Long-term outcome of thoracoscopic extended thymectomy for nonthymomatous myasthenia gravis

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Received 12 September 2008; received in revised form 16 February 2009; accepted 18 February 2009; Available online 31 March 2009

Abstract

Background: Thoracoscopic thymectomy has shown promise in the integrated management of myasthenia gravis (MG) although there is still scant data on long-term results. The aim of this study was to analyze long-term (>5 years) results of thoracoscopic extended thymectomy in nonthymomatous MG.

Methods: We retrospectively reviewed 32 patients operated on between 1995 and 2003. MGFA classification, symptoms' duration, preoperative crisis, anticholinesterase-drugs dosage, steroid use, and acetylcholine receptor antibodies were evaluated in all patients with annual follow-up. Anti-MuSK antibody titer was also assessed at the last follow-up. Results: There were 21 females and 11 males with a median age of 36 years. Ten patients were seronegative for acetylcholine receptor antibodies. Patients in MGFA class I, II, III and IV were 7 (22%), 15 (44%), 9 (28%), 2 (6%) patients, respectively. Median symptoms duration was 11 months. There was no mortality or major morbidity. Median hospital stay was 4.0 days. Ectopic thymic tissue was found in 18 (56%) patients. Median follow-up was 119 months (range 60—156 months). There was no residual thoracic pain. Estimated 10-year remission rate was 50%. At 72 months, 27 (84.3%) patients were improved or in complete remission. At the univariate analysis, shorter duration of symptoms (<12 months) and absence of oropharyngeal involvement were both predictors of response to thymectomy (p < 0.02) whereas positivity for anti-MuSK antibody was a predictor of non-response (p = 0.0007).

Conclusions: Thoracoscopic extended thymectomy yields satisfactory long-term results in patients with nonthymomatous myasthenia gravis although anti-MuSK positivity correlated with poor response to operation.

1. Introduction

Myasthenia gravis is an organ-specific autoimmune disease in which autoantibodies to nicotinic acetylcholine receptors (anti-AChRab) are produced causing impaired neuromuscular transmission and muscular weakness.

Thymectomy is an effective surgical therapy integrating the medical care of patients with myasthenia gravis and has shown to increase the probability of remission or improvement of symptoms [1]. Beneficial effects of thymectomy are thought to be maximized by complete removal of thymus and ectopic thymic tissue that can be scattered throughout the mediastinal and cervical fat [2,3]. On the other hand, there is evidence that thymectomy can be less effective in patients with positive serum titer of antibodies against the muscle-specific receptor tyrosine kinase (anti-MuSKab) [4,5].

Amongst the different surgical approaches employed for thymectomy, thoracoscopic thymectomy is now considered a reliable alternative to standard open approaches due to its low morbidity, improved cosmesis and equivalent efficacy although so far, there is still scant data on long-term outcome of this minimally invasive surgical option [6—9].

The aim of this study was to analyze long-term (>5 years) results of thoracoscopic extended thymectomy employed in nonthymomatous myasthenia gravis.

2. Materials and methods

Between May 1995 and April 2008, 41 patients with myasthenia gravis underwent thoracoscopic extended thymectomy at the Tor Vergata University. Out of these, 32 patients with nonthymomatous disease and a minimum follow-up of 60 months were considered eligible for the
The Myasthenia Gravis Foundation of America (MGFA) [10]. Thereafter, severity of the disease was classified according to comparing the preoperative clinical status with the status in all patients. Anti-MuSKab serum titer was also assessed at the last follow-up.

The therapeutic effect of thymectomy was established by comparing the preoperative clinical status with the status recorded postoperatively after 6 months and every 12 months thereafter. Severity of the disease was classified according to the Myasthenia Gravis Foundation of America (MGFA) [10]. This classification was applied retrospectively for patients operated on up to December 2000 and in a prospective manner thereafter. Medications (i.e., pyridostigmine, steroids and/or azathioprine) and dosages taken at the time of surgery were recorded.

Patients with severe symptoms, who were considered at risk for postoperative respiratory failure, underwent plasma exchange or intravenous immunoglobulins prior to operation. Pyridostigmine was given as needed before and after the surgical procedure, whereas, whenever feasible, steroid treatment was avoided preoperatively.

Symptomatic response was rated in four ranks: complete remission meaning no symptoms off medication; pharmacologic remission meaning no symptoms with medication; clinical improvement meaning improvement in symptoms with medication; and no improvement that included stable symptoms despite medications or symptoms deterioration. Yet, ranks of complete remission, pharmacologic remission and symptomatic improvement were included in the wider definition of response to thymectomy.

2.1. Surgical technique

The surgical technique has been described previously in detail [6]. Thymectomy was performed under general anesthesia with double-lumen tube placement and with the patient lying in a 45° off-center position. A left or right sided 4-trocar access was employed. A utility collar minicervicotomy was added in 21 patients (66%) in whom long cervical extension of the upper thymic horns were intraoperatively identified (Fig. 1). The procedure routinely included removal of the entire gland and all anterior mediastinal perithymic tissues including fatty tissue in the aorto-caval groove, the aortopulmonary window, both cardiophrenic sinuses, and the lower cervical area.

2.2. Statistical analysis

Group descriptive statistics are presented as the median with quartile range. The relationship between potential prognostic factors and response to thymectomy has been initially tested with the Spearman test whereas an analysis of dichotomized factors has been carried out with the two tailed Fisher’s exact test taking median values as cut-off points and considering outcome data at 72 months.

Estimated remission rates were calculated by the Kaplan—Meier method and differences between curves were analyzed by the log rank test. Finally to test whether the number of new remissions plateaued over time, response to thymectomy has been artificially dichotomized at three fixed time intervals (36, 72, and 108 months) and the nonparametric Cochran Q test has been employed to analyze whether the three matched proportions differed significantly amongst themselves.

3. Results

There were 21 females and 11 males with a median age of 36 years (QR: 27—47.5 years). Median duration of preoperative symptoms was 11 months (QR: 6.0—13.5 months). Serum dosage of anti-AchRab was positive in 22 patients and negative in 10. Clinical MGFA class at maximum preoperative severity was as follows: class I, 7 patients; class II, 14 patients; class III, 9 patients; class IV, 2 patients. Amongst these, oropharyngeal involvement was present in 8 patients (3 in class IIb, 4 in class IIIb and 1 in class IVb). Thoracoscopic thymectomy was successful in 30 patients while 2 obese patients required conversion to median sternotomy (6%) because of technical difficulties in dissecting the thymus in one patient and diffuse uncontrolled bleeding in another. Both these patients received steroid therapy preoperatively. Median operative time was 150 min (QR: 140—180 min).

Hystopathologic examination showed hyperplasia in 18 patients, normal thymus in 9 patients and thymic involution in 5 patients.

Ectopic thymic tissue was found in 18 (56%) patients. It was located within the anterior mediastinum adipose tissue in 10 patients, in the pretracheal fat in 4 patients, in the aorto-pulmonary window and the pericardiophrenic angles in 3 patients each. Two patients had ectopic thymic tissue at two different sites (anterior mediastinum and pretracheal fat in one patient and anterior mediastinum and aortopulmonary window in another). There was no operative mortality or major morbidity. Median hospital stay was 4 days (QR: 3—5.5 days). One female patient died at home while sleeping 55...
days after thymectomy due to an unknown cause. No patient was lost to follow-up.

No exacerbation occurred in any patient after that complete remission was achieved.

During follow-up, all patients underwent serum dosage of anti-MuSK antibodies that resulted positive in five patients (16%). All these patients had preoperatively seronegative myasthenia gravis. Overall, response to thymectomy was achieved in 27 patients (84%) at 72 months.

Analysis of factors that might be potentially related to response showed a direct relationship with positivity for anti-AchRab ($r = 0.37$, $p = 0.03$) and an inverse relationship with both the presence of ectopic thymic tissue ($r = -0.42$, $p = 0.01$) and positivity for anti-MuSKab ($r = -0.89$, $p < 0.00001$). Yet, when analyzing frequencies of the aforementioned factors by the two-tailed Fisher’s exact test (Table 1), shorter symptoms’ duration, no oropharyngeal involvement, and negativity for anti-MuSK antibodies were significantly correlated with response whereas a trend in the same direction was observed for absence of ectopic thymic tissue.

Postoperatively, 14 patients received pyridostigmine alone, 16 patients received steroids with or without pyridostigmine whereas 2 patients received steroids and azathioprine. During follow-up, complete remission was achieved by 8 patients receiving sole pyridostigmine (57%), 6 patients receiving steroids (38%), and no patient receiving azathioprine. Pharmacologic remission was achieved by 5 patients (16%) of whom 3 received sole pyridostigmine and 2 received steroids.

The median follow-up was 119 months ranging from 60 to 156 months. Median time from thymectomy to complete remission was 88 months ranging from 11 to 154 months. Overall 14 patients (44%) obtained complete remission during follow-up. None of these patients had positive anti-MuSKab titer. Estimated remission rates calculated by the Kaplan—Meier method are illustrated in Figs. 2—5.

Overall, 10-year remission rate was 50%. There was no significant difference in estimated remission rate according to MGFA class (class I vs class >I) and symptoms duration (<12 months vs $\geq$12 months) whereas patients without oropharyngeal involvement had a higher remission rate ($p = 0.04$).

When assessing the crude number of remissions occurring at three fixed time intervals (36, 72, and 108 months), these increased at each time interval for up to 108 months and the three matched proportions were significantly different (Cochran Q test, $p = 0.0094$)(Fig. 6).

One patient developed non-Hodgkin lymphoma during follow-up while one patient in the positive anti-MuSKab group needed hospital readmission 31 months after the operation due to severely deteriorating myasthenic symptoms.

At the last follow-up, no patient complained of chronic thoracic pain and all patients declared to be highly satisfied with the eventual cosmetic effect of the operation.

### Table 1

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* Complete and partial remissions versus no improvement.
4. Discussion

Thymectomy integrates pharmacological management of myasthenia gravis and benefits deriving from the operation have been widely reported particularly in patients with seropositive nonthymomatous myasthenia associated with thymic hyperplasia [11]. Yet, the possibility to analyze in more detail the immunologic profile of many patients suggests that myasthenia gravis is a more complex disease than previously thought and that different immunologic profiles can be associated with heterogeneous clinical pictures and variable response to thymectomy [12].

The most striking results of our study are twofold. First, we have documented that following thoracoscopic extended thymectomy, highly satisfactory long-term results occurred in a cohort of patients with nonthymomatous myasthenia. In particular, complete remission and symptomatic improvement rates observed in our series are comparable to those reported by others through open approaches [3,11]. Secondly, we have shown that the majority of our patients who did not respond satisfactorily to thoracoscopic thymectomy had a positive titer of anti-MuSKab, which proved a predictor of nonresponse at the univariate analysis. In addition, in our analysis, shorter symptom duration and absence of oropharyngeal involvement predicted response to thymectomy. Finally, we have found that remission rate did not differ between anti-AchR seropositive and seronegative patients. This finding confirms other studies’ results [11,13] and indicates that, provided patients are seronegative for anti-MuSK antibodies, they should not be denied thymectomy.

The main advantages of thoracoscopic thymectomy are thought to be a wide and detailed visualization of the anterior mediastinal and lower cervical regions, a minimal surgical trauma and an optimal cosmetic result, which facilitate acceptance of the procedure both by patients and neurologists [6].

Intermediate follow-up data of recent thoracoscopic thymectomy series showed satisfactory results with remission rates ranging between 14% [8] and 60% [7]. However, as properly reported by Roth and co-workers [14], long-term results of different thymectomy approaches must be carefully analyzed since surgery-related sequelae and fluctuation of clinical results can occur during follow-up in myasthenic patients.

In our series, 88% of the patients had a meaningful symptomatic improvement and 10-year remission rate was 50%. These results parallel those reported by Mantegazza and co-workers [11] by the video-assisted extended thymectomy entailing a bilateral thoracoscopic approach plus a collar cervicotomy.

In addition, when analyzing the behaviour of new remissions at three fixed time intervals we have noted that these continued to increase over time and the three matched proportions differed significantly amongst themselves. This feature confirms that results of thymectomy continue to improve over time and an adequate length of follow-up is needed to assess the efficacy of any thymectomy technique. Our study reinforces these assumptions and extends previously reported data suggesting that by this approach, complete anatomic thymectomy can be associated with an extended removal of the perithymic fatty tissue [6—9]. This need is sustained by the finding that ectopic thymic tissue can be found in the adipose tissue located at variable sites within the anterior mediastinum and cervical area and that lack of removal of this tissue can reduce the benefit of thymectomy.
Jaretzki and Wolf [15] noted that 98% of patients with myasthenia gravis had anatomic variability in the distribution of thymic tissue in the mediastinum whereas Masaoka and co-workers [16] found that 72% of myasthenic patients had ectopic thymic tissue in the anterior mediastinal fat. In a more recent study, Ashour [17] found ectopic thymic tissue in 63% of patients in the neck and in 21% in the cardiophrenic angles. It is worth noting that in the same study, Ashour [17] first reported that presence of ectopic thymic tissue can be a negative prognostic factor indicating poorer response to thymectomy. A possible explanation might be that in patients with ectopic thymic tissue, multiple unrecognized sites sustaining abnormal immunologic response do exist. If this is the case, extended surgical resection could be revealed as unnecessary since identification of ectopic thymic tissue cannot modify the poor response to thymectomy. On the other hand, one might also assume that provided a clinical role of ectopic thymic tissue, this can be completely removed in some patients by the most radical current surgical techniques whereas only patients with residual ectopic thymic tissue fail to respond to thymectomy.

We have found that ectopic thymic tissue was present in 56% of our patients and was slightly and inversely correlated with response although we failed to demonstrate a difference in remission rate between patients with and without ectopic thymic tissue. However, the satisfactory complete remission rate observed in our series reinforces the belief that the more radical the thymectomy the better the outcome [15,16].

As far as the potential effect of severity of disease on clinical outcome is concerned, we have found no difference in complete remission rate between patients with generalized myasthenia and those with pure ocular disease. This result corroborates previous studies’ data [2,18] and suggests that even in patients with ocular myasthenia thoracoscopic thymectomy can be beneficial. On the other hand, we have observed that absence of oropharyngeal involvement resulted in a higher remission rate than in patients with stages b MGFA class. Similar findings have been recently reported by Yu and co-workers [19] who found that oropharyngeal muscle involvement causing difficulty in swallowing, slurred speech and dysphagia correlated with poor prognosis. However, in our series, this result might be affected by the coexistence of positive anti-MuSKAb titer that was found in 5 out of 9 patients with oropharyngeal involvement whereas no data on anti-MuSKAb is reported in the study of Yu and co-workers [19]. Conversely, in agreement with our results, Evoli and co-workers [4] have found that anti-MuSK positive myasthenia gravis is frequently associated with more severe involvement of cranial and bulbar muscles, high frequency of respiratory crises and poor response to thymectomy.

Regarding preoperative symptoms’ duration, our current analysis confirms previous findings indicating shorter duration of symptoms as a predictor of satisfactory response to thymectomy although we failed to demonstrate a significant difference in estimated remission rate in this patients’ subgroup [6].

The beneficial effect of a short interval between diagnosis and thymectomy is likely due to a reduced damage to the neuromuscular plate. However, other authors reported no relationship between symptoms duration and outcome [20,21].

4.1. Limitations

The main limitation of our study is its retrospective nature. Furthermore, the small cohort negated the possibility of performing a multivariate analysis of independent factors potentially affecting outcome. However, in our series, all patients have been operated in the same institution by the same surgeons (TCM and EP) and underwent the same extent of removal of both thymic gland and perithymic fatty tissue according to the criteria outlined by Masaoka and co-workers [2].

4.2. Conclusions

The analysis of a historical thymectomized cohort according to recently available immunologic testing has offered us the possibility of improving our understanding of what was initially thought simply as a surgical failure.

Our data show that thoracoscopic extended thymectomy results in highly satisfactory long-term outcome in non-thymomatous myasthenia gravis with a 10-year remission rate of 50% and an overall response rate of about 90%. Positive anti-MuSKAb titer resulted in a predictor of nonresponse and could account for some of the surgical failures reported in historical cohorts. On the other hand, short duration of symptoms and absence of oropharyngeal involvement were both predictors of response to thymectomy. Larger controlled studies with long-term follow-up are needed to draw further information on outcome of thoracoscopic thymectomy in nonthymomatous myasthenia gravis.

References

Appendix A. Conference discussion

Dr A. Oliaro (Torino, Italy): In our department of thoracic surgery we continue to perform thymectomy between the cervicotomy and splitting the sternum, and our operating time is about 50 min. You have reported an operative time of 165 min. What do you think about the long operative time?

Dr Pompeo: Well, one problem is that with thoracoscopic thymectomy, there is a learning curve. As you have seen, this series goes back to 2003, and now we have shortened our operative time a bit. It did not reach less than 60 min actually, I must say, but anyway, it is somewhat shorter. The second point is that the extension of this dissection is also important when you calculate your operating time. I suppose that for a maximal thymectomy as proposed by Jaretzki, you need more time than for doing a simple thymectomy. We believe that great attention must be paid in removing all the mediastinal fatty tissue we can to maximize the results, and I hope that the outcome can justify this approach.

Dr A. Maat (Rotterdam, The Netherlands): Is it correct that you sometimes open the cervical part to remove more tissue?

Dr Pompeo: Yes, that is correct.

Dr Maat: I have always been struggling with this cervical part, and I think of this publication by Shigemura from Osaka. He did 20 patients with bilateral VATS thymectomy, and after the VATS, he opened the neck, and in all patients he found additional thymus tissue, and more than 70% contained Hassall’s bodies. So don’t you think that we should always open the neck after a VATS thymectomy in order to obtain maximal results for the patient?

Dr Pompeo: I am convinced of this point. I have to say that we now always perform a minimal cervicotomy. I have to say that we now always perform a minimal cervicotomy. It is correct that quite frequently we can find ectopic thymic tissue on that side. And another important technical problem is that through this minimal cervicotomy, you can lift the sternum and help surgical maneuvering during thoracoscopy as well.