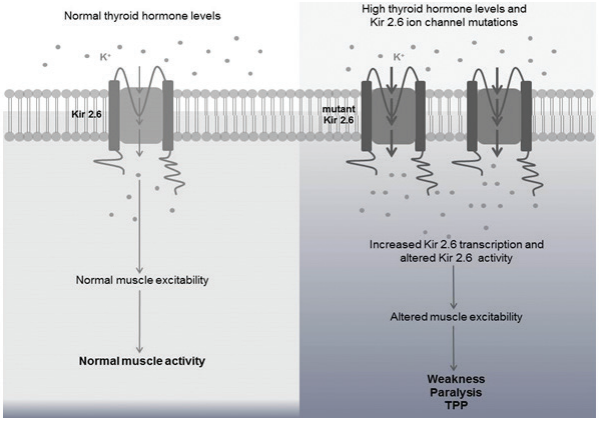
	At Admission	After 5 days	After 30 days	After 120 days
Potassium (normal range 3.5-5.1 mmol/L)	1.9	4.4	4.2	3.8
TSH (thyroid-stimulating hormone) (normal range 0.4-5.0 mUI/L)	< 0.02	<0.02	0.34	1.3
Total T4 (thyroxine) (normal range 5.53-11.0 ng/dL)	24.2	–	–	–
Free T4 (thyroxine) (normal range 0.78-2.17 ng/dL)	–	3.55	1.78	1.14
Total Bilirubin (normal range 0.2-1.3 mg/dL)	4.3	1.7	0.9	–

DISCUSSION

The pathophysiology of the thyrotoxic periodic paralysis (TPP) includes a rapid and massive shift of potassium from extracellular to intracellular compartment under the stimulus of high thyroid hormone circulating levels[4] (Figure 1). Current knowledge about TPP establish that this shift of potassium (in minor extent, also phosphate and magnesium) to the intracellular compartment is a result of stimulus of insulin and catecholamines at the 3Na+/2K+ ATPase, which is enhanced by the thyroid hormones, especially in patients with mutations in Kir channels. This results in serum hypokalemia, which triggers a paradoxical depolarization and inactivation of Na+ channels at myocytes[5].

The complete sequence of molecular events that leads to this shift remains to be understood, but recent studies showed that ion channelopathies has an important role in predisposition to TPP[6]. A multicentric group study demonstrated that mutations in the potassium channel Kir2.6 leads to a high susceptibility to TPP[7]. This channel, codified by the KCNJ1[8] gene, is selective for potassium (like some others Kir family channels), and has the important function of stabilize the resting membrane potential near the potassium equilibrium potential[7]. The chromosome 17q24.3, located near the KCNJ2 gene (that encodes the Kir2.1 channel), has been recently described as another potential susceptibility locus associated with TPP[8].

Figure 1. *Increased potassium influx at myocytes triggered by high thyroid hormone levels and augmented transcription of ion channels like Kir 2.6 leads to altered muscle excitability and TPP (adapted from reference 7).*



Any form of hyperthyroidism can cause TPP, including factitious hyperthyroidism and excessive intake of levothyroxine for non-approved indications (like weight loss), but the absolute majority has been linked to Graves' disease[2]. TPP is more common in Asian people, with median age of first presentation about 20-45 years, and predominates in male patients (Table 2). This predominance in male patients is explained because androgens, like testosterone, increase 3Na+/2K+ ATPase activity, while estradiol probably is a protecting factor against TPP, reducing 3Na+/2K+ ATPase activity[2].

The clinical triad of the TPP includes flaccid paralysis, signs of thyrotoxicosis and hypokalemia during a paralytic crisis[2]; the signs of thyrotoxicosis could not be considered by the physician if there's no previous history of thyroid illness. Otherwise, about three quarters of the patients do not recognize their thyrotoxic symptoms previously to the first TPP attack. Some triggers were identified, like strenuous exercise, heavy meal, high alcohol intake[5] or high carbohydrate diet[9]. Usually the attack starts while the patient is in bed, during the night, or early in the morning following a day of vigorous exercise and/or consumption of a large amount of food[2]. Duration of the attacks is high variable, since few minutes to several hours; indeed, some patients report a "prodromal symptom", like stiffness, pain or cramping in muscles of the limbs[2]. An interesting clinical finding in TPP is that deep tendon reflexes, which is commonly exacerbated in hyperthyroidism, are usually absent or depressed during an acute TPP attack; but this finding is not specific for TPP[2].

Table 2. *Clinical features of thyrotoxic periodic paralysis (adapted from reference 2).*

Clinical feature	Typical findings
Age of onset (years)	20-45 (90% of cases)
Male to female ratio	30:1
Ethnicity most frequently affected	Asian
Family history of paralysis	No
Family history of thyroid disease	Frequent
Precipitating factors	High intake of carbohydrate and/or salt; rest after strenuous exercise
Severe respiratory muscle weakness	Very rare
Deep tendon reflexes	Usually absent or depressed
Duration of the attacks	30 minutes to 6 hours
Potassium levels during the attack (mmol/l)	1.5–3.0
Main treatment	For thyrotoxicosis
Clinical course	Remission after thyrotoxicosis is corrected
Genetic inheritance	Mutations in skeletal muscle potassium Kir2.6 channel in up to 33% of patients

Laboratory hallmarks of TPP include a markedly hypokalemia (usually 1.5-3.0 mmol/L), due to the intracellular shift previously described (there's no loss of total body potassium pool), associated with suppressed levels of TSH and raised levels of thyroid hormones (T3 and T4)2. The electrocardiogram usually shows a prolonged PR interval associated with U waves, that's a sign of hypokalemia[10]; first or second degree heart block can also occur.

The differential diagnosis has to be established with familial periodic paralysis, a condition also related with channel mutations but with no relationship with thyroid illness. Guillain-Barré syndrome, an acute polyneuropathy affecting the peripheral nervous system, usually triggered by an infection, also must be excluded; eventually, an analysis of cerebral spinal fluid should be performed to exclude this condition.

The management of an acute episode of TPP includes the correction of acid-base disturb, with carefully replacement of potassium (and, if necessary, magnesium). The use of glucose solutions should be avoided, because this may stimulate the entry of potassium at the cells (potassium is a co-factor of insulin action), worsening the hypokalemia and eventually leading to death[11]. If there's no previous diagnosis of hyperthyroidism, it's mandatory a laboratory profile including TSH, free T4 and T3. After confirmation of thyrotoxicosis as the underlying disease leading to the symptoms, an anti-thyroid drug (propylthiouracil or methimazole) should be immediately started. The use of beta-blockers is also recommended, even if there's no tachycardia, because the blockade of catecholamines action contributes to impair the potassium influx that leads to the TPP. Corticosteroids could be used to impair the peripheral conversion of T4 in T3 by deiodinases. Ideally, those patients should be admitted in an Intensive Care Unit until the complete recovery of the acute attack.

The prevention of recurrence attacks is based in adequate control of hyperthyroidism, nutritional counseling to avoid intake of salt and sugar-rich foods, and restrict intense physical activity. Beta-blockers, like propranolol, probably are the most effective drugs to prevent new attacks, allied with proper hyperthyroidism treatment. Most authors suggest definitive treatment of hyperthyroidism with radioiodine[2], because, after attaining permanent euthyroidism, there's no recurrence of TPP attacks.

CONCLUSION

The authors suggests that any patient that has a sudden muscle weakness associated with serum potassium abnormalities should be screened to hyperthyroidism by the attending physician, regardless of presence or absence of thyrotoxicosis symptoms. An early diagnosis usually provides a rapid improvement of the clinical symptoms and prevents recurrence of the thyrotoxic periodic paralysis.

ACADEMIC LINKING

This article is a part of the academic profile of Joaquim Custódio da Silva Júnior in the Postgraduate Program of Organs and Systems' Interactions (Health and Science Institute, Federal University of Bahia) to obtain the grade of Academic Master, under the guidance of Professor Helton Estrela Ramos.

REFERENCES

*1. MAIA, A. L. et al. [The Brazilian consensus for the diagnosis and treatment of hyperthyroidism: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism]. **Arq. Bras. Endocrinol. Metab.**, São Paulo, v. 57, n. 3, p. 205-232, abr. 2013.*

*2. MACIEL, R. M.; LINDSEY, S. C.; DIAS DA SILVA, M. R. Novel etiopathophy-siological aspects of thyrotoxic periodic paralysis. **Nat. Rev. Endocrinol.**, London, v. 7, n. 11, p. 657-667, nov. 2011.*

*3. BAHN, R. S. et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. **Endoc. Prac.**, Jacksonville, v. 17, n. 3, p. 456-520, may-jun. 2011.*

*4. KUNG, A. W. Clinical review: Thyrotoxic periodic paralysis: a diagnostic challenge. **J. Clin. Endocrinol. Metab.**, Philadelphia, v. 91, n. 7, p. 2490-5, jul. 2006.*

*5. FALHAMMAR, H.; THOREN, M.; CALISSENDORFF, J. Thyrotoxic periodic paralysis: clinical and molecular aspects. **Endocrine**, Brescia, v. 43, n. 2, p. 274-284, apr. 2013.*

*6. ROLIM, A. L. et al. [Ion channelopathies in endocrinology: recent genetic findings and pathophysiological insights]. **Arq. Bras. Endocrinol. Metab.**, São Paulo, v. 54, n. 8, p. 673-681, nov. 2010.*

*7. RYAN, D. P. et al. Mutations in potassium channel Kir 2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. **Cell.**, Cambridge, v. 140, n. 1, p. 88-98, jan. 2010.*

*8. CHEUNG, C. L. et al. Genome-wide association study identifies a susceptibility locus for thyrotoxic periodic paralysis at 17q24.3. **Nat. Genet.**, New York, v. 44, n. 9, p. 1026-1029, sep. 2012.*

*9. EL-HENNAWY, A. S.; NESA, M.; MAHMOOD, A. K. Thyrotoxic hypokalemic periodic paralysis triggered by high carbohydrate diet. **Am. J. Ther.**, Philadelphia, v. 14, n. 5, p. 499-501, sep.- oct. 2007.*

*10. LOPEZ, S.; HENDERSON, S. O. Electrocardiogram changes in Thyrotoxic Periodic Paralysis. **West. J. Emerg. Med.**, Orange, v. 13, n. 6, p. 512-513, dec. 2012.*

*11. CHEN, D. Y. et al. Fatality after cardiac arrest in thyrotoxic periodic paralysis due to profound hypokalemia resulting from intravenous glucose administration and inadequate potassium replacement. **Thyroid**, New York, v. 22, n. 9, p. 969-972, sep. 2012.*

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