Surg Today (2003) 33:666–670
DOI 10.1007/s00595-003-2584-5

SURGERY TODAY

Results of Surgical Treatment for Nonthymomatous Myasthenia Gravis

TURKAN TANSEL, ERTAN ONURSAL, SEMIH BARLAS, EMIN TIRELI, and UFUK ALPAGUT

Department of Cardiovascular Surgery, Istanbul University School of Medicine, Çapa, Istanbul 34390, Turkey

Abstract

Purpose. To clarify the factors that influence improvement and remission after thymectomy for patients with nonthymomatous myasthenia gravis (MG).

Methods. We retrospectively reviewed 204 patients with nonthymomatous MG who underwent thymectomy and anterior mediastinal dissection through a partial median sternotomy, between 1980 and 2001, and examined whether age, sex, preoperative classification, and duration of symptoms influenced their prognosis.

Results. There was no perioperative or hospital mortality. The mean follow-up period was 7.2 ± 1.2 years, with early and late postoperative remission rates of 44.6% and 73%, respectively. Seven patients died; two from pneumonia and five from causes unrelated to MG. Preoperative treatment and classification, duration of symptoms, age, and sex did not seem to have a significant influence on remission, but the response to thymectomy was greater in patients with thymic hyperplasia. Remission and improvement rates were significantly better at the end of the first year, with the same status found at the last follow-up.

Conclusion. Thymectomy is an effective and highly curative method of treatment for patients. with MG. It provides excellent symptomatic improvement, which is enhanced over the long term.

Key Words Myasthenia gravis · Thymectomy · Surgery · Prognosis

Introduction

Myasthenia gravis (MG) is a relatively uncommon autoimmune disease, the pathogenesis of which almost certainly involves the thymus.[1] Although MG was clinically defined over 300 years ago by the physiologist Thomas Willis, the role of circulating autoantibodies against the acetylcholine receptors (AChR) at the neuromuscular junction was only reported in 1973.[2] MG is a neuromuscular disorder characterized by progressive weakness and fatigability of the skeletal muscles following repetitive muscle contractions, and the transitory improvement of symptoms by antiacetylcholinesterase drugs to enhance neuromuscular transmission.[1,3] The clinical, histopathological, and epidemiological findings of this disorder show heterogeneity.

In 1939, Blalock et al.[4] reported that excision of the cystic thymic tumor resulted in remission in a patient with generalized MG, since when thymectomy has become very important in the treatment of MG. However, the effects of age, sex, preoperative severity of disease, duration of symptoms, and surgical techniques on prognosis are still controversial. The purpose of this study was to clarify the factors which may influence improvement and remission rates after thymectomy for patients with nonthymomatous MG.

Patients and Methods

Between 1980 and 2001, thymectomy was performed on 204 patients with nonthymomatous MG. Of the 204 patients, 149 (73%) were girls or women ranging in age from 9 to 61 years, and 55 (27%) were men ranging in age from 19 to 70 years. The female : male ratio was 2 : 7. The percentages of female and male patients younger than 30 years of age were 69% and 45%, respectively. The diagnosis was made on clinical grounds by positive edrophonium and electromyography tests. Antiacetylcholine receptor antibody levels were obtained in 98 patients and were positive in 72. The indications for thymectomy included severe and incapacitating MG that compromised lifestyle, the progression of symp-

Reprint requests to: T. Tansel
Received: July 1, 2002 / Accepted: March 11, 2003

toms despite long-term conservative therapy, and suspicion of thymoma. The mean interval between the onset of symptoms and thymectomy was 2 years, with a range of 8 months to 6 years. The severity of the disease was classified according to the modified Osserman classification:[2] into group I, ocular myasthenia; group IIa, mild generalized myasthenia with ocular involvement; group IIb, moderate generalized myasthenia with ocular involvement and mild bulbar and respiratory involvement; group IIc_1, acute fulminating myasthenia with severe bulbar involvement; and group IIc_2, late onset generalized myasthenia with severe bulbar involvement and gradual development from classes 1 and 2. The number of patients in groups I, IIa, IIb, IIc_1, and IIc_2 were 13 (6.4%), 88 (43.1%), 72 (35.3%), 11 (5.4%), and 20 (9.8%), respectively. The medical treatment regimens given were anticholinesterase therapy in 51 patients (25%), corticosteroid therapy in 25 (12.2%), anticholinesterase and corticosteroid therapy in 107 (52.4%), corticosteroid and immunosuppressive therapy in 11 (5.4%), and no medication in 10 (4.9%). Plasmapheresis was performed in five patients with very severe and rapidly progressive symptoms and resumed in only one postoperatively. Furthermore, four patients who had been intubated prior to the surgery due to rapidly generalized MG remained intubated for 7–23 (median 9 days) days postoperatively. Partial median sternotomy was performed in 192 (94.1%) patients and the remaining 12 (5.9%) patients required conversion to complete median sternotomy. All anterior mediastinal adipose tissue and soft perityhmic tissues were excised in addition to the entire thymus. We were extremely careful to avoid injuring the phrenic nerves. The pleura was opened when necessary to improve exposure and allow easier dissection. Patients who had no bulbar or respiratory involvement were able to be extubated in the operating room, while the remaining patients who required ventilatory assist were extubated later in the intensive care unit. Of the 204 patients, 193 (94.6%) were extubated in the first 24 h and 11 (5.4%) required mechanical ventilator support for periods ranging from 1 week to 3 months. Prolonged intubation was required by 1 (0.5%) patient in group IIa, 2 (1%) in group IIb, 5 (2.5%) in group IIc_1, and 3 in group IIc_2. Four (2%) patients required reintubation, but were subsequently weaned off the ventilator.

Histopathological examination revealed thymic hyperplasia in 55%, normal thymus tissue in 41%, and cystic thymus tissue in 4% of the patients. A normal thymic gland was noted in four patients who required reintubation.

Postoperative outcome was classified as: "in remission" (asymptomatic, and requiring no medication), "improved" (a lower Osserman stage or the same stage but requiring less medication), "unchanged," or "symptomatically worse." Postoperative assessment was based on follow-up findings after 1 month, 6 months, and 1 year in all patients. The last follow-up information was obtained in 161 (78.9%) of the 204 patients after a mean follow-up period of 7.2 ± 1.2 years.

Survival function was estimated using the Kaplan-Meier method. The statistical significance of associations was evaluated by the χ^2 test, exact Fisher test, and Wilcoxon test. A P value of less than 0.05 was considered significant.

Results

There was no perioperative or postoperative mortality. Postoperative pneumonia, pneumothorax, and wound infection developed in 7 (3.4%), 2 (0.9%), and 4 (1.96%) of the patients, respectively. Survival was 100% from 1 to 5 years and 95.6% after 10 years. Seven patients died in the latter period; two from pneumonia and five from causes unrelated to MG.

Data obtained in the sixth postoperative month and the first postoperative year are summarized in Tables 1 and 2, respectively. Data on the relationship between preoperative classification and remission rates were evaluated and no significant correlation was found ($P = 0.43$), although patients with class I or IIc_2 disease tended to benefit more from thymectomy (84% and 90%, respectively). Preoperative treatment did not

Table 1. Influence of preoperative classification on the results of thymectomy (early remission rates)

Osserman stage	Remission *n* (%)	Improved *n* (%)	Unchanged *n* (%)	Worse *n* (%)	Total
I	9 (69.2)	4 (30.8)	—	—	13
IIa	45 (51.1)	28 (31.8)	10 (11.4)	5 (4.5)	88
IIb	20 (27.7)	19 (26.4)	28 (38.9)	5 (6.9)	72
IIc_1	5 (45.5)	2 (18.2)	2 (18.2)	2 (18.2)	11
IIc_2	12 (60)	8 (40)	—	—	20
Total	91 (44.6)	61 (29.9)	40 (19.6)	12 (5.9)	

Data are expressed as frequencies and percentages

Table 2. Influence of preoperative classification on the results of thymectomy (late remission rates)

Osserman stage	Remission *n* (%)	Improved *n* (%)	Unchanged *n* (%)	Worse *n* (%)	Total
I	11 (84.6)	2 (15.4)	—	—	13
IIa	55 (62.5)	24 (27.3)	5 (5.7)	4 (4.5)	88
IIb	57 (79.2)	6 (8.3)	5 (6.9)	4 (5.6)	72
IIc_1	7 (63.6)	2 (18.2)	—	2 (18.2)	11
IIc_2	18 (90)	2 (10)	—	—	20
Total	148 (72.5)	36 (17.6)	10 (4.9)	10 (4.9)	

Data are expressed as frequencies and percentages

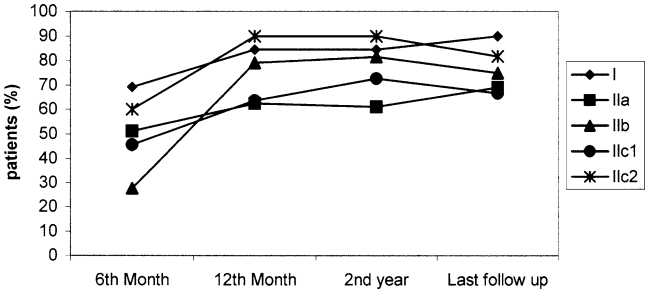

Fig. 1. Remission rates on time scale from thymectomy

have a significant influence on outcome ($P = 0.35$). Patients taking steroids did not have a significantly higher incidence of complications than those not taking steroids ($P = 0.69$). The age and duration of symptoms did not influence remission or improvement rates ($P = 0.42$ and $P = 0.67$, respectively). Evaluations of the relationship between gender and remission rates revealed a 74.5% remission rate in female patients and a 73.5% remission rate in male patients ($P = 0.97$).

Histological findings were significantly related to patient outcome. There was a favorable trend toward remission in patients with thymic hyperplasia, with remission achieved in 67% *vs* 62% of patients with normal thymic tissue ($P < 0.001$).

The early remission rate achieved after thymectomy had increased significantly by the end of the first year (Tables 1 and 2) ($P < 0.001$). The clinical condition of patients at last follow-up was unchanged, and a close correlation was found between their status at 1 year and that at last follow-up (Fig. 1).

Discussion

MG is an autoimmune, acquired disease of the neuromuscular junction that occurs at an incidence of 1/75000.[5] The diagnosis and treatment of MG has improved in the last 20 years with increasing knowledge of its pathogenesis, immunology, and molecular biology. Although thymectomy is the standard treatment of choice, improvements in surgical techniques, and advances in anesthesia, respiratory support techniques, and medical treatment regimens have all contributed to decreasing perioperative mortality and morbidity to almost nil. Since the preoperative clinical status greatly influences postoperative morbidity, the widespread use of plasmapheresis is considered to decrease the peroperative severity of disease.[6] This disease is more prevalent in women, in accordance with all series, including ours. Thymomas are found in 9%–16% of patients with MG.[7] In addition to thymoma, hyperthyroidism, hypothyroidism, and other autoimmune diseases may accompany MG. Autoimmune diseases can result in a poor prognosis by complicating the treatment with immune dysregulation.[8] Other factors determining a poor prognosis have been defined as: the duration of myasthenic symptoms preoperatively, sex, age, and preoperative classification.[9,10] Some authors concluded that patients who experience short periods of symptoms have better remission rates after thymectomy.[7,11,12] In contrast, Jaretzki et al.[13] and Frist et al.[8] reported that the duration of symptoms did not affect prognosis. Similar data were obtained in our series. Although Frist et al.[8] and Hatton et al.[9] detected higher remission rates in female patients, Jaretzki et al.[13] and Papatestas et al.[11] could not define such a relationship. Our results that gender is an independent factor on outcome, are consistent with the findings of these investigators.[11,13] Although a strong association between younger age and better outcome was noted,[8] Cosi and coworkers[14] reported that older age disease onset was associated with a greater tendency to achieve pharmacological remission. This result may be attributed to the better response to steroids in older patients.[14] We found no association between remission rates and age in the present series.

Another controversial association is the relationship between response to thymectomy and the AChR antibody level. According to most investigators,[13,15–17] there is no obvious relationship between the preoperative presence of the AChR antibody and better outcome

after thymectomy. It was also reported that the clinical characteristics of seronegative patients did not differ from those of patients with high antibody levels.[16] The AChR antibody was assessed in only 48% of our patients and the number of patients showing seronegativity was too small (26 patients) to be significant.

Although many investigations have been conducted to clarify the etiology of MG, the relationship between MG and the thymus is still not clearly defined. However, the fact that a thymic anomaly exists in 80% of all patients with MG holds the thymus responsible for its pathogenesis.[18] Thymic hyperplasia and thymoma are present in 85% and 15% of myasthenic patients, respectively, and thymectomy results in remission in these patients.[19] This remission may occur after months or even years postoperatively,[19] which is consistent with our findings.

Most clinicians do not consider thymectomy appropriate for patients with ocular myasthenia, since the benefit is uncertain.[9,20] However, it has been reported that gradual development into generalized MG occurs in about two thirds of patients with ocular myasthenia,[7,11,15] and that ocular MG is usually associated with positive clinical provocation tests.[21] Although few of our patients had ocular MG, the remission rate was high (69.2%). Based on these events, we suggest that thymectomy might be beneficial for this population.

A number of hypotheses to explain the mechanisms of remission after thymectomy have been proposed. First, thymectomy triggers an immune response by extracting the source of continued antigenic stimulation if those thymic myoid cells are the real source of autoantibodies.[22] Second, thymic lymphocytes secrete AChR antibodies, and thymectomy may remove a source of B lymphocytes.[23] Third, thymectomy may correct a disturbance in immune regulation in the myasthenic patient by an unknown mechanism.[1] The fact that specific autoantibodies directed against postsynaptic AChR are detected in 80%–90% of all MG patients gives rise to the speculation that the neuromuscular dysfunction is an autoimmune event related to autoantibodies.[1,2] Because thymectomy results in dramatic clinical improvement and 10% of patients do not have these autoantibodies, the role of AChR antibodies in the etiology of MG is questionable.[1,19] It is generally accepted that abnormal titers of AChR antibodies confirm MG and are not required for diagnosis.[13,24] Additional factors in the etiology of MG are the presence of AChR antibodies directed against receptors, damage to AChR in the postsynaptic membrane by activation of the complement system, a reduction AChR at the neuromuscular junction, and a decrease in AChR production.[2,3,25]

Improvements in diagnosis have also led to improvements in treatment strategies. The main purpose of surgical treatment in MG is to excise all thymic tissue. Since the first report by Blalock and coworkers[4] in 1939, thymectomy has been accepted as a therapeutic alternative for patients with MG, although there is still controversy about the selection of patients, the optimal surgical approach, and the extent of resection. The starting point of these discussions is the variable localization of thymic tissue in the neck and mediastinum.[25–27] Some authors recommend the transcervical approach because of its low morbidity and better cosmetic healing.[28] However, thymic tissue may remain after transcervical thymectomy, without complete resolution of symptoms. Residual thymic tissue can also potentially cause thymoma.[29] From their studies on the mediastinal distribution of thymic tissue, Masaoka et al.[25] concluded that the transsternal approach allows better visibility, and therefore better chance of total removal of the thymic tissue and anterior mediastinal soft tissues, considering that more than 70% of patients have histological evidence of extracapsular thymic tissue in the fat surrounding the thymus. Moreover, Jaretzki et al.[13,27,30] defined maximal thymectomy and recommended combined transcervical-transsternal en bloc resection of the thymus and all mediastinal tissues. Although maximal thymectomy and total thymectomy are still being discussed, their results seem to be similar.

Based on surgical-anatomical studies of the distribution of thymic tissue in the neck and mediastinum, our standard surgical approach involves a partial median sternotomy in most cases. This approach allows excellent visualization and complete resection of the thymus, including the cervical extensions, and perithymic tissue with all the anterior mediastinal lipoid tissues and soft tissues from phrenic nerve to phrenic nerve. Since the postoperative risks and morbidity may be considerably greater when the sternum is completely split, we prefer to operate through a partial sternotomy.

In conclusion, our findings showed that sex, age, duration of symptoms, and preoperative classification did not affect the remission rate after thymectomy, and patients with generalized MG improved in the late follow-up period. According to our experience, the beneficial effect of thymectomy is characterized by a higher remission rate in patients with thymic hyperplasia. Improvements in anesthesia, perioperative care, and surgical techniques, especially transsternal thymectomy with extended mediastinal dissection, provide excellent symptomatic improvement, which is enhanced over the long term.

References

1. Drachman DB. Medical progress: myasthenia gravis. N Engl J Med 1994;330:1797–810.

2. Fambroug DM, Drachman DB, Satyamurti S. Neuromuscular junction in myasthenia gravis: decreased acetylcholine receptors. Science 1973;182:293–5.
3. Engel AG. Myasthenia gravis and myasthenic syndrome. Ann Neurol 1984;16:519–34.
4. Blalock A, Mason M, Morgan H, Riven S. Myasthenia gravis and tumors of the thymic region. Ann Surg 1939;110:544–59.
5. Olanov CW, Wechsler AS. The surgical management of myasthenia gravis. In: Sabiston DC, Spencer FC, editors. Surgery of the chest. 5th ed. Philadelphia: Saunders; 1990. p. 974–94.
6. Machens A, Emskötter T, Busch C, Izbicki JR. Postoperative infection after transsternal thymectomy for myasthenia gravis: a retrospective analysis of 125 cases. Surg Today 1998;28:808–10.
7. Osterman PO. Current treatment of myasthenia gravis. Prog Brain Res 1990;84:151–61.
8. Frist WH, Thirumalai S, Doehring CB, Merrill WH, Stewart JR, Fenichel GM, et al. Thymectomy for myasthenia gravis patient: factor influencing outcome. Ann Thorac Surg 1994;57:334–8.
9. Hatton PD, Dihl JT, Daly BDT. Transsternal radical thymectomy for myasthenia gravis: a 15 year review. Ann Thorac Surg 1989;47:838–40.
10. Budde JM, Morris CD, Gal AA, Mansour KA, Miller JI. Predictors of outcome in thymectomy for myasthenia gravis. Ann Thorac Surg 2001;72:197–202.
11. Papatestas AE, Genking G, Kornfeld P. Effects of thymectomy in myasthenia gravis. Ann Thorac Surg 1987;206:79–88.
12. Mulder DG, Graves M, Herrmann C. Thymectomy for myasthenia gravis: recent observation and comparisons with past experience. Ann Thorac Surg 1989;48:551–5.
13. Jaretzki A III, Penn AS, Younger DS, Wolff M, Olarte MR, Lovelace RE, et al. "Maximal" thymectomy for myasthenia gravis; results. J Thorac Cardiovasc Surg 1988;95:747–57.
14. Cosi V, Romani A, Lombardi M, Raiola E, Bergamaschi R, Piccolo G, et al. Prognosis of myasthenia gravis: a retrospective study of 380 patients. J Neurol 1997;244:548–55.
15. Roth T, Ackerman R, Stein R, Inderbitzi R, Kösler K, Schmid RA. Thirteen years follow-up after radical transsternal thymectomy for myasthenia gravis. Do short term results predict long-term outcome. Eur J Cardiothorac Surg 2002;21:664–70.
16. Soliven BC, Lange DJ, Penn AS, Younger D, Jaretzki A III, Lovelace RE, et al. Seronegative myasthenia gravis. Neurology 1988;38:355–64.
17. Roses AD, Olanow CW, McAdams MW, Lane RJ. No direct correlation between serum antiacetylcholine receptor antibody levels and clinical state of individual patients with myasthenia gravis. Neurology 1981;31:220–4.
18. Marx A, Wilisch A, Schultz A, Gattenlöhner S, Nenninger R, Müller-Hermelink HK. Pathogenesis of myasthenia gravis. Virchows Arch 1997;430:355–64.
19. Lindenberg C, Anderson O, Larsson S, Oden A. Remission rate after thymectomy in myasthenia gravis when the bias of immunosuppresive therapy is eliminated. Acta Neurol Scand 1992;86:323–8.
20. Tellez-Zenteno JF, Remes-Troche JM, Garcia-Ramos G, Estanol B, Garduno-Espinoza J. Prognostic factors of thymectomy in patients with myasthenia gravis; a cohort of 132 patients. Eur Neurol 2001;46:171–7.
21. Roberts PF, Venuta F, Rendina E, De Giacomo T, Coloni GF, Follette DM, et al. Thymectomy in the treatment of ocular myasthenia gravis. J Thorac Cardiovasc Surg 2001;122:562–8.
22. Weatley LM, Urso D, Tamas K, Maltzman J, Loh E, Levinson A. Molecular evidence for the expression of nicotinic acetylcholine receptor a-chain in mouse thymus. J Immunol 1992;148:3105–9.
23. Scadding GK, Vincent A, Newson-Davis J, Henry K. Acetylcholine receptor antibody synthesis by thymic lymphocytes correlation with thymic histology. Neurology 1981;31:935–43.
24. Penn AS, Schotland DL, Lamme S. Antimuscle and anti-acetylcholine receptor antibodies in myasthenia gravis. Muscle Nerve 1986;9:407–15.
25. Masaoka A, Nagaoka Y, Kotake Y. Distribution of thymic tissue at the anterior mediastinum. J Thorac Cardiovasc Surg 1975;70:747–54.
26. Fukai I, Funato Y, Mizuno T, Hashimato T, Masaoka A. Distribution of thymic tissue in the mediastinal adipose tissue. J Thorac Cardiovasc Surg 1991;101:1099–102.
27. Jaretzki A III, Wolf M. "Maximal" thymectomy for myasthenia gravis; surgical anatomy and operative technique. J Thorac Cardiovasc Surg 1988;96:711–6.
28. Cooper JD, Al-Wilaihawi AN, Pearson FG, Humprey JG, Humprey HE. An improved technique for transcervical thymectomy in myasthenia gravis. Ann Thorac Surg 1988;45:243–7.
29. Austin EH, Olanow CW, Wechsler AS. Thymoma following transcervical thymectomy for myasthenia gravis. Ann Thorac Surg 1983;35:548–50.
30. Jaretzki A III, Bethea M, Wolff M, Olarte MR, Lovelace RE, Penn AS, et al. A rational approach to total thymectomy in the treatment of myasthenia gravis. Ann Thorac Surg 1977;24:120–30.