lation of motor nerve branches, and the variability of one NMJ is recorded. The normal range of jitter values has been determined empirically and differs among muscles and according to age (32). Abnormal jitter does not distinguish between presynaptic and postsynaptic defects of transmission. However, by stimulation of the motor nerve electrically, the discharge frequency at which maximal jitter occurs can help distinguish patterns suggestive of pre- or postsynaptic defects (33).

Comparison of Diagnostic Techniques

A suggestive clinical history and examination provides the impetus to proceed with confirmatory clinical, electrophysiologic, and serologic laboratory studies in MG. Diagnostic specificity for MG comes close to 100% when ACh receptor antibody titers are present, although their absence does not exclude the diagnosis. The edrophonium test, repetitive nerve stimulation, and SFEMG are specific for the defect in NMJ transmission. The sensitivity of the edrophonium test and repetitive nerve stimulation depends on the distribution and severity of symptoms. Ocular and mild generalized MG may present difficulty when the findings are subtle or mild. SFEMG is more sensitive in ocular MG and mild generalized involvement because it detects abnormalities that do not cause blocked transmission. A direct comparison of antibody testing, the Tensilon test, repetitive nerve stimulation, and SFEMG performed in the same patients has been made (Table 5) (34). SFEMG was the most sensitive for both ocular and generalized weakness when affected muscles were studied (99% to 89%). Antibody tests were more sensitive for generalized MG (80%) and less for ocular MG (55%). Repetitive nerve stimulation was almost as sensitive in the generalized form (76%), but least in the ocular form (48%).

Mediastinal Imaging

Approximately 10% of patients with MG will have evidence of a thymoma on computed tomography (CT) of the chest. Thymomas are clinically silent except for their association with weakness in MG; even so, only 40% of thymomas are associated with MG (35). Their presence cannot be predicted by the clinical features of MG, and therefore imaging is necessary. CT of the chest, not magnetic resonance imaging, is still the test of choice (36).

Treatment

Concepts

MG is a chronic disease with no cure at this time. The goal of treatment is sustained and complete remission, defined as the absence of symptoms and signs, with no medication. For many patients, complete remission may be elusive, and partial remission is a more practical goal (37). Therapy can be divided into three categories: drugs that improve NMJ transmission and the symptoms of weakness but do not affect the course of the disease, including the AChE inhibitors; procedures that affect the immune system over a limited time period but probably do not affect the natural history of the disease, such as plasma exchange and intravenous immunoglobulin (IVlg); and drugs and procedures that modify the course of MG such as the immunosuppressants prednisone and azathioprine, and thymectomy.

Quantitative Testing

In certain patients, it may be difficult to determine if a particular therapeutic regimen is effective. For example, some may report worsening of symptoms, whereas strength appears unchanged or even improved. Under these circumstances, it is helpful to have quantitative data for objective comparisons. One quantitative scale that was developed as an end-point measure in a drug trial can be used clinically to determine overall function (38); however, it is important to try to carry out the measurements at the same time of the day or regularly at the time of the last dose of pyridostigmine. A frequently encountered problem is the differentiation of steroid myopathy from MG, especially when weakness advances on prednisone. Summing the values of decrement to repetitive nerve stimulation of several nerves or average neuromuscular jitter from SFEMG measurements can be helpful. Electrodiagnostic values are usually unchanged or improved in steroid myopathy and worse during an exacerbation of MG, so emphasizing the importance of establishing baseline electrodiagnostic values even in those whose diagnosis is made on the basis of elevated ACh receptor antibody titers.

<table>
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<tr>
<th>TABLE 5. Comparison of a series of diagnostic tests performed in 550 patients with myasthenia gravis</th>
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<td>SFEMG in any muscle</td>
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<td>Gen MG</td>
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<td>Percent abnormal</td>
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Gen MG, generalized weakness; Ext dig com, extensor digitorum communis muscle, commonly used studied with SFEMG; Ocular MG, weakness restricted to ocular muscles; SFEMG, single-fiber electromyogram; Rep Stim, repetitive stimulation. Modified from Ref. 34.
**Acetylcholinesterase Inhibitors**

Pyridostigmine (Mestinon) is the most commonly used AChE inhibitor. It reversibly binds to ACh and slows the hydrolysis of ACh, raising the concentration of ACh at the junctional folds and increasing the probability of ACh remaining attached to functional receptors. This leads to EPPs with a more rapid rise time and a higher amplitude and thus a greater likelihood of generating APs in previously blocked muscle fibers. It reaches peak serum concentrations in 90 to 120 minutes and has a similar half-life. Doses of 60 to 120 mg every 3 to 4 hours are most effective, but patients may modify their dose to match their level of activity and to reduce the common adverse side effects of cramping and diarrhea. It is rare for pyridostigmine alone to improve transmission to a satisfactory level, and therefore most patients require more definitive therapy (39).

**Plasmapheresis and Intravenous Immunoglobulin**

Plasmapheresis and IVIg rapidly influence the immune system but are of limited duration (40). A recent comparison of plasmapheresis and IVIg demonstrated equal effectiveness (41) and probably equivalent expense; however, they differ in their proposed mechanisms of action and thus may be complementary therapies in MG. Plasmapheresis removes antibodies, presumably those that act at the NMJ but may also modulate the immune system. The response to plasmapheresis occurs over hours to days and is useful to treat or abort myasthenic crisis, but it requires special equipment to separate blood into components and trained personnel and is thus not widely available. A therapeutic trial usually consists of four to six exchanges on alternate days. The procedure is well tolerated but requires good venous access, and patients may require placement of a central venous catheter. Most complications are those associated with central catheters. IVIg consists of pooled exogenous antibodies from thousands of donors. Although the precise mechanisms of action are not well understood, exogenous antibodies interact at several different sites, including binding to the autoantibodies, to idiotypic antigenic sites, and to T cells to modulate the immune system (42,43). It does not require special equipment, and infusions can be performed easily with routine nursing care. The recommended total monthly dose is 2 g/kg in five daily doses, administered slowly enough to avert rate-related side effects. Repeat doses are usually 1 g/kg over 1 to 2 days. The most effective schedule has not yet been determined; however, the half-life of IVIg is about 4 weeks, and monthly doses are reasonable, with the goal of slowly tapering the frequency of treatments based on the clinical status. Clinical responses occur over 2 to 4 weeks.

**Corticosteroids**

Corticosteroids occupy a central role in the treatment of MG because of their effectiveness and reliability in initiating and maintaining a prolonged remission. Corticosteroids affect the immune system at several different levels (44), but the mechanism of influence on MG has not been established. Prednisone is the most widely used oral agent given initially at doses of 40 to 60 mg daily for 3 to 6 weeks and then slowly tapered after a beneficial response is seen. For unclear reasons, a high percentage of MG patients experience temporary worsening of their weakness that sometimes culminates in crisis after high initial doses; accordingly, patients receiving 100 g or more should probably be monitored initially in a hospital setting. Alternatively, the patient can be given a low dose and slowly increased over weeks (40). Although many prednisone taper protocols are followed, one goal is to convert relatively early in the taper schedule to alternative-day dosing to reduce the short-term side effects of weight gain and hyperglycemia, osteopenia, gastric and duodenal erosion, and cataracts (45). A short course of 2 g intravenous methylprednisolone followed by a second infusion 5 days later is sometimes effective in aborting myasthenic crisis, but this has never been formally studied (46).

**Azathioprine**

Azathioprine (Imuran) has been used in patients with poor responsiveness, intolerance, or frequent relapses with corticosteroids and as a steroid-sparing agent in conjunction with prednisone to reduce the long-term side effects (47); however, azathioprine is less effective than prednisone as monotherapy (48). Dosage varies, with some investigators raising the dose to achieve an elevation in the mean corpuscular volume or a drop in the white blood cell count, whereas others give a fixed dose based on weight, usually 3 to 5.0 mg/kg/day (49). There are several caveats of azathioprine therapy. First, there is a long delay in the onset of action, 24 months for the steroid-sparing effects to become evident (50). Second, side effects occur in about 10% of patients, including flu-like symptoms with nausea, fever, chills, arthralgias, or gastrointestinal complaints that usually resolve promptly with cessation of therapy (51). Third, bone marrow suppression occurs in all patients but is rarely a reason to stop therapy with careful monitoring. Fourth, there is the concern for an increased risk of cancers, primarily lymphomas after 10 to 20 years of therapy (52).

**Thymectomy**

The thymus has a central position in the pathogenesis of MG, and thymectomy has been an important treatment of MG. The earliest transsternal thymectomies for MG were performed for the removal of thymic tumors (53); however, the beneficial results in nontumorous patients were appreciated afterward. Nonetheless, it has been difficult to judge the efficacy of thymectomy for several reasons. First, there has not been a placebo-controlled trial. Second, it has been difficult to ascertain the
absolute effectiveness of one type of operative procedure over another and the optimal extent of thymic resection necessary to obtain a maximal clinical response. The surgical approaches to the thymus gland include cervical, transsternal, combined cervical and transsternal, and thoracoscopic procedures (54). Third, there is a delay in the effectiveness that may be prolonged for years after surgery, yet long-term it carries the best likelihood for a sustained remission. Whether all thymic tissue needs to be removed to guarantee the best outcome is not truly known, although most authorities agree that the transsternal approach reduces the risk of leaving thymic tissue behind (54,55,56).

Thymectomy should be included in the initial and primary therapy of patients with generalized limb and bulbar involvement. In one study (56), two thirds of patients were asymptomatic after transsternal surgery, and of those, one sixth had ocular symptoms alone, whereas the remainder had mild generalized weakness. Younger patients, including those with juvenile MG, and older patients respond equally well. Plasmapheresis can improve the preoperative status and later immediate outcome of patients with bulbar weakness and a poor cough that may be a risk for prolonged postoperative intubation. One series (54), based on extensive surgical exploration of the anterior mediastinum and neck for thymic tissue, reported a progressive number of patients in full remission of up to 90% after 7 years of follow-up.

The role of the thymus and thymectomy is one of the more controversial therapeutic issues in MG. Nonetheless, the following guidelines appear to be reasonable. Radiographic evidence of an anterior mediastinal mass on chest CT warrants a thymectomy at any age because approximately 10% of patients with MG will have a thymoma. When there is no mediastinal mass, it seems appropriate to counsel the patient to undergo thymectomy to increase the probability of sustained remission. Plasmapheresis, corticosteroids, and IVIg can be used to optimize the clinical status in the meantime. Transsternal procedures that maximally visualize the anterior mediastinum are preferable to cervical and thoracoscopic procedures that remove less thymic tissue and can miss thymic tissue or a small thymoma.

**Cyclosporine**

Cyclosporine was found to be effective in a small trial as a steroid-sparing agent (38); however, the associated side effects include renal insufficiency, hypertension, headache, and hirsutism.

It must be emphasized that MG is a highly variable disease and therefore treatment of the myasthenic patient is an art and must be individualized. There are very refractory patients who remain weak and require a variety of medications for unpredicted exacerbations. In these situations, finding the optimum combination of medications can be a challenge.

**JUVENILE MYASTHENIA GRAVIS**

**Clinical Features**

Juvenile MG is an immune-mediated disorder that has its onset before age 20 (57). Although similar to the disorder of adults, there are clinical differences. Juvenile MG is less likely to have an ocular presentation. Patients with an onset before puberty are more likely to be seronegative, with the percentage of seropositivity increasing with older age. This is probably due to the propensity of the mature immune system to produce circulating antibodies and the effect of sex hormones on immunoglobulin levels (58). The ACh receptor antibody titer may be a clue in distinguishing between congenital, genetic, or acquired forms of MG. The racial differences in juvenile MG are minor; African-American patients have a female-to-male affected sex predictor of 2:1, whereas in white patients the ratio is nearly equal. Disease severity and long-term prognosis is better when onset is before puberty. White patients have more frequent spontaneous remissions than African-American patients (59).

**Treatment**

The specific therapy is similar for juvenile and adult MG patients because seronegative and seropositive children and adult patients with acquired MG respond equally well to treatment (57). However, plasmapheresis may be more difficult to perform in young patients because of their small blood volumes. In children, there is an additional concern of the effect of prednisone on growth retardation. Azathioprine is a second-choice drug in this group because of the long-term risk of lymphoma. Thymectomy is effective in children; in fact, patients with juvenile MG may even have a more favorable prognosis than adults (56,58). There are racial differences that may affect the surgical outcome. The remission rate in African-American children is lower than in whites (59). Although concerns have been voiced for the long-term effects of thymectomy on the maturation of the immune system, such has never been seen in children with MG or among children that have had the thymus gland removed in the course of cardiac surgery for other reasons (56).

**NEONATAL MYASTHENIA GRAVIS**

**Clinical Features**

Neonatal MG is a transient form of NMJ transmission failure due to the passive transfer of maternal antibodies across the placenta. Symptoms include a poor suck, cry, facial weakness, dysphagia, and hypotonia (60). Clues to the diagnosis in utero may be the presence of reduced fetal movements. These infants appear to have more severe weakness, including respiratory failure at birth. Weakness in utero may also lead to joint contractures, and
neonatal MG is included in the differential diagnosis of arthrogryposis. Although the overall probability of neonatal MG is low, it occurs in about 1 in 10 births to myasthenic mothers, and most infants born to myasthenic mothers are normal (61). Neonatal MG can occur in infants of myasthenic mothers who are in remission (62). The antibody type can be different between mother and affected infant, suggesting that affected infants can synthesize ACh receptor antibodies. Host factors are probably important in determining whether an infant becomes symptomatic, but the nature of these factors is unclear (61). There are no reliable predictive factors based on maternal severity of disease. However, mothers that have had an infant with neonatal MG have a higher likelihood of another affected child (60). Thus, every infant born to a myasthenic mother should be watched carefully in an intensive care unit for weakness and respiratory failure. Conversely, if there is no sign of neonatal MG after 5 to 10 days, the likelihood of an infant developing weakness because negligible. Once weakness begins, respiratory failure can occur precipitously; however, the course is usually a self-limited disorder with symptoms lasting weeks to months. Diagnosis is made by a test dose of edrophonium or diagnostic repetitive nerve stimulation (63,64).

**Treatment**

Treatment is based on severity of symptoms (65). Pyridostigmine alone is generally sufficient. Exchange transfusions have been performed with variable results, presumably because some infants with neonatal MG synthesize their own ACh receptor antibodies (61). Respiratory support may be necessary.

**CONGENITAL OR GENETIC MYASTHENIA GRAVIS**

Congenital MG represents a different spectrum of disorders, each due to a unique genetic defect in NMJ transmission (65). Most are genetic mutations with autosomal dominant and recessive modes of inheritance that alter NMJ structure or enzymatic function (66). Table 6 lists the known forms of congenital MG. Antibodies to the ACh receptor are never present. Before the acquired autoimmune nature of MG was realized, families of patients with congenital MG were known as familial infantile myasthenia.

Congenital MG is clinically characterized by early and relatively fixed degrees of weakness. The pattern of weakness is similar to immune-mediated MG and includes ptosis and extraocular, proximal limb, oropharyngeal, and even respiratory muscle weakness. There can be clinical exacerbations with marked increases that culminate in crisis. Weakness or hypotonia in early childhood may erroneously be ascribed to other genetic or birth problems. Alternatively, early weakness may be so mild as to escape appreciation and not come to clinical attention again until childhood or even adulthood. Under these circumstances, a diagnosis of immune-mediated MG may be entertained.

Congenital MG responds poorly to pyridostigmine and usually not at all to immunomodulating therapy. A course of ephedrine given 15 mg orally three times daily may be effective in suspected cases.

The diagnosis of congenital MG should be entertained in any child with a diagnosis of MG that has been refractory to all modes of therapy. Further support for the diagnosis comes from inspection of early childhood pictures, looking for ptosis or hyperextension of the neck to achieve forward gaze. It should also be considered when other family members have had similar symptoms. Routine electrophysiologic testing does not differentiate between immune-mediated and congenital cases; however, certain presynaptic forms of congenital MG may show facilitation after exercise, and two forms, one due to end-plate AChE deficiency and the other to a slow-channel syndrome, may show a repetitive discharge after the CMAP following a single shock (Table 6). The meaningful investigation of these syndrome requires sophisticated morphologic and electrophysiologic studies of the NMJ usually available at only a few centers with a specific interest in these disorders.

**LAMBERT-EATON MYASTHENIC SYNDROME**

The association of small cell lung cancer (SCLC) and a myasthenic syndrome clinically and electrophysiologically was described by Lambert and coworkers in 1957 (67). The so-called LEMS is one of the best examples of an antibody-mediated paraneoplastic disease.