A new approach to late onset myasthenia gravis

C WARREN OLANOW, MD and ALLEN ROSES, MD

Delay in removing thymomas may increase the likelihood of a benign tumour invading local tissue and becoming malignant. Prolonged steroid therapy in older patients carries with it the risk of serious complications. By contrast, there were no complications of sternal-splitting thymectomy in the late onset myasthenia gravis patients.

We have demonstrated that thymectomy alone can improve many patients with myasthenia gravis, including those with the late onset form of the disorder. A key advantage to this approach is that it avoids the necessity of concurrent medication. While a drug-free approach has advantages for any patient, it is particularly well suited for those over the age of 55. Based on the results of our study, we believe that early, total thymectomy is the preferred treatment for patients with myasthenia gravis.

Background

Myasthenia gravis is the result of an autoimmune attack directed against postsynaptic acetylcholine receptors in muscle. As a result, there is a reduction in the number of acetylcholine receptors, which leads to impaired neuromuscular transmission and the clinical features of weakness and fatigue.

Although the role of the thymus gland in the pathogenesis of myasthenia gravis has not been clearly identified, we have postulated that a thymic factor is essential to the development of clinical weakness. This may act by promoting complement-mediated lysis of the acetylcholine receptor, which has been marked by the antiacetylcholine receptor antibody. Certainly, the thymus gland is known to be capable of modulating cellular and humoral immune reactions and is known to be abnormal in most myasthenia gravis cases. A possible explanation is that the thymus gland contains cells with acetylcholine receptor antigen and is capable of generating antibody to this antigen.

Myasthenia gravis generally affects young patients, but, in some series, as many as one-third develop symptoms after the age of 55. Most of these are men; women are more likely to present at earlier ages.

In its fully-developed form, myasthenia gravis may result in severe weakness with involvement of bulbar musculature; at its onset, the symptoms and signs may be insidious and easily overlooked. Because early thymectomy may effectively prevent the development of symptoms and signs in many patients, early diagnosis is extremely important. The primary care doctor dealing with the geriatric population must therefore be familiar with the presenting features of late onset myasthenia gravis.

Clinical features

Myasthenia gravis is characterised by weakness and fatigability of voluntary muscles.
Myasthenia gravis is the result of an autoimmune attack against acetylcholine receptors – with a thymic component.

Weakness increases with sustained exercise and is improved by rest. The patient may feel well on awakening, only to become fatigued during the course of his daily activities. Individual muscles may be affected selectively, with one muscle being weak while another muscle remains strong.

The cranial nerves are generally the first to be involved; this should alert the doctor to the possible diagnosis. Most patients present with ptosis, diplopia, or both, which may initially be intermittent. Approximately 90% of patients develop external ocular muscle weakness sometime during the course of their illness. Dysfunction may be confined to the ocular musculature (ocular myasthenia), but in the majority, generalised weakness eventually develops.

Other cranial nerves may also be affected. In patients over the age of 55, weakness of the muscles of mastication and swallowing may be prominent early features. One must take particular care with the late onset population not to presume that these symptoms are due to poor dentition or faulty bridgework.

Respiratory disturbances are potentially dangerous features of myasthenia gravis and may occur at any time during the course of the illness. Fortunately, in most situations, the diagnosis can be made before these muscle groups become involved.

The proximal muscles of the upper and lower extremities are generally more severely affected than the distal muscles. In early cases, it may be necessary to “fatigue” these muscles by exercising them in order to bring out weakness. Complaints may be relatively nonspecific, so care must be taken not to attribute these to arthritis, Parkinson’s disease, diabetes, stroke, or other disorders likely to affect older patients. The development of nonspecific complaints of weakness and fatigue, coupled with unusual features – such as inability to hold the head up or distinct worsening during the course of the day – should raise the possibility of myasthenia gravis. In severe cases, virtually any voluntary muscle group may be affected, resulting in profound weak-

### TABLE 1

**Modified clinical classification of patients with myasthenia gravis**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Ocular myasthenia</th>
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<tbody>
<tr>
<td>Involvement of ocular muscles only.</td>
<td>May progress to generalised muscle weakness.</td>
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<tr>
<th>Group 2</th>
<th>Mild generalisation</th>
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<tr>
<td>Frequently ocular at onset with gradual spread to involve skeletal muscles.</td>
<td>Respiratory bulbar muscles not involved.</td>
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<table>
<thead>
<tr>
<th>Moderate generalisation</th>
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</thead>
<tbody>
<tr>
<td>Gradual onset with frequent ocular presentations, progressing to more severe generalised involvement of skeletal and bulbar muscles.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Severe generalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fulminating. Rapid onset of severe bulbar and skeletal muscle weakness with early involvement of respiratory muscles.</td>
</tr>
</tbody>
</table>

Source: Author
As many as one-third of patients develop symptoms after the age of 55 — most of these are men.

Clinical function is often graded by a modified Osserman classification, as outlined in the accompanying table.

**Diagnostic tests**

When the diagnosis of myasthenia gravis is suspected, a prompt neurological consultation should be obtained. Studies should then be performed to try to establish the diagnosis of myasthenia gravis by pharmacological, electrical, and serological criteria shown in the accompanying figure.

The studies we have relied on most include the edrophonium (Tensilon) test, EMG, and a measure of anti-acetylcholine receptor antibodies in the serum.

**Pharmacological tests**

Tensilon is a short-acting anticholinesterase agent that may reverse the clinical and electrical features of myasthenia gravis. This effect is noted within minutes after an intravenous injection. We generally perform this test in a blind manner, using saline and nicotinic acid as controls. The administering doctor must be prepared to deal with possible allergic and cholinergic reactions to the drug. Eighty to 90% of patients with myasthenia gravis will have a positive response to Tensilon. This effect may be least pronounced for the ocular features of myasthenia gravis.

**Electrical tests**

The Jolly’s reaction can be tested in most electromyography laboratories. One looks for a reduction in the ampli-

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**Diagnostic phase in the treatment of myasthenia gravis**

**Myasthenic symptoms**

- Careful history
- Careful physical

**Pharmacological**

- Tensilon

**Electrical**

- Jolly’s reaction

**Serological**

- ACh R antibodies

**Associated conditions**

- Thyroid
- TH panel antibodies
- Thymoma
- CT antibodies
- Antistriated muscle antibodies
- Collagen vascular disease (SLE, polymyositis)
- LE prep
- FANA
- CK
- SED rate
- Red cell aplasia
- MS
- Drug-induced (penicillamine)

*Figure 1. This schematic diagram outlines a diagnostic approach to patients suspected of having myasthenia gravis.*

*Source: Authors*
The cranial nerves are generally the first to be involved, especially with ptosis, diplopia or difficulty with swallowing.

The amplitude of the evoked muscle action potentials following repetitive nerve stimulation. In normal patients, stimulation rates of 50 per second or greater are required to induce significant decrement. In patients with myasthenia gravis, decrement can be seen with stimulation rates as low as two to three per second. This test is valuable in more severely affected myasthenia gravis patients, but values may remain normal in early stages of the disease.

The single-fibre or "jitter" study has proved to be more sensitive. It measures fluctuations in the latency of action potentials of two muscle fibres innervated by the same motor unit. In normal patients, the latency between these potentials is relatively constant. In patients with myasthenia gravis, there may be considerable alteration in these latencies, or "jitter", and in severe cases there may actually be blocking of one of these potentials. Ninety to 95% of patients with myasthenia gravis have abnormal single-fibre studies, although it may be necessary to study several muscle groups.

**Serological tests**
Acetylcholine receptor antibodies are present in the serum of approximately 90% of patients with myasthenia gravis. These antibodies are highly specific and considered to be diagnostic. A laboratory report indicating no measurable acetylcholine receptor antibody level, however, does not rule out myasthenia gravis.

The combination of a careful history and physical examination along with these diagnostic studies allows the diagnosis of myasthenia gravis to be made in the vast majority of instances. Patients with myasthenia gravis restricted to the ocular muscles may be more difficult to identify because laboratory studies are more often nondiagnostic. In circumstances in which the diagnosis cannot be defined, patients should be followed, as the clinical picture may become more clear on subsequent visits.

**Associated conditions**
Several conditions may be associated with myasthenia gravis, including thyroid disorders, polyglandular failure syndrome, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and red cell aplasia. These conditions are generally autoimmune disorders in which other receptors have presumably been affected.
The diagnosis is best confirmed by the edrophonium test, EMG and a measure of antiacetylcholine receptor antibodies.

Disorders of the thymus are noted in 85 to 90% of myasthenia gravis patients. Ten to 15% have a thymoma, which is generally detected by CT of the mediastinum. These are usually benign tumours, but as many as 43% have been reported to be malignant in some series. Malignancy does not usually reflect alterations in the histological pattern; rather, it represents infiltration into neighbouring tissues, such as the pericardium and pleura. It is our impression that delay in removing thymomas very probably increases the likelihood of a benign tumour invading local tissue and becoming malignant.

In most young patients and occasionally in patients over the age of 55, the thymus is hyperplastic. Most late onset patients, however, have involuted atrophic thymus glands. Still, there may be immunologically active thymic remnants. Furthermore, thymic epithelial cells have been found scattered throughout the anterior mediastinal fat. These cells show excessive staining for thymosin-α-1, a potent immunopotentiating agent that may play a role in the pathogenesis of myasthenia gravis.

**Treatment**

The management of patients with myasthenia gravis has involved anti-cholinesterase agents, steroids, plasmapheresis, immunosuppressive agents, and thymectomy. Although there are reports indicating each of these may be effective, there have been no randomised controlled studies comparing one form of therapy with another. A retrospective study suggested that thymectomy was the pre-
ferred form of therapy. It is difficult to analyse studies in the literature as there is considerable variability in patient selection, preoperative preparation, and concomitant treatment.

Even less clear is the situation regarding patients with late onset myasthenia gravis, as most studies concentrate on younger patients. Tindall arbitrarily excluded patients older than the age of 45 from thymectomy in favour of steroids. He described clinical improvement and suggested that steroids were the preferred form of therapy in this age group. He attributed benefit to a reduction in the acetylcholine receptor antibody level.

By contrast we have reported marked improvement following thymectomy without concomitant steroid therapy and without a reduction in acetylcholine receptor antibody levels, indicating that a reduction in this antibody is not essential to clinical improvement. It is our feeling that a thymic factor is critical to the development of clinical weakness in myasthenia gravis. We discussed this view in a recent hypothesis.

**Thymectomy**

Since 1977, all presenting pa-
Our treatment is based on early thymectomy with a gratifying response.

Patients at Duke University Medical Centre have been treated according to a prospective treatment protocol we instituted that is based on this hypothesis. All patients are treated by a sternal-splitting 'total' thymectomy performed as early as possible after the appearance of generalised features of myasthenia gravis. All efforts are made to avoid or discontinue drug therapy. The medical status of patients is optimised before surgery by a course of plasmapheresis without immunosuppression. The results of this approach have been reported in detail elsewhere.

In brief, there have been no significant perioperative complications. All patients have improved, and 87% are free of generalised weakness and are in clinical remission (mean follow-up, 27 months). Sixty percent are on no medication and 25% receive low-dose alternate-day steroids solely for ocular dysfunction.

During the course of this study, no patient was denied thymectomy because of reason of age. We have performed thymectomy on 17 late onset myasthenia gravis patients. The first 12 have been reported separately. There were no complications of surgery in this age group. The response to thymectomy was similar to that seen in our younger patients. These patients have now been followed for approximately 30 months. Seventy-one percent remain free of generalised weakness and 50% are on no medication. One patient has shown transient deterioration in his clinical status; this was easily reversed with a short course of prednisone. The results in general were striking, although not quite so dramatic as in our younger patients. This may reflect the fact that several of our late onset patients were more seriously affected at the time of referral. It is our impression that the best clinical results occur when thymectomy has not been delayed. Long-standing myasthenia gravis may result in irreversible change of the acetylcholine receptor or a fixed myopathy that is not responsive to intervention.

The clinical results occurred independently of thymic pathology; patients with thymic hyperplasia, thymoma, and atrophic involuted thymus glands all showed improvement. However, our general impression was that patients with involuted thymus glands did not improve as dramatically as those with hy-
A thymic factor is critical to the development of clinical weakness in myasthenia gravis.

perplasia or thymoma. There was no significant change in the acetylcholine receptor antibody levels of these patients, indicating again that a reduction in antibody titre is in and of itself not essential for clinical improvement.

Steroids
We compared our series of thymectomy-treated late onset myasthenia gravis patients with those reported to respond to steroid therapy. Although all patients in both groups improved, the percentage of patients free of generalised weakness was higher in our series. Furthermore, all steroid-treated patients continued to require medication, whereas 50 of our patients were on no medical treatment. Prolonged steroid therapy carries with it the risk of serious complications in older patients, including compression fractures, hypertension, glucose intolerance, fluid retention with congestive heart failure, cataracts, mental changes, and possible predisposition to infection. By contrast, there were no complications of sternal-splitting thymectomy in the late onset myasthenia gravis patients. Therefore, we prefer to hold off steroids and all other anti-myasthenia medications during the postoperative period unless patients fail to respond or clinically deteriorate after thymectomy.

References for this article are obtainable from the Editor, P O Box 375, Claremont 7735.

When nature overdoes it

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Reg. No. HB1751 (Act/Wet 10/1965)