Original Article

Clinical Outcomes of Myasthenia Gravis with Thymoma and Thymic Hyperplasia Undergoing Extended Transsternal Thymectomy: A Single-Center Experience

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Abstract

Background: Despite the widespread use of thymectomy in myasthenia gravis (MG) patients, it has remained controversial as to whether this procedure is of a similar efficacy and clinical outcome among MG patients with thymoma and thymic hyperplasia. **Aim:** We sought to determine the long-term clinical outcomes of MG patients who received extended transsternal thymectomy associated with pyridostigmine and prednisolone postoperatively. **Materials and Methods:** In a retrospective study from January 1999 to December 2013, MG patients who underwent thymectomy were followed up. Out of 41 MG patients admitted in our center, 25 patients had undergone thymectomy adjunctive to pyridostigmine and prednisolone therapy postoperatively. The primary endpoints included improvement in individual diplopia, ptosis, dysphagia, dysarthria, dyspnea, and limb weakness. In addition, according to the MG Foundation of America (MGFA) criteria, response to therapy was defined as complete stable remission (CSR), pharmacologic remission (PR), and minimal manifestation (MM) as secondary endpoints. **Results:** Majority of the patients were male (60%) and the mean age of the patients was 32.2 ± 13.9 years. Fifteen (60%) and 10 patients (40%) had thymoma and thymic hyperplasia, respectively. All the patients were followed up during a mean period of of 86.9 ± 50.3 months (minimum 10 months and maximum 168 months). The rates of CSR, PR, and MM were comparable between the thymoma and thymic hyperplasia groups ($P = 0.584$). Based on the Kaplan Meier analysis, the probabilities of CSR, PR, and MM were not significantly different between patients with thymoma and thymic hyperplasia. **Conclusion:** The extended transsternal thymectomy, along with the postoperative regimen of pyridostigmine and prednisolone was associated with a high rate of clinical improvement among MG patients with thymoma or thymic hyperplasia.

Keywords: Complete stable remission (CSR), extended transsternal thymectomy, myasthenia gravis (MG), thymoma, thymic hyperplasia

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Introduction

Myasthenia gravis (MG) is an autoimmune disease affecting approximately 100 patients per million

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populations. In MG, autoantibodies are developed against acetylcholine receptors at neuromuscular junctions, leading to fatigue and weakness after the repetitive use of voluntary muscles.[1,2] MG occurs in a bimodal age of onset including early-onset form in women less than 40 years of age and late-onset type in old men.[2] Early symptoms include extraocular muscle weakness, ptosis, diplopia, and progressively developed limb and bulbar muscle weakness.[2,3] Generalized muscle weakness and the involvement of respiratory muscles may result in death if no therapy is applied.[4]

Medical therapy targeted at autoimmune response is able to control MG symptoms but spontaneous remission rate is low and chronic consumption of agents is more likely to induce adverse effects.[5] Thymectomy, as a surgical modality, has been performed for the first time by Sauerbruch in 1911 using the transcervical approach, and then Blalock developed the transsternal operation in 1936 with favorable outcomes.[6] Transsternal thymectomy has been tuned into the main method of treatment even for the severe form of MG, which has been associated with high rates of complete clinical remission, particularly in patients with nonthymomatous disease.[7,8] We herein sought to determine the long-term clinical outcomes of MG patients who underwent extended transsternal thymectomy and received pyridostigmine and prednisolone postoperatively.

Materials and Methods

Patients and protocol

In a retrospective study, the medical charts of MG patients who underwent thymectomy from January 1999 to December 2013 were evaluated. Out of 41 MG patients admitted in our center, 25 patients had undergone transsternal thymectomy. They were followed up concerning the impact of surgical therapy on outcomes through their visits in the neurology clinic of our institution. The preoperative and postoperative clinical features were obtained by the attending neurologist. Since our study was retrospective, the institutional review board of our center and the local ethics committee in our university approved the study. Furthermore, consent forms were obtained from all the patients.

Diagnosis and treatment modalities

The diagnosis of MG was confirmed by neurologists according to the clinical symptoms, anticholinesterase test results, and electromyographic findings. Patients were diagnosed with MG when they had new-onset generalized MG, failing long-term conservative therapy, or myasthenic symptoms accompanied by thymoma. In our cohort, surgery technique was constant during the study period and two surgeons performed all the operations. Thymectomy was performed through an extended transsternal sternotomy removing mediastinal fat tissue. All patients postoperatively received pyridostigmine with a dose of 10 mg three times per day and prednisolone 1 mg/kg daily. Moreover, all the patients were divided into two groups based on the onset of MG, early-onset versus late-onset. The late-onset was defined as patients whose MG had begun at the age of 50 years and above.

Follow-up data

During the follow-up period, the effect of thymectomy on clinical outcomes was defined based on the MG Foundation of America (MGFA) criteria.[9] Accordingly, complete stable remission (CSR) as a favorable outcome was identified when a patient had no symptoms or signs for at least 1 year and had received no therapy for MG during that period. In addition, pharmacologic remission (PR) was also defined as patients in whom the same criteria as for CSR existed except that they consumed some drugs for MG. They also did not take cholinesterase inhibitors, which is an indicator of muscle weakness. Minimal manifestation (MM) was another group in which the patient had no symptom of functional limitations caused by MG but had some muscle weakness upon physical examination accompanied by taking immunosuppression and/or cholinesterase inhibitors during that time.

Statistical analysis

Continuous and categorical variables were reported as mean ± standard deviation and number (percentage), respectively. Continuous variables were analyzed by *t*-test and categorical ones were analyzed using chi-square test or Fisher's exact test as appropriate. The Kaplan-Meier survival analysis was used to identify the differences between groups with different thymus pathologic features concerning response to treatment at the postoperative follow-up period. All *P* values of less than 0.05 were considered to be statistically significant. All analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The majority of patients were male (60%) and the mean age of the patients was 32.2 ± 13.9 years. Of total subjects undergoing thymectomy, 15 (60%) patients and 10 (40%) patients had thymoma and thymic hyperplasia, respectively. No differences regarding the study variables were observed between patients with thymoma and thymic hyperplasia [Table 1]. There were trends

Table 1: Demographics and clinical manifestation of patients according to pathological features

Clinical characteristics	Total (n = 25) (%)	Thymoma (n = 15) (%)	Thymic hyperplasia (n = 10) (%)	P value
Age, years	32.2±13.9	34.3±14.5	29±13	0.364
Female, no. (%)	15 (60)	10 (66.7)	5 (50)	0.405
Preoperative presentation, no. (%)				
Diplopia	13 (52)	8 (53.3)	5 (50)	0.596
Ptosis	19 (76)	10 (66.7)	9 (90)	0.198
Dysphagia	12 (48)	9 (60)	3 (30)	0.144
Dysarthria	3 (12)	3 (20)	0 (0)	0.198
Dyspnea	5 (20)	5 (33.3)	0 (0)	0.057
Limb and axial weakness	13 (52)	7 (46.7)	6 (60)	0.404
Generalized MG	15 (60)	11 (73.3)	4 (40)	0.096
Clinical outcome, no. (%)				0.584
CSR	8 (32)	5 (33.3)	3 (30)	
PR	12 (48)	8 (53.3)	4 (40)	
MM	5 (20)	2 (13.3)	3 (30)	
Follow-up duration, months	86.9±50.3	89±52.1	83±50	0.802

Data are presented as mean ± standard deviation or number (percentage), All P values are calculate by chi-square or t-test, MG = Myasthenia gravis, CSR = Complete stable remission, PR = Pharmacologic remission, MM = Minimal manifestation

Table 2: Clinical outcomes of patients according to the onset of MG

	Early-onset (n = 21) (%)	Late-onset (n = 4) (%)	P value
Female, no. (%)	14 (66.7)	1 (25)	0.119
Pathologic finding, no. (%)			0.504
Thymoma	12 (57.1)	3 (75)	
Thymic hyperplasia	9 (42.9)	1 (25)	
Generalized MG	12 (57.1)	3 (75)	0.504
Clinical outcome, no. (%)			0.078
CSR	5 (23.8)	3 (75)	
PR	12 (57.1)	0 (0)	
MM	4 (19)	1 (25)	
Follow-up duration, months	83.4±52.6	105±34.9	0.443

Data are presented as mean ± standard deviation or number (percentage), All P values are calculate by chi-square or t-test, MG = Myasthenia gravis, CSR = Complete stable remission, PR = Pharmacologic remission, MM = Minimal manifestation

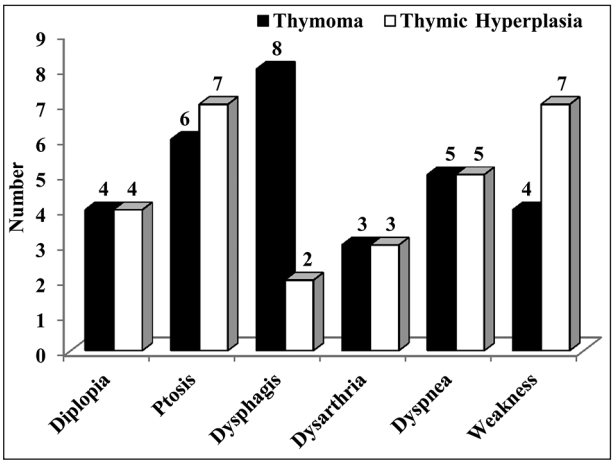

Figure 1: Comparison of MG signs and symptoms between patients with thymoma and thymic hyperplasia

showing that patients with thymoma tended to have more dyspnea (33.3% vs 0%, P = 0.057) and generalized MG at the baseline (73.3% vs. 40%, P = 0.096) compared to those with thymic hyperplasia. All the patients were followed up during a mean period of 86.9 ± 50.3 months (minimum 10 months and maximum 168 months).

Subgroup analysis

All patients were also categorized into two groups including 21 early-onset (84%) and 4 late-onset (16%) patients. Accordingly, there was a trend showing that late-onset MG patients tended to have more CSR during the postoperative period than early-onset MG patients; however, this difference was not significantly different [Table 2]. In addition, when comparing the early-onset and late-onset groups by log-rank test, there were no significant differences between the groups regarding the survival of MM, PR, and CSR (P = 0.807, P = 0.103, and P = 0.228, respectively).

Follow-up outcomes

When comparing the improvements of MG signs and symptoms between patients with thymoma and thymic hyperplasia, there were no significant differences [Figure 1]. Furthermore, the rates of CSR, PR, and MM were comparable between the thymoma and thymic hyperplasia groups [Table 1]. According to the Kaplan-Meier survival curve and log-rank test analysis, the probabilities of CSR [Figure 2], PR [Figure 3], and MM [Figure 4] during long-term follow-up, postoperatively were not significantly different between patients with thymoma and thymic hyperplasia.

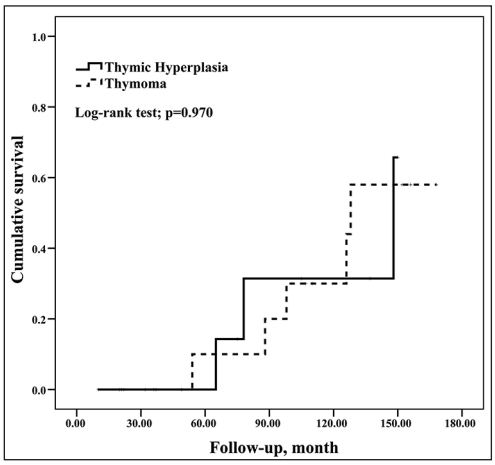

Figure 2: Kaplan-Meier curve comparing the probability of CSR between patients with thymoma and thymic hyperplasia during postoperative follow-up

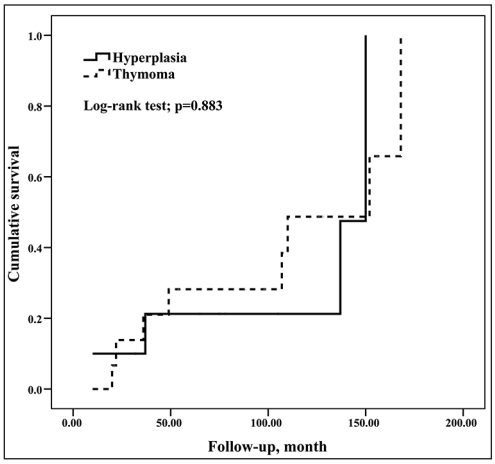

Figure 3: Kaplan-Meier curve comparing the probability of PR between patients with thymoma and thymic hyperplasia during postoperative follow-up

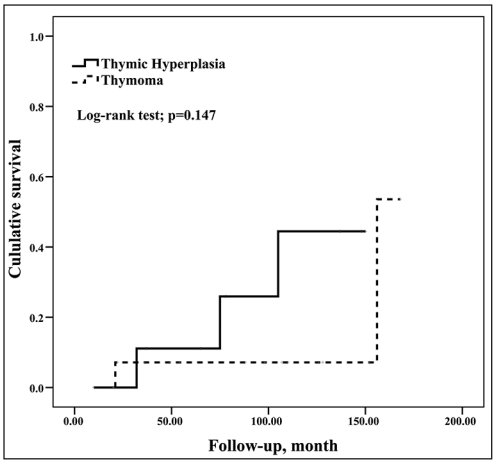

Figure 4: Kaplan-Meier curve comparing the probability of MM between patients with thymoma and thymic hyperplasia during postoperative follow-up

Discussion

In this retrospective study with long-term clinical outcomes, 86.9 ± 50.3 months follow-up duration, we demonstrated that transsternal thymectomy, along with postoperative prednisolone and pyridostigmine in MG patients was associated with favorable outcomes regardless of pathologic features, thymoma versus thymus hyperplasia. The rates of CSR, PR, and MM were 32%, 48%, and 20%, respectively, among all patients. Moreover, there were no significant differences between patients with thymoma and thymus hyperplasia regarding preoperative and postoperative clinical features. The rates of early-onset and late-onset MG were 84% and 16%, respectively. In addition, we showed that long-term postoperative clinical outcomes were not significantly different between the late-onset and early-onset groups regardless of their thymus pathologic features. This study confirmed the safety and efficacy of transsternal thymectomy, which showed neither postoperative MG crisis nor mortality. As we know, this is the first report showing similar outcomes for MG patients with and without thymoma who underwent transsternal thymectomy.

Thymectomy is a well-established treatment modality for MG, which is associated with favorable clinical outcomes.[5] Some different definitions for MG have been developed to help neurologists identify clinical response to treatment and the deterioration of symptoms and signs. Definition tools for the remission and improvement of MG are inconsistent among studies including the Osserman classification, Osserman modified classification, Oosterhuis score, Besinger score, de Filippini, and MGFA.[3] Since the MGFA criteria is a most comprehensive and extendedly used tool, we applied it in our study.[9] The endpoint of our study was CSR defined by MGFA as patients without symptoms or signs of MG for at least 1 year and those who did not receive medical therapy during that time. In addition, the second endpoints included PR and MM as defined in the method section based on the MGFA criteria.

In terms of thymectomy outcomes in MG patients, some studies have shown the effectiveness and safety of this modality. Tansel *et al*.[10] in a retrospective study of 204 nonthymomatous MG patients showed that transsternal thymectomy with mediastinal dissection yielded significant improvement and remission rate, enhancing over time. In contrast, Choi *et al*.[11] have demonstrated that thymectomy in thymomatous MG may be associated with myasthenic crisis within 2 years follow-up that was directly correlated with worse preoperative respiratory function. In our study, no myasthenic crises were observed and all subjects had an improvement of symptoms in some degree to complete

remission. It may be supposed that the lack of efficacy of thymectomy in Choi's study resulted from short-term follow-up since some reports have disclosed that the favorable outcomes following transsternal thymectomy increased over time.[10,12]

The main factors predicting the prognosis of MG patients undergoing thymectomy have been inconsistent among studies mainly owing to them being retrospective. Glinjongol *et al*.[13] in a retrospective study of 30 MG patients undergoing transsternal thymectomy have shown high remission and improvement rates during the 14-year follow-up period. They also found that the female sex, absence of thymoma, thymus hyperplasia, and patients with mild disease significantly predicted favorable outcomes. Soleimani *et al*.[14] evaluated the prognosis of nonthymomatous MG patients and demonstrated that lower age at the baseline and those undergoing thymectomy were associated with less myasthenic crisis. In addition, Budde *et al*.[15] have demonstrated that sex, age, and thymic pathology independently predicted the outcome of thymectomy. All these studies recommended transsternal thymectomy as a safe and efficacious treatment modality in MG patients with and without thymoma. Regarding the effect of pathology of thymus on thymectomy outcomes, there have been controversies. When compared to thymoma, the presence of thymic hyperplasia has been associated with either more improvement or CSR rates.[12,13,16,17] However, some other reports have found no significant difference concerning the prognosis of MG between patients with and without thymoma.[18,19] In our cohort, the frequencies of CSR, PR, and MM were comparable between patients with thymic hyperplasia and thymoma. In addition, no differences in the survival of patients with regard to the presence of CSR, PR, or MM were observed. We think that future randomized studies in a homogenous cohort of MG patients will clarify these notions.

The age at the onset of MG has been found to be associated with outcomes and most studies use more than 40-50 years as a cutoff in the epidemiologic data.[17] In general, early-onset MG has been shown to be an indicator of better prognosis.[17] Park *et al*. in a retrospective cohort of MG patients showed that early-onset MG was a good prognostic factor for CSR among nonthymomatous patients.[5] On the other hand, Uzawa *et al*. studied clinical outcomes of late-onset MG patients with a rate of 12.8% thymic hyperplasia. They have demonstrated that the rate of improvement was more pronounced among MGFA II although this beneficial effect was not significant. They concluded that thymectomy may be of benefit for late-onset MG, particularly in thymic hyperplasia.[20] In our cohort, only 16% of the patients had late-onset MG and thymic hyperplasia was observed in one subject. The rate of MM, PR, and CSR was not significantly different between early- and late-onset MG patients and survival analysis was also comparable between them. We think that, similar to previous studies, thymectomy can be of great benefit for late-onset cases; however, regarding the effect of thymoma or nonthymomatous on late-onset MG outcomes, we need further large-scale study to find such a relationship and our results are not conclusive.

The new surgical techniques were also developed to increase the probability of complete thymic tissue removal for enhancing the rate of CSR in MG patients. Meyer *et al*.[21] evaluated the outcome differences between transsternal thymectomy and video-assisted thoracoscopic surgery (VATS) approaches in MG patients and they found that thymectomy using both transsternal and VATS was a safe and effective modality with equivalent clinical outcomes. In another study comparing VATS and transsternal thymectomy in 60 nonthymomatous MG patients, it has been demonstrated that VATS thymectomy was more advantageous due to shorter hospital stay, less tissue injury, better cosmetic results, and equivalent CSR rate compared with classic transsternal thymectomy.[22] Unfortunately, there is no randomized study in the literature comparing the difference of these two techniques, and we are unable to definitely conclude about which approach will be of more safety and efficacy for each group of MG patients, thymoma and nonthymomatous.

Study limitation

Our study had some limitations. First, this report was a retrospective study and it was therefore, subject to more bias. Second, we postoperatively prescribed prednisolone and pyridostigmine for all patients and this may have led to a significant effect on the CSR rate in our study.

Conclusion

The extended transsternal thymectomy, along with postoperative regimen of prednisolone and pyridostigmine, regardless of the preoperative duration of MG is a safe and effective treatment modality for MG patients with either thymoma or thymic hyperplasia. In addition, transsternal thymectomy was associated with high rates of CSR and PR among this cohort of MG patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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