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Correlation between the atypical presentation of myasthenia gravis and radio-pathological classification of the thymus – A retrospective cohort study

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Abstract

Myasthenia gravis (MG) is a disease of neuromuscular junction and mainly autoimmune in aetiology. The state of thymus is a critical determinant for the prognosis. In this retrospective review study, we aimed at clarifying the relationship between the mode of clinical presentation of MG and the radio-pathological classification of the thymus. We identified patients with MG from the database of our medical center from 1988 – 2017. The patients were classified into two groups according to their clinical presentation: those with a typical presentation with diurnal variation, and those with an atypical presentation of persistent weakness or respiratory failure from the beginning. The underlying thymic state was categorized into six groups: normal, abnormal by imaging (if no operation was performed), hyperplasia, benign thymoma, cortical type thymoma, and malignant thymoma. In total, 227 patients (133 females and 94 males) were included in the analysis, of whom 68% were classified into the typical presentation group. The atypical presentation correlated significantly with thymic categories ($p = 0.014$) and sex ($p = 0.026$) but not age at onset ($p = 0.232$). The atypical presentation was more common in the male patients and in those with thymic carcinoma.

Keywords: Myasthenia gravis, thymus, clinical course

INTRODUCTION

Myasthenia gravis (MG) is a disease of the neuromuscular junction, with a prevalence of about 20 per 100,000[1-3] and an average annual incidence of about 2 - 3 per 100,000 population.[1,2,4] The mechanism of most cases of MG is believed to be autoimmune, with antibodies produced mainly by the thymus and targeting the receptors on the postsynaptic muscular membrane. The disease is best recognised by fluctuations in weakness, characteristically a diurnal variation, as well as fatigability and recovery after rest.

There are many known aetiologies of MG, and the clinical presentations of MG varies with regards to the mode and course of presentation, the affected body area and the severity of weakness. Many classification schemes have been proposed[5], and according to the aetiology, MG can be categorised into six different subtypes, including early-onset MG, late-onset MG, thymoma-associated MG, MG with anti-muscle-specific tyrosine kinase antibodies, ocular MG, MG with no detectable antibodies against acetylcholine receptor antibody and muscle-specific tyrosine kinase.[3] MG can be classified into five categories according to the clinical features, the severity of symptoms and the response to treatment as proposed by the Myasthenia Gravis Foundation of America.[6] MG patients can also be classified according to the radio-pathological classification of the thymus.[7]

Few studies have investigated the relationship between clinical presentations and the underlying thymic pathology. In this study, we aimed at clarifying the relationship between the mode of clinical presentation of MG and the radio-pathological classification of the thymus.

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METHODS

This was a retrospective case review study. We searched the database of National Cheng Kung University Hospital from 1988 to 2017 for cases of MG. Patients aged under 18 years were not enrolled to exclude the possibility of congenital myasthenic syndrome. The patients' age, sex, imaging reports, pathology reports and the initial presentations of MG in the first medical record either in the outpatient clinic or upon admission were collected. This study was approved by the Ethics Committee of National Cheng Kung University Hospital. No identifiable personal data of the patients were revealed.

The patients were classified into two groups according to the clinical presentation: those with a typical presentation, i.e., there is diurnal variation during presentation, recovery after rest or fluctuations, and those with an atypical presentation, i.e., presenting as persistent weakness or respiratory failure from the beginning. The underlying thymic state was categorized into six groups: Normal, abnormal by imaging (if no operation was performed), hyperplasia, benign thymoma (thymoma with indolent behavior, or 2015 WHO Histopathological Classification types A and AB), cortical type thymoma (2015 WHO Histopathological Classification types B1 and B2), and malignant thymoma (types B3 and C, or thymic carcinoma in 2015 World Health Organization classification) groups. We then investigated the relationship between the types of clinical presentation and the thymic state. The effects of sex and age at onset on this relationship were also investigated.

The statistical analyses were conducted using Fisher's exact test with post hoc Bonferroni and Holm correction and the Wilcoxon rank sum test.

RESULTS

The records of 279 patients were initially collected, of whom 22 were under 18 years of age, 10 came to our hospital for other purposes and lacked data of the initial relevant presentation, 16 were excluded due to insufficient records at our hospital, and another two were excluded due to changes in the clinical presentation from typical to atypical during the course.

A case each of typical and atypical presentation will be described followed by the group summary.

The patient of typical presentation was a 49 year old female without underlying disease, who visited our neurologic clinic complaining of insidious binocular diplopia for about half a year. The diplopia was more severe in the afternoon and evening. She also complained that she could hardly drive as before due to the diplopia which became more severe after driving for 20 minutes. The diplopia was partially relieved by closing her eye for a short rest. No focal numbness or any bulbar dysfunction was noted. Repetitive nerve stimulation test showed decremental change in the tested muscles. Chest CT showed thymic hyperplasia.

The patient of atypical presentation was a 51 year old female without underlying diseases was admitted due to a sudden onset and rapid progressive quadriparesis for 2 weeks. She had weakness of right arm initially, followed by left arm and, then, bilateral lower limbs. She denied diplopia, blurring of vision, dysarthria, dysphagia, choking, or sensory symptoms. Repetitive nerve stimulation test showed decremental change in the tested muscles. Chest CT showed the presence of a retrosternal mass.

In total, 227 patients (133 females and 94 males) were included in the analysis (Figure 1). The demographic data of the patients with a typical presentation (n=155, 68%) and those with an atypical presentation (n=72, 32%) is shown in Table 1. As shown, there was no significant difference in age between the two groups ($p = 0.232$), however there was a significant difference in sex between the groups ($p = 0.026$). The distribution of thymic states in all patients and the percentages of atypical presentation in each thymic category are also shown in Table 1. While overall the distribution of thymic states skewed to the benign side, i.e., more patients had a normal or hyperplastic thymus, the percentage of atypical presentation tended to increase with the degree of malignancy of the thymus. The correlation between the radio-pathological classification of the thymus and the mode of MG presentation was statistically significant ($p = 0.014$), and the post hoc test showed a significant differences in the percentages of atypical MG presentations between the normal group versus the malignant thymoma group ($p = 0.04$), and the hyperplasia group versus the malignant thymoma group ($p = 0.04$).

We further investigated whether a sex effect contributed to the different presentations of the thymic groups. Although there was a trend of more males presenting with atypical features, the differences in percentages were insignificant ($p > 0.05$) for all thymic categories, and there was no interaction between the type of thymic state and sex. We also investigated the influence

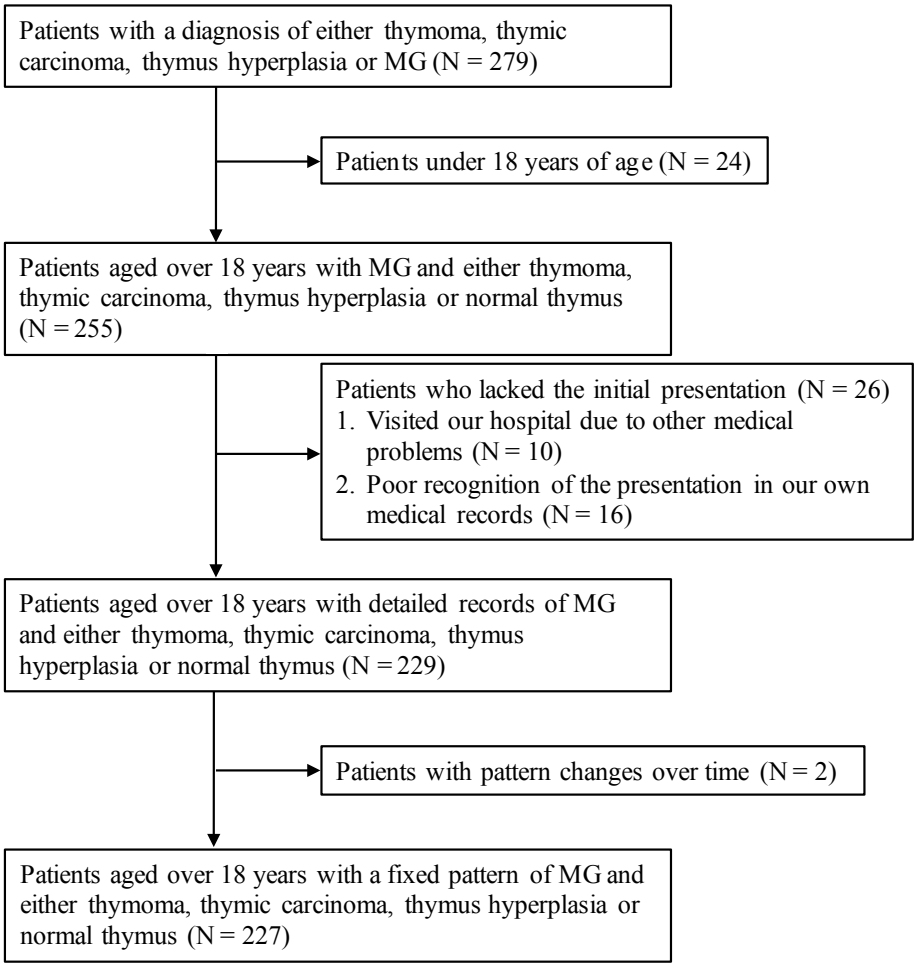

Figure 1. The recruitment of patients for this study.

Table 1: Demographic data of the patients with typical and atypical clinical presentations

	(n)	Typical (n = 155)	Atypical (n = 72)	Difference (*p*)
Age (years)		51.5	54.0	0.232
Sex (M/F)		56/99	38/34	0.026
Clinical feature				<0.001
Diurnal change	101	101	0	
Resting benefit	30	30	0	
Fluctuating	24	24	0	
Atypical	72	0	72	
Thymic category				0.014
Normal	89	66	23	0.167
Abnormal by imaging	13	10	3	0.702
Hyperplasia	58	43	15	0.344
Benign thymoma	15	9	6	0.670
Cortical type thymoma	36	22	14	0.416
Malignant thymoma	16	5	11	0.003

of the age at onset to test whether the older patients presented with more atypical features. Thirteen patients (6 atypical and 7 typical) had missing data with regards to the age at onset, so they were excluded from the analysis. The Wilcoxon rank sum test revealed that there were no significant differences in the age at onset in all thymic categories (Figure 2).

In summary, the atypical presentation was correlated with thymic categories and sex, but not age at onset. The atypical presentation was more common in male patients and in those with thymic carcinoma.

DISCUSSION

MG is mainly an autoimmune disease and is known to be associated with antibodies directed against acetylcholine receptors, muscle-specific kinase, lipoprotein-related protein 4, and agrin in the postsynaptic membrane at the neuromuscular junction. Classifying MG into subgroups according to the aetiology or autoantibodies can help in making therapeutic decisions and in predicting the prognosis.[8]

MG associated with antibodies against acetylcholine receptors accounts for about 80% of MG patients and presents with prototypic clinical presentations, including fluctuating muscle weakness, diurnal change, as well as fatigability and recovery after rest.[9] However, some patients present with acute onset and persistent weakness, although the prevalence rate and pathogenesis of this mode of presentation is still uncertain. In the current study, 32% of the patients presented with the atypical presentation, i.e., persistent limb weakness or respiratory failure at the first visit. However, some studies[10] have defined the atypical presentation differently, including involvement of atypical body parts without mentioning the presentation mode, such as fluctuation of symptoms. A few case reports have described patients with acute and persistent muscle weakness who were eventually diagnosed with MG, however no underlying mechanism were discussed.[10-12] MG patients with antibodies against muscle-specific kinase have been reported to predominantly present with bulbar symptoms which might pose a diagnostic difficulty due to minimal or absent fluctuations of symptoms.[13,14] Again, no definite pathogenesis was discussed in these papers.

The relationship between thymoma and MG has been extensively studied. Approximately 10% to 15% of patients with MG have thymoma, and conversely 20% to 25% of patients with thymoma have MG. Thus, thymus plays a unique and important role in the pathogenesis of the different subtypes of MG.[15] It is accepted that most patients with thymoma-associated MG have antibodies against acetylcholine receptors.[16] Earlier stage, smaller size or Type B thymomas as defined by the WHO pathological classification seem to be more frequently associated with MG, especially types B1 to B2 cortical thymomas, which indicates that the number of CD4+CD8+ double-positive immature T lymphocytes infiltrating the thymoma may be related to the onset of MG.[17-20]

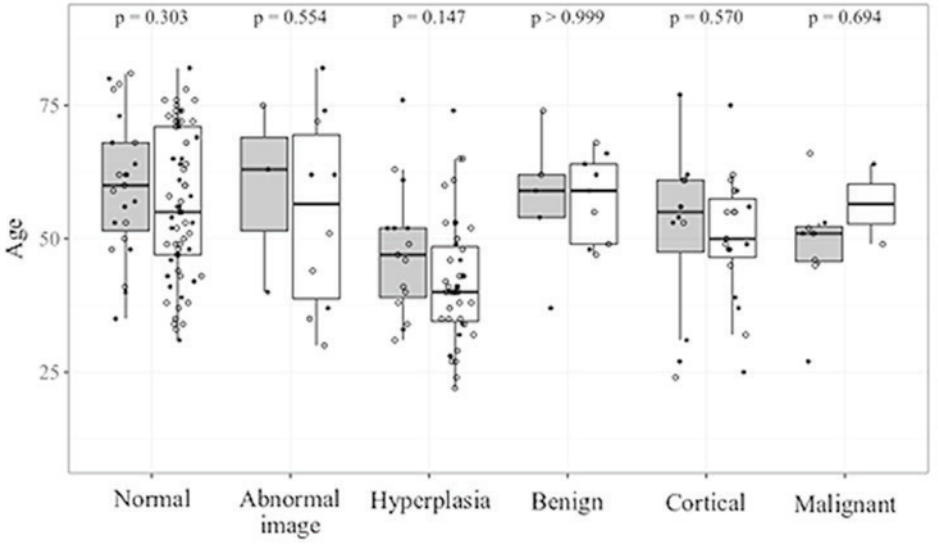

Figure 2. The age distribution in dot-whisker-box format for each clinical presentation type and thymic category. Gray boxes: atypical presentation and white boxes: typical presentation.

Few data are available on MG patients with invasive thymoma, although MG patients with invasive thymoma have been noted to have a poorer outcome, with difficulty in controlling the myasthenic symptoms and to have other clinically important autoimmune diseases concomitantly.[21] In general, thymic carcinoma is not associated with MG, however some cases of benign or malignant thymoma-associated seronegative MG have recently been reported, with a dramatic variation in the incidence ranging from 1% to 32.5%.[17,22] The impact of thymic carcinoma on MG has rarely been discussed. The overall survival rate of patients with thymic carcinoma and MG has been reported to be better than in those without MG, possibly because patients with MG have unique clinical features leading to an early diagnosis of thymic carcinoma, and also higher rates of complete surgical resection.[23]

To the best of our knowledge, no previous studies have focused on the correlation between the presentation modes of MG and the pathological types of the thymus. Our data suggest that the patients in the malignant thymoma group, i.e., those with Type B3 thymoma and thymic carcinoma, tended to develop the atypical presentation more than the patients with a normal thymus or thymic hyperplasia, and that the age at onset and sex did not contribute to the relationship. The latest WHO classification separates thymic carcinoma from thymoma as an independent entity.[5]

There is increasing evidence of the accumulation of gene mutations and alterations from types A, AB, B1, B2 and B3 thymoma to thymic carcinoma. Genomic profiling can be used to distinguish type B3 thymoma and thymic carcinoma from type A to B2 thymomas[24], and the genetic differences may eventually affect the presentation of different antigen epitopes and the selection of different T cell lineages and the following immune responses.[25-27] We propose that the genetic background of thymic lesions may be one of the factors explaining our study results. Thymomas and thymic carcinomas also differ in functional and molecular characteristics, such as KIT pathway, epidermal growth factor pathway, and the insulin-like growth factor-1/IGF-1 receptor system.[28] We hypothesise that a combination of different targeting of the immune networks and autoantibodies from malignant thymoma and thymic carcinoma may cause the presentation of the diseases to become more severe than classical MG.

There are several limitations to this study. First, this was a retrospective study, and history taking and neurological examinations were not performed by a single experienced neurologist. It is possible that the lack of a typical presentation may be due to inadequate personal skills in obtaining information about the clinical course. Second, the data were collected in a single medical center with a relatively limited number of patients. Third, the profile of autoantibodies was incomplete, and the underlying biochemical or immunological mechanism of this relationship was not ascertained.

In conclusion, genetic differences among different types of thymoma may lead to variable production of cytokines and autoantibodies, resulting in different presentations and clinical courses. We found a significant relationship between the radio-histopathological classification of the thymus and the percentage of atypical MG presentation, with a higher percentage of male patients and atypical presentation toward the malignant end of thymic pathology.

DISCLOSURE

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