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Learning Outcomes

On completion of this exercise, the participant should be able to:

- describe neurologic diseases such as myasthenia gravis (MG) and chronic inflammatory demyelinating polyneuropathy (CIDP);
- identify neurologic tests that are used to diagnose these diseases; and
- discuss treatment options for these diseases.

Educational Commentary

Neurologic autoimmune diseases are caused by antibodies against the body’s own nervous system structures, most often neural receptors. Diseases such as myasthenia gravis (MG) and chronic inflammatory demyelinating polyneuropathy (CIDP) are neurologic disorders mediated by immune dysregulation.

Myasthenia Gravis

Myasthenia gravis affects 8 to 10 per 1 million persons annually.\(^1\) It has a bimodal age distribution, affecting individuals in either the second to third decades or sixth to eighth decades.\(^2\)

Generalized and ocular MG are the two clinical forms of the disease. This neuromuscular transmission disorder is caused by the development of autoantibodies to neural receptors at neuromuscular junctions, such as the acetylcholine receptors (AChR), muscle-specific kinase receptors (MuSK), and the lipoprotein receptor–related protein 4 (LRP4).\(^1,3\) When bound, these antibodies cause symmetric, proximal skeletal muscle weakness, which worsens with repetitive muscular activity. The muscles that are predominantly affected are the muscles of the mouth and throat, respiratory tract, and limbs. When present, ocular weakness affects the eyes asymmetrically.\(^1,4\) Ocular MG is present in 15% of patients diagnosed as having MG.\(^1,4\) This symptom causes weakness and fatigability of the extraocular muscles, leading to drooping of the eyelids and double vision.

Myasthenia gravis can be further subgrouped by the presence or lack of a detectable antibody (seropositivity or seronegativity, respectively); if seropositive, it is further classified by the receptor to which the antibody binds, or the presence of thymoma.\(^1\) Prognosis and treatment of MG may vary depending on subgroup. For example, patients who are MuSK antibody–positive respond to treatment with therapeutic plasma exchange (TPE) rather than intravenous immunoglobulin (IVIG).
EDUCATIONAL COMMENTARY – NEUROLOGIC AUTOIMMUNE DISEASES (cont.)

Diagnosis

In the natural progression of MG, symptoms are mild early in the disease, with worsening and persistence as the disease progresses. For most patients, maximal weakness develops within two to three years of disease onset.\textsuperscript{5,6} Myasthenia gravis is diagnosed by reviewing the patient’s medical history and laboratory testing and imaging results. Tests include the edrophonium test, the ice pack test, and serologic and electrophysiologic testing.

Bedside testing includes edrophonium testing and the ice pack test. Edrophonium chloride is an acetylcholinesterase inhibitor that causes an increase in ocular muscle strength.\textsuperscript{7} This test should be performed in patients with drooping eyelids or ptosis only. The test is very sensitive, meaning that there is a high chance of a false-positive result. The ice pack test is an alternate bedside test, performed by placing an ice pack on the eyelid to improve neuromuscular transmission, thus strengthening the eyelid.\textsuperscript{8}

Serologic testing for autoantibodies is the laboratory confirmation of the disease. Blood for this test should be drawn before initiating immunotherapy. AChR antibodies are found in approximately 98% of patients with MG and thymoma.\textsuperscript{9} However, antibody titers do not correlate well with disease severity. MuSK antibodies are found in approximately 40% of patients who are seronegative for AChR antibodies.\textsuperscript{10} Persons who are MuSK positive usually do not have associated thymic disease. Seronegativity is also seen in patients with MG, as there are potentially many antibodies mediating MG that have not yet been identified.

Electrophysiologic testing includes repetitive nerve stimulation and single-fiber electromyography. Repetitive nerve stimulation is performed by stimulating the motor nerve to a particular muscle. The nerve stimulation is recorded by an electrode placed over the endplate regions of the muscle. A decrement in nerve response indicates disorders of neuromuscular transmission, including MG. Single-fiber electromyography is a more sensitive test for MG than repetitive nerve stimulation. This test is more technically challenging, as it records the neuromuscular transmission of several muscle fibers by one motor axon.\textsuperscript{11}

Mediastinal imaging can be used to detect a thymoma, which can affect the patient’s prognosis.

Treatment

There are multiple treatment options for MG, including cholinesterase inhibitors, thymectomy, immunosuppression, TPE, and IVIG.\textsuperscript{12}

Cholinesterase inhibitors are effective in MG and work by increasing the release of acetylcholine in the presynaptic cleft.\textsuperscript{1} Patients who are MuSK positive do not respond as well to this treatment as persons with the other subgroups of MG. This is an effective sole treatment for those with mild disease.
Immunosuppressive treatments such as prednisone, azathioprine, mycophenolate mofetil, and rituximab are also options in patients whose symptoms are not adequately controlled by cholinesterase inhibitors. These medications have different mechanisms of action to decrease the persistent MG symptoms of weakness and fatigue. They can produce adverse effects, such as abdominal cramping, decreased heart rate, and sweating, and it may take months before a therapeutic benefit is seen.

Removal of the thymus gland, thymectomy, leads to delayed improvement with some patients experiencing improvements years postthymectomy.

Therapeutic plasma exchange is used to decrease the titers of the autoantibodies by removing the patient’s plasma and exchanging it with a replacement fluid such as albumin. According to the American Society for Apheresis guidelines, TPE is a category I treatment for moderate to severe MG and individuals with MG before thymectomy. The term category I treatment for a disease or indication means that it can be used as a first-line treatment for that disease. The treatment protocol is a 1.0 plasma volume exchange daily or every other day for 2 weeks followed by a taper. Although the therapeutic benefit of TPE may be seen early, the effect is not sustained long-term unless immunosuppressive therapies are part of the treatment regimen.

Intravenous immunoglobulin treatment uses pooled donor immunoglobulin. The mechanism of action is unknown but symptomatic improvement can be seen early, with improvement lasting 3 to 6 weeks. A comparison of TPE and IVIG showed that TPE was potentially more effective than IVIG in patients with impending respiratory failure.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy is an autoimmune disease that affects the peripheral nerves and nerve roots. Similar to MG, it is a common autoimmune neuropathy. The cause of CIDP remains uncertain but the disease is believed to be mediated by both antibody and T-cell immune responses. The target antigens of the antibodies are currently unknown. Studies have postulated several antibodies to myelin components including β-tubulin and GM1. There is also an increase in inflammatory cytokines such as tumor necrosis factor and interleukins. This disease, which is believed to be underdiagnosed, affects 1 to 2 per 100,000 adults. It affects individuals in the third and sixth decades. CIDP is heterogenous and has many subgroups including Lewis-Sumner syndrome, sensory-predominant CIDP and CIDP with central nervous system involvement. The classic form of the disease causes symmetric proximal and distal muscle weakness, peripheral nerve tingling, depressed reflexes, and balance problems. The disease progressively worsens within 2 months of onset.
EDUCATIONAL COMMENTARY – NEUROLOGIC AUTOIMMUNE DISEASES (cont.)

Diagnosis

Chronic inflammatory demyelinating polyneuropathy is diagnosed by reviewing the patient’s medical history, laboratory testing, and muscle biopsy showing peripheral nerve demyelination. Because of the complexity in diagnosing CIDP, many diagnostic criteria have been published to aid the physician, including the Koski classification and the European Federation of Neurological Societies / Peripheral Nerve Society (EFNS/PNS) Guideline. Electrodiagnostic testing shows slow conduction velocity, conduction blocks, and reduced evoked potential amplitude. Cerebrospinal fluid analysis shows dramatically elevated protein levels (6-fold increase) with a normal white blood cell count. Muscle biopsy shows demyelination and remyelination of the peripheral nerves. Cerebrospinal fluid testing and muscle biopsy are not required for diagnosing CIDP but are helpful in patients with inconclusive electrodiagnostic results.

Treatment

Treatment for CIDP includes corticosteroids, immunosuppressive therapies, TPE, and IVIG to help increase strength, motor performance, and balance. Patients with CIDP are first treated with high-dose steroids (80-100 mg/d) for at least 1 month. The medication is slowly tapered. There are long-term adverse effects, including triggering of diabetes, osteoporosis, and the formation of cataracts. Immunosuppressive drugs such as cyclosporine, azathioprine, and methotrexate can be used as secondary treatment in patients with progressive CIDP symptoms. Therapeutic plasma exchange and IVIG are equivalent treatments based on clinical trials that compared their efficacy.

Therapeutic plasma exchange is a category I treatment for CIDP, used as a first-line treatment for this disease. In clinical trials, patients with CIDP who were treated with TPE had better motor function, motor amplitude, and nerve conduction. Patients with CIDP who are not ambulatory cannot be tapered from corticosteroids, and nonresponders to IVIG should receive TPE as part of their treatment plan. The treatment plan varies but a suggested plan is two to three TPE treatments per week until the patient improves, followed by a taper.

Conclusion

Neurological disorders such as MG and CIDP are autoimmune disorders affecting nervous system structures. These disorders can be appropriately diagnosed using various neurologic and laboratory testing methods and can be treated with medications and therapies such as therapeutic plasma exchange.
References


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