Original Article

Therapeutic Outcomes in Thymectomied Patients with Myasthenia Gravis

Iwao Takanami, MD, Tomohiro Abiko, MD, and Satoko Koizumi, MD

Purpose: Transsternal thymectomy is well established in the treatment of myasthenia gravis (MG). The objectives of this study were to evaluate the influence and prognostic factors of thymectomy as treatment for MG.

Patients and Methods: Surgical results of 54 patients with MG who underwent transsternal thymectomy were retrospectively reviewed. We investigated clinical outcomes of extended transsternal thymectomy in MG, and we analyzed the data to clarify the effect of prognostic factors on clinical outcome.

Results: A total of 54 patients, including 28 males and 26 females, were analyzed. At their last visit, 5 patients (9%) were in complete remission; 36 (67%) reported clinical improvement; and 18 (33%) had no change. There were no operative or late deaths. Clinical improvement was not detected by a patient's age, sex, presence or absence of thymoma, or acetylcholine receptor (AchR) antibodies titer. Patients in which the duration of illness before operation was equal to or less than 24 months (p = 0.018), and patients in the advanced Myasthenia Gravis Foundation of America (MGFA) stage (p = 0.014), showed a greater degree of clinical improvement.

Conclusion: Transsternal thymectomy for MG is safe and effective. Those patients with severe symptoms and a shorter duration of illness showed more benefits from thymectomy. (Ann Thorac Cardiovasc Surg 2009; 15: 373–377)

Key words: transsternal thymectomy, myasthenia gravis, outcome, prognostic factor

Introduction

Myasthenia gravis (MG) is an autoimmune disorder caused by an antibody-mediated attack directed against acetylcholine receptors (AchR) at neuromuscular junctions. It is clinically characterized by muscular weakness and easy fatigability.

In the treatment of MG, thymectomy has generally been accepted as the standard therapy combined with the use of corticosteroid, immunosuppressive, and/or anticholinesterase agents. Today, even with the advancements in medical therapy, thymectomy remains an integral part of the treatment of patients with MG. Controversy, however, still exists about the indication of surgery. Moreover, the most appropriate surgical approach is still under question. Factors that influence the response to thymectomy still remain controversial. To evaluate the effect of thymectomy and to analyze the factors influencing outcome, we performed a retrospective review of 54 MG patients treated with transsternal thymectomy.

From Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

Received February 6, 2008; accepted for publication November 26, 2008

Address reprint requests to Iwao Takanami, MD: Department of Surgery, Teikyo University School of Medicine, 2–11–1 Kaga, Itabashi-ku, Tokyo 173–8605, Japan.

Material and Methods

Patients

From January 1991 to December 2005, a total of 54 consecutive patients with a diagnosis of MG undergoing transsternal thymectomy at our institution were enrolled

Table 1. The preoperative clinical characteristics of 54 patients with MG

Number of patients	54
Age (years)	17–84 (50.6 ± 19.0)
Sex	
Male	28 (52%)
Female	26 (48%)
Time to thymectomy (months)	1–240 (19.3 ± 37.2)
Follow-up (years)	1–16 (6.0 ± 3.9)
MGFA clinical classification	I–V (2.5 ± 1.3)
Class I	12 (22%)
Class IIa/IIb	21 (39%)
Class IIIa/IIIb	8 (15%)
Class IVa/IVb	8 (15%)
Class V	5 (9%)
Histopathology	
Normal thymic tissue	30 (56%)
Hyperplasia	11 (20%)
Thymoma	13 (24%)

MGFA, Myasthenia Gravis Foundation of America.

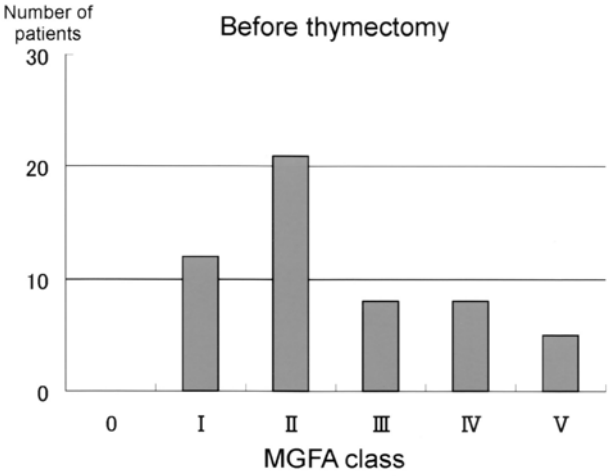

Fig. 1. Myasthenia Gravis Foundation of America (MGFA) stage before thymectomy.

in the study. The diagnosis of MG was made on the basis of the following findings: typical history, fluctuating weakness of voluntary muscles, a clear response to the edrophonium chloride test, and/or positive findings in electromyographic studies. An increase in serum levels of circulating AchR antibodies also supported the diagnosis of MG. All patients underwent computed tomography (CT) scanning of the chest to ascertain whether they had pathological abnormalities of the thymus. The preoperative severity of the disease was classified according to the Myasthenia Gravis Foundation of America (MGFA) clinical classification, whereas the postsurgical clinical status of the patient was assessed according to the MGFA postintervention status.[1] Most patients were taking anticholinestrase agents preoperatively. Plasmaphresis and steroids were used in cases of severe symptoms to reduce the operative risk. Before thymectomy, anticholinestrase agents (60–180 mg/day) were used in 34 patients (63%), corticosteroids (10–30 mg/day) were given in 4 (7%), and plasmaphresis (5–7 sessions) was done in 7 (13%). All patients had undergone extended transsternal thymectomy that includes complete en bloc extirpation of thymic and adjacent tissues, including fatty tissue through median sternotomy. Postoperatively, most patients were administered corticosteroids, other immunosuppressive agents, or anticholinestrase agents. After thymectomy, corticosteroids (50–80 mg/day) were used in 35 patients (65%), and immunosuppressive agents (3–5 mg/day) were given to 11 (20%). Anticholinestrase agents (60–180 mg/day) were used in 15 patients (28%). In our study, the factors that presumably influence the prognosis after extended thymectomy are as follows: age of patient, sex, symptom duration before operation, clinical status according to MGFA classification, presence or absence of thymoma, and AchR antibody titers. All patients had clinical follow-up by the same team of neurologists. Follow-up information was obtained by reviews of hospital records or telephone interviews.

Statistical analysis

Statistical analysis was performed using the StatView 4.02 software (Abascus Concepts, Berkeley, CA, USA). The normally distributed continuous data were expressed as mean ± standard deviation. Categorical variables were expressed as counts and proportions. By use of the Student's t-test and the chi-square test or Fisher exact test, the continuous and categorical variables were compared. The level of significance was $p < 0.05$ in all analyses.

Results

Patient profile

The characteristics of the patients are shown in Table 1. There were 28 men and 26 women with a mean-age onset of 50.6 years (range 17–84). The mean interval from the onset of MG symptoms to surgery was 19.3 months (1–240). The mean preoperative MGFA class was 2.5 ± 1.3. A distribution of preoperative MG classification (Fig. 1) was as follows: 12 patients in class I, 21 in class II, 8 in class III, 8 in class IV, and 5 in class V. Raised AchR antibody titers were found in 91% (49/54) of patients pre-

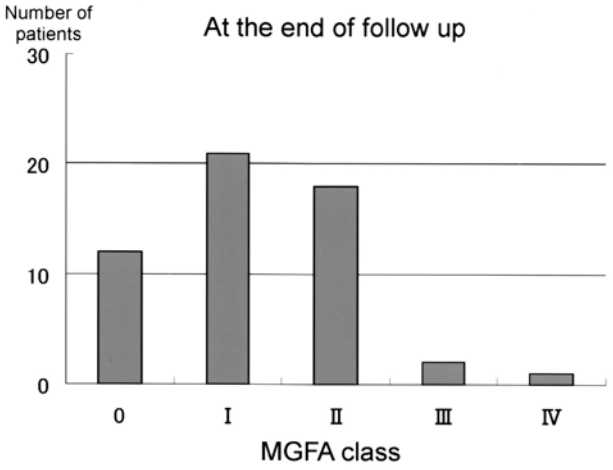

Fig. 2. Myasthenia Gravis Foundation of America (MGFA) stage at the end of follow-up.

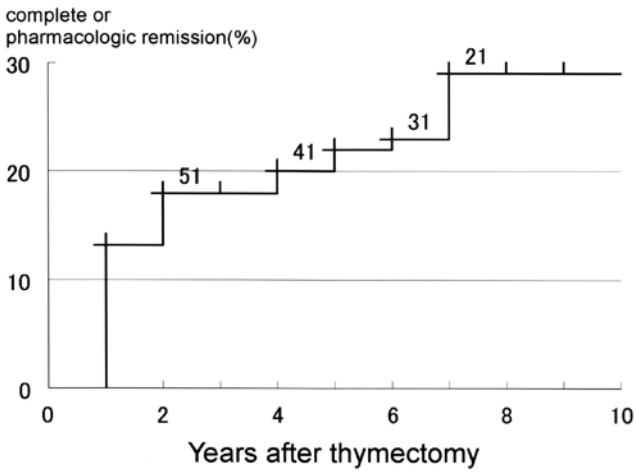

Fig. 3. Complete or pharmacological remission rate after thymectomy.

operatively. The mean preoperative Ach-R antibody titer was 48.4 ± 16.5 nmol/L.

Operative results

Postoperative pathological study of the thymus revealed normal thymic tissue in 30 cases (56%), hyperplasia in 11 (20%), and thymoma in 13 (24%). Morbidity developed in 14 (26%). Myasthenic crisis within 1 month after thymectomy was noted in 10 of the 54 patients (19%). Five had myasthenia crisis from preoperation, and 5 had myasthenia crisis after operation. The MGFA scores before thymectomy in these patients were as follows: 1 in MGFA IVa, 4 in MGFA IVb, and 5 in MGFA V. Pneumonia occurred in 1 patient (2%), postoperative atelectasis in 1 (2%), and wound infection in 1 (2%). No patients died in the postoperative period or during the follow-up period. No other major complications arose in patients with MG after thymectomy.

Neurological outcomes

At the end of follow-up, 5 patients (9%) were in complete stable remission, defined as absence of symptoms, and not receiving antimyasthenia treatment. Figure 2 shows the MGFA scores of thymectomized patients who had been followed up for more than 12 months. Twelve patients (22%) were in remission (no symptoms: MGFA score, 0), 21 (39%) had only ocular symptoms (MGFA score, I), 18 (33%) had mild generalized weakness (MGFA score, II), 2 (4%) had moderate generalized weakness (MGFA score, III), and only 1 (2%) had severe generalized weakness (MGFA score, IV). Thirty-six patients (67%) reported clinical improvement, and 33 (61%) were asymptomatic or in stage I on no or minimal treatment (in complete or pharmacological remission or in minimal manifestation class). Figure 3 showed complete or pharmacological remission rate after thymectomy. The best complete or pharmacological remission was over 7 years after thymectomy. The mean postoperative MGFA class was 1.4 ± 0.8. The mean postoperative Ach-R antibody titer was 13.4 ± 5.3 nmol/L. Eighteen patients (33%) reported no change in their symptoms. There was no worse or death case. The clinical outcomes were dichotomized as improvement/remission and clinical no-change for statistical comparisons. Table 2 shows the results of comparisons of the clinical improvement and clinical no-change. Patients whose duration of illness before operation was equal to or less than 24 months ($p = 0.018$) and patients in the advanced stage ($p = 0.014$) showed a greater degree of clinical improvement. Patient's age, sex, presence or absence of thymoma, and AchR antibody titers predicted no clinical improvement.

Discussion

The value of thymectomy in improving the symptoms of patients with MG is well established. Controversy, however, remains in regard to the extent of surgery and the indications for it. The surgical approach can be transsternal, transcervical, or video assisted, and they remain controversial. The rationale for transsternal thymectomy is based on the thymus arising from several sites, and there may be ectopic nests of thymic tissue scattered throughout

Table 2. Characteristics of patients with myasthenia gravis regarding clinical outcomes

Variables	(n = 54)	Improvement/remission (n = 36) (%)	Clinical no change (n = 18) (%)	p value
Age Y (mean ± SD)	50.6 ± 2.6	48.7 ± 19.7	54.6 ± 19.7	0.2885
Age (years)				
≦60	33	24 (73%)	9 (27%)	
>60	21	12 (57%)	9 (43%)	0.7890
Gender				
Male	28	21 (75%)	7 (25%)	
Female	26	15 (58%)	11 (42%)	0.2895
Duration of symptoms	14.3 ± 0.2	14.6 ± 40.1	28.8 ± 27.4	0.1875
Duration of symptoms				
≦ 24 months	42	33 (79%)	9 (21%)	
> 24 months	12	3 (25%)	9 (75%)	0.018
MGFA stage (mean ± SD)	1.4 ± 0.1	2.9 ± 1.3	1.7 ± 0.7	0.003
MGFA stage				
I/IIa/IIb	41	23 (56%)	18 (33%)	
IIIa/IIIb/IVa/IVb/V	13	13 (100%)	0 (0%)	0.014
Thymic history				
Thymoma	13	9 (69%)	4 (31%)	
Nonthymoma	41	27 (66%)	14 (34%)	0.8211
AchR ab, nmol/L (mean ± SD)	48.4 ± 16.5	34.5 ± 9.3	76.1 ± 46.0	0.2378

SD, standard deviation; MGFA, Myasthenia Gravis Foundation of America.

the anterior mediastinum and even in the retrothyroid space. Clinicians may recommend surgery for severe generalized disease refractory to medical treatment.[2] Opinions vary as to whether thymectomy should be performed in cases of ocular MG, which is not a life-threatening illness, and some natural remission would occur without surgery.[3] Hatton et al.[4] concluded that most patients with ocular disease did not benefit from thymectomy. But we have used thymectomy to treat not only generalized MG, but also ocular MG, because ocular MG often progresses to the generalized type and may be complicated by occult thymoma undetected before operation.

Patients with MG are currently treated with a variable combination of thymectomy and mediation because of the lack of standard treatment regimens. Our study showed that complete remission rate was 9%, and that complete or pharmacological remission rate was 22%. Complete remission rate following surgery ranges from 10 to 42%.[4–6] Complete or pharmacological remission rate was reported to be 34% in analyses of Japanese patients with MG.[7] Remission and improvement following thymectomy are occasionally delayed. Maggi et al.[8] found that the best remission rate in patients is seen during the 5-10–year postoperative period. Our data showed that the best complete or pharmacological remission rate was seen over 7 years after thymectomy. More follow-up period may have been needed in some cases in our study.

Our data demonstrated improvement in 67% of patients with MG after transsternal thymectomy. The factors influencing the outcome of patients undergoing thymectomy are still detectable. Most studies have been conducted to determine the prognostic factors of thymectomy, and a variety of prognostic predictors have been identified, including age at operation, preoperative duration of symptoms, severity of MG, and presence of thymoma.[9–11] We tried to find the prognostic factors that would influence the outcome of patients as other studies did. We learned that a shorter duration of illness enabled favorable prognostic factors for patients following transsternal thymectomy. Most clinicians have noted that a shorter duration of symptoms is associated with more favorable results after thymectomy.[12,13] A better outcome after thymectomy for MG has been reported in patients with severe symptoms.[2] On the other hand, some authors[14,15] reported that patients in the early stage had better outcomes. The advanced stage was a more-favorable prognostic factor for patients following thymectomy than the early stage in this study. But ocular MG following thymectomy did not progress to generalized MG in the study; thus thymectomy was thought to be beneficial for patients with ocular MG. A patient's age, sex, presence or absence of thymoma, or AchR antibodies titer did not influence the remission or

the improvement. Previous studies[16,17] have demonstrated that thymectomy in patients with thymoma is associated with a poorer outcome than in patients without it. But there is a recent report[18] stating that neurological outcomes of the thymoma group were no worse than those of the nonthymoma group.

The absence of any early or late death demonstrates that the transsternal thymectomy is safe. In our study, myasthenia crisis occurred within 1 month after surgery in 19% of the thymectomized patients. The myasthenia crisis occurred significantly more often in patients with bulbar palsy before thymectomy than in patients without it. Therefore our results suggest that the involvement of bulbar muscles is an important risk factor for respiratory crisis after surgery.

In conclusion, our review demonstrates that transsternal thymectomy for MG is safe and effective in relieving the symptoms of the disease. The patient's age, sex, and presence or absence of thymoma were not found to be significant predictors. Patients with severe symptoms and shorter durations of illnesses showed a greater degree of postoperative improvement.

References

1. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000; **55**: 16–23.
2. Kattach H, Anastasiadis K, Cleuziou J, Buckley C, Shine B, et al. Transsternal thymectomy for myasthenia gravis: surgical outcome. *Ann Thorac Surg* 2006; **81**: 305–8.
3. Evoli A, Batocchi AP, Minisci C, Schino CD, Tonali P. Therapeutic options in ocular myasthenia gravis. *Neuromuscul Disord* 2001; **11**: 208–16.
4. Hatton PD, Diehl JT, Daly BD, Rheinlander HF, Johnson H, et al. Transsternal radical thymectomy for myasthenia gravis: a 15-year review. *Ann Thorac Surg* 1989; **47**: 838–40.
5. Bril V, Kojic J, Ilse WK, Cooper JD. Long-term clinical outcome after transcervical thymectomy for myasthenia gravis. *Ann Thorac Surg* 1998; **65**: 1520–2.
6. Ashour MH, Jain SK, Katten KM, al-Daeef AQ, Abdal Jabbar MS, et al. Maximal thymectomy for myasthenia gravis. *Eur J Cardiothorac Surg* 1995; **9**: 461–4.
7. Kawaguchi N, Kuwabara S, Nemoto Y, Fukutake T, Satomura Y, et al. Treatment and outcome of myasthenia gravis: retrospective multi-center analysis of 470 Japanese patients, 1999–2000. *J Neurol Sciences* 2004; **224**: 43–7.
8. Maggi G, Casadio C, Cavallo A, Cianci R, Molinatti M, et al. Thymectomy in myasthenia gravis. Results of 662 cases operated upon in 15 years. *Eur J Cardiothorac Surg* 1989; **3**: 504–11.
9. Blossom GB, Ernstoff RM, Howells GA, Bendick PJ, Glover JL. Thymectomy for myasthenia gravis. *Arch Surg* 1993; **128**: 855–62.
10. Mantegazza R, Beghi E, Pareyson D, Antozzi C, Peluchetti D, et al. A multicentre follow-up study of 1152 patients with myasthenia gravis in Italy. *J Neurol* 1990; **237**: 339–44.
11. Frist WH, Thirumalai S, Doehring CB, Merrill WH, Stewart JR, et al. Thymectomy for the myasthenia gravis patient: factors influencing outcome. *Ann Thorac Surg* 1994: **57**: 334–8.
12. Masaoka A, Yamakawa Y, Niwa H, Fukai I, Kondo S, et al. Extended thymectomy for myasthenia gravis patients: a 20-year review. *Ann Thorac Surg* 1996; **62**: 853–9.
13. Venuta F, Rendina EA, De Giacome TD, Della Rocca G, Antonini G, et al. Thymectomy for myasthenia gravis treated by thymectomy: a 27-year experience. *Eur J Cardiothorac Surg* 1999; **15**: 621–5.
14. Sharager JB, Nathan D, Brinster CJ, Yousuf O, Spence A, et al. Outcome after 151 extended transcervical thymectomies for myasthenia gravis. *Ann Thorac Surg* 2006; **82**: 1863–9.
15. Ozdemir N, Kara M, Dikmen E, Nadir A, Akal M, et al. Predictors of clinical outcome following extended thymectomy in myasthenia gravis. *Eur J Cardiothorac Surg* 2003; **23**: 233–7.
16. Papatestas AE, Genkins G, Kornfeld P, Eisenkraft JB, Fagerstrom RP, et al. Effects of thymectomy in myasthenia gravis. *Ann Surg* 1987; **206**: 79–88.
17. Perlo VP, Poskanzer DC, Schwab RS, Viets HR, Osserman KE, et al. Myasthenia gravis: evaluation of treatment 1,355 patients. *Neurology* 1966; **16**: 431–9.
18. Kim HK, Park MS, Choi YS, Kim K, Shim YM, et al. Neurologic outcomes of thymectomy in myasthenia gravis: comparative analysis of the effect of thymoma. *J Thoracic Cardiovasc Surg* 2007; **134**: 601–7.