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Thyrotoxic Periodic Paralysis (TPP) in a Chinese patient as first presentation of basedow disease

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Abstract

Introduction: Hypokalaemic periodic paralysis secondary to thyrotoxic state is a unusual complication of hyperthyroidism characterised by sudden onset weakness in the proximal muscles secondary to hypokalaemia. This condition most often occurs in east Asian men, but, due to population migration, is increasingly common in Western countries. An association with potassium channel-related mutations have been reported.

Case presentation: We describe a Chinese 35-year-old man presenting with hypokalemic periodic paralysis associated with Graves' disease. He reported symptoms characterized by painless lower limb weakness that arose during the night and that prevented him from standing and walking. Physical examination disclosed tachycardia and neurological signs of bilateral proximal leg weakness with normal arm strength. The laboratory tests and the electrocardiogram showed the presence of severe hypokalaemia while the dosage of thyroid hormones revealed the presence of hyperthyroidism.

The patient was diagnosed as having Graves' hyperthyroidism and THPP. He was successfully treated with potassium supplements and anti-thyroid medication.

Conclusions: It is important for physicians to be able to differentiate thyrotoxic periodic paralysis from familial hypokalemic periodic paralysis, a more common cause of periodic paralysis.

Keywords

Thyreotoxicosis; Periodic paralysis; Hypokalaemia; Basedow diseases; Hyperthyroidism.

Introduction

Thyrotoxic Periodic Paralysis (TPP) is a rare disorder characterized clinically by the appearance of repeated episodes of paralysis associated with hypokalaemia and thyrotoxicosis [1-3]. TPP is triggered by a state of thyrotoxicosis. The most frequently associated disease is Graves' disease but any disease that induces a state of thyrotoxicosis can trigger it [4]. It is very common in Asian males during the third decade of life. The annual incidence in the Asian population with thyrotoxicosis is about 1/50, while it is estimated at 1-2/1,000 in Caucasian patients with thyrotoxicosis [5,6].

Almost all cases of TPP are associated with muscle weakness and can affect respiratory musculature as well as the cardiac conduction system. The attacks are typically nocturnal and sometimes preceded by muscle cramps, pain, and stiffness. Therapy is based on the early and correct administration of potassium to avoid dangerous cardiac arrhythmias [7].

TPP is usually sporadic and the pathogenesis is unknown. Some genetic alterations appear to predispose to PPT such as single nucleotide polymorphisms (SNPs) of the CACNA1S (1q32) and GABRA3 (Xq28) genes reported in some Asian populations [8,9]. Recently, a population-based Genome-Wide Association study identified two new TPP-specific susceptibility loci, DCHS2 on 4q31.3 and C11orf67 on 11q14. In addition the authors observed that 2 risk loci (MHC and Xq21.1) were shared by Graves disease and TPP [10].

We report a case of a 35-year-old Chinese man who presented to the our hospital emergency room with acute bilateral lower extremity weakness associated with hypokalemia who was subsequently diagnosed with TPP due to thyrotoxicosis by Grave's diseases. The written inform consent was obtained from the patient.

Case Report

A 35-year-old Chinese man was being transported to the hospital emergency room with leg weakness. The patient reported a painless lower limb weakness that arose during the night that prevented him from standing and walking. There was no history of trauma, ingestion of toxic substances and fever. No gastrointestinal, cardiovascular or respiratory symptoms were reported. His past and family medical history were both negative. His physical examination did not reveal anything in particular except for tachycardia and neurological signs of bilateral proximal leg weakness with normal arm strength. Tendon reflexes were reduced. Laboratory tests revealed hypokalemia of 1.9 mmol/L (normal 3.5-5.3 mmol/L). Other laboratory tests were normal (Table 1). The EKG confirmed the presence of tachycardia. Head angio-MRI and Vertebral spine MRI showed no evidence of acute pathology. The patient was admitted to a Neurology Department of our hospital and medical therapy with intravenous fluids and potassium replacement were given. Hypokalemia was corrected after a few hours and was followed by complete resolution of the patient's symptoms. As the patient reported weight loss in the previous four weeks, the thyroid function was assessed revealing the presence of biochemical thyrotoxicosis, as shown in Table 2. Thyroid Stimulating Hormone (TSH) receptor antibodies (TRAb) assay was positive. A radioactive iodine

thyroid uptake scan was consistent with Graves' disease. The patient was started on methimazole 5 mg four times a day. After 2 months of follow-up the patient remains euthyroid and symptom free. We performed HLA genotyping, performed by HLA SPP (Sequence Specific Primers) kit I and II class (Biorad), and found A2, B40(Bw22), DR 9, DQB1* 03:03 results that has been reported to be associated in China Zhejiang Han (Table 3).

Table 1: Laboratory tests results at the moment of admission in Emergency department.

Laboratory parameters	Results	Normal range
Potassium	1,9	3,5-5,1 mEq/L
Sodium	143	136-145 mEq/L
Inorganic Phosphate	3,9	2,5-4,5 mg/dl
Magnesium	1,64	1,50-2,60 mg/dl
Ionized calcium	1,21	1,13-1,32 mMOL/L
Urea	23	13-49 mg/dl
Creatinine	0,78	0,67-1,17 mg/dl
Creatine kinase	102	39-308 UI/l

Table 2: Thyroid hormones tests results at the moment of the hyperthyroidism diagnosis.

TSH	<0.0005	(0.2-4.2 uUI/mL)
FT4	31	(12-22 pmol/L)
FT3	10,2	(3.1-6.8 pmol/L)
AbTg	12	(<115 IU/mL)
AbTPO	<9	(<34 IU/ml)
TRAb	3,6	(<1.7 IU/mL)
thyreoglobulin	38	1,4-78 ng/ml

Table 3: HLA Haplotype.

HLA	ALLELS	ALLELS
A	02	24
B	40	56
Cw	03	01
DQA1*	03	05
DQB1*	03:03	03:01
DRB1*	09	13

*= HLA typing in molecular diagnostic.

Discussion

Thyrotoxic Periodic Paralysis (TPP) is an infrequent complication of hyperthyroidism but can begin suddenly and represent a medical emergency. The first report of TPP was published in 1931 and concerned 4 patients with hyperthyroidism and periodic paralysis [11]. TPP represents a common complication of hyperthyroidism in Asian men, but is increasingly seen in Europe and USA because of rising immigrant populations [12,13]. The higher predilection for male sex and Asian populations is probably associated with a genetic predisposition. Some studies have identified specific susceptibility loci that involve the risk of TPP and mutations in the KCNJ18 gene, encoding Kir2.6 channels that are under transcriptional regulation of thyroid hormones [14-16]. TPP-causing mutations in Kir2.6 include loss-of-function mutations but also gain-of-function mutations that hyperpolarize the skeletal muscle, leading to a reduced excitability [14]. The Human Leukocyte Antigen (HLA) B46, DR9, A2, Bw22, AW19, B17, and DRW8 have also been reported [17-19]. A role for testosterone in the pathogenesis for thyrotoxic PP is suggested by the predominance of this condition in men and the demonstration that testosterone increases sodium-potassium ATPase activity in animals [20].

The pathogenesis of TPP remains uncertain. Hypokalemia induced by thyreotoxicosis is a cardinal feature of TPP probably for a direct increase in the genetic transcription of genes coding for the Na-K ATPase pump and an increase in the pump's intrinsic activity [21]. The affected patients present recurrent episodes of flaccid paralysis affecting proximal more severely than distal muscles, and occasionally, are reported to have bulbar weakness and respiratory failure. The degree of hypokalaemia determines the severity of symptoms that improve after correcting the levels of hypokalaemia and thyrotoxicosis [22,23]. Usually, the age of onset of symptoms in the majority of patients is between 20 and 39 years. The appearance of the symptoms of TPP can be triggered by high-carbohydrate meal, physical exertion, preceding febrile illness and often on getting up from sleep probably reflecting an increase in sodium-potassium ATPase pump and may act synergistically with thyroid hormone to drive potassium into cells [24]. Furthermore, insulin and catecholamines have also been shown to inhibit Kir channels [25]. Rare complications include colonic pseudo-obstruction and ventricular arrhythmias [26]. Potassium levels remain the same and the correction must be done with caution. Normalization of serum potassium precedes the recovery of muscle weakness. Diagnosis of TPP can be suspected when a patient complains of recurrent proximal muscles weakness, mainly involving lower limbs with no family history of hereditary neurological disorders. Furthermore, the patient might present with signs and symptoms of hyperthyroidism and hypokalemia which can be confirmed through laboratory investigations. Serum phosphorus can be low and serum Alkaline Phosphatase (ALP) is raised in half of the patients with TPP. To distinguish TPP from familial hypokalemic PP can be considered the urine calcium to phosphate ratio >1.7 [22]. Other conditions that can cause periodic paralysis must be ruled out like drug induced (tocolytics, chloroquine toxicity, barium poisoning), botulism, myasthenia crisis and Guillain Barré Syndrome [27].

The adequate repletion of potassium (total dose of < 90 mEq/24 hours) is recommended with close cardiac monitoring [28]. Once the euthyroid condition has been restored, there will no longer be the risk of TPP episodes [29]. The management of hyperthyroidism differs according to the underlying etiology.. The administration of beta-blocking medications such as propanolol (40 to 120 mg daily) with or without potassium supplementation has also been shown to decrease the frequency and severity of attacks. A nonselective beta blocker (eg, propranolol) should be given. Replacement of potassium may be insufficient to resolve an attack and in these cases intravenous propanolol has been reported to reverse weakness and hypokalemia in patients with thyrotoxic PP that is unresponsive to potassium administration. Promptly diagnosing this condition is very important because it is potentially reversible. On the contrary, a delay in diagnosis could lead to very dangerous complications such as hypercapnic respiratory failure and ventricular fibrillation.

Conclusions

The aim of this study is to alert clinicians to the recognition of a complication of Basedow's disease, which, although rare, is very frequent in Asian populations and which, with the increase of immigration phenomena, is not uncommon to observe also in Western countries.

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