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Preoperative Preparation of the Patient with Myasthenia Gravis

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The combination of symptoms of myasthenia gravis (MG) was first described in the latter part of the 19th century [1]. The role of the thymus in the pathogenesis of MG was theoretical until the work of Sauerbruch and Blalock [2]. In 1939, Blalock et al [3] reported performing a thymectomy in a myasthenic woman who had dramatic postoperative symptom improvement. Blalock et al [4] reported their first myasthenic thymectomy series 2 years later. Several features, including the timing of surgery from the time of diagnosis, the age of the patient, and the degree of symptoms and the extent of the thymic resection, seem to correlate with remission [5]. Residual tissue (2 g) after thymectomy may perpetuate the symptoms [6].

The role of thymectomy in the treatment of MG is not well defined. Identification of an appropriate patient depends on a variety of characteristics. First, does the patient have MG? A thorough evaluation of the classic symptoms of the disease and others that are in the differential diagnosis should be performed. Provocative tests may assist in modifying the diagnosis; disease classification by symptoms and treating drugs helps to determine the likelihood of surgical resection success. Are there comorbid diseases that might pose a significant obstacle to surgery? Would thymectomy benefit the patient? These are a few of the questions that are addressed in this article.

MG is the fatigue of voluntary muscles that worsens with repetitive or continuous use and improves with rest. The symptoms worsen as the day progresses. The proximal muscle groups are predominantly affected and usually symmetrically. The shoulders and upper extremities are more commonly involved than the lower extremities. Sudden or gradual weakness of the skeletal musculature, even with minimal exertion, is the classic presentation. Ptosis, diplopia, and blurring are the presenting symptoms in nearly 50% of patients, and in 15%, they are the sole symptoms. Of patients, 85% develop generalized muscle weakness. In 20%, the bulbar muscles alone are affected.

The physical examination may show a loss of smile, facial weakness, and nasal speech. Patients frequently may sit slumped forward, unable to hold their head erect. Patients may be febrile and have rhonchi, rales, and wheezing from the recurrent aspiration. The gag reflex may be absent. In contrast to other potential diseases, the pupils in MG should react to light and accommodation, and the corneal reflex should be preserved. Placing an ice pack over the eyelids of myasthenic patients with ptosis temporarily improves the lagging lid. Signs of exophthalmos may represent coexistent thyroid disease. Limitation of neck flexion and extension may be a sign of coexistent rheumatoid arthritis. Myasthenic patients may have associated atrial fibrillation and signs of heart failure. Provocative testing during the examination to show weakness with repetitive action includes hand grip strength with a dynamometer, head raising, and arm and leg raising. Stepping up and down on a footstool may prove difficult as the exercise is repeated. Patients may have an elevated white blood cell count, fever, and chest x-ray findings

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consistent with pneumonia. A thorough history and physical examination by the MG surgeon often provides sufficient information to make the diagnosis and determine the appropriate test to confirm it. To assist in grading the disease and following the course of therapy, Barohn et al [7] developed a quantitative MG score that has been adopted by the Myasthenia Gravis Foundation (Table 1).

MG is an autoimmune disease. Nearly 90% of MG patients test positive for acetylcholine receptor (ACh-R) antibodies [8]. The serum from affected patients may be transferred experimentally to and induces symptoms in test animals. Plasmapheresis reduces or relieves the symptoms. A complex interaction of the thymic myoid cells with the local cytokine and complement pathways is believed to initiate and perpetuate the disease [9]. Neither ACh-R antibody concentration nor antibody binding seems to correlate with the severity of the disease or the prognosis. Ultimately, there is a gradual destruction of the nicotinic postsynaptic motor end plate ACh-R. The decrease in the number of receptors seems to correlate with the severity of disease [10]. Symptoms usually occur when the amount of receptors is less than 30% of normal [11]. Other abnormalities identified in the synaptic cleft include a reduction in the end plate folds and an increase in the distance of the synaptic cleft. The result is less ACh released with repetitive stimulation, in essence a "rundown" phenomenon, and less effect from the ACh released [12]. Drugs,

Table 1
Quantitative myasthenia gravis score for disease severity

Test item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision on lateral gaze right or left (circle one), seconds	61	11–60	1–10	Spontaneous	
Ptosis (upward gaze), seconds	61	11–60	1–10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz water (½ cup)	Normal	Minimal coughing or throat clearing	Severe coughing/ chocking or nasal regurgitation	Cannot swallow (test not attempted)	
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30–49	Dysarthria at 10–29	Dysarthria at 9	
Right arm outstretched (90° sitting), seconds	240	90–239	10–89	0–9	
Left arm outstretched (90° sitting), seconds	240	90–239	10–89	0–9	
Vital capacity, % predicted	≥80	65–79	50–64	<50	
Right-hand grip, kgW					
Men	≥45	15–44	5–14	0–4	
Women	≥30	10–29	5–9	0–4	
Left-hand grip, kgW					
Men	≥35	15–34	5–14	0–4	
Women	≥25	10–24	5–9	0–4	
Head lifted (45° supine), seconds	120	30–119	1–29	0	
Right leg outstretched (45° supine), seconds	100	31–99	1–30	0	
Left leg outstretched (45° supine), seconds	100	31–99	1–30	0	
			Total quantitative myasthenia gravis score (range, 0–39)		

From Barohn RJ, McIntire D, Herbelin L, et al. Reliability testing of the quantitative myasthenia gravis score. Ann N Y Acad Sci 1998;841:769–72; with permission.

Box 1. Myasthenia Gravis Foundation classification*

I—May have weakness of eye closure
All other muscle strength is normal
II—Mild weakness affecting other than ocular muscles
Also may have ocular muscle weakness of any severity
IIa—Predominantly affecting limb or axial muscles or both
Also may have lesser involvement of oropharyngeal or respiratory muscles or both
III—Moderate weakness affecting other than ocular muscles
Also may have ocular muscle weakness of any severity
IIIa—Predominantly affecting limb or axial muscles or both
Also may have lesser involvement of oropharyngeal muscles
IIIb—Predominantly affecting oropharyngeal or respiratory muscles or both
IV—Severe weakness affecting other than ocular muscles
Also may have ocular muscle weakness of any severity
IVa—Predominantly affecting limb or axial muscles or both
Also may have lesser involvement of oropharyngeal muscles
IVb—Predominantly affecting oropharyngeal or respiratory muscles or both
V—Defined by intubation, with or without mechanical ventilation except when employed in routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb

* It is recommended that the most severely affected muscles be employed to define the patient's class. The maximum severity—the most severe pretreatment status determined by this classification—is recommended as a permanent point of reference.

Data from Appendix: Myasthenia Gravis Foundation of America Recommendations for Clinical Research Standards. In: Kaminski HJ, editor. Myasthenia Gravis and related disorders. Totowa (NJ): Humana Press; 2003. p. 373–80.

body temperature, and emotions may worsen the neuromuscular transmission.

The age of presentation is bimodal. The most typical patients are young women in their 20s and 30s (mean 26 years). The male-to-female ratio is 1:4, and for patients younger than 30, it is 1:5. Among older patients, men are more common. The symptom onset may be slow or rapid. The prevalence is 1 to 14 per 100,000 [13]. Since the 1980s, the mortality associated with MG has decreased. As a result, the number of living patients has increased. Ten percent of patients have an additional associated autoimmune disorder; 4% have thyroid abnormalities, more commonly hypothyroidism.

The Myasthenia Gravis Foundation has made numerous modifications to the Osserman Classification (Box 1). The classification provides a means to evaluate the natural history, assist in developing a treatment plan, and assist in determining a prognosis. It is not a linear grading system. The examiner simply determines whether there is presence of ocular, bulbar, generalized, or proximal muscle weakness and makes a rough subjective assessment of the severity.

A general understanding of the diagnostic tests assists in confirming the diagnosis. Before surgery, it is helpful to have a neurologist who is experienced in the disease examine the potential surgical patient. Electromyography (EMG) has been used since 1895. The "jolly test" repetitively stimulates a peripheral motor nerve at 2 to 3 Hz while recording the muscle action potential from two surface electrodes. The test is considered diagnostic when the height of the measured action potential decreases by 15% or more with the repetitive stimulation. Accuracy is optimized when the symptomatic muscle groups are tested. Fifty percent of MG patients have false-negative EMG, especially patients with mild generalized symptoms or ocular symptoms only. The test is simple to perform, but interpretation varies by observer.

Single-fiber EMG or "jitter test" requires an experienced neurophysiologist and is expensive to perform. Fine-needle electrodes are placed between two muscle fibers innervated by a single motor neuron. The variation and the action potential between

the two muscle fibers are measured. The test is 95% sensitive and is best done in patients with generalized MG. The specificity is 50% because other nerve disorders may produce a false-positive result. This test typically is used to assess response to therapy.

The Tensilon (edrophonium) test is fairly simple to perform: 0.1 to 0.2 mg of Tensilon is given intravenously initially to determine if symptoms improve. If there is no response, an additional 2 mg of the drug is administered. If there is no symptom improvement, 9 mg is given. The onset of action is usually within 30 seconds and lasts approximately 5 minutes. The gradual increase in edrophonium dose is meant to avoid a cholinergic crisis. This test is least sensitive in patients with ocular symptoms only, but is 95% sensitive in the general MG population. Observer variability occurs. A test has its maximum sensitivity when the patient is at his or her weakest. To evaluate better equivocal or weak test results, neostigmine (Prostigmin), a cholinesterase inhibitor, may be given to prolong the response.

The binding, blocking, and modulating antibody test is a radioimmunoassay using radioactive iodine–tagged α-bungarotoxin, which binds specifically and irreversibly to the ACh-R antibody. The test is 80% to 90% sensitive. The modulating or blocking antibodies are positive in 5% of patients who are binding antibody negative [14]. The 10% to 20% who are antibody negative still have a circulating immune complex that affects the motor nerve end plate and can cause symptoms on passive transfer of serum [15]. Among patients with ocular symptoms, 50% are antibody positive. The test is the most specific of the tests used, although patients with amyotrophic lateral sclerosis, biliary cirrhosis, tardive dyskinesia, thyroiditis, thymoma without MG, and lupus erythematosus can have false-positive antibody tests [16]. The antibody levels do not correlate with the symptoms or the effectiveness of therapy [17,18]. Anti–striated muscle antibodies are associated with patients who have a thymoma [19]. Seronegative patients are more likely female and more frequently have either ocular and bulbar symptoms only or severe bulbar, neck, and respiratory symptoms. As a group, these patients are less likely to respond to thymectomy [20]. A relatively rare group of ACh-R antibody–negative MG patients express antibodies against the muscle receptor tyrosine kinase [21]. These patients are much less likely to benefit from thymectomy because they are less likely to have thymic pathology.

Box 2 lists the other potential diseases that may be confused with myasthenia gravis. The first, congenital myasthenic syndrome, is not a single disease, but rather a group of several rare congenital myasthenic syndromes associated with weakness in neonates and infants [22]. Typically, there is a family history of the abnormality, there is no ACh-R antibody present, and the Tensilon test is negative. These syndromes represent a host of synaptic abnormalities that result in weakness [23].

Box 2. Differential diagnosis of patients with myasthenia gravis

- Congenital myasthenic syndromes
- Drug-induced myasthenic syndromes
  - Penicillamine, organophosphates
  - Curare
  - Procainamide
  - Quinines
  - Aminoglycosides
  - Metoclopramide
- Eaton-Lambert syndrome
- Amyotrophic lateral sclerosis
- Muscular atrophy
- Hyperthyroidism
- Graves' disease
- Botulism
- Progressive external ophthalmoplegia (Kearns-Sayre syndrome)
- Intercranial mass compressing cranial nerves
- Psychoneurosis

MG syndrome can develop in a small percentage (<1%) of patients treated with penicillamine. Frequently the syndrome begins with ocular symptoms and can progress to generalized myasthenia. The Tensilon test, EMG, and the ACh-R antibody tests are positive. Organophosphates, procainamide, quinines, aminoglycosides, and metoclopramide all can cause MG-type symptoms. The symptoms usually improve with discontinuation of the drugs.

Botulism also can result in ocular and bulbar weakness. In botulism, the pupils do not respond to light or accommodation. With repeated nerve stimulation, EMG shows an increased response, rather than the decrease seen with MG.

Brainstem pathology, such as tumors or aneurysms, can cause dysfunction in the cranial nerves. On physical examination, evaluation of cranial nerves III through VI may prove beneficial. The loss of a corneal reflex is not a finding in MG, whereas it is in brainstem lesions. MRI of the brain and skull base may be beneficial to differentiate these lesions

from MG. Generalized symptoms of myasthenia reduce the likelihood of brainstem pathology.

Kearns-Sayre syndrome is a mitochondrial disorder that presents in children as ptosis and ophthalmoplegia and may continue to progress to generalized muscle weakness. There is associated retinal degeneration and progressive cerebellar disease. Muscle biopsy specimens also may help to differentiate this disease from MG.

Thyroid disease may coexist with MG and may be difficult to differentiate from it. When exophthalmos is present, the eye disease is more likely due to Graves' disease than MG. The presence of MG warrants performing thyroid function studies.

Amyotrophic lateral sclerosis can cause progressive muscular weakness, including the bulbar muscles. The peripheral nature of the weakness and the associated hyperreflexia and Babinski sign can help to differentiate this disease from MG. Amyotrophic lateral sclerosis can have a positive Tensilon test and ACh-R antibody.

Psychoneuroses and depression may simulate or may appear similar to MG. With psychoneuroses and depression, the fatigue is greater in the morning, in contrast to the worsening fatigue through the day with MG. Provocative testing also may help to differentiate MG from psychoneuroses and depression.

Eaton-Lambert syndrome may have similar characteristics to MG and is associated with small cell lung cancer and Hodgkin's disease in 85% of cases. Pelvic muscle and truncal weakness is more frequently an early symptom, making it difficult for patients to stand up out of a chair. Bulbar and ocular symptoms are rare; however, ptosis may be seen. The shoulders are less frequently involved with Eaton-Lambert syndrome. Eaton-Lambert symptoms are more pronounced in the morning and seem to improve through the day; there also may be associated autonomic abnormalities, such as dry mouth. EMG shows an increased response rather than the decreased response in MG. Autoantibodies to the P/Q-type calcium channels are found in more than 95% of patients with Eaton-Lambert syndrome. These autoantibodies also may be found in patients with MG, but are relatively rare (<5% of patients).

After reviewing the history and physical examination findings and the provocative testing results, excluding other potential diseases, the degree of disease or the Myasthenia Gravis Foundation Association classification is determined (see Box 2). The neurologist chooses medication that minimizes the symptoms with minimal side effects. Cholinesterase inhibitors or anticholinesterases increase the synaptic cleft ACh. Prolonged use may enhance the destructive effect of MG [24,25]. Medications include neostigmine and pyridostigmine (Mestinon). Pyridostigmine has a longer half-life and usually is started at 60 mg three times per day; it may be increased to 1500 mg/d. After the drug is initiated, most patients experience symptomatic improvement. The improvement is short-lived, and it is beneficial to have a second agent to treat the patient in preparation for surgery. The side effects are diarrhea, rhinorrhea, nausea, increased salivation and tears, bronchorrhea, and abdominal pain. Excessive dosing may result in a cholinergic crisis, which is characterized by myosis, paralysis, salivation, tearing, bronchorrhea, diaphoresis, and wheezing. Progressive weakness associated with anticholinesterases may be difficult to differentiate from undertreatment or overtreatment of MG in the postoperative period.

Corticosteroids are used at doses of 50 to 100 mg/d of prednisone (1–2 mg/kg/d for children). Symptoms may worsen significantly 4 to 8 days after corticosteroids are started, prompting some physicians to admit patients for steroid initiation. Approximately 3 to 6 weeks are required for symptoms to improve. When symptom management is optimized (usually 3–6 months), the dose may be adjusted for lifelong use. Side effects of steroid use include cataracts, cushingoid features, aseptic necrosis of the femoral heads, obesity, psychosis, hypertension, glucose intolerance, osteoporosis, and gastrointestinal ulceration. Prednisone doses of less than 10 mg/d may reduce the likelihood of complications before a median sternotomy is performed, although the presence of steroids may serve to reduce poststernotomy complications [26].

Immunosuppressive medications also may be beneficial and are used in a significant percentage of patients. Azathioprine (Imuran) is used frequently to decrease steroid doses or to benefit patients who are incompletely treated with steroids or unable to tolerate steroids. More specifically, immunosuppressive therapy attempts to target the T cells. Azathioprine most frequently is used lifelong, and its onset effect takes approximately 3 to 12 months. The dose is started at 50 mg/d for the first week, then increased 2 to 3 mg/kg/d until the desired effect is achieved. Nearly half of patients show some improvement. Approximately 10% of patients have flulike reaction, and there is associated bone marrow suppression, nausea, vomiting, and biliary stasis.

Cyclosporine is an alternative immunosuppressive agent that inhibits interleukin-2 by helper T cell. Cyclosporine seems to have a more rapid response than azathioprine; the dose is 5 mg/kg/d. Side effects include hypertension, hirsutism, and renal dysfunction.

Intravenous immunoglobulin improves symptoms for periods of weeks to months. Patients are given a daily dose of 400 mg/kg/d intravenously over a 5-day period. It is generally well tolerated. This medication may be useful in controlling symptoms in children with more advanced disease before thymectomy.

Plasmapheresis may be performed removing 1 to 3 L of plasma each session every other day for three to five sessions. The goal is to achieve the desired effect after the plasmapheresis has been performed. The improvement may last several weeks and may occur in antibody-positive or antibody-negative patients. Plasmapheresis seems to be significantly effective in patients with respiratory dysfunction (with vital capacity <2 L) and patients who may be on a ventilator [27,28] and is superior to anticholinesterase medication [29,30]. Patients with advanced disease who receive preoperative plasma exchange required less long-term ventilation and shorter ICU stays [31]. Plasmapheresis may allow the discontinuation of anticholinesterase drugs preoperatively, reducing the bronchorrhea that is associated with anticholinesterase drugs.

Other diseases may coexist with MG and should be screened preoperatively. Associated thyroid disease may exist in 5% to 10% of MG patients. Patients may be hypothyroid or hyperthyroid, and the associated thyroid disease may worsen the symptoms of myasthenia. It is recommended that thyroid function tests be performed routinely before surgically treating patients with MG. Other autoimmune diseases include rheumatoid arthritis and systemic lupus erythematosus; measuring a screening serum antinuclear antibody and rheumatoid factor may be beneficial as well.

Thymic hyperplasia is found in 70% and thymic atrophy in 20% of surgically resected patients [32]. Thymomas are found in approximately 10% to 20% of patients with MG. These tumors are rare in patients younger than age 20; the incidence is greatest in older men. Patients with thymomas are less likely to benefit from thymectomy. In the initial evaluation and preoperatively, patients should have a screening chest CT scan for thymoma (Fig. 1), which is approximately 88% sensitive [33]. There is no evidence that MRI is superior to CT in screening for thymomas.

Before surgery, assessing the areas of potential organ dysfunction may be of significant benefit. Inspiratory and expiratory muscles may be dysfunctional [34,35]. Spirometry may show a normal total lung capacity, but a low vital capacity with a normal-to-high residual volume [36]. Patients who are at risk for prolonged ventilatory support include patients with advanced disease; a Myasthenia Gravis Foundation classification II or higher (see Box 2); duration of MG for more than 6 years; history of steroid requirement; and a prior history of MG-induced respiratory insufficiency, vital capacity less than 2.9 L, pyridostigmine dose greater than 750 mg/d 48 hours before surgery, or maximal expiratory force less than 40 to 50 cm H_2O [37–40]. The upper airway may be affected or obstructed by bulbar muscular dysfunction or potential mediastinal thymic compression from an anterior thymic mass [41]. There may be a risk of airway obstruction at the time of intubation. A flow-volume loop may be beneficial in evaluating these patients. If this is present, the patient may need to be intubated using an awake intubation technique of local anesthesia and mild sedation.

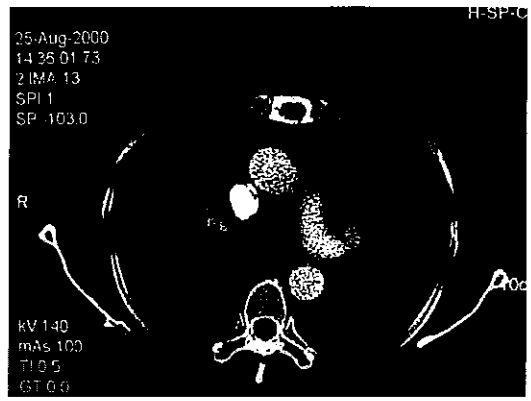

Fig. 1. CT scan of patient who presented with myasthenia and was found to have a large, malignant thymoma.

Patients with MG also may have associated cardiac dysfunction [42]. They may have conduction defects and arrhythmias, including sinus bradycardia, premature ventricular contractions, and atrial fibrillation. There also may be some primary left ventricular filling dysfunction—a condition that seems to be more frequent in patients with thymoma [43,44]. A preoperative ECG and possibly an echocardiogram may be warranted, particularly if symptoms and signs of cardiac dysfunction are present.

In preparing a patient for surgery, the goals are to suppress the immune response, decrease the circulating antibodies, and optimize the neuromuscular transmission. The anticholinesterase medication should be minimized over several weeks before surgery to reduce the likelihood for postoperative bronchorrhea and rhinorrhea, while maintaining symptom control. On the morning of surgery, a half dose of anticholinesterase inhibitor should be given to patients with mild symptoms, and a full dose should be given to patients with moderate-to-severe symptoms

[45]. Steroids should be minimized to reduce the likelihood of postoperative wound healing problems, infection, and pulmonary complications.

From the anesthetic standpoint, some inhalation agents should be avoided in MG patients [46,47]. Propofol has been used and does not seem to affect neuromuscular transmission [48]. Depolarizing muscle relaxants, such as succinylcholine, are less likely to be effective. Preoperative plasmapheresis may delay significantly the reversal of succinylcholine. The nondepolarizing agents, such as atracurium, are not dependent on plasmacholinesterases and are better agents [49].

The role of thymectomy in the management of MG is controversial. Although there is long-standing evidence that the procedure is beneficial, the timing of surgery and the surgical approach are controversial. Some authors believe that thymectomy is valuable as an initial form of therapy because it reduces the likelihood for long-term sequelae of MG. Other authors believe that thymectomy should be reserved for patients who fail medical management or have excessive medication-related side effects. Thymectomy is rarely, if ever, an emergent procedure. The procedure has a mortality of less than 1%, although morbidity may be substantial in the most severely affected patients; 22% of patients with preoperative respiratory insufficiency may require long-term mechanical ventilation [50].

In a meta-analysis of 21 nonthymomatous MG cohorts from 1953 to 1998, patients who received thymectomy were 2.1 times more likely to develop treatment-free remission, 1.6 times more likely to become asymptomatic, and 1.7 times more likely to have improved symptoms compared with patients who did not undergo surgery [51]. Median sternotomy is the most frequently used approach, but other techniques, including the transcervical thoracoscopic and robotic approaches, have been described. The patient selection for each of these approaches has not been completely elucidated.

Summary

All patients who are to undergo a thymectomy should be evaluated thoroughly by a neurologist—ideally one with special training and interest in the diagnosis and management of MG. Confirmatory tests to diagnose MG and other potential diseases should be reviewed. The antibody test seems to be most specific, but there are rare cases of other diseases that are ACh-R antibody positive. In 10% of MG patients, serology is negative, and other tests are necessary to confirm the diagnosis. All patients should undergo a contrast-enhanced high-resolution CT scan with 5- to 8-mm slices because thymoma or thymic carcinoma may be present. Pulmonary function tests, including vital capacity, forced expiratory volume, maximal expiratory force, arterial blood gas, and a flow-volume loop, should be performed. Exercise testing to evaluate for hypoxia and hypotension with exercise and ambulation also may be appropriate. A thorough assessment for cardiac dysfunction, including echocardiography, nuclear medicine studies, or a formal cardiology evaluation, may be beneficial. Because MG is a complex autoimmune disease, preoperative blood tests should include thyroid function testing, antinuclear antibody, and rheumatoid factor in addition to routine preoperative studies. Plasmapheresis or intravenous immunoglobulin should be considered for patients with advanced disease, bulbar symptoms, or poor pulmonary function. Given these guidelines, careful selection of candidates for surgery should optimize the long-term results for patients with MG.

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