Thymectomy in Myasthenia Gravis: Response and Complications

Kondov Goran, MD1; Trajkovska Trajanka, MD2; Ljapcev Risto, MD3; Gogova Lodi, MD1; Kondova Irena, MD4

1Clinic of Thoracic Surgery, Clinical Centre, Medical Faculty, Skopje, Republic of Macedonia
2Clinic of Anaesthesiology, Clinical Centre, Medical Faculty, Skopje, Republic of Macedonia
3Clinic of Neurology, Clinical Centre, Medical Faculty, Skopje, Republic of Macedonia
4Clinic of Infectious Diseases, Clinical Centre, Medical Faculty, Skopje, Republic of Macedonia

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Abstract

Background: Thymectomy is considered as the most effective treatment for achieving sustained improvement in patients with myasthenia gravis (MG).

Goal: To evaluate outcome of surgical management for MG and the prognostic factors that influence outcome.

Methods: Sixty-eight myasthenia patients treated by thymectomy in a 10-year period (1993-2003) were analyzed retrospectively. Correlations, multiple regression analyses and discriminate analyses were calculated using the Statistica 5 program.

Results: Forty-two of 68 patients were women. Mean age was 24.1±16.3 years. Time elapsed from diagnosis to surgery was 9.1±12.1 months. Complete thymectomy was performed in all patients through median sternotomy. A good response to thymectomy was seen in 82.4% of patients; 22.2% achieved remission, 42.6% showed improvement and stabilization of the disease occurred in 17.6%. Important factors influencing the outcome of thymectomy were age, preoperative Osserman stage, histology of the thymus, use of corticosteroids and period of time between onset of the clinical manifestation and the operation. The most important variables associated with remission were <40 years of age, preoperative Osserman stage I or II A, duration of preoperative symptoms, presence of hyperplastic thymus and use of mestinon. Factors related with poor response were >40 years of age, the preoperative Osserman stage II B, III or IV, use of high doses of mestinon, use of corticosteroids, and the presence of atrophy or of thymoma in histopathological analysis. There were no postoperative deaths or severe complications.

Conclusions: Patients with MG undergoing thymectomy showed improvement and a mean remission rate of 82.4%. Age, length of symptoms, pathology of the thymus, and medications appear to be predictors of response to thymectomy in MG patients.

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Introduction

Myasthenia gravis (MG) is a neuromuscular disease of autoimmune origin characterised by sporadic muscular fatigability and weakness of voluntary muscles (1-5).

Thymectomy is considered as the most effective treatment for achieving sustained improvement as well as remission in patients with MG (1-5).

The purpose of this paper is to assess the results of surgical treatment in myasthenia gravis in the patients of the Clinic of Thoracic Surgery and to determine the factors predicting the response.
Materials and Methods

The records of 68 patients who were treated for myasthenia gravis by thymectomy in a 10-year period (1993-2003) were analyzed. Diagnosis was made at the Clinic of Neurology by clinical examination and clinical tests (tension test). CT of the mediastinum with IV contrast, with sections 5 mm apart, were made prior to surgery in all patients. According to clinical manifestations, appearance of signs and evolution of the disease, the patients were divided in four stages according to the Osserman classification (6).

Before the surgery, all patients were treated with mestinon (cholinesterase inhibitor) and corticosteroids. Plasmapheresis was used in a small number of patients who had severe symptoms. All patients were in good condition with minimal motor failure at the time of the surgery.

The extended thymectomy was done by median sternotomy in all patients. This operation entails the removal of the whole thymus tissue, all the tissue that surrounds the thymus gland, especially the fat tissue and the fat tissue that extends to the phrenico-mediastinal space. In most the parietal pleura was opened. In cases of thymoma, the tissue surrounding the pleura and the pericardium was removed.

Postoperatively, most patients regain consciousness early, while still on the operating table or in the recovery room. Patients who show severe muscular fatigue symptoms before surgery and especially older patients receive mechanical ventilation for 24 hours.

All patients continued further medical treatment at the Clinic of Neurology.

The results of the surgery were assessed three months later. The patient’s state was scored as “excellent” if complete remission of neurological symptoms had been accomplished and there was no need for any further medication, “very good” if small doses of medications were needed, “good” if the doses of the medications were the same as before surgery, and “poor” or “failure” if larger doses of medications, induction with stronger immunosuppressant (cell sept), or plasmapheresis were needed.

The outcome of the operation was assessed as excellent in 15 (22%), very good in 29 (42.6%), good in 12 (17.6%) and poor in 12 (17.6%) patients. Thus, positive responses (excellent, very good and good) to thymectomy were seen in 82.4% of the patients.

Results

Female patients constituted a larger proportion (61.7%) of the 68 thymectomies. The female/male ratio was 1.6:1.0 (42 F/26 M).

The patients were divided in two groups by age as “young” (<40 years) and “old” (>40 years). There were 55 patients (80.1%) in the “young” group. The mean age of Group I was 18.2 years. Seventy-one percent of these patients were females. There were 13 patients in the “old” group (Group II), with a mean age of 49.1 years. Male patients were dominant in this group (76.9%). Mean age of the total group was 24.1±16.3 years.

Time from diagnosis to surgery was 9.1±12.1 months. Histologically, the thymuses were hyperplastic in 35 (51.5%) of the patients. Thymus persistence was noted in 18 (26.5%), regressive thymus glands in 11 (16.2%) and thymomas in 4 (5.9%) of the patients (Table 1). Knowing the pathogenesis of the myasthenia gravis, it seemed very important to remove all parts of the thymus gland. There was no postoperative mortality among our patients.

Complications or adverse effects found postoperatively were:
1. Prolonged chest pain in 10 patients (14.7%).
2. Wound complications (aseptic infections which required no treatment) in 4 patients (5.8%).
3. Need for prolonged mechanical ventilation in 2 patients (2.9%).

The outcome of the operation was assessed as excellent in 15 (22%), very good in 29 (42.6%), good in 12 (17.6%) and poor in 12 (17.6%) patients. Thus, positive responses (excellent, very good and good) to thymectomy were seen in 82.4% of the patients.

Results of the surgery, using correlation analysis, were found to be correlated with age ($\rho=0.66$), Osserman stage ($\rho=0.46$), histology of the thymus gland ($\rho=0.57$), doses of mestinon ($\rho=-0.45$), doses of corticosteroids ($\rho=-0.61$) and time from the beginning of symptoms to surgery ($\rho=0.62$).

Multifactorial analysis of the data revealed the following figures: $R=0.914855$, $F=52.19$, $R^2=0.8369$, df=6.61, adjusted $R^2=0.8209$ with $p<0.0017$. In this calculation values for beta ($\beta$) for these factors were: age 0.388, Osserman stage 0.259, histology of the thymus gland 0.158, doses of mestinon -0.07, doses of corticosteroids -0.28 and time from the beginning of symptoms to surgery 0.28. From these analyses, the factors that significantly affect the results of surgery were: age, Osserman stage, histology of thymus gland, doses of corticosteroids and the time from the beginning of symptoms to surgery.

Using discriminate analysis and independent above-mentioned factors we calculated wilks lambda as 0.159, $F$ as 10.43 with $p<0.0001$. Separate values for wilks lambda for independent factors were: Osserman stage 0.24, histology of thymus gland 0.26, doses of mestinon 0.37, doses of corticosteroids 0.19 and time from onset of symptoms to surgery 0.258.

### Table 1. Distribution of the patients by histological findings of the thymus

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Hyperplasia</td>
<td>35</td>
<td>51.5</td>
</tr>
<tr>
<td>Thymus persistence</td>
<td>18</td>
<td>26.5</td>
</tr>
<tr>
<td>Atrophy of the thymus</td>
<td>11</td>
<td>16.2</td>
</tr>
<tr>
<td>Thymoma</td>
<td>4</td>
<td>5.9</td>
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</table>
Discussion

Myasthenia gravis is a neuromuscular disease, with an autoimmune pathogenesis, which manifests itself with weakness of voluntary muscles. Dysfunction of postsynaptic acetylcholine neuromuscular junction is the causative mechanism leading to the clinical symptoms (1-5).

Removal of the thymus gland is thought to lead to improvement in patients with myasthenia gravis, through one of the mechanisms below:

- By removing the thymus gland, the muscular cells that are in the thymus are removed. It is supposed that these cells are embryonic muscle cells and that antibodies against them are produced in the thymus. These antibodies attack and destroy the acetylcholine receptors of the muscle cells.
- Killer T cells, which can destroy neuromuscular junction, are produced in the thymus. These are removed by removing the thymus gland.
- By removing the thymus gland, the place where helper T cells are produced is also removed. These cells are responsible for production of antibodies against acetylcholine receptors.
- By removing the thymus gland, the place where the thymus factor is produced is also removed. This factor may also play a role in activating the complement pathway leading to membrane lysis (1,7).

In our patients, the diagnosis was made by clinical examination and CT of the mediastinum to determine the changes in the size of the thymus. CT can be helpful in detecting thymomas, but is not helpful in the detection of other pathological findings of the thymus (8,9).

Most investigators prefer thymectomy as the standard method in treatment of myasthenia gravis, especially in the generalized form. Thymectomy leads to improvement in the symptoms and lowering of the dose of the medication. However, there are no prospective randomised studies (10-19).

Only Wernneck states that there was no difference, especially with respect to survival, between groups treated with and without thymectomy (20).

Numerous authors prefer the transcervical approach to the thymus gland, because it is a less mutilating operation and leads to a better postoperative recovery (21-23). Other authors prefer a more radical removal of the thymus gland, and they use a combined transternal and transcervical approach (24-26). Trasterek recommends the transternal approach to the thymus gland with partial resection of the sternum, making a compromise between functional and aesthetic results (27). Sugerbaker suggests thymectomy by thoracotomy (28).

In our study, all patients were operated by complete resection of the sternum. We believe that the transternal approach to the thymus gland, with complete resection of the sternum may be a more mutilating method but gives better visualisation and also enables the surgeon to remove the whole thymus tissue as well as all the tissue which surrounds the thymus gland (accessory thymus tissue) and extends to the phrenico-mediastinal space. Control of the haemostasis is also easier with this operation, which is performed under direct visualisation. With this method, we did not encounter any intraoperative complications.

Myasthenia gravis, according to its clinical expression, occurs in two forms, ocular and generalized (1,6,7). In this study we surgically treated 30 myasthenia gravis patients with mild symptoms (Osserman I and II A) and 38 with severe forms (generalized myasthenia, Osserman II B, III and IV).

Adequate preoperative preparation of the patients reduces significantly the complications after surgery. We prepared the patients for surgery by treating them with mestinon (cholinesterase inhibitors) and corticosteroids in the preoperative period. In patients with the severe form of myasthenia gravis, we used plasmapheresis. Thus the patients presented to surgery in good condition with minimal motor failure.

Mechanical ventilation, after surgery, was used only in 2 patients with severe myasthenia gravis, but for periods no longer than 24 hours.

Comparison of the results of this study with our previous experience 10 years ago shows that now we have fewer complications. This is probably a result of better technique and better coordination of the team (3,4).

In this study, improvement in the symptoms of myasthenia gravis after thymectomy was found in 56 (82.4%) patients. This figure is similar to those reported in other studies around the world. De Assis (22) reported improvement in 70%, Osaki (29) in 73.9%, Bertram (13) in 76.9%, De Filippi (5) in 81%, Beghi (30) in 84%, Frist (14) in 87%, Venuto (31) in 89%, Evoli (16) in 89.1% and Nussbaum (17) in 94% of their patients (11-13,15,17-19,32).

Preoperative estimation of ventilatory function and ventilatory reserve and appropriate preparation reduces the percentage of deaths. It is known that death is common in patients with bad ventilatory reserve and in patients with myasthenia crisis in the postoperative period. These conditions require the use of mechanical ventilation.

The multifactorial analysis in our study has shown that the outcome of the operation is influenced by the length of time between the onset of the clinical manifestations of the disease and the operation, by the preoperative Osserman stage of the disease, by the age of the patient, and by use of mestinon and of corticosteroids. This finding is also similar to previous reports (30,33-37).

Use of discriminate analysis and interpretation of wilks lambda values has shown that all factors listed above are effective, separately and in combination.

In our study, factors related with good response were <40 years of age, preoperative Osserman stage (I, II A), use of low doses of mestinon, no treatment with corticosteroids, and presence of hyperplasia in histopathological analyses.
Factors related with poor response were >40 years of age, preoperative Osseman stage (II B, III), use of high doses of mestinon, use of corticosteroids, and presence of atrophy or of thymoma in histopathological analysis.

Conclusion

Improvement and remission rates in our MG patients who underwent thymectomy were similar to those reported in other studies. Age, length of symptoms, pathology of the thymus and muscles appear to be predictors of response to thymectomy in these patients.

• Early thymectomy appears to increase the chance for complete improvement.
• Good preoperative preparation reduces postoperative morbidity and mortality.
• Transternal approaches to the thymus gland enhance the safety of the surgical intervention.
• Complete removal of the thymus gland and of the surrounding soft tissue is very important for a good outcome.
• A trained team including an anaesthesiologist and a retractor is an important factor influencing prognosis, especially in severe cases in myasthenic crisis or in respiratory insufficiency in the postoperative period, requiring mechanical ventilation.

An essential condition for the successful treatment of MG patients and for reduction of postoperative morbidity is the presence of a coordinated team consisting of the neurologist, surgeon and anaesthesiologist.

References