DISORDERS OF NEUROMUSCULAR TRANSMISSION

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Neuromuscular transmission depends on the release of acetylcholine from synaptic vesicles that are stored in the terminal boutons of the motor nerve axon (Fig. 1). Invasion of the motor nerve terminal by the action potential opens voltage-gated calcium channels, resulting in the Ca$^{2+}$-dependent release of the vesicular contents into the synaptic space. Acetylcholine binds to the acetylcholine-gated ion channels (acetylcholine receptors) on the postsynaptic membrane, leading to the opening of these channels and a local depolarization, the end plate potential. If the end plate potential exceeds the critical firing threshold, voltage-gated sodium channels open (sited at the bottom of the postsynaptic folds), generating the muscle action potential that propagates along the muscle fiber and activates muscle contraction. The action of acetylcholine is terminated by its dissociation from the acetylcholine receptors, which close spontaneously after 1 to 4 msec; hydrolysis of acetylcholine by acetylcholinesterase; and acetylcholine diffusion from the synaptic cleft. Meanwhile, in the motor nerve terminal, the voltage-gated calcium channels close spontaneously, and the resting membrane potential is restored through the transient opening of voltage-gated potassium channels.

The extent to which the amplitude of the end plate potential exceeds the threshold for activation of the voltage-gated sodium channels is called the safety factor. In healthy individuals, the amplitude decreases during repeated activity but does not fall below the threshold for activation of the action potential; thus, neuromuscular transmission is not compromised. However, if there is a reduction in the amplitude, failure of neuromuscular
transmission at any individual neuromuscular junction may occur. Causes include defects in the release of acetylcholine, the postsynaptic response to acetylcholine, or the number or sensitivity of the voltage-gated sodium channels. Morphologic changes to the pre- or postsynaptic components or to the basal lamina between them may also influence the efficacy of transmission. Although myasthenia gravis and some neurotoxic envenomations are the most common disorders of neuromuscular transmission, a number of different conditions have been implicated (Table 1).

Table 1 - DISORDERS OF NEUROMUSCULAR TRANSMISSION

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target</th>
<th>Pathobiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUTOIMMUNE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptors</td>
<td>Antibodies to the acetylcholine receptor in 85% of patients reduce the number of acetylcholine receptors and the amplitude of the end plate potential</td>
</tr>
<tr>
<td>Transient neonatal myasthenia</td>
<td>Acetylcholine receptors, muscle-specific kinase</td>
<td>Maternal antibodies cause transient disease in neonates; not seen commonly if mother receiving treatment</td>
</tr>
<tr>
<td>Arthrogryposis</td>
<td>Fetal acetylcholine receptor</td>
<td>Maternal antibodies that inhibit fetal acetylcholine receptor function paralyze the baby in utero, leading to joint contractures; very rare cause of arthrogryposis</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>Voltage-gated calcium channels</td>
<td>Antibodies to voltage-gated calcium channels in 90% of patients reduce the number of voltage-gated calcium channels, the release of acetylcholine, and the amplitude of the end plate potential</td>
</tr>
<tr>
<td>Acquired neuromyotonia</td>
<td>Voltage-gated potassium channels</td>
<td>Antibodies to voltage-gated potassium channels in 40% of patients probably lead to spontaneous and repetitive motor unit discharges</td>
</tr>
<tr>
<td><strong>GENETIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine receptor deficiency</td>
<td>Acetylcholine receptor</td>
<td>Recessive mutations in acetylcholine receptor genes reduce the expression of the acetylcholine receptor</td>
</tr>
<tr>
<td>Acetylcholine receptor deficiency</td>
<td>Recessive mutations in rapsyn gene reduces anchoring of acetylcholine receptors on the postsynaptic membrane</td>
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</tr>
<tr>
<td>Disease</td>
<td>Target</td>
<td>Pathobiology</td>
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<tr>
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</tr>
<tr>
<td>Acetylcholine receptor kinetic abnormalities</td>
<td>Acetylcholine receptor</td>
<td>Dominant or recessive mutations in acetylcholine receptor genes cause kinetic defects—slow and fast channel syndromes</td>
</tr>
<tr>
<td>Choline acetyltransferase deficiency</td>
<td>Choline acetyltransferase</td>
<td>Recessive mutations in the gene for choline acetyltransferase, which synthesizes acetylcholine, reduce the release of acetylcholine</td>
</tr>
<tr>
<td>Acetylcholinesterase deficiency</td>
<td>Acetylcholinesterase</td>
<td>Recessive mutations in the collagen tail (Col Q) that anchors acetylcholinesterase at the neuromuscular junction cause absence of acetylcholinesterase</td>
</tr>
<tr>
<td>Arthrogryposis</td>
<td>Can occur with rapsyn and δ-subunit acetylcholine receptor mutations</td>
<td>Fetal akinesia</td>
</tr>
<tr>
<td>CMS with proximal muscle weakness (limb girdle type)</td>
<td>Dok-7</td>
<td>Recessive mutations in Dok-7 impair interactions with MuSK and lead to a “synaptopathy”</td>
</tr>
</tbody>
</table>

**NEUROTOXIC**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target</th>
<th>Pathobiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulism</td>
<td>Presynaptic acetylcholine release</td>
<td>Botulinum toxin gains entry into the presynaptic motor nerve and cleaves proteins involved in the release of acetylcholine</td>
</tr>
<tr>
<td>Envenomation following bites from snakes, spiders, scorpions, and so on</td>
<td>Varied sites of action</td>
<td>Neurotoxins specific for voltage-gated calcium channels, voltage-gated potassium channels, acetylcholinesterase, acetylcholine receptors, voltage-gated sodium channels, and other targets are frequent in many animal venoms and either inhibit or enhance function</td>
</tr>
<tr>
<td>Drugs/insecticides</td>
<td>Varied sites of action</td>
<td>Muscle relaxants and other drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Many antibiotics and quinine-related drugs can alter neuromuscular transmission at high doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organophosphates and other insecticides block acetylcholinesterase</td>
</tr>
</tbody>
</table>
AUTOIMMUNE DISEASES

1. Myasthenia Gravis

Epidemiology

Myasthenia is the commonest disorder of neuromuscular transmission, with a prevalence of about 15 per 100,000 in Western countries. All races can be affected. It can occur at any age from about year 1 onward, showing a small peak in the third decade. It is being increasingly recognized in elderly persons, with the annual incidence rising above 5 per 100,000 in individuals older than 70 years, making it important in the differential diagnosis of limb or bulbar muscle weakness in older people.

Myasthenia gravis itself is heterogeneous and can be divided into different subtypes; the relative frequency of these different forms is not known, but relatively mild childhood forms are more frequent than older cases in some Asian countries. Neonatal myasthenia gravis, caused by the placental transfer of maternal antibodies to the acetylcholine receptor or to the muscle-specific kinase, affects up to one in eight babies born to mothers with myasthenia gravis. Autoimmune myasthenia gravis needs to be distinguished from congenital myasthenic syndromes, which are caused by gene mutations.

Pathobiology

Pathophysiology

Myasthenia gravis is the result of a defect in neuromuscular transmission. The postsynaptic response to acetylcholine, the end plate potential, is reduced so that the threshold for activation of the muscle action potential is not reached. At a severely affected end plate, this deficiency can occur at the initiation of contraction, but it is most common during repetitive activity when the end plate potential naturally declines. This phenomenon, occurring across many end plates within a muscle, is responsible for the decrement in the amplitude of the compound muscle action potential on repetitive nerve stimulation that is diagnostic of a disorder of neuromuscular transmission.

In myasthenia gravis, the reduced end plate potentials result from loss of functional acetylcholine receptors on the postsynaptic membrane and also from morphologic damage to the membrane. This damage leads to loss of acetylcholine receptor–containing membrane and to simplification of the postsynaptic folds, which contain the voltage-gated sodium channels. The result is a raised threshold for generation of the action potential, further compromising neuromuscular transmission. These changes are caused by antibodies to the acetylcholine receptors in most patients. The pathophysiology in patients without detectable antibodies to the acetylcholine receptor, including patients with muscle-specific kinase antibodies, is not well studied.

Like most synapses, the neuromuscular junction is highly regulated. If the nerve is cut, leading to loss of neuromuscular transmission, the muscle responds by upregulating the expression of acetylcholine receptors that revert to a fetal phenotype (see Fig. 1). Alternatively, if the activity of the postsynaptic muscle decreases, the motor nerve attempts to compensate. Consequently, in myasthenia gravis, there is some increase in the release of acetylcholine from the motor nerve and an increase in the synthesis of acetylcholine receptors in the muscle fiber.

Pathogenesis

Myasthenia gravis is an antibody-mediated autoimmune disease. Evidence includes its association with other autoimmune diseases, most often thyroid disease, and, in younger
patients, with an increased incidence of the human leukocyte antigen HLA-B8,DR3 haplotype that also is associated with several other autoimmune diseases. Placental transfer of autoantibodies from myasthenic mothers can cause transient symptoms of neonatal myasthenia. Conversely, removal of the antibodies by plasma exchange (plasmapheresis) produces a marked improvement in symptoms, starting within days and lasting a few weeks. Moreover, injection of patients’ plasma into mice causes weakness with loss of acetylcholine receptors. In addition, experimental animals immunized against purified acetylcholine receptors develop clinical and pathologic changes of myasthenia gravis.

The antibodies act by three main mechanisms (Fig. 2). First, a few antibodies directly inhibit the binding of acetylcholine to the acetylcholine receptor and cause a pharmacologic-like blockade of function. Second, because of their divalence, antibodies can bind simultaneously to two adjacent acetylcholine receptors through the α-subunits that are present in duplicate in each receptor to form acetylcholine receptor–antibody complexes that are internalized and degraded by the muscle fiber, leading to loss of acetylcholine receptors. Third, most of the antibodies are immunoglobulin G1 (IgG1) subclass, a subclass that binds and activates complement. As a result, the membrane attack complex is activated, leading to destruction of the postsynaptic membrane and probably causing the morphologic damage that is frequently seen. All of these effects are strictly limited to the neuromuscular junction; the remainder of the muscle fiber is essentially normal.

Figure 2. Mechanisms of loss of the acetylcholine receptor (AChR) at the neuromuscular junction. Antibodies can act (a) by directly blocking ACh binding or ion channel function; (b) by cross-linking the AChRs in the membrane, thereby leading to increased internalization and degradation; or (c) by complement-dependent lysis of the AChR-containing postsynaptic membrane. In myasthenia gravis, complement-dependent lysis is likely to be the most important mechanism overall. Interestingly, there is no evidence of complement-dependent mechanisms in either the Lambert-Eaton myasthenic syndrome or acquired neuromyotonia, in which cross-linking of the respective ion channels with increased internalization is the main mechanism.

The acetylcholine receptor antibodies are IgG, high affinity, and highly specific for the native human acetylcholine receptor. Although the antibodies are the effector mechanism for the loss of acetylcholine receptors, their characteristics indicate that specific antibody production requires helper T cells that can recognize acetylcholine receptor epitopes. The thymus gland, which is often abnormal in myasthenia, is at least one site where the immune response occurs. In early-onset myasthenia gravis, the thymus is often “hyperplastic,” with numerous T- and B-cell lymphocytic infiltrates in the medulla. These infiltrates are very similar to the germinal centers that are found in lymph nodes, and some of them can be shown to contain B cells that express surface immunoglobulin specific for
acetylcholine receptors. Plasma cells are also present and synthesize acetylcholine receptor antibodies. In the thymic medulla, there are muscle-like “myoid” cells that have acetylcholine receptors on their surface in both normal and myasthenic individuals; these cells probably provide the antigenic stimulus responsible for the germinal center formation and acetylcholine receptor antibody production in myasthenia gravis. Numerous attempts to characterize the T-cell response in myasthenia have been only partly successful, perhaps because the number of such T cells in patients with an ongoing highly specific autoimmune disease is small.

In late-onset myasthenia gravis, the thymus is probably normal for age. In patients without acetylcholine receptor antibodies, the thymus gland is more likely to appear normal for age, particularly in patients with muscle-specific kinase antibodies. However, in patients without either acetylcholine receptor or muscle-specific kinase antibodies, some lymphocytic infiltrates and germinal centers can be present.

**Thymoma**

Thymoma occurs in about 10% of myasthenic patients, reaching a peak in middle age. Thymomas are epithelial cell tumors and correspond mainly to the World Health Organization type B1 and B2. The epithelial cells attract large numbers of T lymphocytes, which may be sensitized to the acetylcholine receptor in the tumor and then exported to the periphery. Myasthenia gravis can also arise several years after thymoma removal.

**Clinical Manifestations**

Myasthenia gravis arises with fatigable muscle weakness, that is, painless weakness that increases with muscle use and improves after rest. In many patients, the weakness starts in the eye muscles, resulting in double vision or ptosis (drooping eyelids). In others, it may first affect bulbar muscles or limb muscles. Virtually any skeletal muscle may be involved as the illness progresses. Typically, the weakness varies in distribution and severity from day to day or from week to week, and it is often worse in the evening. It may first appear following an infection. Established weakness can increase with anxiety, with infection, or with the menstrual period and tends to improve with rest.

Ocular muscle weakness is characterized by ptosis (often asymmetrical) and diplopia that initially can be transient and first noticed while driving, for example. Severity can range from mild unilateral ptosis or minimal diplopia to profound bilateral ptosis, which obscures vision, combined with almost complete ophthalmoplegia. Bulbar symptoms include weakness of mouth closure, difficulty in chewing, a “snarling” smile, nasal or slurred speech that can noticeably deteriorate as speech continues, impaired swallowing sometimes associated with nasal regurgitation of fluids, reduced tongue movements, and head droop related to neck weakness.

Limb muscle involvement is common, and proximal muscles are usually more involved than distal. Proximal weakness of the legs can lead to collapse when walking and can be misinterpreted as a functional (psychogenic) disorder. Weakness of elbow extension and of finger abduction may be prominent. By contrast, ankle dorsiflexion is rarely affected except in severe disease.

Respiratory muscle involvement is less common but can be life-threatening, especially if associated with dysphagia. Selective involvement of the diaphragm can cause severe breathlessness in the supine posture. Wasting is uncommon but can affect the facial muscles and tongue, for example, in long-standing disease. Tendon reflexes are typically brisk. Bladder disturbances are rare, and sensory symptoms do not occur.
Subtypes of Myasthenia Gravis

Several subgroups can be distinguished on the basis of clinical and pathologic criteria, as set out subsequently, and can help to inform treatment protocols.

Ocular Myasthenia Gravis

Ocular myasthenia gravis describes symptoms that are confined to extraocular muscles. If they remain localized for at least 2 years, subsequent generalization of weakness is unlikely. Acetylcholine receptor antibody levels are generally low and are undetectable in about 50%. Thymoma is rare in this group. The neuromuscular junction of ocular muscles shows structural and physiologic differences from typical limb muscles. Ocular weakness is often the presenting symptom not only in myasthenia gravis but also in neurotoxin poisoning, for example, botulism. Thus physiologic factors or accessibility of the neuromuscular junctions of ocular muscles to circulating factors may make them particularly vulnerable to antibodies in myasthenia gravis.

Generalized Myasthenia Gravis with Acetylcholine Receptor Antibodies

Among patients with generalized disease and acetylcholine receptor antibodies, there are three clinical subgroups. Early-onset myasthenia gravis is more frequent in females and associates strongly with HLA-A1,B8,DR3. The thymus is often hyperplastic. Acetylcholine receptor antibody titers are usually high and decline to varying degrees after successful treatments, including thymectomy.

Late-onset myasthenia gravis is becoming increasingly common with the aging of the population and, when arising with bulbar weakness, may be mistaken for amyotrophic lateral sclerosis or brain stem cerebrovascular disease. Among older patients, males are more frequently affected, and the thymus is usually normal for age. Thymoma-associated myasthenia gravis is an important distinction because thymectomy or other specific tumor therapy is required. Most patients with thymomas and myasthenia gravis present between the ages of 30 and 60 years.

Generalized Myasthenia Gravis with Muscle-Specific Kinase Antibodies

About 15% of all myasthenic patients with generalized symptoms do not have detectable acetylcholine receptor antibodies. A variable proportion of these patients have antibodies to another neuromuscular junction protein, the muscle-specific kinase. Muscle-specific kinase antibodies are mainly IgG4 and are absent or very infrequent in patients with acetylcholine receptor antibody–positive myasthenia gravis, patients with persistent ocular myasthenia gravis, or patients with thymoma. Muscle-specific kinase antibodies are found relatively often in younger females, including children, with marked ocular, bulbar, neck, or respiratory muscle weakness but are seen less frequently in older patients. It is not yet clear how these antibodies cause the neuromuscular junction defect.

Generalized Myasthenia Gravis with neither Acetylcholine Receptor nor Muscle-Specific Kinase Antibodies

There remain some patients with generalized myasthenia gravis who have neither acetylcholine receptor nor muscle-specific kinase antibodies. These patients can develop severe disease but in general respond better to treatment than muscle-specific kinase antibody–positive patients. It is possible that they have acetylcholine receptor antibodies at levels not detected by current laboratory tests.

Diagnosis

Diagnosis is based on the clinical features, serologic testing for specific antibodies, clinical electrophysiology, and, if doubt still remains or specialized facilities are not available, the
clinical response to anticholinesterase medication (Table 2). Mediastinal imaging is needed to exclude a thymoma in patients with acetylcholine receptor antibodies.

### Table 2 - Diagnostic Evaluation of Syndromes Causing Reduced Neuromuscular Transmission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acetylcholine Receptor Myasthenia Gravis</th>
<th>Muscle-Specific Kinase Myasthenia Gravis</th>
<th>Seronegative Myasthenia Gravis</th>
<th>Neonatal Myasthenia Gravis</th>
<th>Lambert-Eaton Myasthenic Syndrome</th>
<th>Congenital Myasthenic Syndrome</th>
<th>Botulism</th>
<th>Mitochondrial Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset birth, recovery within 2 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Onset birth plus arthrogryposis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Rapsyn or AChR δ-subunit mutations</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Onset at &lt;1 year and persistent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Any CMS. Rapsyn-AChR deficiency and SCS may arise later</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Infantile apneas</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>AChR-ε, rapsyn, or ChAT mutation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acetylcholine receptor antibody positive</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Muscle-specific kinase antibody positive</td>
<td>-</td>
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<td>-</td>
<td>±</td>
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<tr>
<td>Voltage-gated calcium channels antibody positive</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>EMG decrement &gt;10%</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>EMG jitter increased</td>
<td>+</td>
<td>+ especially face muscles</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Post-tetanic potentiation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitor response</td>
<td>+</td>
<td>Often weak</td>
<td>+</td>
<td>+</td>
<td>Often weak</td>
<td>Except SCS and ChAT deficiency</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thymoma</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

AChR = acetylcholine receptor; ChAT = choline acetyltransferase; CMS = congenital myasthenic syndrome; EMG = electromyogram; SCS = slow channel syndrome.

Acetylcholine receptor antibodies are present in about 85% of patients with generalized symptoms but only 50% of patients with purely ocular involvement. In the absence of acetylcholine receptor antibodies, the diagnosis can be more difficult, but detection of muscle-specific kinase antibodies can be helpful.

The electrophysiologic abnormality is an abnormally large decrement (>10%) in the amplitude of the compound muscle action potential upon stimulation with 3 Hz, with increased jitter or blocking on single-fiber electromyography (EMG). In patients with
muscle-specific kinase antibodies, EMG abnormalities may be detectable only in facial muscles. These EMG changes are not specific for myasthenia gravis but can occur in any disorder that interferes with neuromuscular transmission.

Intravenous edrophonium (Tensilon®), a short-acting cholinesterase inhibitor, transiently improves myasthenic weakness but requires an appropriate medical setting, including resuscitative facilities and the availability of atropine, because of the risk of adverse events and severe cholinergic reactions, including syncope. A test dose of 2 mg is given intravenously, followed 30 seconds later by 6 to 8 mg if no adverse event has occurred. The equivalent doses in children are a 20 μg/kg test dose followed by 60 to 80 μg/kg. Some patients improve sufficiently with the test dose that it is not necessary to give the full dose. An alternative pharmacologic test in adults is a single dose of subcutaneous or intramuscular neostigmine (1 to 2.5 mg) or of oral pyridostigmine (60 mg).

**Differential Diagnosis**

Congenital acetylcholine receptor deficiency syndromes should be considered in patients who have clinical and EMG evidence of myasthenia but are seronegative for acetylcholine receptor and muscle-specific kinase antibodies. Lambert-Eaton myasthenic syndrome almost always arises with difficulty in walking; ocular symptoms are rare, and specific laboratory tests are available. The ocular muscle involvement that characterizes the Miller-Fisher syndrome is more rapid in onset than is usual in myasthenia gravis and is associated with GQ1b antibodies. Mitochondrial myopathy may show signs that are similar to those of myasthenia gravis (e.g., asymmetrical ptosis and limitation of eye movements), and there may be increased jitter on single-fiber EMG, but this condition and oculopharyngeal dystrophy can be distinguished from myasthenia gravis by the nonfluctuating weakness and by muscle biopsy. In neurasthenia and chronic fatigue syndrome, the laboratory tests for myasthenia gravis are negative.

**Treatment and Prognosis**

Many patients respond to oral pyridostigmine 30 to 60 mg four or five times daily; in patients with mild disease, this dose may adequately control symptoms. Doses in excess of 90 mg are likely to cause gastrointestinal side effects, abdominal cramps and diarrhea, which can be controlled with oral propantheline bromide (Pro-Banthine) 15 mg or loperamide 2 mg.

**Neonatal Myasthenia Gravis**

Pyridostigmine 5 to 10 mg can be given every 4 hours to about an hour before a feeding. Close monitoring and respiratory support in a special unit may be required.

**Ocular Myasthenia**

Diplopia can sometimes be helped by the use of prisms. Ocular symptoms responding incompletely to pyridostigmine are often improved or completely corrected by low-dose prednisone therapy (e.g., 5 mg every other day) increasing by 5 mg at weekly intervals either until symptoms are completely controlled or until a ceiling dose (e.g., 1 mg/kg) is reached. When remission is established, the dose can be slowly reduced (e.g., by 5 mg at 2-weekly intervals) until symptoms recur and then adjusted upward to define the effective minimal dose. Full withdrawal of prednisone is usually followed by a symptomatic relapse. Most centers do not recommend thymectomy for nonthymomatous ocular myasthenia gravis. In patients who fail to respond adequately to prednisone or who are intolerant of the medication, the addition of azathioprine (2 to 2.5 mg/kg body
weight) or ocular muscle surgery is an option. However, the diagnosis should be reviewed in patients who show no improvement with high-dose prednisone treatment.

**Thymoma**

Thymoma usually requires surgery, but removal of the tumor typically does not result in improvement in muscle weakness. If the tumor is found to be locally invasive, radiotherapy is indicated. If tumor spread is more extensive, chemotherapy is necessary.

**Generalized Nonthymomatous Myasthenia Gravis**

When generalized symptoms are inadequately controlled by pyridostigmine, thymectomy is often recommended empirically even for patients without a thymoma, especially patients younger than 45 years, despite the absence of trials and no clear consensus from observational data. However, many patients respond to alternate-day prednisone, started at a low dose (e.g., 10 mg qod) and increasing by 5 to 10 mg per dose to 1.0 to 1.5 mg/kg. Because starting prednisone can temporarily exacerbate the disease, patients are usually best managed in the hospital, especially if they have bulbar or respiratory muscle involvement. When remission is established, the dose can be reduced by 5 to 10 mg every 2 weeks (or more slowly) until symptoms recur, when it can then be adjusted upward, aiming to define the effective minimal dose. Prophylactic treatment for steroid-induced bone disease should be considered in all patients.

Additional immunosuppressive medication is likely to be required in patients who can be controlled only by high-dose prednisone or who are intolerant of it. Azathioprine 2.5 mg/kg/day is often the medication of choice. In fact, a randomized double-blind trial comparing azathioprine plus prednisone with placebo plus prednisone showed that the combined treatment was better tolerated, allowed a substantially lower dose of prednisone to be used, and was associated with fewer relapses than prednisone alone. Mycophenolate 1 g/kg twice daily, cyclosporin 3 to 5 mg/kg daily, and methotrexate 5 to 15 mg weekly are options for those intolerant of azathioprine, but results of long-term randomized studies using the latter therapies have not yet been reported. When remission has been achieved, doses can be reduced slowly and cautiously; full withdrawal is likely to be followed by relapse.

Plasmapheresis (plasma exchange) or immunoglobulin infusion can lead to short-term improvement, typically lasting 4 to 6 weeks, and can be used to prepare patients for thymectomy, to cover the initiation of prednisone therapy, or to control an exacerbation of myasthenic weakness. These two treatments are equally efficacious. An immunoglobulin infusion of 1 g/kg given on day 1 only is as effective as 1 g/kg given on day 1 and again on day 2. Because of the short-lived benefits of these therapies, they must be accompanied by additional immunosuppressive therapy, as noted previously.

**Prognosis**

The increasing use of immunologic therapies, coupled with advances in critical care, has improved the prognosis in nonthymomatous myasthenia gravis. Many patients can expect substantial improvement or remission with a normal life expectancy. The prognosis is less good, however, in those with invasive thymoma.
2. The Lambert-Eaton Myasthenic Syndrome

Definition and Epidemiology

The Lambert-Eaton myasthenic syndrome is a rare disorder that can occur in paraneoplastic and nonparaneoplastic forms and affects all races. The incidence of the former is much higher, but its shorter survival results in a similar prevalence of the two types. The paraneoplastic form affects about 2% of patients with small cell lung cancer and can also occur with lymphoma. The nonparaneoplastic form associates with HLA-A1, -B8, and -DR3, as in myasthenia gravis.

Pathobiology

Lambert-Eaton myasthenic syndrome is an antibody-mediated presynaptic disorder characterized by a reduced number of acetylcholine quanta (vesicles) released by each nerve impulse. End plate potentials recorded from intercostal muscle biopsies are consequently much reduced in amplitude. During repetitive nerve stimulation, the end plate potential amplitude increases, probably because of build up of calcium in the motor nerve terminal, leading to increased release of acetylcholine. Freeze-fracture electron microscopic studies of motor nerve terminals show that the “active zone” particles, which represent voltage-gated calcium channels, are reduced in number and disorganized. IgG can be identified bound to the presynaptic nerve terminal at the sites of acetylcholine release. Similar changes can be reproduced in mice injected with IgG from patients with the Lambert-Eaton myasthenic syndrome, indicating that the electrophysiologic and morphologic changes are due to antibodies. The mice have reduced end plate potential amplitudes and quantal contents, and IgG is bound to their motor nerve terminals. The IgG also interferes with transmitter release from postganglionic parasympathetic and sympathetic neurons in injected mice, providing an explanation for the autonomic dysfunction observed in many patients.

The antibodies in Lambert-Eaton myasthenic syndrome appear to act principally by cross-linking the voltage-gated calcium channels on the surface of the presynaptic motor nerve membrane, leading to their clustering and internalization. There is no evidence that the antibodies activate complement, and the motor nerve terminal is morphologically intact. Direct inhibition of voltage-gated calcium channel function by antibody is infrequent.

Clinical Manifestations

Almost all patients present with difficulty in walking, which exhibits a rolling characteristic. Weakness in ocular, bulbar, and respiratory muscles is less common than in myasthenia gravis. Weakness predominantly affects proximal muscles, which may show augmentation of strength during the first few seconds of a maximum contraction. Reflexes are absent or depressed but can increase following 10 seconds of maximum contraction of the muscle (post-tetanic potentiation). Autonomic symptoms (dry mouth, constipation, erectile dysfunction) are present in most patients. Occasionally, cerebellar ataxia may be present. Patients with nonparaneoplastic Lambert-Eaton myasthenic syndrome may have other autoimmune diseases, notably vitiligo.

Diagnosis

Diagnosis is based on the clinical features, on a positive serum voltage-gated calcium channel antibody test, and on the characteristic EMG findings. Antibodies specific for the α1A (P/Q) subtype of voltage-gated calcium channels are found in 90% of patients, both with and without small cell lung cancer. Patients may not respond convincingly to intravenous edrophonium. On EMG, the amplitude of the resting compound muscle action potential is reduced, but it increases by more than 100% following 10 seconds of voluntary
contraction of the muscle or during high-frequency (40 Hz) nerve stimulation. Chest imaging is required in those at risk for tumor.

**Differential Diagnosis**

Botulinum poisoning causes blockade of presynaptic transmitter release at the neuromuscular junction as well as EMG changes similar to those in the Lambert-Eaton myasthenic syndrome. Botulinism is detected by finding the toxin in serum or the *Clostridium botulinum* bacteria in the wound or feces. Myopathies can mimic Lambert-Eaton myasthenic syndrome clinically, but autonomic changes do not occur, EMG findings are different, and muscle biopsy is abnormal.

**Treatment and Prognosis**

Plasma exchange leads to clinical improvement within a few days in acutely ill patients, and most patients respond to immunosuppressive drugs or intravenous immunoglobulin therapy. Intravenous immunoglobulin therapy (1 g/kg for 1 to 2 days) improves strength, with an associated decline in specific antibody. Patients may also respond to plasmapheresis.

Specific tumor treatments (resection, local radiotherapy, chemotherapy) often lead to improvement of the neurologic disorder. Most patients respond to 3,4-diaminopyridine (10 to 20 mg four times daily; *this drug had not been approved by the U.S. Food and Drug Administration at the time of publication*), which increases transmitter release from motor nerve terminals; however, excessive doses can lead to seizures.

Long-term immunosuppressive treatment with prednisone, azathioprine, or cyclosporin may be required in those with severe weakness, using doses similar to those described previously for myasthenia gravis.
ACQUIRED NEUROMYOTONIA

Definition and Epidemiology

Neuromyotonia, or Isaacs' syndrome, is a rare disorder primarily characterized by myokymia (spontaneous undulating muscle contractions) that can be intermittent or continuous and may be present during sleep or general anesthesia. It results from the hyperexcitability of motor nerves. A milder variant, the cramp-fasciculation syndrome, is more common. Autoimmunity underlies many cases.

Pathobiology

Neuromyotonia may be associated with other autoimmune diseases or other autoantibodies, and cerebrospinal fluid analysis may show oligoclonal bands. In about 15% of patients, it is paraneoplastic, usually associated with thymoma and occasionally with lung cancer. Evidence for an antibody-mediated pathogenesis includes improvement following plasma exchange, passive transfer to mice by patients' plasma/IgG, and the effects of patients' IgG on cultures of dorsal root ganglia or neuroblastoma cell lines.

Antibodies to voltage-gated potassium channels can be detected in about 40% of patients by radioimmunoprecipitation. Occasionally, neuromyotonia appears to be triggered by infection.

Clinical Manifestations

Acquired neuromyotonia is rare, and the clinical presentation is heterogeneous. There is a combination of muscle stiffness, cramps, myokymia (visible undulation of the muscle), pseudomyotonia (e.g., failure to relax after fist clenching), and weakness. Increased sweating is common. Myokymia persists during sleep. Cramp-fasciculation syndrome shares some features with neuromyotonia. Some patients have sensory symptoms, including transient or continuous paresthesias, dysesthesia, and numbness, and a proportion have central nervous system features of an encephalopathy, including insomnia, hallucinations, delusions, and mood change. Rare cases have constipation and cardiac irregularities.

Diagnosis

EMG shows spontaneous motor unit discharges that occur as distinctive doublet, triplet, or multiplet bursts with high intraburst frequency (40 to 300 per second), longer continuous bursts, and postactivation contraction. The abnormal muscle activity may be generated at different sites throughout the length of the nerve, but in most cases it is principally distal. Antibodies to voltage-gated potassium channels are found in 40% of patients. The differential diagnosis includes neuromyotonia caused by acquired and inherited neuropathies and by voltage-gated potassium channel gene mutations (Kv1.1) that can associate with episodic ataxia.

Treatment and Prognosis

Neuromyotonia can be improved by anticonvulsant drugs, such as carbamazepine (up to 800 to 1000 mg daily), phenytoin (up to 300 mg daily), or lamotrigine (up to 100 mg daily), that downregulate sodium channel function, thereby reducing the hyperexcitability of nerves. Plasma exchange and intravenous immunoglobulins, using the same regimen as for myasthenia gravis, may be followed by short-term improvement. Immunosuppressive medications, again using the same drugs as for myasthenia gravis, are effective in some patients.
GENETIC MYASTHENIC SYNDROMES

Epidemiology
These conditions (see Table 1) are rare inherited disorders, mostly autosomal recessive except for the slow channel syndrome, that result from mutations in genes encoding key proteins at the neuromuscular junction. Their frequency in the population is unknown but could be as high as 3 per million.

Pathobiology
The genetic mutations can be presynaptic, synaptic, or postsynaptic. The most common site for mutations is the acetylcholine receptor ε-subunit gene, where the mutations can be single nucleotide substitutions or deletions and usually result in complete loss of function of the acetylcholine receptor ε-subunit. Because this subunit replaces the acetylcholine receptor γ-subunit around the time of birth, the babies are normal in development but show weakness during late pregnancy and in the neonatal period. Survival probably depends on the continued expression of the γ-subunit. Acetylcholine receptor deficiency can also result from defects in the gene for rapsyn, a cytoplasmic protein required for the clustering of the acetylcholine receptors at the neuromuscular junction. Single nucleotide changes in genes for any of the acetylcholine receptor subunits can affect acetylcholine-induced receptor channel openings, leading to kinetic defects. In the fast channel syndrome, the result is reduced function of acetylcholine receptor, whereas in the slow channel syndrome, the channel opens for prolonged periods, resulting in subsynaptic accumulation of ions and degenerative changes.

Mutations in the ColQ gene, which gives rise to the collagen tail that anchors acetylcholinesterase in the synaptic cleft, are uncommon. The resulting continuous exposure of the postsynaptic membrane to acetylcholine leads to degenerative changes and progressive muscle weakness. Mutations in choline acetyltransferase, the enzyme responsible for the synthesis of acetylcholine, do not necessarily lead to dysfunction at rest; during repetitive activity, however, the amount of acetylcholine in each packet decreases, with consequent failure of neuromuscular transmission. Mutations in Dok-7 cause a “synaptopathy” with small, simplified neuromuscular junctions.

Clinical Manifestations
There may be a history of fetal akinesia. Most cases present in infancy with hypotonia and with difficulties in feeding and breathing. Arthrogryposis multiplex congenita often associates with rapsyn mutations. Life-threatening episodic apneas can occur with mutations in choline acetyltransferase or rapsyn. However, some patients do not present until adolescence or young adulthood, including some with rapsyn mutations and the slow channel syndrome. The age at presentation can differ even within a family.

Diagnosis
The EMG findings in the acetylcholine receptor deficiencies and fast channel syndromes are similar to those in typical myasthenia gravis. In the slow channel syndrome and acetylcholinesterase deficiency syndrome there may be a double response to a single nerve stimulus (see Table 2). Most patients show a response to cholinesterase inhibitors (edrophonium or neostigmine), with the exception of the slow channel syndrome and acetylcholinesterase deficiency. DNA screening for congenital myasthenic syndromes is essential. Genetic analysis can confirm the diagnosis, although there remain many families in which the faulty gene has not been identified. A precise genetic diagnosis can help in treatment, prognosis, and counseling.
The principal differential diagnoses are spinal muscular atrophy, infant botulism, hereditary neuropathies, and congenital myopathies or muscular dystrophies. Onset in early childhood, adolescence, or adulthood, as can occasionally occur, may mean that the genetic nature of the disorder is not recognized or initially leads to the incorrect diagnosis of seronegative myasthenia gravis.

**Treatment and Prognosis**

Many of the congenital myasthenic syndromes respond to acetylcholinesterase inhibitors as used for myasthenia gravis. However, no specific treatment is available for acetylcholinesterase deficiency (ColQ mutations). For the slow channel syndrome, some adult patients have responded to fluoxetine, but the use of fluoxetine in children or adolescents requires psychiatric supervision. Although these congenital disorders can be fatal during infancy, usually because of apneic episodes during infections, most tend to be nonprogressive and stable or even may improve during adolescence or adult life. The exceptions are the slow channel syndrome and acetylcholinesterase deficiency, which, owing to the excess acetylcholine receptor activations that they cause, can be associated with progressive degenerative changes at the neuromuscular junction.