Thymectomy in Myasthenia Gravis

Myasthenia Gravis'de Timektomi

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ABSTRACT

In recent years, thymectomy has become a widespread procedure in the treatment of myasthenia gravis (MG). Likelihood of remission was highest in preoperative mild disease classification (Osserman classification 1, 2A). In absence of thymoma or hyperplasia, there was no relationship between age and gender in remission with thymectomy. In MG treatment, randomized trials that compare conservative treatment with thymectomy have started, recently. As with non-randomized trials, remission with thymectomy in MG treatment was better than conservative treatment with only medication. There are four major methods for the surgical approach: transcervical, minimally invasive, transsternal, and combined transcervical transsternal thymectomy. Transsternal approach with thymectomy is the accepted standard surgical approach for many years. In recent years, the incidence of thymectomy has been increasing with minimally invasive techniques using thoracoscopic and robotic methods. There are not any randomized, controlled studies which are comparing surgical techniques. However, when comparing non-randomized trials, it is seen that minimally invasive thymectomy approaches give similar results to more aggressive approaches.

Keywords: Extended thymectomy, follow-up, myasthenia gravis, thoracoscopic thymectomy

ÖZ

Miyastenia gravis tedavisinde son yıllarda timektomi giderek yaygınlaşan bir prosedür haline geldi. Preoperatif hafif hastalık sınıflaması (Osserman sınıflaması 1, 2A) olanlarda remisyon ihtimali en yüksek olarak gösterildi. Timoma veya hiperplazi yokluğunda timektomi ile remisyon sağlamada yaş ve cinsiyetin ilişkisi gösterilemedi. Miyastenia gravis tedavisinde timektomi ile konservatif tedaviyi karşılaştıran randomize çalışmalar yeni yayınlanmaya başlandı. Nonrandomize çalışmalarda olduğu gibi Miyastenia gravis tedavisinde timektomi ile remisyon, sadece ilaçla konservatif tedaviden daha iyi bulundu. Cerrahi yaklaşım için transservikal, minimal invaziv, transsternal ve kombine transservikal transsternal timektomi olmak üzere dört major yöntem bulunmaktadır. Transsternal yaklaşımla timektomi yıllardır kabul gören standart cerrahi yaklaşımdır. Son yıllarda torakoskopik ve robotik yöntemin kullanıldığı minimal invaziv tekniklerle timektomi sıklığı artmaktadır. Cerrahi teknikleri karşılaştıran randomize, kontrollü çalışmalar bulunmamaktadır. Ancak nonrandimize çalışmalar arasındaki karşılaştırmalara bakıldığında minimal invaziv timektomi yaklaşımlarının daha agresif yaklaşımlara benzer sonuçlar verdiği görülmektedir.

Anahtar Kelimeler: Myasthenia gravis, ekstended timektomi, torakoskopik timektomi, izlem

Introduction

Myasthenia gravis (MG) is a disease caused by abnormal neuromuscular transmission. It may be congenital or acquired. In recent years, studies have shown that the incidence of the disease, which is thought to be affecting the younger age group, has increased by 50 years and over. The most common starting age for women is bimodal, which is between 20 and 30 years and older than 50 years, and men older than 50 years. In other words, while it is seen more frequently in women at younger ages, it is seen equally in both sexes in advanced ages [1].

Surgical removal of the thymus has been an alternative treatment for this disease since Blalock et al. [2] performed a successful thymectomy in a 26-years-old woman with MG and thymus cysts. Then, Blalock et al. [2] published their study about 20 patients with MG treated with transsternal thymectomy. In the following decade, a large number of studies investigating the role of thymectomy in MG have been reported from the United States and the United Kingdom [2]. Over time, with improvements in perioperative care, results of thymectomy have improved, and thymectomy has found its place in the treatment integrity of MG. The benefit of the thymec-

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tomy still continues to be questioned by some authors. In addition, there are still debates on the timing of thymectomy, treatment type in early ages, and surgical approaching techniques.

MG diagnosis

Diagnosis can be easily done in a patient with advanced oculobulbar symptoms and a typical myasthenic face. However, diagnosis may be delayed in patients who are only suffering from ptosis, diplopia, and chewing or speaking difficulties. Diagnostic steps in MG are:

1. The presence of increased complaints with activity and spontaneous remissions in anamnesis.

2. Improvement in muscle strength with acetylcholine esterase (Edrophonium test).

3. Repetitive nerve stimulation test: Stimulation potentials are recorded by giving three stimulations to a nerve in a second. More than 15% reduction in response is considered as positive.

4. Single-fiber electromyography

5. Anti-acetylcholine receptor (AChR) antibody detection: It can be investigated by radioimmunoassay. It is specific for MG. It is 85% positive in generalized disease, but in ocular myasthenia, positivity is less than 50% [3, 4].

Classification

MG has two clinical forms: ocular and generalized. Weakness in the ocular form is limited to the eyelids and extraocular muscles. However, in generalized patients with myasthenia, in addition to these, there are weaknesses at different degrees in the bulb, extremity, and respiratory muscles. Myasthenic weakness typically fluctuates during the day; it is usually the least in the morning and worsens later in the day especially after prolonged use of involved muscles.

The progress of the disease is variable and usually progressive. Maximal weakness develops during the first year in two-thirds of the patients. In 15%-25% of patients, myasthenic crisis, usually with severe respiratory failure, occurs within the first 3 years. Over the years, myasthenic complaints have diminished, but the disease is characterized by fluctuations in remissions and relapses [5]. Untreated weakness becomes permanent after 15 to 20 years, and atrophy can occur in the most affected muscles. Modified Osserman classification is used to determine the clinical status of the patients (Table 1) [6].

Separation of MG by subtypes is useful in terms of pathogenesis, diagnosis, and treatment approach. The disease is classified according to the muscles involved, starting age, presence of antibodies, and thymoma. The most classic form is generalized, early-onset, anti-AChR-positive, and thymoma-free form (Table 2) [3].

Table 1. Osserman classification system

Class	Symptoms
I	Only ocular involvement
IIa	Generalized muscle involvement without pulmonary involvement
IIb	Bulbar manifestation
III	Rapid progression of generalized bulbar disease and weakness in respiratory muscles
IV	Class 1 or 2 patients presenting progressive symptoms within 2 years

Table 2. Classification of MG disease

According to involved muscles	Generalized
	Ocular
According to onset age	Early (before 40-50 years old)
	Late (after 40-50 years old)
According to antibody	Anti-AChR-positive
	Anti-MuSK-positive
	Seronegative
According to thymoma presence	Thymoma
	No thymoma

Treatment options in MG

There are four primary approaches in the treatment of MG:

1. Symptomatic treatment with anticholinesterase agents: Pyridostigmine (Mestinon) is the most commonly used drug. Its effect starts in 30 minutes and reaches maximum level in 2 hours.

2. Immunosuppressive treatment: Corticosteroids, azathioprine (Imuran), and cyclosporine (Sandimmune) are used for this purpose. Prednisone is often preferred as a corticosteroid. It must be known that at the beginning of the treatment, myasthenic complaints may exacerbate in the first weeks; the dose should be gradually increased and moderate-to-severe generalized patients should be treated by admission. Recovery starts within weeks; the dose should be adjusted by reducing once the desired level is reached within the months. Azathioprine is used in patients who do not receive steroids, who do not respond to steroids, and who are trying to reduce steroid doses. Cyclosporine is a potent immunosuppressant that stops the interleukin (IL)-2 release from T-helper cells.

3. Plasma exchange and rapid immunomodulating treatments with intravenous immunoglobulins: They are used in situations requiring rapid recovery, such as myasthenic crisis, or preparation for thymectomy operation.

4. Thymectomy: Thymus is considered to play a role in MG pathogenesis. Most patients with MG and AChR autoantibodies have thymus anomalies. Hyperplasia in 60%-70% of cases and thymoma in 10%-15% of cases were detected [7, 8]. The reason for thymectomy in patients with MG is based on the above observations.

Indications of thymectomy

One of the topics that have been debated in MG treatment for many years and not reached consensus is indications for thymectomy. Before the discussions about surgery approach types, even the superiority of thymectomy to medical treatment is still a matter of serious debate. Patient's age, sex, the presence of thymoma, the severity of MG, presence of AChR antibodies or MuSK antibody, and seronegative myasthenia formation affect the decision of thymectomy [9]. As a general rule, indication, timing, and pre- and post-operative care of a thymectomy-planned MG patient should be managed by the surgeon in close cooperation with an MG-specialized neurologist.

Thymomatous MG

There is an indication of thymectomy in all thymoma cases, regardless of whether MG is generalized, bulbar, or ocular. Complete resection of thymoma should be targeted. If this is not possible, medical treatment can be given to both relieve myasthenic symptoms and prevent local invasion. It has been reported that remission and recovery rates of MG in patients with thymoma are similar or slightly worse than those without thymoma [10].

Non-thymomatous MG (anti-AChR antibody-positive)

In the absence of thymoma, thymectomy is generally thought to be beneficial to generalize MG and AChR antibodies-positive patients [11-13]. Appropriate age for surgery, stage in which surgery will be performed during the course of the disease, surgery approach type, role of thymectomy in ocular MG, seronegative MG, and MuSK antibodies-associated MG cases are still questions to be answered.

Age, gender, and severity of the MG

Response to thymectomy appears to be roughly comparable in mild, moderate, and severe MG [14]. Mao et al. [15] evaluated prognostic factors of remission in MG after thymectomy by evaluating findings of 18 retrospective studies. Prevalence of remission after thymectomy was higher in patients with preoperative mild MG disease. Gender, age, and absence of thymoma were not associated with post-thymectomy remission.

An age limit for thymectomy in patients without thymoma has not been demonstrated with any study until today [14]. It is thought that elderly individuals may not respond well to thymectomy because of high thymic involution incidence and that risks of thymectomy may be serious than potential benefits. For this reason, most centers do not perform thymectomy for patients older than 60 years. However, some authors suggest individual assessment for patients by evaluating benefit and risk and believe that older age is not an excluded factor for surgery [7].

The role of thymectomy in the treatment of prepubertal patients with MG is unknown. However, in children with generalized, AChR antibody-positive MG, if the response to pyridostigmine and immunosuppressive therapy is unsatisfactory or it is wanted to prevent potential complications of immunosuppressive therapy, thymectomy should be considered.

Seronegative myasthenia

Anti-AChR antibody-negative MG is divided into two subgroups according to serological findings: anti-MuSK antibody-positive MG (anti-MuSK MG) and double-seronegative MG (anti-AChR antibody-negative and anti-MuSK antibody-negative) [16].

The role of thymectomy in patients with double-seronegative MG is not yet fully understood. However, most clinics recommend thymectomy in these cases. Guillermo et al. [17] reported that AChR antibody-positive and -negative cases have similar response rates at least 3 years follow-up, in a retrospective cohort study. Similar to anti-AChR-positive MG, generalized MG has been reported to have a double-seronegative MG as an indication for thymectomy [18].

In children with seronegative generalized MG, congenital myasthenic syndrome or other neuromuscular conditions should be assessed before the decision of thymectomy [7].

MuSK antibody-positive myasthenia

MuSK antibody-associated patients with MG have much less thymus pathology than AChR antibody-associated patients with MG, except patients with thymoma. Present findings in the literature do not support the benefit of thymectomy in MuSK antibody-associated MG [11]. Guptill et al. [19] compared the post-surgical status of 40 patients who underwent thymectomy with 70 patients who were not operated in their series consisting of 110 patients with MuSK-positive MG. A possible benefit of thymectomy was not excluded in this study. However, many clinics do not recommend thymectomy in MuSK-positive without patients with thymoma MG. Medical treatment should be the first choice in these cases.

Ocular myasthenia

The role of thymectomy in ocular MG is controversial. While thymectomy may be beneficial in patients with the generalized disease, some clinics do not recommend thymectomy for patients with ocular MG [20]. In some clinics, it is recommended as a treatment option with less invasive procedures. No significant indications for thymectomy have been shown in patients with ocular-type double-seronegative MG as well as in ocular-type anti-AChR antibody-associated cases [18].

MG in pregnancy

MG causes an increase in myasthenic exacerbation and crisis tendency during pregnancy, especially during early puerperium. Pregnancies with MG enter the high-risk pregnant group and the disease state cannot be predicted. Thymectomy should be postponed until post-pregnancy because it is unlikely to benefit during pregnancy [7].

Efficiency of thymectomy

In 2016, Wolfe et al. [13] (MGTX Study Group) report the results of a randomized, controlled trial comparing the effects of thymectomy and prednisone therapy versus prednisone therapy alone. The results supported the benefit of thymectomy in patients with non-thymomatous MG. In the study, 126 patients with generalized AChR antibody-associated MG and less than 5 years' duration of disease (age, 16-65 years; median age, 33 years) were observed. Results were recorded by giving daily prednisone in addition to randomized extended transsternal thymectomy cases or only by giving daily prednisone [13]. During a period of 3 years, time-dependent averaged mean quantitative MG score of thymectomy group was found to be significantly lower than of the prednisone alone group. During the 3 years, daily average prednisone-requiring was significantly lower (44 vs. 60 mg) in the thymectomy group. The proportion of immunosuppression-requiring cases by azathioprine was significantly lower in the thymectomy group (17% vs. 48%). The proportion of hospitalized patients for MG exacerbations was significantly lower in the thymectomy group (9% vs. 37%).

Findings from non-randomized studies showed that thymectomy has contributed to MG remission and recovery [14, 21], although before the MGTX study, usefulness of thymectomy was found to be controversial in the treatment of AChR antibody-associated MG in absence of thymoma.

Taioli et al. [22] compared conservative treatment results with thymectomy in patients with non-thymomatous MG (10.140 patients: 5,275 thymectomies, 4,865 medication) in their review in 2016. They determined that thymectomy was superior to conservative treatment with only medication in MG remission.

The benefit of thymectomy does not start very quickly. Remission rates in the first year are less than 20%. However, the remission rates have increased up to 50% over 7-10 years [7, 9, 23].

Thymectomy is generally recommended by most centers for patients between puberty and 60 years of age as a long-term treatment of AChR antibody-associated MG [11, 12].

Adverse effects of thymectomy

Patients with MG are generally at high risk for surgical intervention due to impaired respiratory function. However, along with advances in surgical and anesthesia techniques, now the operations can be done safely. Mortality rates associated with thymectomy are ≤1% even in cases with insufficiently controlled MG symptoms [14]. Complications related to thymectomy include crisis (6%), infections (11%), and recurrent laryngeal nerve / phrenic nerve injury (2%) [18].

Surgical method

The purpose of thymectomy is to remove as many thyroid tissues as possible safely. Mediastinal and cervical adipose tissues may contain varying amounts of thymic tissues in addition to itself [20]. Surgical approach should provide as much resection as possible for this ectopic thymic tissue without damaging recurrent laryngeal, left vagus, and phrenic nerves. Four major surgical approaches are used:

1. Transcervical thymectomy

2. Minimally invasive thymectomy (video- or robot-assisted)

3. Transsternal thymectomy

4. Combined transcervical-transsternal thymectomy

In all of these procedures, the thymus is resected, but the resection of extracapsular mediastinal and cervical fat tissue varies. There is no persuasive evidence of superior efficacy or long-term remission rates in MG for either of these approaches [18].

Median sternotomy (extended transsternal thymectomy or combined transcervical-transsternal thymectomy) is preferred by many chest surgeons and neurologists [9, 23]. This approach provides a broad exploration area from mediastinum to neck, allowing complete resection of all thymic and associated fat tissues.

Some authors advocate extended-cervical thymectomy for minimizing postoperative pain and so ventilator need [24, 25]. In this approach, hospitalization is usually as short as a day and incisions are small. A special manubrial retractor has been developed to improve mediastinum exposition and facilitate resection. It is the controversial part of this approach that it may be inadequate to reveal thymus fully and that residual thymus tissue may remain in the left posterior side. However, clinical improvement similar to transsternal thymectomy has been reported in various series [26-28].

The simple transcervical approach is rarely performed. Surgical excursion of the thymus is inadequate, and residual thymus tissue remains in most patients [23, 29].

Thymectomy operations by minimally invasive procedures such as video-assisted thoracoscopy or robot-assisted approaches are associated with low morbidity and mortality rates [30-34]. Meyer et al. [35] compared video-assisted thymectomy with the extended transsternal approach in a retrospective study. Video-assisted thoracoscopic surgery (VATS) was performed in 48 patients, and transsternal approach was performed in 47 patients. Equivalent clinical results were obtained in both approaches in the treatment of MG cases. However, larger clinical trials are needed to compare the effectiveness of minimally invasive approaches with complete sternal thymectomy.

It is controversial that which surgical technique is more effective in MG. However, there is no doubt that minimally invasive approaches have a lower morbidity and shorter hospitalization time than those with more invasive approaches. Meyer et al. [35] reported significantly shorter average length of hospital stay in the VATS group than in the transsternal approach group, in the mentioned studies (1.9 vs. 4.6 days). In addition, Khicha et al. [36] reported that almost none of the 151 patients with extended transcervical thymectomies required overnight hospitalization and a 0.7% of major complication rate. Being able to avoid potential complications of sternotomy via avoiding to cut sternum in less invasive methods is a significant advantage.

Thoracoscopic and robotic approach rates are increasing in thymectomy. They have successful results in experienced centers [37]. There are no randomized, controlled comparison studies. However, based on comparisons of studies, less invasive thymectomy approaches give similar results to more aggressive approaches [38-41].

Time for surgical treatment

Thymoma cases should be evaluated for surgical treatment without delay. However, the optimal time for thymectomy has not been determined in thymoma-free MG cases. In addition, to avoid perioperative complications, under-controlled patients with MG with minimal bulbar and respiratory symptoms are the most appropriate group. It is also useful to reduce glucocorticoids to sufficiently lowest level that clinical situations permit to reduce problems associated with postoperative infection and wound healing. Some authors argue that thymectomy response is better in early-disease phase. It is due to better remission rates of early-stage thymectomies than late ones. In addition, remission rates of cases are higher in early phases of the disease [14, 42]. Although early thymectomy does not have a proven benefit, it is mostly recommended to be done within first 3 years of the disease [11, 12].

Preoperative preparation

Contrast-enhanced thorax computerized tomography must be performed in a patient with MG who is planned to undergo surgery. If MG is accompanied by a thymoma, tomography is inevitable to assess anterior mediastinal mass and to show possible vascular invasions. Although the importance of transthoracic needle aspiration is controversial, it may be helpful in the preoperative diagnosis of thymoma [43].

Thymectomy-scheduled patients with MG are only advised for surgery when their medical condition is optimal. In the preoperative evaluation of patients with MG, recent progress of the disease, affected muscle groups, applied drug treatments, and co-morbid diseases should be focused and pulmonary function tests should be examined. Teamwork of anesthesia, neurology, surgery in all preoperative, intraoperative, and postoperative periods is absolutely important for patients with MG who will undergo thymectomy. Detailed evaluation of pulmonary function tests should be performed in the preoperative period. Forced vital capacity (FVC) may be a useful indicator of estimated postoperative prognosis. Rapid immunotherapy with plasmapheresis or intravenous immunoglobulin should be performed before thymectomy in patients with preoperative respiratory or bulbar signs. This will help in the postoperative period as well as in reducing preoperatively given corticosteroid levels [44]. Seggia et al. [45] showed that plasmapheresis significantly improves respiratory functions and muscle strength in patients with myasthenia treated with thymectomy and significantly reduces hospitalization times.

Continuation of regular anticholinesterase treatment until surgery and even giving the last drug dose in morning of operation day is very important. The medication should be continued with a small amount of water as soon as patients regain consciousness. It is a very important lack of symptoms such as oropharyngeal and respiratory weakness during surgery.

Postoperative follow-up

Following the surgery, patients were awakened and evaluated closely by an anesthesiologist. Extubation is performed if the respiratory strength and blood gas test results are good. Nearly all of the patients can be extubated early. Patients should be kept in close observation by surgery, intensive care, or neurology specialists as well as emergency respiratory support and reintubation conditions are ready and should be alert to weakness, progressive weakness, and respiratory failure. To assess respiratory status, vital capacity measurements can be done in every 6 hours by inspiratory-expiratory pressures. Aggressive bronchopulmonary cleaning precautions should be taken. Starting anticholinesterase agents early in the postoperative period will reduce oral and tracheal secretion problems and possibility of cholinergic crisis. If the patients' breathing worsens, plasmapheresis should be considered immediately. A patient who is observed to have stabilized breathing can be shifted from the intensive care unit to the clinic room. Drains can be removed as early as possible, and discharge can be planned [46].

Sometimes, there can be a postoperative temporary increase in myasthenic symptoms. Several factors have been reported related to postoperative myasthenic crisis or need for long-term mechanical ventilation. These include preoperative expiratory weakness, the vital capacity of less than 2.0 L, bulbar symptoms, myasthenic crisis story, AChR antibody serum level greater than 100 nmol/L, and intraoperative bleeding of more

than 1 L [44, 47-50]. Patients with these worse prognostic factors need more attention in the postoperative period.

Conclusion

Regardless of MG condition, all cases with thymoma should be operated by resection if possible. If complete excision of thymoma is not possible, radiotherapy and chemotherapy should be given both to control myasthenic symptoms and to prevent local invasions. Thymectomy is recommended for patients younger than 60 years with non-thymomatous, generalized AChR antibody-associated MG. The role of thymectomy in ocular MG is controversial. Plasmapheresis or intravenous immunoglobulin is recommended before thymectomy in patients with preoperative respiratory or bulbar symptoms. The goal of thymectomy is to remove as much thymic tissue as possible. There is no consensus on whether the transsternal approach is better than less-invasive extended-transcervical and video-assisted approaches.

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