CASE REPORT
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Hypokalemic thyrotoxic periodic paralysis in a young Serbian male

Hipokalemijska tireotoksična periodična paraliza kod mladog muškarca u Srbiji

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Abstract

Introduction. Hypokalemic thyrotoxic paralysis is a very rare form of periodic paralysis in Caucasian population. In this population, a more frequent form is familiar hypokalemic periodic paralysis with the same clinical presentation. It is flaccid paralysis of proximal muscles in extremities. Having in mind that clinical presentation of hyperthyroidism in these patients is milder than it could be expected with given values of thyroid hormones, differential diagnosis to other forms of hypokalemic paralysis is essential. **Case report.** We presented a case of a young male with hyperthyroidism and severe periodic flaccid paralysis particularly of leg muscles. Laboratory findings showed elevated thyroid hormones levels and hypokalemia during the attacks with normalized potassium levels between attacks. The patient had no relatives with the similar condition. Also, he never had anything like these attacks prior to development of hyperthyroidism. After differential diagnosis, other reasons for hypokalemic periodic paralysis were excluded. We intensified the hyperthyroidism treatment and resolved hypokalemic periodic paralysis attacks with potassium chloride (KCl) infusions. The patient was advised to start a definitive treatment of hyperthyroidism after stabilization of hormonal levels. **Conclusion.** Hypokalemic thyrotoxic paralysis is a rare and potentially dangerous condition which, if recognized, can be prevented by resolving hyperthyroxinemia and the use of nonselective β blockers.

Key words:
hyperthyroidism; hypokalemia; paralysis, drug therapy; treatment outcome.

Apstrakt

Uvod. Hipokalemijska tireotoksična paraliza je veoma retka forma periodične paralize u beloj populaciji. U ovoj populaciji je zastupljenija familijarna hipokalemijska periodična paraliza sa istom kliničkom slikom. To je flacidna paraliza proksimalne muskulature ekstremiteta. Imajući u vidu činjenicu da je kod ovih bolesnika klinička slika hipertireoidizma blaža nego što bi se očekivalo, kada su u pitanju vrednosti hormona štitaste žlezde, veoma je važna diferencijalna dijagnoza u odnosu na ostale forme hipokalemijskih paraliza. **Prikaz bolesnika.** U radu je prikazan mlađi muškarac sa hipertireoidizmom i teškim oblikom flacidne paralize najizraženije u mišićima donjih ekstremiteta. Laboratorijska analiza ukazala je na povišene vrednosti hormona štitaste žlezde i na hipokalemiju tokom napada, uz normalizaciju vrednosti kalijuma u periodima remisije. Porodična anamneza je bila negativna na slična stanja, a bolesnik u prethodnom periodu nije imao ovakve napade. Nakon isključenja drugih potencijalnih uzroka ovog poremećaja, započeto je sa intenzivnom terapijom hipertireoidizma, a napadi hipokalemijske periodične paralize su kupirani primenom infuzije kalijum hlorida (KCl). Bolesniku je savetovano da nakon stabilizacije nivoa hormona štitaste žlezde započne sa definitivnom terapijom hipertireoidizma. **Zaključak.** Hipokalemijska tireotoksična paraliza je retko i potencijalno opasno stanje koje, ukoliko se na vreme prepozna, može biti kupirano terapijom hipertireoze i upotrebom neselektivnih β blokatora.

Ključne reči:
hipertireoidizam; hipokaliemija; paraliza; lečenje lekovima; lečenje, ishod.

Introduction

Hypokalemic thyrotoxic periodic paralysis (HTPP) is a very rare form of periodic paralysis in Caucasian population. In this population, a more common form of hypokalemic paralysis is familiar hypokalemic periodic paralysis (FHPP). Both conditions have similar clinical presentation with flaccid paralysis of proximal muscles on

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extremities, which stresses the importance of differential diagnosis (Table 1) [1].

Table 1
Difference between hypokalemic thyrotoxic periodic paralysis (HTPP) and familiar hypokalemic periodic paralysis (FHPP)

Parameters	HTPP	FHPP
Race	Asian	Caucasian
Age	20–40 years	Adolescence
Heredity	Usually no	Autosomal dominant
Thyrotoxicosis	Always	No effect
Prevention	Normalization of FT3 and FT4 level	Acetazloamide

FT3 – free T3; FT4 – free T4.

Hyperthyroxinemia is necessary for development of HTPP and it can be caused by various reasons: Graves disease, thyroiditis, thyroid stimulating hormone (TSH) secreting pituitary tumor, toxic nodular goiter or toxic adenoma, excessive T4 or excessive iodine ingestion [2–8]. For the occurrence of HTPP, the origin of hyperthyroidism is not important [9].

Pathophysiology of HTPP involves potassium shift in intracellular space and consequent hypokalemia without real potassium loss. In the center of HTPP pathophysiology is Na-K-ATPase pump which can be stimulated by increased insulin and catecholamine response.

HTPP is a treatable condition that can be prevented with the correction of hyperthyroidism and the use of nonselective β blockers.

We reported the case of a young Serbian male with HTPP, provoked by Graves disease.

Case report

A male, age 21, was admitted to our Clinic with severe muscle weakness especially in his legs and worsening of previously treated hyperthyroid state. His hyperthyroidism had been controlled for four years with propylthiouracil, propranolol and an anxiolytic. Parallelly to hyperthyroidism, the patient had periodic attacks of muscle weakness and in his opinion mostly in the evenings. Flaccid paralysis usually ceased spontaneously after a short period of time. Muscles involved in the attacks were predominantly proximal muscles of legs and shoulders. Never before this onset of hyperthyroidism, he had anything like these attacks. None of his relatives had similar condition. He could not relate these episodes to intensive physical activity but insisted that he could feel the incoming attacks. During attacks blood pressure was normal but usually they were followed by tachycardia. Never, even during the most severe attacks, he had deterioration of consciousness. During these four years he was free of HTPP in periods with normalized thyroid hormones levels.

Tree days prior to the admission to our Clinic the patient had developed severe muscle weakness. It was so intense that he could not get up or stand. He denied diarrheas in connection to periodic paralysis. There was no allergy or other significant medical condition prior to onset of hyperthyroidism.

On the day of the admission the patient was anxious, exhausted and hypodynamic. He had faster heart rate and sweating, particularly during the night. There were no signs of dehydration. Palms were warm and moist with discrete tremor of fingers. There were no signs of ophthalmopathy. Palpation revealed diffuse enlargement of thyroid with no signs of infiltration or palpable nodes. Auscultation of lungs and heart showed normal findings. Arterial tension was 120/80 mmHg and heart frequency 118/min. During the attacks the patient had flaccid paralysis and lack of reflexes. Between attacks, neurological exam was normal.

Laboratory examination revealed higher values of thyroid hormones: free T4 (FT4) > 100 pmol/L, free T3 (FT3) > 50 pmol/L with TSH < 0.005. Blood count and basic biochemical values [creatinine, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase, erythrocyte sedimentation rate (ESR)] were in referent range. The lowest plasma potassium level, detected during the attack, was 2.4 mmol/L. This came with the notion that the patient had been prone to self-medication with oral KCl when he believed attack was coming. This behavior usually occurred at night when attacks were most common. After one such night when 3.0 grams of KCL was ingested, potassium level was measured 5.3 mmol/L. Kaliuria was 81.0 mmoL/24 h (normally 25–120 mmoL/24 h) with diuresis of 1,000 mL/24 h.

Electrocardiogram (ECG) findings are presented on Figures 1 and 2.

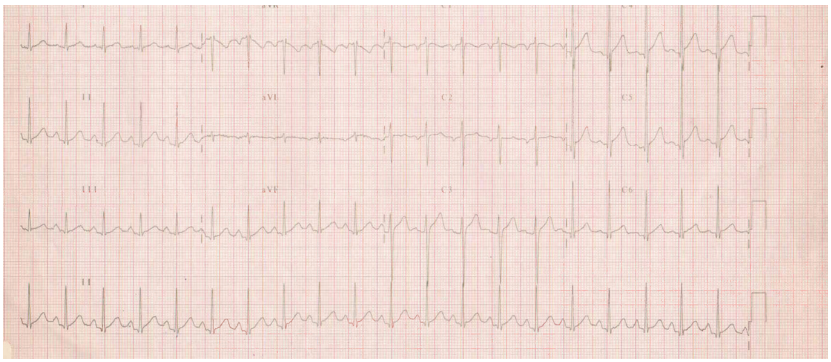

Fig. 1 – Electrocardiogram (ECG) in the period without hypokalemic thyrotoxic periodic paralysis (HTPP).

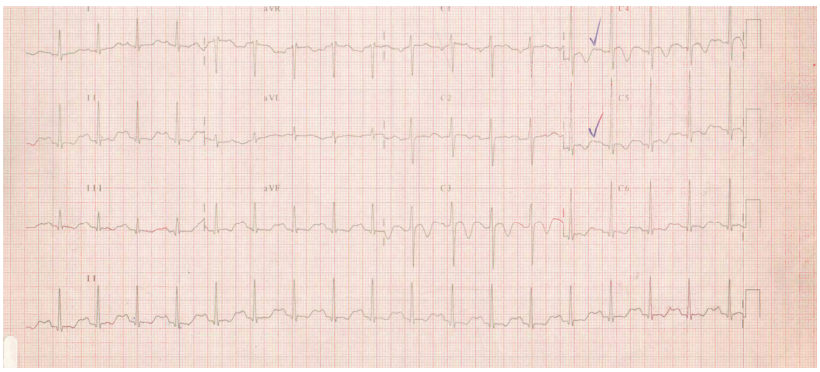

Fig. 2 – Electrocardiogram (ECG) during hypokalemic thyrotoxic periodic paralysis (HTPP) attack.

ECG on admission showed sinus rhythm (heart rate 118/min), PR interval was 145 ms, QRS duration 72 ms, QTc 403 ms, with normal repolarization pattern. During the attack, ECG showed sinus rhythm (heart rate 107/min), PR interval 168 ms, QRS duration 86, QTc 412 ms, negative T waves in D3, aVF and from V2 to V6. U wave was presented in D2, D3, aVF and from V4 to V6.

Ultrasound of thyroid gland showed diffuse enlargement of thyroid. Transversal diameter of the right lobe was 26 x 29 mm and of the left lobe 27 x 26.2 mm. Parenchyma was hypoechogenic and heterogenic with diffusely increased vascularization. No thyroid nodes or regional lymph nodes were found.

During hospitalization HTPP episodes were corrected with 40 mEq of intravenous potassium chloride in the emergency department and was then started on a normal saline infusion with 20 mEq/L of potassium. Also, hyperthyrosis was treated with propylthiouracil (PTU) 300 mcg daily and non-selective β blocker propranolol was given 40 mg twice daily. In support, we temporarily added an anxiolytic. The patient was clinically stabilized and properly informed about necessity of definitive treatment of his hyperthyroidism. Unfortunately there was no compliance from patient. He did not accept to undergo thyroidectomy after reaching euthyroid state nor was interested ine th treatment with I-131 at the time. The patient had such attitude in the first four years prior to the hospitalization in our clinic. Taking medication and KCl supplementation on need was more acceptable to him. Later treatment was conducted in regional medical center. Several years after hospitalization he accepted treatment with I-131, but hyperthyroidism remained. However, he was free of periodic paralysis attacks during the periods with normalized thyroid hormones levels.

Discussion

HTPP is periodic flaccid paralysis caused by transitory hypokalemia and, by rule, it happens during the hyperthyroxinemic state. Common causes for acute systemic paralysis include neurological, metabolic/toxicological or infectious/inflammatory conditions. Neurological ones may be myasthenia gravis, Sy Lambert Eaton, cataplexy, multiple sclerosis, transitory ischemic attack or hyperventilation sy ndrome. In metabolic/toxicological group, there are electrolyte imbalances, porphyries, medicaments, botulismus, alcoholism, opiates, hypoglycemia or some endocrinopathies. Finally, possible causes from infectious/inflammatory group are poliomyelitis, poliomyositis, diphtheria, dermathomyositis, Sy Guillain Barre, and inflammatory myopathy.

Hypokalemia itself might be due to real potassium loss or without real potassium loss. FHPP, HTPP, barium poisoning, insulin excess and alkalosis comprise the latter group. For differential diagnosis it is necessary to explore all reasons for potassium loss including renal ones: mineralocorticoid effect, renal disease, diuretic treatment and hypomagnesemia as well as non renal reasons like reduced food intake, diarrhea, villous adenoma-colon, fistulas, ureterosigmoid stoma or laxative abuse.

HTPP is metabolically induced systemic paralysis without real potassium loss; instead, potassium is shifted to intracellular space. Other causes of hypokalemic periodic paralysis need to be taken in consideration for differential diagnosis.

Rosenfeld [10] was the first who described HTPP in 1902. HTPP is a rare medical condition in our region. Recent epidemiological references have indicated that it is more common in Asian population, up to 1.8–1.9% of thyrotoxic patients in China and Japan compared to 0.1–0.2% in North America [11, 12]. There are reported cases in Caucasians, Aborigines, South American population and rarely in women [13].

Although hyperthyroidism is up to 10 times more common in females, HTPP predominantly affects males [14]. In Chinese population HTPP occurs in 13% of male compared to 0.17% female thyrotoxic patients [15]. Male to female ratio in other studies was reported to be 17–70 : 1 [16]. Usually, HTPP patients are 20–40 years old. Human leukocyte antigen (HLA) evaluation, although with some regularity, is not universally characteristic.

For HTPP to emerge, a patient needs to be in hyperthyroxinemia for some time. Muscle weakness begins usually 3–4 hours after dinner, during rest or sleep. It is believed that this is due to more prominent insulin or adrenalin release. Common provocative factor is a meal rich in carbohydrates, as it was in the case of our patient, and it may also be physical activity or stress. Interestingly, moderate physical activity might stop an incoming attack [17].

Clinical presentation of all hypokalemic paralyses, regardless of their origin (HTPP or FHPP), is the same. It is flaccid paralysis differing in severity of presentation.

Dominantly, it affects proximal muscles of extremities and it is followed by the lack of reflexes. Legs are usually affected first. Walking and standing up from a sitting position are compromised. Respiratory or bulbar muscles are not affected. Patients often claim that they could feel an incoming attack, as it was in the case of our patient. Paralysis usually starts at night and may last form a few minutes up to 48 hours, but usually a few hours. Between attacks, neurological findings are normal [1, 2].

Every HTPP patient has hyperthyroxinaemia. Hyperthyroidism in case of HTPP can be very mild so it can be unnoticed. This requires caution in diagnostic evaluation of hypokalemic paralysis. Our patient had severe hyperthyroxinaemia on admission. Despite the notion that clinical presentation of hyperthyroidism in the case of our patient was clearly present, it could have been more pronounced considering extremely elevated levels of thyroid hormones.

Although paralysis can stop spontaneously, the best way to stop attack is oral or intravenous administration of KCl. Recommended doses are 60–130 mEq orally or 20 mEq dissolved in saline infusion, intravenously [18]. The effect is expected within 15–20 min. The above was confirmed in our experience. Caution is required due to possible hyperkalemia. The other recommended treatment is initial use of non-selective beta blocker propranolol 3 mg/kg, with the notion that such an approach is efficient and free of hyperkalemia. After the normalization of thyroid hormones plasma levels, HTPP patients remain free of attacks. Besides reaching euthyroid state, for the prevention of HTPP, we can use propranolol, too. It is believed that the effects of β2 adrenergic receptor blockade are beneficial in this situation. Sympathetic stimulation of insulin release from β-cells might be the argument for such treatment [1]. Spirinolactone was also reported as useful in prevention of HTPP and, of course, avoiding known provocative factors is highly recommended [19]. On the other hand, taking preventive doses of oral KCl is not effective. Our patient was previously convinced that oral KCl could prevent attack but during the hospitalization in our Clinic we advised him otherwise.

Hypokalemia can be severe during attack but in-between attacks potassium levels are normal. Daily potassium excretion is normal so it is obvious that potassium is shifted from circulation during attacks. It is believed that potassium is shifted to intracellular space. During attacks patients have temporary hypomagnesemia and hypophosphatemia. Patohistological finding by electronic microscopy includes vacuolization of sarcolema and contractile parts of fibrils. Degenerative changes in myofibrils are also seen.

During attacks, ECG changes include tachycardia, negative T waves, U waves, first degree AV block, shortening of QT interval and elongation of QRS complex. Atrial fibrillation may occur; on the other hand, ventricular fibrillation is extremely rare [20]. Our patient during the attacks had U wave, elongation of QRS complex and negative T wave but QT interval was not shortened, instead it was a bit longer. Between attacks, ECG was normal.

Pathogenesis of HTPP is still not clear. Muscle weakness is a consequence of altered depolarization, which disturbs readiness for the next depolarization-contraction cycle. Persistence of mild depolarization state on sarcolema is a combined effect of reduced activity of adenosine triphosphate (ATP), dependent potassium channel and prolonged Na-K-ATPase activity. Earlier, it was found that insulin and catecholamines stimulate Na- K- ATPase, and also that insulin reduces the activity of ATP dependent potassium channel. Thyrotoxicosis in HTPP stimulates the activity of Na-K-ATPase and increases the number and density of adrenergic receptors which all together facilitates development of hypokalemia caused by insulin and catecholamines [21, 22]. Reduced activity of Ca^{2+} pump and increased intracellular Ca^{2+} concentration are reported [23–25].

In 2010 Puwanant and Ruff [26] reported that outward potassium channels (Kir) current is decreased in intercostal myofibrils in both, HTPP and FHPP. In addition to the activation of Na-K ATPase, insulin and catecholamines also decrease the activity of Kir [27]. Genetic mutation of gene encoding Kir2.6 channels was found in 33% Cacausans with HTPP [28].

During rest or sleep, potassium increasingly enters into cells; on the other hand, during physical activity potassium is released in circulation. This data amplify importance of potassium transport in HTPP [23, 29, 30].

For differential diagnosis, the most important condition is FHPP. FHPP is a hereditary condition. In FHPP, mutation is on 1q chromosome and leads to alteration of α subunit on dihydropyridine sensitive L-type calcium (L-Ca) channels. They are slow Ca^{2+} channels. Also, these channels act as voltage sensors for so called excitation-contraction linking. Mutation on genes for Na^+ and K^+ channels are also seen in FHPP. Several patients with HTPP had a mutation on K^+ channel [23]. Presence of hyperthyroxinemia is essential for development of HTPP and has no influence on FHPP.

Our patient had an overwhelming level of evidence for diagnosis of HTPP. The problem with his attitude toward definitive treatment of diffuse toxic goiter kept him away from preventive normalization of thyroid hormones level. The reason for hospitalization in this occasion was a severe and prolonged paralysis caused by worsening of the thyroid hormones level. His previous experience with mild self-ceasing attacks sealed him in his decision to avoid thyreoidectomy. Later attempt in a regional hospital with I-131 did not permanently solve hyperthyroidism and HTPP remained to some extent, except in periods with normalized thyroid hormones levels. At least, during hospitalization in our Clinic, he was educated how to avoid other povocative factors and hopefully reduce his health risk.

Conclusion

HTPP is rare in Caucasians, including Serbs as a part of Slavic population. Hyperthyroidism in HTPP patients is often milder in clinical presentation than it could be expected according to levels of FT4 and FT3. This may be misleading and points to the necessity of careful differential diagnosis in every patient with hypokalemic paralysis. Resolving reasons for hyperthyroxinemia and preventive nonselective β-blockade are recommended.

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