UPDATE ON MYASTHENIA GRAVIS

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Update on Myasthenia Gravis

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The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AAEM.
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## Update on Myasthenia Gravis

### Contents

<table>
<thead>
<tr>
<th>Faculty</th>
<th>ii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>v</td>
</tr>
<tr>
<td>Course Committee</td>
<td>vi</td>
</tr>
<tr>
<td><strong>Epidemiology of Myasthenia Gravis: An Electrodiagnostic Perspective</strong></td>
<td>1</td>
</tr>
<tr>
<td>Lawrence H. Phillips, II, MD</td>
<td></td>
</tr>
<tr>
<td><strong>The Clinical Features and Diagnosis of Myasthenia Gravis</strong></td>
<td>7</td>
</tr>
<tr>
<td>Vern C. Juel, MD</td>
<td></td>
</tr>
<tr>
<td><strong>The MuSK Antibody—Positive Myasthenia Gravis</strong></td>
<td>13</td>
</tr>
<tr>
<td>Donald B. Sanders, MD</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment of Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome</strong></td>
<td>19</td>
</tr>
<tr>
<td>Richard Barohn, MD</td>
<td></td>
</tr>
<tr>
<td><strong>Quality-of-Life Issues in Myasthenia Gravis</strong></td>
<td>29</td>
</tr>
<tr>
<td>James M. Gilchrist, MD</td>
<td></td>
</tr>
<tr>
<td><strong>CME Self-Assessment Test</strong></td>
<td>37</td>
</tr>
<tr>
<td><strong>Evaluation</strong></td>
<td>41</td>
</tr>
<tr>
<td><strong>Future Meeting Recommendations</strong></td>
<td>43</td>
</tr>
</tbody>
</table>

**OBJECTIVES** Myasthenia gravis is one of the most common autoimmune neuromuscular diseases, yet many physicians misunderstand how to diagnose and treat the disease. Participants in this course will learn (1) to recognize the clinical features of the disease, including new and emerging concepts about varying presentations of the disease, (2) the diagnostic strategy for confirming the disease, and (3) how to choose the most appropriate treatment for individual patients with myasthenia gravis.

**PREREQUISITE** This course is designed as an educational opportunity for residents, fellows, and practicing clinical EDX consultants at an early point in their career, or for more senior EDX practitioners who are seeking a pragmatic review of basic clinical and EDX principles. It is open only to persons with an MD, DO, DVM, DDS, or foreign equivalent degree.

**ACCREDITATION STATEMENT** The AAEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

**CME CREDIT** The AAEM designates attendance at this course for a maximum of 3.5 hours in category 1 credit towards the AMA Physician’s Recognition Award. This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he/she actually spent in the activity. The American Medical Association has determined that non-US licensed physicians who participate in this CME activity are eligible for AMA PMR category 1 credit.
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INTRODUCTION

Clinicians are accustomed to the study of disease in individual patients. Those who have an interest in clinical research will sometimes collect information about groups of patients, or case series, in an effort to learn more about the full clinical spectrum of a disease. What is learned from individual patients or case series instructs physicians about a disease, but it is unlikely that all manifestations of a disease will be observed in any one patient or group of patients. Even large case collections may not provide a true picture of the full clinical spectrum of a disease, since there are many biases inherent in the generation of case collections.

The only way to be absolutely certain that one has collected all possible information about a disease is to examine every patient with it. With dedicated effort and much time, one might be able to accomplish this in a rare disorder. In the vast majority of diseases, no one individual or group of individuals can possibly examine every patient with a given disorder. Since it is impossible, the closest one can come is to study the behavior of the disease in an unbiased sample selected from a defined population. Alternatively, examining the population itself for evidence of the disease can reveal some information that is not available otherwise. The science of epidemiology is the study of disease in a population, thus many manifestations of a disease can be defined most accurately through the use of epidemiological methods.

Epidemiology as a discipline first evolved as a method of studying infectious diseases, hence the derivation of the name from the root word, “epidemic.” The epidemiological approach has been used to identify patterns of disease occurrence in populations that provide clues about the etiology and source of the infection. This is the basis for public health investigations into such diseases as meningococcal meningitis, poliomyelitis, and West Nile virus encephalitis. Identification of the source of the epidemic and its mode of spread has allowed acute treatment and prevention strategies to be developed. A similar approach can also be applied to more chronic conditions like the prion diseases. Thus, the epidemiologic study of variant Creutzfeldt-Jacob disease has identified potential sources of disease transmission based on animal feed production techniques, and public health measures designed to end risky feeding practices have been proposed.

Noninfectious, chronic diseases can also be studied by the use of epidemiologic techniques. The same methods that are used to identify victims of infections can be used to define the occurrence of a chronic disease like myasthenia gravis (MG). The findings of epidemiologic investigations can instruct clinicians about how they can expect to encounter patients with this relatively rare disease.

The data from an epidemiologic study of a disease is usually expressed in the form of a rate. This is an expression of how frequently some measure of the disease occurs as a fraction of the non-affected population. Commonly used rates include incidence, prevalence, and mortality. The incidence rate is the number of new cases (incident cases) of the disease that occur in a population in a defined period. The most commonly described
incidence rate is the average annual incidence, expressed as the average number of new cases of the disease that occur per year. The prevalence rate is the number of cases of a disease that are present at a specified time. This is usually expressed as the point prevalence, or the number of affected patients in a population on a given day (known as the prevalence day). Lastly, the mortality rate is the number of deaths that occur over a defined period of time. Like incidence, mortality is usually expressed as the average number of deaths per year. It can be expressed as a cause-specific rate, i.e., the number of deaths due to the disease, but more commonly it is expressed as the overall number of deaths of affected individuals from all causes. It is important to realize that each of these rates is expressed as the number of individuals with the disease in the overall population. For a rare disease like MG, the number of affected individuals is a very small fraction of the total population, and the rate is usually expressed as the number of cases in 100,000 or 1,000,000.

**THE EPIDEMIOLOGY OF MYASTHENIA GRAVIS**

Of what value is knowledge of the epidemiology of MG for an electrodiagnostic (EDX) physician? Quite honestly, most EDX consultants can conduct their daily business effectively with absolutely no knowledge of the epidemiology of MG. There is some value, however, to knowing how the incidence and prevalence of the disease affect one’s experience in the EDX laboratory.

From discussions with colleagues, this author is aware that many EDX consultants feel somewhat uneasy about their ability to perform an adequate study of a patient with MG. There seems to be an underlying concern that the diagnosis is being missed in many cases. At least part of this unease is based on the fact that most EDX physicians encounter few MG patients in their practices. There is, however, a good explanation for why so few patients with MG are encountered by the typical practitioner.

Myasthenia gravis is a rare disease. It has been the subject of more than 50 population-based epidemiologic studies over the past 50-60 years. The studies have established that the prevalence rates of the disease have increased progressively over time. The reasons for the increasing rate are not entirely clear, but they must be related in large part to steady improvements in diagnosis and treatment of the disease. In spite of the increasing rate, the prevalence is still small. The highest reported prevalence rate for MG is 20.4 per 100,000. The expression of the rate as a number per 100,000 is a way of indicating that only a tiny percentage of the population is affected. The rate of 20.4 per 100,000 is actually 0.0204% of the population. One way to visualize this is to think of a large football stadium that holds 100,000 people, for example, the Rose Bowl. Statistically speaking, one would expect that a typical New Year’s Day crowd in the Rose Bowl should include 20 individuals with MG (assuming that all MG patients were football fans and they were equally distributed in the population in the stadium). If you were to try to identify even one of those MG patients, you would probably need to examine at least 5000 fans. You might expect this to take a significant amount of time, and it would certainly cut into the amount of time you had to enjoy the football game!

Another way to understand how the epidemiology of the disease has an impact on a physician’s practice is to consider the incidence of the disease. Remember that incidence is a measure of the number of new cases that occur over a defined period of time. The MG patients who are referred for an EDX examination are most likely to be those who have had recent disease onset. They are thus best measured in an incident cohort. For any chronic disease there are fewer incident cases in any period than there are prevalent cases, thus average annual incidence rates in MG are expressed as the number of cases per million. The highest reported rates have been 15 per million in the population of Cyprus and 21.27 per million in the population of Barcelona, Spain.

One can estimate the average number of new MG cases per year by doing some simple calculations. It can be assumed that the incidence and prevalence rates for MG in the United States are similar to those reported in other locales, since the available evidence indicates that there is a fairly uniform distribution of the disease world-wide. If one assumes that the United States incidence is 21 per million, and the total population for the country is approximately 280 million, the average number of new cases of MG in a given year would be the product of 21 multiplied by 280, or 5880. There are approximately 5000 members in the American Association of Electrodiagnostic Medicine (AAEM). If one assumes that every incident case of MG is referred to a member of the AAEM for EDX study, then the average member of the organization would expect to see about one new case per year. One recent study, for example, found that only 60% of patients were correctly diagnosed with MG within their first year of symptom onset. It is thus unlikely that all patients who have MG within their first year of symptom onset are referred for EDX studies. It is also known that patient referrals are not equally distributed. In other words, some physicians are more likely to encounter cases of MG than are others. It is therefore unlikely that the typical AAEM member will encounter a new case of MG more than once every few years.
The Impact of the Epidemiology of Myasthenia Gravis on Electrodiagnosis

There is a potential collision between the rarity of MG in the population and the performance characteristics of EDX tests for the disease. Physicians are often lulled into thinking that medical tests provide clear-cut, black and white answers to clinical questions. This is infrequently true. For example, if a physician performs a study that provides evidence for a diagnosis of peripheral neuropathy, then the physician probably feels certain that there is such a disease present in the patient. In reality, however, there are few, if any, diagnostic tests that are perfect. In other words, there is a potential for a false positive test result. Likewise, the fact that an EDX test does not demonstrate abnormality does not mean that there is absence of disease in the patient. There can certainly be false negatives. Thus, when an electrodiagnosis of peripheral neuropathy is made, the patient may not, in fact, have a disease of the peripheral nerves.

How does this concept apply to the diagnosis of MG? None of the tests that are performed for the diagnosis of MG are perfect. A variety of tests can be performed, including EDX studies, but there is no one test that will distinguish between individuals with MG and normal subjects in all cases. When the manifestations of the disease are severe, the clinical presentation may be so clear that support from laboratory tests is not necessary. Experienced clinicians can often be certain of the diagnosis at the bedside, and in emergent, life-threatening situations, treatment decisions are made before any supporting laboratory tests can be performed. However, even experienced clinicians can be fooled at times. This author is aware of several patients who were given an initial diagnosis of MG only to have the correct diagnosis of amyotrophic lateral sclerosis made after the progression of their disease made it more obvious.

Ironically, the diagnosis of MG is often most difficult when the disease is very mild. The likelihood that all of the diagnostic tests will be normal is much higher when the degree of weakness is mild and its distribution is limited. To understand the role of diagnostic tests, a review of some of the measures of test performance is needed.

The two most common measures of test performance are the sensitivity and the specificity. The sensitivity of a test is also known as the true positive rate (TPR). It is defined as the number of diseased patients who have an abnormal test result divided by the total number of diseased patients in the population. It is an expression of the likelihood that a diseased individual will have a normal test result. These measures are generated when the results of a given test are compared with a “gold standard.” A gold standard is a test whose performance characteristics are well established, and there is general agreement on its accuracy.

Unfortunately, gold standards are difficult to define, and many diagnostic tests in common use have not been evaluated against such a standard. This is certainly true of the tests for MG. The EDX tests for MG include repetitive nerve stimulation (RNS) and single-fiber electromyography (SFEMG). The sensitivity of RNS is much lower than SFEMG in all forms of MG. A number of studies have established that SFEMG is the most sensitive test available for the diagnosis of MG, particularly in the case of ocular MG. Since a number of other disorders can produce abnormal SFEMG results, the specificity of the test is somewhat lower. There is, however, only one study that has looked at both the sensitivity and specificity of the test.

Application of the data from this study illustrates some pitfalls in the use of the test in patients with ocular MG.

In addition to the sensitivity and specificity of a test, physicians should also be concerned with its positive predictive value (PV+) and its negative predictive value (PV-). These two measures give a clearer picture of the clinical reliability of a test result. The PV+ is defined as the fraction of patients in a population who have an abnormal test result and have the disease in question. It can be calculated from the number of true positives (TP) and false positives (FP):

\[ PV_+ = \frac{TP}{(TP+FP)} \]

The PV- is the fraction of patients in a population who have a normal test result and do not have the disease. It is calculated from the number of true negatives (TN) and false negatives (FN):

\[ PV_- = \frac{TN}{(TN+FN)} \]

If the data from the Rouseev and colleagues paper is used, calculations of the PV+ and PV- indicate that EDX consultants should be cautious in how even a very sensitive test like SFEMG is used. The definition of a gold standard for MG in this study was based on “strict clinical criteria.” As one might imagine, this somewhat ambiguous definition produced some equally ambiguous results. The results were expressed in three categories as: (1) definite MG, (2) definite “other” disease, and (3) no final diagnosis. In the text, the authors indicate that most patients who were classified as “no final diagnosis” most likely had MG. The
strict clinical definition used by the authors required a positive response to a trial of cholinesterase medication, and the patients in the latter category had not been exposed to that therapy. For the purpose of analysis, those patients can be lumped into the MG category. The authors also used two different definitions of abnormality on SFEMG. The least strict definition required two or more fiber pairs to have abnormal jitter. The more strict definition required that the mean jitter had to exceed an abnormal cutoff value. The paper can be reviewed for more detail, but the numbers from this study can be plugged into the formulae for PV+ and PV-.

A total of 41 patients were studied, and the TP, FP, TN, and FN values are indicated in the cells in the top portion of Table 1. The PV+ calculated from the data in the upper half of the table produces a value of 72.7%. This means that at least one patient in four who has an abnormal SFEMG result will have some diagnosis other than MG. Even if one uses the more strict definition of abnormality, the PV+ only increases to 88.8%. In other words, even under the best of circumstances, more than 10% of patients will be misdiagnosed as having MG if the results of SFEMG alone are relied on.

### Table 1

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<thead>
<tr>
<th>Classification of ocular myasthenia gravis by single-fiber electromyography results (modified from Rouseev and colleagues.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Least Strict Definition</strong></td>
</tr>
<tr>
<td>MG</td>
</tr>
<tr>
<td>Not MG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>More strict definition</strong></th>
<th><strong>SFEMG Abnormal</strong></th>
<th><strong>SFEMG Normal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>MG</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Not MG</td>
<td>2</td>
<td>16</td>
</tr>
</tbody>
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| MG = myasthenia gravis; FN = false negative; FP = false positive; SFEMG = single-fiber electromyography; TN = true negative; TP = true positive. |

Bayes’ Theorem

A final cautionary note comes from the application of Bayes’ theorem to this data. In Bayes’ theorem, the prevalence of the disease becomes a factor. Some physicians use EDX studies to screen their patients for MG. A common example is the patient who complains of non-specific whole body “weakness” that becomes more pronounced as the day progresses. Experienced neuromuscular physicians readily recognize that this complaint of “weakness” is an expression of fatigue rather than a true loss of muscle power, but physicians who lack neuromuscular expertise can conclude mistakenly that this complaint is a symptom of MG. If such a patient is referred to the EDX laboratory for SFEMG studies to screen for MG, there is an especially high risk of incorrect diagnosis.

The formula for Bayes’ theorem incorporates the true prevalence rate into a calculation of the likelihood that a patient has the disease in question when an abnormal test result is obtained. (See Schulzer for more details.)

\[
P[D+ | T+] = P[T+ | D+] \times P[D+] / (P[T+ | D+] \times P[D+] + P[T+ | D-) \times P[D-])
\]

Where \(P[D+ | T+]\) is the probability that a patient with an abnormal test result has the disease, \(P[T+ | D+]\) is the sensitivity of the test, \(P[D+]\) is the prevalence of the disease in the population, \(P[T+ | D-]\) is the false positive rate \((= 1 - \text{sensitivity})\), and \(P[D-]\) is the probability that an individual from the test population is disease free \((= 100\% - \text{prevalence})\). Although the terminology makes the formula appear to be daunting, one can actually plug the numbers detailed above into a simple arithmetic calculation.

The key number here is the prevalence. If the value for the highest prevalence rate quoted so far is used, 20.4 per 100,000, the calculated probability that a positive test result indicates the patient has MG is 0.05%. In other words, using the SFEMG study as a tool to screen for MG in the general population is more than 10,000 times more likely to make a misdiagnosis than it is to identify a patient with the disease. This figure is based on the data from the Rouseev paper, but the calculated sensitivity from that study is only 70%. Other studies, however, have shown the sensitivity to be as high as 99%. Even if the higher sensitivity figure is plugged into the Bayesian calculation, the probability that a positive test result indicates the patient has MG is only 1.98%. This improves the chance of making a correct diagnosis by two orders of magnitude, but it is still much more likely that a patient with an abnormal test result has some disease other than MG.

Other manipulations of the data to examine various “what-if” scenarios can be performed. For example, better results from a screening test might be expected if a selected population were examined. A neuro-ophthalmologist colleague of this author prefers to refer virtually every one of his patients with diplopia for SFEMG. His clinic population is a highly selected one, and it can be estimated that 10% of the patients he examines ulti-
imately have MG. If one considers this to be the prevalence in the
Bayesian calculation, the diagnostic yield is 20.6%. Thus, only 1
in 5 patients from that clinic who have an abnormal SFEMG
study will actually have MG. If the percentage of patients re-
ferred from that clinic who have MG is 50%, then the diagno-
stic yield is 70%. This is much better, but still 3 out of 10 patients
who have abnormal SFEMG will have some other disease.

SUMMARY

The incorrect conclusion that can be made from these calcula-
tions is that EDX studies are not useful for disease screening,
since MG is rare. However, the correct conclusion is that EDX
studies are appropriate to confirm the diagnosis of MG follow-
ing examination by an experienced clinician who is able to
analyze the data in light of all the information available.

REFERENCES

INTRODUCTION

In 1895, Friedrich Jolly demonstrated declining muscle responses to electrical stimulation in a patient with “myasthenia gravis pseudoparalytica” and theorized that such fatigue may localize to muscle. Early clinical descriptions of myasthenia gravis (MG) emphasized both the fluctuating and fatigable nature of the disorder as well as the high mortality associated with progressive MG. Over the last half-century, MG has become increasingly well-characterized in terms of clinical findings, neurophysiology, and immunology. The contemporary outlook for patients with MG has significantly improved, and life expectancy is now nearly normal. This attributes mainly to improved treatment and intensive care, but may also relate to better recognition of the disorder following advances in diagnostic electrophysiology and immunology.

PATHOPHYSIOLOGY

Most patients with MG have an autoimmune disease related to antibody-mediated, T-cell dependent immunologic attack involving the postsynaptic membrane of the neuromuscular junction. This autoimmune process reduces the probability of successful neuromuscular transmission following quanatal release of acetylcholine (ACh) by the motor nerve terminal and it ultimately results in clinical weakness in striated muscles. Transitory neonatal MG follows passive transfer of maternal antibodies to the newborn. Rare congenital myasthenic syndromes result from various genetic mutations that compromise neuromuscular transmission. Although many symptoms and findings for congenital myasthenic syndromes are often identical to that of autoimmune MG, the following discussion pertains specifically to autoimmune MG.

In MG and other autoimmune disorders, loss of immunological self-tolerance occurs. The thymus is considered essential for establishing self-tolerance, and thymic abnormalities have long been recognized in association with MG. Thymoma occurs in about 10% of patients with MG. Most thymic tumors are benign and encapsulated. Approximately 70% of patients demonstrate thymic hyperplasia with active germinal centers. In the germinal centers, B-lymphocytes interact with T-helper lymphocytes to produce antibodies. Thymomas are often associated with an earlier age of onset, more fulminant disease, and higher titers of acetylcholine receptor (AChR) antibodies.

FORMS OF MYASTHENIA GRAVIS

Myasthenia gravis is termed ocular myasthenia when weakness is exclusive to the eyelids and extraocular muscles, and generalized myasthenia when weakness extends beyond these ocular muscles. Seropositive (SP) MG refers to patients with circulating antibodies to the AChR, while seronegative (SN) patients lack these antibodies. About half of patients with ocular MG are SN,
patients. While 80% of patients with generalized MG are SP. Seronegative patients are more likely to have purely ocular myasthenia or more mild disease. 

**CLINICAL PRESENTATION AND COURSE**

Patients with MG present with complaints of fluctuating and fatigable weakness of specific muscle groups, rather than with generalized fatigue or pain. The weakness is variable from day to day and from hour to hour, but it is usually worse later in the day. Sustained exercise and increased body temperature may increase the degree of weakness.

Most patients develop initial symptoms of extraocular muscle weakness involving asymmetric ptosis and diplopia. The course is frequently variable, particularly within the first year of the disease. Nearly 85% of patients with initial ocular symptoms progress to develop weakness of bulbar and limb muscles within the first 3 years. Initial presentations with oropharyngeal and limb weakness are less common. Maximum disease severity is reached within the first year of disease in almost two-thirds of patients. Ventilatory failure due to myasthenic weakness or myasthenic crisis occurs in about 20% of patients, usually within the first year of illness. Myasthenic symptoms and signs may worsen in a setting of systemic illness, particularly viral upper respiratory infections, thyroid disease, pregnancy, increased body temperature, and exposure to drugs that impair neuromuscular transmission.

Early in the course of MG, symptoms may fluctuate and occasionally remit, although such remissions are rarely permanent. Three overall stages of generalized MG have been proposed. An active stage lasting approximately 7 years is characterized by relapses and remissions. This is followed by an inactive stage lasting about 10 years. The inactive stage is characterized by less volatility, but patients may experience exacerbations related to intercurrent illnesses, pregnancy, or exposure to medications that compromise neuromuscular transmission. Finally, in the burned-out stage, untreated weakness may become fixed in association with muscle atrophy.

### Ocular Muscles

Ocular weakness presents as fluctuating, fatigable, and sometimes alternating ptosis and binocular diplopia which resolves with closing or covering one eye. Many patients report difficulties with driving, reading, or watching television. Bright lights may be quite bothersome. Retrospectively, many patients report periods of intermittent blurred vision before they were able to discern dual visual images. Examination may demonstrate asymmetrical weakness of multiple extraocular muscles that cannot be attributed to a single cranial neuropathy. Pupillary function is normal. Ptosis may be elicited or increased with sustained upgaze. It is generally asymmetrical, and it may be associated with ipsilateral frontalis muscle contraction to help compensate for the weak levator palpebrae. Excessive lid elevation or Cogan’s lid twitch sign may be observed when gaze is directed from down to upward.

Dysthyroid (Graves) ophthalmopathy may coexist with ocular MG. Although external ophthalmoplegia may occur in either disorder, dysthyroid ophthalmopathy produces proptosis, not ptosis, owing to enlarged extraocular muscles. The enlarged muscles may be demonstrated by orbital magnetic resonance imaging (MRI).

### Jaw Muscles

Jaw closure muscles are frequently affected in MG, but strength is usually normal in jaw opening muscles. Patients may complain of difficulty in chewing candy or tough meats, and some modify their diet to compensate for this difficulty. Patients may assume a thoughtful resting posture by placing the thumb beneath the chin in order to hold the jaw closed. The jaw closure muscles can be examined by exerting several seconds of sustained downward pressure on the chin while the patient attempts to hold the jaw closed. Jaw opening muscles are assessed by exerting upward pressure on the jaw while the patient attempts to hold it open.

### Facial Muscles

Many patients exhibit a depressed or expressionless facial appearance. Whistling, using straws, or blowing up balloons may be impaired. A “myasthenic snarl” may be observed when the patient attempts to smile. The snarl follows contraction of the middle portion of the upper lip while the upper mouth corners fail to contract. On examination, many patients exhibit weak forced-eye closure that can easily be overcome by the examiner. Bell’s phenomenon with upward and lateral rotation of the eyes on attempted closure is observed when the patients’ forceful eye closure is defeated by the examiner. In the lower face, patients with overt lower facial weakness develop a transverse pucker when they attempt to hold air within the cheeks.

### Oropharyngeal Muscles

Oropharyngeal muscle weakness produces dysarthria and dysphagia. With weakness of palatal muscles, speech becomes hypernasal as air escapes through the nose. This may become more apparent with prolonged speaking. Liquid may also escape through the nose during attempted swallowing with nasal regurgitation. Involvement of laryngeal muscles is associated with a hoarse, breathy voice. Incomplete glottic closure during swallowing may produce aspiration. Examination may reveal
reduced or absent palate elevation. Tongue weakness may be demonstrated when the patient attempts to protrude either cheek with the tongue against the resistance of the examiner’s finger applied to the cheek. With marked tongue weakness, the patient may not be able to protrude either cheek with the tongue. With severe weakness, the tongue may not protrude beyond the lips.

**Neck Muscles**

Neck flexor and extensor muscles are often weak in MG. Though the neck flexors are usually weaker, a “dropped head syndrome” due to neck extensor weakness may occur. Although painless weakness is the rule in MG, patients with neck extensor weakness may experience posterior neck myalgias.

**Limb Muscles**

Limb weakness in MG tends to involve proximal muscles. It may be associated with complaints of difficulty performing overhead tasks with the arms, and there may be difficulty climbing stairs due to lower extremity weakness. Examination reveals asymmetrical weakness involving any muscle group in the limbs, though the deltoids, triceps brachii, wrist and finger extensors, and foot dorsiflexors are often involved.

**PHARMACOLOGIC TESTING**

**Edrophonium Chloride Testing**

Edrophonium chloride is a short-acting acetylcholinesterase inhibitor. Its pharmacologic action has rapid onset (approximately 30 seconds) and short duration (approximately 5 minutes). Edrophonium chloride temporarily improves the safety factor of neuromuscular transmission and elicits improved strength in patients who have abnormal neuromuscular transmission. When there is unequivocal improvement in strength following administration of edrophonium, the test is considered positive. However, the development of increased weakness may also suggest abnormal neuromuscular transmission. The main limitation of edrophonium testing relates to the choice of an objective muscle strength parameter for assessment. Accordingly, edrophonium testing is most useful in patients who have significant ptosis or restricted extraocular movements which can be graded objectively. In other muscles, volition and the muscarinic effects of edrophonium may complicate strength measurement and render the test uninterpretable.

Although the exact sensitivity of edrophonium testing is difficult to determine accurately, it has been estimated to be about 86% for ocular MG and 95% for generalized MG. False positive edrophonium testing may occur in other neurological conditions including lower motor neuron disorders and brainstem tumors.

Up to 10 mg of intravenous edrophonium chloride can be administered to patients suspected of having myasthenic weakness. Because of the potential for serious muscarinic side effects, including bronchospasm and bradycardia, atropine should be readily available. More common muscarinic side effects include increased sweating, lacrimation, salivation, nausea, and diarrhea. An incremental dosing schedule should be utilized. If muscle strength improves clearly within 1 minute following any dose increment, the test is considered to be positive and the procedure ended. In this fashion, the risk of giving excess edrophonium and eliciting untoward muscarinic side effects is reduced. Initially, a 2 mg dose of intravenous edrophonium is given, and the patient is observed for 1 minute for improvement in the prespecified strength parameter (e.g., ptosis). If there is no improvement, a second 2 mg dose of edrophonium is given. If no improvement occurs after 1 minute more, a third dose of 3 mg is given. If no improvement is observed after an additional minute, the remaining 3 mg of edrophonium is administered.

**ELECTROPHYSIOLOGIC TESTING**

**Repetitive Nerve Stimulation Studies**

At low rates of motor nerve stimulation (2-5 Hz), repetitive nerve stimulation (RNS) studies deplete the immediate stores of ACh at the neuromuscular junction. This reduces the safety factor and probability of successful neuromuscular transmission. In neuromuscular junction disorders where the safety factor is marginal at baseline, further reduction by RNS causes some end-plate potentials to fail to reach depolarization threshold. This results in a failure to elicit muscle fiber action potentials. With a reduced number of individual muscle fiber action potentials, the compound muscle action potential (CMAP) becomes reduced in both amplitude and area, and the result is a decremental response.

In MG, RNS findings are abnormal when the amplitude of the fourth CMAP is reduced more than 10% from the baseline value. This may not be present in stimulus trains recorded following rest, but it may only develop in trains collected subsequent to an exercise period as a consequence of postactivation exhaustion. The sensitivity of RNS is increased when recordings are made from clinically weak muscles. To avoid erroneous results, careful attention to technical detail is important. There must be adequate immobilization of the stimulating and recording electrodes, delivery of supramaximal stimuli, muscle warming to 35°C, and withholding of acetylcholinesterase inhibitors for at least 12 hours prior to the testing. In general, proximal muscles including facial muscles, trapezius, deltoid, and
biceps brachii are more likely to exhibit abnormal findings. In MG, when RNS studies are performed in a hand and in a shoulder muscle, the overall sensitivity is approximately 60%. Repetitive nerve stimulation studies are relatively more sensitive in generalized MG and relatively less sensitive in ocular MG.\textsuperscript{12}

**Needle Electromyography**

During conventional needle electromyography (EMG), variability in the size and shape of the motor unit action potential (MUAP) may be observed during sustained muscle activation. This phenomenon, termed MUAP instability or “jiggle,”\textsuperscript{30} reflects delayed or failed neuromuscular transmission in individual muscle fibers that contribute to a MUAP. Jiggle is not exclusive to MG, and it may also be seen in peripheral nerve and muscle disease.

**Single-Fiber Electromyography**

Single-fiber EMG (SFEMG) is the most sensitive diagnostic test for detecting abnormal neuromuscular transmission. In SFEMG, individual muscle fiber action potentials generated by the same motor neuron are recorded by a specialized concentric needle with a 25 µm diameter recording surface and a 500 Hz high-frequency filter. In most normal muscles, this arrangement facilitates recordings from two individual muscle fiber action potentials. The variability in time interval between the firing of one muscle fiber potential with relation to the other is termed the neuromuscular jitter.\textsuperscript{31}

Serological Testing

**Acetylcholine Receptor Antibodies**

The AChR-binding antibody assay utilizes purified human skeletal AChRs which are incubated with a patient’s serum immunoglobulin. The assay is very specific, and positive antibody studies confirm MG in a patient with appropriate symptoms and clinical findings. As noted previously, AChR-binding antibodies are present in approximately 80% of patients with generalized MG, but in only 55% of patients with ocular MG.\textsuperscript{14,33} About one-half of prepubertal children with MG are SN.\textsuperscript{2} Though relatively less sensitive than SFEMG, AChR-binding antibodies are highly specific for autoimmune MG. Rarely, false positive results in AChR-binding antibody assays have been observed in patients with other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and inflammatory neuropathy. False positive results have also been reported in motor neuron disease, patients with thymoma without MG, and relatives of patients with MG.\textsuperscript{25} Some initially SN patients may seroconvert within the first several months of disease. Seroconversion may be identified in these patients by repeating the AChR-binding antibody studies after 6 months of symptoms.\textsuperscript{23}

Acetylcholine receptor modulating antibodies bind to exposed portions of the AChR on skeletal muscle membranes. Acetylcholine receptor blocking antibodies bind near the AChR and block ACh binding to the receptor. The modulating and blocking assays are probably useful only when the binding antibody assay is negative, since they increase diagnostic sensitivity only slightly. Approximately 4% of patients with a negative binding antibody assay demonstrate elevated modulating antibodies, and approximately 1% of patients with a negative binding antibody assay demonstrate blocking antibodies.\textsuperscript{11}

**Anti-Striated Muscle Antibodies**

Anti-striated muscle (anti-striational) antibodies react with contractile elements of skeletal muscle. They are found in 30% of patients with adult-onset MG, and they appear to be more common in patients with later disease onset.\textsuperscript{3} These antibodies may be useful as a serological marker for thymoma in younger patients. Anti-striated muscle antibodies have been demonstrated in 80% of myasthenics with thymoma, and 24% of patients with thymoma in the absence of MG. Following
thymoma resection, a rise in anti-striated muscle antibody titer may suggest recurrent tumor.\textsuperscript{3} In one series, thymomas were demonstrated in 60\% of patients with anti-striated muscle antibodies and MG beginning before age 50, and in less than 2\% of patients without these antibodies.\textsuperscript{26}

**Muscle-Specific Tyrosine Kinase Antibodies**

Muscle-specific tyrosine kinase (MuSK) appears to facilitate clustering of AChR at the neuromuscular junction. Antibodies to MuSK have been demonstrated recently in about one third of patients with generalized SN-MG,\textsuperscript{5,9,24} though the role of MuSK antibodies in producing neuromuscular junctional disease has not been defined.

**Other antibodies**

Antibodies against the intracellular skeletal muscle protein titin may be present in patients with thymoma, but they are also present in about half of patients with late-onset MG without thymoma.\textsuperscript{29,34} Ryanodine antibodies are also associated with late-onset MG. Patients with ryanodine antibodies may exhibit severe, treatment-resistant myasthenia associated with malignant thymomas.\textsuperscript{17} Although the role of these antibodies in the diagnosis of MG has yet to be determined, they may have prognostic value and expedite chest imaging studies for detection of thymoma.

**Other testing**

Chest computerized tomography (CT) should be performed in patients with MG to exclude the presence of thymoma. Chest CT is more sensitive than chest radiograph for delineating anterior mediastinal masses, and chest MRI does not improve diagnostic sensitivity. Since MG often co-exists with other autoimmune disorders, particularly autoimmune thyroid disease, patients should undergo thyroid function testing along with testing for other autoimmune disorders when clinically appropriate.

**SUMMARY**

Myasthenia gravis remains one of the most challenging medical diagnoses due to its dynamic character and to the similarity of its symptoms to other disorders. The clinician must consider the possibility of MG in patients with fluctuating and fatigable weakness, particularly when such weakness involves extraocular and bulbar muscles. A clinical diagnosis may be supported by pharmacologic, electrophysiologic, or serologic testing. Edrophonium testing is sensitive when it is performed in patients with significant ptosis or external ophthalmoparesis. Repetitive nerve stimulation testing may demonstrate impaired neuromuscular transmission, especially when it is recorded in a clinically affected muscle, but it is relatively insensitive in ocular and in mild generalized MG. The most sensitive test for MG is SFEMG, and normal SFEMG findings in a clinically weak muscle exclude MG. In the clinical context of fluctuating and fatigable weakness, AChR antibodies confirm the diagnosis of MG, though nearly half of patients with ocular myasthenia are SN. The recent demonstration of MuSK antibodies in many SN patients with generalized MG suggests an alternate pathophysiology for autoimmune MG which awaits further characterization.

**REFERENCES**

30. Stålberg EV, Sonoo M. Assessment of the variability in the shape of the motor unit action potential, the “jiggle” at consecutive discharges. Muscle Nerve 1994;17:1135-1144.
MuSK Antibody—Positive Myasthenia Gravis

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INTRODUCTION

An autoimmune etiology for acquired myasthenia gravis (MG) was first hypothesized by Simpson in 1960, based on clinical observations. The current understanding of the immunological events that produce this disease began when the antibody to the acetylcholine receptor (AChR) was demonstrated in the serum of affected patients by Lindstrom and colleagues in 1976. The following statement in the latter paper has proven to be an understatement: “Assay of antireceptor antibody should prove a useful test in the diagnosis of myasthenia gravis.” These antibodies are found in the blood of approximately 80% of patients with generalized MG, and about 50% of those with ocular MG. It is now known that the physiologic abnormality in MG is caused by an immunological reaction against components of the post-synaptic muscle end-plate region. The target of the immunologic attack in most cases of MG is the main immunogenic region on the AChR (Figure 1). The binding of antibodies to AChR increases the rate of receptor degradation, blocks acetylcholine (ACh) binding sites on the receptor, and induces complement-mediated disruption of the post-synaptic end-plate membrane. This reduces the effective concentration of AChR at the muscle end-plate and lowers the safety factor of neuromuscular transmission, resulting in ineffective neuromuscular transmission and weakness.

ACETYLCHOLINE RECEPTOR ANTIBODIES

Antibodies that bind to the AChR are detected by co-precipitation of the patient’s serum immunoglobulin G (IgG) with human skeletal muscle AChR. Acetylcholine receptor antibodies can also be detected by two other assay techniques: (1) “modulating” antibodies, which bind selectively to exposed segments of AChR on living muscle and increase their degradation, and (2) “blocking” antibodies, which interfere with ACh binding to the AChR. Acetylcholine receptor antibodies are the most specific diagnostic markers for MG. Binding AChR antibodies have been found in 81% of generalized MG, and 55% of ocular MG in this author’s clinic. Modulating antibodies were found in 10% of the patients without binding antibodies, but only rarely were blocking antibodies found in the absence of binding antibodies. Patients with circulating AChR antibodies are said to be “seropositive” and the disease is termed seropositive MG (SP-MG). Patients without these antibodies are “seronegative” and the disease is termed seronegative MG (SN-MG). In about 10%
of patients who are seronegative early in their disease, AChR antibodies become elevated later, usually within 6 months of disease onset. Thus, if AChR antibody testing is normal early on, repeat testing may be diagnostic later.

The frequency of seropositivity and the mean maximum binding antibody level increase with disease severity, but antibody titers vary greatly among patients with similar severity. Thus, disease severity cannot be inferred from the antibody level in individual patients. Virtually all MG patients with thymoma are SP. Seronegative patients are more likely to have ocular or mild generalized disease, but 15% of patients with moderate or severe generalized disease also are SN. Up to 50% of children with MG onset before puberty are SN.1

Acquired SN-MG is also an autoimmune disease, as demonstrated by passive transfer to mice,11 modulation of AChR function14 or expression13 in vitro by SN plasma, transient neonatal MG in babies born to women with SN-MG,6,12 and clinical and electrophysiological improvement after immunotherapy, such as plasma exchange (PLEX).11

ANTI-MUSK ANTIBODIES

Antibodies to muscle specific tyrosine kinase (MuSK) are found in more than 40% of patients with generalized SN-MG.3,4,10,15,18 MuSK plays an essential role in the developing neuromuscular synapse by initiating clustering of AChRs at the end-plate. Preliminary information suggests that MuSK antibodies are mainly IgG4, and they disrupt the neuromuscular junction without mobilizing complement.21 Plasma containing MuSK antibodies initially stimulates, but then subsequently prevents AChR clustering in developing muscle.4 The role of MuSK in mature, innervated muscle is not yet known, and it is not clear what effect MuSK antibodies have on mature muscle.
The cell-mediated immune system also plays a role in autoimmune MG, but at this time, the role of cell-mediated immunity in MuSK-positive (MuSk+) MG is not clear. MuSK+ patients do not have thymic hyperplasia\(^{18}\) and thymectomy has produced little response in the patients reported to date.\(^{15,18,21}\)

Thus, there are at least two autoimmune, antibody-mediated processes underlying autoimmune MG, targeting the AChR in the majority and MuSK in a minority of patients. Among SN/MuSK-negative patients, other, as-yet-unidentified-antigens are probably the targets of the autoimmune process.\(^{21}\)

### MUSK-POSITIVE MYASTHENIA GRAVIS

#### Clinical Patterns

In 1996, Evoli and colleagues identified a subset of patients with generalized SN-MG who frequently had a characteristic clinical pattern of weakness. They had predominantly ocular-bulbar weakness, frequent respiratory failure, and a poor response to immunotherapy.\(^{2}\) Most of these patients were subsequently found to have serum anti-MuSK antibodies.\(^{3,18}\) Anti-MuSK antibodies have not been reported in purely ocular MG, nor in SP-MG. Two patients with anti-MuSK antibodies had profound muscle wasting, especially of facial and oropharyngeal muscles (unpublished observations, J. Newsom-Davis and colleagues.)

Among the patients with MuSK+ MG reported to date, there have been several different clinical presentations. In reports from Italy and England, many had predominantly oculo-bulbar weakness, frequently with a poor response to treatment, and atrophy of chronically weak muscles.\(^{3,10}\) This author has found anti-MuSK antibodies in 17 patients with generalized SN-MG (Table 1). Seven had typical MG findings, i.e., fluctuating ocular, oropharyngeal, and limb muscle weakness. Eight initially had weakness limited to a few limb muscles, particularly neck extension and shoulders or muscles of respiration. There was little or delayed ocular muscle weakness. Two, including the only man this author has seen with MuSK antibodies, had progressive facial and pharyngeal muscle weakness and atrophy. The following cases demonstrate these three clinical presentations.

#### Case 1 – Typical Myasthenia Gravis

A 42-year-old woman began having intermittent blurred vision. Over the next several months, she developed slurred and nasal speech and mild generalized limb weakness. Tensilon testing was positive, and assay for AChR binding, blocking and modulating, and anti-striated muscle antibodies was negative. Jitter was increased in the extensor digitorum communis (EDC) muscle, and more so in the frontalis. Her symptoms improved slightly with pyridostigmine, and she achieved a Myasthenia Gravis Foundation of America Post-Intervention Status score of “marked improvement” on high-dose prednisone.\(^{3}\) She underwent thymectomy; histologic examination found no germinal centers. Symptons recurred when the prednisone dose was reduced, and she was intolerant of azathioprine. Mycophenolate mofetil for 6 months produced no improvement, but she again achieved “marked improvement” after beginning cyclosporine. At this point, anti-MuSK antibodies were found to be elevated.

#### Case 2 – Facio-pharyngeal Weakness and Atrophy

A 45-year-old woman had onset of fatigable lingual dysarthria and nasal speech. One year later, she had transient lid ptosis and dysphagia, which cleared spontaneously. Dysarthria became severe and constant. When seen at age 53, she had severe lingual dysarthria, marked weakness of upper facial muscles, and severe atrophy of the tongue and upper face. There was only minimal lid ptosis, and strength was normal in the extraocular muscles and limbs. Electromyography (EMG) was normal in the limb muscles, but showed complex, unstable motor unit action potentials (MUAPs) in the tongue. Repetitive nerve stimulation testing found no decrement in the abductor digiti minimi (ADM), trapezius, or nasalis muscles. Single-fiber EMG (SFEMG) jitter was slightly increased in the EDC, and was markedly abnormal, with frequent impulse blocking, in the frontalis and orbicularis oculi muscles. Acetylcholine receptor antibody testing was normal; MuSK antibodies were found in the serum. Pyridostigmine produced no improvement in her symptoms, but she again achieved “marked improvement” after beginning cyclosporine.

#### Case 3 – Neck Weakness - Myopathy

A 26-year-old pregnant woman noted difficulty holding her head up and lifting her arms over her head. These symptoms

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Table 1 Demographics and clinical features in 17 MuSK+ patients

<table>
<thead>
<tr>
<th>Pattern</th>
<th>“Typical” MG</th>
<th>Restricted</th>
<th>Facio-pharyngeal</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>7</td>
<td>8</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>F:M</td>
<td>7:0</td>
<td>8:0</td>
<td>1:1</td>
<td>16:1</td>
</tr>
<tr>
<td>Age at onset</td>
<td>34.9 (18-59)</td>
<td>36.3 (21-54)</td>
<td>32-45 (18-59)</td>
<td>35.9</td>
</tr>
<tr>
<td>Race</td>
<td>5:2</td>
<td>3:5</td>
<td>1:1</td>
<td>9:8</td>
</tr>
</tbody>
</table>

B = black; F = female; M = male; MG = myasthenia gravis; MuSK = muscle specific tyrosine kinase; W = white.
became worse after delivery of a normal infant. Electrodiagnostic (EDX) studies showed evidence of myopathy, but no further information about EDX testing is available. Most symptoms improved without treatment, but she continued to have difficulty holding her head up. Two years later, she noted hand weakness, mild dysarthria, and orthopnea. Examination then revealed normal eye movements, slight difficulty holding air in the cheeks, minimally weak neck and elbow flexion, and moderate weakness of neck extension. There was no definite fatigability. Creatine kinase and AChR antibody measurements were normal. Electromyography showed abnormalities consistent with a widespread but patchy myopathy, most marked in the shoulder and neck muscles, with fibrillation potentials in hand muscles. Repetitive nerve stimulation testing showed a 9% amplitude decrement in the ADM, and a 10% decrement in the trapezius muscle. Single fiber EMG jitter was normal in the EDC and frontalis muscles, but was markedly abnormal, with frequent impulse blocking, in neck extensor muscles. Pyridostigmine produced no symptomatic improvement. Anti-MuSK antibodies were elevated in the blood. After a course of PLEX, she had only minimal residual weakness of neck flexion and extension.

These patients represent three distinct clinical presentations that have been reported in MG patients with anti-MuSK antibodies. The first is typical for SP-MG. The second has severe facial and pharyngeal muscle weakness and atrophy, and the third has a clinical pattern consistent with a myopathy, including predominant neck, shoulder, and respiratory muscle weakness, and minimal or delayed ocular muscle weakness. The latter two patterns are unusual in MG (Figure 2). Among more than 900 MG patients seen in the Duke Myasthenia Gravis Clinic, ocular symptoms were present at onset in two-thirds of SP-MG, and in over 70% of SN-MG, but in less than half of the 17 MuSK+ patients. Weakness began in the limbs in over 40% of the MuSK+ patients, but in less than 10% of those without MuSK antibodies.

**Electrodiagnostic Findings**

Electrodiagnostic findings vary markedly among MuSK MG patients (Table 2).\(^5,15,17\) Repetitive nerve stimulation and SFEMG jitter may be normal in forearm, hand, and shoulder muscles in those with predominantly facial or neck extensor weakness. Jitter was normal in an arm muscle (EDC) in 7 of 17

![Figure 2](image)

**Figure 2** Presenting symptoms in 900 myasthenia gravis (MG) patients. Ocular symptoms were present at onset in 2/3 of SP-MG, and in over 70% of SN-MG, but in less than half the MuSK+ patients. Weakness began in the limbs in over 40% of MuSK+ patients, but in less than 10% of those without MuSK antibodies. (Copyright D.B. Sanders, 2004)

* p<.05 compared to non-MuSK patients

SP-MG = seropositive myasthenia gravis; SN-MG = seronegative myasthenia gravis; MuSK = muscle specific tyrosine kinase
MuSK+ patients, and in both the arm and facial muscles in two. In three patients, increased jitter was found only or predominantly in neck extensor or shoulder muscles. This pattern of distribution is unusual in generalized MG, in which abnormal jitter is usually found diffusely, even in muscles that are not weak.16 In MuSK+ patients with predominantly neck and shoulder muscle weakness, needle EMG may show findings consistent with myopathy in the most severely involved muscles. There are fibrillation potentials, positive sharp waves, and excessively recruited complex short duration MUAPs. Muscle biopsy has shown only type II atrophy, without evidence of inflammation. In several MuSK+ patients at this author’s institution, the suspicion of MG first arose when MUAPs in neck muscles were noted to have excessive “jiggle.”20

Response to Treatment

The Tensilon test is frequently negative in MuSK+ patients. The response to oral acetylcholinesterase (ChE) inhibitors is quite variable; they can make some patients weaker. Plasma exchange has consistently produced a dramatic improvement in MuSK+ patients, and many have ultimately had a good response to selected immunotherapy.15 Others have recurrent crises or persistent facial weakness and progressive atrophy despite aggressive immunotherapy.3 No MuSK+ patients have been reported to improve after thymectomy.3,15 The best treatment approach for these patients has yet to be determined (Table 3).

<table>
<thead>
<tr>
<th>Pattern</th>
<th>“Typical” MG</th>
<th>Restricted</th>
<th>Facio-pharyngeal</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridostigmine</td>
<td>5/7***</td>
<td>3/7</td>
<td>0/2</td>
<td>8/16**</td>
</tr>
<tr>
<td>Prednisone</td>
<td>6/6</td>
<td>3/5</td>
<td>1/1</td>
<td>10/12</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0/4</td>
<td>0/2</td>
<td>-</td>
<td>0/6</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4/4</td>
<td>2/3</td>
<td>-</td>
<td>6/7</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>3/3</td>
<td>4/5</td>
<td>-</td>
<td>7/8</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>6/6</td>
<td>6/6</td>
<td>-</td>
<td>12/12</td>
</tr>
<tr>
<td>IVIg</td>
<td>1/1</td>
<td>-</td>
<td>-</td>
<td>1/1</td>
</tr>
</tbody>
</table>

*Number of patients who improved/total treated
**One became worse

IVIg = intravenous immunoglobulin; MG = myasthenia gravis; MuSK = muscle specific tyrosine kinase.

CONCLUSIONS

Up to 50% of patients with generalized SN-MG have serum antibodies to MuSK. Because many patients with anti-MuSK antibodies have clinical features, EDX findings and responses to ChE inhibitors that differ from typical MG, correct diagnosis can be difficult. In some patients, MG can only be confirmed by SFEMG in weak muscles. Responses to therapy are variable, though PLEX produces consistent, marked benefit. Many patients achieve an excellent response to various forms of immunosuppression, but others have persistent weakness and atrophy despite aggressive immunotherapy. Benefit from thymectomy has not been demonstrated.

Assay for MuSK antibodies promises to be of value in confirming the diagnosis in patients with generalized SN-MG. It may also be useful in guiding therapy.

Drs. Janice Massey and Robert Kurtzke generously provided clinical information about their patients with MuSK+ MG. Assay for anti-MuSK antibodies was performed by Dr. Angela Vincent and by Athena Diagnostics.

*Dr. Sanders has received consultation fees from Athena Diagnostics and grant support from Roche Pharmaceutical Company.
REFERENCES

INTRODUCTION

Auto-immune myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) can now be managed with a number of relatively safe and effective therapies. This review will discuss the various treatment modalities for these disorders.

TREATMENT OF MYASTHENIA GRAVIS

Anticholinesterase Drugs

Acetylcholinesterase inhibitors are typically the first line of treatment for MG. These medications boost the amount of acetylcholine (ACh) available for neuromuscular transmission by impairing its breakdown at the synaptic cleft. Pyridostigmine is the main acetylcholinesterase inhibitor used. Other agents, such as neostigmine methylsulfate, are available, but are used rarely. Pyridostigmine provides symptomatic treatment, but in some patients it is the only therapy needed. The effects of pyridostigmine are noticed 15-30 minutes after taking a dose (Table 1). Beneficial effects last for 3-4 hours. However, it can often be dosed successfully 4 times daily (qid) or even 3 times daily (tid). Pyridostigmine comes as 60-mg pills. These are double scored, permitting easy dosing in 15-mg increments. The typical starting dose is 30 mg tid. Many patients can be well controlled on 60 mg tid to qid. Pyridostigmine can be increased in 30 mg per dose increments, and can be safely used in doses up at 120 mg qid. However, if a patient has significant weakness at a dose of 60-90 mg qid, the MG is not under control, an immunomodulating treatment should be added, as will be discussed.

A slow-release form of pyridostigmine is also available in a 180 mg pill with delayed absorption and therefore a longer time of action. This is not a good choice for daytime use because absorption is variable. It can be difficult to regulate the total pyridostigmine dose. Some patients take this preparation at night to avoid significant weakness in the morning. Most patients do not have significant morning weakness and the use of regular release

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time to Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridostigmine</td>
<td>10-15 minutes</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>1-4 weeks</td>
</tr>
<tr>
<td>IVlg</td>
<td>1-4 weeks</td>
</tr>
<tr>
<td>Prednisone</td>
<td>2-8 weeks</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>2-6 months</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2-6 months</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>3-18 months</td>
</tr>
</tbody>
</table>

IVlg = intravenous immunoglobulin.
pyridostigmine after awakening is sufficient. In a small number of patients who do have severe weakness upon awakening, a bedtime dose of slow release pyridostigmine can be helpful.

At high doses, pyridostigmine can cause muscle weakness through effects on nicotinic ACh receptors (AChR). However, in the current era of MG management, in which immunomodulating therapies are often utilized, the doses of pyridostigmine used are not (or should not be) high enough to cause weakness. In the past, some patients developed so-called “cholinergic crisis”, which was difficult to distinguish from the deterioration associated with MG. As previously stated, if a patient does not respond to moderate doses of pyridostigmine, other treatments should be added. Limb and bulbar weakness typically show a good response to pyridostigmine, but ocular symptoms such as ptosis and diplopia may not respond as well.

At standard pyridostigmine doses, patients may experience fasciculations rather than weakness. Other common adverse effects of pyridostigmine are muscarinic, and include abdominal cramps and diarrhea. These symptoms, which may limit the use of pyridostigmine, can often be mitigated by anticholinergic medications. Hyoscyamine sulfate 0.125 mg can be taken as needed or prophylactically with each dose of pyridostigmine.

Pyridostigmine can be given intravenously if oral medications cannot be taken. This usually is used only during hospitalization for myasthenic crisis. The intravenous dose is 1/30 the oral dose, and the dosing frequency is the same. When an MG patient is in crisis, pyridostigmine may be beneficial, but this author’s practice is to hold cholinesterase inhibitors and treat the patient aggressively with immunomodulating therapies, which will be discussed later. When the patient is off mechanical ventilation and is improving as a result of the other therapeutic interventions and bed rest, oral pyridostigmine is resumed. Pyridostigmine is probably not a key deciding factor in getting the patient through an episode of crisis. In addition, it may increase bronchial secretions and precipitate cardiac arrhythmias. Furthermore, the effects of pyridostigmine can mask the response to immunomodulating therapy. It is best to titrate the immunomodulator to a point where the patient reaches maximal improvement while avoiding the use of pyridostigmine.

**IMMUNOMODULATING THERAPIES**

**Corticosteroids**

Corticosteroids can suppress the immune system in a number of ways; the precise explanation for their effect in MG is unknown. Prednisone has been shown to reduce AChR antibody levels and this decrease often correlates with clinical improvement. The ideal prednisone dose has not been established, but initial doses are usually 60-100 mg per day. The dose can be calculated at 1-1.5 mg/kg, but in most adults it is typical to begin with 100 mg per day. After 2-4 weeks change to a dose of 100 mg every other day. This helps minimize side effects. Most patients tolerate alternate day dosing, but some feel poorly on the off day, so daily dosing is often resumed. Patients with diabetes are treated more effectively with the same prednisone dose each day to minimize blood sugar fluctuations.

After the initiation of corticosteroid therapy at moderate to high doses, improvement is typically seen within 2-3 weeks (Table 1). A problem with starting treatment at high doses is that as many as 50% of patients may experience transient deterioration in strength. The exact cause is unknown, but it may involve prednisone-induced worsening of neuromuscular transmission. The worsening can be serious; in one study, almost 10% of patients who experienced deterioration required intubation. If an MG patient has significant weakness, initiate high-dose prednisone therapy only in the hospital where respiratory and bulbar function can be closely monitored. Unfortunately, deterioration can occur up to a week after corticosteroid initiation. It is sometimes difficult to obtain approval for such a hospitalization unless a patient already has significant weakness and requires plasmapheresis or intravenous immunoglobulin (IVIg). For patients with milder baseline weakness, corticosteroids can be started at low doses and then built up slowly. Start with 10-20 mg per day and increase the dose by 5 mg every 3-5 days. While this will minimize the risks of deterioration, the onset of improvement will be significantly prolonged. After reaching the target daily dose of 100 mg per day (within 6-8 weeks), the patient can be switched to alternate day dosing.

A study from the University of Virginia has provided good data regarding the efficacy of prednisone in MG. In the treatment of 116 patients with prednisone, a marked improvement was seen in 52% of patients (minor symptoms and return to activities of daily living), a moderate improvement in 15% of patients (functional limitations), no improvement in 5% of patients, and pharmacologic remission (asymptomatic on medication) in 28% of patients. The mean time to maximum prednisone benefit was 5.5 months (range: 2 weeks to 6 years). This study also demonstrated that only 14% of patients were able to be completely taken off of prednisone.

After improvement is achieved, the prednisone dose should be decreased. It is important not to taper prednisone too early or too quickly. As with the initial dose, there are no established guidelines for tapering. In general, maintain patients on 100 mg every other day for 2-4 months before tapering. Deterioration may not occur for 1-2 weeks following a decrease in corticosteroid dose, therefore, taper by only 5 mg per day every 2 weeks. When the prednisone dose is decreased to 20 mg every other...
day, taper even more slowly. Although the goal is to get patients completely off prednisone, many patients require low doses (5-10 mg every other day) for years or indefinitely.

Corticosteroids have a number of advantages for the treatment of MG—they are inexpensive, have a quick onset of action, and have an established track record. The main drawback is their adverse effects, which range from cosmetic (weight gain, cushingoid facies) to serious medical problems (e.g., infection, diabetes mellitus, hypertension, osteoporosis, depression, and psychosis). Although side effects cannot be entirely avoided, there are some measures, such as every other day dosing, that can help minimize them. To minimize weight gain, patients are placed on a calorie-restricted, low carbohydrate, low sodium diet. All patients are placed on calcium (1500 mg per day) and vitamin D (400-800 IU per day) supplementation to minimize bone mineral loss. Bone density is measured at baseline and, if it is satisfactory, it is measured every 6 months. If osteopenia develops, patients are treated with a bisphosphonate, such as alendronate. Prescribing histamine-2 blockers or proton pump inhibitors should not be done routinely, but can be used when symptoms of gastric irritation develop. Serum electrolytes, glucose, and blood pressure should be monitored regularly.

**Azathioprine**

Azathioprine is an anti-metabolite that blocks cell proliferation. Inhibition of T-lymphocytes is the presumed mechanism for benefit. Acetylcholine receptor antibody levels are decreased with azathioprine treatment. Azathioprine is used most often in patients who have relapsed while on prednisone. It is used as a steroid-sparing agent in patients who have been taking prednisone for long periods of time. A number of clinicians start both corticosteroids and azathioprine concurrently. Using azathioprine as a first-line immunosuppressant agent instead of prednisone is not recommended, but this practice is more common in Europe. In retrospective studies of azathioprine therapy, 70-90% of MG patients improve whether the drug is used as a first- or second-line therapy. The clinical response is slow, ranging from 3-18 months (Table 1). In an important double-blind study that compared oral prednisolone therapy versus prednisolone plus azathioprine, patients who received both medications had fewer relapses, a higher incidence of remission, and ultimately achieved a lower corticosteroid dose. The beneficial effects of azathioprine were not seen until after 18 months. On the basis of these data, many clinicians use both corticosteroids and azathioprine when they begin immunomodulating treatment in patients with MG. This author still frequently uses prednisone monotherapy, especially in patients without risk-factors for steroid-induced morbidity (e.g., obesity, diabetes, hypertension, or osteopenia). This controlled study underscores the long latency before clear benefit from azathioprine may be seen. Therefore, for patients in whom a more rapid effect is needed, other treatments should be considered.

Begin azathioprine at 50 mg per day. If, after 1 week, there are no systemic side-effects, increase the dose to 2-3 mg/kg/day. Therefore, after the initial test dose, most MG patients are placed on 150-200 mg/day. Azathioprine is usually well-tolerated, but there are a few limiting adverse effects. Within the first several weeks of treatment, approximately 10% of patients will have an idiosyncratic reaction consisting of fever, anorexia, nausea, vomiting, and abdominal pain. Patients feel as if they have the flu. These symptoms resolve quickly after the drug is stopped. The same symptoms usually return if the patient is re-exposed to azathioprine. Leukopenia and hepatotoxicity are important adverse events. Blood counts and liver function tests should be monitored monthly. If the white blood cell count decreases below 4000 cells/mm$^3$, the dose should be decreased. If the count falls below 3000 cells/mm$^3$, azathioprine should be stopped. Medication should also be held if liver enzymes become significantly increased. In these circumstances, patients can be rechallenged with azathioprine although, in many patients, recurring toxicity will require discontinuation of the drug. Following long-term use of azathioprine, patients are at increased risk of developing malignancies. Azathioprine is teratogenic and can impair fertility in women.

**Cyclosporine**

Cyclosporine, a drug designed to prevent rejection in organ transplantation patients, became a popular MG treatment in the 1990s. This drug inhibits helper T-lymphocytes, facilitates suppression of interleukin-2. Cyclosporine is unique among MG therapies in that it is the only treatment for which successful randomized, blinded, placebo-controlled trials have been performed. Tindall and colleagues studied this drug in new-onset MG patients and in corticosteroids-dependent patients. In both studies, cyclosporine was more effective than placebo in improving clinical assessments and in lowering AChR antibody levels. The corticosteroid dose could be reduced with cyclosporine therapy.

Clinical benefit can be seen 2 months after starting cyclosporine (Table 1). The time to effect is slower than that seen with prednisone, but faster than that seen with azathioprine. The dose of cyclosporine is 4-6 mg/kg/day in 2 divided doses taken 12 hours apart. Side effects include hirsutism, tremor, gum hyperplasia, paresthesias, anemia, and hepatotoxicity. However, hypertension and nephrotoxicity are the main limitations to therapy. Blood pressure, renal function, and trough plasma cyclosporine levels

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should be followed monthly. The risk of malignancy with long-term use may also be increased.12 Although it is effective, the role of cyclosporine has largely been usurped by mycophenolate mofetil due to concerns about renal injury and hypertension.

**Mycophenolate Mofetil**

Mycophenolate mofetil (MM) is another immunosuppressant agent used in organ transplantation. By selectively blocking purine synthesis it suppresses both T- and B-cell proliferation. A multicenter, double-blind, placebo-controlled study of MM as a steroid-sparing agent is currently ongoing. However, based on retrospective case series9,11,47 and a small pilot, double-blind, placebo-controlled study,48 MM seems to be an effective adjunct therapy for MG. It appears to improve function and allow for decreased doses of prednisone and pyridostigmine.47 Onset of benefit is probably similar to cyclosporine (Table 1). In one large retrospective review of 85 patients treated with MM, the mean time to objective improvement was 10 weeks (range: 4-40 weeks).47 The mean time to maximal objective improvement was 27 weeks (range: 8-104 weeks). Sixty-two patients (73%) improved with the addition of MM. Corticosteroid dosage could be decreased in the majority of the patients. Of the 19 patients treated with MM as the sole therapy, 17 (89%) improved. However, in the 14 patients started on MM because they were refractory to other therapies, only 43% improved. Mycophenolate mofetil appeared to be well tolerated. Side effects were noted in 27% (mainly nausea and diarrhea) but discontinuation due to side effects was necessary in only 6% of patients.

Standard doses are 2000-3000 mg per day in 2 divided doses. Begin patients on 500 mg twice a day (bid) and, after 1-2 weeks, increase to 1000 mg bid. In transplant patients, myelosuppression is common, but in MG patients who take lower MM doses, this does not seem to be a frequent problem.9,11,47 Nevertheless, blood counts should be checked monthly. In contrast to azathioprine and cyclosporine, MM may not raise the risk of malignancy.27 Therefore, MM appears to have efficacy similar to cyclosporine with less toxicity. Currently, there is an ongoing multi-center, randomized, controlled trial where patients will be randomized to prednisone plus MM or prednisone plus placebo for 3 months.

**Cyclophosphamide**

Cyclophosphamide is a nitrogen mustard alkylating agent that blocks cell proliferation and affects both T- and B-cells. There are limited data regarding the benefits of cyclophosphamide in MG.17,60 It is a potent immunosuppressant medication, but it is not typically used in MG due to significant potential adverse effects, such as myelosuppression, hemorrhagic cystitis, and an increased risk of malignancy. As previously outlined, there are a number of effective, less toxic immunosuppressant agents available. Cyclophosphamide may be of benefit in MG patients refractory to other treatments.17 Recently, a novel approach to treatment of refractory patients was proposed by Drachman and colleagues using a one-time course of high-dose cyclophosphamide to “reboot” the immune system.20 They took advantage of the fact that stem cells are resistant to cyclophosphamide. This allowed the immune system to be reconstituted after they administered high doses of cyclophosphamide to ablate cellular components in circulation. Based on prior success in animal MG models and in the treatment of other autoimmune diseases in humans, Drachman and colleagues treated three refractory MG patients with this same method.20 All three tolerated the procedure well. They showed significant clinical improvement, and the dose of other immunosuppressant medications could be lowered. Benefit from this procedure has persisted for several years. The best approach to treating refractory MG patients is uncertain. Further studies are needed to compare chronic conventional immunosuppressant medications, repeated pulse-dose cyclophosphamide, and one-time high-dose cyclophosphamide. The long-term benefits and risks of these therapies have not been determined.

**Plasmapheresis**

Plasmapheresis, a procedure that removes AChR antibodies from circulation, is an effective treatment for MG.16 However, it is surprising that a controlled trial of plasmapheresis for MG has never been performed. Improvement following plasmapheresis occurs within a few days—much faster than for other immunomodulating therapies (Table 1). Plasmapheresis is an established therapy for patients in myasthenic crisis and is often used to improve the strength of a patient (if necessary) prior to thymectomy. Another situation in which plasmapheresis is employed is to treat weak patients admitted to the hospital for initiation of corticosteroids. Infrequently, chronic, intermittent plasmapheresis is used in patients refractory to other therapies.

The effects of a course of plasmapheresis last several weeks. It can be performed through peripheral veins, but usually a large-bore, double-lumen subclavian catheter is necessary. The risks of a chronic indwelling catheter (pneumothorax in the short-term, and infection and thrombosis in the long-term) make chronic plasmapheresis a relatively unattractive long-term treatment option.

A course of plasmapheresis usually consists of four to six exchanges. Three to 5 liters of plasma are removed with each treatment, and treatments are performed daily or every other day. There is no precise prescription governing the number, volume, and frequency of exchanges. This is dependent to a large extent on how well a patient tolerates the procedure, and how quickly and thoroughly the patient responds. Plasmapheresis produces large fluid shifts and patients are susceptible to hypotension and, in individuals at risk, myocardial infarction.
Intravenous Immunoglobulin

Intravenous immunoglobulin is frequently used by physicians for a number of immune-mediated neuromuscular disorders. Although clear efficacy demonstrated by a placebo-controlled trial is lacking, there is experimental and anecdotal evidence of the benefit of IVIg in MG.1,2,14,15,22,24,33 In this series of evidence, the response rate was approximately 60-70% and improvement occurred within days to weeks. The specific mechanism of action of IVIg in patients with MG is not known.37

A randomized study that compared IVIg to plasmapheresis in 87 MG patients with exacerbations found the two therapies to be equally effective with IVIg having fewer side effects.23 A retrospective series found plasmapheresis to be superior to IVIg in patients in myasthenic crisis.62 Stricker and colleagues77 reported four patients in myasthenic crisis who had no response to IVIg, but improved with plasmapheresis. A double-blind, placebo-controlled trial of IVIg in mild to moderately weak outpatients refractory to other immunomodulating therapies. In this situation, following a 2 g/kg dose, two or three additional infusions of 0.4 g/kg given at monthly intervals are scheduled. After these additional infusions, the patient is subsequently re-evaluated to determine if further treatments are needed. Because of the expense, insurers are often reluctant to approve IVIg for this indication. If improvement occurs, it generally takes 1-4 weeks (Table 1).

The advantages of IVIg are the low side effect profile compared to immunosuppressant medications and plasmapheresis. Most adverse effects are related to the rate of infusion, and they include headache, lightheadedness, and chills. Nephrotoxicity can occur in patients with underlying renal impairment and hypertension.78 This appears to be related to the osmolality of the IVIg solution, and it depends largely on sugar content, which varies among brands of IVIg. Although uncommon, significant thrombotic events, including myocardial infarction and stroke, may occur.7,76

Thymectomy

In 1939, Blalock6 reported the remission of generalized MG in a 21-year-old woman following removal of a thymoma. Since then, thymectomy, with or without the presence of thymoma, has gained widespread acceptance as a form of treatment for MG. Thymectomy was therefore the first attempt at “immunotherapy” for MG, and it continues to be one of the most frequently utilized treatments for this disease. Key questions regarding thymectomy include: (1) which patients are most likely to respond; (2) when should thymectomy be performed; (3) which patients should undergo the procedure; and (4) which type of surgical procedure is most effective. Unfortunately all studies that address the effectiveness of thymectomy are retrospective or case control series.47

Gronseth and Barohn26 recently reviewed 21 thymectomy series from 1953 to 1998, involving 8490 MG patients. Patients who underwent thymectomy were more likely to achieve medication-free remission, to become asymptomatic, or to show clinical improvement compared with patients who did not have thymectomy (median relative rates: 2.1, 1.6, and 1.7, respectively). However, among the patients who had undergone thymectomy, the median rates of remission, asymptomatic state, or improvement were only 25%, 39%, and 70%, respectively (the mean rates are approximately 50% lower for each). Therefore, although a patient who undergoes thymectomy may be two times more likely to experience improvement, the majority of patients who have this operation will not experience remission or become completely asymptomatic. A recent multivariate analysis of 756 MG patients found thymectomy to be significantly associated with remission, but the odds ratio was only 1.6.42 Patients and physicians should be aware that even in the most favorable reports, the response to thymectomy is not immediate. In one early study among the patients who attained remission, 25% remitted in the first year, 40% in the second year, and 55% in the third year.61 Other series have shown that the “benefit” of a remission from thymectomy may take as long as 7-10 years.52,65 The prolonged latency to improvement raise the question of whether other confounding factors might account for the perceived benefit (Table 1).

Thymectomy can be performed in children, but it should probably be avoided during the first few years of life.64 Whether or not ocular MG patients should have thymectomy is controversial.36,73 Thymectomy is generally not advised for such patients.
In addition, thymectomy is probably less effective in the elderly due to atrophy of the thymus. An upper age limit has not been established, and some authors do not regard age as exclusionary. Typically, patients over 60 should not undergo thymectomy.

For the reasons outlined above, there is much uncertainty about the benefit of thymectomy. In a 1990 survey of 56 experts, only 3 expressed no reservations in recommending thymectomy for patients with generalized MG. For several years, there have been calls for randomized studies of thymectomy. A multicenter, multinational study is currently being planned. This author recommends physicians start treating MG patients with pyridostigmine and, if necessary, a course of immunomodulating therapy. If patients do not show a good response, or cannot be reduced to a small dose of medication, then consider thymectomy. Some authors suggest that thymectomy is most effective when it is performed soon after diagnosis, but significant methodological issues limit interpretation of that data. This author tends to favor thymectomy for newly diagnosed young women, although admittedly this is not based on firm empirical data. The option of thymectomy should be presented to all patients. Physicians should explain that there may be an increased likelihood of improvement and describe the limitations of the available data and point out that most patients—despite surgery—will not go into remission or become asymptomatic.

Another controversy is whether a sternal splitting surgical approach is superior to techniques that offer less exposure, such as transcervical approach or fiberoptic thorascopy. A similar lack of controlled data hampers comparison of different surgical procedures. With current techniques, surgical mortality and morbidity from thymectomy are each less than 1%. The presence of a thymoma is, of course, the one absolute indication for thymectomy. All newly diagnosed MG patients should have a computerized tomography scan or magnetic resonance imaging of the chest to look for thymoma. Chest radiographs are not sensitive enough to exclude thymoma. Interestingly, MG may sometimes develop weeks or months after removal of a thymoma.

Other Immunosuppressant Therapies

Tacrolimus, a transplant medication similar in mode of action and toxicity to cyclosporine, has been found to be effective in MG in a few small series. It may have less nephrotoxicity than cyclosporine. Rituximab is a monoclonal antibody directed against antigens on B-cells. It was devised to treat lymphomas, but it has theoretical applicability to the treatment of MG. It has a low side effect and toxicity profile. There are two case reports that describe benefit from its use in MG.

Bilevel Positive Airway Pressure in Myasthenia Gravis

A recent study suggested that bilevel positive airway pressure (BiPAP) may prevent intubation in patients with myasthenic crisis. Eleven episodes of crisis in 9 patients were initially managed with BiPAP and endotracheal intubation was avoided in 7 of these 11 trials.

Treatment of Seronegative Patients

For years the management of MG patients seronegative (SN) for AChR antibodies has not differed from that of seropositive (SP) patients. For the most part, this is still true, but recent findings are modifying our approach to SN patients. A proportion of SN patients will have antibodies against muscle specific tyrosine kinase (MuSK). The percentage of SN patients who are MuSK-positive has ranged from 38-71%. Only limited data are available for MuSK-positive patients, but they appear to have a variable response to pyridostigmine. They have an excellent response to plasmapheresis, and an overall good response to immunosuppressant medications. In the small number of patients studied to date, there has not been improvement after thymectomy.

TREATMENT OF LAMBERT-EATON MYASTHENIC SYNDROME

Neoplastic Lambert-Eaton Myasthenic Syndrome

In neoplastic LEMS, the therapy is initially directed at the tumor. If the tumor responds to chemotherapy or radiation therapy the LEMS symptoms may improve. Usually patients with neoplastic disease require additional therapy for LEMS.

Pharmacologic Therapy

Guanidine hydrochloride increases the release of ACh vesicles and can produce improvement of strength in LEMS patients. The starting dose is 5-10 mg/kg/day in divided doses. Side effects are prohibitive in most patients and include bone marrow depression, renal failure, gastrointestinal distress, ataxia, hypotension, paresthesias, confusion, dry skin, and atrial fibrillation. Because of toxicity, guanidine is seldom used for LEMS treatment.

3,4-Daminopyridine

Recent literature suggests that 3,4-diaminopyridine (3,4-DAP) therapy can improve the symptoms of LEMS. The agent works by blocking the outward potassium current of the nerve action potential...
potential, which increases the duration of voltage gated calcium channels activation. The increased activation allows for more effective calcium entry into the nerve terminal. Two double-blind, placebo-controlled studies have corroborated the findings of earlier trials that demonstrate improved strength and resolution of electrophysiologic abnormalities in LEMS patients treated with 3,4-DAP. The starting dose in the trial by Sanders and colleagues was 20 mg tid. Noted improvement with doses as low as 5 mg tid have been reported. The medication is usually well tolerated, but a few patients experience perioral and anal paresthesias. It is recommended that doses not exceed 80 mg per day, as higher doses may induce seizures. When combined with pyridostigmine, 3,4-DAP may have synergistic effects. Unfortunately, 3,4-DAP is not approved by the Food and Drug Administration, or on a compassionate-use basis.

Immunosuppressive Therapy

Anecdotal reporting suggests that plasmapheresis, corticosteroids, or azathioprine can be effective for patients with either neoplastic or nonneoplastic LEMS. Plasmapheresis has a peak effect in 2 weeks, but the benefit disappears by 6 weeks. No controlled trials exist for these agents. In a retrospective analysis, IVIg was reported to be effective in LEMS. Subsequently, a randomized, placebo-controlled cross-over study of IVIg in LEMS reported significant improvement in myometric limb strength. The resting compound muscle action potential amplitude also increased with IVIg but it did not reach statistical significance. A recently published Cochrane Database review of LEMS treatment concluded that the three randomized controlled trials of 3,4-DAP and IVIg cited above may improve muscle strength scores and CMAP amplitude. No controlled trials exist for corticosteroids or other immunosuppressive agents.

SUMMARY

Both MG and LEMS can now be well managed with a number of relatively safe and effective therapies. Management involves a graded approach from pharmacologic therapy at the neuromuscular junction to various immunomodulating strategies. While great strides have been made in this field, we are optimistic that there will be further developments for the treatment of these auto-immune disorders.

REFERENCES


Quality of life (QOL) is an important concept, yet it remains difficult to define and each physician might define it differently. Myasthenia gravis (MG) may affect QOL, but the individualistic nature of QOL means that this author's opinion of how MG may affect QOL is unlikely to be shared by all, or even any, patients with MG. The question then is how can one determine what QOL issues are important to patients with MG? This leads to a corollary question, how does one measure QOL?

Why are physicians interested in QOL? Thirty years ago, researchers were satisfied using survival and morbidity statistics, or specific physiologic, pathologic or other "hard" measurements to determine a successful or failed outcome. In the intervening decades, a general consensus has arisen that such surrogates are inadequate to fully define patient experiences. Quantity of life does not equal quality of life. Health-related QOL (HRQOL) has become an attractive way to describe more accurately the actual experience of patients.

But QOL, and even HRQOL, is not an isolated concept. Many investigators fail to actually define HRQOL, but among those who do, the usual definition of HRQOL is the preservation of a sense of well-being. Well-being can be affected by many aspects of life. One patient with MG may be cheerful, friendly, proud of her educational accomplishments, surrounded by friends and family, and eager to talk about her career in marketing, in spite of being severely affected by the disease and its treatment, and having a high level of dependence on others for her activities of daily living (ADLs). Another patient equally affected with the same disease, may be angry, bitter, and resentful. The patient may have few or no friends and several failed experiences in education and work. The first patient will have a normal overall QOL, but the second patient will not. It will not take a sophisticated battery of tests to distinguish between the QOLs in the two patients. Thus, "it is important to recognize that a patient may experience greater symptom severity during times of emotional distress, despite no change in the pathophysiology of the disease. This point represents the critical distinction between a biomedical condition and how patients interpret and experience symptoms of the condition," i.e., the former is the disease, the latter is the illness. The biomedical condition (disease) and the experience of the condition (illness) tend to co-vary, but not perfectly. A full range of illness severity is possible for any given burden of disease, and psychological health is an important determinant of where in the range of illness a patient lies. When under stress or depressed, patients may experience greater symptoms, even though there has been no change in the underlying biomedical disease. Any measure of QOL must pay attention to those variables that affect illness behavior.

Quality of life can also be viewed as the gap between hope and expectation, and reality. The wider that gap, the worse QOL will be. In this sense, QOL may be improved by narrowing the gap, either by lowering expectations or by improving reality. Physicians consistently underestimate the QOL of disabled patients, and QOL is likely maintained at a high level in large part due to the conscious or unconscious lowering of expectations, keeping them in line with reality. Those individuals with the greatest capacity to adapt expectations to reality will have the best QOL. Helping patients to accept their disease (i.e., lower
It is quite possible that the response to a single, simple question may suffice to give an accurate indication of QOL. For example, in general, “would you say your life is excellent, very good, good, fair, or poor?” But this would not tell much about how the two patients described previously came to such different conclusions about their QOL. This has led to the development of tests that measure different components of QOL, such as separating the physical aspects of health from the emotional or mental aspects. In the two patients, sub-measures, or domains, of QOL might show that physical factors of health are similarly limited but that emotional responses, coping abilities, differences in personality and mental health are quite different. Additional domains of QOL might include social support mechanisms available to patients for their physical and emotional realms of existence, or their perception of control over life and illness. This last item may be an important factor in MG, as the unpredictable and fluctuating nature of the disease makes life uncertain and planning for the future difficult. The frequent misdiagnosis of MG symptoms can also contribute to feelings of inadequate control and a lower QOL. This is potentially rectifiable by making an accurate diagnosis and appropriate prognosis. Other factors can include instillation of confidence in the physician, the support staff, and the treatment, as well as education of the patient about the disease, and inclusion of the patient in decision making. Therefore, measurement of QOL and its domains can potentially teach physicians much about MG as a disease and as an illness. It can provide targets for intervention in individual patients with the aim of more directly improving QOL, and it may allow measurement of the success or failure of those interventions.

THE BROWN EXPERIENCE

In 2000, this author and a group of colleagues began a series of investigations of the psychosocial aspects of MG. A set of psychometric tools designed to assess the impact of fatigue and mood on cognition and QOL in a group of patients with MG was used.13,14,15,17,18 Little is known about how MG affects the psychological and cognitive health of patients or how patients respond to MG. Many patients with MG complain of memory loss, and, despite suggestions that acetylcholine receptor antibodies may also attack central receptors, there is no evidence to support that possibility.17 Regardless, a review of the literature revealed that 7 of 10 studies reported significantly poorer performance on cognitive measures. Methodologic limitations permeated all the studies,13 and this author’s group attempted to address these limitations by studying a group of patients with MG.13 No significant difference was found from healthy control subjects similar in age and education on measures of attention, retention of learned verbal information, and retention of learned visual information. The MG patients performed significantly poorer on response fluency, information processing speed, and learning of visual and verbal information.13 This is a different pattern from degenerative dementias that affect central cholinergic neurons, and may best be explained by mental or physical fatigue, as perceived levels of mental and physical fatigue tend to increase or decrease together. In a subsequent study, this author’s group showed that MG patients experience significantly more mental and physical fatigue than do control subjects.15 Perception of both mental and physical fatigue increases after demanding cognitive effort, and this lends support to the contention that both forms of fatigue may underlie cognitive complaints in MG.16 A significant relationship was found between change in mental fatigue and performance on tests of response fluency, information processing speed, verbal learning, and visual retention. The scores decreased as perceived mental fatigue increased. There was no relationship between perceived physical fatigue and cognitive measures.16

Studies into the presence of anxiety and depression among patients with MG have obtained contrasting results. This may be due in part to small sample sizes, varying ranges of disease severity, and methodology. Another factor is the overlap in vegetative symptoms between depression and MG, especially the symptom of fatigue. This author’s research group published two studies that examined depression and mental health in MG.15,18 The Chicago Multiscale Depression Index was used which independently examined mood symptoms (e.g., feeling sad) and vegetative symptoms (e.g., feeling tired) of depression. No significant difference was found in the mood subscale (MG mean 20.9, control subjects mean 18.6), but there was a significant group difference on the vegetative subscale (MG mean 35.6, control subjects mean 24.0).15 Only on the vegetative subscale did the percentage of abnormal individuals reach significance (MG 41%, control subjects 8%). This study indicated that mood disturbances are not increased in frequency in patients with MG, and it implies that depression may be over-diagnosed in MG due to the shared vegetative symptoms. A second investigation examined QOL in MG patients,18 which will be discussed in more detail later. No difference was found in mental health between MG patients and healthy control subjects, and there was no significant difference in overall rating of QOL.

QUALITY-OF-LIFE INSTRUMENTS: AN ABUNDANCE OF POSSIBILITIES

In the author’s studies, the Medical Outcomes Study Short Form survey (SF-36)11 was used to measure QOL, but its limitations were noted for use in MG. The perfect tool does not exist, but a disease specific QOL measurement tool built upon, or in addition to, either the SF-36 or another generic metric would potentially repair many of the deficiencies. No such disease-specific QOL measure for MG exists currently. The options for non-
MG-specific instruments are many and bewildering. In a 1994 review of 75 medical publications concerned with QOL, 159 different QOL devices were in use, and the most commonly used was employed in only 10 of the studies. The website www.qolid.org “aims to identify and describe QOL instruments to help you choose appropriate questionnaires and facilitate your access to them.” Currently, 447 QOL instruments are included. A review of the qualities of each method is beyond the scope of this paper and the competence of the author, but it would be worthwhile to peruse some of the ostensible QOL instruments which have been used in MG or related diseases. Four will be discussed: the McGill Quality of Life Questionnaire (MQOL), the European Organization for Research and Treatment of Cancer quality-of-life questionnaire as adapted for myasthenia gravis (EORTC-MG),3 the Sickness Impact Profile (SIP)4 and its disease specific version, SIP/ALS-19,2,10,20 and the SF-36.22

To better understand the process of measuring QOL, it is best to begin with a definition of commonly used terms. An item is a single question. The scale is the mechanism of response, e.g., a visual analog line, a blank space for an open response, or a series of choices ranging from worst to best, either in words or numbers. The scale may be non-specific, with no demarcation of specific criteria for each response, or it may contain instructions, e.g., “10 equals constant eye drooping interfering greatly with visual function and 0 indicates no eyelid drooping at all. A domain identifies a particular area of interest, such as physical health, mental health, spirituality, or social status, and it is comprised of the answers to a single item or multiple items. To confuse matters, sometimes scale or subscale is used interchangeably with domain. An instrument is the group of items used to collect the responses, and it may consist of a single item or multiple items, which may or may not be separable into domains. The output of an instrument can be viewed as either a single global score, or as a profile, the latter being the results of the component domains of the instrument cited individually and in tandem. Measurement can be by summation of scores, often normalized to a 100 point scale. Alternatively, a population-based mean and standard deviation, which has been the standard, or item response theory can be used. Most instruments are scored using an algorithm which includes internal weighting of items and scales. Reliability is the ability of an instrument to discriminate between better or worse QOL. A valid instrument is one which actually measures what it was intended to measure, i.e., HRQOL.

The MQOL was developed to measure QOL in people with a life-threatening or terminal disease. It has been validated in patients with cancer and human immunodeficiency virus. It has not, to this author’s knowledge, been used in MG, which is rarely a terminal disease. It has been used in amyotrophic lateral sclerosis. It consists of four domains: physical (4 items); psychological (4 items); existential (6 items), and support (2 items). It is measured with an 11-point scale scored from 0 (terrible) to 10 (well) concerning the prior 2 days. The MQOL, unlike many QOL instruments, puts less emphasis on physical function, and it includes an existential domain, which may be important in end-of-life QOL assessment. A study in ALS patients showed a correlation between the existential domain of the MQOL and a measure of religiosity/spirituality. The MQOL was thought to be the best measure of overall QOL in ALS.

The EORTC QOL questionnaire was developed in 1993 for use in cancer trials. It consists of 30 applicable but non-specific items arranged into 8 domains, including functional (5 items), working ability (2 items), general symptom (12 items), cognition (2 items), emotional (4 items), social (2 items), financial strain (1 item), and global (2 items). In addition, there is a module of 20 disease-specific items. These include symptom (14 items), treatment scale (5 items), and overall hope and confidence (1) domains. “To accommodate the unique appearance of myasthenia gravis,” this instrument was altered to omit 9 items from the general symptom domain, and 15 from the disease-specific symptom and treatment strain domains. The remaining three items from the general symptom domain and three from the disease-specific symptom domain were then joined to form a vegetative domain. The three disease-specific items retained are not necessarily specific to MG, but they are more relevant than the others. It is unclear and doubtful that the rearranged questionnaire was studied for reliability or validity in MG.

The SIP was developed to provide a measure of perceived health status that is broadly applicable but sufficiently sensitive to detect changes in health status over time and across types of diseases and social groups. It has existed for approximately 25 years, and is a well-known and oft-used instrument. It has been validated in many diseases, but not as yet in MG. The full SIP consists of 136 items, and it requires considerable time and energy on the part of the researcher and the patient. It consists of 12 domains or categories which are: sleep and rest; eating; work; home management; recreation and pastimes (all considered independent categories); ambulation; mobility; body care and movement (the physical dimension; social interaction; alertness behavior; emotional behavior; and communication (the psychosocial dimension). The SIP has been shown to correlate with aspects of the Tufts Quantitative Neuromuscular Exam Combination Megascrore (TQNE CM) in patients with ALS, but it was judged to be too lengthy. A shorter version was constructed from the 23-item body care and movement domain and the 10-item home management domain (SIP-33). These were the domains that most closely correlated with the TQNE CM. A separate, shorter version of 19 items (SIP/ALS-19) was generated by neuromuscular specialists who selected items most important to QOL in ALS. Both the SIP-33 and SIP-19 correlated nearly as well as the full SIP with the TQNE CM. The SIP-19, however, includes items from eight domains of the SIP rather than two, and it is less redundant clinically than the
studies that did not assess QOL, but instead looked at related

LITERATURE

populations, and between diseases.

the ability to compare results across demographic and social

benefit of a widely-used generic instrument such as the SF-36 is

to measure how illness interferes with completion of activities

physical function. A particular strength of the SF-36 is its intent

emotional problems (4 items); vitality (4 items); general health

problems (4 items); social functioning (2 items); bodily pain

status was 80%. There was a suggestion that certain aspects of

lowest scores were in working ability (50%), vegetative (62%),

interpret as abnormal or significant. For the failed group, the

mean of 100% for the group, meaning QOL was not affected in

correlation. In the responders, many of the domains indicated a

106 patients were followed continuously for 10 years. Eighty-six

average follow-up time was not indicated, but 26 of the original

were available for assessment; 61 were placed in the re-

response group, and the rest were in the failure group. The results

hard to interpret, as there were no normative data for com-

comparison. In the responders, many of the domains indicated a

mean of 100% for the group, meaning QOL was not affected in

any way for any of the patients! Mild decreases were found in

emotional, global, and vegetative domains, but in the 83-95%

range, which in the absence of normative data, is impossible to

interpret as abnormal or significant. For the failed group, the

lowest scores were in working ability (50%), vegetative (62%),

and emotional/social (both 67%) domains. The physical status

domain was 80%. There was a suggestion that certain aspects of

this instrument corresponded to Osserman class, including the

physical, social, and vegetative domains. No global score was cal-

culated. The authors concluded that QOL was completely re-

stored to normal after thymectomy, though the absence of

pre-operative QOL measurement makes that a difficult claim to

verify. They also concluded that the domains of emotional and

vegetative functioning seemed to be sensitive indicators of residu-
al myasthenic activity. Given the aforementioned deficiencies, it

is hard to be confident in that claim.

In 1996, a German group used the EORTC QOL-MG to assess

long-term outcome in 65 patients who had transternal thymec-
tomy for MG.3 As noted above, the altered instrument may not

have been either valid or reliable. It was administered only at the

time of last follow-up, thus no longitudinal or comparison data

was available. A failed thymectomy was defined as no change or

worsening of modified Osserman class after operation, while re-

sponse was defined as any improvement in Osserman class. The

average follow-up time was not indicated, but 26 of the original

106 patients were followed continuously for 10 years. Eighty-six

patients were available for assessment; 61 were placed in the re-

response group, and the rest were in the failure group. The results

QUALITY OF LIFE IN MYASTHENIA GRAVIS IN THE

LITERATURE

The literature on QOL in MG is not extensive. There are two

studies that did not assess QOL, but instead looked at related

concepts. Doering and colleagues’ studied coping mechanisms

in patients with MG. Coping behavior was assessed using the

Bernese Coping Modes, patient self evaluation and a semi-struc-
tured interview. They found no difference from the average pop-

ulation in personality, anxiety, or depression. They found a

variety of coping strategies, including passive cooperation (trus-

ting in the physician), acceptance, stoicism, altruism, distraction,

and relativism in all the patients, who were universally charac-
terized by an attitude of calmness and acceptance. Coping styles

were independent of severity or duration of disease. The authors

attributed successful coping to the availability of effective

“somatic” therapies. This resulted in MG being “a part of these

patients’ lives without necessarily being the center.”25 Though

QOL was not addressed, the ability to effectively cope with MG

is vital in the process of re-aligning expectations to the reality of

MG, and it would make a positive impact on QOL.

Wolfe and colleagues23 published an MG ADL profile, which

they compared to the Quantitative Myasthenia Gravis (QMG)
score (a measure of disease activity) for reliability, and from

which it was derived. The authors acknowledged it was not a

QOL instrument. The MG ADL profile consists of eight items

and a 4-level scale, with normal being 0 and a maximum dis-

ability being 24. The ADL and QMG scores exhibited a positive

correlation (0.583). This was not surprising, as several of the

same functions were assessed quantitatively by the QMG and

subjectively by the ADL profile. Several of the activities in ques-
tion had scales which assessed frequency of occurrence rather

than interference with ADLs. It is unclear how a particular score

correlates with the level of interference in ADLs, and it is unclear

that equal scores indicate an equal level of interference. For

example, a score of 3 could be constant eyelid drooping, or it

could be breathing problems so severe as to require ventilator de-
pendency. This author would posit that those two are not equal

in level of interference with ADLs. The successful ability to ne-

gotiate ADLs is an important aspect of improved physical func-
tion, and it would improve QOL by narrowing the gap with

expectations. An instrument that accurately measures ADLs is an

important adjunct to QOL assessment.

Two studies from separate groups that used the SF-36 as their

QOL instrument were published in 2001.12,18 This author’s re-

search group studied 27 MG patients recruited from regional

chapters of the National Myasthenia Gravis Foundation.18 It was

predicted that MG patients would rate poorly on domains
related to physical function and that overall QOL would be negatively impacted. This was partially correct. Several domains were negatively affected in MG patients (Table 1), but bodily pain and mental health were not. When a criterion of 1.5 standard deviations from the mean of normative data was applied, only the domain of role disruption-physical was abnormal. This domain measures the change in activities due to physical limitations. Overall QOL was also lower in MG patients, but it did not reach the level of being abnormal. Overall, QOL correlated with scores on the mood subscale of the Chicago Multiscale Depression Index, which is not unexpected. In comparison, a much greater impact on physical function was found in MG than in patients with other chronic diseases such as arthritis, hypertension, or congestive heart failure. Mental health was less affected in MG than the other groups. Disease duration did not correlate with QOL, but since all patients were Osserman class 2, it was not possible to determine the effect of disease severity or treatment. This author’s group was pleasantly surprised that, on the whole, QOL was maintained at a reasonably high level.

Shortly thereafter, an Italian group published the results of their study of QOL.12 They used the SF-36, in 46 patients with MG. Most of the study subjects were inpatients who were admitted for worsening symptoms. Osserman classes varied from class 0 to class 3. The patients were also given the Disabilities of the Arm, Shoulder, and Hand questionnaire, thus combining a generic instrument (SF-36) with an anatomically specific instrument. The authors found significant correlations between the Osserman class and the domains of physical functioning, role-physical, general health and vitality, but all domains were decreased, including those having to do with mental health (Table 2). They found no effect of thymectomy or other treatments on QOL ratings. The negative impact on physical domains of QOL mirrored the author and colleagues study, but there was a highly significant difference in the impact of MG on mental domains,11 and the mental domains scale was more than 4 standard deviations below the mean of patients with other chronic diseases.11 One possible explanation is methodologic. This author’s patients were stable outpatients recruited from a support group, while the Italian group’s patients were mostly inpatients with unstable disease.

### Table 1  Scores for each scale of the SF-36 for all participants.*16

<table>
<thead>
<tr>
<th>SF-36 Scale</th>
<th>MG Patients mean (SD)</th>
<th>Normative Data mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>52.7 (24.9)</td>
<td>84.5 (22.9)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>72.2 (22.2)</td>
<td>83.6 (22.4)</td>
</tr>
<tr>
<td>Role Disruption-physical</td>
<td>25.9 (35.0)</td>
<td>81.2 (33.8)</td>
</tr>
<tr>
<td>Role Disruption-emotional</td>
<td>70.3 (39.5)</td>
<td>81.3 (33.0)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>74.2 (14.5)</td>
<td>74.8 (18.0)</td>
</tr>
<tr>
<td>Vitality</td>
<td>45.1 (22.8)</td>
<td>61.1 (20.9)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>70.5 (27.9)</td>
<td>75.5 (23.6)</td>
</tr>
<tr>
<td>General Health</td>
<td>56.4 (20.4)</td>
<td>72.2 (20.2)</td>
</tr>
<tr>
<td>Overall QOL</td>
<td>58.4 (25.9)</td>
<td>73.0 (24.3)</td>
</tr>
</tbody>
</table>

*Possible range, 0 to 100 (worst to best).

QOL = quality of life; SD = standard deviation; SF-36 = Medical Outcomes Study Short Form Survey

### Table 2  Correlation of Italian sample between SF-36 scores, Osserman class, and USA sample*11

<table>
<thead>
<tr>
<th>Patient Oriented Scores (SF-36)</th>
<th>Mean Scores (SD)</th>
<th>Correlation With Osserman Class</th>
<th>Difference With USA Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>48.5 (28.3)</td>
<td>P = 0.01; r = -0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>13.0 (30.2)</td>
<td>P = 0.004; r = -0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>54.2 (33.2)</td>
<td>NS</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>General Health</td>
<td>25.6 (35.7)</td>
<td>P = 0.009; r = -0.4</td>
<td>P &lt; 0.002</td>
</tr>
<tr>
<td>Vitality</td>
<td>36.5 (21.2)</td>
<td>P = 0.002; r = -0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>41.8 (28.3)</td>
<td>NS</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>32.0 (17.3)</td>
<td>NS</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Mental Health</td>
<td>45.6 (21.5)</td>
<td>NS</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

* Possible range 0 to 100 (worst to best).

SD = standard deviation; SF-36 = Medical Outcomes Study Short Form Survey
TOWARD A DISEASE-SPECIFIC QUALITY-OF-LIFE INSTRUMENT FOR MYASTHENIA GRAVIS

The assessment of HRQOL may be individualistic, but more detailed instruments can be of value. The combination of a generic and a disease-specific instrument would provide many advantages over either one alone. Generic instruments are readily available. They have already been tested for reliability and validity and have established norms, usually for such demographic categories as age, gender, social class, economic status, and culture. They allow comparisons to non-diseased populations and to populations with other diseases. Generic instruments, however, do not take into account the unique features of a given disease. Alzheimer’s disease poses different challenges to QOL than does MG, and a generic QOL instrument will not assess those differences. Developing such a disease-specific measure is not easy, but it has been accomplished for cancer, heart disease, and arthritis, among others. Two examples of neurologic diseases where development of a disease-specific instrument is well underway are Alzheimer’s disease and ALS, although in neither disease could consensus be said to exist. Myasthenia gravis is clearly far behind in this regard. The actual construction and mechanics of developing a disease-specific QOL instrument should follow rigorous guidelines, for which examples exist.

In 1994, Gill and Feinstein proposed a set of criteria by which QOL instruments could be judged. Their article is worth reading by anyone interested in measuring QOL, as is the accompanying editorial that offers alternative criteria. Quality of life must be defined before it can be measured, and the tool for doing the measuring must then be shown to actually measure the defined purpose (establish validity). Gill and Feinstein recommended that a global rating of QOL by the patient be incorporated into any disease-specific instrument. It can be supplemented by more detailed items specific to the disease in question and of importance to patient’s lives, as determined by both patients and physicians. These items of importance should be assessed for the extent to which reality matches expectations. The relative importance of the items should then be determined through input from each patient, as each patient may value aspects of QOL differently. All patients with MG likely view the impact of diplopia on their lives as a factor in QOL, but they will rank its importance variably as compared with other aspects of the disease, such as fatigue, ptosis, dysphagia, or dysarthria. A further aspect of QOL, which is also patient-centric, is the importance of any determined difference. In this author’s study, 1.5 standard deviations from the normal mean was used, but what does that really mean? Determining what numeric difference actually denotes a significant change in assessment of QOL has been called the interpretability, and it can be elusive. Lastly, it should be remembered that the use of QOL measurements is just one aspect of health care research and assessment. Improving patients’ QOL by lowering expectations or improving physical functioning should not preclude the fact that the disease remains, and physicians must still find ways to better diagnose and treat it. This will require continued analysis of physiologic, immunologic, pathologic, and other non-psycho metric measures.

REFERENCES


Update on Myasthenia Gravis

CME SELF-ASSESSMENT TEST

Select the ONE best answer for each question.

1. The prevalence of a disease in a population is:
   A. The number of new patients affected in a given year.
   B. The rate at which patients with the disease die in a given year.
   C. The outcome of treatment interventions for the disease.
   D. The number of affected patients at a specified point in time.
   E. The frequency of medical complications associated with the disease.

2. The sensitivity of a diagnostic test is the same as:
   A. The specificity of the test.
   B. The true positive rate of the test.
   C. The positive predictive value of the test.
   D. The prevalence of the disease for which the test is being done.
   E. The true negative rate of the test.

3. The incidence of a disease in a population is:
   A. Equal to the prevalence minus the mortality.
   B. The number of affected patients at a specified point in time.
   C. The number of new patients affected in a given year.
   D. The rate at which patients with disease die in a given year.
   E. The outcome of treatment interventions for the disease.

4. Over the past 50 years, the prevalence of myasthenia gravis (MG) has:
   A. Increased steadily.
   B. Not changed.
   C. Increased, then decreased in the past decade.
   D. Declined.
   E. Increased only in those under the age of 40.

5. Factors involved in the prevalence pattern for MG include all of the following EXCEPT:
   A. Aging of the population at risk.
   B. Improved diagnosis.
   C. Improved treatment strategies.
   D. Increased mortality from other diseases.
   E. Ready availability of skilled intensive care.

6. Which of the following represents the most specific diagnostic test for MG?
   A. Single-fiber electromyography (EMG) recording in the extensor digitorum communis.
   B. Acetylcholine receptor (AChR) binding antibodies.
   C. Repetitive nerve stimulation (RNS) studies recording in the abductor digiti quinti manis.
   D. Edrophonium test.
   E. Anti-striated muscle antibodies.

7. Which of the following represents the most sensitive diagnostic test in a patient with bulbar MG?
   A. Single-fiber EMG recording in the extensor digitorum communis.
   B. Single-fiber EMG recording in the frontalis.
   C. Concentric needle EMG recording in the upper extremity.
   D. Anti-ryanodine antibodies.
   E. RNS studies.

8. Potential side-effects of edrophonium testing include all of the following EXCEPT:
   A. Bradycardia.
   B. Asystole.
   C. Tachycardia.
   D. Increased weakness.
   E. Diaphoresis.
9. Which patient is most likely to have an elevated titer of AChR antibodies?
   A. An 18-year-old with generalized MG and thymoma.
   B. A 55-year-old with ocular MG.
   C. An 80-year-old with ocular MG.
   D. An 8-year-old with generalized MG.
   E. A 45-year-old with proptosis and binocular diplopia.

10. Which patient is most likely to develop myasthenic crisis?
    A. A man with 15-year history of stable generalized MG.
    B. An elderly woman with anti-striated muscle antibodies and ocular MG.
    C. A man with a 5-year history of ocular MG and normal chest computed tomography.
    D. A man with a 1-month history of alternating ptosis with thymic hyperplasia.
    E. A pregnant woman with 3 weeks of symptomatic generalized MG and an upper respiratory infection.

11. All of the following statements are true EXCEPT:
    A. Muscle specific tyrosine kinase (MuSK) antibodies are found in about 50% of patients with generalized seronegative MG.
    B. MuSK antibodies impair neuromuscular transmission by interfering with the interaction of acetylcholine (ACh) with its receptor on the muscle membrane.
    C. MuSK plays a critical role in the developing neuromuscular junction.
    D. The role of MuSK in the mature neuromuscular junction is not clear.
    E. Patients with anti-MuSK antibodies may have clinical features that are typical for seropositive MG.

12. Some antibodies in MG:
    1. Bind to the ACh receptor (AChR).
    2. Increase the turnover of AChR.
    3. Reduce the release of ACh from the nerve terminal.
    4. Block the interaction of ACh with its receptor.
   A. None are correct.
   B. Only 1 and 3 are correct.
   C. Only 1 is correct.
   D. Only 1, 2, and 4 are correct.
   E. All are correct.

13. Which of the following statements is (are) true?
    1. Seronegative MG (SN-MG) can be passively transferred to mice.
    2. SN-MG is an autoimmune disease.
    3. Transient neonatal myasthenia does not occur in the absence of binding antibodies to the AChR.
    4. Plasma exchange relieves weakness in SN-MG.
   A. None is correct.
   B. Only 1 and 3 are correct.
   C. Only 1 is correct.
   D. Only 1, 2, and 4 are correct.
   E. All are correct.

14. Which of the following statements is NOT true?
    A. Repetitive nerve stimulation testing is usually abnormal in patients with MuSK-positive MG.
    B. Jitter may be normal in forearm and facial muscles in MuSK-positive MG.
    C. Electromyography may show myopathic findings in MuSK-positive MG.
    D. Muscle biopsy shows non-specific changes in MuSK-positive MG.
    E. MG should be suspected if motor unit action potentials have varying (unstable) waveforms.

15. Which of the following is most likely to be abnormal in MuSK-positive myasthenia gravis?
    A. Repetitive nerve stimulation in a shoulder or facial muscle.
    B. Tensilon test.
    C. Jitter measurement in the frontalis.
    D. Muscle biopsy.
    E. Jitter measurement in the extensor digitorum communis.

16. Which drug can be used to treat the muscarinic gastrointestinal side effects of pyridostigmine?
    A. Corticosteroids.
    B. Azathioprine.
    C. Hyoscyamine sulfate.
    D. Time-release form of pyridostigmine.
    E. Mycophenolate mofetil
17. Corticosteroid side effects include all of the following EXCEPT:
   A. Ataxia.
   B. Weight gain.
   C. Psychosis.
   D. Osteoporosis.
   E. Hyperglycemia

18. The response to therapy with azathioprine for MG usually occurs in:
   A. 18 hours.
   B. 18 days.
   C. 18 months.
   D. 18 years.
   E. 18 weeks.

19. All of the following are true regarding intravenous immunoglobulin (IVIg) therapy for MG except:
   A. Anecdotal studies suggest a response rate of 60-70%.
   B. IVIg is superior to plasmapheresis in the treatment of myasthenic crises.
   C. The specific mechanism of action of IVIg with respect to MG is not known.
   D. Adverse reactions such as headache are often due to the infusion rate.
   E. Induction dose is generally 2 g/kg.

20. Thymectomy as a therapy for myasthenia gravis:
   A. Should be performed through a fiberoptic thoracoscopy in all patients.
   B. Has a surgical mortality and morbidity of 20%.
   C. Should only be done in patients with MG and invasive thymoma.
   D. Has not been studied yet in a randomized prospective trial.
   E. Is only performed after a patient has failed therapy with prednisone and at least one more immunosuppressive agent.

22. QOL can be improved by:
   A. Lowering the level of physical function.
   B. Lowering the level of patient expectations.
   C. Raising the level of patient expectations.
   D. Widening the gap between expectations and reality.
   E. All of the above.

23. Most QOL instruments:
   A. Are generic and not specific to a particular disease.
   B. Are the same.
   C. Can be altered and adjusted easily to meet the needs of a particular disease.
   D. Are improved by ignoring individual patient concerns.
   E. All of the above.

24. Myasthenia gravis:
   A. Has quality of life issues similar to other chronic neurologic diseases, such as Alzheimer’s disease.
   B. Has no significant effect upon physical aspects of quality of life.
   C. Has been shown to affect mental health aspects of quality of life equally across different populations.
   D. Affects physical functioning aspects of quality of life much more than emotional functioning.
   E. All of the above.

25. Myasthenia gravis:
   A. Is the disease and a patient’s actual experience is the illness.
   B. Has no unique features compared to other neurologic disease.
   C. Seriously compromises mental health.
   D. Has no effect on mental fatigue.
   E. All of the above.
Update on Myasthenia Gravis

EVALUATION

Select ANY of the answers that indicate your opinions.

Your input is needed to critique our courses and to ensure that we use the best faculty instructors and provide the best course options in future years. Please use the computer form to answer the following questions. For the purpose of tabulating evaluations, please enter the last 4 digits of your telephone number in the ID NUMBER box beginning with the left column and fill in the appropriate ovals below each number. Make additional comments or list suggested topics or faculty for future courses on the comment form provided at the end.

26. How would you rate the quality of instruction received during Dr. Phillips’ presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

27. Select any item(s), that, if changed, would have appreciably improved Dr. Phillips’ presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

28. How would you rate the quality of instruction received during Dr. Juel’s presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

29. Select any item(s), that, if changed, would have appreciably improved Dr. Juel’s presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

30. How would you rate the quality of instruction received during Dr. Sanders’ presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

31. Select any item(s), that, if changed, would have appreciably improved Dr. Sanders’ presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

32. How would you rate the quality of instruction received during Dr. Barohn’s presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

33. Select any item(s), that, if changed, would have appreciably improved Dr. Barohn’s presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.
34. How would you rate the quality of instruction received during Dr. Gilchrist's presentation?
A. Best possible.
B. Good.
C. Average.
D. Fair.
E. Worst possible.

35. Select any item(s), that, if changed, would have appreciably improved Dr. Gilchrist's presentation:
A. Quality of slides.
B. Quality of handout.
C. Amount of clinically relevant information in the presentation.
D. Amount of scientific content in the presentation.
E. Other: please explain on the comment form at the back of this handout.

36. As a result of your attendance at this course, did you learn anything that will improve the care of your patients?
A. Yes, substantially.
B. Yes, somewhat.
C. Not sure.
D. Probably not.
E. This course was not applicable to my patients.

37. Select ALL items where improvement was needed.
A. The accuracy of advance descriptions of this course.
B. The specific topics selected for presentation.
C. The number of speakers in this course.
D. The amount of time allotted for discussion in this course.
E. Other: please add other areas and outline specific recommendations for areas needing improvement on the comment form at the back of this handout.

38. Should this topic be presented in the future by a different method of presentation.
A. No, the topic of presentation should remain as a course.
B. Yes, the topic should be presented as a dinner seminar.
C. Yes, the topic should be incorporated into the plenary session.
D. Yes, the topic should be discussed during a breakfast session.
E. Yes, the topic should be organized as a special interest group.
FUTURE MEETING RECOMMENDATIONS

Select ANY of the answers that indicate your opinions.

The following questions are included with all dinner seminar, course, and plenary session evaluations. It is only necessary to answer these questions once during the course of the entire meeting.

39. Please indicate below your specialty:
   A. Neurologist.
   B. Physiatrist.
   C. PhD.
   D. Other.

40. How often do you attend AAEM meetings?
   A. Annually.
   B. Every 2-3 years.
   C. Every 4 or more years.
   D. This is the first AAEM meeting I have attended.

41. With regard to this year's meeting, which of the smaller group sessions did you attend? (mark all that apply)
   A. Experts' roundtables.
   B. Workshops.
   C. Dinner seminars.
   D. None of the above.

42. If you answered none of the above to the previous question, please answer the following. The reason I did not attend the small group sessions was due to:
   A. The timing of the event.
   B. The cost of the event.
   C. My lack of interest in the topics offered.
   D. The session was full.

43. Did this meeting provide information that will enhance care of your patients?
   A. Extremely.
   B. Somewhat.
   C. Very little.
   D. Not at all.

44. With regard to the social event:
   A. I am signed up to attend the social event.
   B. I did not sign up because of the cost of the event.
   C. I did not sign up because of the day the event was offered.
   D. I did not sign up because I am not interested in attending this type of function.

45. How would you rate this meeting?
   A. Poor.
   B. Fair.
   C. Good.
   D. Very good.
   E. Excellent.

46. Did this meeting meet your expectations?
   A. Not at all.
   B. Somewhat.
   C. As expected.
   D. Exceeded expectations.
   E. Best ever.

47. Was the printed program clear and easy to follow?
   A. Yes.
   B. No.

48. With regard to the meeting hotels:
   A. I stayed at one of the meeting hotels.
   B. I did not stay at one of the meeting hotels.

49. If you answered B to the question above, please explain why you did not stay at one of the meeting hotels (please make your comments under Comments, page 45).

50. How did you first learn about the meeting? (choose the method where you first learned about the meeting)
   A. Preliminary brochure mailing.
   B. Registration brochure mailing.
   C. The internet.
   D. Email message.
   E. From a friend.

51. Did you perceive any commercial bias in any of the educational sessions offered by the AAEM at this meeting?
   A. Yes.
   B. No.
52. Did you attend any of the Industry Forums provided this year?
   A. Yes.
   B. No.

53. If you answered yes to question 52 and you attended the Pfizer Industry Forum, how would you rate the quality of the session?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.
   On page 45 under comments, please provide any other comments you have about your attendance at the Pfizer Industry Forum.

54. If you answered yes to question 52 and you attended the Allergan Industry Forum, how would you rate the quality of the session?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.
   On page 45 under comments, please provide any other comments you have about your attendance at the Allergan Industry Forum.

55. How do you prefer to learn new information?
   A. Lecture only.
   B. Lecture in conjunction with questions and answers.
   C. Small group hands-on.
   D. Small group discussion.

56. I plan to attend the 2005 AAEM meeting in Monterey, California, September 21-24.
   A. Yes, definitely.
   B. No, definitely.
   C. Will wait to see the program content.
   D. Will wait to see if budget allows my attendance.

57. I would be more likely to attend the 2005 AAEM meeting if (please make your comments under Comments, page 45):
COMMENTS

Given time and budget constraints, is there something we could do in terms of altering the format of the meeting that would significantly increase the likelihood of your attendance at future AAEM meetings? Explain:

Write out any additional comments about specific courses or the plenary session (please indicate which), and list suggestions for topics and speakers for future meetings. Leave at the AAEM Registration and Information Center or mail to the AAEM Executive Office at 421 First Avenue SW, Suite 300 East, Rochester, MN 55902.