Thymectomy for myasthenia gravis: a 27-year experience

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Received 21 September 1998; received in revised form 13 January 1999; accepted 27 January 1999

Abstract

Objective: Thymectomy is considered an effective therapeutic option for patients with myasthenia gravis (MG). We reviewed our 27-year experience with surgical treatment of MG with respect to long-term results and factors affecting outcome.

Methods: Between 1970 and 1997, we performed 232 thymectomies for MG. Fifteen patients were lost to follow-up; the remaining 217 form the object of our study.

Sixty-two patients (28.4%) had thymoma. Myasthenia was graded according to a modified Osserman classification: 51 patients (23.5%) were in class I, 81 (37.3%) in class IIA, 52 (24%) in class IIB, 26 (12%) in class III and seven (3.2%) in class IV. Mean duration of symptoms before the operation was 12 ± 10 months. Fifty-eight thymectomies for thymoma were performed through a median sternotomy and four through a clamshell incision. Forty-six thymectomies for non-thymomatous MG were performed through a standard cervicotomy, 101 procedures through a partial upper sternal-splitting incision and eight through a complete median sternotomy.

Results: Operative mortality was 0.92% (two patients). After a mean follow-up of 119 months, 71% of all patients improved their clinical status (25% without medications and asymptomatic; 46% with a reduction of medications and/or clinically improved); 39 (18%) have a stable disease with no clinical modifications; 12 (5%) presented a deterioration of their clinical status with worse symptoms, required more medications, or both. Thirteen patients (6%) died because of MG (mean survival 34.3 ± 3.6 months). The presence of a thymoma negatively influenced the prognosis. Younger patients showed a more favorable outcome as well as patients with a shorter duration of symptoms before the operation; patients with lower classes of myasthenia showed a higher rate of remission.

Conclusions: Thymectomy is effective in the management of patients with MG at all stages with low morbidity. Patients with thymoma present a less favorable outcome.

Keywords: Myasthenia; Surgery

1. Introduction

Myasthenia gravis (MG) is characterized by an impaired neuromuscular transmission with symptoms of weakness and fatigue; it is generally related to an accelerated degradation or complement-related damage to acetylcholine receptors mediated by auto-antibodies. Extensive clinical experience with a variety of medical treatments is actually available [1]: anticholinesterase drugs can enhance neuromuscular transmission and decrease the immune response; steroids, plasmapheresis and immunoglobulin administration contributes to improve the clinical performance. Plasmapheresis is also used in the acute setting and to prepare patients for the operation [2]. Thymectomy has been employed extensively to remove the major source of antibodies production; in recent years it has gained increasing acceptance as the most effective form of treatment with the goals of achieving prolonged improvement. In fact, patients with MG who undergo thymectomy, demonstrate a superior response of clinical symptoms and medication requirements when compared with those patients treated non-surgically [3]. However, controversy persists regarding the proper selection of patients, the optimal sur-
2. Patients and methods

Between 1970 and 1997, we performed 232 thymectomies for MG. Fifteen patients were lost to follow-up; the remaining 217 (136 females and 81 males; mean age 37 ± 15.3 years) form the object of our study. MG was staged according to a modified Osserman classification (Table 1). Mean duration of symptoms before the operation was 12 ± 10 months (from 0.5 to 42). 62 patients (28.4%) had thymoma. Thymoma was classified histologically according to Marino, Muller-Hermelink and Pescarmona [4,5]: 38 (62.3%) were cortical, 19 (30.6%) were mixed and five (8%) were medullary. Clinical staging was accomplished according to the modified Masaoka classification [6]: 19 (30.6%) were stage I, 19 (30.6%) were stage II, 18 (29%) were stage III and six (9.7%) were stage IV. Fifty-eight thymectomies for thymoma were performed through a complete median sternotomy and four through a clamshell incision to resect radically an invasive primary tumor and/or the pleural metastases. Forty-six thymectomies for non-thymomatous myasthenia were performed through a complete median sternotomy and four through a clamshell incision to resect radically an invasive primary tumor and/or the pleural metastases. Forty-six thymectomies for non-thymomatous myasthenia were performed through a transcervical approach, 101 through a partial upper sternal -splitting incision and eight through a complete median sternotomy. Current follow-up information was obtained in 217 (93.5%) patients by physician examination, questionnaire or phone conversation; no information was obtained in 217 (93.5%) patients by physician examination.

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients (n)</th>
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<tbody>
<tr>
<td>Stage I: ocular</td>
<td>51 (23.5%)</td>
</tr>
<tr>
<td>Stage II: mild generalized</td>
<td>81 (37.3%)</td>
</tr>
<tr>
<td>Stage II: moderate generalized</td>
<td>52 (24%)</td>
</tr>
<tr>
<td>Stage III: acute fulminating</td>
<td>26 (12%)</td>
</tr>
<tr>
<td>Stage IV: late severe</td>
<td>7 (3.2%)</td>
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Differences in terms of remission and palliation between the different groups were analyzed by χ² test; the differences were considered statistically significant with P-values lower than 0.05. Survival rates were calculated according to the Kaplan–Meier method; zero time was the time of surgery; death related to causes other than myasthenia was treated as a censoring case to construct disease-related survival curves.

3. Results

The age distribution of patients with and without thymoma showed some differences: the non-thymomatous group peaked between 20 and 40 years with a mean age of 34.9 ± 15.4 years; thymoma showed a higher incidence between 30 and 60 years (mean 42.4 ± 13) (P = 0.002). The distribution of the different classes of MG is reported in Table 1. The pattern of distribution of MG in the group of patients with and without thymoma was quite similar. In the thymomatous group, there was no significant correlation between the type of MG and the clinical stage of thymoma with an homogeneous distribution of the disease: 13 patients (21%) had class I MG, 16 (26%) class IIA, 20 (32%) class IIB and 13 (21%) class III. Histologically, cortical thymomas were more frequent (62.3%). Preoperative duration of symptoms in the non-thymomatous group ranged between 11 and 74 months (mean 12 ± 10) while in patients with thymoma it was 11.5 ± 9 (range between 13 and 72) (P = 0.7). The titer of the acetylcholine receptor antibody was measured only in 112 patients; the mean values of titer in the thymomatous and non-thymomatous group did not differ (mean: 62.3 vs. 56.4 pmol/ml, respectively). All patients received anticholinesterase drugs before operation; 89 patients (41%) received steroids (30 in the thymomatous group; 48.3 and 59–48.3% in the non-thymomatous group), 22 underwent plasmapheresis and five received immunoglobulins to equilibrate symptoms of MG and reduce the dose of steroids. After the operation, the medical treatment was continued as preoperatively and subsequently modified after discharge by the neurologist. Only one patient required plasmapheresis in the immediate postoperative period.

Two hundred and twelve patients (97.7%) were extubated in the operatory room, immediately after the operation. There were two operative deaths (0.9%) due to respiratory failure in patients with postoperative bleeding requiring reoperation. Minor complications were arrhythmia (1.8%) and infection (1.8%). Mean hospital stay after the operation was 6.4 days (7.9 days before 1980, 4.8 between 1980 and 1990 and 3.7 after 1990). Thirteen patients (6%) died because of MG (mean survival: 34.3 ± 3.6 months) (Fig. 1): six in the group with thymoma (9.7%) and seven in the non-thymomatous group (4.5%). MG wasn’t a negative prognostic factor in the thymoma population as previously reported by our group [6,7]. The distribution of deaths related to MG is similar when comparing the duration of symptoms (more or less than 18 months), the age of the patients (above or below 45 years) and class of MG (Fig. 2). Thirty-nine patients died for causes unrelated to myasthenia and recurrent thymoma was the most frequent cause of death (14 patients – 39%);
two patients developed a colonic and hepatic cancer and died, 10 and 26 years after thymectomy.

After a mean follow-up of 119 months (6–324 months) 54 patients (25%) are free of disease without medications (complete remission); 99 (46%) improved their activities and/or received less medications (palliation); 39 (18%) have a stable disease with no clinical change if compared to their clinical status before the operation; 12 (5%) presented a deterioration of their clinical status with worse symptoms, required more medications, or both. The group of patients with thymoma presented a lower remission rate (14.5 vs. 29%; \( P = 0.032 \)) when compared with the non-thymoma group; they also presented a higher incidence of deaths due to MG as reported, but the difference was not statistically significant \( (P = 0.12) \). Patients younger than 45 years did better than older patients: in fact, respectively 27 and 48% of the former group did not receive any medication or improved their clinical status, while in the latter group of patients the remission and palliation rates were 19.7 and 39.7%, respectively; however, the differences were not statistically significant. Also patients with a shorter duration of symptoms before the operation \( (<18 \text{ months}) \) did better (remission: 26.8 vs. 17.1%, \( P = 0.049 \); palliation: 51.8 vs. 19.5%, \( P = 0.041 \)). The stage of MG affected the outcome: in fact, remission and palliation considered together were 77% in patients with ocular myasthenia, 86.4% for class IIA MG, 55.8% for class IIB and only 38.5% (five patients in complete remission) for class III \( (P = 0.028) \). Remission and palliation were similar in patients operated through cervicotomy and upper sternal splitting. The curve of remission and palliation plotted against time could not be constructed since the retrospective collection of the data didn’t allow the establishment of the exact time of remission and palliation of symptoms.

4. Discussion

The progress in medical therapy have attenuated the debilitating and life-threatening characteristics of the natural history of MG. Thymectomy has been considered beneficial as part of a multidisciplinary approach and the positive results have been repeatedly demonstrated since the initial report by Blalock et al. in 1939 [8–10]. However, the specific indications to the operation remain controversial. Most centers consider the operation suitable for selected patients with generalized disease, with specific consideration to age, severity of symptoms, type of MG, response to medical treatment and duration of symptoms [9]. The indications to thymectomy for ocular MG are still ill-defined; in fact, type I MG is not a life-threatening disease and may also have natural remission. However, ocular MG often progresses to generalized MG [11,12] and may be complicated by thymoma. Surgical treatment is generally considered effective also at this stage and able to allow a complete remission in 50–70% of patients [12,13].

It is generally believed that ‘radical thymectomy’ should include the removal of all the thymic gland and the surrounding mediastinal fat tissue. Different surgical approaches have been proposed, from the simple transcervical thymectomy [14,15] to the ‘extended thymectomy’ [13] and the ‘maximal thymectomy’ [17]. After the initial 46 transcervical thymectomies, we have approached the anterior mediastinum through a partial upper sternal splitting incision. This incision allows a good exposure with direct control of the inferior region of the neck and, after placement of a retractor behind the sternum, also the fat located anteriorly to the pericardial sac can be removed. It is necessary to remove of the thymus and all the surrounding mediastinal fat and this can be well-achieved through a partial sternotomy. Our results are in line with those reported in the literature, with remission rates ranging between 13 and 46% [14–19]. Our careful attempts to remove all the mediastinal tissue is confirmed by the high number of patients in which we opened the mediastinal pleura during the dissection (140 patients, 64.5%). Previous reports did not show any relationship between preoperative Osserman classification and outcome after thymectomy [14]; however, even if our population was more weighted in favor of class I and II A patients, we observed a better improvement in the lower classes of MG, especially when
compared with MG class III, and this is in line with other reports [14,16–18,20]. Patients with pure ocular myasthenia showed a remission rate significantly higher (53%). Younger patients showed improved results if compared with the older group, but the difference was not statistically significant, as in other series [13].

Thymoma associated to MG present special clinical features. Most of the lesions were histologically classified as cortical thymomas, however, the distribution among the different Masaoka stages and MG classes was uniform; we have previously demonstrated that MG is not a negative prognostic factor for patients with thymoma [6], however, patients with thymomatous MG present worse results in terms of functional improvement and long-term survival. In fact, especially in the era preceding the multimodality treatment of these tumors [6], the recurrence of the mediastinal lesion was the most frequent cause of failure (14 patients, 6.5%). The improved control of the tumor with neoadjuvant chemotherapy and postoperative treatment will contribute to modify also the outcome of patients with thymomatous MG.


References


Appendix A. Conference discussion

Mr J. Dussek (Leuven, Belgium): Did you notice a change in symptom response with time? At what time did you assess the patients’ condition for this paper?

Dr. Venuta: When we decided to review retrospectively all our patients, we wanted to design a curve in terms of the time when symptoms disappeared or get worse after the operation. This would have been possible only in patients operated in the last 10 years; in fact, the time of appearance of symptoms couldn’t be assessed in patients operated many years ago. So I don’t have all the data to plot a curve with regard to these parameters. I would say that most of the patients that showed functional improvement, had it within 12 months after the operation.

Dr P. De Leen (Leuven, Belgium): Did you do any reoperations for myasthenia, and can you tell us anything about it?

Dr. Venuta: We did only two reoperations for myasthenia, and these patients were not included in this study. One patient was operated by us 11 years before and another patient was operated at another institution through a lateral thoracotomy 20 years before. We performed a median sternotomy in both patients with a radical extended thymectomy according to Jaretzky, since we wanted to be radical. One patient is alive and his condition is improved, and the other one died in the postoperative course.

Dr P. De Leen: At this moment, what are your indications for reoperation for myasthenia?

Dr. Venuta: We usually discuss this with the neurologist, we consider an indication to reoperation if there is an improvement and then there is a decline after the operation, or the patient is not happy with his condition and has to take steroids again after the operation, or needs plasmapheresis;
there are very serious cases, even 5, 6 years after the first operation and these patients should be considered for reoperation.

Dr P. Van Schil (Edegem, Belgium): Do you use a special preoperative preparation, like plasmapheresis in the severe cases of myasthenia? Did you encounter some respiratory insufficiency after thymectomy?

Dr Venuta: We have used plasmapheresis in 22 cases before the operation, and it’s mainly been used to improve preoperative functional status. If we can treat these serious patients before the operation, we try to do plasmapheresis also to lower the dose of steroids before surgery. We had only three patients with respiratory failure after the operation and two died. Ninety-seven percent of the patients have been extubated inside the operating room, and I would say that the postoperative course has been without major problems in most of them.

Dr D. Skinner (New York, NY, USA): You pointed out the Jaretzky approach to a more radical thymectomy. You did 46 patients through a cervicotomy. Was there any difference between the median sternotomy and the cervicotomy group?

Dr Venuta: The 46 patients operated through the transcervical approach were the first group in our series and the transcervical approach was the standard one for thymectomy in patients with myasthenia gravis. Then the papers from Masaoka and other Japanese authors came out, and we switched to what we thought was a more suitable approach to reach the lower part of the mediastinum, without performing a median sternotomy. We have used the Jaretzky approach in the two patients who required reoperation.

Now, in terms of results, we are a little disappointed because there was a difference between patients operated through a partial median sternotomy and the previous series. They did better. However, the statistical analysis showed that there was no significant difference between the two groups. So this is one of the cases where we must trust the statistics; however, we think that these patients should be considered for the more extended approach to completely clean the mediastinum.

Dr J. Benfield (Sacramento, CA, USA): I noted that you had a small but real experience with patients with ocular myasthenia. What is your policy regarding the postoperative management of these patients?

Dr Venuta: I'm glad you have such a good relationship with your neurologist. Our situation is a little more difficult. We try to keep these patients without medications for the first 48 h, unless they do need something. Our patients go routinely to the intensive care unit for at least 24 h, even if they are extubated in the operating room and medications are given by the intensivists, after that period most of our patients take the same medications that they took before the operation, and then they lower them when they go back to the neurologic clinic after the operation.