

Clinical Features and Prognosis of Ocular Myasthenia Gravis Patients with Different Phenotypes

Li-Li Wang, Yun Zhang, Mao-Lin He

Department of Neurology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder caused by anti-acetylcholine receptor antibodies (AChR-Abs) or other etiologies. Ocular symptoms were the first presentations in 40–50% of MG patients. Ptosis and diplopia were the most common symptoms of ocular MG (OMG). Limited studies demonstrated that patients presented with initial symptoms of only ptosis in 47%, only diplopia in 14% and both ptosis and diplopia in 39% of OMG.^[1] Variations of diplopia or ptosis did not significantly affect the physical or mental status of OMG. Initial presentation of concurrent ptosis and diplopia was significantly associated with insensitivity to pyridostigmine for OMG patients. However, the differences of clinical features including age of disease onset, gender, thymoma, as well as other autoimmune disease between various phenotypes of OMG remain unidentified.

OMG developed to generalized MG (GMG) in about 50–80% patients within the first 1 or 2 years after disease onset and 38% of the MG patients experienced remission during 30 years of observation.^[2,3] Early thymectomy and administration of prednisolone can decrease relapse and secondary generalization of OMG. Late age of onset, anti-AChR-Ab, and thymoma increased the risk of secondary generalization. Anti-Kv1.4 antibody and thymus hyperplasia increased MG relapse. Time of diagnosis from onset and age at onset (≤ 40 years) predicted MG remission. Gender does not seem to predict the course of MG. However, less attention was paid on the effect of initial OMG symptoms of disease onset such as ptosis and diplopia concurrence or alone, ptosis on one or both eyes on both MG relapse and OMG second generalization. Our study aimed to explore the clinical characteristics and prognosis of OMG with different phenotypes.

METHODS

Eighty-three MG patients recruited in this study were examined in the Neurology Department of Beijing Shijitan Hospital between January 2002 and October 2014. Among 83 MG patients, 59 patients presented with only ocular signs and symptoms at disease onset. The diagnosis of MG was based on the combination of clinical features and one of the laboratory criteria including favorable effect of cholinesterase inhibitors, positive results of repetitive nerve stimulation or single fiber electromyography and anti-AChR-Abs highly specific for MG.^[4] The study was approved by the hospital ethics committee on clinical research and written informed consent was obtained from all of the patients in this study.

There were no well-accepted criteria for the diagnosis of OMG relapse. In this study, OMG relapse was diagnosed with the reappearance of any symptoms and signs of extra-ocular muscles weakness. The reappeared symptoms and signs should last more than 24 h. And the duration between the OMG relapse and last remission should be more than 30 days. Also, a minimal period of 2 years without generalization is required to classify a patient with initial ocular manifestations as having a pure ocular form.

The computed tomography scan explores the presence of a thymoma or thymic hyperplasia. Autoimmune thyroid

Address for correspondence: Dr. Li-Li Wang,
Department of Neurology, Beijing Shijitan Hospital, Capital Medical
University, Beijing 100038, China
E-Mail: bitljq2012@163.com

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diseases such as Graves' disease and antibody positive thyroid disease were diagnosed on the basis of clinical features, thyroid ultrasonography, and serum thyroxin and related autoantibody levels. The diagnosis of rheumatoid arthritis was based on the guideline of The American College of Rheumatology.

Age, gender, thymus abnormality, and associated autoimmune diseases, as well as prognosis including OMG relapse and second generalization were compared between different OMG groups. In addition, disequilibrium caused by treatment between the groups was precluded in order to assure the accuracy of this current analysis.

Statistical analysis was performed with SPSS 22 software (SPSS Inc., USA). Categorical variables were analyzed using the Chi-square and Fisher exact test. Continuous variables were analyzed with *t*-test. $P < 0.05$ was considered as statistically significant.

RESULTS

Clinical features of ocular myasthenia gravis patients with different phenotypes

There were 33 female and 26 male OMG patients in this study, with a median age of 46.1 ± 18.5 years (range: 4.0–72.0 years). This study demonstrated that patients presented with the initial symptom of only ptosis were in 62.7% of OMG patients, only diplopia were in 10.2% and both ptosis and diplopia were in 27.1% of OMG patients. These patients were divided into two groups: single ptosis or diplopia group ($n = 43$) and concurrence diplopia and ptosis group ($n = 16$) based on the initial symptoms of disease onset. Results showed that age of onset, gender, thymus histology, and other autoimmune disease had no significant difference between the two groups.

Also, OMG with ptosis were further divided into unilateral group ($n = 14$) and bilateral group ($n = 23$) based on ptosis on one or both eyes. Other autoimmune diseases such as Graves' disease and rheumatoid arthritis were observed significantly more frequently in bilateral group than those in unilateral group ($P = 0.006$).

Prognosis of ocular myasthenia gravis patients with different phenotypes

OMG relapse and second generalization were investigated between bilateral ptosis and unilateral ptosis groups. MG relapse in the first 2 years after disease onset was observed more frequently in bilateral group (58.3%) than that in unilateral group (30.4%). However, the frequency and the time of MG relapse did not show statistically significant difference between the two groups. Also, there was no difference of OMG second generalization occurrence between the two groups (87.5% vs. 90.0%). Also, the time and the first symptom of OMG generalization between the two groups also had no statistical significance.

Prognosis features were also compared between the group with single ptosis or diplopia and the group with the

concurrence of diplopia and ptosis. OMG relapse occurred more frequently in single ptosis or diplopia group (41.5% vs. 28.6%) than in the group with concurrence of diplopia and ptosis. But the frequency and the time of MG relapse showed no statistical significance between the two groups. In addition, the ratio of OMG second generalization in the first 2 years after disease onset was found without differences in the two groups (82.1% vs. 91.7%). OMG progressed more rapidly in single ptosis or diplopia group. Time of OMG generalization showed statistically significant differences between the two groups ($P = 0.019$, Fisher exact test). However, the first symptoms of OMG generalization between these two groups did not show statistical difference.

DISCUSSION

The purpose of this study was to investigate clinical features and prognosis of OMG with different phenotypes. This analysis showed that concurrent autoimmune disease was observed more commonly in bilateral ptosis patients (64.3%) than that in unilateral ptosis patients (17.4%). Patients with initial bilateral ptosis can predict the presence of concurrent autoimmune disease. OMG developed to GMG more rapidly in single ptosis or diplopia group compared to that in both ptosis and diplopia group. Initial single symptom ptosis or diplopia could serve as potential indicators for the generalization of OMG in the first 6 months.

Previously no studies have addressed the relationship of ptosis, diplopia with the occurrence of thymus abnormality and with the concurrence of other autoimmune diseases. This study demonstrated that thymus abnormality occurred more frequently in both ptosis and diplopia group although the difference was not statistical significant. Associated autoimmune diseases occurred significantly more frequently in bilateral ptosis group. This study also demonstrated that age of disease onset and gender had no relationship with the different presentations of OMG.

In the present study, 62.7% of OMG patients presented with ptosis, 10.2% with diplopia and 27.1% with the concurrence of ptosis and diplopia. The ratio of ptosis was higher in our study compared with that in a previous study that reported that ptosis, diplopia, ptosis, and diplopia were present in 47%, 14%, and 39% of OMG patients, respectively.^[1] This discrepancy may be related to the different race and heritage background between the two studies.

Until now, little attention was paid on the relationship of ptosis, as well as diplopia with OMG relapse and second generalization. This study demonstrated that OMG patients with single presentation of ptosis or diplopia developed early generalization in the first 6 months. To the best of our knowledge, there was no other related study reported.

The mechanisms underlying why different presentations of ptosis and diplopia have different clinical features and prognosis remain unclear. The previous study implied that

Th17 cell was the key factor in the development of both MG and associated Graves' disease. Also, Concurrent autoimmune diseases such as Hashimoto's thyroiditis and rheumatoid arthritis were found in muscle-specific kinase (MuSK) antibody positive patients (9.6%) and Graves' disease was found in AChR-Ab positive patients. Therefore, Th17 cell and MuSK antibody, as well as AChR-Ab might contribute to OMG with the concurrence of other autoimmune diseases.

Treg percentage was significantly lower in the relapse stage than in the remission stage of childhood OMG.^[5] Th17 and Treg contributed to immunologic disorders in MG patients. Therefore, we speculated that Th17 and Treg might be related to the prognosis of OMG. Also, genetic risk factors have been shown to have relevance to MG development. Further studies should be conducted to address these issues in the future.

In summary, our study demonstrated that patients with initial bilateral ptosis can predict the presence of concurrent autoimmune disease. Initial single symptom ptosis or diplopia could serve as potential indicators for the generalization of OMG in the first 6 months.

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Conflicts of interest

There are no conflicts of interest.

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