**TABLE 461-1 DIAGNOSIS OF MYASTHENIA GRAVIS (MG)**

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| History |
| Diplopia, ptosis, dysarthria, dysphagia, dyspnea |
| Weakness in characteristic distribution: proximal limbs, neck extensors, generalized |
| Fluctuation and fatigue: worse with repeated activity, improved by rest |
| Effects of previous treatments |
| Physical examination |
| Ptosis, diplopia |
| Motor power survey: quantitative testing of muscle strength |
| Forward arm abduction time (5 min) |
| Vital capacity measurement |
| Absence of other neurologic signs |
| Laboratory testing |
| Anti-AChR radioimmunoassay: ~85% positive in generalized MG; 50% in ocular MG; definite diagnosis if positive; negative result does not exclude MG; ~40% of AChR antibody–negative patients with generalized MG have anti-MuSK antibodies |
| Repetitive nerve stimulation: decrement of >15% at 3 Hz: highly probable |
| Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific |
| Edrophonium chloride (Enlon®) 2 mg + 8 mg IV; highly probable diagnosis if unequivocally positive |
| For ocular or cranial MG: exclude intracranial lesions by CT or MRI |

***Abbreviations:*** AChR, acetylcholine receptor; CT, computed tomography; MRI, magnetic resonance imaging; MuSK, muscle-specific tyrosine kinase.

patients, the weakness becomes generalized, affecting the limb muscles as well. If weakness remains restricted to the extraocular muscles for 3 years, it is likely that it will not become generalized, and these patients are said to have *ocular MG*. The limb weakness in MG is often proximal and may be asymmetric. Despite the muscle weakness, deep tendon reflexes are preserved. If weakness of respiration becomes so severe as to require respiratory assistance, the patient is said to be in *crisis*.

## DIAGNOSIS AND EVALUATION

(Table 461-1) The diagnosis is suspected on the basis of weakness and fatigability in the typical distribution described above, without loss of reflexes or impairment of sensation or other neurologic function. The suspected diagnosis should always be confirmed definitively before treatment is undertaken; this is essential because (1) other treatable conditions may closely resemble MG and (2) the treatment of MG may involve surgery and the prolonged use of drugs with potentially adverse side effects.

**Antibodies to AChR, MuSK, or lpr4** As noted above, anti-AChR antibodies are detectable in the serum of ~85% of all myasthenic patients but in only about 50% of patients with weakness confined to the ocular muscles. The presence of anti-AChR antibodies is virtually diagnostic of MG, but a negative test does not exclude the disease. The measured level of anti-AChR antibody does not correspond well with the severity of MG in different patients. However, in an individual patient, a treatment-induced fall in the antibody level often correlates with clinical improvement, whereas a rise in the level may occur with exacerbations. Antibodies to MuSK have been found to be present in ~40% of AChR antibody–negative patients with generalized MG, and their presence is a useful diagnostic test in these patients. MuSK antibodies are rarely present in AChR antibody–positive patients or in patients with MG limited to ocular muscles. These antibodies may interfere with clustering of AChRs at neuromuscular junctions, as MuSK is known to do during early development. A small proportion of MG patients without antibodies to AChR or MuSK may have antibodies to lrp4, although a test for lrp4 antibodies is not yet commercially available. Finally, antibodies against agrin have recently been found in some patients with MG. Agrin is a protein derived from motor nerves that normally binds to lrp4 and thus may also interfere with clustering of AChRs at neuromuscular junctions. There may well be other—as yet undefined—antibodies that impair neuromuscular transmission.

**Electrodiagnostic Testing** Repetitive nerve stimulation may provide helpful diagnostic evidence of MG. Anti-AChE medication is stopped 6–24 h before testing. It is best to test weak muscles or proximal muscle groups. Electric shocks are delivered at a rate of two or three per second to the appropriate nerves, and action potentials are recorded from the muscles. In normal individuals, the amplitude of the evoked muscle action potentials does not change at these rates of stimulation. However, in myasthenic patients, there is a rapid reduction of >10–15% in the amplitude of the evoked responses.

**Anticholinesterase Test** Drugs that inhibit the enzyme AChE allow ACh to interact repeatedly with the limited number of AChRs in MG, producing improvement in muscle strength. Edrophonium is used most commonly for diagnostic testing because of the rapid onset (30 s) and short duration (~5 min) of its effect. An objective end point must be selected to evaluate the effect of edrophonium, such as weakness of extraocular muscles, impairment of speech, or the length of time that the patient can maintain the arms in forward abduction. An initial IV dose of 2 mg of edrophonium is given. If definite improvement occurs, the test is considered positive and is terminated. If there is no change, the patient is given an additional 8 mg IV. The dose is administered in two parts because some patients react to edrophonium with side effects such as nausea, diarrhea, salivation, fasciculations, and rarely with severe symptoms of syncope or bradycardia. Atropine (0.6 mg) should be drawn up in a syringe and ready for IV administration if these symptoms become troublesome. The edrophonium test is now reserved for patients with clinical findings that are suggestive of MG but who have negative antibody and electrodiagnostic test results. False-positive tests occur in occasional patients with other neurologic disorders, such as amyotrophic lateral sclerosis, and in placebo-reactors. False-negative or equivocal tests may also occur. In some cases, it is helpful to use a longer-acting drug such as neostigmine (15 mg PO), because this permits more time for detailed evaluation of strength.

**Inherited Myasthenic Syndromes** The congenital myasthenic syndromes (CMS) comprise a heterogeneous group of disorders of the neuromuscular junction that are not autoimmune but rather are due to genetic mutations in which virtually any component of the neuromuscular junction may be affected. Alterations in function of the presynaptic nerve terminal, in the various subunits of the AChR, AChE, or the other molecules involved in end-plate development or maintenance, have been identified in the different forms of CMS. These disorders share many of the clinical features of autoimmune MG, including weakness and fatigability of skeletal muscles, in some cases involving extraocular muscles (EOMs), lids, and proximal muscles, similar to the distribution in autoimmune MG. CMS should be suspected when symptoms of myasthenia have begun in infancy or childhood and AChR antibody tests are consistently negative. By far the most common genetic defects occur in the AChR or other postsynaptic molecules (67% in the Mayo Clinic series of 350 CMS patients), with about equal frequencies of abnormalities in AChE (13%) and the various maintenance molecules (DOK7, GFPT, etc.; ~14%). In the forms that involve the AChR, a wide variety of mutations have been identified in each of the subunits, but the ε subunit is affected in ~75% of these cases. In most of the recessively inherited forms of CMS, the mutations are heteroallelic; that is, different mutations affecting each of the two alleles are present. Features of the four most common forms of CMS are summarized in Table 461-2. Although clinical features and electrodiagnostic and pharmacologic tests may suggest the correct diagnosis, molecular analysis is required for precise elucidation of the defect; this may lead to helpful treatment as well as genetic counseling.

**Differential Diagnosis** Other conditions that cause weakness of the cranial and/or somatic musculature include the nonautoimmune CMS discussed above, drug-induced myasthenia, Lambert-Eaton myasthenic syndrome (LEMS), neurasthenia, hyperthyroidism (Graves' disease), botulism, intracranial mass lesions, oculopharyngeal dystrophy, and mitochondrial myopathy (Kearns-Sayre syndrome, progressive external ophthalmoplegia). Treatment with penicillamine (used for scleroderma or rheumatoid arthritis) may result in true autoimmune