

Neuromuscular Junction (NMJ) Disorders (Dr. Merchut)

The Neuromuscular Junction (NMJ)

1. Normal and abnormal physiology

During normal muscle contraction, specific lower motor neurons are depolarized and fire action potentials. When action potentials reach the motor neuron terminals, calcium influx facilitates presynaptic release of acetylcholine (ACh) from vesicles. ACh binds at specific nicotinic acetylcholine receptors (AChR) in the end plates of the postsynaptic muscle membrane, activating ion channels and creating an end plate potential (EPP). Normally, the EPP far exceeds the threshold required to generate a muscle fiber action potential, which then spreads through the muscle fiber, causing it to contract. When many muscle fibers are simultaneously activated, the muscle can be observed to contract.

This effect of ACh and its EPP are limited by synaptic acetylcholinesterase (AChE), which breaks down ACh. During repetitive muscle contractions or exercise, lesser amounts of ACh are released from motor neuron terminals. Although the EPP amplitudes are thereby decreased, they still remain above the threshold for generating muscle fiber action potentials, and adequate muscle contraction is still achieved. This is the "safety factor" at normal neuromuscular junctions. In myasthenia gravis, in which many AChR are degraded or blocked, less ACh is able to bind, producing EPPs which are either initially below the threshold for generating muscle fiber action potentials or which become too low during repeated muscle contractions. Clinically weakness then occurs at rest or after repeated activity or exercise. Myasthenic weakness can be improved by drugs that inhibit AChE, effectively increasing the amplitude and duration of the EPP.

Myasthenia gravis (MG) is an autoimmune disorder of the **postsynaptic** NMJ. Although less common than MG, two other NMJ disorders worth mentioning involve the **presynaptic** NMJ, where the release of ACh is impaired. Lambert-Eaton myasthenic syndrome (LEMS) is also an autoimmune disease, but the target is the voltage-gated calcium channel at the presynaptic membrane, not the AChR. In botulism, which will be discussed further in the section on Intoxications of the Nervous System, a bacterial toxin binds presynaptically at the NMJ, preventing ACh release and causing weakness. (Congenital myasthenia refers to a few rare inborn disorders of the NMJ which are usually familial and will not be discussed further here.)

Myasthenia Gravis (MG)

1. The immune system and MG

Myasthenia gravis is an autoimmune disease, where the otherwise normally functioning immune system inappropriately reacts to a specific, normal self-antigen. With the help of T-cells, B-cells produce antibodies which block and destroy AChRs faster than new AChRs can be synthesized. The normal architecture and folding of the postsynaptic NMJ is lost when viewed under electron microscopy. The thymus gland,

critical for T-cell development, appears to be an important factor in the etiology of MG. In most myasthenic patients, abnormalities of the thymus occur, consisting more commonly of glandular enlargement or hyperplasia, and less commonly of a thymic tumor or thymoma. The thymus may be where myasthenic autoimmunity begins, but the actual triggers or inciting events are unknown.

2. Clinical features of MG

Autoimmune myasthenia gravis can begin at any age, from childhood to late adult life, with a prevalence of 20 people per 100,000 (Phillips LH. Ann NY Acad Sci 2003). As a neuromuscular junction disorder, it causes only motor symptoms manifest as weakness and fatigue of skeletal muscles, without pain, sensory or cognitive impairment. Fatigue here refers to muscular weakness encountered during non-strenuous activity, such as chewing a meal, climbing a flight of stairs, having a conversation, or watching a movie. Fatigue here does not refer to lack of sleep, exhaustion or feeling "tired all over." The most common initial symptoms include **ptosis** (eyelid drooping), **diplopia** (double vision from asymmetrically weak extraocular muscles), **dysarthria** (slurred speech), and **dysphagia** (weakness of swallowing). These may be present on awakening and remain fairly constant throughout the day in some patients. Others will feel fine in the morning after a night's rest, but develop symptoms later in the day, especially after sustained activity or exertion. For example, dysarthria may occur only after a long conversation, or diplopia may occur after reading for an hour; both may improve or resolve after a period of rest. Some patients have milder or more localized symptoms which only slowly become troublesome, while others may have more severe, fulminant weakness that involves most of the body. Asymmetrical weakness is common, with more droopiness of one eyelid, or more "crookedness" of one eye. When attempting to smile, a horizontal snarl may result, or the face may sag (see Fig. 1). One or more limbs can likewise weaken, while respiratory weakness or choking are ominous signs. The severity or extent of weakness and fatigue may vary from hour to hour or day to day. On examination, sensation, muscle stretch reflexes, cognition, and higher cortical functions remain normal, with muscle atrophy developing only rarely in severe MG of long duration.

Although many myasthenic patients have initial symptoms of only ptosis or diplopia, only a minority of them, about 10-20%, will continue to have only these visual symptoms after 2 to 3 years time. This is **ocular myasthenia**, a restricted form of MG. The majority of MG patients, about 80-90%, eventually develop **generalized myasthenia gravis**, having more than just visual or ocular symptoms. In **neonatal myasthenia**, healthy newborns of myasthenic mothers may have MG symptoms for a few days, until maternal antibodies "wash out" of their system. In **myasthenic crisis**, profound weakness may cause quadriplegia, with the patient unable to speak, swallow or breathe. Myasthenic crisis may be suddenly triggered by a serious infection or other systemic illness in a myasthenic patient, or may unpredictably develop over days in someone with severe MG. It is a neurological emergency often requiring intubation and mechanical ventilation, intensive care in the hospital, treatment of any concurrent infection and acute, aggressive treatment of MG itself.

It should be noted that a few other neurological conditions besides myasthenic crisis cause acute paralysis of speech, chewing, swallowing, limb and respiratory

muscles. All these patients need emergent intensive care and ventilatory support, often before the specific cause is identified. The differential diagnosis includes an extensive infarction of the brain stem, where hyper-reflexia may be noted, and the lesion confirmed by MRI scan. Guillain-Barre syndrome usually evolves over a few days, with areflexia and sensory impairment accompanying the weakness, the diagnosis confirmed by electromyography (EMG) and an elevated cerebrospinal fluid protein (see "Neuropathy, Myopathy and Motor Neuron Disease"). Acute paralysis from a spinal cord lesion spares the cranial nerves and has a localizing level of sensory loss, sometimes with neck or back pain (see "Spinal Cord Disorders"). Spinal cord MRI reveals any causative tumor or inflammation (multiple sclerosis, viral myelitis), which may begin to improve with intravenous corticosteroids. In myasthenic crisis, sensation and reflexes remain normal.



Fig. 1 Signs of myasthenia gravis. Despite contraction of forehead muscles, the eyelids still droop (ptosis). An open-mouthed snarl demonstrates facial weakness when smiling.

3. Diagnosis of MG

The clinical history should be very suggestive or typical of MG, since the examination of a rested patient early in the day may be neurologically normal. If a truly objective sign of weakness is present, such as ptosis, marked improvement after injection of an acetylcholinesterase inhibitor drug like edrophonium (Tensilon) strongly suggests

MG. In the electromyography laboratory, myasthenic patients undergoing repetitive nerve stimulation or single fiber jitter analysis may show NMJ abnormalities typical of MG. The **most specific** diagnostic test for MG is the presence of **serum AChR antibodies**. These are detected in 80-90% of patients with generalized MG, but only in about half of those with the restricted form of ocular MG. Some of the 10-20% of seronegative patients with generalized MG have been found to have serum antibodies to MuSK (muscle specific receptor tyrosine kinase), an NMJ protein important for the clustering of AChRs.

4. Treatment of autoimmune MG

Historically, weak myasthenic patients appeared similar to those poisoned by curare, an NMJ antagonist, and their muscles would weaken when given very small amounts of curare which had no effect on normal muscles. This led in 1934 to the first successful use of a cholinesterase inhibitor in treating MG by Mary Walker, a London medical resident. Today, oral **anticholinesterase drugs**, most commonly pyridostigmine (Mestinon), are the first treatment of MG. Dose escalation must be monitored closely since high doses may produce a **cholinergic crisis**, consisting of weakness, sweatiness, salivation, diarrhea, and excessive urination. Anticholinesterase drugs may be the only treatment needed in some patients, whereas others require the addition of immunosuppressant drugs. Some patients go into remission, whether spontaneously or after treatment, and their symptoms gradually disappear.

In 1939, Blalock removed a thymoma, previously irradiated, from a myasthenic woman who struggled through several myasthenic crises, only to slowly improve postoperatively and achieve remission years later. From then on, **thymectomy** was often performed in younger myasthenics without thymoma, benefitting some patients. A controlled, randomized trial of thymectomy for MG remains to be completed however.

Various **immunosuppressant drugs** are also used to treat MG, unfortunately not selectively inhibiting production of AChR antibodies, but suppressing the immune system as a whole. These include **corticosteroids**, especially prednisone, and drugs commonly given to organ transplant patients, like azathioprine, mycophenolate, and cyclosporine. In the setting of myasthenic crisis, where severe weakness is life-threatening and rapidly effective treatment is needed, **intravenous immunoglobulin (IVIG) or plasmapheresis** are used. The gamma globulin component of plasma, containing all circulating antibodies as well as anti-AChR, is physically removed by a plasmapheresis machine through which a patient's blood is pumped. This removal of circulating anti-AChR temporarily improves MG symptoms. The exact mechanism by which IVIG helps MG is less clear, but may involve down-regulation of the immune system triggered by high levels of infused circulating antibodies, or infusion of unknown antibodies which attack or block the action of anti-AChR. IVIG also has a temporary therapeutic benefit.

Lambert-Eaton Myasthenic Syndrome (LEMS)

1. Clinical features of LEMS

As another NMJ disorder, muscle fatigue and weakness occur in LEMS, but tend to affect the proximal muscles of the shoulders and hips as well as the trunk, mimicking the weakness also seen in a myopathy. Symptoms do not usually involve the eyes, swallowing, or speech. Muscle stretch reflexes may appear decreased, but reappear along with improved strength after a brief period of isometric exercise, which can be tested during the bedside examination. LEMS also differs from MG in that autonomic symptoms may occur, such as dry mouth, orthostatic hypotension, or erectile dysfunction. In a majority of LEMS patients, the autoimmune dysfunction is related to an underlying cancer, most often **small cell carcinoma of the lung**, while in a minority of patients the autoimmune trigger remains unknown. Again, sensory deficits, cognitive symptoms, and pain are not usually found in LEMS.

2. Diagnosis and treatment of LEMS

Repetitive nerve stimulation and other tests in the electromyography laboratory usually show presynaptic NMJ abnormalities typical of LEMS. In many patients a serum antibody to the voltage-gated calcium channel is found. A thorough search for a small cell carcinoma of the lung is needed, as this cancer may be only present as a tiny endobronchial lesion. If detected, treatment is primarily directed towards the underlying cancer. Strength and fatigue may improve with drugs that enhance the release of ACh, such as guanidine or 3,4-diaminopyridine. Immunosuppressant drugs and plasmapheresis benefit some patients. However, the treatment of LEMS is generally not as effective as that for MG.