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□ Case Report □

Hypokalemic Periodic Paralysis in Graves' Disease

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그레이브스씨병에서 발생한 저칼륨성 주기적 마비증

서영진 · 김 욱 · 전정수

Thyrotoxic hypokalemic periodic paralysis is a rare endocrine disorder, most prevalent among Asians, which presents as proximal muscle weakness, hypokalemia, and with signs of hyperthyroidism from various etiologies. It is an autosomal dominant disorder characterized by acute and recurrent episodes of muscle weakness concomitant with a decrease in blood potassium levels below the reference range, lasting from hours to days, and is often triggered by physical activity or ingestion of carbohydrates. Although hypokalemic periodic paralysis is a common complication of hyperthyroidism among Asian populations, it has never been documented since in Korea. We report a case of male patient with Graves' disease accompanied by hypokalemic periodic paralysis that was treated by total thyroidectomy, and present a literature review. **(J Korean Surg Soc 2002;62:344-347)**

Key Words: Thyrotoxicosis, Paralysis, Hypokalemia
중심 단어: 갑상선중독증, 마비, 저칼륨증

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INTRODUCTION

Periodic paralyses - include hypokalemic and hyperkalemic periodic paralyses - and nondystrophic myotonias constitute a group of hereditary muscle disorders implicating an abnormal function of ion channels. (*1,2*) These ion channelopathies include hypokalemic and hyperkalemic periodic paralysis, paramyotonia congenita, and myotonia congenita. Primary hypokalemic periodic paralysis (HPP) is a rare entity first described by Shakanowitch in 1882, (*1*) and is an autosomal dominant disease. We hereby report a case of HPP in a male adult, successfully managed by total thyroidectomy for his Graves' disease and hypokalemic periodic paralysis.

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CASE REPORT

A 30-year-old male patient presented with complaints of recurrent attacks of quadriparesis especially after vigorous exercises for the last 5 years, which had been started 2 months after the diagnosis of and medications for Graves' disease. He had taken medications of methimazole (15 mg/day) and propylthiouracil (50 mg/day) initially but discontinued medications on his own intermittently and paralysis together with hypokalemia developed. Each episode of paralysis used to start with symmetrical lower limb weakness progressing to the upper limbs over a period of 3～4 hours. Spontaneous recovery occurred over 3～4 days every time. Many of the episodes started in the early morning hours without any particular precipitating factor. The general physical examination was normal and he had a family history of having an aunt who experienced a unilateral thyroid lobectomy for her nodular hyperplasia. There was hypotonia and proximal muscle weakness in the limbs but deep tendon jerks were not depressed. No other neurological signs were present. His initial serum potassium level was 2.0 mEq/L and sodium level was 142 mEq/L. His electrocardiogram showed findings of QT prolongation. Considering the clinical pattern and biochemical abnormalities, a diagnosis of thyrotoxic hypokalemic periodic paralysis was made and the patient was admitted for surgical care due to his poor compliance with antithyroid medications. Thyroid ultrasonogram revealed diffusely enlarged thyroid glands. Strong hot uptake was seen on the scintigram. Thyroid-stimulating hormone receptor antibody level rose up to 35 U/L that was over three fold of reference range. His potassium level was being corrected before the operation with potassium supplementation

and elevated thyroid functions (elevated free T4 2.59 ng/dl (0.8～1.8), T3 3.59 ng/ml (0.6～1.7), T4 18.79μg/dl (4.5～12) and decreased TSH 0.0021μU/ml (0.4～5)) were suppressed with propylthiouracil. Three months later he was euthyroid and symptom free. Total thyroidectomy was performed and L-thyroxin prescribed. Since one month after the operation, his serum potassium level showed normal value and he suffered no more muscle weakness ever after. On his follow up of 17 months, he has been a good condition and no other symptoms yet.

DISCUSSION

Hyperkalemic periodic paralysis, paramyotonia congenita, and their variants are transmitted with an autosomal dominant inheritance with complete penetrance and variable expressivity. But myotonia congenita displays both autosomal dominant and recessive modes of transmission. By analogy with murine model of myotonia congenita and using interspecies conservation of syntenic loci, both forms of myotonia were shown to implicate the muscle chloride channel CLCN1. (*2,3*) By a candidate gene approach, these muscle disorders were seemed to be caused by allelic mutations of the muscle sodium channel gene SCN4A located on chromosome 17q22-23. (*4*)

Hypokalemic periodic paralysis (HPP) is an autosomal dominant disorder with incomplete penetrance in females or rarely sporadic in 20% of the cases. In the present case, however, no family member was affected. Though the exact etiology of hypokalemia in HPP is not known, a possibility of abnormally reduced surface membrane permeability to potassium in muscles has been proposed. (*5*) Thus, low serum potassium coupled with high muscle potassium levels produce hyperpolarization of the muscle membrane, making it inexcitable. (*5*) Muscle weakness during attacks is due to the persistent depolarization of the sarcolemmal membrane. An abnormal influx of sodium was recorded in muscle fibers of HPP patients when decreasing the extracellular level of potassium. (*6*)

The hypokalemia is due to a massive shift of potassium from the extra- to the intracellular compartment. It is suggested that the mechanism for the development of the hypokalemic periodic paralysis is the intracellular blockade of potassium by the surplus of thyroid hormones. (*7*) The pathogenesis of hypokalemic periodic paralysis involves the ATPase-dependent sodium-potassium pump whose activity is stimulated by thyroid hormones. (*8*) The mechanism may be based on potassium shift into the muscle cell due to higher activity of the Na-K-ATPase pump, under the influence of beta-adrenergic stimulation and thyroid hormone, (*9*) but there is another explanation for the increased activity of the Na-K-ATPase pump. (*10*) The exact nature of the abnormal ion channel and the mechanisms leading to hypokalemia are still unknown. However, sarcolemmal ion channels or the genes regulating their function are candidate genes for the defect. In this context, HPP was shown to be non-allelic to the other ion channelopathies. (*11-13*)

An increased frequency of HLA-DR3 was found in Graves' patients without paralysis but not in those with paralysis, as compared to the general population. (*14*) The fact that muscle disorders caused by different defective genes exhibit the same phenotype suggests that the products of the implicated genes may cooperate in a still undetermined manner to result in an appropriate muscle contraction. The identification of these genes through studies of families presenting ion channelopathies may lead to a better understanding of the interaction between ion channels or with the genes regulating their function.

Periodic paralysis manifests only in the thyrotoxic patient, occurring sporadically almost exclusively in young Asian men in the third decade with a negative family history. Graves' disease is the most common cause of hyperthyroidism, (*15-17*) but any cause of thyrotoxicosis (including administration of excessive amounts of exogenous thyroid hormone) can trigger attacks of thyrotoxic periodic paralysis (TPP) in susceptible subjects. The reasons for the ethnic and male predominance are poorly elucidated. The onset of the disease is usually in the second decade, and the first attack occurs before 16 years of age in 60%. (*18*) The attacks started at night or early after awakening, frequently triggered by a high carbohydrate diet and physical exertion. Reflexes were brisk at the onset of the attack and reduced or absent during the course of the episode. Prior to diagnosis patients presented one to five attacks of thyrotoxic periodic paralysis each lasting between one to ninety-six hours. Attacks resolved after treatment of the hyperthyroid state. Interestingly, many attacks about half seemed to occur between July and October, most commonly in August. (*19*) Except for the fact that hyperthyroidism is an absolute requirement for expression of the disease, TPP is identical to familial periodic paralysis (FPP) in its clinical presentation. TPP affects predominantly males (to an even greater degree than FPP), is rarely associated with a positive family history, and has a later onset of presentation than FPP (reflecting the need for hyperthyroidism to occur before the disorder can be expressed). Involvement of respiratory muscles in usually uncommon during an attack. (*18*) Patients present with acute and reversible attacks

of muscle weakness accompanied by a fall in blood potassium levels. The severity of paralysis did not correlate with the degree of either hypokalemia or hyperthyroidism. (*14*)

Hypokalemic periodic paralysis is not often highlighted as an endocrine emergency. Early diagnosis is important so as to be able to establish antithyroid treatment and avoid further episodes of weakness. Diagnosis of HPP rests upon excluding secondary causes of hypokalemia. (*18*) Intermittent attacks and normal serum potassium values in between attacks point to a primary cause in present case. Clinical features of thyroid disease may be very subtle or virtually nonexistent, therefore thyroid function tests along with the determination of the plasma levels of potassium are part of the diagnostic workup of hypokalemic periodic paralysis.

Low carbohydrate low sodium diet, spironolactone and diclofenamid have also been tried in the management of HPP. Current treatment consists of conventional management for thyrotoxicosis including thyroidectomy. (*9*) Definitive treatment of hyperthyroidism leads to cessation of periodic hypokalemic paralysis, but symptoms can return with recurrence of the hyperthyroid condition. Potassium supplementation during an acute attack will shorten the duration and alleviate the symptom of the episode, and the treatment with antithyroid drugs with or without beta-blocker may prevent attacks in some patients.

CONCLUSION

Thyrotoxic hypokalemic periodic paralysis is an underdiagnosed but probably frequent complication of hyperthyroidism mostly in Asian males. Early recognition of the attacks is essential to investigate and treat the underlying thyroid dysfunction whose symptoms are usually mild and whose myalgias and flaccid weakness predominated over proximal leg muscles, sparing bulbar and respiratory musculature. The episodes of periodic paralysis resolve with the correction of the hyperthyroidism. In case of noncompliance with antithyroid medications, thyroidectomy may be considered positively to correct both abnormalities. Thyrotoxic periodic paralysis should be considered in the differential diagnosis of all acute episodes of motor paralysis or acute muscle weakness in young male patients. Absence of clinical thyrotoxicosis does not exclude the diagnosis. Plasma potassium should be monitored carefully during treatment to prevent rebound hyperkalemia.

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