Clinical News /alert

Myasthenia Gravis

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CONTINUUM, Myasthenia Gravis
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DISCLOSURE

The faculty, reviewer, and editor report no financial interests, arrangements, or affiliations with any commercial entity whose products may be mentioned in this monograph.

GOAL

To provide health care professionals in pharmacy, medicine, and nursing with an overview of myasthenia gravis and related myasthenic disorders, their etiology, diagnosis, and treatment options.

OBJECTIVES

Upon completion of this lesson, the reader should be able to:

1. Explain the autoimmune basis of myasthenia gravis;
2. Describe the clinical evaluation of patients presenting with myasthenic symptoms;
3. Discuss treatment options for myasthenia gravis and related disorders;
4. List some of the side effects of treatments used for these disorders;
5. Identify the characteristics that distinguish acquired myasthenia gravis from Lambert-Eaton myasthenic syndrome; and
6. Name the three types of childhood myasthenia gravis conditions and describe some of the differences among them.

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ANSWERS TO QUESTIONS

1.A	11.B
2.D	12.A
3.D	13.B
4.B	14.C
5.A	15.E
6.B	16.D
7.E	17.E
8.C	18.E
9.D	19.A
10.B	20.E

Myasthenia Gravis

INTRODUCTION

Myasthenia gravis (MG), an uncommon and once relatively obscure condition of interest primarily to neurologists, is now the best characterized and understood autoimmune disease. MG affects the transmission of nerve impulses at the neuromuscular junction, causing the characteristic fluctuating weakness in voluntary muscle groups that include ocular, oropharyngeal, shoulder, hip, and limbs. A wide range of potentially effective treatments is available for MG and the much rarer Lambert-Eaton myasthenic syndrome (LEMS), and the clinician is challenged to select the approach most appropriate for each patient. To do so is extremely gratifying, however, because few neuromuscular diseases respond as well to appropriate treatment. Left untreated, however, both diseases can be life threatening when "grave muscular weakness," from which the disease derives its name, hinders respiration.

There are an estimated 70 000 patients with MG in the United States. At least 39 studies of the epidemiology of MG have been published since the early 1950s. In that half century, the reported prevalence has steadily grown—the increase believed largely due to a deeper understanding of the disease as well as improved diagnostic techniques and treatments. Increased survival and longevity are also factors.

The most common age at onset of MG is often the second and third decades in women and the seventh and eighth decades in men. Early studies have shown that women were more often affected than men. As the age of the US population has increased, this has changed. Men are now more affected than women, and the age of symptom onset is usually after age 50. The implication of these prevalence studies and demographic trends is that clinicians can expect to see larger numbers of MG patients in the future. These patients will live longer and require treatment for longer periods.

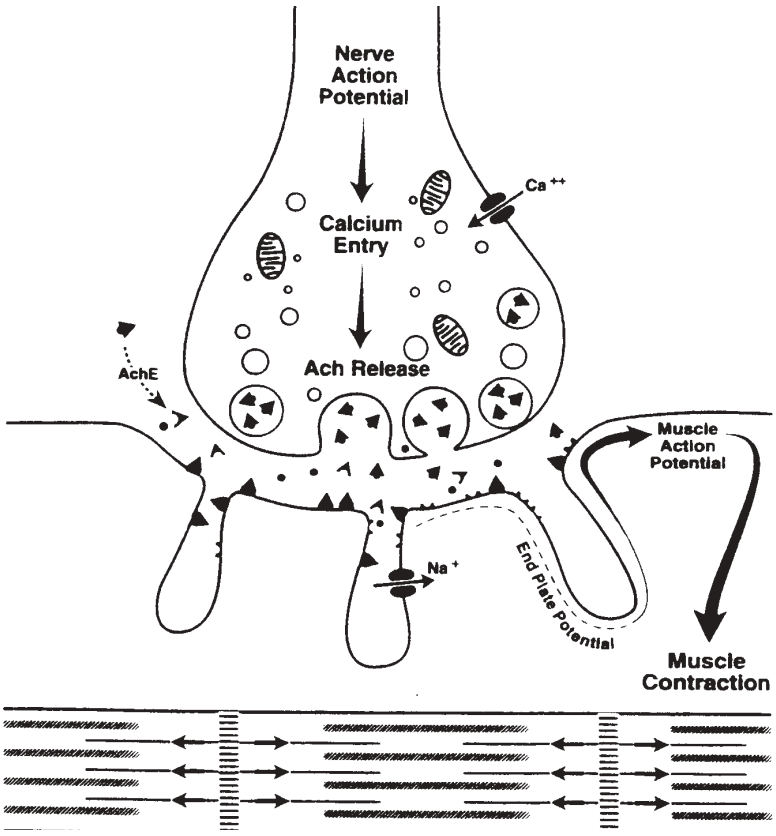

Figure 1. The neuromuscular junction. From Wolfe GI, Barohn RJ, Galetta SL. Drugs for the diagnosis and treatment of mysathenia gravis. In: Zimmerman TJ, ed. *Textbook of Ocular Pharmacology*. Philadelphia, Pa: Lippincott-Raven Publishers. 1997 with permission.

PATHOPHYSIOLOGY

In the past 20 years, much has been learned about the pathophysiology and immunopathology of MG. The immune-mediated nature of the disease was suspected as early as 1960, when Simpson[1] speculated that MG was an autoimmune disease with antibodies directed against the motor endplate at the neuromuscular junction. A series of breakthroughs in the 1970s confirmed that speculation.[2-4]

Acetylcholine (ACh) acts as the neurotransmitter of the neuromuscular junction (Figure 1). ACh is synthesized and stored in vesicles in the motor nerve terminal. Each vesicle contains a quantum, or about 10 000 molecules, of ACh. At rest, individual vesicles spontaneously release their quanta of

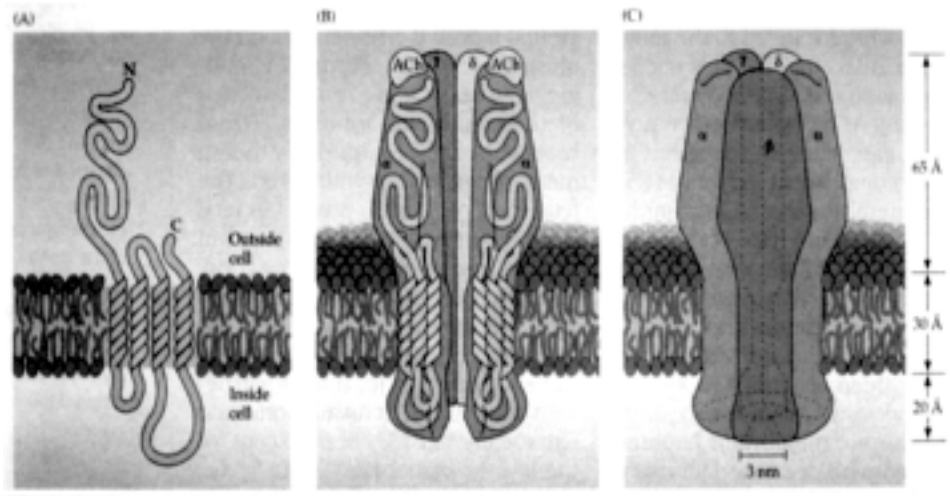

Figure 2. The structure of the acetylcholine receptor channel. (A) Each receptor subunit crosses the membrane four times. (B) Five subunits form a complex structure around a central pore. (C) The openings at each end of the receptor channel are approximately 3 nm in diameter, and the lowest portion of the pore is 0.6 nm in diameter. By comparison, the diameter of Na^+ is less than 0.3 nm. From Purves D, ed. *Neuroscience*. Sunderland, Mass: Sinauer Associates. 1997 with permission.

ACh at special release sites on the presynaptic membrane. The released neurotransmitter migrates across the synaptic cleft and binds to ACh receptors on the postsynaptic membrane, producing a transient increase in the permeability of sodium and potassium ions. The local endplate depolarization that results is known as a miniature endplate potential (MEPP). MEPPs help to maintain resting muscle tone by producing a constant background of cholinergic stimulation.

MEPPs are minuscule compared to the larger depolarizations that occur when nerve action potentials arrive at the presynaptic terminal. These depolarizations produce an influx of calcium ions into the motor terminal, leading to the exocytosis of anywhere from 150 to 200 quanta of ACh vesicles. The postsynaptic depolarization that results is called an endplate potential (EPP). Normally, the number of quanta released by each nerve volley is more than enough to produce an EPP large enough to generate an action potential along the muscle membrane. At the threshold of the EPP, propagation of the muscle action potential leads to a cascade of events that drive muscle contraction.

The size of the EPP is directly related to the number of ACh molecules that bind to their receptors on the postsynaptic muscle membrane. Normally there are more than required. This so-called safety factor ensures an adequate number of neurotransmitter-receptor interactions to produce a muscle action potential. The entire sequence takes only milliseconds and is terminated by the diffusion of ACh from the synapse and its rapid hydrolysis by acetylcholinesterase.

In a patient with MG, there is a physiologic abnormality that results from reduction in the concentration of acetylcholine receptor (AChR) on the muscle endplate; from distortion and simplification of the post-synaptic muscle membrane; and, at least in some cases, from the blockade of the AChR by antibodies attached to the muscle membrane. ACh is released normally from the nerve, but its effect on the muscle is reduced as a consequence of these endplate changes.

The AChR is a large glycoprotein composed of five subunits (two alpha subunits, one beta and one delta subunit, and either a gamma subunit in the fetal form of the receptor or an epsilon subunit in the adult form) arranged circumferentially around a central channel through the muscle membrane (Figure 2). Binding sites for ACh are found on each of the two alpha subunits. These receptors are continuously being metabolized and resynthesized.

AChR antibodies can be found in the blood of most patients with MG. These antibodies are heterogeneous, but it is likely that most are directed against a region on the extracellular side of the alpha subunit of the AChR called the main immunogenic region (MIR). The initial event in MG probably involves a break in immunologic tolerance to the MIR. This is followed by production of autoantibodies and complement-mediated lysis of the postsynaptic muscle membrane. The role of serum antibodies against AChR in the pathophysiology of the disease is not fully understood. But several observations substantiate a major role, including the fact that removing circulating factors including antibodies by thoracic duct drainage or plasma exchange can produce rapid and marked improvement in many patients with MG.

Although antibody levels are usually higher in patients with more severe disease, levels vary widely among patients. In up to 25% of them, antibodies cannot be detected by available assay techniques. The antibodies responsible for the neuromuscular abnormality may not always be those that are measured, and the serum antibody level may not reflect the amount of antibody attached to the muscle endplate.

Several observations indicate that T lymphocytes play a crucial role in the pathogenesis of the disease. For example, T cell–independent antibody formation produces IgM antibodies only, whereas IgG anti-AChR antibodies are found in the serum and bound to the endplate region in MG patients. This suggests that anti-AChR B cells switch T cells to synthesize the IgG isotype. In addition, anti-AChR-reactive $CD4^+$ T cells are found in the serum and thymus glands of myasthenic patients. Thymectomy, which produces improvements in many patients with MG, reduces the anti-AChR reactivity of circulating T cells. Finally, synthesis of human anti-AChR antibodies and abnormal neuromuscular transmission can be transferred to severe combined immunodeficiency disease (SCID) mice following engraftment of blood lymphocytes from myasthenic patients, if they have not been depleted of $CD4^+$ cells.

The thymus plays an integral, if incompletely understood, role in MG. Ten percent to 15% of patients with MG have a thymic tumor, and 70% have hyperplastic changes in the germinal centers of the thymus, indicating immunologic activity. This gland may contribute to both the induction and maintenance of the immunologic reaction against the AChR.

CLINICAL EVALUATION

The two most characteristic clinical features of MG are: (1) weakness that begins in, and predominantly involves, ocular and oropharyngeal muscles, and (2) dramatic changes in the severity of weakness over brief periods, typically worsening as the day goes on. Virtually all patients with MG have some weakness of the ocular muscles. If none can be demonstrated, the diagnosis should be reconsidered. Eyelid ptosis that involves one eye initially and then switches to the other is virtually diagnostic of MG. Finally, myasthenic weakness frequently increases when the body temperature is raised.

Symptoms

Patients with MG usually seek medical attention because of specific muscle dysfunction. Ptosis or diplopia is the usual initial symptom in two-thirds of patients, and almost all have both symptoms within the first 2 years of onset. Difficulty in chewing, swallowing, or talking is the initial symptom in one-sixth of patients. In about 10%, the initial symptoms are due to weakness of single muscle groups, such as neck or finger extensors, hip flexors, or ankle dorsiflexors.

Muscle weakness typically fluctuates throughout the day. It is usually least severe in the morning and becomes progressively worse as the day wears on. Weakness typically worsens after prolonged use of affected muscles. Patients' ocular muscle weakness generally increases while reading, watching television, or driving, especially in bright sunlight. Jaw muscle weakness gets worse during prolonged chewing. The patient's voice may become nasal or hoarse, particularly after talking for a long time. If the palate is weak, liquids may be regurgitated nasally, and if swallowing is impaired, patients may cough or clear their throats frequently during and after eating because of aspiration.

The course of MG is variable, but commonly progresses over time. In about 10% of patients, weakness remains limited to ocular muscles; the remainder exhibit oropharyngeal and limb muscle weakness within 2 years of onset. In two- thirds of patients, maximum weakness occurs during the first year. Left untreated, the weakness becomes fixed, and severely involved muscles become atrophic.

Factors that may worsen symptoms include systemic illness, especially viral respiratory infections; hypothyroidism or hyperthyroidism; pregnancy and the menstrual cycle; increased body temperature; emotional upset; and drugs that affect neuromuscular transmission, including some antibiotics, antiarrhythmics, and beta-adrenergic blocking agents.

Physical Examination

Examination of patients with known or suspected MG must be performed in a way that will detect varying weakness in specific muscle groups. Strength should be assessed repeatedly during maximum effort and after brief rest periods. It is important to keep in mind that performance in these tests may fluctuate in diseases other than MG, especially if testing causes pain. Strength fluctuations in MG are best elicited by examining ocular and oropharyngeal muscle function, since these are less likely to be affected by inconsistent effort.

Close examination is sometimes required to detect weakness of the ocular muscles, which occurs in virtually all MG patients. Asymmetrical weakness of several muscles in both eyes is typical. Oculomotor weakness is usually most severe in the medial rectus muscles. Mild weakness of the medial rectus can be demonstrated on lateral gaze by observing lateral deviation of the adducted eye when it is covered. To compensate for ptosis, the frontalis muscle may be chronically contracted, producing a worried or surprised look. Unilateral frontalis contraction is a clue that the lid elevators are weak on that side; that may be the only visible evidence of eyelid weakness. Ocular muscle weakness is usually accompanied by weak eye closure.

Myasthenic patients, particularly those with severe or long-standing disease, may have a characteristic facial appearance. At rest, the corners of the mouth droop and the patient appears depressed. Attempts to smile may produce the appearance of a snarl.

Palatal weakness produces nasal speech, while weakness of the laryngeal muscles causes hoarseness and difficulty in making high-pitched sounds. If jaw muscles are weak, the patient may hold the jaw closed with the thumb under the chin and the middle finger curled under the nose or lower lip, giving a studious or attentive appearance.

Any trunk or limb muscle can be weak in MG, but some are affected much more often. Neck flexors are usually weaker than neck extensors, and the deltoids, triceps, extensors of the wrist and fingers, and dorsiflexors of the ankles are frequently weaker than other limb muscles.

Although the differential diagnosis of muscle weakness or oculomotor symptoms is broad, the diagnosis is usually clear in patients with typical MG. This is particularly true if lid ptosis fluctuates or alternates from side to side. In patients with less typical manifestations, the differential includes motor neuron disease, primary muscle disease, CNS lesions affecting the brainstem nuclei, cavernous sinus thrombosis, various toxins, botulism, and diphtheritic neuropathies, among other rare conditions.

Diagnostic Procedures

Appropriate diagnostic procedures will greatly narrow the differential and usually lead to the correct diagnosis. They include the Tensilon® test, measurement of acetylcholine receptor antibody levels, and electromyography.

Edrophonium Chloride (Tensilon®) Test—Weakness caused by abnormal neuromuscular transmission characteristically improves after the administration of the anticholinesterase edrophonium chloride (Tensilon®). With the exception of the ocular and pharyngeal muscles, the examiner must rely on the patient to exert maximum effort before and after drug administration to assess its effect. For this reason, the test is

most reliable when the patient has ptosis or nasal speech. The Tensilon® test is positive in more than 90% of patients with MG. However, improved strength after Tensilon® is not unique to MG. It may also occur in motor neuron disease in which neuromuscular transmission is abnormal during certain phases of denervation and reinnervation. Eye movement may also improve after Tensilon® in patients with lesions of the oculomotor nerves and in muscle disease affecting the ocular muscles.

The ideal dose of Tensilon® cannot be determined. For this reason, an incremental dosing schedule is recommended. Two milligrams are injected intravenously and the response is monitored for 60 seconds; this is followed by an injection of 3 mg, another 60-second monitoring period, and then a 5 mg injection. If unequivocal improvement is seen within 60 seconds after any dose, the test is positive and no further injections are necessary. An AMBU® bag and atropine sulphate for intramuscular injection should be readily available, since some people are supersensitive to even small doses and may develop respiratory arrest. Patients who fail to respond to Tensilon® may need IM neostigmine because of its longer duration of action. This is particularly true of infants and children whose response to Tensilon® may be too brief for adequate observation.

Acetylcholine Receptor Antibodies—Eighty percent of patients with acquired generalized MG and 55% with ocular myasthenia have serum antibodies that bind human AChR (Figure 3). Serum concentration of AChR antibody varies widely among patients of similar severity, and thus does not predict disease severity in any given individual. Because of inconsistent changes in AChR antibody levels, they are not useful in monitoring the effect of treatment. In general, an elevated concentration of AChR binding antibodies in a patient with compatible clinical features confirms the diagnosis of MG, but normal antibody levels do not exclude the diagnosis. Virtually all patients with MG and thymoma have elevated AChR binding antibodies. However, many patients without thymoma also have high concentrations of these antibodies, and thus these serologic patterns cannot be used to predict the presence of thymoma.

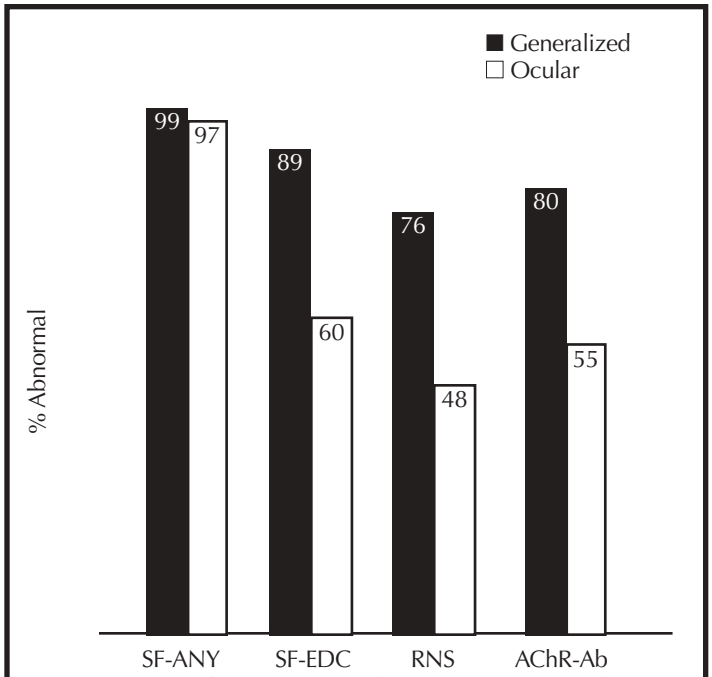

Figure 3. Percent of 550 patients with ocular or generalized autoimmune MG in whom results of various diagnostic tests were abnormal. SF-ANY=increased jitter measured by SFEMG in at least one tested muscle; SF-EDC=increased jitter in extensor digitorum communis; RNS=decrement to repetitive nerve stimulation in a hand or shoulder muscle; and, AChR-Ab=elevated serum levels of binding antibody to acetylcholine receptor. (Sanders DB, Howard JF Jr, Massey JM. Unpublished data.)

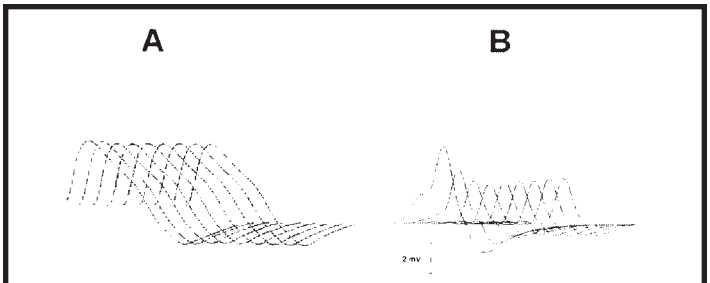

Figure 4. Repetitive nerve stimulation studies (3/second) demonstrating a normal response (A) and a response characteristic of MG (B).

Electromyography—Electrodiagnostic tests can be particularly valuable when clinical findings, antibody testing, and response to cholinesterase (ChE) inhibitors are not conclusive. The most common test involves the demonstration of a decrementing muscle response to repetitive nerve stimulation (RNS) (Figure 4). Such a response is seen more often in the facial muscles, biceps, deltoid, and trapezius than in distal muscles; a diagnostic response to RNS is found in the hand or shoulder muscles in 60% of patients with MG (Figure 3). Single-fiber electromyography (SFEMG) is the most sensitive clinical test of neuromuscular transmission. Increased jitter is noted in some muscles in almost all patients with MG (Figures 3 and 5). Jitter is greatest in weak muscles, but may be abnormal even in muscles with normal strength. Patients with mild or ocular muscle weakness may have increased jitter only in the facial muscles. It should be emphasized that normal jitter in a weak muscle excludes abnormal neuromuscular transmission as the cause of weakness. If there is any weakness in any limb muscle or in the oropharyngeal muscles, jitter should be measured in the extensor digitorum communis (EDC) muscle of the forearm, which is abnormal in 89% of patients (Figure 3). If weakness is limited to the ocular muscles, jitter is increased in the EDC in only 60% of patients. In such patients, EMG testing can begin with jitter measurements in a facial muscle, which demonstrates abnormal neuromuscular transmission in virtually all MG patients.

TREATMENT

In most clinical circumstances, the goals of therapy in MG are to make the patient as functionally normal as possible with fewest side effects, and as quickly as possible at the lowest cost while using the simplest treatment regimen. No single regimen is appropriate for every patient. The approach to each individual should be determined by many factors

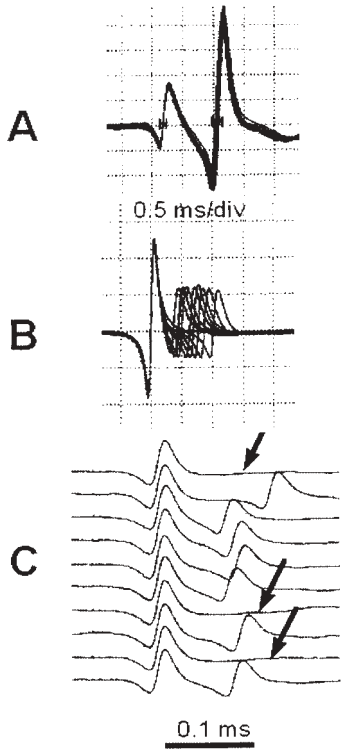

Figure 5. Single-fiber EMG recordings performed during voluntary activation of the muscle demonstrating (A) normal jitter, (B) increased jitter, and (C) increased jitter with intermittent impulse blocking. Each trace contains ten consecutive oscilloscope sweeps, superimposed in (A) and (B), rastered in (C). Arrows indicate blocking of the second action potential.

including the severity, distribution, and rate of progression of weakness; the age and sex of the patient; the degree of functional impairment; and, the presence of other diseases. There are pharmacologic as well as nonpharmacologic treatment options available. The patient should participate actively in determining immediate and long-term goals and should be well informed about the prognosis and predicted responses to treatments under consideration.

Cholinesterase Inhibitors

Cholinesterase (ChE) inhibitors retard the enzymatic hydrolysis of ACh at cholinergic synapses, so that the neurotransmitter accumulates at the neuromuscular junction and its effect is prolonged. ChE inhibitors bring about considerable improvement in some patients with MG and little or none in others. Strength rarely becomes normal with this treatment alone. Pyridostigmine bromide (Mestinon®) and neostigmine bromide (Prostigmin®) are the most commonly used ChE inhibitors. (See Table 1 for equivalent doses.)

Pyridostigmine is generally preferred because of fewer gastrointestinal side effects and more prolonged action. The initial oral dose in adults is 30 to 60 mg every 4 to 6 hours. The equivalent dose of neostigmine is 7.5 to 15 mg. In infants and children, the initial oral dose of pyridostigmine is 1.0 mg/kg and of neostigmine is 0.3 mg/kg. Pyridostigmine is available as a syrup (60 mg/5 mL) for children or for nasogastric tube administration in patients with impaired swallowing. Both pyridostigmine and neostigmine can also be administered by nasal spray or nebulizer. A timed-release oral dosage form of pyridostigmine (Mestinon Timespan® tablets 180 mg) is available as a bedtime dose for patients too weak to swallow in the morning. Its absorption, however, is erratic, leading to possible over- or underdosage, and it should not be used during waking hours. Even at night, it is sometimes preferable for patients to awaken at the appropriate dosing interval to take the regular 60 mg tablet.

TABLE 1. EQUIVALENT DOSES OF CHOLINESTERASE INHIBITORS

	Route and Dose (mg)			
	Oral	IM	IV	Syrup
Neostigmine bromide (Prostigmin® bromide)	15			
Neostigmine methylsulfate (Prostigmin® methylsulfate)		1.5	0.5	
Pyridostigmine bromide (Mestinon®)	60	2.0	0.7	60 mg/5 mL
(Mestinon Timespan®)	90-180			
Ambenonium chloride (Mytelase® chloride)	7.5			

Note: These values are approximations only. Appropriate doses should be determined for each patient based on the clinical response.

No fixed dose schedule suits all patients. The dose and schedule should be adjusted day to day, as well as during the same day, to produce the optimal response in muscles that cause the greatest disability. For example, patients with oropharyngeal weakness need doses timed to provide optimal strength during meals. The attempt to eliminate all muscular weakness by increasing the dose or shortening the interval may cause overdosage at the time of peak effect. To avoid this, a dose should be used that produces definite improvement 30 to 45 minutes after administration and begins to wear off before the next dose is due, minimizing the possibility of the dose being increased to the point of causing cholinergic weakness.

Central nervous system (CNS) side effects are rarely seen with doses of ChE inhibitors used to treat MG. Adverse reactions are predominantly peripheral and result from ACh accumulation at muscarinic receptors on smooth muscle and autonomic glands and at nicotinic receptors of skeletal muscle. Gastrointestinal (GI) complaints including queasiness, loose stools, nausea, vomiting, abdominal cramps, and diarrhea are among the most common side effects. Increased bronchial and oral secretions are a serious problem in patients with swallowing or respiratory insufficiency. These symptoms of muscarinic overdosage should be taken as a warning that nicotinic overdose (weakness) may also be occurring. GI side effects can be suppressed with loperamide, propantheline, and diphenoxylate.

Bromism, presenting with acute psychosis, is a rare complication in patients taking large amounts of pyridostigmine bromide and can be confirmed by measuring the serum bromide level. Some patients are allergic to bromide and develop a rash, even at modest doses. A chloride formulation, ambenonium chloride (Mytelase®) is available under such circumstances.

When patients have achieved an optimal response to

thymectomy or immunosuppression, two other therapy options discussed below, there should no longer be a need for or benefit from ChE inhibitors.

Thymectomy

In 1939, Blalock and colleagues reported the remission of generalized MG in a 21-year-old woman following removal of a cystic thymic tumor.[5] Subsequently, he performed thymectomy on MG patients without thymoma, found hyperplasia in the thymus glands, and reported improvement in at least half of his patients. Blalock's experience prompted others to perform thymectomy in MG patients.

The procedure has since gained wide acceptance as a treatment for MG. Thymectomy was the first attempt at "immunotherapy" for MG and continues to be one of the most frequently used treatments for this disease. However, all studies on the possible effectiveness of thymectomy are based on retrospective studies. A randomized study has yet to be done, despite calls for such a trial by experts in the neuromuscular community.

There are several problems inherent in retrospective studies of the efficacy of thymectomy. A determination of the status of remission and improvement by a retrospective unblinded chart analysis is potentially fraught with error. The definitions for "remission" and "improvement" are often subjective and arbitrary. The majority of the published series have only a surgical group: these reports often seem to have very high remission rates (60% to 80%). In the few series that include a nonthymectomy treatment group, surgical and nonsurgical treatment groups are often different with respect to extent of disease, severity, age and sex, and even the time period from which cases were analyzed.

In 1977, McQuillen and Leone compared remission rates between patients receiving medical and surgical management reported in several large series performed, with one exception, prior to 1965.[6] They could find no significant differences between the two treatment groups, with a remission rate of 24% in the nonsurgical group and 28% in the thymectomy group. (McQuillen and Leone's analysis is summarized in Table 2.)

The large retrospective study of Perlo and colleagues,[7] which is frequently cited to support the benefit of thymectomy, reported a complete remission rate of 35% and improvement in an additional 41% (76% remission or improvement). Of nonthymectomized patients, 17% achieved remission and 11% improved (28% remission or improvement). This supports the contention of many experts that thymectomy provides improvement in 60% to 80% of patients. However, even in the most favorable reports, the response to thymectomy is not immediate, and patients should be so informed.

TABLE 2. REMISSION RATES[6]

Nonsurgical Therapy			Surgical Therapy		
Author	**n**	**%**	**Author**	**n**	**%**
Kennedy and Moersch	87	31	Simpson	258	21
Grob	202	23	Perlo et al	267	34
Simpson	99	16	Mulder et al	73	36
Oosterhuis	180	31	Emeryk and Strugalska	112	23
Perlo et al	417	24	Papatestas et al	111	25
OVERALL	985	24	OVERALL	821	28

The American Academy of Neurology Quality Standards Subcommittee recently formed the Myasthenia Gravis Practice Parameter Group to perform a detailed review of the thymectomy literature, addressing the question: should patients with autoimmune myasthenia gravis without thymoma undergo thymectomy? The analysis was limited to published reports that included outcomes of both thymectomy and nonthymectomy treated groups. Between 1953 and 1998, 20 cohorts of patients have been reported in this manner.

The drug-free remission rate in the nonthymectomy groups ranged from 6% to 50% with a mean of 16%. Patients who underwent thymectomy were 2.1 times more likely to achieve a drug-free remission, 1.6 times more likely to attain either drug-free or drug-dependent remission, and 1.7 times more likely to improve compared to the nonthymectomy patients. Some of the studies included confounding variables that could affect these outcomes. These indicated that patients were more likely to benefit from thymectomy if they were female or had generalized or more severe disease. Older, male patients were less likely to have a better outcome after thymectomy. Some studies, such as the Mayo Clinic cohort of pediatric patients,[8] suggest that if a thymectomy is done within the first year or two after diagnosis, the likelihood of remission is greater.

Based on this analysis, patients with generalized MG should be informed that thymectomy will more likely than not improve their outcome. However, they should be told that this potential benefit has not been established with reasonable medical certainty by appropriate clinical trials and that remission and improvement can occur without thymectomy. In addition, even if there is a potential benefit, not all patients obtain it. Finally it is not known how long it will take for the potential benefit from thymectomy to appear or how long it will last.

Thymectomy can be done in children, though there is some controversy about the role of the procedure in very young children with autoimmune MG. Thymectomy is generally not performed in patients with ocular myasthenia only, but sustained remission may follow thymectomy in such patients. Thymectomy is probably less effective in the elderly, but the exact age above which a thymectomy should not be performed is difficult to determine. Many clinics do not undertake thymectomy when MG begins after age 50 or 60. Some clinics do not find age a significant restricting factor.

One of the most vexing thymectomy-related issues in MG involves how long to wait for improvement after surgery before considering immunosuppression. If immunosuppression is begun early after thymectomy, the benefit from surgery may not be appreciated. On the other hand, prolonged

disability after surgery should not be permitted. The degree and distribution of residual post-thymectomy weakness in the individual patient usually determines the length of delay before beginning immunosuppression.

For patients with relatively mild post-thymectomy symptoms that can be controlled adequately with ChE inhibitors, it is reasonable to wait for up to 12 months before considering alternative therapy. However, if there is persistent and disabling weakness after surgery, especially if oropharyngeal muscles are involved, immunosuppressive therapy should be started without undue delay.

It is not known whether thymectomy provides additional benefit to patients who are in remission from immunosuppression. Despite the absence of data, it is reasonable to recommend thymectomy in young patients who have responded well to immunosuppression based on the presumption that the potential benefit from thymectomy is not eliminated by prior immunotherapy.

It should be pointed out that even if a patient goes into remission after thymectomy, there is no certainty that the remission will last indefinitely. It is common to find patients who have had a complete resolution of weakness after thymectomy developing a recurrence of symptoms sometimes years later.

Thymomas occur in approximately 10% to 15% of patients with MG. Tumors are found most often in patients with onset of MG in the third and fourth decade, with almost 20% having a thymoma. Most patients with thymoma have circulating antibodies to striated muscle. Although these latter antibodies are also found in one third of MG patients without thymoma, their absence provides strong evidence that no thymoma is present. On occasion, the first symptoms of MG develop weeks or months after the removal of thymoma. Although there are exceptions, thymomas should almost always be removed along with all identifiable thymic tissue. Improvement or even remission may follow thymectomy in some cases, but patients with thymomas usually respond less well to thymectomy than patients without tumors. All newly diagnosed MG patients should have a chest CT to look for a thymoma, since routine chest radiographs miss up to 25% of thymic tumors.

Corticosteroids

Corticosteroids suppress multiple facets of the humoral, cell-mediated, and nonspecific arms of the immune system and are used in MG patients to supplement treatment with ChE inhibitors and thymectomy.

Marked improvement in symptoms or even complete relief occurs in more than 90% of patients treated with prednisone. Some improvement is seen in most of the rest (Table 3). Much of the improvement is seen in the first 6 to 8 weeks of therapy, but progress may continue to total remission in the weeks that follow. The best responses occur in patients with recent onset of symptoms, but patients with chronic disease may also respond. The severity of the disease does not predict ultimate improvement. Patients with thymoma have an excellent response to prednisone before or after tumor removal.

TABLE 3. CORTICOSTEROIDS IN MYASTHENIA GRAVIS

Advantages
- Produce rapid improvement in most patients
- Produce total remission or "marked improvement" in 90% of patients (high-dose daily steroids)
- Predictable time of response
- Relatively simple drug schedule
- May reduce the morbidity and mortality of subsequent thymectomy
- Low cost

Disadvantages
- Steroid side effects
- Exacerbation of weakness after initiation
- Require chronic administration for maximum benefits

Major role
- As initial definitive therapy, producing rapid, virtually complete improvement in the majority of patients
- As secondary treatment, producing improvement in most patients who fail to respond to thymectomy or other immunosuppressive therapy

The most predictable response to prednisone occurs when treatment begins with a daily dose of 60 to 80 mg (Table 4). This dose is given until sustained improvement occurs, usually within 2 weeks. The dosing is then changed to an alternate-day schedule beginning with 100 to 120 mg. The dose should be gradually decreased over many months to the lowest dose necessary to maintain improvement. This is usually less than 20 mg every other day. Dosage tapering should be done based on individual response.

One-third of patients become temporarily weaker after starting prednisone or after major dose increments. Weakening usually begins within 7 to 10 days and lasts for up to 6 days. Increased weakness can usually be managed on an outpatient basis with ChE inhibitors. Patients with oropharyngeal or respiratory involvement may, however, require hospitalization to begin high-dose prednisone. Plasma exchange may be used before beginning prednisone in these patients to prevent or reduce the severity of steroid-induced exacerbations and to produce a more rapid response. Once improvement begins, further exacerbations are unusual.

An incrementing dose regimen is used by some in order to minimize exacerbations and steroid side effects. But patients

TABLE 4. HIGH-DOSE DAILY PREDNISONE REGIMEN

1. In patients with oropharyngeal or respiratory dysfunction, hospitalize and use plasmapheresis until definite improvement occurs
2. Begin 60 to 80 mg prednisone/day
3. Maintain this dose at least 10 days or until definite prednisone-induced improvement has been present for 3 to 4 days
4. Begin alternate-day prednisone, 100 to 120 mg every other day
5. Reduce dose slowly over many months to the minimum necessary level
6. If weakness recurs as the dose is reduced, recommence high daily dose, use plasmapheresis or IVIG, begin other immunosuppressant medication, or combinations of these

on an incrementing dose regimen may end up taking more prednisone for a longer time than if they started with high daily doses. Further, the onset of improvement is less predictable and the ultimate response may be less complete. If satisfactory improvement is not seen within 1 to 2 months using an incrementing regimen, alternative treatment, including high-dose prednisone and plasmapheresis, should be considered.

The high-dose prednisone regimen can be used for both generalized and purely ocular MG. An alternative approach for ocular myasthenia is to begin with prednisone 5 or 10 mg daily and increase 5 mg every 3 to 4 weeks until improvement begins. The dose is then kept constant until maximum improvement is achieved, then tapered over 4 to 6 months to a maintenance dose of 5 to 10 mg every other day.

The major disadvantages of chronic corticosteroid therapy are the side effects. Hypercorticism occurs in half the patients treated with the suggested regimen. The severity and frequency of adverse reactions increase when high daily doses are continued for more than a month. Fortunately, this is rarely necessary, especially if plasma exchange is begun at the same time as prednisone. Most side effects subside as prednisone is tapered and become minimal at doses less than 20 mg every other day. Side effects can be minimized by a low-fat, low-sodium diet and supplemental calcium. Postmenopausal women should also take supplementary vitamin D. Patients with peptic ulcer disease or symptoms of gastritis require H_2 antagonists.

Immunosuppressant Medications

Immunosuppression produces marked, sustained improvement in most patients with MG, including many who have not responded well to corticosteroids or thymectomy. Disadvantages include delayed onset of improvement, adverse effects, cost, and the need to continue treatment chronically. After prednisone, azathioprine and cyclosporine are the most frequently used immunosuppressants in MG. Tables 5, 6, and 7 present information on advantages, disadvantages, costs, adverse reactions, and interactions.

TABLE 5. IMMUNOSUPPRESSANT DRUGS IN MYASTHENIA GRAVIS

Advantages
- Produce marked, sustained improvement in most patients

Disadvantages
- Long delay before improvement
- Serious side effects
- Expensive
- Require monitoring for side effects

Major role
- As initial definitive therapy in patients with late-onset myasthenia gravis or in whom corticosteroids are contraindicated
- As secondary treatment when patients fail to respond to corticosteroids or thymectomy
- In combination with prednisone to enhance the response or to permit more rapid reduction of prednisone dose

Azathioprine is the most frequently used nonsteroidal immunosuppressant in MG. It is administered when prednisone is relatively contraindicated and when a less rapid response to therapy is acceptable. It may also be used for its "steroid-sparing" effects in patients who have developed unacceptable side effects to prednisone, in whom it has not been possible to reduce the dose of prednisone to acceptable levels, or when the response to prednisone alone has not been satisfactory.

The initial dose is 50 mg per day. It is increased weekly to a target of 1.5 mg/kg, or an approximate daily dose for an average-size patient of 150 to 200 mg/day. A complete blood count and liver function studies should be performed each week for 1 month after beginning therapy and then each month for 6 months. As many as 20% of patients have an untoward reaction to azathioprine, the most frequent being a flu-like syndrome with chills, low-grade fever, and malaise, usually 2 weeks after beginning therapy. Some patients develop a skin rash, fever, and malaise. If either syndrome occurs, azathioprine must be discontinued. Hepatic toxicity may also develop at any time; if that occurs, the dose should be reduced by 50 to 100 mg per day and liver function tests performed weekly until normal. After several weeks, the dose may be increased by 25 to 50 mg per day. If liver dysfunction persists, the dose should be reduced further or discontinued. If the white blood count falls below 4×10^9/L with a downward trend, the dose should be reduced by 50 mg per day every week until the WBC is stable. If it falls below 3×10^9/L, azathioprine should be withheld until it rises above 4×10^9/L, then recommenced at a lower dose. It can then be titrated upward to therapeutic levels.

Cyclosporine is being used in the treatment of MG more frequently now, primarily because it produces improvement in most patients with relatively few side effects. Cyclosporine is a potent immunosuppressant that inhibits predominantly T lymphocyte-dependent immune responses by suppressing interleukin 2 activity. Well-controlled studies have established the value of the agent in MG. Improvement usually begins within 1 to 2 months and is maximal by 3 to 4 months. Cost is the main limitation to its use. Moreover, there are some serious side effects—in particular, renal toxicity and hypertension—which require a rigorous dose schedule, attention to other drugs that may interact, and frequent blood tests to monitor renal function.

Treatment usually begins with a dose of 5 to 6 mg/kg per day, divided into two doses taken at 12 hour intervals. Blood levels of cyclosporine should be measured monthly and the dose adjusted to achieve a value of 100 to 150 ng/L until the therapeutic response is maximum. Blood for these must be

TABLE 6. TYPICAL COSTS OF MYASTHENIA GRAVIS MEDICATIONS IN THE UNITED STATES[9]

Per Month	Usual Dose	Average Retail
Pyridostigmine	60 mg TID	$54.00
Prednisone	60 mg/day	$16.50
	10 mg QOD	$4.50
Azathioprine (generic)	150 mg/day	$90.00
Cyclosporine	150 mg BID	$482.00

TABLE 7.

DRUGS THAT MAY CAUSE KIDNEY DAMAGE WHEN TAKEN WITH CYCLOSPORINE

Antibiotics: gentamicin, tobramycin, vancomycin, trimethoprim (Bactrim®, Septra®), ciprofloxacin (Cipro®)

Antifungals: amphotericin B (Fungizone®), ketoconazole (Nizoral®)

Antivirals: acyclovir (Zovirax®)

Antiulcer: cimetidine (Tagamet®), ranitidine (Zantac®)

Nonsteroidal anti-inflammatory drugs: diclofenac (Voltaren®), ibuprofen (Advil®, Motrin®, Nuprin®), piroxicam (Feldene®), indomethacin (Indocin®), naproxen (Naprosyn®, Anaprox®)

Chemotherapy: melphalan (Alkeran®), etoposide (VePesid®)

Cardiac/blood pressure: captopril (Capoten®), acetazolamide (Diamox®), furosemide (Lasix®), disopyramide (Norpace®)

DRUGS/FOOD THAT MAY RAISE BLOOD CYCLOSPORINE LEVELS

Antibiotics: erythromycin

Antifungals: ketoconazole (Nizoral®), fluconazole (Diflucan®)

Food: grapefruit juice

Stomach/ulcer: metoclopramide (Reglan®), cimetidine (Tagamet®)

Cardiac/blood pressure: diltiazem (Cardizem®, Dilacor®), nicardipine (Cardene®), verapamil (Calan®, Isoptin®, Verelan®)

Hormones: danazol (Danocrine®), oral contraceptives, methylprednisolone

Miscellaneous: bromocriptine (Parlodel®)

DRUGS THAT MAY DECREASE BLOOD CYCLOSPORINE LEVELS

Antibiotics: rifampin (Rifadin®, Rifamate®), imipenem (Primaxin®), nafcillin (Unipen®), trimethoprim (Bactrim®, Septra®)

Anticonvulsants: phenytoin (Dilantin®), phenobarbital, carbamazepine (Tegretol®)

DRUGS THAT MAY ACCUMULATE IN THE BLOOD WHEN TAKEN WITH CYCLOSPORINE

Steroids: prednisone, prednisolone

Cardiac: digoxin (Lanoxin®)

drawn before the morning dose to assure trough values are measured. The dose can then be reduced over many months to the minimum necessary to maintain the therapeutic response. Blood levels of creatinine should be measured monthly as long as cyclosporine is taken and the dose adjusted to keep the value less than 150% of the pretreatment level. Elevated blood pressure should be treated with antihypertensive medications or by reducing the dosage of cyclosporine, or both. Patients taking cyclosporine should avoid nonsteroidal anti-inflammatory agents or potassium-sparing diuretics, which may increase nephrotoxicity. Many other medications interfere with the metabolism of cyclosporine and its levels in the blood, and these should be used with caution.

Cyclophosphamide is a nitrogen mustard that has been used to treat MG resistant to other therapies. Because the reported experience with this drug in MG is limited, it should be used only in severe cases after other treatments have failed.

There is a risk of infection in all immunosuppressed patients. The long-term risk of malignancy in chronically immunosuppressed patients is not known, nor is the teratogenetic potential in child-bearing women.

Plasma Exchange

Plasma exchange (PEX), or plasmapheresis, is used as a short-term intervention in patients with worsening weakness; it produces rapid improvement before thymectomy to reduce perioperative morbidity. It may also be utilized on a chronic intermittent basis in patients who have failed to respond to another therapy.

The frequency of PEX is determined by clinical response. Typically up to 3 liters of plasma are removed three times a week until a plateau of improvement has been reached, generally with six or fewer exchanges.

PEX produces improvement in virtually all patients with acquired MG. Typically improvement lasts for weeks or months, with weakness returning thereafter, unless thymectomy is performed or there has been a change in immunosuppressive therapy. Repeated exchanges alone have no apparent cumulative benefit, but long-lasting improvement occurs when PEX is combined with immunosuppressives.

The main advantages of PEX are the speed of improvement and the potential to induce improvement in patients who have not responded to other therapies. The potential risks result from large or rapid fluctuations of plasma volume, alteration of serum constituents, inhibition of normal clotting mechanisms, the abrupt reduction in levels of circulating plasma-bound drugs, and infection, especially if indwelling lines are used for venous access. If PEX is done in preparation for thymectomy, at least 24 hours should be allowed between the last exchange and surgery. Any situation in which a rapid, albeit temporary, improvement in strength would be of benefit can be an indication for PEX.

Intravenous Immunoglobulin

Approximately 70% of autoimmune MG patients improve after a course of high-dose intravenous immunoglobulin (IVIG). Improvement usually begins within 1 week after completing a course of treatment, becomes maximal within the next 2 weeks, and lasts for several weeks, or occasionally several months in patients receiving long-term immunosuppression. Indications for IVIG are similar to PEX: to reduce perioperative morbidity prior to thymectomy; to produce rapid improvement in patients with severe disease until immunosuppressive therapy takes effect; and, in selected patients, for long-term treatment. The standard dose is 2 g/kg, given as a slow infusion over 2 to 5 days; a dose of 1 g/kg daily over 2 consecutive days has been shown to be beneficial in children with autoimmune MG.

The relative ease of administration makes IVIG an attractive acute therapy for young patients and patients with poor venous access. Principal side effects include headache and aseptic meningitis, especially in migraineurs, and transient flu-like illnesses. Congestive heart failure, deep vein thrombosis, and acute renal failure have been reported in adults, most of whom had other risk factors.

Drugs that Worsen Myasthenic Weakness

Drugs that compromise neuromuscular transmission

frequently exacerbate weakness in MG as well as in LEMS (Tables 8 and 9). It is not uncommon for the disease to come to clinical attention when prolonged weakness or apnea follows administration of neuromuscular blocking agents during anesthesia. Drugs that have significant neuromuscular blocking effects include certain antibiotics, particularly aminoglycosides, some anti-arrhythmics and beta-adrenergic blocking agents. With the possible exception of d-penicillamine, no drugs are absolutely contraindicated in MG.

TABLE 8. DRUGS THAT MAY ADVERSELY AFFECT PATIENTS WITH MYASTHENIA GRAVIS

DRUGS THAT CAN UNMASK OR EXACERBATE MG

Neuromuscular blocking agents (eg, Vecuronium®)

Excessive anticholinesterases (eg, pyridostigmine)

Adrenocorticosteroids and ACTH (eg, prednisone)

Magnesium preparations

Anti-arrhythmics

—Lidocaine (Xylocaine®) intravenously, but not locally administered

—Quinidine and quinine preparations (eg, Quinaglute®, Quinidex®, Quinora®, Cardioquin®)

—Procainamide (eg, Procamide®, Procan SR®, Pronestyl®)

Phenytoin and related drugs (eg, Dilantin®)

Antibiotics

—Aminoglycosides: gentamicin (Garamycin®), tobramycin, amikacin, neomycin, streptomycin

—Polypeptides: polymyxin B (Aerosporin®), Colistin (Coly-Mycin®)

—Miscellaneous: clindamycin (Cleocin®), ciprofloxacin (Cipro®), erythromycin

DRUGS THAT MAY INDUCE MG BY PRECIPITATING AN AUTOIMMUNE REACTION

d-penicillamine (Cuprimine®)

Trimethadione (Tridione®)

DRUGS THAT HAVE BEEN IMPLICATED IN ISOLATED INSTANCES OF MG EXACERBATIONS

Cimetidine (Tagamet®)

Anesthetic agents (including alcohol)

Chloroquine

Cocaine

Diazepam (Valium®)

Lithium (eg, Eskalith®)

Propranolol (Inderal®)

Timolol maleate drops (Timoptic®)

Tetracyclines: chlortetracycline (Aureomycin®), oxytetracycline (Terramycin®), tetracycline (Achromycin®), demeclocycline (Declomycin®), doxycycline (Vibramycin®), minocycline (Minocin®)

Trihexyphenidyl (Artane®)

TABLE 9. MYASTHENIA GRAVIS DRUG ALERT

d-penicillamine should never be used in myasthenic patients.

The following drugs produce worsening of weakness in most MG patients who receive them. Use with caution and monitor patient for exacerbation of myasthenic symptoms:

—Succinylcholine, d-tubocurarine, vecuronium, or other neuromuscular blocking agents

—Quinine, quinidine, or procainamide

—Certain antibiotics, particularly tobramycin, gentamicin, kanamycin, neomycin, streptomycin, colistin, erythromycin, and ciprofloxacin

—Beta-blockers: propranolol, timolol maleate eyedrops

—Calcium channel blockers

—Iodinated contrast agents

—Magnesium products

Many other drugs are reported to exacerbate the weakness in some patients with myasthenia gravis. All patients with myasthenia gravis should be observed for increased weakness whenever any new medication has been started.

OTHER FORMS OF MYASTHENIA

Seronegative Myasthenia Gravis

Approximately one-quarter of patients with acquired, immune-mediated MG do not have detectable AChR antibodies and are referred to under the umbrella of seronegative myasthenia gravis (SN-MG). Patients may have normal AChR antibody levels within the first months of symptoms and elevated AChR antibodies thereafter. Patients with SN-MG improve after immunotherapy such as plasma exchange, immunosuppression, and thymectomy. SN-MG is rare among myasthenic patients with thymoma. Seronegative patients as a group have less severe disease and are more likely to have purely ocular myasthenia. Fifty percent of children with prepubertal onset of acquired myasthenia are seronegative, but after puberty the proportion of SP-MG increases dramatically.

Childhood Myasthenia

Three forms of myasthenia are recognized in infants and children: autoimmune MG, sometimes known as juvenile myasthenia gravis (JMG); congenital MG (CMG), otherwise known as genetic MG; and transient neonatal MG (TNMG). The most important disorder to be distinguished from autoimmune MG, especially in young children, is CMG. It is essential to make this distinction so that one may offer potentially effective immunotherapies to those with autoimmune MG and avoid ineffective therapies in those with CMG.

Autoimmune Myasthenia Gravis—In North America, onset of autoimmune MG before age 20 accounts for about 10% to 15% of all patients with MG. Most frequently, weakness is manifest in the extraocular muscles with variable ptosis and diplopia. Bulbar weakness is also common. Fatigue and weakness, usually of the extraocular muscles, are the cardinal findings.

A positive assay of AChR antibodies in the appropriate

clinical context is diagnostic of autoimmune MG. However, 30% to 50% of prepubertal patients are seronegative, compared with 18% to 32% of peripubertal patients and less than 9% of postpubertal adolescents with acquired MG. Repeated AChR antibody measurements over years may demonstrate conversion from seronegative to seropositive, confirming a diagnosis of autoimmune MG. SFEMG (single-fiber electromyography) is the most sensitive method to detect abnormal neuromuscular transmission, but it will not distinguish between autoimmune MG and CMG.

Therapeutic strategies for autoimmune MG in children are similar to those in adults. There are reports of significant improvement in 10% to 61% of pediatric patients treated with corticosteroids. Side effects of chronic corticosteroid therapy are many and potentially serious, but may be reduced by alternate-day dosing. Since myasthenic children may face a lifetime of therapy, it is prudent to consider steroid-sparing therapies such as thymectomy, azathioprine, cyclosporine, intermittent pulsed methylprednisolone, or intermittent IVIG.

Dramatic improvement, even complete remission, is frequently seen in young patients following thymectomy. Other potential benefits of thymectomy include reduction of long term side effects of steroids and other immunosuppressants, and identification and treatment of the very rare pediatric patient with thymoma. Thymectomy in experienced hands is a safe and usually beneficial treatment for autoimmune MG even for young children.

Fetal and Transient Neonatal Myasthenia Gravis—About 10% to 20% of infants born to mothers with autoimmune MG develop transient neonatal myasthenia gravis (TNMG). Postnatal symptoms of TNMG usually begin within a few hours after birth but may be delayed for up to 3 days. The symptoms of TNMG are transient and typically last about 3 weeks, but have been known to persist for up to 3 months. AChR antibody levels fall progressively in infants with TNMG because the maternal AChR antibodies no longer enter the infant via the placenta.

Treatment is supportive, since the disease has a self-limited course of days to months. Ventilatory support and nasogastric feeding may be required in more severely affected infants. Pyridostigmine, 4 to 20 mg/dose every 4 hours, usually with feeding, and titrated according to beneficial effects and side effects, may be helpful. Exchange transfusion and IVIG have also been used with good effect.

Congenital/Genetic Myasthenia Gravis—Classically, congenital myasthenia gravis (CMG) syndromes present at birth or in the first few months of life (Table 10). Immunotherapy and thymectomy are of no benefit in CMG. Diagnosis in the newborn period is relatively straightforward in patients with previously diagnosed relatives. In the older child, a history of weakness and of respiratory and feeding difficulties from birth or early infancy argues in favor of a diagnosis of CMG rather than autoimmune MG. Because weakness in slow-channel syndrome typically begins in late childhood or early adult life, it is frequently confused with acquired MG. The clinical presentation is distinct, with predominant weakness in hand and proximal limb muscles and relatively little weakness of ocular muscles. ChE inhibitors may cause worsening.

TABLE 10. CHARACTERISTIC FINDINGS IN NEUROMUSCULAR TRANSMISSION DISEASES IN INFANTS

Clinical Features	CMG	TNMG	Botulism
Alert and responsive	Yes	Yes	Yes
Feeding problems	If severe	If severe	Common
Respiratory problems	If severe	If severe	Common
Pupillary reactions	Normal	Normal	Usually impaired
Ptosis, ophthalmoplegia	Most syndromes	Uncommon	Frequent
Hypotonia	Yes	Yes	Yes
Weakness	Yes	Yes	Yes
Reflexes	Normal	Normal	Normal or reduced
Sensation	Normal	Normal	Normal

Most other CMG syndromes do respond to ChE inhibitors. however. Therefore a transient improvement in strength following an injection of edrophonium (Tensilon®), 0.1 mg/kg would support a diagnosis of CMG, but lack of response does not exclude it. Anticholinesterase medications are the mainstay of treatment in CMG.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a rare condition in which weakness results from a presynaptic abnormality of ACh release at the neuromuscular junction. First described in association with lung cancer, it is now clear that LEMS results from an autoimmune attack against the voltage-gated calcium channels (VGCC) on the presynaptic motor nerve terminal. Although LEMS is similar to MG in some ways, the clinical presentations of the two conditions are usually quite distinct. The weakness in LEMS is rarely life threatening, and in most cases the differential diagnosis would include cachexia, polymyositis, or other paraneoplastic neuromuscular disease. LEMS usually begins in later life and in early studies males were much more commonly diagnosed than females, at a frequency of almost 2 to 1. In 50% of patients, a malignancy is found or known to be present when the disease begins, or develops within 1 to 2 years after the diagnosis of LEMS.

Weakness of proximal muscles, especially in the lower limbs, is the major symptom. Strength may improve after exercise. Tendon reflexes are reduced or absent on routine testing, and most patients experience dry mouth. Some patients exhibit other manifestations of autonomic dysfunction, including impotence, postural hypotension, and impaired ocular accommodation. LEMS is similar to MG in some ways. Both diseases respond at least to some extent to many of the same treatments. Treatment with prednisone, PEX, and IVIG produces improvements with many patients with LEMS.

The diagnosis of LEMS may be confirmed by demonstrating characteristic findings on electrodiagnostic studies (Table 11). Facilitation of the muscle response to nerve stimulation greater than 100% is the cardinal electrodiagnostic finding in LEMS, but is not seen in all muscles or all patients with LEMS.

TABLE 11. LEMS PROTOCOL

The electrodiagnostic findings characteristic of LEMS will be demonstrated if the following protocol is followed:

1. Measure the amplitude of a single CMAP elicited from the rested muscle by supramaximal nerve stimulation. Abnormalities of these measurements may be partially masked by low muscle temperature; thus, the muscle should be warmed to a surface temperature of at least 34°C and rested for several minutes before testing.

2. Have the patient contract the tested muscle maximally for 10 seconds and then completely relax. Deliver a supramaximal nerve stimulus when relaxation is complete. Compare the amplitude of the CMAP with that obtained in the rested state.

3. This sequence should be performed three times; the average change in CMAP amplitude is used to assess the degree of facilitation.

4. Nerve stimulation at 20 to 50 Hz for 5 to 7 seconds also may be used to demonstrate facilitation. The amplitude of the maximum CMAP at the end of stimulation is compared with that of the initial response.

5. Perform these measurements in at least one hand and one foot muscle.

In patients with LEMS who do not have cancer, aggressive immunotherapy is justified. ChE inhibitors do not usually produce significant improvement in LEMS, although they may give dramatic improvement from weakness or dry mouth in some patients. Pyridostigmine (30 or 60 mg every 4 to 6 hours) is the preferred agent and should be taken for several days before assessing the response. Guanidine hydrochloride increases the release of ACh and produces temporary improvement with many patients with LEMS. It should be used with extreme caution because of the frequent occurrence of side effects such as bone marrow suppression, arrhythmia, hepatic toxicity, chronic interstitial nephritis, and others. Hematologic, hepatic, and renal function must be evaluated frequently.

Aminopyridines have a similar mechanism of action as guanidine. 3,4-Diaminopyrimidine (3,4-DAP) produces improvement in strength and autonomic function in most patients. The drug is given orally in doses of 5 to 25 mg, three to four times a day. The effects of 3,4-DAP are augmented by the concurrent administration of pyridostigmine. Side effects are usually negligible. When weakness is severe, PEX or IVIG may be used initially to induce rapid, albeit transitory improvement. Immunosuppressants should be added for more sustained improvement. Prednisone and azathioprine are the most frequently used immunosuppressants, given alone or together.

CONCLUSION

A wide range of pharmacologic and nonpharmacologic therapies are available to treat patients with MG and related myasthenic conditions, including cholinesterase inhibitors, thymectomy, corticosteroids, immunosuppressants, intravenous immunoglobulin, and plasmapheresis. While patients with many other neuromuscular diseases tend to get progressively worse over time, those with MG and LEMS are usually able to achieve and maintain good muscle function if diagnosed and treated in a timely manner. With appropriate treatment, most MG patients can lead an essentially normal life free from myasthenic weakness. Treatment is a lifelong process.

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QUESTIONS

1. Which of the following is most useful in the treatment of severe acute myasthenic weakness?
a. plasma exchange
b. thymectomy
c. azathioprine
d. cyclosporine
e. Cytoxan®

2. Which of the following is true concerning acetylcholine receptor antibody measurement?
a. it is useful in monitoring response to therapy in MG
b. it is useful in assessing disease severity in MG
c. a normal reading excludes the diagnosis of MG
d. an elevated level in a patient with compatible clinical features generally confirms MG diagnosis
e. none of the above

3. Which of the following drugs would be contraindicated in a patient with Lambert-Eaton myasthenic syndrome?
a. guanidine
b. prednisone
c. 3,4-diaminopyridine
d. d-penicillamine
e. azathioprine

4. What is the estimated number of cases of MG in the United States?
a. 50,000
b. 70,000
c. 85,000
d. 100,000
e. 140,000

5. What is the most likely side effect of guanidine?
a. bone marrow suppression
b. fasciculations
c. diarrhea
d. temporary worsening of weakness
e. muscle cramps

6. What is the most likely explanation for LEMS?
a. it is a paraneoplastic syndrome
b. it is an autoimmune disease
c. it reflects heavy metal intoxication
d. it results from exposure to an environmental toxin
e. it is an acute inflammatory neuropathy

7. The physiologic abnormality essential in LEMS is:
a. block of acetylcholine receptors by antibodies
b. abnormal conduction in the distal nerve fibers
c. increased numbers of active zone particles (AZP on the motor nerve terminal)
d. impaired syntheses of acetylcholine
e. impaired release of acetylcholine from the nerve terminal

8. When advising MG patients about thymectomy, it is appropriate to indicate that:
a. they will go into remission
b. they will improve
c. they are more likely to go into remission or improve compared to MG patients who do not have a thymectomy
d. they will most likely have a relapse after surgery
e. the symptoms most likely to improve after surgery are ocular

9. If an MG patient does not have a thymectomy, but undergoes most appropriate medical therapy, he or she:
a. will never go into remission
b. will never improve
c. is at risk for developing a thymoma
d. can still go into remission or improve
e. will note improvement in ocular, but not bulbar, symptoms

10. What percentage of MG patients have a thymoma?
a. 1% to 5%
b. 10% to 15%
c. 50% to 60%
d. 75%
e. 90%

11. How many quanta of acetylcholine vesicles are normally released at the neuromuscular junction as a result of each nerve action potential?
a. <100
b. 150 to 200
c. 300 to 500
d. 750 to 1000
e. 10,000

12. What presenting symptom(s) are noted most often in patients with MG?
a. ptosis or diplopia
b. difficulty in swallowing
c. hoarseness or nasal speech
d. difficulty in breathing
e. all of the above

13. Which test is least sensitive in diagnosing MG?
a. edrophonium chloride (Tensilon®)
b. measuring serum concentration of AChR antibody
c. single-fiber electromyography (SFEMG)
d. jitter measurement in a facial muscle
e. all of the above tests are equally reliable

14. What is the normal starting dose of pyridostigmine in adult MG patients?
a. 30 to 60 mg per day
b. 60 to 120 mg every other day
c. 30 to 60 mg every 4 to 6 hours
d. 30 to 60 mg twice daily
e. 60 to 120 mg every 4 to 6 hours

15. What side effect(s) is (are) rarely encountered in patients using ChE inhibitors?
a. paresthesia
b. vomiting and diarrhea
c. increased oral and bronchial secretions
d. bromism
e. both a and d

16. When the American Academy of Neurology Quality Standards Subcommittee examined published reports of outcomes of thymectomy and nonthymectomy in MG patients, which of the following was among the findings?
a. older, male patients were more likely to have a better outcome from thymectomy than female patients
b. patients with more severe disease were less likely to benefit from thymectomy
c. the mean rate of drug-free remissions in nonthymectomy patients was 50%
d. thymectomy patients were 1.7 times more likely to improve than nonthymectomy patients
e. 85% of thymectomy patients showed improvement

17. What factor(s) should be of concern to the clinician in the decision to use cyclosporine to treat MG?
a. serious potential side effects including renal toxicity and hypertension
b. potential interactions with agents that interfere with cyclosporine's metabolism
c. cost of treatment
d. patient's increased susceptibility to infection
e. all of the above

18. What are the main risks of plasma exchange as a treatment for patients with MG?
a. rapid fluctuations in plasma volume
b. alteration of serum constituents
c. inhibition of normal clotting mechanisms
d. abrupt reduction in levels of plasma-bound drugs
e. all of the above

19. Which statement(s) is (are) not true of seronegative MG?
a. 25% of children with prepubertal onset of acquired MG are seronegative
b. seronegative MG is rare among myasthenic patients with thymoma
c. approximately one-quarter of patients with acquired, immune-mediated MG do not have detectable AChR levels
d. patients with seronegative MG improve after immunotherapy such as immunosuppression, plasma exchange, and thymectomy
e. all of the above

20. What factors may worsen symptoms of MG?
a. viral respiratory infections
b. hypothyroidism
c. pregnancy
d. emotional upset
e. all of the above