

Classic therapies revisited

Thymectomy for myasthenia gravis

John D Urschel, Raji P Grewal

Summary

The pathophysiological role of the thymus in myasthenia gravis, and the mechanism of therapeutic effect of thymectomy, are incompletely understood. Nevertheless, thymectomy is a valuable treatment modality in selected patients with generalised myasthenia gravis. There are several types of thymectomy operation, but no one operative approach is clearly superior to the others. Total removal of the thymus gland is essential. Additional excision of associated mediastinal and cervical tissue, that may harbor ectopic thymic rests, is a controversial surgical issue. Surgeons that advocate thymectomy through small, cosmetically favourable, incisions usually believe that simple removal of the thymus gland is an adequate operation. Surgeons that emphasise the importance of removing extrathymic tissue, in addition to the thymus gland, usually favour greater operative exposure through a median sternotomy. To minimise operative morbidity, surgery for myasthenia gravis requires a multidisciplinary (neurology, surgery, anaesthesia) approach to peri-operative care.

Keywords: myasthenia gravis; thymectomy; pre-operative care; postoperative care

Myasthenia gravis is an autoimmune disease characterised by muscular weakness and fatigability.¹ At one time myasthenia gravis was disabling or fatal in most patients. With modern medical and surgical management, death is uncommon and most patients lead productive lives.² Thymectomy plays a central role in the treatment of myasthenia gravis. This article will briefly summarise the pathophysiology of myasthenia gravis, and review its surgical treatment (thymectomy) in detail.

Pathogenesis

The weakness of myasthenic patients is due to an antibody-mediated autoimmune attack against acetylcholine receptors at neuromuscular junctions.¹⁻³ This autoimmune process causes a reduction in the number of acetylcholine receptors and reduced transmission of neural signals to skeletal muscle.⁴⁻⁵ Reduction of acetylcholine receptors is a reversible process; receptors regenerate if the autoimmune process is controlled. Anti-acetylcholine receptor antibodies are produced by B cells, but T cells and other immune cells are important for B cell stimulation and antigen processing.¹⁻⁶ The thymus gland plays a central role in the pathophysiology of myasthenia gravis.⁷ It contains the key cellular elements of the myasthenic autoimmune process (antigen presenting cells, T cells, and B cells). In addition, the 'targets' of the autoimmune process (acetylcholine receptor antigens) are also found in the thymus.⁸ Thymic myoid cells possess a surface acetylcholine receptor that is identical to that found on skeletal muscle cells. The normal function of thymic myoid cells, and the physiological purpose of their acetylcholine receptors, remains unknown. Similarly, the initial event that triggers the autoimmune process in myasthenia gravis remains unknown.¹⁻⁷

The pathophysiological role of the thymus in myasthenia gravis is supported by histological observations. Approximately 75% of myasthenic patients have abnormalities of the thymus.⁹ Thymic hyperplasia is the commonest abnormality. Thymomas are present in approximately 10% of patients with myasthenia gravis.

Clinical features, diagnosis, and medical treatment

Myasthenia gravis has a prevalence of approximately 10 cases per 100 000 population. It has a bimodal age distribution; young adult females and older adults of both sexes are typically affected.¹⁰⁻¹¹ Skeletal muscle weakness, and fatigability with repetitive activity, are characteristic.¹⁻¹² In most patients, extraocular and eyelid muscle weakness are the first symptoms of disease. Generalised weakness eventually develops in approximately 85% of patients. If weakness of the diaphragm and accessory muscles is severe, mechanical ventilation is required (myasthenic crisis). Before the widespread use of immunosuppressive therapy and thymectomy, approximately 25% of patients with myasthenia gravis died of their disease.¹³⁻¹⁵ Modern disease mortality is less than 5%.

Patients with myasthenia gravis may be classified or 'staged' according to the severity of their disease.¹⁶ Indications for medical and surgical therapies, and treatment results, vary with clinical stage of disease. Osserman's classification is

Department of Thoracic Surgery,
Roswell Park Cancer Institute, Buffalo,
NY 14263-0001, USA
JD Urschel

Department of Neurology, University of
Southern California, Los Angeles,
California, USA
RP Grewal

Table 1 Osserman's classification of disease severity

Stage	% of cases	Comments
I Ocular	20	Good prognosis; thymectomy rarely indicated
IIa Mild generalised	35	Thymectomy beneficial
IIb Moderate generalised	25	Thymectomy beneficial
III Severe generalised - acute	10	Medical stabilisation needed; thymectomy occasionally indicated
IV Severe generalised - late	10	Poor prognosis; thymectomy rarely indicated

Thymectomy: general principles

Pre-operative

- medical stabilisation of myasthenia

Anaesthesia

- avoid muscle relaxants

Operative

- total thymectomy
- avoid phrenic nerve injury

Postoperative

- multidisciplinary team
- early extubation
- resume anticholinesterase medication (reduced dose)

the most commonly used staging system (table 1). Most patients have ocular (I), mild generalised (IIa), or moderate generalised (IIb) disease. Severe generalised myasthenia (III and IV) is differentiated from moderate myasthenia by the presence of respiratory muscle involvement. In acute-severe myasthenia (III), symptoms rapidly progress to the point of myasthenic crisis. In late-severe myasthenia (IV), progressive involvement of the respiratory muscles occurs several years after disease onset.

No single investigation is diagnostic of myasthenia gravis. In a patient with clinical features suggesting myasthenia gravis, the diagnosis is confirmed by a combination of anticholinesterase testing, electrophysiological testing, and anti-acetylcholine receptor antibody assay.^{17 18} Once a diagnosis of myasthenia gravis is made, patients should have a screening chest computed tomography (CT) scan for possible thymoma¹⁹ (figure).

Medical therapies for myasthenia gravis can be classified into three groups: anticholinesterase drugs, immunosuppressive drugs, and short-term immunotherapies (plasmapheresis and immunoglobulin).^{1 12 20} Anticholinesterase drugs are the first line of treatment for myasthenia gravis. They enhance neuromuscular transmission by inhibiting cholinesterase activity at the neuromuscular junction. Because they have no impact on the underlying autoimmune process, anticholinesterases do not alter the natural history of myasthenia gravis.¹³

Most patients note improvement in muscle weakness with anticholinesterases, but relief of symptoms is often incomplete. Therefore, the addition of second-line agents (immunosuppressive drugs), or surgical treatment (thymectomy), is eventually required in most patients.^{12 20 21} Second-line medical therapies and surgical thymectomy should not be viewed as competitive treatment modalities. Immunosuppressive therapy and thymectomy are often used together, in a complementary fashion.¹²

Thymectomy

INDICATIONS

The goal of thymectomy in myasthenia gravis is to cause remission of disease, or failing that, to allow dose reduction of potentially harmful immunosuppressive drugs.⁷ Indications for thymectomy remain somewhat controversial, but several generalisations can be made (table 1). Most experienced clinicians recommend thymectomy for patients with mild or moderate generalised disease.^{7 12 22} In these patients, thymectomy should be done early in the course of the generalised disease, as the results appear to be better with earlier surgery.^{7 23} Most patients with purely ocular myasthenia are well controlled with medical treatment, and do not require thymectomy.^{12 24} At the other end of the clinical spectrum, most patients with late-severe generalised myasthenia respond poorly to thymectomy and are at higher risk for peri-operative complications. Therefore, thymectomy is infrequently performed in this group of patients. Patients with acute-severe generalised myasthenia may benefit from thymectomy, but they require initial intensive medical therapy to stabilise their condition. All myasthenics suspected of having a thymoma should undergo thymectomy for oncological reasons.^{7 23 25} Thymectomy for thymoma is reviewed elsewhere and will not be discussed in this article.^{26 27}

In addition to clinical stage of disease, the decision to recommend thymectomy is influenced by patient age. Juvenile myasthenics are more likely than adults to experience spontaneous disease remission.^{12 28} Therefore, thymectomy is only considered after a prolonged period of medical therapy. Patients over 60 years old are not good candidates for thymectomy. The thymus is often atrophic in this age group, and results of thymectomy are disappointing.²⁹ Moreover, operative morbidity is higher in elderly patients.

GENERAL PRINCIPLES OF PERI-OPERATIVE MANAGEMENT

For thymectomy to be an effective treatment modality in myasthenia gravis, total removal of the thymus gland must be accomplished with minimal peri-operative morbidity.⁷ The need for total thymectomy is a basic surgical tenet; it will be discussed later in this review. Peri-operative morbidity is kept to a minimum by careful attention to detail in pre-, intra-, and post-operative care (box). A multidisciplinary team of neurologist, anaesthesiologist, and surgeon is essential.⁷

Thymectomy is never an emergency operation. Pre-operative medical stabilisation of myasthenic symptoms is necessary.⁷ In severely affected patients, pre-operative plasmapheresis may be needed. An experienced neurologist should manage this aspect of peri-operative care. Besides medical stabilisation of myasthenia, respiratory function must be optimised. Cessation of cigarette smoking is highly desirable. Pre-operative teaching by a chest physiotherapist facilitates postoperative respiratory care.

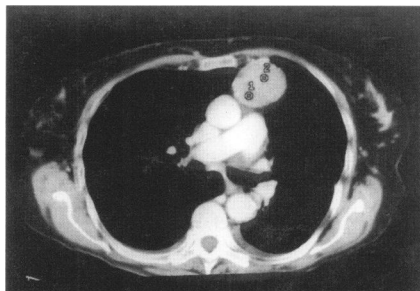


Figure Chest CT scan showing a thymoma in a patient with myasthenia gravis

Intra-operative anaesthesiology concerns include sensitivity of myasthenic patients to skeletal muscle relaxants, and the possible need for corticosteroid administration.³⁰ Skeletal muscle relaxants are best avoided.³¹ Parenteral corticosteroids are given to patients who have been treated with prednisone before operation.

Extubation within several hours of surgery is desirable, but not essential.^{32 33} Assessment of mental status, arterial blood gases, and weaning parameters (indicators of mechanical ventilatory function) is done before extubation.^{30 33 34} Generally, myasthenic patients can be safely extubated if they fulfill these criteria: $p\text{CO}_2 < 6$ kPa, inspiratory force more negative than -25 cm H_2O , tidal volume > 7 ml/kg, and vital capacity > 10 ml/kg. In patients with marginal muscle strength, and borderline weaning parameters, mechanical ventilation is continued and weaning parameters are re-assessed at frequent intervals.^{32 33} In these difficult cases, early postoperative neurological consultation is valuable; cautious administration of anticholinesterase drugs usually results in safe and successful extubation.

Postoperative care should initially take place in an intensive treatment unit. Serial assessments of arterial blood gases, negative inspiratory force, tidal volume, and vital capacity, provide useful information to guide anticholinesterase dosage. After thymectomy, patients may become acutely sensitive to anticholinesterases, and develop profound weakness from their use. This is called a cholinergic crisis.^{7 12} Although some clinicians advocate withholding anticholinesterases in the early postoperative period, it is common practice to restart the medication immediately after thymectomy, but at a reduced dosage. This strategy avoids cholinergic crisis while preventing early postoperative myasthenic weakness. Under the direction of a neurologist, anticholinesterase dosage is slowly increased to control myasthenic symptoms adequately. Anticholinesterases may cause troublesome bronchorrhea after surgery. Close cooperation between neurologist and surgeon is essential in the first few days after thymectomy.

Most major morbidity after thymectomy is respiratory in nature, so the importance of chest physiotherapy and general respiratory supportive care is obvious.⁷ To help deep breathing and coughing, incisional pain must be aggressively treated. Thoracic epidural analgesia and patient-controlled analgesia systems are helpful.³⁵ They provide good pain control while minimising sedation. Bronchial secretions, in part related to anticholinesterase medication, must be cleared. Coughing and chest percussions are usually successful, but invasive tracheobronchial toilet measures may be required. Nasotracheal suctioning, mini-tracheostomy suctioning, or bronchoscopy can be used to clear bronchial secretions.

OPERATIVE APPROACHES

Whilst all surgeons agree that subtotal thymectomy is an inadequate operation for myasthenia gravis, debate continues over the best operative approach to the thymus, and the exact definition of total thymectomy.⁷ Total thymectomy is a simple concept physiologically, but it is very nebulous as an anatomic concept. To some surgeons, total thymectomy means removal of the thymus gland proper. To others, total thymectomy is only accomplished if all possible sites of aberrant thymic tissue are excised. In reality, it may be impossible to achieve total thymectomy consistently; the extent and anatomic location of aberrant thymic rests are too variable. Thymic rests are commonly found in the anterior mediastinal fat, but they may also occur in the neck and in all compartments of the mediastinum.³⁶⁻³⁸ The issues of operative approach and extent of thymectomy are interrelated. Surgeons who advocate thymectomy through small, cosmetically favourable, incisions usually believe that removal of the thymus gland proper is an adequate operation. Surgeons who emphasise the importance of removing extrathymic tissue, in addition to the thymus gland, require greater operative exposure through, at minimum, a complete median sternotomy. The advantages and disadvantages of commonly used operative approaches are summarised in table 2.

It is difficult to designate one type of thymectomy as the standard operation, against which other operations are compared. Nevertheless, thymectomy done through a median sternotomy is the most common operation performed.⁷ The thymus gland is completely removed, while preserving other mediastinal tissues. This is called a 'simple' thymectomy. Simple thymectomy through a complete sternotomy is technically easy, safe, and effective.⁷ Operative exposure is good, so intra-operative complications such as bleeding and phrenic nerve injury are uncommon. Phrenic nerve injury must be avoided in all types of thymectomy. Paralysis of even one hemidiaphragm can be catastrophic for a patient with myasthenia gravis. One disadvantage of the sternotomy approach is postopera-

Table 2 Thymectomy: operative approaches

<i>Approach</i>	<i>Advantages</i>	<i>Disadvantages</i>
Sternotomy	Technically simple	Cosmetic concerns; pulmonary morbidity
Transcervical	Cosmetically good; minimal morbidity	Technically difficult; risk of subtotal thymectomy
Maximal (sternotomy + cervical)	Most complete resection	Highest morbidity; two incisions; risk of recurrent laryngeal nerve injury
Thoracoscopic	Cosmetically good; reduced incisional pain?	Technically difficult; risk of subtotal thymectomy; post thoracoscopy neuralgia

tive pain, which is often considerable. Fortunately, postoperative analgesia has improved in recent years.³⁵ The cutaneous scar from complete sternotomy often concerns patients, especially young woman. Some patients cite it as a reason for delaying surgical treatment.

Several variations of the sternotomy approach to thymectomy exist. Simple thymectomy can be done through a partial median sternotomy.³⁹⁻⁴⁰ In another variation of the sternotomy thymectomy, both pleural spaces are deliberately opened to facilitate thymectomy and removal of all anterior mediastinal fat (which may contain rests of thymic tissue). This operation, which is done through a complete sternotomy, is called an 'extended' thymectomy.²³⁻⁴¹⁻⁴³

Thymectomy can be accomplished through a neck incision, without splitting any part of the sternum (cervical thymectomy).⁴⁴⁻⁴⁷ With the aid of a specially designed retractor, the sternum is retracted to create room to operate within the mediastinum. The thymus can be removed with this operative approach, but it is not feasible to remove surrounding mediastinal fatty tissue. Considerable experience is required to do this operation well; it is not recommended for occasional thymus surgeons. Incomplete removal of the thymus is a potential problem, even in experienced hands.⁴⁸⁻⁵¹ An occasional patient will have a good result after cervical thymectomy, and then subsequently develop recurrent myasthenic symptoms. Re-operation in these patients, through a sternotomy approach, has shown residual thymic tissue in the mediastinum.⁴⁶⁻⁴⁹⁻⁵¹ One advantage of the cervical thymectomy is its lack of significant postoperative pain, which in turn minimises pulmonary complications. Another major advantage of cervical thymectomy is the favourable cosmetic result. It is acceptable to young women, and this can influence them to accept surgical intervention earlier in the course of their disease.⁴⁵

Maximal thymectomy is the most extensive of the thymectomy operations.⁵²⁻⁵³ It involves a sternotomy and a neck incision. Thorough dissection of the mediastinum, pleural spaces, and neck is done to remove as many sites of potential aberrant thymic tissue as possible.³⁶⁻³⁸ In this way a 'maximal' thymectomy is accomplished. Its proponents claim that this gives better therapeutic results for myasthenia gravis than the other less extensive operations. However, operative morbidity is higher with this operation. The extensive neck dissection may result in recurrent laryngeal nerve injury. Even temporary vocal cord paralysis can have adverse physiological effects in myasthenic patients. It makes coughing difficult, and therefore pulmonary problems are more likely. Maximal thymectomy does not enjoy widespread popularity in the surgical community; its use is confined to a few centres.⁵²⁻⁵⁴

Thoracoscopic thymectomy is relatively new, and experience is therefore limited.⁵⁵⁻⁶⁰ It shares a common surgical paradigm with the cervical approach; cosmesis and postoperative pain reduction are sought, but there is a risk of subtotal thymectomy and superior technical skill is needed. Some surgeons have even combined the thoracoscopic approach with a neck incision to reduce the possibility of subtotal thymectomy.⁶¹⁻⁶³ With this combined cervical-thoracoscopic approach, the extent of mediastinal dissection may equal that obtained with a sternotomy.⁶²⁻⁶³ Although thoracoscopic thymectomy would appear to be advantageous in minimising postoperative pain, chronic neuralgia can occur from the trauma of intercostal instrument placement. This complication of thoracoscopic surgery has been increasingly recognised.⁶⁴ Follow-up data for thoracoscopic thymectomy are still quite immature. However, it is conceptionally similar to cervical thymectomy, and it may compete with that approach in centres favouring a less invasive approach to thymectomy.

RESULTS OF THYMECTOMY

Thymectomy benefits approximately 80% of patients who undergo the operation. Approximately 30% experience complete remission of their myasthenia gravis and do not require any medication.⁷⁻²³⁻⁴¹⁻⁴⁵⁻⁴⁶⁻⁵²⁻⁶⁵⁻⁶⁹ An additional 50% improve sufficiently to allow reduction of medication dosage. In the case of long-term steroid use, this dosage reduction can be quite beneficial.

It is difficult to compare the therapeutic efficacy of the various thymectomy operations. Patient selection and criteria for postoperative improvement vary from series to series. Nevertheless, the results of the three traditional operations are remarkably similar.^{45 47 52 66} Further data on thoracoscopic thymectomy are awaited.

The therapeutic effect of thymectomy is somewhat unpredictable. It may take months or years for improvement to be seen,^{7 23} and this raises the possibility of spontaneous remission, unrelated to the thymectomy. Randomised trials have not been done. Buckingham performed a retrospective computer-matched study of medical treatment alone compared to medical treatment plus thymectomy.⁷⁰ The thymectomy group had more frequent complete remissions (35% vs 8%) and a lower incidence of death from myasthenia gravis (14% vs 44%) than the group treated without thymectomy. This report, and other retrospective clinical series, support the use of thymectomy in myasthenia gravis.^{14 67 71 72}

Not all patients with myasthenia gravis are equally likely to benefit from thymectomy. Patients in Osserman stages IIa and IIb have better results than those with stages III and IV disease.^{7 42 46 68} There is some evidence that younger patients, and those having thymectomy early in the course of their disease, also do better.^{7 23 46 67 74} Only 40–50% of myasthenic patients with thymomas are improved by thymectomy, but the operation is nevertheless indicated to remove their tumours.^{7 23 26}

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