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Neuromuscular Junction Disease

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Neuromuscular junction diseases are caused by abnormal neuromuscular transmission of the action potential from the nerve terminal to the muscle, and they can be autoimmune (myasthenia gravis, Lambert Eaton Syndrome), hereditary (congenital myasthenic syndromes), or toxic (botulism, organophosphate intoxication).

MYASTHENIA GRAVIS

Definition/Epidemiology/Pathology

Myasthenia gravis (MG) is a rare autoimmune disease caused by antibodies against the postsynaptic acetylcholine receptors (AChR Ab) in the neuromuscular junction. All ages are affected but incidence is higher in women younger than 40, and in men older than 50. Prevalence is approximately 20 in 100,000. Transient neonatal MG occurs in about 12% of newborns of myasthenic mothers and is caused by transplacental passive transfer of antibodies from the mother to the fetus. Thymoma is found in 10% of patients with MG and thymic hyperplasia is present in 65%.

Clinical Presentation

MG is characterized by fluctuating, fatigable weakness either isolated to the ocular muscles (ocular MG), or involving ocular as well as limb, bulbar, and respiratory muscles (generalized MG). The majority of patients present first with ocular symptoms (blurred vision, double vision, droopy eyelids), but about 15% of cases present with bulbar symptoms first (dysarthria, dysphagia, shortness of breath), or limb weakness. Ptosis is usually asymmetric. Myasthenia crisis is a true neurological emergency that occurs in 15% to 20% of patients and consists of severe dysphagia or respiratory failure requiring ventilator support and/or tube feeding in an ICU setting.

Diagnosis and Differential Diagnosis

The diagnosis of MG is based on a combination of clinical history, physical examination, and confirmatory tests. The ice pack test is a simple and relatively sensitive test to differentiate ptosis caused by MG from other causes of ptosis. In this test an ice pack is applied to the ptotic eye for 2 minutes and an improvement of 2 mm or more in ptosis supports MG.

Edrophonium chloride (Tensilon) is a short-acting acethylcholinesterase inhibitor administered IV to demonstrate symptom improvement in patients with MG. A positive Tensilon test is defined as an unequivocal improvement in strength in an affected muscle after 2 to 5 minutes from administration of 2 mg incremental doses up to 10 mg. Atropine should be available during a tensilon test because bradychardia and hypotension are possible side effects. Edrophonium testing can be positive in other disorders.

Electrodiagnostic testing with 3 Hz repetitive nerve stimulation (RNS) demonstrates a compound muscle action potential (CMAP) decrement more than10% in about 50% to 75% of patients with generalized MG, but is abnormal in less than 50% of patients with purely ocular symptoms. Single fiber electromyography (SFEMG) is the most sensitive test in the diagnosis of MG and reveals increased jitter and blocking in 99% of patients with generalized MG, and in 97% of those with purely ocular MG when a weak muscle is tested. SFEMG is usually available only in specialized EMG laboratories.

Serum antibody testing for AchR Ab (binding antibody) is positive in about 80% of patients with generalized MG, and 50% of patients with purely ocular symptoms. Anti MuSK antibody is detected in a portion of seronegative patients, usually men.

Chest CT should be performed to rule out thymoma. Thyroid function should be evaluated because thyroid disease is commonly associated with MG. Electrodiagnostic and serum antibody testing help with differentiating MG from motor neuron disease, Lambert-Eaton myasthenic syndrome (LEMS), and Guillain-Barre syndrome (GBS).

Treatment

Pyridostigmine 30 to 60 mg every 4 hours improves symptoms in most patients with MG; it is used alone to treat purely ocular and generalized cases with only minimal or mild weakness, or in combination with immunosuppressant drugs in patients with more severe manifestations. Prednisone is effective in improving muscle weakness in a short period of time, but long-term use is associated with side effects. Azathioprine and mycophenolate mofetil are used for long-term treatment and as steroids-sparing agents. Plasmapheresis and IVIG are used for cases with severe bulbar or generalized weakness, respiratory crisis, and in refractory patients who do not respond to oral immunomodulating medications. Thymoma resection is indicated in all patients with MG and thymoma. Thymectomy is also recommended as an option in patients with nonthymomatous autoimmune MG to increase the probability of remission or improvement. Thymectomy is usually not recommended in patients over age 60. Some medications may exacerbate the symptoms of MG or precipitate the initial signs and symptoms of the disease (Table 123-1).

Prognosis

Most patients with MG who are optimally treated experience improvement or remission of their symptoms. About 10% of