Myasthenia Gravis Accompanied by Premature Ovarian Failure and Aggravation by Estrogen

Yi Li, Bo Xiao, Lan Xiao, Ning Zhang and Huan Yang

Abstract

The association of myasthenia gravis (MG) and premature ovarian failure (POF) has rarely been recognized, and the influence of hormone replacement therapy on MG in patients with POF has not been reported. We describe a patient diagnosed with MG and POF, whose myasthenic symptoms were precipitated by estrogen treatment. Such combined clinical symptoms of MG and POF may reflect potentially common autoimmune disease mechanisms, although the precise pathogenesis remains to be defined.

Key words: myasthenia gravis, premature ovarian failure, estrogen, anti-AChR antibody, anti-ovarian antibody

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Introduction

Myasthenia Gravis (MG) is an autoimmune disease characterized by weakness of striated muscles, which is commonly due to the existence of anti-acetylcholine receptor antibody (anti-AChR-Ab). Even though it is not uncommon for MG to accompany autoimmune disorders such as thyroidites, systemic lupus erythematosus (SLE) or diabetes, the association between POF and MG has rarely been documented in the literature (1-3). Furthermore, the influence of hormone replacement therapy on MG in patients with POF has not been reported.

Here, we describe a rare case of a young woman diagnosed with generalized MG accompanied with POF, where both anti-AChR-Ab and anti-ovarian antibodies (AOA) were positive, and her symptoms of MG were aggravated by estrogen from hormone replacement therapy.

Case Report

A 20-year-old woman was hospitalized for myasthenic crisis. At age 19, she started having progressive ptosis, easy fatigability, and cessation of menses, and went to an outside hospital three months later. The neostigmine test was positive. The sex hormone measurement showed: FSH: 86.79 mIU/mL, LH: 117.89 mIU/L, E$_2$: 33.45 pg/mL, P: 0.29 ng/mL, and PRL: 15.06 ng/mL. The age of her menarche was 13 years, and her menses were regular until the onset of MG. She was diagnosed with MG accompanied with secondary amenorrhea, and received pyridostigmine (60 mg orally three times daily) and sex hormone replacement therapy. However, after taking estrogen for a week, her symptoms of MG were acutely aggravated and the myasthenic crisis occurred. She was then referred to our hospital. Before the deterioration, she did not show symptoms of infection, emotional stress, or overwork, which are common factors that could trigger MG. We also excluded the possibility of pyridostigmine toxicity, since she did not show excessive cholinergic stimulation symptoms. She stopped the hormone replacement therapy immediately, despite one subsequent menstruation. When she was admitted to our hospital, the physical examination showed bilateral ptosis, generalized muscle weakness, dyspnea and cyanosis. The quantitative MG score was 35 out of 39. The laboratory tests revealed positive results for serum anti-AChR-Ab and AOA (Fig. 1). Computed tomography of the chest showed normal size thymus. Brain MRI showed a normal pituitary gland. The sex hormone measurement showed: FSH: 86.79 mIU/mL, LH: 117.89 mIU/L, E$_2$: 33.45 pg/mL, P: 0.29 ng/mL, and PRL: 15.06 ng/mL. The age of her menarche was 13 years, and her menses were regular until the onset of MG. She was diagnosed with MG accompanied with secondary amenorrhea, and received pyridostigmine (60 mg orally three times daily) and sex hormone replacement therapy. However, after taking estrogen for a week, her symptoms of MG were acutely aggravated and the myasthenic crisis occurred. She was then referred to our hospital. Before the deterioration, she did not show symptoms of infection, emotional stress, or overwork, which are common factors that could trigger MG. We also excluded the possibility of pyridostigmine toxicity, since she did not show excessive cholinergic stimulation symptoms. She stopped the hormone replacement therapy immediately, despite one subsequent menstruation. When she was admitted to our hospital, the physical examination showed bilateral ptosis, generalized muscle weakness, dyspnea and cyanosis. The quantitative MG score was 35 out of 39. The laboratory tests revealed positive results for serum anti-AChR-Ab and AOA (Fig. 1). Computed tomography of the chest showed normal size thymus. Brain MRI showed a normal pituitary gland. The sex hormone measurement showed: FSH: 86.79 mIU/mL, LH: 117.89 mIU/L, E$_2$: 33.45 pg/mL, P: 0.29 ng/mL, and PRL: 15.06 ng/mL. She underwent a tracheotomy and was treated with pyridostigmine, plasmapheresis.
Figure 1. Changes of serum anti-AChR-Ab and AOA level in the patient before treatment and three months after treatment. The OD value of ELISA revealed that both serum anti-AChR-Ab-IgG and anti-ovarian-Ab-IgG showed an evident decrease at 3 months after treatment compared to that before treatment.

Table 1. Summary of the Current and Three Previous Three Cases of MG Accompanied by POF

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Current study</th>
<th>Kuki et al., 1981 (1)</th>
<th>Chung et al., 1993 (2)</th>
<th>Ryan et al., 2004 (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset (Years)</td>
<td>19</td>
<td>19</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Clinical course &amp; Response to treatment</td>
<td>Suffer from MG and POF at the same time</td>
<td>Firstly diagnosed as MG, then diagnosed as POF in two years</td>
<td>Diagnosed as MG shortly after POF symptoms occurred</td>
<td>First diagnosed as POF, then diagnosed as MG in 12 years</td>
</tr>
<tr>
<td>Related to MG</td>
<td>No thymectomy</td>
<td>MG symptoms increased in severity</td>
<td>Spontaneous pregnancy after thymectomy and then hormone replacement</td>
<td>Symptoms of MG characteristically worsened during menstrual period</td>
</tr>
<tr>
<td>Related to POF</td>
<td>Anti-AChR-Ab (+)</td>
<td>N/A</td>
<td>N/A</td>
<td>Anti-AChR-Ab (+)</td>
</tr>
<tr>
<td>Ovarian biopsy</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A (+)</td>
</tr>
</tbody>
</table>

Discussion

MG is an autoimmune disease in which autoantibodies interfere with neuromuscular transmission. POF is defined by the presence of amenorrhea for at least four months, and FSH values greater than 40 IU/L (obtained twice with more than one month interval) in women younger than 40 years (4). Its symptoms usually include amenorrhea along with hot flashes, night sweats and mood changes. The combination of MG and POF are seldom seen; a summary of three previous case reports (1-3) and the current one is given in Table 1.

POF is a heterogeneous disorder with various causes, including genetic abnormalities, autoimmune imbalance, injury, dysfunction of hypothalamus-pituitary-adrenal axis, etc. For this patient, we propose that the POF was induced by an autoimmune attack on the ovaries. This hypothesis is supported by the existence of serum AOA, a negative family history for ovarian relevant disorders, normal pituitary on brain MRI and intact ovaries in the patient. This hypothesis is also strengthened by previous reports showing that autoimmunity is present in 18-92% of POF patients who have AOA or other auto-antibodies (5), and some of them simultaneously exhibit other autoimmune disorders.

This combination of MG and POF is interesting since impaired immunoregulatory mechanisms could contribute to both diseases. Previous case reports of patients with MG and POF showed that thymectomy either resolved the and intravenous dexamethasone. She was then treated with oral prednisone for several months. The patient declined thymectomy. After treatment, her symptoms of myasthenic crisis were resolved. Three months later, the laboratory examinations revealed decreased levels of both anti-AChR-Ab and AOA (Fig. 1), although there was no resumption of her menses.
amenorrhea (7) or made a spontaneous pregnancy happen (2), indicating that the thymus may play an important role in both diseases. It has been known that the thymus is involved in the pathogenesis of MG. Moreover, an increased expression of estrogen receptor α has been found on thymocytes and peripheral T lymphocytes in MG patients (6); this dysregulation might influence the progression of the autoimmune response for POF. However, the details of pathogenic mechanisms involved in both diseases need further exploration.

Another interesting phenomenon in the present case is that the treatment of estrogen was temporarily related to the aggravation of the muscle weakness. One study demonstrated that treatment of 17β-estradiol enhanced the production of anti-AChR-Ab in experimental autoimmune MG (8), which implies that estrogen might contribute to the aggravation of MG. Furthermore, the influence of estrogen as an immunoregulator has also been observed to increase the risk of other autoimmune diseases such as SLE (9). In addition, the present case makes us more cautious about the possible influence of sex hormone replacement therapy on other MG patients, such as those in menopause. Further clinical surveys are necessary for more insight.

The serum titer of AOA and anti-AChR-Ab decreased after the patient received immunosuppression therapy for MG. This indicated that the treatment did affect the levels of both autoimmune antibodies although it could not reverse all clinical symptoms, but the long-term effects need further observation.

Overall, this case highlights a rare association of the two disorders which may share common pathogeneses, it raises the possibility that estrogen may contribute to the aggravation of MG, and also puts forward the question about the effects of hormone replacement therapy on MG patients.

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References