Extended thymectomy in myasthenia gravis: a team-work of neurologist, thoracic surgeon and anaesthesist may improve the outcome

Alfredo Mussi, Marco Lucchi, Luigi Murri, Roberta Ricciardi, Luca Luchini, Carlo Alberto Angeletti

Abstract

Objective: We reviewed our overall experience on 163 patients, affected by myasthenia gravis, who underwent thymectomy between 1976 and 1998. A comparison between the oldest series of 72 patients (January 1976–December 1992), referred by various neurologists and operated on through different approaches, and the last 91 patients (January 1993–December 1998), taking part in a strict diagnostic-therapeutical programme, was made. Methods: Anagraphic data, duration of symptoms, the surgical approach, necessity of respiratory assistance, the hospital stay, histopathological findings, preoperative and postoperative Osserman classification, as well as medications, were globally analyzed and then compared in the two groups. Results: Significant differences in the length of hospitalization (8.7 days vs. 4.2 days; \( P < 0.00001 \)) and in the prolonged intubation rate (18 vs. 0; \( P < 0.000001 \)) were observed in the most recent series. Patients in the preoperative Osserman stage I and operated on in the second period had a higher complete remission rate at the univariate analysis (\( P < 0.001 \) and \( P < 0.0001 \), respectively). At the multivariate analysis the only parameter which affected the outcome was to be operated on in the second period (\( P < 0.01 \)).

Conclusions: Our experience confirms the role of the extended thymectomy in the treatment of myasthenia gravis. Whenever an extended thymectomy was performed through a complete sternotomy it was a quick procedure, with short hospitalization and acceptable cosmetic results. A careful pharmacological control of the myasthenic symptoms and the presence of team-work among neurologist, thoracic surgeon and anaesthesist in the peri-operative setting reduce the incidence of complications and might increase the efficacy of the thymectomy. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Myasthenia gravis; Osserman classification; Median sternotomy; Thymectomy; Complete remission rate

1. Introduction

The efficacy of thymectomy in achieving improvement, as well as complete remission in myasthenic patients, has been widely determined [1–3]. Moreover, several factors such as the preoperative Osserman stage, the thymic histology, the symptoms duration, the extent of thymic resection have been reported to affect the patient’s response to thymectomy [4–7].

Unfortunately, different indications and approaches to thymectomy, with various extent of mediastinal fat exeresis, have produced consequent heterogenous and limited populations of patients [8–11].

In 1976 we started performing the thymectomy in myasthenic patients, referred by various neurologists, and, at that time, different surgical procedures and pharmacological control of the symptoms were adopted.

From January 1993, as a consequence of a strict collaboration with a dedicated neurologist and a anaesthesist, all the patients were inserted in a diagnostic-therapeutical programme consisting of a careful pharmacological control of the myasthenia gravis (MG) in the pre-, peri-, and postoperative period, an extended thymectomy, performed through a median sternotomy, and the prevention of postoperative myasthenic complications in the intensive care unit.

We reviewed our overall experience with thymectomies
in myasthenic patients analyzing the factors, which may influence the clinical outcome.

A retrospective comparison between the two groups concerning complications, medical requirements and complete remissions after thymectomy was attempted in order to evaluate whether the growing experience and an effective multidisciplinary collaboration play any role in improving the efficacy and safety of thymectomy in myasthenic patients.

2. Material and methods

The medical records of 163 patients who underwent thymectomy for myasthenia gravis between January 1976 and December 1998 were reviewed retrospectively.

Table 1
Preoperative characteristics of the patients

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Gender male vs. female</td>
<td>37 vs. 35</td>
<td>32 vs. 59</td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>43.1 ± 15.4</td>
<td>42.7 ± 16.7</td>
</tr>
<tr>
<td>Osserman stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>IIA</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>IIB</td>
<td>16</td>
<td>42</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Duration of symptoms (months) mean (range)</td>
<td>19 (1–324)</td>
<td>19.6 (3–132)</td>
</tr>
<tr>
<td>Acetylcholine receptor Ab positive vs. negative</td>
<td>–</td>
<td>72 vs. 19</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinesterase</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Steroid</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anticholinesterase + steroid</td>
<td>37</td>
<td>56</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>–</td>
<td>3</td>
</tr>
</tbody>
</table>

At the beginning, patients were referred for the surgical procedure by various neurologists and operated on through different approaches; from January 1993 all the patients were referred, and followed, by a single neurologist (R.R.); the thymectomy was performed through a complete median sternotomy, with a skin incision sparing about 3 cm from the jugulum and the xiphoid.

The diagnosis of MG was made on clinical criteria (fluctuating ocular or skeletal weakness that worsened with repeated efforts, and improved with rest or injection of anticholinesterase drugs), and confirmed by a decremental response to repetitive nerve stimulation and high titers of AchR antibodies.

The preoperative preparation, as well as the anaesthesia management and postoperative medical care, varied in the first period according to the neurologists and anaesthesists preferences; contrarily they were uniform and mediated by our previous experience in the second period.

Preoperative data, clinical characteristics, duration of symptoms, pre- and post-operative Osserman classification [12], pre- and post-operative medication requirements, time to extubation after surgery, pathological findings, and complications were evaluated, and their distribution in the two groups is shown in Tables 1–3.

All patients were optimally stabilized before surgery, and no patient was operated on while in crisis. Preoperatively, severity of symptoms was determined by the patient’s maximum symptoms at any time before operation and classified according Osserman’s classification.

The surgical procedure was, at the beginning, performed through various approaches (mostly sternotomy, in few cases cervicotomy, cervicotomy plus partial sternotomy, thoracotomy), while after 1993 it was always performed through a complete median sternotomy with a skin incision sparing about 3 cm from the jugulum and the xiphoid. In one case the resection of an invasive thymoma required an anterior thoracotomy associated to the sternotomy. Whenever
the surgical procedure was performed through a median sternotomy the thymectomy was always ‘extended’ or ‘radical’. The mediastinal dissection began at the diaphragm with the removal of all mediastinal fat. The pleura was frequently violated on both sides. The mediastinal fat was elevated and the dissection continued with the lower lobes. The phrenic nerves were identified and the dissection continued to the superior lobes in the vicinity of the thyroid gland. The superior thymic veins from the internal mammary and innominate veins as well as the thymic arteries from the internal mammary arteries were ligated. One small tube was placed in the mediastinum.

Patients were visited at 1, 3 and 6 months from the operation, thereafter yearly or whenever it was required by the deterioration of the symptoms.

Postoperative results were also classified as follows:

- Complete remission: no myasthenic symptom and sign for at least 6 months without drug treatment.
- Remission with medications: no myasthenic symptom but permanent anticholinesterase therapy even at lower dosage than preoperatively.
- Improved: still symptomatic but in a lower Osserman stage than before thymectomy and with less drug requirement.
- Unchanged: minimal changes.
- Worsened: worse than before thymectomy.

All the considered variables were statistically analyzed in the overall series and in two time-related subgroups: (A) from 1976 to 1992 and (B) from 1993 to 1998.

### 2.1. Statistical analysis

Data were analyzed uncorrected and corrected for length of follow-up. Life table analysis by the Kaplan–Meier method [13] was used to assess the effect of the evaluated variables on the distribution of complete remission (interval from thymectomy to the occurrence of complete remission) and difference among patient subgroups.

The influence of multiple variables on complete remission distribution was estimated by the Cox proportional hazard model [14].

\( P < 0.05 \) was considered statistically significant. The data were processed by the Statistica software.

### 3. Results

Ninety-three women and 70 men were operated on. The mean age at time of the operation was 42.9 years (range 12–77 years). At the maximal deterioration before surgery the clinical grading according to the Osserman classification was: stage I in 45 patients; stage IIA in 54 patients; stage IIB in 58 patients; stage III in three patients and stage IV in three patients.

Anti-acetylcholine receptor antibody (AntiAchRAb) assays, routinely performed after 1993, were positive in 72 patients. Patients underwent thymectomy when their symptoms were optimally controlled. The control of the symptoms in 67 patients required anticholinesterase medication, in 93 patients anticholinesterase and steroid drugs, and in three cases both of these in association with azathioprine.

The anticholinesterase and steroid therapy was unchanged during the perioperative period and then gradually decreased in dosage according to the absence of myasthenic symptoms. The surgical procedures lasted from 70 to 200 min (mean 95 min). The length of anaesthesia was from 90 to 225 min (mean 115 min). There were 18 prolonged intubations in the first period while all of the last 91 patients were extubated in the operating room. There was no perioperative mortality, nor there were major complications. The mean hospital stay was 6.2 days (range 3–19 days). With regard to pathological characteristics, there were 69 thymomas, 82 hyperplasias and 12 atrophic thymuses. The Masaoka stage of the thymic neoplasms was: 34 I, eight IIA, 14 IIB, nine III, four IVA.

With an overall mean follow-up of 93 months (134 and 52 months for the first and second period, respectively) 51 patients had a complete remission, 50 a remission with medications, 54 an improvement of the symptoms with decrease in drug requirement, seven remained nearly in the same status and one worsened. Two of the last eight patients were operated on again. No patient died because of myasthenia gravis. Four patients died for causes unrelated to myasthenia gravis (one recurrence of invasive thymoma, one car accident, one lung cancer, one myocardial infarction 3 years after the operation).

Considering first all the 163 patients and then the two historical groups, the only variable indicating a more favorable outcome was the Osserman stage before operation \( (P < 0.001) \), with the highest complete remission rate in patients with stage I (Fig. 1). Patients with thymoma had a higher complete remission rate than those without but the difference was not statistically significant. Age of the patients, sex, time from diagnosis to operation, medication
requirements failed to significantly affect the outcome even when we excluded patients with stage I and patients with thymoma.

Comparing patients operated on in the first period with those who underwent operation in the second, we found that remission rate was significantly higher \( (P < 0.0001) \) for those operated on after January 1993 (Fig. 2). Significant differences in the length of hospitalization (8.7 vs. 4.2 days; \( P = 0.00001 \)) (Fig. 3) and in the necessity of respiratory assistance (18 vs. 0; \( P < 0.000001 \)) were also observed in the most recent series. Multivariate analysis did not show significant differences in the distribution of complete remissions for any of the considered variables except for the two time-related series \( (P < 0.01) \).

4. Discussion

The role of the thymus in the pathogenesis of myasthenia gravis remains a question to become clear, but several reasons for the beneficial effect of thymectomy have been suggested [15].

Unfortunately, neurologists, as well as thoracic surgeons, have no fixed parameters to predict the effect of the thymectomy on myasthenic patients. Numerous studies [4,6–8,16] have detected some prognostic factors of a favorable outcome in thymectomized myasthenic patients, but, unfortunately, as emphasized by Jaretzki in a recent review of the literature [17], there is an absence of standardized methods for assessing patient status before and after surgery and in the assessment of correct criteria of success, so that the data are confusing and conflicting.

In agreement with Jaretzki [8,17], we believe that complete and permanent remission rate is the real measure of response to thymectomy, just as the rate of patients who find themselves in worse conditions or who die in crisis represents the failure of therapy. Moreover, life-table analysis by the Kaplan–Meier method is the best statistical technique to analyze remissions after thymectomy and to compare the role of different variables [17–18]. Furthermore, different thymectomy techniques, from the ‘basic’ transcervical [9] to the ‘maximal’ transcervical-transsternal [8], and the recent thoracoscopic technique [11], seem to offer differing extents of thymic resection, and, as a consequence, may represent a further variable in the analysis of the results. In the beginning we performed the thymectomy through different approaches, but, after the anatomical studies by Masaoka [19] and Jaretzky [20], and the evidence that the thymic gland must be removed with all the surrounding fat from the thyroid gland to the diaphragm and between the two phrenic nerves, we considered the complete sternotomy the best approach to the anterior mediastinum. Progressively we reduced the length of the skin incision, and, since 1993, we always spare at least 3 cm from the jugulum and the xiphoid.

That decision gave excellent cosmetic results and, associated to the use of absorbable suture (Maxon loop) in place of wire for the sternal synthesis, made the transternal approach to thymectomy well-accepted by all patients, even by the youngest and females.

With growing experience the morbidity rate of the thymectomies and length of hospitalization progressively
and has intrinsic limits; a prospectively randomized study with affected by time variations. It is a retrospective comparison treatment on the myasthenic symptoms should not be ed by the natural evolution of the techniques in medicine. or with the general trend that has affected all operations. better surgical and anaesthetic technique in the recent series the shorter hospitalization, somebody may argue with the due to many reasons. Concerning the earlier extubation and results, we strongly support the extended thymectomy in was performed for a thymoma, but, on the basis of our other Osserman stages.

In most of the reports the presence of a thymoma is associated with a lower remission rate [2–4,18–19], indicating that the thymomectomy, even if necessary for oncological reasons, influences less the symptoms regression. In our series, on the contrary, the thymomatous group had a more favorable outcome (even if not statistically significant) than the non-thymomatous group, but the reason is not clear. One possible explanation may be that most of the thymomas were early stage and that in the 13 stage III–IVA thymomas an excellent control of the disease was obtained through both neoadjuvant and adjuvant therapies [21].

In the same way the age of the patients, at disease onset, and the duration of the symptoms failed to affect the outcome (even if the group of patients with a length of symptoms less than 1 year has a higher complete remission rate, the difference is not statistically significant).

An important consideration regards the thymectomy in stage I myasthenia gravis (ocular symptoms) which is a controversial indication. Even if unsatisfactory results have been reported in some cases, and natural remissions have been also described, it is true that two-thirds of these patients will develop a generalized disease in their natural history, and in some cases stage I myasthenia gravis is associated with thymomatous disease. We experienced an extremely favorable outcome in this group of patients with a complete remission rate significantly higher than in the other Osserman stages.

In 23 cases of stage I myasthenia gravis, the operation was performed for a thymoma, but, on the basis of our results, we strongly support the extended thymectomy in all patients with ocular symptoms whenever there isn’t a complete remission after medication or when the required doses of medication are too high.

The better results obtained in the second period may be due to many reasons. Concerning the earlier extubation and the shorter hospitalization, somebody may argue with the better surgical and anaesthetic technique in the recent series or with the general trend that has affected all operations. However the difference is so marked that it cannot be justified by the natural evolution of the techniques in medicine.

More important the analysis of the results of the surgical treatment on the myasthenic symptoms should not be affected by time variations. It is a retrospective comparison and has intrinsic limits; a prospective randomized study with two groups of patients (team approach vs. non-team approach) is necessary to draw some valid conclusions but it is our feeling that the presence of an effective collaboration among a dedicated neurologist, thoracic surgeon, independently by the surgical technique preferred in performing a extended thymectomy, and anaesthetist, with solid experience in the treatment of myasthenic patients plays a main role in achieving good results.

As a matter of fact operative volume has been postulated to be a source of surgical outcome difference. This hypothesis has been validated both in cardiac surgery and general thoracic surgery [22–24] with a significant increase in mortality and morbidity when the specific surgical procedure was performed occasionally vs. frequently.

The low incidence of complications and the apparent increase of the efficacy of the thymectomy obtained in our practice prompt us to suggest that such a relatively ‘rare disease’ should be treated in a few, well-trained centers.

A method to detect ectopic thymic tissue or postoperative thymic remnants would be desirable in order to indicate an exeresis for selected patients which could be more extensive than an ‘extended’ or ‘maximal’ thymectomy.

To achieve well-supported conclusions, it is necessary to start a multicenter randomized, prospective study with a sufficient number of patients in a short period, a uniform classification of the symptoms and an adequate statistical method of analysis [25]. Until such a time we will simply not have enough evidence regarding how extensive a given thymectomy must be and which patients could maximally benefit from the operation.

References


