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Transsternal Maximal Thymectomy is Effective for Extirpation of Cervical Ectopic Thymic Tissue in the Treatment of Myasthenia Gravis

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Purpose: Extensive extirpation of cervico-mediastinal adipose tissue increases the chance of removing ectopic thymic tissues, thus potentially improving the prognosis of myasthenia gravis after thymectomy. We sought to increase efficacy and safety of transsternal maximal thymectomy (TSMT). **Materials and Methods:** Twenty four patients who underwent TSMT from July 2006 to June 2007 were retrospectively reviewed and compared with 73 patients who underwent transsternal extended thymectomy (TSET) from January 2004 to May 2006. Ectopic thymic tissue in additionally excised cervicomediastinal fat tissue was examined histologically. **Results:** In TSMT group, operation time, amount of cumulative drainage and duration of drainage were significantly higher than TSET group. However, the difference in hemoglobin count, amount of transfusion, duration of intensive care, postoperative hospital stay, and complication rates were not statistically different. There was no operative mortality in either group. Ectopic thymic tissue was found in 50% of patients. All patients had ectopic thymic tissues in the cervical area. Two patients had additional ectopic tissue in the aortopulmonary window, and 1 patient had ectopic tissue at posterior of the left bracheocephalic vein and lateral of the right phrenic nerve. **Conclusion:** TSMT is more effective in the extirpation of ectopic thymic tissues than TSET without significant impairment of safety, especially in the cervical area.

Key Words: Thymectomy, myasthenia gravis

INTRODUCTION

Thymectomy is an important and reliable treatment modality for myasthenia gravis (MG).[1,2] However, the route of approach and extent of thymectomy vary.[3-7] Theoretically, a more extended resection of cervico-mediastinal adipose tissue increases the chances of ectopic thymic tissue removal, thus increasing the chance of remission from myasthenic symptoms.[7-9] A maximal thymectomy is the most extensive method for extirpation of cervical and mediastinal adipose tissue with ectopic thymic tissue.[3,8] Although Jaretzki and colleagues reported excellent long term prognosis with this technique, maximal thymectomy is still reported to be undertaken in a minority of cases of thymectomy in the literature. Since June 2006, the authors performed transsternal maximal thymectomy (TSMT) and considered it the procedure of choice for the treatment of MG, expecting improved neurologic outcomes over those of transsternal extended thymectomy (TSET). TSMT is a modification of transcervical transsternal maximal thymectomy, and cervical extirpation is performed beneath the retracted cervical skin and strap muscles without a separate cervical incision.[10] We intended to evaluate the efficacy and feasibility of TSMT for the removal of ectopic thymic tissue through a histologic evaluation of ectopic thymic tissue in the cervico-mediastinal adipose tissue.

MATERIALS AND METHODS

Twenty-four patients with MG who underwent TSMT from July 2006 to June 2007 were retrospectively compared with 73 patients who underwent

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TSET from January 2004 to June 2006. MG was diagnosed using the anticholinesterase test and electromyography. All patients were managed by 2 attending neurologists. All thymectomies were conducted through a median sternotomy. Borders of the TSET were the same as previously reported.[5] In the case of TSMT, additional dissection of adipose tissues was performed at the aortopulmonary window, at lateral of both phrenic nerves from phrenic nerve to both pleural reflections, in the cervical area between both recurrent laryngeal nerves from the lower border of thyroid to the upper border of the right brachiocephalic artery, and posterior to the left brachiocephalic vein.[10] Each specimens from additionally dissected area were named as cervical, aortopulmonary window, lateral of phrenic nerve, and posterior brachiocephalic vein for evaluation of ectopic thymic tissue distribution. Two chest tubes were inserted through subxiphoid stab incisions, and no separate drain was inserted at the cervical area. Demographic and clinico-pathologic data such as age, gender, body surface area (BSA), Myasthenia Gravis Foundation of America (MGFA) preoperative clinical classification, acetylcholine receptor binding antibody titer, thymic pathology, presence of ectopic thymic tissue, operation time, duration of intensive care, amount of cumulative drainage, duration of drainage, decrease of hemoglobin count, amount of transfusion required, postoperative hospital stay, and complications were obtained by a retrospective review of medical records. In 14 non-thymomatous MG patients in the TSMT group, the presence of ectopic thymic tissue outside the extended thymectomy field was evaluated microscopically with hematoxylin-eosin staining. All specimens were embedded in paraffin block after fixed in 10% formalin solution for 3 days, and each 50 micrometer-thick tissue section at 450 micrometer interval was stained for evaluation. This study was approved by the local institutional review board.

Categorical variables were compared by the χ^2 or Fisher's exact tests. Unpaired t-test was used for the comparison of continuous variables. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed with Statistical Package for Social Science (SPSS 12.0, Chicago, IL, USA).

RESULTS

Out of 24 patients who underwent TSMT, 18 (75%) were female and their mean age was 36.0 years. There was no statistical difference in age, gender distribution, BSA, acetylcholine receptor binding antibody titer, or preoperative MGFA clinical classification between TSMT and TSET groups. The proportion of patients with thymomatous MG was higher in the TSMT group (p = 0.046), but the incidence of follicular hyperplasia and atrophy were not significantly different (Table 1).

Surgical outcomes

The operative time, duration of chest tube drainage, and amount of cumulative drainage were increased in the TSMT group. However, the range of hemoglobin count decrease, duration of intensive care, and post-operative hospital stay were not different between the 2 groups (Table 2). In the TSET group, 1 case of chylothorax and 1 case of postoperative bleeding requiring reoperation developed. In the TSMT group, 1 patient experienced left vocal cord palsy due to an injury to the cervical recurrent laryngeal nerve. There was no injury to the recurrent laryngeal nerve at the aortopulmonary window and phrenic nerves. No operation-related mortality occurred in either group.

Ectopic thymic tissue

Of 14 patients evaluated for the presence of ectopic thymic tissue, 7 (50%) had ectopic thymic tissues outside the TSET fields. All of these 7 patients had ectopic thymic tissues in the cervical area (Fig. 1). Ectopic thymic tissues were widely distributed in cervical area. The proportions of ectopic thymic tissue positive sections to adipose tissue section examined are shown in Table 3. Two patients had additional ectopic thymic tissue at the aortopulmonary window, and proportions of positive section to tissue section examined in these patients were 2/7 and 3/4, respectively. One patient had ectopic thymic tissue at posterior of the left brachiocephalic vein (2/5) and lateral of the right phrenic nerve (3/7).

Table 1. Demographic, Clinical and Pathologic Characteristics of the Patients

Characteristics	TSMT (n = 24)		TSET (n = 73)	
	n	%	n	%
Gender				
Male	6	25	21	8.8
Female	18	75	52	71.2
Age (yrs)	35.9 ± 13.1		35.2 ± 12.3	
BSA (m^2)	1.63 ± 0.13		1.65 ± 0.16	
Seropositive MG	24	100	58	93.5*
AchR Ab (nmol/L)	9.158 ± 4.946		8.187 ± 5.363	
MGFA clinical classification				
I	3	12.5	12	16.4
II	16	66.7	49	67.1
III	4	16.7	10	13.6
IV	1	4.2	2	2.8
V	0	0	0	0
Thymic pathology				
Normal	4	16.7	8	11.0
Follicular hyperplasia	14	58.3	54	73.9
Atrophy	6	25	11	15.1
Thymoma	9	37.5	13	17.8
Masaoka stage I	8	33.3	6	8.2
II	1	4.2	7	9.6

TSMT, transsternal maximal thymectomy; TSET, transsternal extended thymectomy, BSA, body surface area; AchR Ab, acetylcholine receptor binding antibody; MGFA, Myasthenia Gravis Foundation of America.
Plus-minus values are mean ± SD.
*The percentage of this category is calculated by dividing the number of seropositive patients (58) into number of patients (62) with available data.

DISCUSSION

This study revealed that TSMT is more effective in the extirpation of ectopic thymic tissues than TSET especially in the cervical area without significant increase of morbidity and mortality. Maximal thymectomy is considered to be an ideal thymectomy.[4,8] However, there are few reports about this procedure. Many surgeons are not willing to perform maximal thymectomy, because of the belief that the procedure carries a higher rate of morbidity without definitive evidence of promising long-term neurologic outcomes compared with extended thymectomy.[6,11,12] TSET had been used to be the procedure of choice at our clinic, because it is easy, safe and effective.[11,12] Complete stable remission (symptom free without medical treatment for more than 1 year) rates of non-thymomatous MG were 29.6% at 5 years and 45.2% at 10 years.[5] Since June 2006, however, we have performed TSMT to increase the rate of ectopic thymic tissue removal by extending the thymectomy field. TSMT was first introduced as an anterior-superior cervicomediastinal exenteration

Table 2. Comparison of Surgical Outcomes

Variables	TSMT	TSET	*p* value
Operation time (min)	137 ± 27	108 ± 23	0.00
Cumulative Drainage (mL)	1,123 ± 691	714 ± 493	0.002
Duration of Drainage (day)	5.1 ± 1.7	4.2 ± 1.7	0.03
Hemoglobin decrease (g/dL)	2.35 ± 1.18	2.31 ± 1.66	0.93
Transfused packed RBC (unit)	0.12 ± 0.57	0.17 ± 0.47	0.41
Duration of intensive care (day)*	2 (1 - 28)	3 (1 - 13)	0.61
Duration of hospital stay (day)*	9 (5 - 90)	10 (5 - 300)	0.81

TSMT, transsternal maximal thymectomy; TSET, transsternal extended thymectomy; RBC, red blood cell.
Plus-minus values are mean ± SD.
*median (range).

Table 3. Proportion of the Number of Ectopic Thymic Tissue Positive Section to the Number of Total Cervical Adipose Tissue Section

Patient No.	Total (n)	Positive (n)	Proportion (%)
1	10	1	10
2	8	1	13
3	8	4	50
4	10	6	60
5	13	13	100
6	8	8	100
7	6	6	100
Total	63	39	62

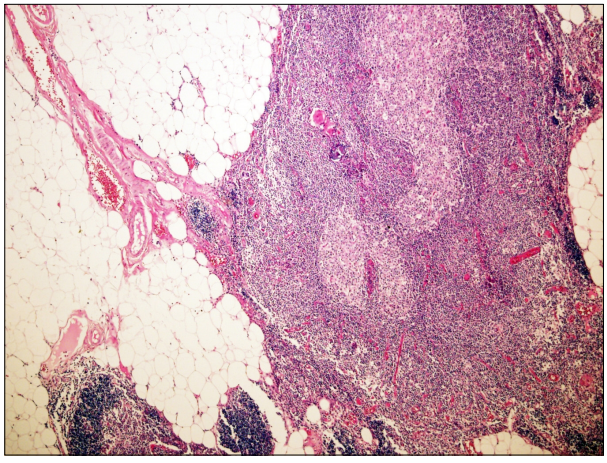

Fig. 1. Low power view of the ectopic thymus in cervical adipose tissue showing germinal centers in the medulla (hematoxylin-eosin, × 40).

by Chen and colleagues.[10] Difference between this technique and transcervical trans-sternal maximal thymectomy is that cervical dissection is performed under the cervical flap after a full-length midsternotomy without transverse cervical incision. By this method, almost all cervico-mediastinal adipose tissues can be extirpated. Two main concerns about maximal thymectomy are surgical safety and clinical efficacy. In terms of safety, surgical outcomes of this study indicate that TSMT does not have a higher rate of morbidity and mortality than extended thymectomy. Although TSMT increased operation time, cumulative drainage, and days of chest tube maintenance, the overall recovery and complication rates were not significantly different from TSET. Increased cumu-

lative drainage and prolonged chest tube maintenance in TSMT might be due to more extended field of dissection than TSET. Different proportion of thymoma patients between 2 groups might not be influenced by the amount and duration of drainage and chest tube. Because all thymomas were in Masaoka stage I or II and thymoma itself did not complicate the procedure. No operation-related mortality occurred in either group. The most dreaded complication of maximal thymectomy is functional impairment due to nerve injury. One episode of recurrent laryngeal nerve injury developed in a second patient in this series. No more recurrent nerve injury occurred thereafter. Recurrent laryngeal nerve injury at the cervical area in that patient might be a technical failure due to unfamiliar approach method. However, this could be overcome in a short time because cervical dissection and preservation of recurrent laryngeal nerves through cervical incision are familiar procedures through the experience about surgical treatment of esophageal disease, tracheal disease, and other cervical diseases. There was no injury to the phrenic nerves or recurrent laryngeal nerve at the aortopulmonary window. Dissection of the phrenic nerve and left recurrent laryngeal nerve at the aortopulmonary window is also a familiar procedure for thoracic surgeons who perform systematic lymph node dissections in lung cancer surgery, and can safely be done. A few studies of maximal thymectomy also reported no thymectomy-related mortality and low complication rates. Jaretzki and colleagues reported no mortality and a 4.5% complication rate in 157 patients after maximal thymectomy. Almost all their complications were wound-related, and only 1 case of chylothorax was attributed specifically to maximal thymectomy.[13] Ashour and colleagues also reported two cases of re-exploration due to postoperative bleeding, 6 cases of pulmonary complications, and 2 cases of septicemia in 48 patient without any mortality.[14] In the following report, however, they experienced no complications in 30 pediatric patients.[15] Both authors reported no recurrent laryngeal or phrenic nerve injury. Zielińsky and colleagues reported only 1 case of temporary recurrent laryngeal nerve injury in 100 patients who underwent maximal cervical dissection.[4] Although the incidence and distribution of ectopic thymic tissues varies, the presence of ectopic thymic tissue is evident.[4,16,17] Theoretically, a more radical resection of ectopic thymic tissue results in a larger decrease in the antigenic focus for autoimmune disease, therefore maximal thymectomy is regarded as the most effective method of thymectomy.[4,8] Some studies have provided more promising results.[8,15] However, comparison of the prognostic value of various methods of thymectomy is difficult at present, because almost all these studies were conducted in a retrospective setting and used subjective parameters for end points with inappropriate statistical analysis methods.[2,8] Furthermore, no prospective randomized studies have been reported. The efficacy of ectopic thymic tissue removal appeared to be a useful indirect indicator for the long-term neurologic efficacy of TSMT in a short time. Ectopic thymic tissues embedded in the aortopulmonary window, lateral to the phrenic nerves, and posterior to the left brachiocephalic vein could additionally be removed in 21% of patients by TSMT. The most significant finding of this study is that extirpation of cervical adipose tissues through TSMT is essential, because 50% of patients have a chance of having residual thymic tissue in the cervical area after TSET. Moreover, the burden of residual thymic tissue in cervical area is also considerable. The reported prevalence of ectopic thymic tissue in the cervical area is 10 to 63%.[3,4,17] The importance of extirpation of cervical adipose tissues can also be recognized through experiences with transcervical thymectomy. Comparable clinical outcomes with transcervical thymectomy indicate that the burden of ectopic tissue in the cervical area is not insignificant, compared with the lower mediastinal area.[6,18,19] Thus, extirpation of cervical adipose tissue must be considered as a routine aspect of thymectomy, since it is in lower mediastinum and the TSMT is one of ideal approachs for thymectomy.

Recently, interest in minimally invasive thymectomy has increased.[4,7,20] From our results, we can recommend that, in minimally invasive thymectomy, a bilateral approach to dissection of the lateral area of each phrenic nerve and the aortopulmonary window with separate cervical dissection is an ideal method for radical removal of thymic tissues.

A limitation of this study is a small number of study subjects and short study time, which suggest the need for a large-volume study and estimation of neurologic outcomes. At present, it is impossible to predict how many patients will get more clinical benefit by TSMT. Furthermore, no extra ectopic tissue was found in 50% of patients with TSMT in this study. Therefore, the benefit and risk of TSMT might be estimated by further long-term study. Another limitation is that this study provided no information about the quantitative analysis of ectopic thymic tissues and the proportion of additionally removed ectopic thymic tissues to the whole burden of thymic tissue. This information might be more representative of the improvement of outcomes. In conclusion, TSMT is effective and feasible method for the treatment of myasthenia gravis, and extirpation of cervical adipose tissues must be incorporated into the standard procedure of thymectomy.

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