Endocrinol Nutr. 2012;59(6):394–400

ENDOCRINOLOGÍA Y NUTRICIÓN

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SCIENTIFIC LETTERS

Thyrotoxic periodic paralysis: An increasingly common complication of hyperthyroidism☆

Parálisis periódica tirotóxica: complicación del hipertiroidismo cada vez más frecuente en nuestro medio

To the Editor,

Thyrotoxic periodic paralysis (TPP) is a complication of hyperthyroidism mainly reported in Asian males. It is uncommon in other races, although its incidence is increasing in Western countries. We report the case of a Caucasian patient diagnosed with thyroid hyperfunction who experienced episodes of loss of strength in the lower limbs.

The patient was a 35-year-old male with an unremarkable personal history who attended the emergency room reporting a loss of strength in the proximal lower limbs, with no pain or sensory changes, mainly occurring in the evening and related to intense work activity. The episode had occurred at other times during the previous three months. Clinical history found hyperhidrosis, distal tremor, and occasional palpitations, which did not occur at the same time as muscle weakness. The main finding in neurological examination was an asymmetric decrease in lower limb strength with generalized hypoactive bone and tendon reflexes. Urgent supplemental tests requested found hypokalemia (2.7 mequiv./L, NV: 3.8–5.2 mequiv./L), elevated creatine kinase level (253 U/L, NV: 45–135 U/L), and sinus tachycardia at 110 bpm. The condition improved with water and electrolyte replacement, and the patient was admitted for a complete work-up.

Medullary compression and infection were ruled out as the cause during his hospital stay, and electromyography consistent with non-specific myopathy of a probable metabolic origin suggested muscle disease (Fig. 1). Primary hyperthyroidism was also found. On neck examination, grade 2 diffuse goiter was palpated. Supplemental tests for antithyroid peroxidase antibodies (TPO) and anti-TSH receptor antibodies (TSI) were positive, and thyroid gammagraphy showed an increased gland size with homogeneous distribution of the radioactive agent. The patient was diagnosed with Graves disease, and treatment was started with thiamazole 30 mg and propranolol 40 mg daily. The patient's course was satisfactory, and he is currently symptom-free and in an euthyroid state after a therapeutic radioiodine dose (Table 1). Because of the clinical characteristics of the condition, its triggers, the finding of hypokalemia, the

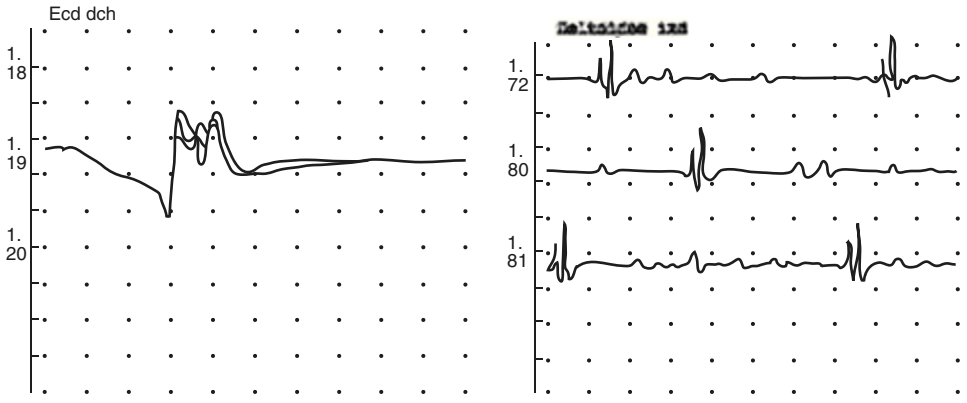

Figure 1 Electromyography: mild, non-specific chronic myopathy of probable metabolic origin.

☆ Please cite this article as: García-Martín A, et al. Parálisis periódica tirotóxica: complicación del hipertiroidismo cada vez más frecuente en nuestro medio. Endocrinol Nutr. 2012;59:394–6.

Table 1 Laboratory parameters and treatment diagnosis and monitoring.

	NV	Baseline	2 m	3 m	7 m	*12 m*
TSH (μIU/mL)	0.27–4.20	0.01	0.01	1.90	0.01	*2.34*
Free T4 (ng/dL)	0.90–1.71	5.01	0.98	0.38	1.61	*1.52*
Free T3 (ng/dL)	1.50–4.10	19.99	2.81	1.45	4.49	*2.34*
Autoantibodies						
TSI (IU/L)	1.20–2.00	5.5				
TPO (IU/L)	0.00–50.0	453				
Daily thiamazole dose		30 mg	30 mg	20 mg	20 mg	
Daily propranolol dose		40 mg	40 mg	40 mg	40 mg	

Values after the therapeutic dose of 15 mCi of radioiodine are given in italics.
T4: thyroxine; TPO: peroxidase antibodies; TSH: thyrotropin; TSI: anti-TSH receptor antibodies; T3: triiodothyronine; NV: normal values.

absence of a family history of periodic paralysis, and symptom improvement after antithyroid treatment was started, the condition was diagnosed as thyrotoxic hypokalemic periodic paralysis.

TPP is a well-known complication in Asian populations, where it occurs in 1.8–1.9% of hyperthyroid patients.[1] However, there has been a recent increase in the number of cases of TPP in Western countries.[2] Most cases reported in Europe occur in Mediterranean areas, including Spain.[3,4] TPP occurs in young men aged 20–40 years, such as our patient, who experience transient, recurrent episodes of muscle weakness with flaccid paralysis lasting for hours. Proximal muscles are affected, sensitivity is preserved, and bone and tendon reflexes are decreased or absent. Episodes are commonly triggered by the intake of carbohydrate-rich meals, alcohol, or strenuous exercise. Clinically, TPP is similar to familial hypokalemic periodic paralysis. Differential features such as epidemiological characteristics, family history and, especially, coexistent hyperthyroidism must therefore be sought.[5]

Hypokalemia is the characteristic biochemical finding. The degree of hypokalemia is correlated to paralysis severity, but not to hyperthyroid clinical signs and symptoms or hormone levels. It is produced by a rapid, massive potassium entry from the extracellular to the intracellular space, mainly to myocytes because of increased activity of the Na/K-ATPase pump. Patients with TPP are predisposed to activation of the Na/K-ATPase pump, either directly through thyroid hormone excess or indirectly by adrenergic, insulin, or physical exercise stimulation.[6] Two-thirds of patients are found to have increased creatine kinase levels, particularly in episodes triggered by physical exercise. Electrocardiographic findings are highly variable, including sinus tachycardia, high QRS voltage, or first-degree AV block.[7] The electromyogram shows myopathy with decreased amplitude of muscle action potentials and no marked changes after epinephrine stimulation.[6]

Most cases of TPP detected are due to hyperthyroidism caused by Grave's disease, but other causes of thyroid hyperfunction are possible and have been reported. As regards genetic predisposition, various genes have been considered responsible. Polymorphisms have been found in the nucleotide sequence of subunit alpha-1 of voltage-dependent calcium channel Cav1.1, with differences from the mutations occurring in familial hypokalemic periodic paralysis.[8]

Urgent treatment consists of electrolyte replacement with potassium by either the intravenous or oral route in order to prevent cardiovascular complications.[9] Oral non-selective beta-blockers are helpful for preventing paralysis attacks, and in order to avoid triggering factors. Final remission is achieved when hyperthyroidism is controlled.[5]

TPP is a complication associated with hyperthyroidism which is becoming increasingly common in Western countries. It should be considered in patients with episodes of muscle paralysis, for whom thyroid function tests should be part of the diagnostic process.

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Endocrine and psychological changes in polysomy 48,XXXY☆

Alteraciones endocrinológicas y psicológicas en la polisomía 48,XXXY

A 14 year-old male patient was referred to the endocrinology outpatient clinic for hypogonadism. He had an unremarkable family and personal history. He was born in China, and had lived in Spain with his biological family since the age of three.

This boy was referred by the urology outpatient clinic due to delayed genital development possibly due to hypergonadotropic hypogonadism with a total testosterone level of 3.7 nmol/L (reference range: 9.9–27.8), FSH 18.3 IU/L, and LH 13.3 IU/L (1–25).

His family reported poor academic performance, difficulties in relations with other students, and progressive behavioral changes (attention deficit, irritability, impulse control problems) in the previous two years.

Physical examination found a weight of 50.5 kg, a height of 169 cm (97th percentile of height and 50th percentile of weight for Chinese adolescents of similar chronological age),[1] and an arm span of 173 cm. He had a longilinear body habitus, pectus excavatum, kyphoscoliotic pattern, prominent elbows, and increased abdominal fat. Low hair implantation, abnormal ears, hypertelorism, and epicanthus were also found. As regards secondary sexual characteristics, he had no pubic and axillary hair and showed infantile genitalia (2-mL testes, 3-cm penis). The rest of the examination was unremarkable (Fig. 1).

Based on these findings, laboratory tests were requested, including a hormone profile, X-rays of the left hand, and karyotype. The patient was also referred to the infantile mental health unit (USMI). Results of supplemental tests were as follows: total testosterone, 5.5 nmol/L; sex hormone-binding globulin (SHBG), 29.9 nmol/L (NV 10–80); LH, 29.6 IU/L; FSH, 37.3 IU/L; 17-beta-estradiol, 24 pmol/L (20–1800); TSH, 3.93 μU/mL (0.4–4); total cholesterol, 106 mg/dL (150–200); and triglycerides, 58 mg/dL (70–170). Basic blood chemistry, liver tests, and complete blood count were normal. Bone age was 13 and a half years. Karyotype showed polysomy 48,XXXY. The patient was assessed by the clinical psychology team of USMI and reported to have mild mental retardation (intelligence quotient (IQ) of 62 with marked retardation in the speech area) and difficulties in cultural adaptation.

A diagnosis of partial hypergonadotropic hypogonadism due to Klinefelter-like syndrome secondary to aneuploidy 48,XXXY was therefore made. Treatment was started with testosterone cypionate 50 mg every 4 weeks by the intramuscular route, with three-monthly dose titration based on total testosterone and gonadotropin (FSH and LH) levels. Drug treatment was well tolerated and had no influence on behavior. Based on recommendations by the USMI, the patient entered a specific support and follow-up program at school.

Klinefelter syndrome encompasses a group of disorders characterized by the presence of at least one X chromosome additional to the normal male karyotype, 46,XY. The classical form is a karyotype 47,XXY, but there are other much more uncommon variants, such as those caused by aneuploidies 48,XXYY, 49,XXXXY, and 48,XXXY.[2] The 47,XXY is the most common chromosome abnormality in humans, with an incidence of one case per 650 males born. The incidence of the 48,XXXY variant is very low and is estimated at approximately 1:50,000 males born.[3]

While patients with these polysomies share common clinical characteristics, there are differential traits between the different forms reported. This syndrome is traditionally characterized by tall height, narrow shoulders, gynecomastia, decreased testicular size and penis length, facial dysmorphism, hypergonadotropic hypogonadism, and mental retardation, among other changes. These traits vary depending on the underlying chromosome abnormality and specifically on the number of surplus X chromosomes. Thus, patients with polysomy 48,XXXY have higher mean heights as compared to those with polysomy 47,XXY (190 cm versus 179–188 cm) and are more likely to have congenital malformations such as radioulnar synostoses or clinodactyly.[3,4] Facial and body dysmorphism (hypertelorism, epicanthus, narrow lid opening, low hairline implantation, flat feet, joint hyperextensibility and hyperlaxity) are also more common in polysomy 48,XXXY. Decreased testicular volume (less than 3 mL and usually lower than 1.5 mL) is a constant trait, and is also more likely in patients with polysomy 48,XXXY.[3] Other frequent changes include metabolic syndrome, type 2 diabetes mellitus, osteoporosis, and breast cancer. It is not known whether the risk of these changes is greater in variants of Klinefelter syndrome.[5]

As regards the cognitive sphere, significant intellectual disability is uncommon in patients with polysomy 47,XXY, in whom mean IQ ranges from 89 and 102. By contrast, more than 50% of patients with aneuploidy 48,XXXY have a variable mental retardation (IQ 40–75). Learning, speech, and motor retardations are more common in variant 48,XXXY,

☆ Please cite this article as: Romero Lluch A, et al. Alteraciones endocrinológicas y psicológicas en la polisomía 48,XXXY. Endocrinol Nutr. 2012;59:396–8.