Hypokalemic Periodic Paralysis Induced by Thymic Hyperplasia and Relieved by Thymectomy

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Case Report/Case Series

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**CONCLUSIONS AND RELEVANCE**

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**OBSERVATIONS**

We report a male patient in his mid-20s with progressive episodes of flaccid muscle weakness, associated low serum potassium levels, and a pathologic decrement in the long exercise test. Because the familial inheritance in the family was initially unknown, thorough diagnostic tests were performed including contrast-enhanced computed tomography scan, which displayed a mass in the anterior mediastinum. The test results for autoantibodies against myasthenia gravis (acetylcholine receptor, muscle-specific tyrosine kinase, and low-density lipoprotein receptor–related protein 4) and other end plate channelopathies were negative, and test results for hypokalemia-inducing hormones (thyroid, corticotropin, and cortisol) were negative. Surgery identified a thymus of $13 \times 8 \times 3$ cm$^3$. Histologic analysis was consistent with thymic hyperplasia of the follicular subtype and immunohistologic analysis showed cytokeratin 5/6 in hyperplastic epithelial cells. A 2-year follow-up revealed the postoperative absence of weakness episodes. As in 30% of familial cases, molecular genetics testing failed to identify a mutation in periodic paralysis genes.

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Chest imaging was performed by radiography and contrast-enhanced computed tomography (CT). The following serum concentrations were determined: electrolytes; corticotropin (ACTH); cortisol; aldosterone; thyroid hormones; creatine kinase; IgA, IgG, IgM, and IgE; light chains k and λ, k/λ; complements C3 and C4; CD3, CD4, CD8, CD19, and CD4/CD8; and natural killer cells. The following autoantibodies were tested: acetylcholine receptor, muscle-specific tyrosine kinase, N- and T-type calcium channels, voltage-gated potassium channel complex, N-methyl-D-aspartate subunit R1, AMPA1/2, γ-aminobutyric acid B receptor, CASPR2, LGI1, RyR1, titin, skm, nuclear, ribonuclear, Sm, Sjögren syndrome A and B, PM-Scl, jo-1, centromere protein B, proliferating cell nucleus, DNA, nucleosome, histone, ribosomal proteins, and mitochondria. The recently reported myasthenia gravis autoantibody against the low-density lipoprotein receptor–related protein 4 (Lrp4), which functions as a muscle-specific tyrosine kinase ligand, was determined using an indirect immunofluorescence test on HEK293 cells, transiently transfected for 48 hours with complementary DNA of human Lrp4–green fluorescent protein, conferring green fluorescence to Lrp4-expressing cells. Membrane-bound anti-Lrp4 antibodies of positive controls were visualized by secondary antibodies exhibiting red fluorescence.

In the long exercise test, the patient, his uncle presenting with hypokalemic PP, and a male healthy control aged 30 years performed 7 rounds of finger spreading of 35 to 40 seconds each against strong resistance, followed by 2 to 3 seconds of relaxation, ensuring blood flow. The ulnar nerve was supramaximally stimulated at the wrist (constant current pulse, 0.2 milliseconds, 125%). Compound muscle action potentials were recorded from the abductor digiti minimi muscle immediately before and after exercise and then every minute for 5 minutes and finally every 5 minutes for up to 60 minutes.

The exons and exon-intron boundaries of \( CACNA1S \), \( SCN4A \), \( KCNJ2 \), and \( KCNJ18 \) were amplified from genomic DNA and bidirectionally sequenced using an automated 373A sequencer.

Results

Family History

The patient and his maternal uncle had hypokalemic PP with episodes of flaccid muscle weakness associated with low serum potassium levels and a pathologic decrement in the long exercise test (Figure 1). The spells were triggered by strenuous muscle work or exposure to a cold environment and improved by potassium intake. The patient’s mother was deceased (stroke) and did not present with weakness episodes.

The Patient’s History

The patient reported episodes of muscle weakness for 5 years. The episodes usually occurred during rest after strenuous exercise or after exposure to a cold environment and consisted of proximal leg weakness or tetraparesis. Hypokalemic was detected during some episodes (lowest potassium value, 2.38 mEq/L [to convert to millimoles per liter, multiply by 1], whereas interictal serum potassium levels were in the normal range [3.5-5.5 mEq/L]). In his early 20s, attacks expanded from paraparesis to tetraparesis. During the first 2 years, the episodes disappeared spontaneously within 2 hours to a few days; however, in the last 3 years, potassium administration was required. During the last 6 months before referral, frequency and severity of attacks further increased and potassium administration became ineffective. The patient reported no other diseases.

Perioperative Findings

The patient was referred to 117 PLA Hospital with complete proximal tetraparesis and reduced muscle stretch reflexes. Although ocular, bulbar, and respiratory muscles seemed to be unaffected, a neostigmine test was performed and results were negative. Except for a reduced serum potassium level of 2.4 mEq/L, all other serum values, including
the autoantibodies listed in the Methods subsection, were not indicative of an autoimmune disorder. Particularly test results for the myasthenia-related autoantibodies, including anti-Lrp4 and the autoantibodies against various neuromuscular ion channels, were negative. Serum cortisol levels taken at 8 AM were in the normal range of 3.5 to 25.0 μg/dL (to convert to nanomoles per liter, multiply by 27.588) (18.1 μg/dL at admission and 15.9 μg/dL at release) as well as serum ACTH level determined at release (24 ng/L; normal range, 10-90 ng/L). Thyroid and renal function, arterial blood pressure, electrocardiogram, radiography of the chest, and a contrast-enhanced CT scan of the adrenal glands revealed no abnormal findings. A contrast-enhanced CT scan of his chest exhibited an enlarged thymus (Figure 2A).

Thoracic surgery was performed right sided and video assisted under particular perioperative measures. In situ, an enlarged yellow-red thymus was observed. The excised thymus weighed 200 g (Figure 2B). Histologically, a lobular architecture with thymic cortex, medulla, Hassall corpuscles, and multiple hyperplastic follicles were observed, composed of adipose tissue and fibrous tissue (Figure 2C). Immunohistology was negative for ACTH but revealed hyperplastic thymic epithelial cells positive for cytokeratin 5/6 (Figure 2D), confirming the diagnosis of follicular thymic hyperplasia.

Follow-up
Examinations performed 1 and 2 years after thymectomy revealed a postoperative absence of both abortive spells and weakness episodes. Genetic studies of both the patient and his uncle revealed no disease-causing mutation in the PP genes, and a contrast-enhanced CT scan of the uncle’s chest was normal.

Additional Information on Unavailable Patients
We obtained the medical reports on (1) a male patient in his early 30s who had frequent hypokalemic weakness episodes and died of an acute paralytic attack associated with a serum potassium level of 2.0 mEq/L; thymic hyperplasia was found in the autopsy and (2) a female patient in her late 40s with familial hypokalemic PP and an enlarged thymus on the CT scan; thymectomy has not been performed because of the absence of end plate autoantibodies.
Discussion
Follicular thymic hyperplasia is seen in more than 50% of patients with myasthenia gravis. The remaining 50% have other autoimmune disorders, such as Graves disease or neuromyotonia, and tumors with increased ACTH or glucocorticoid levels. 11 Our patient exhibited normal ACTH, glucocorticoid, and thyroid serum levels. Additionally, we identified neither clinical hints for myasthenia gravis nor autoantibodies directed to the end plate. Finally, there were no autoantibodies against presynaptic calcium channels causing Lambert-Eaton syndrome or against dendrotoxin-sensitive potassium channels responsible for Morvan syndrome and neuromyotonia. 12

In spite of negative screening results, the presence of autoantibodies in our patient cannot be excluded since even the majority of patients with asymptomatic thymic hyperplasia develop an autoimmune disorder. 13 Evidence for contribution of a putative autoimmune disorder to the phenotype is the late onset and steady progression of the PP, suggesting a minimal required level of follicular thymic hyperplasia for clinical manifestation and a hyperplasia-proportional progression. The cessation of PP after thymectomy also supports this idea. Therefore, autoantibodies against sarcolemmal ion channels encoded by PP (susceptibility) genes should be tested in the future.

The reported familial recurrence indicates contribution of a hereditary disposition, probably due to a variant in an unknown susceptibility gene. This would explain the reduced penetrance in the mother and the lack of mutation in the PP channel proteins Cav1.1, Nav1.4, and Kir. 2 4 despite the occurrence of hypokalemic-related weakness episodes, response to potassium administration, and abnormal long exercise test results.

We conclude that thymic hyperplasia can clinically manifest genetically predisposed hypokalemic PP. For patients with hypokalemic PP and late onset or clinical progression, we recommend screening for an autoimmune disease and, if thymic hyperplasia can be identified, thymectomy. Our findings may stimulate the identification of patients, raise the discussion on which patients should be screened and the need for thymectomy, and finally spark the search for autoantibodies against sarcolemmal ion channels.

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