Factors affecting response rates after thymectomy for myasthenia gravis

Transsternal extended thymectomy for myasthenia gravis

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Abstract

Aim: In our study, we report the clinical response obtained after transsternal extended thymectomy (TSET), the factors affecting the response, and the most appropriate timing of the operation. Material and Method: A total of 35 cases underwent TSET with the diagnosis of myasthenia gravis in our department from December 1996-June 2015. Twenty of the cases were females (57%) and fifteen (43%) were males with a mean age of 42±15 (14-68). The case registry has been analyzed retrospectively. Results: Postoperative histopathological examination revealed non-thymoma thymic pathologies in 19 (54%), thymoma in 16 (46%). Myasthenia gravis symptoms were staged according to the Osserman classification: 8 (22,9%) were stage I, 13 (37,1%) were stage IIa, 11 (31,4%) were stage IIb, and 3 (8,6%) were stage III, with no patients at stage IV. The duration of symptoms of <24 month before the operation was statistically significant for groups with and without thymoma (p< 0,001). However, parameters of age, gender, preoperative Osserman stage, and pathological diagnosis were not statistically significant between groups. Discussion: Transsternal extended thymectomy allows for extended removal of all the mediastinal tissue in the anterior mediastinum with a low complication rate. Symptom duration before operation is the most important factor in response to treatment; therefore, patients must be operated on as soon as possible. Thymectomy also seems to be helpful for early stage MG.

Keywords

Myasthenia; Surgery; Thymectomy

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Introduction

Today, there is absolute agreement about the efficacy of thymectomy for myasthenia gravis (MG). However, discussions continue about the most appropriate surgical technique, especially, since the development of minimally invasive approaches. There are many different thymectomy procedures, such as basic thymectomy, extended thymectomy, maximal thymectomy, and transcervical-subxiphoid videothoracoscopic maximal thymectomy.

The effectiveness of any kind of thymectomy can be described with regard to certain factors such as improvement rate, complete remission rate, and need for immunosuppressive drugs [1]. In our study, we report the clinical response obtained after transsternal extended thymectomy (TSET), the factors affecting the response, and the most appropriate timing of the operation.

Material and Method

A total of 35 cases underwent TSET with the diagnosis of MG in our department from December 1996-June 2015. Twenty of the cases were females (57%) and fifteen (43%) were males with a mean age of 42±15 (14-68). The case registry was analyzed retrospectively. Current follow-up case information was obtained by physician examination, questionnaire, or phone conservation. The age distribution by gender: female cases were 14-68 with a mean age of 39±3,9 and male cases were 20-61 with a mean age of 47±2,7. The most frequently observed symptom during preoperative neurologic evaluation was phytosis in 19 cases. Other symptoms according to frequency were muscle weakness, dysphagia, diplopia, and breathing difficulty. Phytosis was evident preoperatively for 17 of the 19 cases and was the most frequently mitigated postoperatively. Before the operation, all the cases had been evaluated by X-ray, thorax computed tomography (CT), pulmonary function test, and blood tests. Anesthesia induction was generally performed by using an intravenous agent (thiopental, propofol, or etomidate) and by combining an inhalation agent. All the cases were intubated by a one-lumen endotracheal intubation tube.

Based on thorax CT, a thymoma was diagnosed in twenty-one cases and anterior mediastinal giant mass in one case. Twenty-one thymectomies for thymoma were performed through TSET; the thymus tissue and primary tumor together with the surrounding fatty tissue of the neck and mediastinum were resected radically (Figure 1). Unless there was thymoma and the invasion of nearby tissue, removing the mediastinal pleura was not required. However, opening of pleura during dissection was not regarded as a complication and a thorax drain was implanted into the pleural space for these cases. Anterolateral thoracotomy and resection was performed for one case because of an anterior mediastinal mass. In this case, histopathologic examination thymoma was revealed in the postoperative period. After the operation, the medical treatment initially continued unchanged from the preoperative regimen but was subsequently modified postoperatively by the neurologist. For the remaining 13 patients with no thymoma, extended thymectomy with mediastinal fatty tissue was performed through median sternotomy (Figure 2).

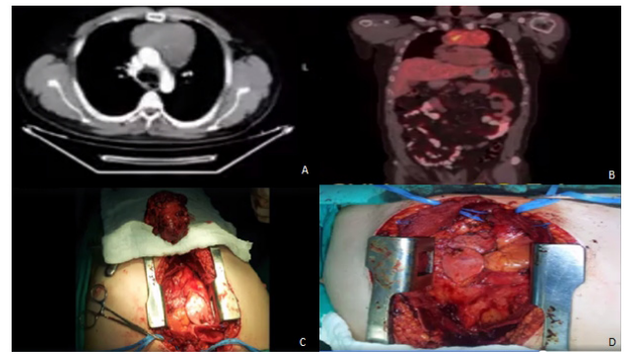

Figure 1. Toraks CT image of thymoma in anterior mediastinum (A). PET-CT image of thymoma with 7,5 SUVmax (B). Intraoperative image of TSET with thymoma (C). Intraoperative image of after TSET (D).

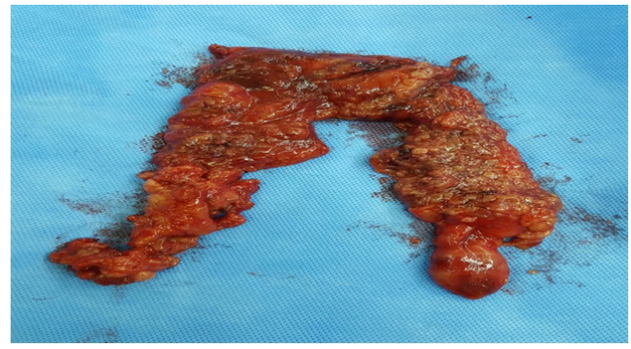

Figure 2. The image of thymus with mediastinal fatty tissue after TSET.

Our cases did not need plasmapheresis in the preoperative or postoperative periods. For all cases, medical treatments before and after the operation, neurological complaints, autoimmune related diseases, surgical indication, and detailed pathological analysis were researched. The cases were classified by the clinical responses to the operation and drugs required during the postoperative period. Responses of increased drug requirement and complaints were defined as "stable," decreased drug requirement but continued complaints as "recovery," and no symptoms without medication as "remission." Cases were divided into two groups according to drug requirement after surgery: Positive (good) response group and negative (poor) response group. Groups were compared by age, gender, preoperative Osserman stage, preoperative duration of symptoms, thymic pathologies, and ectopic thymic tissue presence.

Statistical Analysis

Analysis of qualitative data was performed with the chi-square test. The one-way analysis of variance was performed when suitability to normal distribution was not shown. Patients' age, sex, preoperative Osserman stage, thymic histology, and duration of symptoms were correlated with postoperative improvement and remission rates. A p value of less than 0.05 was considered significant.

Results

Postoperative histopathological examination revealed non-thymoma thymic pathologies in 19 (54%) cases and thymoma in 16 (46%). The gender distribution of the thymoma group was 10 males and 6 females and of the non-thymomatous group,

5 males and 14 females. Myasthenia gravis symptoms were staged according to Osserman classification: 8 (22,9%) stage I, 13 (37,1%) stage IIa, 11 (31,4%) stage IIb, and 3 (8,6%) stage III; no patients were stage IV.

All the cases were extubated in the operatory room and anticholinesterase treatment was started. One case with wound infection was treated with simple antibiotherapy and, no other complications was observed. Mean hospital stay after surgery was 9 (4-20) days. There was no operative mortality. After the operation mean follow-up was 49 (2-135) months. The cases' response to thymectomy after the operation is summarized in Table 1. Overall, a positivepostoperative outcome was found in 23 (66%) patients (improvement and remission).The duration of symptoms before the operation < 24 month were statistically significant for groups with and without thymoma ($p < 0,001$). However, parameters of age, gender, preoperative Osserman stage, and pathological diagnosis did not affect remission or improvement rates. Improvement and remission response more often occurred in patients with early stage MG (Osserman stages I, IIa) and was equal in those with hyperplasia of the thymus and thymoma (Table 1).

Table 1. Outcomes and response to thymectomy following operation.

Factors	p	Improvement (n=21)	Remission (n=2)	Stable/ Worsening (n=12)	Total (n=35)
Age		n	n	n	n
<40 years	0.86	6	1	6	13
>40 years		15	1	6	22
Sex					
Male	0.25	11	1	3	15
Female		10	1	9	20
Duration of symptoms					
<24 months	0.000	21	0	10	31
>24 months		0	2	2	4
Osserman stage					
I, IIA	0.28	13	2	6	21
IIB,III,IV		8	0	6	14
Histopathological outcomes					
Thymoma		10	0	6	16
Hyperplasia	0.37	8	2	6	16
Normal or atrophy		3	0	0	3

Discussion

Myasthenia gravis most frequently appears at ages 20-30 and over age 50 for females, and over age 50 for males, and is more than 4-5 times more prevalent in young females than in males. The male-female ratio over age 50 is equal [2,3]. In our study, 9 of 22 (41%) cases were male and 13 (59%) were female with a mean age of 40±16 (14-68). The age distribution for males was 20-60 (mean 44±12). Seven of the total 13 female cases were under age 30; the number of male cases under age 30 was only one. However, when the cases were evaluated on the relationship between thymic pathology and age, it was seen that the average age was 53±9 for the thymoma group and 30±13 for the group without thymoma. The relationship between older age and thymoma is statistically significant. Consequently, our data are aligned with similar studies in terms of age and gender [2-5].

Myasthenia gravis is the autoimmune disease most often related to thymoma. In a reported series, about 30-65% of cases with thymoma were found to have MG [5,6]. Kondo et al. [6] have summarized the findings in 1089 cases who underwent thymectomy for thymoma and detected MG in 24,8% of cases. Conversely, of the cases with MG, 10-15% had thymoma and 70% had thymus hyperplasia [3,7,8]. Popescu et al. [9] reported the rate of thymic hyperplasia as 78,5% in 107 cases. Kattach et al. [10] showed 11% thymoma and 60% thymic hyperplasia in 85 cases. In our study, the rate of thymoma was 45,4% and the rate of thymic hyperplasia was 40,9%. The reason our thymoma rate was higher than in the literature is because almost all our TSET cases had an initial radiologically-determined diagnosis of thymoma. Remes-Troche et al. [5] explained that one of the most frequent symptoms is bilateral phytosis, followed by extremity weakness. Dysphagia is present in 24% of the cases. In our study the most common symptom was phytosis (19 cases), with concomitant diplopia in 5 of them. The second most common symptom was muscle weakness, seen in half of the cases, followed by dysphagia in 10 cases. Our results are aligned with the literature in terms of myasthenia gravis symptoms.

In our study we observed positive (good) response in 14 cases (63,6%) and negative (poor) response in 8 cases (36,3%). Our complete remission rate was 9,1%. In different studies, remission rates are reported ranging from 19-47%, with positive (good) response rates been ranging from 34-56% [11-16]. Although our remission rate is low, our overall positive (good) response rate corresponds with that in other studies.

Generally, it has been accepted that having a short duration of myasthenic symptoms before surgery is related to better results. Nieto et al. [17] observed that complete remission is seen disease have been running for longer than eight months in cases. Additionally, it is known that longer duration from the disease diagnosis to surgery is related to negative (poor) results. This relation is possibly related to increased damage at the neuromuscular plates [18,19]. Venuta et al. [20] reported in their study of 232 cases that those with MG diagnosis of less than two years responded better to the surgery than those cases with MG diagnosis of more than two years duration. In our study, a significant difference was not found between the preoperative duration of symptoms and the response to operation. The reason is that duration before the operation was less than two years in 86,4% of our cases. To date, many studies have emphasized that there is a strong relationship between age and response to surgery [5,11,16]. It was seen in our study that the positive (good) response group was significantly younger. The relationship between the response to operation and gender has also been analyzed by several authors. Some authors found that female gender is correlated with positive (good) reply, while others found that male gender is a positive prognostic factor [10,21,22]. According to some authors there is no relationship between gender and response to operation [12,23]. A relationship between gender and response to operation was not shown in our study, either.

The relationship between preoperative Osserman stage and the clinical response to operation has been examined in several studies, with varying results. Zielinski et al. [24] pointed out that complete remission rates at stages I, IIa and IIb are better, but there was no remission in stage III cases after surgical treatment. Nieto et al. [17] obtained better clinical response at stage I and II cases. Although Roth et al. [25] obtained better clinical response at stages I and IIa, it was not statistically significant. Remes-Trocheet al. [5] found that stages IIa and IIb cases responded well, although it was not statistically significant, but all the stage I cases responded badly. Masaoka and Budde's studies [11,16] noted that there was no relationship between Osserman stage and response to operation. A statistically significant difference has not been found between preoperative Osserman stage and response to thymectomy [11,16]. However, while all our stage III cases improved, positive (good) response was seen in 60% of our stage I cases.

Thymic structures can be found in different sizes and forms in all mediastinal structures from the neck to the diaphragm and bilaterally from beyond each phrenic nerve. In addition, ectopic thymic structures were found in mediastinal fatty tissue in 22,7% of the cases in our study. Roth et al. [25] found this rate as 22,2% whereas Ashour et al. [22] found it as 39,5%. According to Ashour et al. [22] the cases with ectopic thymus tissue show worse clinical results. However, Roth et al. [25] reported that there is not any significant difference between long and short term results. In 80% percent of our cases, ectopic thymic tissue was clinically recovered. But the relationship between the presence of ectopic thymic tissue and clinical recovery was not found to be statistically significant.

Thymic histology is a partially determining factor in terms of the response of the cases with MG to thymectomy. Although thymic hyperplasia is correlated with increased recovery rates in several studies, other studies found a correlation with poor response [5,12]. Jaretski et al. [12] reported low recovery rates and high mortality rates in cases with thymomatous MG and Kattach et al. [10] noted that thymic histology did not affect clinical response after the operation. Roth et al.[25] supported this point of view. A statistically significant difference between thymic histology and clinical response to operation was not found in our study, either.

Nowadays, there is consensus about thymectomy in MG treatment. However, standard surgical approaches remain controversial. Different surgical approaches have been proposed ranging from the simple transcervical thymectomy to the extended thymectomy and the maximal thymectomy [1,11,14,18,26]. It is accepted that "radical thymectomy" should include the removal of all the thymic tissue and the surrounding mediastinal fatty tissue. Since 1992, the variety of methods has increased with development of thoracoscopic thymectomy [9]. This suggestion is based on comparisons of remission rates between uncontrolled studies. However, such comparisons should be questioned based on other variables including institutional policy, and differences in the invasiveness of medical administrations and result assessments. The results of comparison between uncontrolled studies may not provide conclusive evidence of the superiority of one technique over another. All the studies performed until now put forward advantages and disadvantages of their own methods. The few controlled trials comparing results in MG patients undergoing thymectomy with different surgical techniques demonstrate variable results. Mantegazza et al. [27] and Papatestas et al. [28,29] reported that transcervical thymectomy had better outcomes than their transsternal cases. Masaoka et al. [30] compared results after simple transsternal, simple transcervical, and extended thymectomy, and reported that MG patients who received extended thymectomies had better outcomes. In 21 of our cases the TSET method was performed. Thymectomy with video assisted thoracoscopic surgery (VATS) was not performed in any cases because almost all our surgical cases used radiology for initial thymoma diagnosis. Due to the high possibility of remaining tumor tissue for cases with thymoma, we consider that thoracoscopic resections are not reliable and that all cases with thymoma must receive sternotomy to completely remove fatty tissue with the tumor.

Conclusions

Thymectomy has been considered beneficial as part of a multidisciplinary approach to MG treatment and positive results have been demonstrated since the initial report. TSET allows an extended removal of all the mediastinal tissue in the anterior mediastinum with low complication rate and a shorter postoperative stay. Age is the most important factor in response to treatment. Therefore, younger patients especially should receive surgery immediately. In most published studies, there were numerous differences between the MG patients in each technique group. Thus, controlled trials did not provide convincing evidence that one thymectomy technique was superior. More randomized trials are needed to evaluate the best approach and at which stage and age surgery should be performed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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