THYROTOXIC PERIODIC PARALYSIS AND CHOREA: TWO UNCOMMON NEUROMUSCULAR COMPLICATIONS AS PRESENTING SYMPTOMS IN AN ADOLESCENT WITH NEWLY DIAGNOSED GRAVES' DISEASE: A CASE REPORT

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Abstract. Thyrotoxic periodic paralysis (TPP) and chorea are uncommon neurological complications of hyperthyroidism. Here, we report and describe a case of 14-year-old boy who presented with both TPP and chorea at his initial presentation with signs and symptoms of Graves' disease. After diagnosis, a combination of methimazole (MMI) and propranolol were started to control hyperthyroidism. TPP resolved completely within 48 hours after hypokalemia was corrected with potassium supplementation. Chorea gradually resolved over a period of 4 weeks. The pathogenesis of TPP and chorea in hyperthyroidism was reviewed herein. In addition, this report highlights a clinical importance for awareness of these neurological complications in children with hyperthyroidism, since they may be the only presenting symptoms of hyperthyroidism and could be confusing with the diagnosis of genuine neuromuscular disorders.

Keywords: Graves' disease, periodic paralysis, chorea, adolescent

INTRODUCTION

Thyroid hormones influence several aspects of the neuromuscular system and brain. Muscular and neurologic symptoms may be among presenting features of hyperthyroidism. These include movement disorders, peripheral neuropathy, seizure, encephalopathy, proximal myopathy, myasthenia gravis, thyrotoxic periodic paralysis (TPP) and rhabdomyolysis among thyrotoxic patients (Nandi-Muushi and Taplin, 2015).

TPP and chorea are infrequently reported neurological complications of hyperthyroidism in children and adolescents. Here, we present and describe a case of 14-year-old boy who initially presented with both symptoms together with other signs and symptoms of Graves' disease.

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CASE REPORT

A 14-year-old Thai boy presented to our emergency department with a 5-hour history of acute generalized proximal muscle weakness and myalgia. He denied having poor intake, vomiting and diarrhea. Detailed history revealed increased appetite, heat intolerance and labile mood for 6 months. He also reported gradual onset of involuntary movements of both hands and shoulders. There is no significant family history of thyroid or neuromuscular disease.

Physical examination revealed tachycardia (heart rate 115 beats/min), diffuse enlargement

of his thyroid gland with vascular bruit, mild exophthalmos and moist skin. An innocent murmur grade II/V along the left parasternal border was audibled. Neurologic examination showed generalized proximal muscle weakness and hyporeflexia. No muscle atrophy, tenderness, or fasciculation was noted. Sensation, cranial nerves, and bowel and bladder function were all normal. Involuntary, non-sustained, purposeless movement of mainly the upper extremities and milkmaid signs were present, both of which were consistent with chorea.

Serum thyroid function test showed serum triiodothyronine (T3) >651 ng/dl (normal range 80-185 ng/dl); free thyroxine (free T4) >7.77 ng/dl (normal range 0.8-2.3 ng/dl) and thyroid stimulating hormone (TSH) <0.005 µU/ml (normal range 0.5-4.8 µU/ml) – all of which were consistent with hyperthyroidism. Serum electrolytes revealed hypokalemia (serum potassium 2.1 mmol/l) with normal sodium, chloride, and bicarbonate. Serum creatinine, calcium, phosphorus and magnesium were all normal. Calculated trans-tubular potassium gradient (TTKG) was 3, which indicated that there was no renal potassium wasting. Autoimmune profile showed anti-thyroglobulin (anti-TG) antibody <1:20 (normal range <1:20); anti-thyroid peroxidase (anti-TPO) antibody 1:25,600 (normal range <1:100); anti-cardiolipin IgM <2MPL.U/ml (normal range <12 MPL.U/ml); and negative anti-dsDNA and ASO titer. Other laboratory tests showed serum creatine phosphokinase (CPK) 1,555 U/l (normal range 5-130 U/l) and C-reactive protein (CRP) <3 mg/l (normal range <3 mg/l). Electrocardiograph showed left ventricular hypertrophy (LVH) by voltage criteria with absence of U wave.

These findings of generalized proximal muscle weakness with hypokalemia and thyrotoxicosis were consistent with thyrotoxic periodic paralysis (TPP), therefore the patient was diagnosed with Graves' disease with TPP and chorea. Methimazole (MMI) 30 mg/day and propranolol 1.2 mg/kg/day were started. Intravenous potassium replacement was administered to correct hypokalemia and serum potassium was normalized within 7 hours. Our patient was able to stand and walk normally on the 2nd day of admission. After 4 weeks of treatment, thyroid function test results were consistent with biochemical hypothyroidism; therefore, MMI dose was reduced and propranolol was discontinued. His choreiform movements gradually decreased and resolved completely within 4 weeks after MMI and propranolol were started.

Three years later, the patient underwent radioactive I^{131} treatment due to relapse of hyperthyroidism after an 8-week discontinuation of MMI. Neither TPP nor chorea developed during this relapse.

DISCUSSION

This report described an adolescent boy with a new-onset Graves' disease who developed concomitant TPP and chorea. To the best of our knowledge, this patient is the first pediatric patient with hyperthyroidism who developed these two rare associated neurological complications. Interestingly, our patient's only presenting symptoms were muscle weakness and myalgia. Detailed history and physical examination revealed hyperthyroidism.

Various neurological presentations have been described in patients with hyperthyroidism, with tremor being the most common. Other uncommon neurological manifestations include TPP, myopathy, abnormal movement and encephalopathy (Nandi-Muushi and Taplin, 2015). We identified only one previous case report of a patient with Graves' disease who had both muscular complication and choreoathetosis. Differently from our patient reported herein, the previous patient had thyrotoxic myopathy but not TPP which involved both bulbar and skeletal muscles (Clements *et al*, 1981).

TPP is a potentially lethal complication of

hyperthyroidism that is characterized by muscle paralysis and hypokalemia that results from a massive intracellular transfer of potassium (Kung, 2006). TPP has been reported in various etiologies of hyperthyroidism including Graves' disease, subacute thyroiditis, toxic nodular goiter and thyroid-stimulating hormone (TSH)-secreting tumor (Pothiwala and Levine, 2010). TPP mainly affects Asian adult male patients, with an overall incidence of TPP among Chinese and Japanese thyrotoxic patients of 1.8% and 1.9%, respectively (Kung, 2006). Clinical manifestation of TPP is characterized by acute transient episodes of muscle weakness that affect proximal rather than distal muscle groups and might be asymmetrical. Our patient's clinical signs and symptoms with laboratory evidence of hypokalemia, together with low urinary K excretion, elevated CPK and complete recovery after normalization of serum potassium were all consistent with TPP (Kung, 2006).

The pathogenesis of TPP is still unclear. A rapid and massive transfer of potassium from extracellular into intracellular compartments occurs in patients with TPP. In general, a transcellular K distribution is maintained by sodium-potassium-adenosine triphosphatase (Na/K- ATPase) pump activity (Kung, 2006; Lin and Huang, 2012). Thyroid hormone has been shown to increase Na/K-ATPase activity (Kung, 2006). Enhanced β-adrenergic activity in hyperthyroidism can also enhance Na/K-ATPase activity and administration of non-selective β-adrenergic blockers can abort or prevent TPP (Kung, 2006). Insulin also induces Na/K-ATPase activity; therefore, hyperthyroidism-induced hyperinsulinemia can also trigger TPP (Kung, 2006). Recently, a defect in potassium efflux may play an important role in the pathogenesis of TPP (Lin and Huang, 2012). Mutations in gene encoding Kir2.6, a skeletal muscle-specific Kir channel are also associated with TPP predisposing these patients with genetic variation to acute paralytic attack (Ryan *et al*, 2010).

Besides TPP, our patient also had chorea, which is a rare neurological complication among patients with hyperthyroidism (Shahar *et al*, 1988). In most cases, chorea has a gradual onset and involves limbs bilaterally similar to our patient (Clements *et al*, 1981; Hayashi *et al*, 2003; Seeherunvong *et al*, 2007; Chung *et al*, 2013; Leblicq *et al*, 2013). However, acute onset (Adcock *et al*, 1999; Yu and Weng, 2009; Park *et al*, 2012) and unilaterally involvement (Park *et al*, 2012) have also been reported. In addition, our patient also exhibited classic signs and symptoms of chorea that gradually worsened. Negative ASO titer, ANA and anti-phospholipid antibody excluded other causes of chorea, such as Sydenham chorea, systemic lupus erythematosus and anti-phospholipid syndrome.

The pathogenesis of chorea associated with hyperthyroidism is not well-understood. Several hypotheses including hyperthyroxinemia (Leblicq *et al*, 2013), autoimmunity (Adcock *et al*, 1999), increased sensitivity of dopaminergic (Garcin *et al*, 2008) and adrenergic systems (Hayashi *et al*, 2003) have been proposed. Neuroimaging studies in most patients were normal (Seeherunvong *et al*, 2007; Yu and Weng, 2009; Chung *et al*, 2013; Leblicq *et al*, 2013). However, functional neuroimaging studies such as fluorodeoxyglucose-positron emission tomography (FDG-PET) scan (Chung *et al*, 2013) showed increased metabolism in the basal ganglia. Single-photon emission computerized tomography (SPECT) scan showed decreased perfusion to the basal ganglia (Yu and Weng, 2009). These reported findings suggest transient dysfunction in the basal ganglia.

However, the neuroimaging was not performed in our patient since chorea improved and then completely subsided after the treatment with MMI and propranolol.

The etiology of hyperthyroidism in this patient was Graves' disease. Patients with Hashitoxicosis can present with signs, symptoms, and a high titer

of anti-TPO antibody like patients with Graves' disease (Saravanan and Dayan, 2001). However, Hashitoxicosis in most children usually subsides within 6 months (Nabhan *et al*, 2005). The clinical course of our patient that required 3 years of MMI and the necessity of I^{131} treatment have completely excluded Hashitoxicosis in our patient.

In conclusion, TPP and chorea are uncommon neurological complications in children with hyperthyroidism. Physicians should be aware of the potential hyperthyroidism in children who present with muscle weakness and/or chorea, since the classic signs and symptoms of hyperthyroidism may be obscure.

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CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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