CASE REPORT

Myasthenia Gravis with Thymoma and Coexistent Central Hypothyroidism

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Myasthenia gravis (MG) is a well-known acquired autoimmune neuromuscular disorder. Patients with MG have a higher incidence of autoimmune disease than the normal population. MG is frequently associated with autoimmune thyroid disease, the most common of which is thyrotoxicosis. Associated hypothyroidism is not common, and the central (pituitary) origin, to our knowledge, has not yet been reported. We report an MG patient with thymoma that coexisted with central hypothyroidism, the correction of which is mandatory and significant to achieve remission. [*J Chin Med Assoc* 2009; 72(2):91–93]

Key Words: hypothyroidism, myasthenia gravis, thymectomy, thymoma

Introduction

Myasthenia gravis (MG) is an acquired neuromuscular disorder, characterized by fluctuating weakness of the skeletal muscles, particularly those innervated by motor nuclei of the brainstem. The disorder produces a decrease in the number of acetylcholine receptors in the neuromuscular plates, due to an autoimmune process mediated by antibodies against the alpha subunit of the nicotine receptor of acetylcholine. Patients with MG have a higher incidence of other autoimmune diseases, such as thyroid diseases, polymyositis, systemic lupus erythematosus, and rheumatoid arthritis. The most frequently associated condition is autoimmune thyroid disease, which is present in 5–10% of patients with MG.[1] However, only 0.2% of patients with thyroid disease have MG, with thyrotoxicosis as the most common among them. Hypothyroidism is rare. In the report of Téllez-Zenteno et al, associated conditions in MG accounted for about 26% of the cases, and among them, the incidence of hypothyroidism was less than half the incidence of hyperthyroidism (14% *vs.* 33%).[2] Herein, we present an MG patient with thymoma and coexistent central hypothyroidism, who benefited from the correction of hypothyroidism by thyroxine sodium (eltroxin) supplementation.

Case Report

An 82-year-old married man had hypertension for more than 10 years and received regular medications with good control. One month before admission, he complained of weakness when grasping objects, extending his fingers and after prolonged mastication. The symptoms occurred mostly in the afternoon; no prominent fluctuating course was noted, and the patient felt better after resting. He did not complain of muscle aches or cramps after exertion. Two weeks before admission, he developed drooping of his left eyelid, and a positive intravenous vasostigmine test was noted. Progressive exertional dyspnea and orthopnea were observed in the ongoing 1 week.

Physical examination showed an awake, well-nourished but acutely ill-looking patient, with tachypnea (30 per minute) and exertional dyspnea without wheezing, rhonchi or rales. There were no limb edema, cyanosis, or clubbed fingers. Neurologic examination showed weakness of all 4 limbs but symmetrical muscle power grading of 4/5 in both distal and proximal portions. Prominent weakness of neck flexors and extensors with grades of 2/5 and 3/5 respectively were also noted. Light reflexes, eye accommodation, other brainstem reflexes, swallowing capability and all the

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Table 1. Repetitive stimulation of peripheral nerves at a rate of 3 per second on admission and on the 45th postoperative day

Muscle	On admission			Postoperatively		
	Ampl (mV)	△AMP4 (%)	△AMP10 (%)	Ampl (mV)	△AMP4 (%)	△AMP10 (%)
Right						
APB	12.4	–20.2	–19.1	10.5	–5.3	–8.2
ADM	10.4	–16.1	–18.4	7.4	–4.6	3.6
Nasalis	1.1	–48.2	–43.2	1.3	–4.1	–3.1
Left						
APB	9.4	–22.1	–17.8	7.0	–2.7	0.8
ADM	9.3	–21.2	–15.4	6.7	2.9	1.2
Nasalis	0.8	–36.5	–32.7	1.6	1.1	0.8

APB = abductor pollicis brevis; ADM = abductor digiti minimi; Ampl = amplitude; △AMP4 = difference in amplitude of wave 4; △AMP10 = difference in amplitude of wave 10.

sensory modalities were intact. Symmetrically brief knee and biceps jerks were noted. There were no upper motor neuron signs, no fasciculations, no myotonia, no muscle hypertrophy and no muscle tenderness. Laboratory data revealed no significant findings in routine blood tests and biochemistry study. The acetylcholine receptor antibody using radioimmunoassay was 45.3 nmol/L (normal < 0.2 nmol/L). No hypoxemia or hypercapnia was noted. Noncontrast chest computed tomography (CT) disclosed a soft tissue density measuring about 13 × 4.6 × 2.3 cm in size at the anterior mediastinum. Repetitive stimulation of peripheral nerves (including facial, median and ulnar nerves) at a rate of 3 per second showed significant decremental responses (Table 1).

Double-filtration plasmapheresis was started for 5 consecutive sessions, and postprandial oral pyridostigmine 60 mg thrice a day and oral prednisolone 5 mg twice a day were also given simultaneously. Intravenous methylprednisolone 1,000 mg was given on the day of admission and in the perioperative period. About 11 days after admission, the patient underwent maximal thymectomy via a trans-sternal approach. Histopathologic examination showed a multilocular thymic cyst with multifoci of type A thymoma, and no evidence of malignancy was seen. The endotracheal tube (ET) was removed smoothly after recovery of consciousness on the same day of operation. Neurologically, the patient showed no focal limb weakness and no swallowing difficulty, but marked weakness in neck flexors and extensors were noted as on admission.

On the 6th postoperative day, he became drowsy, and arterial blood gas showed hypercapnia (57 mmHg) without hypoxemia. He regained consciousness soon after intubation of ET tube with ventilator support. Plasmapheresis was restarted for 3 consecutive sessions, along with increased dosage of pyridostigmine to 240 mg and prednisolone to 20 mg a day. On the 10th postoperative day, the patient was weaned from the ventilator, but a similar event occurred 3 days after extubation and arterial blood gas again disclosed hypercapnia (45 mmHg) that soon resolved after re-intubation of ET tube with ventilator support. Stationary neurologic deficits were noted.

Possible associated conditions of MG were surveyed due to repeated failure of weaning from ventilator with ensuing hypercapnia. The results showed low levels of total triiodothyronine (T3; 0.49 ng/mL; normal, 0.7–1.7 ng/mL), total thyroxine (T4; 1.90 μg/dL; normal, 4.5–12.5 μg/dL), and free thyroxine (FT4; 0.45 ng/dL; normal, 0.89–1.8 ng/dL), but normal levels of thyroid-stimulating hormone (TSH; 1.07 μIU/mL; normal, 0.4–4 μIU/mL), prolactin, ACTH, cortisol, follicle-stimulating hormone, luteinizing hormone, erythrocyte sedimentation rate, and immunoglobulins (IgA, IgG, IgM). Antinuclear antibody and rheumatoid factors were negative. Consultation with an endocrinologist confirmed the central origin of hypothyroidism.

Magnetic resonance imaging (MRI) of the brain showed a small pituitary gland with widened empty pituitary fossa (empty sella) and no abnormal contrast enhancement. There was no evidence of other polyglandular autoimmune diseases, which was confirmed after an evaluation by a rheumatologist. Eltroxin supplement with 100 μg daily was given along with respiratory training rehabilitation. Dramatic responses were noted 5 days later. The patient regained full muscle power of neck flexors and extensors and was weaned from the ventilator successfully. The serum level of T4 (8.0 μg/dL) and FT4 (2.05 ng/dL) normalized, although T3 level remained at the lower limit of normal (0.62 ng/mL). TSH (1.9 μIU/mL), cortisol and ACTH remained within normal limits after repeated check-up.

Repetitive stimulation of peripheral nerves was repeated 45 days after operation, and revealed no decremental responses (Table 1). The patient was able to live independently. Medications were continued with oral prednisolone 10 mg, pyridostigmine 180 mg and eltroxin 50 μg a day.

Discussion

We present a patient with definite MG who had thymoma that coexisted with central hypothyroidism. Whether the coexistence of hypothyroidism plays a major role in the clinical expression or plays an adjunctive role is not well known. Since the positive intravenous vasostigmine result, elevated serum acetylcholine receptor antibody, significant decremental responses at 3-Hz repetitive stimulation test, anterior mediastinal mass by CT scan, and histopathologic findings all confirmed the diagnosis of MG with thymoma, we did not pursue further surveying for possible associated conditions. Fortunately, this overlook did not result in any irreversible harm to the patient. Instead, it helped us prove that the correction of hypothyroidism is mandatory for complete remission of MG. This seems to contradict the findings of De Assis et al, who suggested that "there is no clinical correlation between both myasthenia symptomatology and thyroid dysfunction, neither significant influence on myasthenic symptoms when the endocrine disorders improve".[3]

The main symptoms related to hypothyroidism are proximal muscle weakness, muscle cramps, and myalgia, which were lacking in our patient, except for the prominent neck and respiratory muscle weakness. It was also observed that the patient could not be weaned from the ventilator successfully without thyroxin supplementation. Proximal myopathy may rarely be seen as the sole manifestation of hypothyroidism. However, in our patient, the initial manifestations were distal muscle weakness and preserved deep tendon reflexes without evidence of myxedema. These initial manifestations seemed to have no correlation with hypothyroidism, hence, an "atypical" condition was more favored. Severe muscular weakness of acute onset is relatively rare and is encountered in approximately 1% of hypothyroid patients.[4] Conversely, we may not see improvement in spite of thyroxine supplementation without sufficient treatment directed toward MG. In our patient, we were able to achieve complete remission with the proper management of MG and correction of hypothyroidism.

Central hypothyroidism is caused by impaired stimulation of a normal thyroid gland by hypothalamic or pituitary hormones via various etiologies,[5] and pituitary adenomas are the most common cause.[6] The etiopathogenic relationship between the thymus and MG is variable and complex, and immunopathologic as well as immunogenetic possibilities have been proposed. Kuroda et al[7] described a case of exacerbation of myasthenia after removal of a thymoma having a membrane phenotype of suppressor T-cells, while Ghiringhelli et al[8] suggested that the onset of myasthenia can be attributed to the withdrawal, following surgery, of the inhibitory effects of the thymoma on some clones of autoreactive lymphocytes. But in a large series study, regarding thymectomy for MG with associated conditions, no differences were found between patients with and without associated conditions in their clinical data, complications, and response to thymectomy.[2] A multifactorial study clarified the prognostic factors in thymoma, and found that staging was of the greatest usefulness in predicting the biological behavior of thymoma, and other clinicopathologic features (age, sex, tumor size, presence of MG, epithelial subtyping, and lymphocyte/epithelial cell ratio) have no definite influence on survival expectancy.[9]

In our patient, the reason for the pure selective pituitary dysfunction is not clear, and clinical follow-up to search for other possible associated autoimmune diseases should be kept in mind in the future. Surveying of associated conditions in every MG patient should be done routinely even though definite thymoma is present. Correction of the associated conditions is mandatory and may be significant in the achievement of remission.

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