Coexistence of Pernicious Anemia and Myasthenia Gravis—A Rare Combination of Autoimmune Diseases in Taiwan

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About 5–10% of patients with myasthenia gravis concomitantly have other autoimmune diseases. However, the coexistence of myasthenia gravis and pernicious anemia is rare. Here, we report a 73-year-old Taiwanese woman who developed myasthenia gravis 5 months after the onset of pernicious anemia. Her myasthenic and pernicious anemia symptoms markedly improved after pyridostigmine, prednisolone and hydroxocobalamin treatment. It is important to recognize concurrence of myasthenia gravis and pernicious anemia in the same patient because the therapeutic results for both diseases are rewarding. [J Formos Med Assoc 2006;105(11):946–949]

Key Words: myasthenia gravis, pernicious anemia

Myasthenia gravis is an autoimmune disease that affects the neuromuscular junction and has occasionally been found in conjunction with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and thyroiditis.1 There have also been a few reports of the association of myasthenia gravis with pernicious anemia.2,3 Multiple autoantibodies, such as anti-parietal cell and anti-intrinsic factor antibodies, have also been demonstrated in some myasthenia gravis patients.3,4 It is speculated that these associations represent a constellation of hyper-immunity syndromes. Here, we report an elderly Taiwanese woman who developed myasthenia gravis in the course of pernicious anemia.

Case Report

A 73-year-old woman was admitted to our hospital with an 8-month history of oral and lingual pain in September 2002. She was neither a vegetarian nor an alcoholic. She had no history of hyperthyroidism, diabetes mellitus, alopecia, or celiac disease. Physical examination showed beefy red tongue with atrophic papillae and mild cheilosis. The liver and spleen were impalpable. Laboratory studies showed a red blood cell (RBC) count of $1.4 \times 10^{12}/L$ (normal range, 4.5–7.9 $\times 10^{12}/L$), hemoglobin of 66 g/L (normal range, 45–59 g/L), hematocrit of 19.1% (normal range, 41–53%), mean corpuscular volume (MCV) of 134 fl (normal range, 80–100 fl), and mean corpuscular hemoglobin of 46 pg (normal range, 26–34 pg). White blood cell count was $3.8 \times 10^9/L$ (normal range, 3.8–10.6 $\times 10^9/L$) with 54% segmented neutrophils, 40.5% lymphocytes, 2% monocytes, 2% eosinophils, 1% atypical lymphocytes, and 0.5% basophils. Platelet count was $122 \times 10^9/L$ (normal range, 150–400 $\times 10^9/L$). Serum levels of electrolytes, glucose, blood urea nitrogen, creatine, aspartate aminotransferase, alanine aminotransferase,

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Received: August 17, 2005
Revised: September 27, 2005
Accepted: December 6, 2005

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γ-glutamyl transpeptidase, and total bilirubin were all within normal limits. Thyroid screening tests, including free T4 and thyroid-stimulating hormone, were unremarkable.

Diagnostic studies for anemia showed a decreased level of serum vitamin B12 (<36.9 pmol/L, normal range, 118.1–715.9 pmol/L) and a positive gastric parietal cell antibody (titer, 1:80). Serum folate level was normal. Microscopic examination of a peripheral blood smear showed marked hypersegmented neutrophils. Bone marrow aspirate showed megaloblastic hematopoiesis. Atrophic gastric mucosa with absence of parietal cells and chronic inflammation were observed on esophageal endoscopic biopsy. Based on the clinical and laboratory findings, pernicious anemia was diagnosed.

After 3 months of hydroxocobalamine treatment, the oral and lingual pain subsided. Five months later, RBC count, hemoglobin, hematocrit, and MCV were 4.42 × 10^12/L, 126 g/L, 39.8%, and 90.0 fl, respectively. She was re-admitted in February 2003, however, due to bilateral ptosis.

During the second course of hospitalization, binocular diplopia was noted, with free range of eye movement. The pupils were normal in size and promptly reactive to light. Muscle strength was normal in the face and four limbs. Edrophonium hydrochloride administered intravenously in a dose of 10 mg produced a dramatic improvement in ptosis. Nerve conduction studies of the four limbs were normal. Repetitive nerve stimulation at 3 Hz demonstrated a 60% decremental response of the compound muscle action potential amplitude in the deltoid muscle and a 36% decremental response in the triceps muscle. Serum anti-acetylcholine receptor antibody was 5.36 nmol/L (normal, <0.2 nmol/L). Myasthenia gravis was diagnosed based on the clinical and laboratory findings. Thoracic computed tomography revealed no evidence of thymoma.

Ptosis and diplopia improved markedly after pyridostigmine (60 mg, 4 times per day) and oral prednisolone therapy (20 mg daily). Regular pyridostigmine and hydroxocobalamine administration was continued. Prednisolone was tapered and stopped 7 months after discharge, and repetitive nerve stimulation at the rate of 3 Hz demonstrated no significant decremental response. She experienced no recurrence of anemia or myasthenic symptoms over a 2-year follow-up at our outpatient clinics.

**Discussion**

Pernicious anemia is a chronic illness caused by impaired absorption of vitamin B12. It is an autoimmune disease due to atrophic gastritis that produces autoantibodies to the gastric parietal cells or intrinsic factors. The clinical manifestations of pernicious anemia include beefy tongue, loss of papillae, lingual and oral burning pain. The pathologic features of aspirated bone marrow were hypercellularity with large erythroid precursors and hypersegmented neutrophils. Subacute combined degeneration of the lateral and dorsal column of the spinal cord is usually noted as the neurologic presentation. The present case had characteristic features of pernicious anemia including macrocystic anemia, megaloblastic hematopoiesis, positive gastric parietal cell antibody and a low serum level of vitamin B12. The development of ptosis and diplopia later raised the possibility of myasthenia gravis. The symptoms of both diseases were markedly improved after medical treatment.

Myasthenia gravis is an autoimmune disease associated with the presence of anti-acetylcholine receptor antibody. This autoantibody binds to the postsynaptic nicotinic acetylcholine receptor and blocks neuromuscular transmission. Other autoimmune diseases, such as systemic lupus erythematosus, polymyositis, rheumatoid arthritis, and Hashimoto’s thyroiditis are present in 5–10% of patients with myasthenia gravis. However, the combination of myasthenia gravis and hematologic autoimmune diseases is rare. A few cases of pernicious anemia, hemolytic anemia, pure red cell aplasia, thrombotic thrombocytopenic purpura and acute lymphoblastic leukemia associated with myasthenia gravis have been reported.
Simpson reported a total of nine cases of pernicious anemia in 491 patients with myasthenia gravis—an incidence of 1.83%, and concluded that the incidence of pernicious anemia in patients with myasthenia gravis is higher than in the normal population. However, a review of the data from our previous study of 390 patients with myasthenia gravis in this hospital, diagnosed based on clinical features and confirmed by positive anti-acetylcholine receptor antibody and/or decremental repetitive nerve stimulation response, revealed that only one patient (0.26%) had pernicious anemia. From among the 390 patients in that study, 33 (8.46%) had thyroiditis, two (0.51%) had systemic lupus erythematosus, two (0.51%) had rheumatoid arthritis, one (0.26%) had Sjögren’s syndrome, and one (0.26%) had multiple sclerosis. In addition to one case of pernicious anemia, two other cases of myasthenia gravis concomitant with anemia (one case with thalassemia and the other with aplastic anemia) were found in the series. The result of the study indicated that the incidence of pernicious anemia in Taiwanese patients with myasthenia gravis (0.26%) is lower than that reported in Caucasian patients (1.83%). The discrepancy may be attributable to genetic differences, different sampling methods, the possibility that occurrence of both disorders may simply be coincidental, or to different immunopathogeneses involved in myasthenia gravis associated with pernicious anemia in Taiwanese and Caucasians.

Pernicious anemia and myasthenia gravis may share a common cause of autoimmunity. It is possible that different antibodies to various tissues can be expressed in the same patient. Downes et al found gastric parietal cell antibodies in 12% of 74 myasthenic patients. Zittoun et al reported a total of three (3.7%) patients with anti-intrinsic factor antibodies in a study of 81 patients with myasthenia gravis. Other autoantibodies, such as antithyroid and antinuclear antibodies, were also found in some patients with myasthenia gravis. On the other hand, such autoantibodies were also found occasionally in patients with pernicious anemia. Therefore, these two diseases may be classified as involving systemic autoimmunity. Determination of the extrinsic or intrinsic factors that trigger the production of these organ-specific autoantibodies will require further study.

A multicenter study of patients with myasthenia gravis in Italy reported that 70% had hyperplasia of the thymus and 10% had thymoma. A study from the USA reported that among patients with coexisting pernicious anemia and myasthenia gravis, 9% developed thymoma. Thymectomy may result in a striking improvement in patients with systemic lupus erythematosus or autoimmune hemolytic anemia occurring coincidentally with myasthenia gravis. However, the benefit of thymectomy in patients with coexisting myasthenia gravis and pernicious anemia has not been established. In this patient, myasthenia gravis and pernicious anemia were easily controlled with pyridostigmine and prednisolone, and hydroxocobalamine, respectively. As regular hydroxocobalamine administration was continued during follow-up in this case, it is not clear whether the pernicious anemia was cured by prednisolone treatment. However, a good response to short-term steroid treatment may suggest a lower level of autoimmunity and that thymectomy may not be necessary.

Although existing data suggest that the coexistence of myasthenia gravis and pernicious anemia is rare in the Taiwanese population, the presence of pernicious anemia must still be ruled out in any patient with myasthenia gravis who feature anemia or posterior-column symptoms. Conversely, ptosis, diplopia or muscle weakness in a patient with pernicious anemia should arouse suspicion of myasthenia gravis. Antibody testing in a patient with myasthenia gravis to screen for the full range of concomitant autoimmune diseases may be indicated. Recognition of the combination of myasthenia gravis and pernicious anemia is important because the therapeutic result is rewarding.
References