Clinical Features, Diagnostic Approach, and Therapeutic Outcome in Myasthenia Gravis Patients with Thymectomy

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Abstract-

Purpose: Thymectomy has been widely employed in the treatment of myasthenia gravis (MG). However, little data exist in Iran demonstrating the efficacy and morbidity of thymectomy. The aim of this study was to determine the clinical features, diagnostic approach, and therapeutic outcome in patients with MG who underwent thymectomy.

Methods: This historical cohort study was conducted in 3 university hospitals in Tehran. Preoperative and operative indices of 61 patients with MG who had been treated with thymectomy in these hospitals from September 2000 to July 2005 were reviewed. Among them, 20 patients were followed during one year after operation for determination of postoperative complications and one year mortality rate.

Results: The most common manifestations of MG were ptosis (77.0%) and upper limbs weakness (70.4%). CT scans of the thymus showed thymus enlargement, thymoma and thymus hyperplasia in 51.5% (22/43), 11.6% (5/43) and 2.32% (1/43) of patients, respectively. The postoperative complications were found in 13.1% of patients and one year mortality rate of thymectomy was 6.6%.

Conclusion: Regarding to high one year mortality rate of thymectomy in patients of MG in this study, the assessment of the factors related to the mortality and outcome of patients who underwent thymectomy in Iran are necessary.

Key Words: Myasthenia gravis, Thymectomy, Manifestation, Outcome, Treatment

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INTRODUCTION

Myasthenia gravis (MG) is a relatively rare autoimmune disorder of neuromuscular transmission in which antibodies form against acetylcholine (ACh) nicotinic postsynaptic receptors at the myoneural junction. A reduction in the number of ACh receptors (AChR) results in a characteristic pattern of progressively

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reduced muscle strength with repeated use of the muscle and recovery of muscle strength following a period of rest. The prevalence of MG has increased over the past two decades, primarily because of the increased life span of patients with the disease but also because of earlier diagnosis[1].

The association of MG with thymic abnormalities is well recognized. The most common abnormality is thymic hyperplasia, but thymoma may occur in up to 22% of cases of MG. Most series report that thymoma is present in 9-14%[2]. The pathogenesis of MG with thymoma differs from that of non-thymomatous MG, but the exact role of the thymoma in the pathogenesis of MG in those patients has not been determined. Antibodies to AChR are found in both thymomatous and nonthymomatous MG. While the AChR is found in myoid cells in tumour-free thymuses, it is not expressed in thymoma[3].

Thymectomy has been widely employed in the treatment of MG as a standard therapy, particularly for the generalized type. From the viewpoint of the histopathology of the thymus, this surgical procedure is necessary in thymoma-associated cases. In young-onset patients with MG without thymoma, this operation is usually selected because hyperplasia is predominantly seen in the histology of thymus and possibly plays an important role in the production of anti-AchR antibody[4]. Patients with MG, who undergo thymectomy, demonstrate a superior responses of clinical symptoms and medication requirement when compared with those patients treated non-surgically[5]. Thymectomy is associated with a clinical improvement in 85% of cases[6].

However, a few studies were performed to investigate the clinical manifestations, and the diagnostic and treatment protocols in our country. This study was therefore conducted to determine the clinical features, diagnostic approach, and therapeutic outcome in patients with MG who underwent thymectomy.

METHODS

To evaluate the clinical manifestations and the mid-term outcome of thymectomy, we reviewed 61 patients with MG (29 men and 32 women, mean age 33.1 ± 12.9 years) who had been treated with this surgical procedure in three university hospitals in Tehran from September 2000 to July 2005, detailed medical files were available. Patients with other diagnoses (polyneuropathy, myopathy, multiple sclerosis, neurasthenic syndrome) were excluded. The diagnosis of MG was made on the basis of the following findings: (1) muscle weakness and rapid fatigue in one or more muscle groups; (2) muscle weakness aggravated by exercise and relieved by rest; and (3) a significant response to anticholinesterase drugs [7]. Then, we followed 20 patients during one year after operation for determination of postoperative complications and one year mortality rate. We also determined the dose of drug (Mestinon) every three months during one year follow up.

Results were expressed as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. Categorical variables between the groups were compared using Pearson's χ^2-test; continuous variables were compared by independent samples t-test for variables with normal distributions, and Mann-Whitney test for variables with non-normal distributions. P values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS software version 13 and SAS version 9.1 for Windows.

RESULTS

Preoperative clinical manifestations of patients are shown in Table 1. The most common manifestations were ptosis (77.0%) and upper limbs weakness (70.4%).

Table 1. *Preoperative clinical manifestations of patients with MG who underwent thymectomy*

Clinical manifestation	Frequency (n = 61) n (%)
Ptosis	47 (77.0)
Upper limb weakness	43 (70.4)
Lower limb weakness	42 (68.8)
Diplopia	34 (55.7)
Oropharyngeal weakness	32 (52.5)

Electromyography (EMG) (repetitive stimulation test, RST) was performed in 31 patients. The results showed that 87.1% (27/31) of these patients was suggestive of MG and 12.9% (4/31) was normal. Tensilon test was done on 43 of 61 patients, and was positive in all cases. CT scan of the thymus was performed on 43 patients, and showed thymus enlargement, thymoma and thymus hyperplasia in 51.5% (22/43), 11.6% (5/43), and 2.32% (1/43) of the patients, respectively. Thymus was normal in the remaining patients (34.8%).

We also compared the pathologic results of thymus between two genders (Table 2) and between the patients who were ≤ 50 years old and those who were above 50 years old (Table 3). The difference in pathologic reports between the two genders was not statistically significant. However, 3.4% of men and 12.5% of women had normal, pathology of the thymas. However, there was a significant difference in other category of pathologic reports between patients ≤ 50 years old and older patients (Table 3). In 9.3% of patients ≤ 50 years old, pathology of the thymus was normal, whereas in elderly patients none had normal thymic pathology.

The most of the patients treated with piridostigmine or mestinon before operation. However, 4.9% of the patients did not use these drugs as premedication. The mean dose of mestinon before thymectomy was 200.0 ± 101.4 mg daily and the mean time of drug usage was 10 months. 24.6% of patients used prednisolone (100 mg daily for 1.8 months). 59% of patients underwent plasmaphresis 14.8% of patients had received IVIG before surgery.

A history of autoimmune diseases was found in 11 patients (18%), and 6 of them (9.8% of all MG cases) had a history of hyperthyroidism. Diabetes mellitus and rheumatoid arthritis as underlying diseases were found in 2 (3.2%) and 1 (1.6%) patients, respectively. One patient had a family history of MG.

The most important finding during operation was invasive thymoma, whereas in 8 (13.1%) patients, the mass in thymus was found in 4 cases (6.6%). Only two patients underwent concomitant radiotherapy and one patient underwent both radiotherapy and chemotherapy. MG crisis was found in 13 (21.3%) patients and the mean interval between thymectomy and crisis was 2.4 ±

Table 2. *Comparison of the pathologic results of thymus between two genders*

Pathology	Male (29)* number of patients (%)	Female (32)* number of patients (%)	P value
Thymus hyperplasia	14 (48.3 %)	18 (56.3 %)	0.5
Thymoma	11 (37.9 %)	8 (25.0 %)	0.2
Thymolipoma	3 (10.3 %)	2 (6.3 %)	0.5
Normal	1 (3.4 %)	4 (12.5 %)	0.1

*The number indicates total number of patients.

Table 3. *Comparison of the pathologic results of thymus between the patients ≤ 50 years old and older patients.*

Result	Age ≤ 50 years old (54)* number of patients (%)	Age > 50 years old (7)* number of patients (%)	P value
Thymus hyperplasia	30 (55.5 %)	2 (28.61 %)	0.1
Thymoma	16 (29.6 %)	3 (42.81 %)	0.4
Thymolipoma	3 (5.5 %)	2 (28.51 %)	0.03**
Normal	5 (9.25 %)	0	-

*The number indicates total number of patients. **$p<0.05$ is considered significant.

12.3 weeks.

The mean dose of mestinon from the first to forth trimesters was gradually decreased (136 mg in the first trimester vs. 114 mg in the forth trimester). 4 patients (14.8%) used prednisolone (mean dose of 4.7±13.8 mg) after surgery; 2 patients used the immunosuppressive drugs (imuran) (50 mg and 100 mg, respectively) after surgery.

8 (13.1%) patients had postoperative complications which included: respiratory failure and repetitive aspiration in 7 cases (11.4%) and bleeding in one patient (1.6%). One year mortality rate of thymectomy was 6.6% (4 cases), and the most common causes of mortality were cardiopulmonary arrest in 3 patients and MG crisis in one patient.

DISCUSSION

Thymectomy has become recognized as an integral element in the care of patients with MG. Trans-sternal thymectomy is feasible in the management of patients with MG at all stages with high improvement rate and low surgical morbidity[8], in both groups with and without thymoma[4].

In our study, the peak age incidence of MG was 33 years old and the male-to-female ratio was 0.9. In the study of Ojini et al., peak age incidence was in the third decade, and the male-to-female ratio was 0.6[9]. In the study of Liu et al., a significant difference was not seen in sex distribution between the two groups[10].

In our study, the most frequent manifestations were ptosis and upper limb weakness. Similarly, the commonest presentation in Ojini study was ptosis, followed by diplopia and limb weakness, while other features such as dysphonia, dysphagia, and dysarthria were relatively uncommon[9]. In previous studies, the onset of MG symptoms was different between the two genders. The onset of symptoms peaked in the third decade in females, whereas the male distribution was bimodal with peaks in the third and sixth decades[11].

CT scan showed thymoma in 11.6% of MG patients. Althoush thymoma was numerically was more frequent in men, it was statistically similar between two genders. We also found that the incidences of thymoma and hyperplasia were statistically similar between the patients ≤ 50 years old and older patients, whereas in other studies, the incidences of hyperplasia and thymoma were related to patients' age. In the studies of Wang et al. and de Perrot et al., the MG patients with thymoma were significantly older[12,13]. In the study of Liu et al., all of the patients in the pediatric group had thymus hyperplasia, but in the elderly group more than half (56.26%) had thymoma[10]. In our study, the incidence of thymoma in men was lower and in women was higher than those in the study of Monden et al.[14]. Also, in our study, the incidence of thymoma in patients older than 50 years old was dramatically lower than that in the latter study[14].

In our study, acetylcholinesterase blocker was used in most of the patients. However, steroids and IVIG were used in 24.6% and 14.8%, respectively. Acetylcholinesterase blockers are still used as the first-line treatment of MG. Although most of patients benefit from these drugs, the improvement is usually incomplete and often wanes after weeks or months of treatment. When clinical symptoms are not adequately controlled by anticholinesterase drugs, immunosuppressive therapy is suggested, but indications for treatment should take into account of age and clinical symptoms (ocular versus generalised myasthenia). Steroids are the most commonly used and most consistently effective immunosuppressive agents for MG but they also have the highest incidence of potential side effects. IVIG is recommended as an adjunct in the management of MG exacerbations. Recent studies have suggested that there are no pronounced differences in the efficacy between IVIG treatment and plasma exchange[15].

In our study, the postoperative complications were found in 13.1% of patients and the one year mortality rate of thymectomy was 6.6%. The one year mortality of this operation in our study was higher than the previous studies which ranged between 0-1%[5,8,16,17]. Therefore, the assessment of the factors related to the early and late mortality and the outcome of thymectomy such as age[5,18], and the presence of thymoma[19-20] in patients of MG are necessary.

CONCLUSION

Our survey is similar to other studies. The most common manifestations in patients of MG were ptosis and upper limbs weakness. Pathologic results of thymus between the two genders and between the patients older than 50 years old and younger patients were similar. The most common drug used was acetylcholinesterase blocker. Regarding to a high one-year-mortality rate of thymectomy in this study, the assessment of the factors related to the mortality and outcome of patients who underwent thymectomy in this country are necessary.

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