Correlation Analysis of Myasthenia Gravis Thymic Disease with Quantitative Score of Myasthenia Gravis Swallowing Function and Respiratory Function

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Abstract

Introduction: The pathophysiology of myasthenia gravis (MG), an autoimmune disease affecting the neuromuscular junction, is closely related to thymic disorders (thymic hyperplasia, thymic involution, thymic neoplasms). Myasthenia gravis often causes or exacerbates thymus disease, which often occurs together with myasthenia gravis. Further studies are needed to determine the relationship between thymus properties and quantitative myasthenia gravis (QMG), swallowing, and respiratory function in patients with myasthenia gravis.

Methods: From 2021 to 2022, 93 MG patients with definite thymic disease were found by thymic CT or histopathological biopsy in the Myasthenia Gravis Treatment Center of the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine.

The Quantitative Myasthenia Gravis (QMG) score was used by physicians at the deputy high level and above to measure patients' swallowing and respiratory function. The purpose of this study was to observe the relationship between myasthenia gravis thymic disease and QMG score, swallowing function score, and respiratory function score.

Results: The poor swallowing function score (3 points) accounted for 58.9%, 4.8%, and 13.6% in the thymoma group, thymic hyperplasia group, and thymus without abnormality group, respectively, and the difference between the groups was statistically significant ($P<0.05$). The respiratory function score was poor (3 points), and the thymus group accounted for 58.7%, which was significantly higher than the thymic hyperplasia group and the thymus without abnormality group. There was significant difference between groups ($P<0.05$). Myasthenia gravis quantitative score (QMG)>20 points (severe), the thymoma group accounted for 77%, which was significantly larger than the thymic hyperplasia group, and the thymus group had no abnormality, and the difference between the groups was significant ($P<0.05$).

After multiple comparison test results, it was found that the QMG score of the thymoma group was 1.07298 higher than that of the normal thymus, and the difference was significant. The swallowing score of the thymoma group was 1.461 higher than that of the normal thymus group, and the difference was significant. The respiratory function score of the thymoma group was 0.832 higher than that of the normal thymus group, and the difference was significant. The lung function score of the thymoma group was significantly higher than that of the thymic hyperplasia group by 1.509.

Keywords

Myasthenia gravis Thymic disease, Quantitative analysis of myasthenia gravis Respiratory function, Swallowing function, Correlation analysis

Introduction

Myasthenia gravis (MG) is an autoimmune disease that occurs primarily at the neuro-muscular junction. The pathogenesis of myasthenia gravis (MG) has not been clearly studied. Acetylcholine receptor (AChR) antibody, muscle-specific tyrosine kinase (Musk) antibody, other related antibodies found so far include: low-density lipoprotein receptor-related protein 4 antibody, anti-aggregate antibody, Titin antibody, Kv1.4 Antibodies, ryanodine receptor antibody (RYR-Ab), Collagen Q antibody and Cortactin antibody, etc., the pathogenesis of which includes T cell help and complement participation [1,2].

Studies have shown that about 75% of MG is related to thymus abnormalities, 85% to thymic hyperplasia, and 15% to thymoma. Dysphagia, aspiration pneumonia, or other causes of respiratory failure are the most common causes of death in patients with MG. The relationship between the pathogenesis of myasthenia gravis and thymic diseases (thymic hyperplasia, thymic involution, thymoma). The aim of this study was to investigate the correlation of thymic properties with myasthenia gravis (QMG score), respiratory and swallowing function, thymic imaging, and histopathology in patients with myasthenia gravis.

Methods

This single-center, prospective, cross-sectional observational study was investigator-initiated. The Ethics Committee of the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine accepted each experimental protocol (NO. ZYYECK [2019] 055). This research followed the principles outlined in the Declaration of Helsinki. Each participant, or their parent or legal guardian if they were under the age of 18, provided their informed consent. All participants were fully informed about the study's objectives, procedures, potential risks, and benefits, ensuring that their participation was voluntary and based on an understanding of the study.

A total of 93 patients with MG who were hospitalized in the Myasthenia Gravis Treatment Center of the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine and confirmed by thymic imaging or histology from 2021 to 2022 were collected. Physicians with a graduate degree or above used the Quantitative Myasthenia Gravis Score (QMG) to assess patients' breathing and swallowing abilities. The evaluation also included a thorough review of the patients' medical history, with particular attention to any previous treatments or surgeries, as these could influence the progression and presentation of MG.

The 2004 World Health Organization histological classification of thymic tumors identifies the following types of thymic tumors: Type A: stromal cells and tumor cells without lymphocytic infiltration; AB: both types A (fewer lymphocytes) and type B (lymphocytes) Type B1: similar to the normal thymic cortex, but with a small amount of thymic epithelial tumor cells; Type B2: a large number of immature lymphocytes with scattered tumor cells; Type B3: mainly composed of tumor-like epithelial cells. Thymic hyperplasia is a benign lesion of the anterior mediastinum, which can be further divided into true hyperplasia and lymphoid follicular hyperplasia. "True thymic hyperplasia" refers to the diffuse thickening of the thymus, which increases in size or mass compared to the normal age range. Tumor chemotherapy, radiotherapy, thermal burn or postoperative thymus elastic hyperplasia are the most common causes, and the pathological tissue retains the original thymus structure and immunohistochemical characteristics [3,4].

Lymph follicular hyperplasia is characterized by an increased number of thymic lymphoid follicular centers with normal or mildly enlarged thymus. Both true thymic hyperplasia and lymph follicular hyperplasia are benign lesions that require biopsy for diagnosis and are usually classified as thymic hyperplasia under imaging [5,6]. These classifications were crucial in categorizing the patient data for the study, contributing to more

accurate clinical assessments.

Statistical analysis was performed by SPSS (V22), measurement data were expressed as mean ± standard deviation, and the comparison of means among multiple groups was by one-way ANOVA; count data were expressed by rate, using $\chi 2$ test or Fisher's exact test. The chi-square test was used for comparison between groups, and the Bonferroni method was used to correct the P value; the Kruskal-Wallish test was used for ordered categorical variables, and ANOVA analysis of variance was used for the scores between groups. $P<0.05$ indicated a statistically significant difference. These statistical methods ensured the robustness and reliability of the study findings, providing a strong foundation for the conclusions drawn [7].

Results

The characteristics of swallowing function, respiratory function and quantitative myasthenia gravis (QMG) score of patients with thymoma and control group are shown in Table 1. The proportion of respiratory muscle involvement and laryngeal muscle involvement in MG patients in thymoma group was significantly higher than that in thymic hyperplasia group and MG patients with no abnormal thymus.

(1) Male to female sex ratio: thymus group, male patients (44.8%): female patients (55.2%); thymic hyperplasia group, male patients (9.5%): female patients (90.5%); normal group, male patients (27.9%): Female patients (72.1%), there was a significant difference between the two ($P<0.05$).

(2) The spirometry score was poor (3 points), and the thymus group accounted for 58.7%, which was significantly larger than that of the thymic hyperplasia and no abnormal thymus group, and there was a significant difference between the groups ($P<0.05$).

(3) Quantitative myasthenia gravis (QMG) score > 20 was considered severe, and the thymus group accounted for 77%, which was significantly larger than that of the thymic hyperplasia and no abnormal thymus group, with a significant difference between the groups ($P<0.05$).

Table 1. Correlation between thymoma and quantitative score of myasthenia gravis (QMG), swallowing function and respiratory function.

Variable	Thymoma group (n=29)	Hyperplasia group(n=21)	The normal group(n=43)	2/H	P
Gender				7.417	0.025*
Male	13(44.8)	2(9.5)	12(27.9)		
Female	16(55.2)	19(90.5)	31(72.1)		
Antibody group				5.607	0.061
ACHR	10(86.2)	17(81.0)	27(62.7)		
Not ACHR	19(13.8)	4(19.0)	16(37.3)		
Age				3.450	0.178
0-30	4(13.8)	7(33.3)	13(30.2)		
30-50	17(58.6)	12(57.1)	18(41.9)		
50	8(27.6)	2(9.5)	12(27.9)		
Swallowing score				4.614	0.000
0	2(6.8)	7(33.3)	23(53.5)		
1	3(10.3)	11(52.4)	8(18.6)		
2	7(24.0)	2(9.5)	6(13.9)		
3	17(58.9)	1(4.8)	6(13.9)		
Vocal score				0.155	0.925

Variable	Thymoma group (n=29)	Hyperplasia group(n=21)	The normal group(n=43)	2/H	P
0	18(62.1)	14(66.7)	26(60.5)		
1	2(6.9)	1(4.8)	7(16.3)		
2	3(10.3)	3(14.3)	3(7.0)		
3	6(20.7)	3(14.3)	7(16.3)		
Lung capacity score				38.443	0.000
0	0(6.9)	6(28.6)	6(9.2)		
1	5(17.2)	12(57.1)	12(18.5)		
2	7(24.1)	2(9.5)	19(29.2)		
3	17(58.7)	1(4.8)	28(43.1)		
QMG				78.108	0.000
0-10	3(4.0)	5(12.8)	15(20.0)		
11-20	14(18.9)	28(71.8)	50(67.6)		
20	57(77.0)	6(15.4)	9(12.4)		

The characteristics of swallowing function, respiratory function and quantitative myasthenia gravis (QMG) score of patients in AChR serum antibody and control group are shown in Table 2.

(1) The ratio of male to female: the ratio of male to female in the AChR group and the non-AChR group was 22:47 and 5:19, and there was no significant difference between the two.

(2) The condition of thymus: The condition of thymus in AChR group was: thymoma (36.2%), no abnormal thymus (39.1%), 66.7% of non-AChR group had normal thymus, and there was no significant difference between the groups [8].

(3) Swallowing function score: the AChR and non-AChR groups in good condition (0 points) accounted for 62.3% and 58.1%, and the swallowing function was generally better.

(4) Vocal function score: 60.8% and 66.7% of the AChR group and non-AChR group scored 0 points, respectively, indicating that the vocal function was generally better. There was no difference in the quantitative scores of swallowing, respiration and QMG between the AChR and non-AChR groups, which may be related to the fact that the serum antibodies to myasthenia gravis in this patient are mainly AChR (accounting for 74%), which is limited by the sample size. The size does not meet the sample size requirement for logistic regression.

Table 2. Correlation between SERUM receptors of AChR and quantitative score of myasthenia gravis (QMG), swallowing function and respiratory function.

Variable	ACHR(n=69)	Not ACHR(n=24)	2/z	P
Gender			1.055	0.304
Male	22(31.9)	5(20.8)		
Female	47(68.1)	19(79.2)		
The thymus grouping			5.607	0.061
Thymoma group	10(36.2)	19(16.7)		
Hyperplasia group	17(24.6)	4(16.7)		
The normal group	27(39.1)	16(66.7)		
Age			-0.158	0.874
0-30	18(26.1)	6(25.0)		

Variable	ACHR(n=69)	Not ACHR(n=24)	2/z	P
30-50	34(49.3)	13(54.2)		
50	17(24.6)	5(20.8)		
Swallowing score			-0.136	0.892
0	2(5.1)	20(45.5)		
1	6(15.4)	16(36.4)		
2	11(28.2)	4(9.05)		
3	20(51.3)	4(9.05)		
Vocal score			-0.157	0.875
0	42(60.9)	16(66.7)		
1	10(14.5)	0(0.0)		
2	8(11.6)	1(4.2)		
3	9(13.0)	7(29.2)		
Lung capacity score			-0.301	0.763
0	3(7.7)	9(16.7)		
1	9(23.1)	20(37)		
2	14(35.9)	14(25.9)		
3	13(31.3)	11(20.4)		
QMG			-1.182	0.237
0-10	8(20.5)	16(29.6)		
11-20	16(41.0)	31(57.4)		
20	15(28.5)	7(13.0)		

Thymus condition QMG score, swallowing score, respiratory function score and LSD multiple test analysis. See Table 3.

The results of the multiple comparison test are as follows. It can be obtained that the thymus types are different, and the mg. scores are different. It is found that the score of thymoma is 1.07298 higher than that of normal thymus, and it is significant. Swallowing scores were different, and it was found that the thymoma group had a significantly higher score of 1.461 than the normal thymus group. Respiratory function was different in the QMG score, and it was found that the score of the thymoma group was 0.832 higher than that of the normal thymus group, and it was significant. The vital capacity score of the thymoma group was 1.509 higher than that of the thymic hyperplasia group, and it was significant.

Table 3. Multiple comparisons of QMG, swallowing and vital capacity cores among thymus types.

Score	The Thymus(I)	The Thymus (J)	Mean difference (I-J)	The standard error	Signifi-cant	95% A confidence interval	
						The lower limit	Ceiling
QMG	Thymoma	Normal	1.07298	0.12018	0.000	0.8342	1.3117
		Hyperpl-asia	1.10509	0.14331	0.000	0.0204	1.3898
Swallo-wing	Thymoma	Normal	1.461	0.240	0.000	0.98	1.94
		Hyperpl-asia	1.488	0.286	0.000	0.92	2.06

Score	The Thymus(I)	The Thymus (J)	Mean difference (I-J)	The standard error	Signifi-cant	95% A confidence interval	
						The lower limit	Ceiling
Breath-ing	Thymoma	Normal	0.832*	0.202	0.000	0.43	1.23
		Hyperpl-asia	1.509*	0.240	0.000	1.03	1.99

An analysis of variance is shown in Table 4. It can be found that the observed variables swallowing score, breathing score, QMG score, the sum of squares between groups, and the F value can obtain the statistic P value. If the significance level α is 0.05, because the probability P value is less than the significant If the sex level is α, the null hypothesis should be rejected, and the alternative hypothesis should be accepted, and it is believed that there is a significant difference in the swallowing score for different types of thymus glands.

Table 4. Swallowing score, respiration score, QMG score ANOVA.

Score	The Thymus(I)	Sum of squares	Degrees of freedom	The mean square	F	Significant
Swallowing	Between groups	43.125	2	21.562	21.673	.000
	Within the group	89.542	90	.995		
	Total	132.667	92			
Breathing	Between groups	28.648	2	14.324	20.363	.000
	Within the group	63.309	90	.703		
	Total	91.957	92			
QMG	Between groups	23.444	2	11.722	46.861	.000
	Within the group	22.513	90	.250		
	Total	45.957	92			

Discussion

MG (myasthenia gravis) is an acquired autoimmune disease, assisted by T cells, mediated by multiple antibodies and complements, limiting the transmission function of neuro-muscle joints and the pathogenesis is not fully understood. The initial clinical symptoms of MG vary, often involving the muscles of the eyes, trunk muscles of the limbs, respiratory muscles, and swallowing muscles, with ocular symptoms being the most common. Symptoms are mild in the morning and severe in the evening. Currently, there are various classification systems for myasthenia gravis, such as the classic Osterman classification, the American Basic Classification of Myasthenia Gravis (MGFA classification), and more recently, the immunology-based multidimensional classification. MG typing methods based on serum antibodies have also appeared in the clinic [9].

The pathogenesis of MG has not been fully studied. It is generally believed that its pathogenesis is

closely related to the autoimmune antibody AChR antibody. Skeletal muscle acetylcholine receptors (AChRs) are the most common autoimmune receptors in MG and are present in the neuro-muscle junction, the postsynaptic membrane, part of the presynaptic membrane, the synaptic surface of ganglion cells, epithelial cells and surface of other cells, etc. AChR receptor antibodies produced in MG patients accelerate receptor degradation by binding to AChR. Accelerated degradation of AChR leads to post-synaptic membrane nicotinic choline deficiency and disrupts endplate function, but there are other targets of attack, such as muscle-specific receptors. tyrosine kinase (MUSK), ryanodine receptor antibody (RYR-Ab), etc. The latest research shows that the incidence of MG is 1.7-21.3 per million people, and it can occur in all age groups. No significant differences in incidence were found across age groups, but there were more women than men according to age at onset.

It can be divided into early-onset (age of onset < 50 years) and late-onset (age of onset > 50 years); according to the course of the disease, it can be divided into ocular muscle type (accounting for about 20% of MG patients), or systemic type, crisis type, etc.; According to antibody specificity, it is divided into anti-AChR type (80%), anti-muscle-specific receptor tyrosine kinase (MuSK) type (5%-10%), anti-low density lipoprotein receptor-related protein 4 (LRP4) type, TiTin antibody (Titin-Ab) type, ryanodine receptor antibody (RYR-Ab) type. However, because MG serum antibodies often combine a variety of antibodies, there is no unified standard based on antibody typing. TiTin antibody, ryanodine receptor antibody (RYR-Ab), type I interferon, IL-12, and Th17-related cytokines have been reported to be found in more than 90% of MG thymoma patients. These antibodies can be used as indicators of empirical prediction of thymoma risk, but the specific role of these antibodies in thymoma and MG remains to be studied.

Studies have shown that 80%-90% of MG patients have thymus disease. In the diagnosis of imaging or pathological biopsy, 65%-70% suggest thymic hyperplasia, and 10%-15% suggest thymoma. According to thymic biopsy, it can be divided into normal or atrophic thymus, thymic inflammation, thymoma and thymic hyperplasia. Thymic hyperplasia (thymic follicular hyperplasia, diffuse thymic hyperplasia, or thymic inflammation), thymic degeneration, and thymic biopsies are common pathological biopsies in MG thymic disease, of which thymic hyperplasia is the most common. There are five common pathological types of magnesium-related thymoma (A, AB, B1-3). Most studies believe that the histological types of MG thymoma are AB, B1, and B2, of which type B3 has the highest degree of deterioration. In addition, 9% of MG patients had thymic degeneration [10]. The clinical stage of thymoma is also closely related to the occurrence of myasthenia gravis. Types I and II thymoma are more likely to be complicated with myasthenia gravis, while thymoma types III and IV are less likely to be complicated by myasthenia gravis; that is, the clinical stage of thymoma complicated with myasthenia gravis is earlier.

In recent years, there have been many studies on the correlation analysis between MG serum antibodies and thymic diseases. Among them, the latest new guidelines for MG believe that the correlation between ryanodine receptor antibody (RYR-Ab) and thymoma is closely related to the pathogenesis of MG. RYR-Ab MG patients are often associated with thymoma, and their symptoms are often aggravated by thymic surgery and postoperative radiotherapy and chemotherapy. The disease often involves respiratory muscles and medulla, causing pseudobulbar palsy and respiratory weakness. MG crisis due to respiratory muscle weakness usually requires airway support such as artificial mechanical ventilation or tracheotomy. Pseudobulbar palsy is caused by dysphagia, difficulty in removing gastric tubes, and poor quality of life. Serum antibodies in MG with thymic hyperplasia are usually AChR and Musk antibodies. According to research, MG is often associated with thymic disease, usually

accompanied by thymic hyperplasia. RyR receptors are detected in 75% of MG thymoma patients. TiTin serum receptor is a structural protein that plays an important role in establishing and maintaining the elongation elasticity and static tension of muscle fibers. The RYR receptor is more specific than Titin-AB in patients with MG thymoma and has become one of the main antibodies affecting imaging diagnosis and surgical evaluation. MG symptoms in some patients with thymic disease resolve after thymectomy. Combined with the pathological characteristics of the thymus, the symptoms of MG patients with thymoma are often relieved or partially relieved by postoperative radiotherapy, chemotherapy and immunotherapy. The data show that thymus disease is closely related to the pathogenesis of MG, and about 85% of the myasthenia symptoms in MG patients are caused by AChR AB. MG patients with thymoma account for about 15% of MG patients. MG can occur in 30% of thymoma patients, and TYPE B2 accounts for about 50% of the WHO classification.

The Quantitative Myasthenia Gravis Score (QMG) provides an objective evaluation of muscular endurance, the severity of muscle weakness of affected muscle groups, respiratory function and swallowing function for the MGFA classification of MG, and provides a quantitative test of muscle strength to provide a reference for the severity of MG. One of the scales for clinical evaluation of MG treatment effect. The QMG score is the strength of the quantitative test, including the eye muscles, limb trunk muscles, swallowing and breathing scores. The more severe the clinical symptoms of MG with a high QMG score, the higher the MGFA clinical grade. The composite score of trunk muscles, swallowing, and respiration, in addition to the severity of individual muscles, also includes the number of muscle groups involved, so a higher QMG score does not mean a higher level of clinical classification of MGFA. There was no difference in the quantitative scores of swallowing, respiration and QMG between the AChR and non-AChR groups, which may be related to the fact that the serum antibodies to myasthenia gravis in this patient are mainly AChR (accounting for 74%), which is limited by the sample size. The size does not meet the sample size requirement for logistic regression.

Swallowing dysfunction is one of the common clinical manifestations of patients with MG, dysphagia due to autoimmune disorders, antibody attack, medulla oblongata swallowing center damage, caused by bulbar paralysis, bilateral cortical brain stem damage caused by the false bulbar paralysis, eventually cause food by pharyngeal reflex movement of the esophagus disorders, easy cause aspiration pneumonia, It is often the turning point of MG treatment. Reports show that about 40% of patients with MG in the process of disease progression with drinking water choke to cough, difficulty swallowing clinical manifestations, such as gastric tube after treatment, patients often easy to stomach tube depends on tube, difficulty swallowing dysfunction in addition to cause the stomach tube to take off the tube, easy to induce caused by aspiration of aspiration pneumonia, pulmonary infection and other diseases.

Conclusions

This study showed that the proportion of respiratory muscle involvement and laryngeal muscle involvement in MG patients in the thymoma group was significantly higher than that in the thymic hyperplasia group and thymus without abnormality group, and the scores of QMG, swallowing function, and respiratory function were also significantly higher. Patients with thymoma often have severe clinical symptoms due to the involvement of respiratory and swallowing muscles, which may result in choking, coughing, and difficulty swallowing. In severe cases, it can lead to respiratory failure and aspiration pneumonia, becoming one of the important causes of clinical death. It is clinically believed that thymoma is an unfavorable prognostic factor for MG patients. Once a patient develops myasthenic crisis, treatment is difficult, and the mortality rate is high. This study was limited to a single-center, cross-

sectional observational study. The QMG score was used to objectively assess the respiratory and swallowing function of patients with MG complicated with thymic disease. However, the number of patients was small, and there was no significant difference in the correlation analysis between myasthenia gravis and thymoma serum antibodies, respiratory scores, and swallowing scores. QMG scores were performed on MG patients, but only correlation analysis was performed, and statistical analysis was not performed in combination with factors such as treatment drugs, lifestyle, and surgery. Therefore, the results of this study need to be confirmed by large sample size, follow-up studies, and multivariate logistic regression analysis.

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Conflicts of Interest

The authors declare no conflict of interest.

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