Ectopic thymic tissue in the mediastinum: limitations for the operative treatment of myasthenia gravis†

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Abstract

OBJECTIVES: The aim of the study was to investigate the distribution of ectopic thymic tissue in the mediastinum and to evaluate the possible relevance of this distribution to the therapeutic yield of thymectomies in patients with myasthenia gravis.

METHODS: In this prospective autopsy study, mediastinal dissections were performed on 50 cadavers without any previously known intrathoracic pathology. The initial dissection was performed in the same way as during the maximal thymectomy. The second stage consisted of dissecting areas of fatty tissue located out of reach of the standard maximal thymectomy, such as the perithyroid, periaortic, peritracheal and retrotracheal areas, as well as the areas adjacent to the right and left phrenic and recurrent laryngeal nerves. Each specimen was independently examined by two pathologists for ectopic thymic tissue.

RESULTS: There were 41 (82%) male and 9 (18%) female cadavers, with a mean age of 44.3 years (range: 15–75). Ectopic thymic tissue was detected in 32 out of 50 cadavers (64%). In 10 (20%) cadavers thymic foci were found in locations accessible to the standard surgical intervention and in 22 (44%)—in inaccessible locations. Thymic tissue incidence in individual locations was as follows: retrothyroid, 3 (6%); peritracheal, 5 (10%); retrotracheal, 1 (2%); right phrenic nerve, 2 (4%); left phrenic nerve, 14 (28%); right recurrent laryngeal nerve, 2 (4%); left recurrent laryngeal nerve, 2 (4%) and periaortic, 0.

CONCLUSIONS: The incidence of ectopic thymic tissue in the mediastinum is common. Although some improvements in the results of thymectomies may be expected with more extensive dissection, the frequent presence of thymic foci in anatomical locations hardly accessible to surgical intervention may be the true limitation for surgical treatment of myasthenia.

Keywords: Myasthenia • Mediastinum • Anatomy • Thymus • Ectopia • Autopsy

INTRODUCTION

The relevance of the ectopic thymic tissue to the surgical treatment of myasthenia gravis is well recognized, although opinions of different authors in this regard are inconsistent. Since the original paper of Masaoka [1], several anatomical studies were published and a substantial body of evidence has since been gathered regarding the incidence and distribution of this type of tissue [2–4]. Several surgical techniques aimed at removing ectopic thymic foci were developed as a consequence of these studies.

The direct comparison of various surgical techniques, such as the extended and maximal thymectomies and the simple thymectomy, is rather difficult due to the lack of randomized studies, various definitions of response and different time of follow-up. Generally, the best results were reported by authors using more extensive dissection of mediastinal tissue [5–7] with some non-randomized controlled studies showing more favourable results after extended thymectomies [7–9].

However, the results of even the most extensive operative techniques (extended and maximal thymectomy) are suboptimal in 40–50% of patients. It should be stressed that even these techniques do not include removal of all the mediastinal fatty tissue. For technical reasons, some fatty tissue is left around and behind the trachea, around the descending aorta and close to the phrenic and recurrent nerves. We designed this study to elucidate whether the anatomical distribution of ectopic thymic tissue in the mediastinum enables improvement of the efficiency of operative treatment of myasthenia gravis.
MATERIALS AND METHODS

Clinical questions

What is the distribution of the ectopic thymic tissue in particular areas of the mediastinum?
Is it possible to extend the range of dissection of the ectopic thymic tissue during thymectomy?

Setting

Prospective autopsy study.

Location

Department of Anatomy, Jagiellonian University, Cracow, Poland.
Department of Pathology, Jagiellonian University, Cracow, Poland.
Department of Thoracic Surgery, Jagiellonian University, John Paul II Hospital, Cracow, Poland.
Department of Pathology, Sokolowski Pulmonary Hospital, Zakopane, Poland.

Materials

Fifty adult cadavers without any known intrathoracic pathology.

Intervention

The design of the study was accepted by the Bioethical Committee of the Jagiellonian University. The dissection of the mediastinum was performed prior to the routine autopsy, after removal of the sternum and rib cartilages, and included two stages. The initial dissection was performed using the technique of maximal thymectomy. The thymus gland was removed together with the perithymic tissue, the innominate veins were dissected free and both pleural cavities were widely opened. The lateral borders of dissection were set at 1 cm from both phrenic nerves. Both recurrent nerves were identified and the fatty tissue of the lower neck removed, keeping the border of dissection at 1 cm from these nerves. The upper border of dissection was the lower part of the thyroid gland. The fatty tissue located between the superior vena cava, ascending aorta and trachea (aorto-caval groove) and in the aorto-pulmonary window, was excised. Finally, both pericardio-diaphragmatic fat pads were removed (Fig. 1).

The second stage of the dissection included the removal of the fatty tissue from regions of the mediastinum hardly accessible to dissection during thymectomy or unresectable for technical reasons. Both phrenic nerves were excised together with the pericardio-diaphragmatic vessels and surrounding fatty tissue. Then, both recurrent nerves were excised together with the adjacent fatty tissue (Fig. 2). Further dissection was carried out on the side table after removal of the block of organs including lungs, trachea, larynx, heart, aorta, pharynx and oesophagus. The fatty tissue located behind the thyroid gland, around and behind the trachea as well as around the descending aorta was dissected (Figs 3 and 4).

Figure 1: The areas of mediastinum dissected during maximal thymectomy (1: thymus and perithymic tissue; 2: aorto-pulmonary window; 3: aorto-caval groove; 4: right pericardiacophrenic angle; 5: left pericardiacophrenic angle).

Figure 2: The areas of mediastinum not accessible for the standard thymectomy—front view (tissue surrounding the nerves-1: right phrenic; 2: left phrenic; 3: right laryngeal recurrent; 4: left laryngeal recurrent).

Tissue dissected from each anatomical location was placed in a separate container in a buffered 10% formalin and labelled. From every tissue fragment specimens for microscopic examination were taken. The standard tissue work-up using a tissue processor was used. Tissue blocks were then sliced and stained using haematoxylin and eosin. Final specimens were independently examined by two pathologists using standard light
microscope. The criterion of diagnosis of ectopic thymic tissue was the finding of the Hassals corpuscles.

**Variables analysed**

The incidence of ectopic thymic foci in each anatomical location.

**RESULTS**

Fifty adult cadavers without known intrathoracic pathology were examined. There were 41 (82%) male and 9 (18%) female cadavers, the mean age was 44.3 years (range, 15–75). The mean number of specimens for pathological examination per each site was 3.7. Ectopic thymic tissue in mediastinum was detected in 32 cadavers (64%). In 10 (20%) cadavers thymic foci were found in locations accessible to the standard surgical intervention and in 22 (44%)—in inaccessible locations. One focus of ectopic thymic tissue was found in 17 (34%) cadavers, two foci in 10 (20%), three in 4 (8%) and four in 1 (2%) cadaver (Table 1).

The incidence of the thymic tissue in the individual locations is presented in Table 2. Total number of the ectopic foci found in 32 cadavers was 53. Twelve of them were found in the neck and 41 in the mediastinum.
DISCUSSION

In this study, the ectopic thymic tissue was found in 32 cadavers (64%). In 10 (20%) cadavers location of ectopic thymic tissue was accessible for the standard surgery, and in 22 (44%) of them was not accessible for standard surgery. The latter were frequently located along phrenic nerves, especially on the left side. In this area, ectopic thymic tissue was found in 32%. On the neck, in close contact with recurrent laryngeal nerves, ectopic thymic tissue was found in 8% of cadavers.

It should be stressed that not all removed fatty tissue was pathologically examined—the average number of specimens taken randomly per each site was 3.7. Examining of every mm³ of tissue would require enormous work and expense. It must therefore be assumed that the true incidence of ectopic thymic tissue is higher; this reservation also concerns all studies published previously.

Even after the most extensive thymectomy, the rate of complete remission in long-term follow-up was only 62% [6]. It is unlikely that any operative technique will achieve a rate of complete remission close to 100%. This is probably due to the unpredictable distribution of ectopic thymic tissue in every compartment of the mediastinum, on the neck and occasionally in such locations as the base of the skull [10], pericardial cavity [11], lung parenchyma [12] and the pleural cavity [13]. However, highlighting areas of high thymic foci incidence, amenable to surgical intervention, might contribute to the improvement in the completeness of resection and, in consequence, the long-term outcome of thymectomies in patients with myasthenia gravis.

The most critical finding of this study is the high incidence of ectopic thymic tissue in locations that limit surgical intervention because of a risk of serious complications (nerve palsy) or lack of access to the tissue. The total incidence of ectopic thymic tissue in this study is consistent with the results published by Zielinski et al. [4] in myasthenia patients. Lower incidence was reported by Ashour et al. [14] and Ponseti [15] (39.5 and 42.2%, respectively), but in both these studies the perithymic fat was not included (Table 3).

Ectopic thymic tissue were present within aorto-caval groove in 2% and within aorto-pulmonary window in 10%. This is consistent with Ponseti [14], while Zielinski et al. [4, 7] found more thymic foci in both these areas (Table 3). These differences may be attributable to different distribution of ectopic thymic tissue in myasthenia patients and non-myasthenia individuals.

The ectopic thymic foci left in the mediastinum may account for the 40-50% of the suboptimal results after extended or maximal thymectomies [5, 6]. We may theoretically consider extending the range of resection to include the fatty tissue located along the left phrenic nerve, though any such extension would potentially also entail an increase of the risk of nerve damage. Further research and randomized trials may provide insight into the potential risks and benefits of more extensive resection and its impact on the rate of remission. Due to the relatively low incidence of ectopic thymic tissue adjacent to the right phrenic and both recurrent nerves (4% each in our study), it does not seem justified to attempt more radical removal of fatty tissue in these locations, as palsy of these nerves would cause serious morbidity. Peritracheal and retrotracheal fatty tissue, containing thymic foci in 16% of cadavers, is difficult to approach using the median sternotomy. The transpericardial approach, enabling dissection of the lower trachea and the subcarinal region, also seems to be exceedingly invasive. This region is, however, accessible for VATS dissection, as shown in studies concerning VATS lymph node dissection for lung cancer.

The maximal thymectomy performed in patients with identical distribution of the ectopic thymic tissue as found in our study, would remove all thymic tissue in 56% of them. This figure

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Table 2: Incidence of ectopic thymic foci in particular locations

<table>
<thead>
<tr>
<th>Location</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accessible for the standard surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perithymic fat</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Aorto-caval groove</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Aorto-pulmonary window</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Right pericardiacophrenic angle</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Left pericardiacophrenic angle</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inaccessible for the standard surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrothyroid</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Peritracheal</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Right phrenic nerve</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Left phrenic nerve</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Right recurrent laryngeal nerve</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Left recurrent laryngeal nerve</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Retrhostracheal</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Periaortic</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: Incidence of ectopic thymic tissue in thymectomy specimens

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Number of patients</td>
<td>38</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td>Ectopic thymic tissue</td>
<td>15⁶</td>
<td>39.5⁶</td>
<td>71</td>
</tr>
<tr>
<td>Perithymic fat</td>
<td>1</td>
<td>2.6%</td>
<td>33</td>
</tr>
<tr>
<td>Aorto-pulmonary window</td>
<td>1</td>
<td>2.6%</td>
<td>33</td>
</tr>
<tr>
<td>Aorto-caval groove</td>
<td>2</td>
<td>5.3%</td>
<td>7</td>
</tr>
<tr>
<td>Left pericardiacophrenic angle</td>
<td>2</td>
<td>5.3%</td>
<td>7</td>
</tr>
<tr>
<td>Right pericardiacophrenic angle</td>
<td>2</td>
<td>5.3%</td>
<td>7</td>
</tr>
<tr>
<td>Neck</td>
<td>12</td>
<td>31.6%</td>
<td>10</td>
</tr>
<tr>
<td>Laternal to the left phrenic nerve</td>
<td>3</td>
<td>3.6</td>
<td>11</td>
</tr>
<tr>
<td>Laterral to the right phrenic nerve</td>
<td>3</td>
<td>3.6</td>
<td>11</td>
</tr>
</tbody>
</table>

1<sup>*</sup>Calculated for the whole cohort.
2<sup>⁶</sup>No data regarding perithymic fat.
3<sup>⁷</sup>Pericardial fat up to diaphragm.
4<sup>⁸</sup>No data regarding pericalicophrenic angles.
corresponds well with the rate of complete remissions reported in the clinical series of maximal thymectomy. Additional removal of the fatty tissue located along phrenic nerves would increase the rate of complete resections to 88%—the question remains open, whether this would justify the potential increase of risk of the nerve palsy.

CONCLUSIONS

(1) The incidence of ectopic thymic tissue in some compartments of the mediastinum is higher than previously expected.
(2) There may be significant differences in distribution of the ectopic thymic tissue in patients with myasthenia gravis and non-myasthenic individuals.
(3) While a more aggressive approach to the dissection of the left phrenic nerve might be expected to improve the results of thymectomy, the frequent presence of thymic foci outside the reach of standard surgical intervention is an important limitation for the surgical treatment of myasthenia gravis.

Funding

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Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr A. Duranceau (Montreal, QC, Canada): This is a very interesting paper and I have two questions. Firstly, I did not see the definition of ectopic thymic tissue in your abstract, and, secondly, do you have any recommendation to give in regard to minimally invasive thymectomy or extra-radical thymectomy? What are your observations about these approaches? Dr Klimek-Piotrowska: Ectopic thymic foci means the finding of Hassall bodies during pathological examination. Regarding your second question, I am not a thoracic surgeon, I am an anatomist. I am not sure that I am a competent person to answer your clinical question. Maybe I can ask my colleague who is a thoracic surgeon and works together with me.

Dr J. KuzdHAL (Krakow, Poland): Generally, the aim of the study was to show whether we could expand the completeness of mediastinal dissection for myasthenia, after performance of maximal thymectomy. The access we use—sternotomy, bilateral VATS, subxiphoid, neck incision—doesn’t matter, but what is important is the extent of removal of the fatty tissue of the mediastinum. So on the cadavers we performed a so-called maximal thymectomy according to the rules of Jaretzki, and then after completion of this procedure, which should correspond with maximal thymectomy, we also removed the extra fatty tissue, which is in fact inaccessible or difficult to access during surgery. The study was purely anatomical, so we didn’t consider the technique of performance of thymectomy.