Comparison of complete remission rates after 5 year follow-up of three different techniques of thymectomy for myasthenia gravis

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Abstract

Objective: This study aims to analyse the effectiveness of treatment of myasthenia gravis with three different techniques of thymectomy.

Methods: Results of complete remission rates after 5-year follow-up of 60 patients who underwent basic transsternal thymectomies (group A) from 1 January 1996 to 31 December 1997, 75 patients who underwent extended transsternal thymectomies (group B) from 1 January 1998 to 30 June 2000 and 291 patients who underwent transcervical-subxiphoid-videothoracoscopic ‘maximal’ thymectomy (group C) from 1 September 2000 to 31 January 2009 were compared. Results: There were no differences between groups according to patient’s characteristics and postoperative complications’ rate. Ectopic foci of the thymic tissue were discovered in the fat of the neck and the mediastinum in 53.9% of patients from the group B and in 65.9% patients from the group C. After 1, 2, 3, 4 and 5 years of follow-up, complete remission rates were 8.3%, 11.7%, 15.0%, 16.7% and 20.0%, respectively, in group A; 26.7%, 38.7%, 42.7%, 46.7% and 50.7%, respectively, in group B; and 31.5%, 39%, 45.8%, 46.3% and 53.1%, respectively, in group C. The differences between group A and the groups B and C after 1, 2, 3, 4 and 5 years were statistically significant. There were no significant differences between groups B and C. Conclusions: (1) The results of complete remission rates after 5-year follow-up were statistically better in patients with myasthenia gravis (MG), who were operated on with extended transternal thymectomy and transcervical-subxiphoid-videothoracoscopic ‘maximal’ thymectomy than the patients who underwent basic transternal thymectomy. (2) The difference can be explained by the removal of ectopic foci of the thymic tissue from the neck and the mediastinum in these patients.

Keywords: Myasthenia; Surgery; Mediastinum; Thymus; Thymectomy

1. Introduction

The thymus is a shadowy organ whose physiological and pathophysiological role is understood only partially. The importance of the thymus in the development of myasthenia gravis (MG) and the value of surgical removal of this organ in the treatment of MG is a well-known issue. The main principle of the operative treatment of MG is a complete removal of the entire thymic gland. A subtotal thymectomy is unacceptable and should not be performed. A necessity of removal of the ectopic thymic foci is a matter of controversy. There are many variations in the technique of thymectomy. In general, all thymectomies can be classified according to two criteria — the type of surgical approach and the extensiveness of the procedure. There are several types of operative approaches for thymectomy: complete median sternotomy, upper median sternotomy (manubriotomy), transverse sternotomy, lateral thoracotomy, cervical incision, complete median sternotomy with additional cervical incision, upper median sternotomy (manubriotomy) combined with cervical incision, subxiphoid incision and several subtypes of videothoracoscopic (VATS) thymectomies including robot thymectomy [1—13].

Thymectomies can be also classified with regard to the extensiveness of the procedure. Basic thymectomy includes removal of the thymus gland without any surrounding fatty tissue. Extended thymectomy includes removal of the thymus with the surrounding fatty tissue of the neck and the mediastinum [14,15]. The maximally extended procedure introduced by Jaretzki includes removal of the thymus with the fatty tissue, from the level of the upper poles of the thyroid gland, down to the diaphragm, with a wide opening of both pleural cavities and radical en bloc exenteration of the anterior mediastinum with the overlying mediastinal pleural sheets; the laryngeal recurrent, vagus and phrenic nerves are

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The aim of this retrospective study was to compare the late results of thymectomy performed through an upper median sternotomy, the extended transsternal thymectomy performed through a complete median sternotomy and the transcervical-subxiphoid-videothoracoscopic maximal thymectomies.

2. Material and methods

The results of all patients operated on for MG from 1 January 1996 to 31 January 2009 were reviewed. The indication for thymectomy was clinically stable MG, stage I—III according to the Osserman–Genkins classification. The patients with unstable MG were treated with steroids and immunosuppressive drugs for stabilisation of MG before thymectomy. Plasmapheresis was used only in several patients referred to our institution from other hospitals.

There were 60 patients who underwent basic transsternal thymectomies (group A) from 1 January 1996 to 31 December 1997, 75 patients who underwent extended transsternal thymectomies (group B) from 1 January 1998 to 30 June 2000 and 291 patients who underwent transcervical-subxiphoid-videothoracoscopic 'maximal' thymectomy (group C) from 1 September 2000 to 31 January 2009 were compared. The positive (i.e., complete remissions) and negative (i.e., lack of improvement, deterioration and deaths from MG) results of 5-year follow-up of all groups were compared.

All patients with MG in the course of thymoma or who underwent rethymectomy, operated on during this period, were excluded from the analysis.

The operative technique of the basic transsternal thymectomy has been described in detail elsewhere [15]. In brief, the technique of the basic transsternal thymectomy is as follows: a 10-cm longitudinal incision is made above the upper part of the sternum, which is divided in the standard manner. The whole thymus gland is dissected free by blunt and sharp dissection from the mediastinal fat and removed. In general, any pleural cavity is entered, and the mediastinal fat is not removed. The technique of the extended transsternal thymectomy is similar to the method described by Bulkley et al. [19] and is as follows: a complete longitudinal sternotomy is performed; all the fatty tissue of the anterior and (partly) the middle mediastinum is removed by sharp dissection from the level of the lower poles of the thyroid gland to the level of the diaphragm. The mediastinal pleura is widely incised below the inner surface of the sternum and parallel to the phrenic nerves, at a distance of 1 cm from each nerve. The sheets of mediastinal pleura are bilaterally removed en bloc with the specimen.

Generally, both phrenic nerves are the margins of dissection; however, the fatty tissue extending beyond the nerve is also removed. No effort is made to dissect the thymus gland separately, but it is always removed with the whole specimen. The adipose tissue of the lower part of the neck is totally removed from between both carotid arteries, which are dissected free along their anterior surfaces with visualisation of both laryngeal recurrent nerves and lower parathyroid glands, all of which are carefully preserved.

The technique of visualisation of the laryngeal recurrent nerves has been described in detail elsewhere [20]. The fatty tissue from the aorta—caval groove (a space situated posteriorly to the aorta and vena cava superior and laterally to the trachea) and the aorta—pulmonary window are dissected separately, and the rest of the specimen containing the adipose tissue from the paratracheal and the cervical regions, the space behind the left innominate vein, the anterior mediastinum and the right and the left epiphrenic fat pads is removed.

The operative technique of the transcervical-subxiphoid-videothoracoscopic 'maximal' thymectomy is as follows: a patient is positioned supine on the operating table with a roll placed beneath the thoracic spine to elevate the chest and to hyperextend the patient’s neck. Under general anaesthesia, an endobronchial tube is inserted to conduct selective lung ventilation during the latter part of the procedure. To shorten the operative time and to facilitate performance of the procedure, an operation may be performed by two teams—one called the ‘cervical team’ working from above and the second one called ‘the subxiphoid team’ working from below the sternum with control of the videothoracoscope (VTS) (Figs. 1 and 2). Alternatively, the whole operation is performed by one surgical team performing 'the cervical' and 'the subxiphoid' parts of the operation sequentially.

Fig. 1. The position of all members of both teams. Reprinted from ‘open videoassisted techniques: transcervical-subxiphoid-videothoracoscopic maximal thymectomy’ from ‘Thymus gland pathology’ Springer 2008. With kind permission of Springer Science + Business Media.
All operative steps are described without specifying if one or two teams are involved. The cervical part of the operation: a transverse 5–8 cm incision is made in the neck above the sternal notch. The whole thyroid gland is visualised and all foci of the adipose tissue are removed downwards from the level of the upper poles of the thyroid gland. The parathyroid glands and both laryngeal recurrent nerves are visualised and carefully preserved. The fatty tissue containing the superior poles of the thymus is separated from the lower poles of the thyroid gland with 1–4 inferior thyroid veins ligated and divided. Alternatively, such devices as a harmonic knife, LigaSure (Valleylab, Boulder, CO, USA), BiClamp (ERBE) or vascular clips can be used to secure the vessels throughout the procedure. The thymus with the surrounding fat is then separated from the sternohyoid and sternothyroid muscles, the trachea, the internal surface of the sternum, the carotid arteries, the innominate artery, the aorta and the right innominate vein. At this point, a sternal retractor connected to the traction frame (the same as one which is used for traction of the manubrium) is placed under the sternum, which is elevated to facilitate access to the anterior mediastinum from below. A thoracoscopic port for 5 mm, 30° oblique thoracoscope is inserted into the right pleural cavity in the 6th intercostal space in the anterior axillary line. The right mediastinal pleura is cut near the sternal surface up to the level of the right internal thoracic vein, which is left intact. The prepericardial fat and right and left epiphrenic fat pads are dissected from the pericardium and diaphragm with blunt dissection using a peanut sponge and a sharp dissection using scissors or BiClamp (preferably). Dissection of the prepericardial fat containing the thymus gland proceeds upwards under the control of the VTS camera in an en bloc fashion, without any attempt to dissect the thymus gland separately. The right phrenic nerve is a margin of dissection. Ventilation of the right lung is resumed and the ventilation of the left lung is disconnected. A thoracoscopic port for 5 mm, 30° oblique thoracoscope is inserted into the left pleural cavity, as on the right side. Under the control of the VTS camera, the left mediastinal pleura is divided along the sternum and the left prepericardial fat is dissected from the pericardium above the level of the left internal thoracic vein previously divided. The left lower pole of the thymus is separated from the pericardium and the specimen is removed. Dissection of the aorta—pulmonary window is completed, if necessary, at this stage of the operation. Haemostasis is checked, the VTS ports are removed and the chest tubes are inserted into both pleural cavities through the incisions made for insertion of the ports. Ventilation of both lungs is resumed. The cervical and subxiphoid incisions are closed in the standard manner. In general, a patient is extubated immediately after the operation.

In pathological studies, the histological types of the thymus were described as hyperplastic, involuted or normal, and foci of the ectopic thymic tissue were searched for with haematoxylin/eosin staining. To all patients from three groups, questionnaires were sent every year with questions about symptoms (or lack of symptoms), medications (anticholinergic, corticosteroids or immunosuppressive drugs and the doses of drugs), improvement, stabilisation or worsening.
and (in women) the effect of pregnancy on the myasthenia. In selected cases the patients or their physicians were interviewed by phone. Outcomes were based on the patients’ answers and were defined as follows: (1) complete remission — no symptoms of MG and no need of antiamyotrophic medication, (2) improvement — myasthenic symptoms less severe or absent using antiamyotrophic drugs, (3) negative results — no improvement, deterioration or (4) death from myasthenia. Complete remission rates and negative post-operative results rates (lack of improvement, deterioration and death) were compared for the three groups.

Statistical analysis was performed with the STATISTICA software package. Probability values were generated with the chi-square test and the Student’s-t test or the Mann—Whitney test. Probability values \( p < 0.05 \) were considered to be statistically significant. The complete remission rate for 1, 2, 3, 4 and 5 years of follow-up and negative results’ rate were compared between both groups. Impact of age, sex, duration of symptoms and severity of symptoms (Osserman classification) [17], and the histological type of the thymus (hyperplasia, involution and normal) and the presence of ectopic foci of the thymic tissue were examined.

The study was approved by the Scientific Committee of our institution.

3. Results

Patients’ characteristics are shown in Table 1. No differences were found according to the: mean age 30.4 years (range: 14—67 years) in group A, 30.4 years (range: 15—70 years) in group B and 29.7 (15—75 years) in group C \( (p = 0.30) \), sex rate: 51 women and nine men in group A, 61 women and 14 men in group B and 249 women and 43 men in group C \( (p = 0.98) \), median duration of symptoms before an operation 23.5 months (4—108 months) in group A, 34.9 months (1—192 months) in group B and 28.29 months (2—204 months) in group C \( (p = 0.81) \). The rate of patients taking steroids/immunosuppressive drugs before an operation was 33.3\% (20/60) in group A, 20\% (15/75) in group B and 24.6\% (72/292) in group C. There was no significant difference between the groups with regard to this factor.

The mean operative time was 90.1 min (35—165 min) in group A, 175.86 min (115—255 min) in group B and 179.4 min (95—335 min) in group C. \( (p = 0.005) \). There was a significant difference between groups A and B \( (p < 0.0001) \) and between A and C \( (p < 0.0001) \) and no significant difference between groups B and C \( (p = 0.78) \).

There was no postoperative mortality and there were only few serious complications with no difference between groups. All postoperative complications are listed in Table 2.

Pathological studies revealed ectopic thymic tissue in all areas of dissected fatty tissue of the neck and the mediastinum.

During the 5-year follow-up period, five patients died; causes of deaths are listed in Table 3.

Seven of 426 (1.6\%) patients were lost to follow-up; all other patients responded to the questionnaires. The results of follow-up regarding complete remission rates are shown in Fig. 1 after 1, 2, 3, 4 and 5 years of follow-up.

After 1, 2, 3, 4 and 5 years of follow-up, complete remission rates were 8.3\% (confidence interval — CI 1.3—15.1\%), 11.7\% (CI 3.5—19.5\%), 15.0\% (CI 5.9—23.7\%), 16.7\% (CI 7.1—25.7\%) and 20.0\% (CI 9.7—29.7\%), respectively, in the group A; 26.7\% (CI 16.2—35.8\%), 38.7\% (CI 26.8—48.5\%), 42.7\% (CI 30.6—52.6\%), 46.7\% (CI 34.3—56.6) and 50.7\% (CI

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n = 60)</th>
<th>Group B (n = 75)</th>
<th>Group C (n = 292)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51</td>
<td>61</td>
<td>249</td>
<td>0.98</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>14</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>30.4 (14—67)</td>
<td>30.4 (15—70)</td>
<td>29.7 (15—75)</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean duration of symptoms of MG (months)</td>
<td>23.5</td>
<td>34.9</td>
<td>28.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Steroids/immunosuppressive drugs use before operation</td>
<td>20/60 (33.3%)</td>
<td>15/75 (20%)</td>
<td>72/292 (24.6%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Group A: basic thymectomy; group B: extended thymectomy; group C: transcervical-subxiphoid-videothoracoscopic maximal thymectomy.

Table 2

Postoperative complications in the groups A, B and C.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group A (n = 60)</th>
<th>Group B (n = 75)</th>
<th>Group C (n = 292)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory insufficiency (ventilator)</td>
<td>2 (3.3%)</td>
<td>3 (4%)</td>
<td>12 (4.1%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Postoperative bleeding (reoperation)</td>
<td>0</td>
<td>0</td>
<td>5 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Mediastinal haematoma (conservative treatment)</td>
<td>2 (3.3%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>0</td>
<td>1 (1.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>0</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>0</td>
<td>0</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0</td>
<td>0</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>0</td>
<td>0</td>
<td>2 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>1 (1.7%)</td>
<td>2 (2.7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Temporary phrenic nerve palsy</td>
<td>0</td>
<td>1 (1.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Temporary laryngeal recurrent nerve palsy</td>
<td>0</td>
<td>2 (2.7%)</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Permanent nerve palsy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>5 (8.3%)</td>
<td>9 (12%)</td>
<td>23 (7.9%)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Group A: basic thymectomy; group B: extended thymectomy; group C: transcervical-subxiphoid-videothoracoscopic maximal thymectomy.
38.2–60.6%), respectively, in group B; and 31.5% (CI 25.1–37.5%), 39% (CI 32.2–45.3%), 45.8% (CI 38.6–52.6%), 46.3% (CI 38.4–53.7%) and 53.1% (CI 44.1–61.3%), respectively, in group C.

The differences in complete remission rate between both groups were statistically significant in favour of groups B and C in comparison to group A (Figs. 3 and 4).

After 1, 2, 3, 4 and 5 years of follow-up, negative results rates were 5%, 20%, 26.7%, 26.7% and 26.7%, respectively, in group A; 5.3%, 47%, 4%, 4% and 4%, respectively, in group B and 11.7%, 8.9%, 3.1%, 3.1% and 5.7%, respectively, in group C.

Pathologic examination of the specimen revealed ectopic foci of the thymic tissue with Hassall’s corpuscles and the foci were highly probable for the presence of the thymic tissue, but without Hassall’s corpuscles in 53.3% patients from group B and in 65.9% of patients from group C ($p = 0.06$).

4. Comment

There are several controversies regarding the role of thymectomy in the treatment of MG. The most important question is if the extent of the thymectomy can affect the results of the treatment of MG. The general principle is that thymectomy should provide removal of the whole thymus gland; this gland was shown to generate an autoimmune process leading to the occurrence of myasthenic symptoms. The next question is if this is necessary to remove only the main thymus gland or if the fatty tissue containing the ectopic foci of the thymic tissue should be removed as well.

Our current study was an attempt to find an answer for these important questions.

Most studies analysing the results of thymectomy were retrospective and based on small groups of patients, who were operated on over relatively long periods of time, which was an important shortcoming of these studies. In fact, there was no prospective randomised trial comparing results of basic versus extended thymectomies conducted by one surgical team on a uniform group of patients during a relatively short period of time (to exclude any variabilities of management of different surgical teams and changes of management of MG that might occur if the study was conducted over a long period of time). The patients in our study were not randomised to any group; however, the patients were comparable in terms of age, sex ratio, duration of MG before an operation, severity of symptoms and steroids use, with no significant differences in regard to any of these factors between the three groups. The neurologists referring the patients for the operation and the surgeons performing the operation were the same during the years 1996–2008. The period of time when all operations were done is relatively short and no considerable changes in the treatment of MG occurred during that time.

We compared three different techniques of thymectomies, with basic thymectomy comprising removal of the thymus gland, without the surrounding fatty tissue with two very radical techniques – the transternal extended thymectomy and the transcervical-subxiphoid-VATS maximal thymectomy. All three techniques enabled complete removal of the whole thymus gland. The difference of extensiveness between the last two procedures regarded only more radical
dissection of the neck in case of the transcervical-subxiphoid-VATS maximal thymectomy. The transcervical-subxiphoid-VATS maximal thymectomy is the technique developed in our institution to achieve two aims, namely to avoid sternotomy and to enable the maximal completeness, similar to the technique described by Jaretzki et al. [13,16] We are very critical towards unilateral or even bilateral videothoracoscopic approach, including thymectomy performed with the use of robots, which do not enable complete removal of the upper poles of the thymus as was shown by Shigemura et al. [21] Similarly, we are critical of transcervical thymectomy which does not enable complete removal of the left and right epiphrenic fat pads containing ectopic thymic foci in 24.1% and 22.4%, respectively, as we demonstrated previously. Besides, de Perrot et al. reported that 19% of the patients operated upon with use of this approach had to be converted to the upper median sternotomy [22].

In our opinion, any really complete technique of thymectomy for MG must include good access to the area of the neck with visualisation of the thyroid gland, parathyroids and both laryngeal recurrent nerves [15]. We stress that the upper poles of the thymus end just at the level of the thyroid and the specimen should be cut at this level. Any technique of thymectomy that does not enable good visualisation of the thyroid is not sufficiently complete and leaves parts of the upper thymic poles in the neck. Any reliable technique of thymectomy must also provide an access to the aorta—pulmonary window, which was shown to contain ectopic thymic foci in 25.9%, as well as both pericardiophrenic fat pads [15]. The area we also dissect is the area we call 'the aorta—caval groove', which is an equivalent of the right paratracheal space. Dissection of this area, which was shown to contain ectopic thymic foci in 17.2% of specimens, has not been described before by other authors [15].

There were no differences in postoperative morbidity in the three groups despite the operative time being significantly shorter in the basic transcervical thymectomy group than in the extended thymectomy group and the transcervical-subxiphoid-VATS maximal thymectomy group (with no significant difference between the last two groups). We have shown a statistically significant difference in complete remission rates and the negative results’ rates between the basic and the extended thymectomy and the transcervical-subxiphoid-VATS maximal thymectomy groups after 1—5 years of follow-up, with no significant differences between the last two groups. The only explanation for such a difference in results is the technique of thymectomy, with the removal of ectopic foci of the thymic tissue in the extended thymectomy and the transcervical-subxiphoid-VATS maximal thymectomy groups.

Pathologic studies revealed proven ectopic foci of thymic tissue (containing Hassall’s corpuscles) or highly probable ectopic foci of thymic tissue (resembling thymic tissue, but without Hassall’s corpuscles) in 53.3% of specimens after the extended thymectomy and in 65.9% of specimens after the transcervical-subxiphoid-VATS maximal thymectomy group. The difference between both groups is close to significance (p = 0.06) that might indicate that the transcervical-subxiphoid-VATS maximal thymectomy is more complete than extended transsternal thymectomy. An incidence of ectopic foci of thymic tissue in the adipose tissue of the neck and the mediastinum reported by Jaretzki et al. was 98.0%, by Masaoka et al. 72.2%, by Ponseti et al. 42.2% and by Ashour 39.5% [16,23—25].

This finding supports the necessity of the extensive removal of the adipose tissue of the mediastinum and the neck because the complete remission rate of MG may be achieved even if the ectopic foci are present.

5. Conclusions

1 The results of complete remission rates after 5-year follow-up were statistically better in patients with MG, who were operated on with extended transternal thymectomy and transcervical-subxiphoid-videothoracoscopic 'maximal' thymectomy in comparison to the patients who underwent basic transternal thymectomy.

2 The difference can be explained by the removal of ectopic foci of the thymic tissue from the neck and the mediastinum in these patients.

References


