Thymus Surgery in Myasthenia Gravis

Subjects: Surgery

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The thymus is a lymphoid organ involved in the differentiation of T cells, and has a central role in the physiopathogenesis of Myasthenia Gravis (MG). This connection is proved by a series of changes in the level of neuromuscular junctions, which leads to a decrease in the amplitude of the action potential in the post-synaptic membrane. Because of this, the presence of anti-cholinergic receptor antibodies (AChR), characteristic of MG, is found, which causes the progressive regression of the effect of acetylcholine at the level of neuromuscular junctions, with the appearance of muscle weakness. The thymectomy is a surgical variant of drug therapy administered to patients with MG. In the case of patients with nonthymomatous MG, thymectomy has become a therapeutic standard, despite the fact that there is no solid scientific evidence to explain its positive effect. Videothoracoscopic surgery or robotic surgery led to a decrease in the length of hospital stay for these patients.

Keywords: thymectomy myasthenia gravis thoracic surgery acetylcholine video-thoracoscopy (VATS)

1. Indications for Thymectomy

One of the topics debated in recent years in relation to MG, without reaching a consensus yet, is related to the indications of thymectomy for MG [1].

Before discussing the types of surgical approaches, and even the superiority of thymectomy over medical treatment, one more issue must be considered [2].

Patient age, gender, presence of thymoma, specific seropositivity, and severity of MG symptoms are the aspects to consider for the management of thymectomy [1]. As a rule, both the operative indication, the preoperative evaluation, and the postoperative care should be managed with the cooperation of the surgeon, anesthesiologist, and neurologist [2].

In most cases of thymoma, patients should undergo thymectomy, regardless of whether MG is generalized, bulbar, or ocular. A complete resection of the thymoma should be aimed for. If this is not possible, medical treatment can be administered both to relieve myasthenic symptoms and to prevent local invasion. It has been reported that the remission and recovery rates of patients with MG associated with thymoma are similar or slightly worse than in nonthymomatous patients [3] (**Table 1**).

Table 1. Thymectomy indications.

Pacients	Indications	Comments
Thymomatous	- Most of the patients—taking into consideration the staging	- The complete resection of the thymoma must be followed - MG remission is comparable to that of nonthymomatous patients

Pacients	Indications	Comments
Nonthymomatous	- Patients presenting MG with positive specific serology - Young patients with generalized MG, who do not respond to drug treatment - In pediatric patients in whom it is necessary to avoid immunosuppressive treatment	- Elderly patients may have a weaker response to thymectomy - The role of thymectomy in young patients is not fully known

In the absence of thymoma, thymectomy may be indicated in cases of generalized MG with a positive specific serology [4] [5].

The response to thymectomy does not appear to be influenced by the severity of MG [6].

The prevalence of remission of MG after thymectomy is not related to gender or age [7].

It must, however, be taken into account that elderly patients may have a weaker response to thymectomy due to their high degree of thymic involution. Considering this aspect, and the fact that operative risks are higher in elderly patients, most surgeons avoid thymectomy in this category of patients. However, some authors suggest the individual assessment of patients by evaluating the benefits and risks and consider that advanced age is not a factor in excluding this category of patients from the benefits of a thymectomy [8].

The role of thymectomy in young patients is not fully known. However, thymectomy may be considered in children with generalized MG with positive acetylcholine receptor anti-receptor serology who do not respond satisfactorily to pyridostigmine therapy or immunosuppressive therapy. There may also be an indication for thymectomy in children for whom it is necessary to prevent possible complications of immunosuppressive therapy [9].

The role of thymectomy in patients with double-seronegative MG is not fully known. However, most clinicians recommend thymectomy even in these cases. There are studies that highlight the fact that there are comparable results in terms of efficiency, both in patients with negative acetylcholine receptor antibody serology and in patients with positive specific serology [10].

In children with generalized seronegative MG, the feasibility of thymectomy should be evaluated [11].

MG may present an increased risk of exacerbation of symptoms during pregnancy. In particular situations, the occurrence of an acute myasthenic crisis syndrome in pregnant patients could occur. However, thymectomy should be avoided and delayed until after delivery due to the significant risks this surgery may pose to the mother or the fetus [12].

2. Limits and Risks of Surgical Intervention

Patients with MG are at significant risk of having a thymectomy because of the impairment of respiratory function during the disease [13].

However, with the advancement of operative techniques and improved performance in the fields of anesthesia and intensive care, the risks of a thymectomy are now manageable [14].

The mortality rate associated with thymectomy is less than 1%, even in patients with poorly controlled MG [14].

Complications related to thymotomy may occur due to the following conditions: acute myasthenic crisis, nosocomial infections, lesions of the recurrent laryngeal nerves, or phrenic nerves [15].

3. Types of Surgical Approach in Thymectomy

The goal of thymectomy is to remove as much of the thymic tissue as possible. Considering that the mediastinal and cervical adipose tissue may contain traces of thymic cells in varying amounts, the surgical approach should aim to achieve a resection as extensive as possible, avoiding damage to the recurrent laryngeal, left vagus, or phrenic nerves [16].

To achieve these objectives, there is the possibility of choosing between four major surgical techniques:

(a)Transcervical thymectomy,

(b)Minimally invasive thymectomy (video-assisted or robotic);

(c)Trans-sternal thymectomy;

(d)Combined trans-cervical–trans-sternal thymectomy [17].

In all of these procedures, the thymus is resected, but the resection of extracapsular mediastinal and cervical adipose tissue varies. There is no convincing evidence of superior efficacy or long-term remission rates in patients with MG for any of these surgical approaches [17].

Median sternotomy is preferred by most of the surgeons. This approach provides a wide area of exploration from the mediastinum to the neck, allowing complete resection of all thymic and associated adipose tissue [17].

Some authors support the effectiveness of an extended cervical thymectomy, taking into account less postoperative pain. This surgical approach leads to a period of hospitalization approximately equal to that required for patients who benefit from a median sternotomy, but the incisions made in this case are much smaller [18][19].

A special manubral retractor has been developed to improve exposure of the mediastinum and facilitate resection. The controversial element in relation to this approach is related to the impossibility of complete discovery, from an anatomical point of view, of the thymus, which leads to the risk of residual thymic tissue in the posterior part of the mediastinum. However, recent studies have reported comparable results to those obtained in the case of patients who underwent surgical interventions with a median sternotomy approach [20][21].

The simple transcervical approach is rarely preferred because of the risk of remnant thymic tissue in most patients [21].

Thymectomy by minimally invasive procedures such as video-assisted thoracoscopy or robot-assisted approaches is associated with low morbidity and mortality rates [22][23].

There is no doubt that minimally invasive approaches have lower morbidity and shorter hospital stays than more invasive approaches [24].

In addition to the obvious advantage given by the possibility of avoiding sternotomy, video-assisted approach techniques have similar results to those obtained by choosing median sternotomy. Also, a great advantage in the case of video-assisted mediastinal exploration techniques is represented by a much lower rate of postoperative complications, which may occur following thymectomy [25].

The rate of surgical approaches involving the use of video-thoracoscopy or robotic-assisted surgery is increasingly preferred for performing thymectomy in patients with MG. According to the studies carried out so far, the types of minimally invasive thoracic approaches for thymectomy offer comparable results to those obtained by using more aggressive techniques [26].

4. Determining the Moment to Perform the Thymectomy and the Preoperative Preparation of the Patient

Thymoma patients should be evaluated for surgical treatment without delay. However, the optimal time for performing thymectomy has not been determined in patients with MG who do not present thymoma [27].

The most suitable patient for thymectomy is one with minimal bulbar or respiratory symptoms. This must be taken into account to avoid perioperative complications as well as to reduce the doses of corticoids as the time of surgery approaches and to minimize the risk of postoperative infection. Some studies support the idea that thymectomy is more effective in the early stages of MG. This fact is due to the better remission rates of MG in patients with early stages of the disease [28].

Although early thymectomy has no proven benefit, it is mostly recommended to be performed within the first 3 years after the onset of the condition [29].

Any patient with MG for whom a thymectomy is considered should undergo a thoracic computed tomography with a contrast agent. This investigation is all the more useful in patients with thymoma for the evaluation of a mediastinal mass and possible associated vascular invasions. Obtaining a histopathological diagnosis by transthoracic needle aspiration is still controversial [30].

Patients with MG scheduled for thymectomy should be operated on when the clinical condition is optimal. In the preoperative evaluation stage of patients with MG, the following parameters related to the specifics of the disease must be taken into account:

- Recent evolution of the disease,
- Degree of muscle weakness,
- Drug treatments included in the patient's therapy at the time of evaluation,
- Comorbidities,
- Pulmonary function [28].

Interdisciplinary collaboration is extremely important in the approach of a patient with MG who is about to undergo thymectomy. A detailed evaluation of pulmonary function should be performed preoperatively, which could provide an appropriate prognosis related to postoperative care. In patients with bulbar or respiratory symptoms, in the preoperative stage, immunoglobulin therapy or its association with plasmapheresis is necessary. This will also help to reduce the amount of corticosteroids required for drug therapy, both preoperatively and postoperatively, in any patient with MG undergoing thymectomy [31].

Plasmapheresis significantly improves both respiratory function and muscle strength in patients with MG undergoing thymectomy. Also, this therapeutic technique significantly reduces the hospitalization period [32].

Continuation of anticholinesterase therapy until surgery is essential, usually by the morning of the surgery. Also, the administration of anticholinesterases is useful in the postoperative stage, right from the moment patients regain consciousness, because it is extremely important to avoid the appearance of oropharyngeal or respiratory symptoms [33].

5. Postoperative Follow-Up of Thymectomized Patients

Following the operation, the patient is awake and closely monitored by an intensive care specialist. Extubation is performed if respiratory function and blood tests are appropriate. In almost all cases, extubation can be performed early. The postoperative follow-up of the thymectomized patient must be carried out by a multidisciplinary team formed by a surgeon, neurologist, and intensive care specialist. If acute respiratory failure occurs, reintubation should be performed urgently [34].

To assess respiratory status, the vital capacity of the lungs should be assessed every 6 h by inspiratory-expiratory pressure measurements. Aggressive bronchopulmonary clearance measures should also be taken [35].

Early initiation of anticholinesterase therapy in the postoperative period reduces the risk of oral and tracheal secretion problems. By doing so, the risk of a cholinergic crisis may be minimal. If respiratory malfunctions occur in the postoperative period in thymectomized patients, the initiation of plasmapheresis therapy should be considered in absolute emergency conditions. The transfer of the patient from the intensive care unit should be carried out only in a situation where he is stable from a respiratory point of view. It is also important to favor the early removal of drain tubes, taking into account the comfort of the patients and decreasing the risk of infection [36].

There are situations in which a postoperative exacerbation of myasthenic symptoms may occur. There are a number of factors that influence the occurrence of postoperative myasthenic crisis, associated with the need to ensure the continuation of mechanical ventilation in thymectomized patients:

- Weakness of respiratory muscles,
- A vital pulmonary capacity of less than 2 L,
- Bulbar manifestations,

- History of the myasthenic crisis,
- A serum level of anti-acetylcholine receptor antibodies exceeding 100 nmol/L,
- Intraoperative blood loss greater than 1 L [37].

Patients presenting such prognostic factors require increased attention in the postoperative care stage [38].

Cholinergic crisis develop as a result of overstimulation of nicotinic and muscarinic receptors at the level of neuromuscular synapse junctions. This phenomenon usually occurs secondary to the inactivation or inhibition of acetylcholinesterase (AChE), the enzyme responsible for releasing acetylcholine [39].

The excessive accumulation of acetylcholine in the neuromuscular junctions causes the symptoms of muscarinic and nicotinic toxicity, such as muscle cramps, excessive salivation, lacrimation, muscle weakness, paralysis, diarrhea, and vertigo [40].

Cholinergic crisis occurs in the following situations:

- In the case of patients with MG, who receive treatment with acetylcholinesterase inhibitors in high doses;
- In the case of patients who are under post-general anesthesia and have received high doses of acetylcholinesterase inhibitors to neutralize neuromuscular blocking agents during the intervention, such as neostigmine;
- In case of exposure to a chemical substance that causes the inactivation of acetylcholinesterase: sarin gas, some pesticides, and insecticides [41].

Myasthenic crisis is a complication of MG. Among the triggers of myasthenic crisis are: infections, surgical interventions, menstruation, and some drugs (quinidine, calcium channel blockers, and some antibiotics) [42].

The clinical symptomatology of myasthenic crisis is very similar to that of cholinergic crisis. Cholinergic crisis should be evaluated in every case of myasthenic crisis, although they are not completely similar [43].

It is important to identify the type of seizure that is causing the muscle weakness. This is achieved by administering an IV dose of 2 mg of edrophonium, which produces an improvement in the clinical symptoms in myasthenic crisis, whereas in patients who are in cholinergic crisis, the symptoms are aggravated by this drug [44].

The treatment of acute myasthenic crisis consists of the administration of rapid immunotherapy with immunoglobulins administered intravenously, or by using plasmapheresis. During this time, patients should be evaluated for possible infection or other complications, such as the use of medications that may exacerbate MG attacks [45].

In case of immunotherapy or plasmapheresis with limited results within a few weeks, prednisone or methylprednisolone must be administered. Although cholinesterase inhibitors are also available for IV administration, they should be avoided in a crisis because they can increase respiratory tree secretions, complicating airway management. Therefore, all acetylcholinesterase inhibitors will be withheld throughout mechanical ventilation [46].

Regardless of the stage of MG, all cases associated with thymoma should be operated on by resection. If complete excision of the thymoma is not possible, radiotherapy and chemotherapy should be performed both to control myasthenic symptoms and to prevent local invasion. Thymectomy is recommended for patients younger than 60 years with generalized, non-thymomatous MG and anti-acetylcholine receptor antibodies. Plasmapheresis or intravenous immunoglobulin is recommended before thymectomy in patients with preoperative respiratory or bulbar symptoms [47][48].

6. VATS Thymectomy

Thymectomy by video-thoracoscopy (VATS) is necessarily performed under general anesthesia. To achieve this, first of all, selective endotracheal intubation is necessary [49].

Bilateral video-thoracoscopic thymectomy, especially the uniportal one, is a purely endoscopic procedure with direct access to the monitor. The surgical dissection is started to the left, with the patient seated in a lateral recumbent position at an angle of 60°. An incision of 3–5 cm is performed in the fourth intercostal space on the anterior axillary line without affecting the ribs. Thus, the lung is deflated, and through a minithoracotomy, the thoracoscope and conventional thoracoscopic instruments are inserted. The camera is placed at the rear end of the uniportal access. Dissection usually

starts from the left pericardiophrenic angle. Proceeding cranially, the next step is to incise the mediastinal pleura along the anterior line of the phrenic nerve and mobilize the thymus and perithymic fat. Endoscopic vascular clips are used to control the thymic vessels. The dissection is performed in the pre-pericardial plane. Finally, the superior thymic poles are dissected gently and pulled down to achieve their complete mobilization until the thyroid-thymic ligaments are visible for sectioning. After finishing the left thymic dissection, the researchers open the contralateral pleura to push the mobilized part of the thymus into the right pleural cavity while the lung is in apnea for a few seconds. At this point, the residual mediastinal fat is completely dissected from the left phrenic nerve, the innominate vein, and the left pericardiophrenic angle. A single tube is inserted through the incision and curved downward to the costophrenic angle [50][51].

The patient is then placed on the contralateral side, also in lateral recumbent, at an angle of 60°. Similarly, on the left side, a 3–5 cm incision is performed in the fourth intercostal space, at the level of the anterior axillary line, without damaging the ribs. The dissection starts from the right pericardiophrenic angle and continues cranially, along the anterior border of the phrenic nerve. The thymus is then mobilized from the surrounding tissue and from the superior vena cava. Vascular clips are used to secure the thymic veins draining into the superior vena cava. Finally, “en bloc” thymic dissection, with bilateral perithymic and pericardiophrenic fat tissue, is completed, and removed using a 15 cm endosac via uniportal access. At this operative step, the mediastinal fat is completely dissected from the right phrenic nerve, innominate vein, and right pericardiophrenic angle. A single chest drain tube is inserted through the incision, curved downward to the costophrenic angle. The lung is then re-inflated [52].

During the intervention, the surgeon and the assistant are positioned behind the patient. The camera is placed at the posterior end of the uniportal access and is controlled by the assistant. The camera does not interfere with the surgeon’s instruments and provides a stable view of the operative field. It is also mandatory that the surgeon’s action be in the center of the screen. Finally, synchronization between the surgeon and his assistant is essential to reducing the operative time and the success of the procedure [51]. This means there should be trained operative teams for this procedure.

Standardization of technique and maintaining the same surgical team could be very useful ways to achieve performance [53].

Bilateral uniportal video-assisted thoracoscopic extended thymectomy is a safe and feasible technique for surgical resection of thymic hyperplasia and thymoma. This technique could be considered a development of multiportal thoracoscopic thymectomy that offers all the advantages of minimally invasive surgery, such as:

- Reduced postoperative pain,
- Faster mobilization of patients,
- Reduced hospitalization period,
- Better results in terms of the postoperative scar [51].

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