Case Report and Case Series

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Clinical characteristics and relationship between myasthenia gravis and premature ovarian failure: report of two cases

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Abstract

Myasthenia gravis (MG) and premature ovarian failure (POF) are rare. MF and POF greatly affect patients' health. Combined occurrence of MF and POF in young women can have serious consequences. We report two cases of MG with POF. Case 1 was a 20-year-old woman who presented with myasthenic crisis and menopause in September 2015 and November 2015, respectively. The patient's estradiol and follicle-stimulating hormone levels were abnormal. She was administered plasmapheresis and methylprednisolone pulse therapy. She improved and was discharged with normal restoration of menstruation after 3 months. Case 2 was a 21-year-old woman who had right eyelid droop and double vision in June 2014. She presented with menstrual disorder and menopause in August 2014 and September 2014, respectively. Estradiol and follicle-stimulating hormone levels were abnormal. She underwent progesterone therapy. She was admitted to hospital again in March 2016 with a myasthenic crisis. She received methylprednisolone pulse therapy and underwent thymectomy, but menstruation was not restored. In conclusion, there is comorbidity of POF in MG, and there is a close relationship between these two diseases. MG may subsequently lead to development of POF, and timely immunotherapy for MG may normalize POF.

Keywords

Myasthenia gravis, premature ovarian failure, progesterone, immunotherapy, myasthenic crisis, estradiol, methylprednisolone

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Introduction

The pathogenic mechanism of myasthenia gravis (MG), which is an autoimmune disorder, is mediated by acetylcholine receptor (AChR) antibodies. MG is cell-dependent and is associated with neuromuscular junction dysfunction.[1] This disorder is characterized by muscular weakness and fatigue. Premature ovarian failure (POF) is non-physiological cessation of menstruation after puberty and before 40 years old, accompanied by elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and decreased levels of estrogen. Clinical manifestations of POF include hot flashes, infertility, amenorrhea, menopause, and reproductive organ atrophy. Furthermore, estradiol (E2) and gonadotropin levels are reduced in POF.[2] MG and POF are rare diseases. In patients with secondary amenorrhea, the incidence of POF before the age of 30 years is 0.1%.[2] MF and POF have a major effect on patients' health. If both of these diseases occur in young women, fertility can be affected, causing serious consequences. We analyzed the clinical characteristics, treatment, and follow-up results of two patients with MG and POF, with the aim of improving the level of diagnosis and treatment of such problems by clinicians.

Case report

Case 1

A 20-year-old woman was hospitalized in September 2015 for unexplained exhaustion, even on walking short distances. She was hospitalized for 2 months and was diagnosed with MG, systemic lupus erythematosus, and Sjogren's syndrome. The patient was treated with prednisone, an injection of human immunoglobulin, and pyridostigmine, and her symptoms improved. She had experienced her last menstrual period on 11 November 2015. However, she still complained of limb weakness (obvious after exercise) after discharge and was re-admitted to our hospital on January 13, 2016. She did not smoke or drink alcohol. There was no record of family genetic diseases or other special medical conditions. *Tripterygium wilfordii* and other drugs affecting menstruation had not been administered.

The results of further examinations after admission are shown in Table 1. After admission, we found that the patient's symptoms of myasthenia were severe in the afternoon, aggravated after continuous activity, and were resolved after rest. MG was diagnosed on the basis of results of a neostigmine test, single-fiber electromyography, acetylcholine receptor antibody measurement, and measurement of the amplitude of low frequency repetitive nerve stimulation (detailed results are shown in Table 1).[3] During hospitalization, the patient had a cough, difficult expectoration, and MG crisis. Anti-infection treatment, tracheal cannulation, mechanical ventilation, methylprednisolone pulse therapy (0.5 g/day × 3 days by intravenous drip, 0.25 g/day × 3 days by intravenous drip, 0.12 g/day × 3 days by intravenous drip), and plasmapheresis (three times) were administered. Following these treatments, the patient was gradually taken off the ventilator and limb weakness was ameliorated. Since November 2015 up to this time of hospitalization, the patient's menstruation had not been restored. On the basis of this finding and the results for sex hormone tests (Table 1), we diagnosed the patient with POF. The discharged muscular strength was normal without any obvious discomfort. Discharge prescriptions included methylprednisolone (40 mg/day), pyridostigmine bromide (180 mg/day), bailing capsule (3 g/day), and mycophenolate mofetil (1 g/day). The patient insisted on taking these drugs orally in the outpatient

Table 1. Results of various auxiliary examinations.

Examination	Case 1	Case 2
Neostigmine test	Positive	Positive
Amplitude of low-frequency repetitive nerve stimulation	Decreased by >10%	Decreased by >10%
Single-fiber electromyography	Abnormal jitter	Abnormal jitter
Acetylcholine receptor antibody	Positive	Positive
Thymus enhanced CT	No obvious abnormality	Possible thymic hyperplasia
Electrocardiogram	Normal	Sinus bradycardia
Sex hormone test	E2: <10 pg/mL↓ FSH: 48.53 IU/L↑ LH: 21.95 IU/L↑ Prolactin: 19.27 ng/mL Testosterone: 0.19 ng/mL Progesterone: 0.10 ng/mL↓	E2 <10.00 pg/mL↓ FSH: 89.01 IU/L↑ LH: 24.43 IU/L↑ Prolactin: 21.87 ng/mL Testosterone: 0.13 ng/mL Progesterone: 0.20 ng/mL
Routine blood examination	WBC count: 2.15×10^9/L↓ Neutrophil count: 1.18×10^9/L↓	WBC count: 3.89×10^9/L↓ Neutrophils: (%) 0.353↓ RBC count: 3.95×10^{12}/L↓
Approximately normal examination	Routine urine analysis, renal function, lipid levels, and coagulation function tests showed no obvious abnormalities	No significant abnormality was found in pituitary MRI
Completely normal measurements	Anti-thyroid autoantibody, thyroid function, routine stool test, female eight-item tumor screening test, perinuclear-anti-neutrophil cytoplasmic antibody, glycosylated hemoglobin, and erythrocyte sedimentation rate	Procalcitonin, thyroid function, anti-thyroid autoantibodies, routine urine test, myocardial enzymes, routine stool examination, fecal occult blood test, and cardiac ultrasonography
Other abnormal test results	Detection of SLE: anti-nuclear antibody, 1.11 U/mL Anti-double-stranded DNA antibody: 992.99 IU/mL↑ Anti-nucleosome antibody: 283.26 U/mL↑ CRP: 13.60 mg/L↑ Serum amyloid protein A: 8.50 mg/L↑ IgA: 1.10 g/L↓ IgM: 0.64 g/L IgG: 17.90 g/L↑ Anti-cardiolipin antibody was weakly positive	Albumin/globulin ratio: 1.2↓ Creatinine: 52 μmol/L↓ Uric acid: 379 μmol/L↓ Cholinesterase: 4523 U/L↓ Prothrombin activity: 80.1%↓

Note: CT, computed tomography; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; CRP, C-reactive protein; RBC, red blood cell; WBC, white blood cell; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; Ig, immunoglobulin. Auxiliary examinations in Case 1 were in January 2016. Auxiliary examinations in Case 2 were in March 2016.

clinic, and treatment was continued for 2 months. Her condition reversed to normal menstruation. After being discharged for 6 months, a sex hormone test confirmed return to normal menstruation. At a 10-month follow-up, the patient had maintained normal menstruation and continued to be prescribed methylprednisolone (4 mg/days) and mycophenolate mofetil (0.75 g/days).

Case 2

A 21-year-old woman presented with right eyelid droop and double vision in June 2014 with no obvious cause. Symptoms were mildest in the morning and worst in the evening, worsened during fatigue, and resolved after rest. The patient had a menstrual disorder from August 2014 and menstruation ceased from September 2014. Therefore, the patient underwent four consecutive progesterone injection sessions at local hospitals in February 2015 after observing uterine atrophy with ultrasonography. However, the patient's menstruation did not return to normal. In September 2015, the patient was diagnosed with MG at Shenzhen People's Hospital. Symptoms of MG greatly improved with 60 mg/day pyridostigmine bromide treatment.

In March 2016, the patient presented again with a myasthenic crisis (respiratory tract infection induced) at our hospital. *Tripterygium wilfordii* or other antimenstrual drugs had not been previously administered. Additionally, she had no history of hereditary diseases, smoking, or drinking alcohol. We found that the patient's symptoms of myasthenia were severe in the afternoon, aggravated after continuous activity, and resolved after rest. MG was diagnosed on the basis of results of a neostigmine test, single-fiber electromyography, acetylcholine receptor antibody measurement, and measurement of the amplitude of low frequency repetitive nerve stimulation (detailed results are shown in Table 1).[3] After admission, she received methylprednisolone pulse therapy (0.5 g/day × 5 days of intravenous drip, 0.25 g/day × 3 days by intravenous drip, 0.12 g/day × 3 days by intravenous drip, and then oral prednisone 60 mg/day), and parenteral nutrition and symptomatic treatment. The symptoms of myasthenic crisis gradually resolved. The patient had been taking a maintenance treatment of pyridostigmine bromide 60 mg/8 hours. Since September 2014 up to hospitalization in 2016, the patient's menstruation had not been restored. On the basis of this finding and the results for sex hormone tests (Table 1), we diagnosed the patient with POF. Thymectomy was performed in April 2016 and the patient was followed up until December 2016. She did not experience menstruation at this time.

Statement of ethics

The study protocol was approved by the Ethics Review Board of the Third Affiliated Hospital of Shenzhen University. The subjects provided written informed consent.

Discussion

The main pathogenic factors of POF are iatrogenic, environmental, genetic, infection, and immune-associated. Approximately 18% to 92% of patients with POF show comorbidity with other autoimmune diseases.[4] Cellular immunity is important in POF.[5] T cells express and secrete cytokines, which act directly on B cells to produce antibodies that destroy follicles. Systemic lupus erythematosus and Sjogren's syndrome were found in Case 1, but both diseases were inactive at admission. Active immunotherapy in Case 1 ameliorated the symptoms of MG and menstruation was also restored. To the

best of our knowledge, only two other cases of MG with POF have been reported in China,[4,6] and this type of comorbidity has rarely been reported elsewhere. Previous studies [4,6] have reported symptoms of MG after diagnosis of POF, but the effect of immunotherapy on POF was not recorded.

The cases reported in this study showed symptoms of MG earlier than those of POF. Positive early immunotherapy may be effective in treating POF. The findings in our cases and previous studies showed that MG and immune POF comorbidities were associated; however, the exact mechanism remains to be determined.[7] The standard treatment for young women with POF is estrogen/progesterone replacement therapy. However, this treatment in patients with POF (merged MG) can induce an MG crisis.[4] In an autoimmune MG mouse model, estrogen treatment promoted proliferation of AChR-specific Th1 cells, which led to an increase in AChR IgG2b and aggravated MG.[8] Elevated estrogen levels can affect MG via B cell activation through autoantigens in the thymus.[6,9] Therefore, absence of estrogen replacement therapy was favorable for Case 1. Symptoms of MG worsened after progesterone replacement therapy in Case 2. The mechanism of this finding is associated with the thymus and reproductive gland function, and the presence of estrogen receptors in thymic epithelial cells (thymic factor-producing cells). Thymectomy, which eliminates the key target for estrogen in the body, is an effective treatment for MG. Further, this treatment can reduce the risk of an MG crisis induced by estrogen therapy for POF. Active treatment of MG can help to restore POF. Chung[10] reported that a patient with MG and autoimmune POF recovered after thymectomy, oral pyridostigmine, and hormone replacement therapy. The effect of immunotherapy in improving POF is related to the duration of amenorrhea. If this duration is lengthy, it can cause complete atrophy of the uterus, which renders restoration of menstruation difficult, as shown in Case 2.

In conclusion, premature loss of fertility in POF amenorrhea can significantly affect patients and their families. Estrogen or progesterone replacement therapy for POF may induce an MG crisis. MG is closely related to immune POF. Timely and active immunotherapy of MG may restore menstruation and reproductive function. However, the specific immune mechanism underlying these comorbidities still needs to be studied in depth.

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Author contributions

Conceived and designed the study: Liming Cao.

Analyzed the data and provided constructive discussion: Weibin Liu.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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