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Clinical characteristics of myasthenia gravis (MG) patients developing other autoimmune diseases after thymectomy from one single center cohort

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Abstract

Background: Myasthenia gravis (MG) patients are reported to have a high risk of other autoimmune diseases (ADs), and thymectomy may increase the risk further. A cohort of MG patients in which thymectomy was performed were investigated to analyze the prevalence, types and features of the new onset ADs.

Methods: Consecutive patients with MG who underwent thymectomy at Beijing Hospital between January 2012 and August 2021 were retrospectively enrolled. Patients with a postoperative follow-up period shorter than a year or incomplete clinical records were excluded. Clinical and follow-up data were collected. Statistical analyses were performed using SPSS version 22.0.

Results: A total of 445 patients were included in this study. The median follow-up period was 72 months (range, 12–135 months). A total of 63 (14.2%) MG patients had concurrent ADs. The incidence rate was higher than the background prevalence of population (5%), and also higher than that of a former Chinese MG cohort (11.6%). A total of 47 patients (10.6%) were diagnosed with ADs before thymectomy, and 19 (4.3%) developed a new AD after thymectomy. The most common types of new onset ADs after thymectomy were Hashimoto's thyroiditis and rheumatoid arthritis (RA), which were different from those before thymectomy (hyperthyroidism and Hashimoto's thyroiditis). The incidence rate of new onset RA (1.35%) was higher than the frequency of RA before thymectomy (0.45%), and also higher than the incidence rate in a Chinese MG cohort (0.5%). There was a higher proportion of female patients ($p = 0.026$) with postoperative ADs. A younger age at operation may increase the risk of nonthymoma MG patients ($p = 0.040$) developing ADs. The postoperative treatment effect of MG was similar between patients with and without new onset ADs ($p > 0.05$).

Conclusions: We observed a higher incidence rate of autoimmune diseases, especially rheumatoid arthritis, in MG patients after thymectomy. The most common types of ADs after thymectomy were different from those before thymectomy. New onset ADs tended to occur in female and young nonthymoma MG patients. The postoperative effect of MG was not related with the new occurrence of ADs.

KEYWORDS
autoimmune diseases, myasthenia gravis, thymectomy

Wenxin Tian and Jing He contributed equally to this study.

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease (AD) with neuromuscular junction disorder which is characterized by fatigable weakness in skeletal muscles, such as extraocular muscles, neck, limbs, and bulbar muscles. The pathogenesis of MG has been proven to be strongly associated with thymic abnormalities, mainly including lymphofollicular hyperplasia and thymoma,[1] and surgical removal of the thymus gland is one effective treatment previously reported for the management of MG.[2–5] In addition, thymectomy has been tried in an attempt to manage other ADs, with uncertain effect and great controversy.[6,7] Several studies have reported an increased occurrence of other ADs in MG patients.[8–11] The removal of the thymus gland may have a significant impact on the immune function of the body, and further break the balance of the immune system. Other ADs, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), have been reported to occur in MG patients many years after thymectomy.[12–14] However, most of the studies were based on single cases or a small sample size. Here, we investigated the incidence rate in an MG patient cohort of a relatively large sample size, who all accepted thymectomy in our center, and the clinical characteristics of patients who developed a new AD after thymectomy were analyzed.

METHODS

Patients

This study was approved by the Institutional Ethnics Review Board of Beijing Hospital. The informed consent was waived because no additional treatment was planned as this was a retrospective study.

Consecutive MG patients who underwent thymectomy in Beijing Hospital from January 2012 to August 2021 were included in the study. Patients with a postoperative follow-up period shorter than 1 year or incomplete clinical records were excluded. Clinical information was collected including sex, age, smoking index (pack-year), Osserman classification when surgery, preoperative course of MG, serum antibody status, history of malignancies, surgical procedure, thymic pathology, and concurrent ADs before surgery. Smoking index was defined as the average root number per day multiplied by smoking years. Preoperative course of MG was defined as the interval between the date of the diagnosis of MG and thymectomy.

The diagnosis of MG was confirmed by clinical presentations and at least one of the following specific tests: neostigmine test, autoantibodies (antiacetylcholine receptor and anti-MuSK antibodies), and electrodiagnostic tests (repeated nerve stimulation with low and high frequencies and simple-fiber electromyography). MG clinical severity before surgery was graded by the Osserman classification system. The diagnosis of MG was assessed by a skilled neurologist. The diagnosis of autoimmune diseases was based on clinical symptoms and laboratory tests, which was assessed by corresponding skilled specialists.

Surgical procedure

All operations were performed using video-assisted thoracoscopic surgery (VATS) or sternotomy. The removal range of thymectomy for MG patients included removal of the whole thymus gland (including thymic tumor if existing), the anterior mediastinal fat tissue between bilateral phrenic nerves, and the fat tissue from both pericardiophrenic angles.

TABLE 1 Clinical characteristics of patients with MG enrolled

Variables	$n = 445$
Age at operation (years), mean ± SD	47.0 ± 15.7
Sex (male/female)	228/217
Smoke history (n[%])	
Non	360 (80.9%)
Smoking index (pack-year) ≤400	52 (11.7%)
Smoking index, (pack-year) >400	33 (7.4%)
Onset age of MG(n[%])	
< 50 years	198 (44.5%)
≥ 50 years	247 (55.5%)
Preoperative course of MG (n[%])	
≤12 months	295 (66.3%)
>12 months	150 (33.7%)
Dose of pyridostigmine bromide (mg/day)	180 (0,600)
Patients with AD before thymectomy, n (%)	47 (10.7%)
Patients with malignant tumors, n (%)	15 (3.4%)
Surgical procedure, n (%)	
VATS	381 (85.6%)
OT	64 (14.4%)
Osserman classification, n (%)	
I	98 (22.0%)
IIa	121 (27.2%)
IIb	192 (43.1%)
III	19 (4.3%)
IV	15 (3.4%)
Pathology, n (%)	
Thymic hyperplasia	264 (59.3%)
Normal thymus	11(2.5%)
Thymic atrophy	38 (8.5%)
Thymoma	132 (29.7%)
Perioperative complications, n (%)	19 (4.3%)
Postoperative myasthenic crisis, n (%)	47 (10.6%)

Abbreviations: AD, autoimmune diseases; MG, myasthenia gravis; OT, open thoracotomy; SD, standard deviation; VATS, video-assisted thoracoscopic surgery.

Follow-up

All patients were followed up every 6 months in the first 2 years after surgery, and then annually thereafter. Follow-up information was collected including follow-up period, occurrence of new ADs, occurrence of malignancies, survival status, and postoperative treatment effect of MG. For patients with new onset of ADs, related medical records including clinical symptoms, laboratory tests, and pathology results (if necessary) were provided to corresponding skilled specialists to confirm the diagnosis. The follow-up period was defined as the interval between the date of surgical resection and death or last follow-up. The postoperative effect of MG was examined according to the Myasthenia Gravis Foundation of America criteria defining the post-intervention status.[15]

Statistical analysis

Statistical analyses were performed with IBM SPSS version 22.0 statistical software. Continuous data of normal distribution are presented as mean ± standard deviation, while data of abnormal distribution are expressed as medians with interquartile range. Categorical data are presented as frequency and percentage. Continuous variables were compared by Student's *t*-test and categorical variables were compared by Pearson's chi-square test. Survival curves were calculated by the Kaplan–Meier method. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic data

A total of 535 patients with MG underwent thymectomy at the Department of Thoracic Surgery of Beijing Hospital from January 2012 to August 2021. After excluding patients with incomplete records and a short follow-up period, 445 patients were finally included in this study. A total of 261 patients were males, and 253 were females. The mean age at operation was 47.0 ± 15.7 years. The median onset age of MG was 47 years (range, 15–86 years). The median preoperative course of MG was 6 months (range, 0.13–480 months). According to Osserman classification, there were 98 type I, 121 type IIa, 192 type IIb, 19 type III, and 15 type IV. The median dose of pyridostigmine bromide

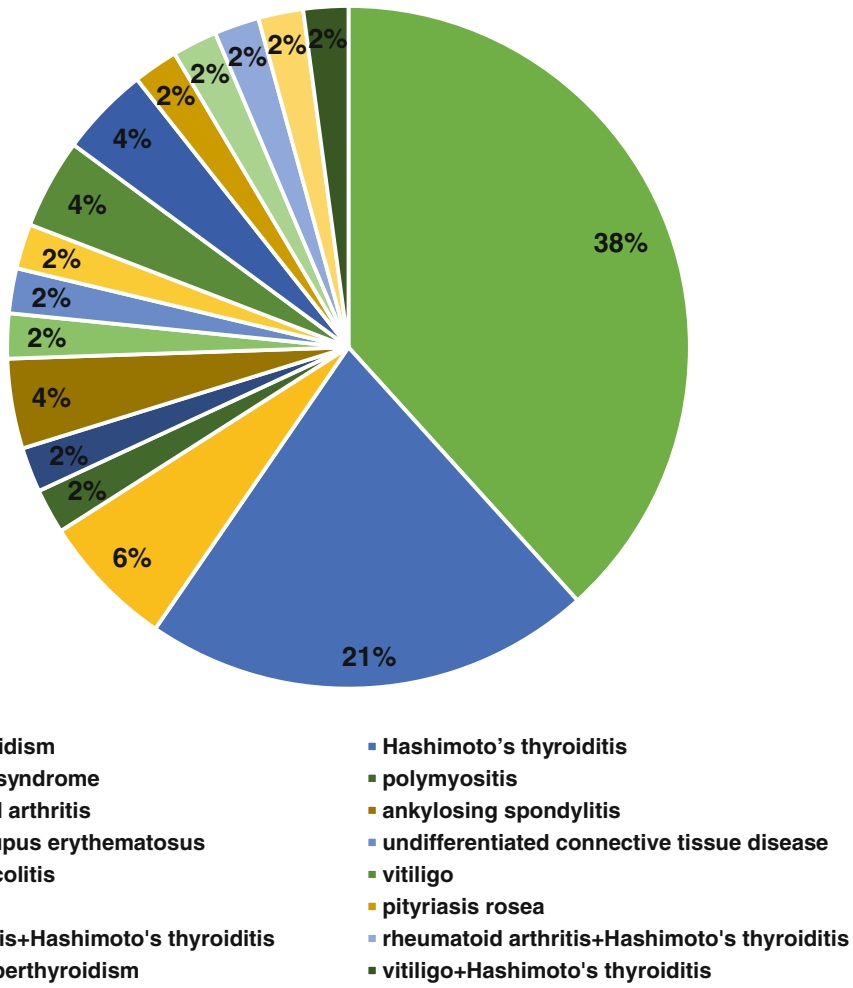

FIGURE 1 Types and proportions of concurrent autoimmune diseases (ADs) before thymectomy

was 180 mg/day (range, 0–600 mg/day). Thymoma was present in 132 (29.7%) patients. A total of 47 (10.6%) patients suffered myasthenic crisis within 1 month after thymectomy. A total of 47 patients were diagnosed with comorbid ADs, and 15 patients had a history of malignant tumors before thymectomy. The demographic characteristics are listed in Table 1.

Follow-up data

The median follow-up period was 72 months (range, 12–135 months). The 5-, 8-, and 10-year overall survival (OS) rates were 96.8, 95.4, and 94.2%, respectively. There were 16 deaths, including five due to MG, five due to thymoma recurrence, one due to pulmonary infection, one due to lung cancer, one due to prostate cancer, one due to gastric cancer, one due to cardiac infarction, and one due to Sjögren's syndrome.

All the patients in this study cohort were evaluated for post-intervention status of MG, including 135 patients (30.3%) with complete stable remission (CSR), 48 (10.8%) with pharmacological remission (PR), 146 (32.8%) with minimal manifestations (MM), 52 (11.7%) with improved condition (I), 28 (6.3%) with unchanged condition (U), 11 (2.5%) with worse condition (W), 18 (4.0%) with exacerbation (E), and seven (1.6%) who died of MG (D). The overall effective rate (CSR + PR + MM + I) was 85.6% (381/445).

Eighteen patients developed one or more malignant tumors, of whom six patients developed lung cancer, three patients rectal cancer, three patients thyroid cancer, two patients lymphoma, one patient urothelial tumor, one patient cervical carcinoma, one patient melanoma, and one patient developed two tumors successively which were lung and prostatic cancer.

Types and percentages of ADs before and after thymectomy

A total of 63 MG patients (24 males and 39 females) had concurrent ADs. The frequency of observed ADs was 14.2%, which was higher than the background prevalence of population (5%),[16] and also higher than the incidence rate in a former study of a Chinese MG cohort (11.6%).[8] Among them, 47 patients (10.6%) were diagnosed ADs before thymectomy (Figure 1). Hyperthyroidism was the most common preoperative concurrent AD with a percentage of 40.4% (19/47), and Hashimoto's thyroiditis was the second with a percentage of 27.7% (13/47). The other types and percentages were Sjögren's syndrome (6.4%, 3/47), polymyositis (4.3%, 2/47), RA (4.3%, 2/47), ankylosing spondylitis (4.3%, 2/47), SLE (2.1%, 1/47), undifferentiated connective tissue disease (2.1%, 1/47), ulcerative colitis (2.1%, 1/47), vitiligo (8.5%, 4/47), psoriasis (4.3%, 2/47), and pityriasis rosea (2.1%, 1/47). One patient both had hyperthyroidism and leukoderma, and three patients with Hashimoto's thyroiditis had another AD, which were RA, polymyositis, and vitiligo, separately.

A total of 19 patients (4.3%) developed a new AD after thymectomy (Figure 2). The frequency was higher than the incidence rate of new onset ADs in patients in whom thymectomy was not performed after the diagnosis of MG (1.73%), and even higher than in MG patients in whom thymectomy was performed (3.3%) in a Taiwanese cohort study.[17] The median postoperative follow-up period at the diagnosis of the new AD was 48 months (range, 6–108 months). In this study, the most common type of new onset ADs after thymectomy was Hashimoto's thyroiditis (47.4%, 9/19), and the second was RA (31.6%, 6/19). The other types were hyperthyroidism (5.3%, 1/19), Sjögren's syndrome (5.3%, 1/19), scleroderma (5.3%, 1/19), and vitiligo (5.3%, 1/19). The proportions of different types were different between pre- and postoperative ADs. The frequency of new onset RA after thymectomy (1.35%, 6/445) was higher than the frequency of RA before thymectomy (0.45%, 2/445), and also higher than the incidence rate in a previous study of a Chinese MG cohort (0.5%).[8] Two MG patients with a concurrent AD before surgery developed another AD after surgery.

Clinical characteristics of MG patients with concurrent ADs

Patients were divided into two groups according to whether they were with or without other ADs. The clinical

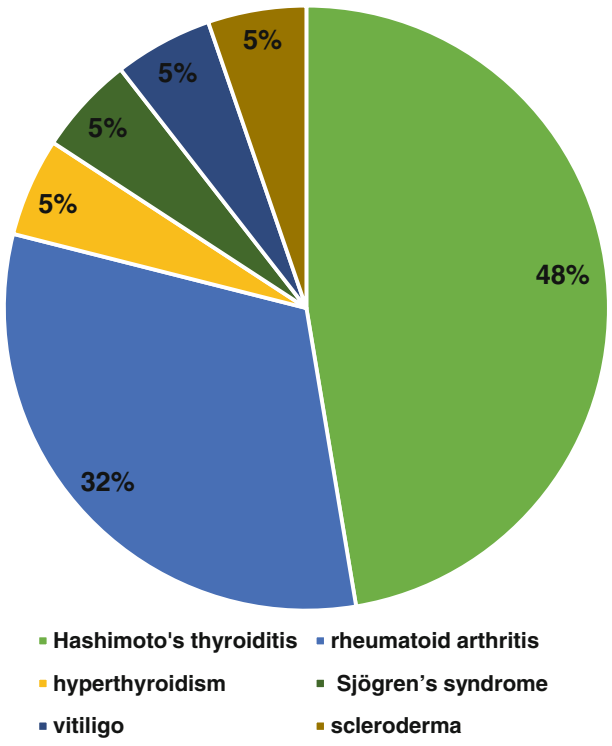

FIGURE 2 Types and proportions of new onset autoimmune diseases (ADs) after thymectomy

characteristics were compared between the two groups (Table 2). In patients with ADs, a higher proportion were females (39/63 vs. 178/382, $p = 0.024$), and a lower proportion had thymomas (6/63 vs. 113/382, $p = 0.001$) than those without ADs. We also compared the treatment effect of MG between the two groups, but no significant differences were observed in CSR rate (19/63 vs. 116/382, $p = 0.973$) or effective rate (CSR + PR + MM + I) (51/63 vs. 330/382, $p = 0.255$). There were no significant differences in other clinical characteristics between MG patients with and without ADs.

Clinical characteristics of MG patients with postoperative onset ADs

More female MG patients developed new ADs than male patients (14/19 vs. 203/426, $p = 0.026$). None developed more than one new AD. No significant differences were found in onset age, age at operation, preoperative duration of MG, thymic pathology, and Osserman types between patients with and without new onset ADs after thymectomy. The CSR rate (8/19 vs. 127/426, $p = 0.254$) and effective rate (CSR + PR + MM + I) (16/19 vs. 365/426, $p = 0.858$) were similar in the two groups (Table 3).

For nonthymoma MG patients with new onset ADs, females also occupied a higher proportion than males (10/13 vs. 138/426, $p = 0.029$). Patients with postoperative new ADs were younger at onset age (37.1 ± 15.1 vs. 46.3 ± 16.2, $p = 0.045$) and operation age (32.2 ± 18.8 vs. 42.9 ± 18.3, $p = 0.040$) than those without. No significant differences were found in other clinical characteristics and postoperative MG treatment effect between nonthymoma MG patients with and without new onset ADs.

We next analyzed the clinical characteristics of MG patients who developed RA after thymectomy. Six patients who developed postoperative RA were all females, and only one patient was older than 50 years at operation. One patient had a thymoma, and the other five had thymic hyperplasia. The shortest period when RA was diagnosed was 24 months after thymectomy, and the longest was 96 months. One patient had hyperthyroidism, and one had an undifferentiated connective tissue disease before thymectomy. Four patients achieved CSR, one achieved PR, and one improved at the end of follow-up. The six patients all survived, and none had malignant tumors.

TABLE 2 Comparison of clinical data between patients with and without ADs

Variables	Patients without ADs	Patients with ADs	*t*-test or x^2	*p*-value
N	382	63		
Age (years), mean ± SD	47.1 ± 15.3	46.5 ± 18.0	−0.313	0.754
Sex (male/female)	204/178	24/39	5.072	0.024
Smoke history			1.122	0.571
Non	309 (80.9%)	51 (81.0%)		
Smoking index (pack-year) ≤400	43 (11.3%)	9 (14.3%)		
Smoking index (pack-year) >400	30 (7.9%)	3 (4.8%)		
Onset age of MG (<50 years/≥50 years)	170/212	28/35	0.000	0.993
Preoperative MG course (≤12 months/>12 months)	256/126	39/24	0.632	0.427
Surgical procedure (VATS/OT)	329/53	52/11	0.565	0.452
Osserman classification, n (%)			2.656	0.617
I	85 (22.3%)	13 (20.6%)		
IIa	106 (27.7%)	15 (23.8%)		
IIb	161 (42.1%)	31 (49.2%)		
III	18 (4.7%)	1 (1.6%)		
IV	12 (3.1%)	3 (4.8%)		
Pathology, n (%)			32.350	0.000
Thymic hyperplasia	226 (59.2%)	38 (60.3%)		
Normal thymus	11 (2.9%)	0 (0%)		
Thymic atrophy	32 (8.4%)	19 (30.2%)		
Thymoma	113 (29.6%)	6 (9.5%)		
Postoperative effect of MG (CSR), n (%)	116 (30.4%)	19 (30.2%)	0.001	0.973
Postoperative effect of MG (CSR + PR + MM + I), n (%)	330 (86.4%)	51 (81.0%)	0.646	0.422
Patients developing postoperative tumors, n (%)	15 (3.9%)	3 (4.7%)	0.097	0.755

Abbreviations: AD, autoimmune diseases; CSR, complete stable remission; I, improved; MG, myasthenia gravis; MM, minimal manifestations; OT, open thoracotomy; PR, pharmacological remission; SD, standard deviation; VATS, video-assisted thoracoscopic surgery.

TABLE 3 Comparison of clinical data between patients with and without new onset ADs after thymectomy

Variables	Patients without postoperative ADs	Patients with postoperative ADs	*t*-test or x^2	*p*-value
N	426	19		
Age (years), mean ± SD	47.2 ± 15.6	42.6 ± 19.0	−1.248	0.213
Sex (male/female)	223/203	5/14	4.933	0.026
Smoke history, n (%)			1.005	0.605
Non	343 (80.5%)	17 (89.5%)		
Smoking index (pack-year) ≤400	51 (12.0%)	1 (5.3%)		
Smoking index (pack-year) >400	32 (7.5%)	1(5.3%)		
Onset age of MG (<50 years/≥50 years)	187/239	11/8	1.443	0.230
Preoperative MG course (≤12 months/>12 months)	285/141	10/9	1.657	0.198
Surgical procedure (VATS/OT)	363/63	18/1	1.340	0.247
Osserman classification, n (%)			2.801	0.592
I	94 (22.1%)	4 (21.1%)		
IIa	117 (27.5%)	4 (21.1%)		
IIb	181(42.5%)	11(57.9%)		
III	19 (4.5%)	0		
IV	15 (3.5%)	0		
Pathology, n (%)			4.935	0.177
Thymic hyperplasia	251(58.9%)	13 (68.4%)		
Normal thymus	11(2.6%)	0 (0%)		
Thymic atrophy	38 (8.9%)	0 (0%)		
Thymoma	126 (29.6%)	6 (31.6%)		
Postoperative effect of MG (CSR), n (%)	127 (29.8%)	8 (42.1%)	1.301	0.254
Postoperative effect of MG (CSR + PR + MM + I), n (%)	365 (85.7%)	16 (84.2%)	0.032	0.858
Patients developing postoperative tumors, n (%)	16 (3.8%)	2 (10.5%)	2.148	0.143

Abbreviations: AD, autoimmune diseases; CSR, complete stable remission; I, improved; MG, myasthenia gravis; MM, minimal manifestations; OT, open thoracotomy; PR, pharmacological remission; SD, standard deviation; VATS, video-assisted thoracoscopic surgery.

DISCUSSION

The thymus is the most important central immune organ of human body, which is the place for development, differentiation, maturation of T cells, and also the center for autoimmune tolerance. Thymus abnormalities can lead to many autoimmune disorders. The most common one is MG. Patients with MG are more likely to have other ADs than the general population.[8–11] Previous studies have reported that the most common AD in MG patients is autoimmune thyroid diseases, such as hyperthyroidism and Hashimoto's thyroiditis.[9,10] Other ADs associated with MG patients include systemic lupus erythematous (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, and so on. A Swedish population-based study suggested that MG patients shared an increased risk to coexist with other ADs especially among younger and female patients.[9] Kanazawa and colleagues[10] from Japan also found that patients with Graves' disease appeared to be younger, with a lower degree of positivity for the antiacetylcholine receptor antibody, and a higher proportion of thymic hyperplasia. A retrospective cross-sectional study observed a higher frequency of concurrent ADs in a Chinese MG cohort, and MG patients with ADs appeared to have a mild presentation, and were less likely to develop myasthenic crisis.[8,14] In our cohort, the proportion of patients with concurrent ADs was 14.2%, which is higher than the incidence rate in the Chinese cohort with MG.[8] However, various incidence rates (9.4%–22.9%) have been reported in different regions.[9–11,18] Similarly, the majority of patients in those studies were female, and the most common types were autoimmune thyroid diseases.

Thymectomy has been proven to be effective in the management of MG, not only for MG patients with thymoma, but also for nonthymoma MG patients.[2–5] However, thymectomy may lead to greater changes in the immune function of the body. In experimental animals, neonatal thymectomy has been reported to lead to various degrees of T cell depletion.[19] Several studies found that multiple immune alterations arose in humans whose thymus gland was removed in early childhood as a result of surgery for congenital heart diseases, and the removal of the thymus may result in a delayed immune response to new antigens later in life.[20–23] Zlamy et al.[24] revealed that early thymectomy in

childhood demonstrated immunological alterations of CD8 + T cells, which mimic features of premature immunosenescence in humans. MG patients with a long term after thymectomy had mild T cell lymphopenia, and also displayed a polyclonal increase in serum IgG and IgM associated with the presence of some antibodies.[25] The function of cytotoxic T cells may be enhanced, and regulatory T cells may be weakened after thymectomy. As a result, the balance of immune homeostasis is broken, leading to new ADs or malignant tumors. There have been many cases of SLE reported in MG patients after thymectomy.[12–14] One cohort study from Taiwan revealed that thymectomy in patients with MG increased the risk of autoimmune rheumatic diseases.[14] Furthermore, thymectomy in patients without MG may also increase the risk of ADs, and the overall incidence rate of ADs has been reported to be 2.68 times higher in thymectomy patients than those who did not undergo thymectomy.[17]

In this study, the incidence rate of patients developing a new AD after thymectomy was 4.3%, which was higher than the incidence rate of new onset ADs in patients without thymectomy after the diagnosis of MG (1.98%), and also higher than MG patients after thymectomy (3.3%) in the Taiwanese cohort.[17] The proportions of different types after surgery changed. The first common AD before surgery was hyperthyroidism (40.4%), while the first common new onset AD after surgery was Hashimoto's thyroiditis (47.4%). The changes in ADs before and after surgery might reflect that thymectomy shifted the development direction of autoimmune reactions. It is possible that the thymus is a protective or promoting factor for different ADs in different individuals. In our study, we found that new onset ADs after thymectomy were more likely to occur in female patients, and young nonthymoma patients. However, the occurrence of new onset ADs was not observed to be related to the postoperative effect of MG. The incidence rate of RA (1.3%) after thymectomy was much higher, but no new onset SLEs were observed in this study, which is different from previous studies. The diversity of the results among different studies may be partly due to the differences in study populations. Thymectomy was performed in all the patients in our study, and in other studies MG patients who underwent removal of thymus only occupied a small fraction.

A large sample size of MG patients undergoing thymectomy with a long period of follow-up was included in this study. Such studies have been limited in this respect until now. However, some limitations of our study should be highlighted. First, this was a retrospective single-center study, and selection bias was therefore inevitable. Second, the follow-up information was collected by telephone, inpatient and outpatient records. The observed new onset ADs were expected to be underestimated, rather than overestimated. Third, the data of autoantibodies of many patients was not available in this study. The relationship between autoantibodies and new onset ADs could not be analyzed. Further studies should not only collect data regarding the autoantibodies associated with MG, but also with other common ADs before and after thymectomy. Finally, the number of patients in this study was not sufficient to analyze the relationship between a single certain type of AD and thymectomy, due to the low prevalence rate. A prospective multicenter study with a huge sample size and a long-period of follow-up is warranted.

In conclusion, we observed a higher prevalence rate of autoimmune diseases, especially rheumatoid arthritis, in MG patients after thymectomy. The most common types of ADs after thymectomy were different from those before thymectomy. New onset ADs tended to occur in female and young nonthymoma MG patients. The postoperative effect of MG was not associated with the new occurrence of ADs.

AUTHOR CONTRIBUTIONS

Wenxin Tian: Conceptualization, data curation, methodology, and writing original draft. **Jing He:** Data curation, methodology, and writing original draft. **Hanbo Yu:** Investigation and methodology. **Yaoguang Sun:** Methodology, supervision, and validation. **Qingjun Wu:** Supervision and validation. **Peng Jiao:** Investigation and supervision. **Chao Ma:** Data curation and investigation. **Chuan Huang:** Data curation and investigation. **Donghang Li:** Data curation, methodology, and validation. **Hongfeng Tong:** Conceptualization, methodology, supervision, and writing-review & editing. All the authors read and approved the final manuscript.

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CONFLICT OF INTEREST

No authors report any conflicts of interest.

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