Neurologic outcomes of thymectomy in myasthenia gravis: Comparative analysis of the effect of thymoma

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Objectives: The objectives of this study were to compare the clinical features and the outcomes after thymectomy between patients with and without thymoma and to evaluate the influence of thymectomy on the subsequent clinical course of myasthenia gravis.

Methods: Between 1995 and 2003, 64 consecutive patients underwent thymectomy, and of these, 60 patients were followed up for at least 12 months postoperatively. The study population was divided into 2 groups based on the presence of thymoma. We performed a retrospective analysis to compare the neurologic outcomes of thymectomy between patients with thymomatous myasthenia gravis and those with nonthymomatous myasthenia gravis.

Results: Twenty-four patients had a thymoma. No significant differences were observed between the 2 groups regarding the preoperative severity of myasthenia gravis. There was no significant difference in the follow-up duration between the 2 groups. There was no significant difference in the overall remission rate between the 2 groups ($P = .064$). The mean time required to reach a remission was 10.6 months and 23.5 months in the thymoma and nonthymoma groups, respectively. The mean duration of remission was 43.1 months and 30.8 months in the thymoma and nonthymoma groups, respectively. In the early phase of follow-up, more patients reached remission in the thymoma group than those in the nonthymoma group ($P = .040$).

Conclusions: Neurologic outcomes of the thymoma group were no worse than those of the nonthymoma group. It is expected that earlier thymectomy is likely to result in a better prognosis by shortening the disease period, even for patients with nonthymomatous myasthenia gravis.

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Myasthenia gravis (MG) is an autoimmune disorder that is caused by an antibody-mediated attack directed against acetylcholine receptors at the neuromuscular junction. Thymoma occurs in 24% to 38% of patients with late-onset MG.^{1,2} Both the clinical severity of MG and the outcomes after thymectomy are different between the patients with and those without thymoma. Thymoma is considered a poor prognostic factor of MG because of either the more severe symptoms or the less responsiveness to treatment.³⁻¹⁰

Thymoma may be a source of autoantigen in thymomatous MG, and therefore we hypothesized that the myasthenic symptoms of patients with thymoma would have

Abbreviations and Acronyms

CT	= computed tomography
MG	= myasthenia gravis
MGFA	= Myasthenia Gravis Foundation of America

better response to thymectomy than would those of patients without thymoma. The objectives of this study were to compare the clinical features and their outcomes after thymectomy between patients with and those without thymoma and to evaluate the influence of thymectomy on the subsequent clinical course of MG.

Materials and Methods

Between January 1995 and December 2003, 64 consecutive patients with a diagnosis of MG underwent thymectomy at our institution. Of these, 60 patients were followed up for at least 12 months postoperatively, and they constituted the study population. Their medical records were retrospectively reviewed to compare the clinical characteristics and long-term results between the patients with thymoma and those without thymoma, and we focused on the neurologic outcomes of MG. The study was reviewed and approved by the Institutional Review Board of the Sungkyunkwan University.

The diagnosis of MG was primarily based on the clinical features and confirmed by 1 or more of the following tests: the positive tensilon test, the repetitive nerve stimulation test, and assay for acetylcholine receptor antibody. All the patients underwent computed tomographic (CT) scanning of the chest to ascertain whether they had pathologic abnormalities of the thymus. The severity of MG was retrospectively evaluated at the time of diagnosis, during the period of medical management, and immediately before the operation according to the clinical classification of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America (MGFA).¹¹

Thymectomy was recommended when either thymoma or hyperplasia of the thymus was detected on the CT scan or when the patients aged 19 through 69 years had generalized symptoms of MG. All thymectomies were performed transternally, as described previously, and every possible effort was made to eliminate all the thymic tissue as completely as possible.⁷ A consistent protocol of perioperative care was used, including preoperative stabilization and postoperative management of the patients.

A histopathologic examination was performed on all specimens and then reviewed by a pathologist. Thymomas were histologically classified based on the new World Health Organization classification of Rosai and Sabin as type A (medullary), AB (mixed), B1 (organoid), B2 (cortical), B3 (epithelial), or C (thymic carcinoma) thymoma. For the patients with thymoma, pathologic staging was done according to the scheme suggested by Masaoka and colleagues.¹² Stage I was defined as macroscopically completely encapsulated thymomas, with no microscopically determined capsular invasion; stage II was defined as macroscopic invasion into the surrounding fatty tissue or mediastinal pleura or microscopic invasion into capsule; stage III was defined as macroscopic invasion into neighboring organs (ie, pericardium, great vessels, and

lung); stage IVa was defined as pleural or pericardial dissemination; and stage IVb was defined as lymphogenous or hematogenous metastasis. Patients with advanced stages of thymoma received adjuvant radiation therapy or both adjuvant radiation therapy and chemotherapy.

All the patients were regularly followed up at intervals of 3 months for the first 2 years postoperatively and then every 6 months thereafter. A detailed report of the MGFA classification and medications for each patient was obtained at every point of follow-up and then reviewed by a neurologist. The clinical outcomes regarding MG were classified according to the MGFA postintervention status¹¹: complete stable remission, pharmacologic remission, improved, unchanged, and worse. The remission rate was defined as the ratio of the number of patients in either complete or pharmacologic remission to the number of patients whose information concerning the neurologic status was available at each follow-up visit. A follow-up CT scan was performed to rule out the possibility of a recurrent thymic tumor in patients with sustained neurologic symptoms.

The study population was divided into 2 groups based on the presence of a thymoma. Descriptive statistics were used to describe the patients' characteristics and outcomes. The normally distributed continuous data were expressed as means $\pm$ SD. Categorical data were expressed as counts and proportions. The Student *t* test and the χ^2 or Fisher exact test were used to compare the continuous and categorical variables, respectively.

Results**Patient Profile**

The clinical characteristics and operative techniques of the study population are presented in Table 1. Twenty-four (40%) patients turned out to have a thymoma. The thymoma group consisted of 8 men and 16 women with a mean age of 46.5 ± 15.3 years. The nonthymoma group was comprised of 10 men and 26 women with a mean age of 36.4 ± 11.5 years. The mean duration of preoperative symptoms was 2.0 ± 5.0 months for the patients with thymoma compared with 22.0 ± 27.3 months for those without thymoma. No significant differences were observed between the thymoma group and the nonthymoma group regarding the severity of MG immediately before the operation. The preoperative antiacetylcholine receptor antibody titer was 7.5 ± 3.2 nmol/L and 6.6 ± 4.2 nmol/L in the thymoma and nonthymoma groups, respectively. In the nonthymoma group, 16 (44.4%) patients required immunosuppression therapy preoperatively, whereas 5 (20.8%) patients of the thymoma group received immunosuppression therapy before their operations.

Operative Results

There was no in-hospital mortality. No patients experienced significant complications related to the operation. Of the 24 patients who underwent thymectomy for both MG and thymoma, 4 (16.7%) were treated for myasthenic crisis postoperatively, whereas none of the patients without thymoma experienced myasthenic crisis. The postoperative

Table 1. Clinical characteristics of the study population

	All patients n = 60	Thymoma (+) n = 24	Thymoma (–) n = 36	P value
Age at diagnosis, y (mean ± SD)	39.3 ± 14.3	46.4 ± 15.2	34.6 ± 11.7	.003
Age at operation, y (mean ± SD)	40.5 ± 14.0	46.5 ± 15.3	36.4 ± 11.5	.009
Male sex/female sex	18/42	8/16	10/26	.645
Duration of symptoms, n (%)				.002
≤1 y	45 (75)	23 (96)	22 (61)	
>1 y	15 (25)	1 (4)	14 (39)	
MG classification, n (%)				.121
Ocular	16 (27)	9 (38)	7 (19)	
Generalized	44 (73)	15 (62)	29 (81)	
MGFA stage, n (%)				.824
I	16 (27)	9 (38)	7 (19)	
IIa	17 (28)	4 (17)	13 (36)	
IIb	22 (37)	8 (33)	14 (39)	
IIIa	1 (2)	1 (4)	—	
V	4 (7)	2 (8)	2 (6)	
MGFA stage (mean ± SD)	2.0 ± 0.9	1.9 ± 1.1	2.0 ± 0.8	.826
Myasthenic crisis, n (%)	6 (10)	3 (13)	3 (8)	.675
Preoperative remission, n (%)	2 (3)	0 (0)	2 (6)	.512
AChR Ab, nmol/L (mean ± SD)	6.9 ± 3.9	7.5 ± 3.2	6.6 ± 4.2	.412
Immunosuppressants, n (%)	21 (35)	5 (21)	16 (44)	.060

SD, Standard deviation; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; AChR Ab, acetylcholine receptor antibody.

antiacetylcholine receptor antibody titer was 7.6 ± 3.7 nmol/L and 6.5 ± 4.2 nmol/L in the thymoma and nonthymoma groups, respectively. A report of the pathologic findings was available for all the patients, which revealed hyperplasia of the thymus in 26 patients, thymoma in 24 patients, thymolipoma in 3 patients, fatty involution of the thymus in 2 patients, and normal thymus in 1 patient. Among the 24 patients who had both MG and thymoma, 13 (54.2%) had stage I disease, 7 (29.2%) had stage II disease, 3 (12.5%) had stage III disease, and 1 (4.2%) had stage IV disease. Except for the 1 patient with pleural dissemination, there was no incomplete resection of the thymoma. Thirteen (54.2%) patients received adjuvant therapy for either invasive thymoma or thymic carcinoma. There were no recurrences of thymic tumors, except for the 1 patient with stage IV thymic carcinoma. A repeat operation was not performed in any group. The histologic classification of the specimens and the pathologic staging of thymoma are listed in Table 2.

Neurologic Outcomes

Follow-up was completed for all the patients, with a mean duration of 58.1 months (range, 15.4-133 months). There was no significant difference in the follow-up duration between the 2 groups. During follow-up, 23 (95.8%) patients in the thymoma group achieved an asymptomatic state, as did 29 (80.6%) in the nonthymoma group, regardless of the length of the symptom-free period. In the thymoma group 16 (66.7%) patients were asymptomatic at the last follow-up, and of these, 11 needed no medication for

MG. In the nonthymoma group 24 (66.7%) patients were asymptomatic at the last follow-up, and of these, 21 required no medication for MG. Among the thymoma group, 18 (75%) patients experienced either complete or pharmacologic remission during the follow-up period. Of these, 12 patients maintained the remission until the last follow-up visit, whereas 6 had a relapse. On the other hand, among the nonthymoma group, 25 (69.4%) patients reached either complete or pharmacologic remission before the last follow-up visit. Of these, 20 patients remained in remission, whereas 5 relapsed thereafter. There was no significant difference in the remission rates between the 2 groups ($P = .064$). The time required to reach a remission was 10.6 ± 9.7 months and 23.5 ± 30.6

Table 2. Histologic classification and pathologic staging of thymoma

WHO classification, n (%)	
B1	5 (20.8)
B2	9 (37.5)
B2 + B3	2 (8.3)
B3	7 (29.2)
C	1 (4.2)
Masaoka stage, n (%)	
I	13 (54.2)
II	7 (29.2)
III	3 (12.5)
IV	1 (4.2)

WHO, World Health Organization.

Figure 1. Comparison of the remission rates between the thymoma and nonthymoma groups.

months in the thymoma and nonthymoma groups, respectively ($P = .059$). The mean duration of remission was 43.1 ± 27.3 months and 30.8 ± 21.1 months in the thymoma and nonthymoma groups, respectively ($P = .151$). The remission rate of

the thymoma group at 1, 2, 3, 4, and 5 years was 54.2%, 60.9%, 66.7%, 61.1%, and 61.5%, respectively (Figure 1). The remission rate of the nonthymoma group at 1, 2, 3, 4, and 5 years was 30.6%, 32.1%, 39.1%, 42.9%, and 41.2%, respectively (Figure 1). There were no significant differences in the remission rates between the 2 groups, except for the 2-year rate ($P = .040$). The data regarding the neurologic outcomes during the follow-up period are summarized in Table 3. Comparisons of the MGFA class and the percentages of asymptomatic or generalized patients with MG with all the patients are shown in Figures 2, 3, and 4.

Discussion

The relationship between MG and the thymus has been recognized for a number of years, because the thymus in patients with MG often shows pathologic abnormalities, such as thymic follicular hyperplasia and thymic tumors. Epithelial tumor of the thymus (ie, thymoma) occurs in approximately 10% of patients with MG, and in turn, MG occurs in approximately 15% of patients with thymomas.¹³ When patients with MG also have a thymoma, their clinical manifestations are significantly distinct from those seen in the patients without thymomas. In comparison with patients without thymomas, the onset of MG in patients with thy-

Table 3. Neurologic outcomes after thymectomy

	All patients n = 60	Thymoma (+) n = 24	Thymoma (-) n = 36	P value
FU duration, mo (mean $\pm$ SD)	58.1 $\pm$ 28.5	63.0 $\pm$ 23.4	54.8 $\pm$ 31.6	.280
ASx during FU, n (%)	52 (87)	23 (96)	29 (81)	.128
Myasthenic crisis, n (%)	4 (7)	4 (17)	—	.022
Last FU visit, n (%)				
Asymptomatic	40 (67)	16 (67)	24 (67)	1.000
Ocular MG	8 (13)	3 (13)	5 (14)	1.000
Generalized MG	12 (20)	5 (21)	7 (19)	1.000
Remission rate (%)				
Overall	72	75	69	.064
At 1 y	40	54	31	.067
At 2 y	45	61	32	.040
At 3 y	52	67	39	.068
At 4 y	51	61	43	.256
At 5 y	50	62	41	.269
TuR, mo (mean $\pm$ SD)	18.1 $\pm$ 24.8	10.6 $\pm$ 9.7	23.5 $\pm$ 30.6	.059
DoR, mo (mean $\pm$ SD)	36.0 $\pm$ 27.5	43.1 $\pm$ 27.3	30.8 $\pm$ 27.1	.151
Relapse, n (%)	11 (26)	6 (33)	5 (20)	.321
Final outcomes, n (%)				.903
CR	23 (38)	8 (33)	15 (42)	
PR	9 (15)	4 (17)	5 (14)	
Improved	16 (27)	9 (38)	7 (19)	
Unchanged	8 (13)	1 (4)	7 (19)	
Worse	4 (7)	2 (8)	2 (6)	
AChR Ab, nmol/L (mean $\pm$ SD)	6.9 $\pm$ 4.0	7.6 $\pm$ 3.7	6.5 $\pm$ 4.2	.371

FU, Follow-up; SD, standard deviation; ASx, asymptomatic; MG, myasthenia gravis; TuR, time until remission; DoR, duration of remission; CR, complete stable remission; PR, pharmacologic remission; AChR Ab, acetylcholine receptor antibody.

Figure 2. Comparison of the Myasthenia Gravis Foundation of America (MGFA) class between the thymoma and nonthymoma groups.

omas tends to be late, with a peak incidence in the sixth and seventh decades, and this combined disease mostly affects men.⁵ Likewise, in our practice patients with MG with thymoma were older than those without thymoma, and men were more frequently affected in the thymoma group than in the nonthymoma group.

Since Blalock and associates¹⁴ reported a remission of generalized MG after removal of a thymic tumor in 1939, numerous studies have demonstrated the favorable outcomes of thymectomy on the natural course of the disease, and thymectomy is currently considered to be effective for treating MG.¹⁵ Many studies have been conducted to deter-

Figure 3. Comparison of the percentages of patients with generalized myasthenia gravis (MG) between the thymoma and nonthymoma groups.

Figure 4. Comparison of the percentages of asymptomatic patients between the thymoma and nonthymoma groups.

mine the prognostic factors of thymectomy, and a variety of prognostic predictors have been identified, including age at operation,^{6,9,10,12,16-18} the severity of MG,^{10,16,19} and the preoperative duration of symptoms.^{3,6,7,10} Among these, the presence of thymoma indicates a poor prognosis after thymectomy for MG.³⁻¹⁰ Jaretzki and coworkers⁴ found a decreased remission rate and increased mortality among patients with thymomas and MG. Masaoka and associates,¹² in their large study of 375 patients, observed that 67.2% of the patients without thymomas achieved remission at 15 years compared with 31.8% of the patients with thymomas. They suggested that the absence of thymoma was one of the favorable prognostic factors.

In our study, however, we found that patients with thymomas appeared to have better neurologic outcomes after thymectomy than did those without thymomas. In the early phase of follow-up, and especially 2 years after the operation, considerably more patients reached a remission state in the thymoma group than in the nonthymoma group ($P = .040$). The longer the duration of follow-up, the less was the difference in the remission rates between the 2 groups, with the long-term results of the nonthymoma group showing improvement. Nevertheless, the thymoma group showed at least no less favorable outcomes than did the nonthymoma group, even in the late phase. The overall remission rate of the thymoma group was no lower than that of the nonthymoma group (75% vs 69%, $P = .064$). Additionally, not only did the patients with thymoma reach a remission earlier (10.6 vs 23.5 months, $P = .059$) but they also maintained it longer (43.1 vs 30.8 months, $P = .151$) than did those without thymomas. Despite this tendency, however, there was no statistically significant difference between the 2 groups. When the patients who achieved remission were

followed up, there were no significant differences in the relapse rates between the 2 groups. Our findings seem to be quite different from the previous series in the literature, which regarded the presence of a thymoma as a poor prognostic factor.

These results could be interpreted from several perspectives. First, when the patients have both MG and thymoma, the overall prognosis could be influenced by invasiveness of the tumors, as well as by the neurologic symptoms. Most of the patients in the thymoma group in our series had less advanced stages of tumor, which could have had less of an adverse effect on the prognosis of MG.

Second, it has been reported that patients with thymoma tend to have more advanced MG preoperatively, and some authors speculated that the poor outcomes for patients with thymomatous MG could be explained by this tendency. In our practice the severity of neurologic symptoms in the thymoma group was no more advanced than that in the nonthymoma group, and this might have led to better results in the thymoma group, which is in contrast to the past reports.

Third, it is likely that patients with thymomas undergo thymectomy earlier than those without thymomas. When myasthenic patients are also given a diagnosis of thymoma, prompt thymectomy is recommended for the treatment of a thymoma per se. Neurologists or physicians could easily decide to suggest an operation for patients with both MG and thymoma. On the contrary, when there is no evidence of a thymic tumor, then there could be a propensity to postpone a thymectomy or to continue medical treatment. In our study 23 of 24 patients with thymoma underwent thymectomy within a year after a diagnosis of MG, whereas 14 of 36 patients without thymoma had to have MG for more than a year before their operations. Given that the short duration of preoperative symptoms has been consistently considered a good prognostic factor in most series,^{3,6,7,10} the reason why the patients with thymoma showed relatively favorable outcomes in our series could be that they received thymectomy almost immediately after diagnosis. In the same context the patients without thymoma would have achieved much better outcomes if thymectomy had been recommended as early as was done for the patients with thymoma.

This study demonstrated different results than did those of the previous reports, and we tried to interpret the implications of our findings. Nonetheless, we could not reveal the mechanism of dissimilar responses to thymectomy between the thymoma and nonthymoma groups. It is generally known that thymomatous MG is distinct from nonthymomatous MG as to the pathogenesis of disease. However, it is still unclear how a thymoma plays a role for patients with MG, although it has been assumed that a thymoma could be the substantial source of continued antigenic stimulation. Had we performed antibody assay for various antigens other than the acetylcholine receptor, it would have been helpful

to elucidate the differences between the 2 groups. In addition, because our data were retrospectively gathered and then analyzed, this study has important limitations. Furthermore, the study population was rather too small to show the significant difference in neurologic outcomes between the thymoma and nonthymoma groups, and there were few cases for which the relationship between relapse of MG and recurrent thymoma could be investigated. If the patients had experienced recurrence of thymoma after a remission and then they had been followed by the relapse of MG, this would have been strong evidence that MG was provoked by a thymoma.

In conclusion, we evaluated the influence of thymomas on the results of thymectomy for patients with MG by comparing the neurologic outcomes between the thymoma and nonthymoma groups. Neurologic outcomes of the thymoma group were no worse than those of the nonthymoma group. It is expected that earlier thymectomy is likely to result in a better prognosis by shortening the disease period, even for patients with nonthymomatous MG. We believe that it is necessary to perform a prospective study under clinical circumstances that would include antibody assays for the various antigens specific to thymomas, and thymomatous MG should be considered a different disease category from nonthymomatous MG.

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