

## Primer of Myasthenia Gravis

General: Myasthenia gravis (MG) is an autoimmune disorder affecting the neuromuscular junction, resulting in fatigable weakness.

Clinical features: MG is an acquired disease affecting transmission at the neuromuscular junction of action potentials from nerve terminals to muscle fibers. Weakness can present at any age, from childhood to late adulthood. The distribution of weakness varies, and has been divided into ocular, bulbar and generalized distributions, with various combinations. Ocular MG primarily affects eye lid strength (resulting in ptosis) and the muscles that move the eyes (resulting in diplopia). Bulbar MG affects the tongue and swallowing (resulting in dysarthria and dysphagia). Generalized MG affects primarily proximal limb muscles and may affect the diaphragm (resulting in respiratory compromise and failure). There is a marked component of fatigue that may become apparent over seconds to minutes of an activity, with partial recovery after seconds to minutes of rest. The overall course includes natural exacerbations and spontaneous

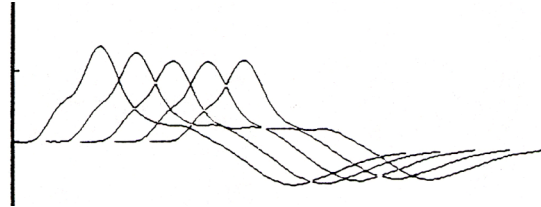
remissions over weeks to months, although in the current era most remissions are based on successful drug treatment and exacerbations during withdrawal. The spectrum and severity of weakness varies markedly, from subtle weakness challenging the accurate diagnosis for years, to life threatening respiratory weakness. In general, the pattern and severity establishes itself within a patient during the first five years after symptom onset. Thus, a patient with only ocular symptoms will likely not develop generalized weakness.

Genetics: MG is an acquired disease and not considered to be a genetic disorder, although there may be genetic susceptibilities with other organ-specific autoimmune disorders (type 1 diabetes mellitus, pernicious anemia, thyroiditis, vitiligo) with the patient or within the family. There is another distinct and unrelated disorder called congenital MG that represents genetic mutations affecting any of a number of enzymatic steps and proteins that are part of neuromuscular junction transmission. Congenital MG presents in infancy while autoimmune MG rarely presents in late childhood.

Diagnosis: The diagnosis of MG is based on clinical features of fatigable weakness in the above distributions. There are several tests that can aid in the diagnosis. MG is believed to be caused by antibodies attaching to proteins at the neuromuscular junction. Specific antibodies to the acetylcholine receptor can be detected in the serum in about 65% of patients (seropositive MG). Antibodies are more common in generalized MG (80%) and least in ocular MG (55%). The antibody titer value does not predict the severity of MG and serve primarily as a diagnostic marker.

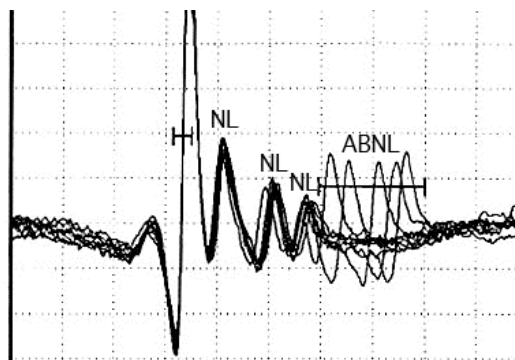
Seronegative MG is also felt to be antibody-mediated, but specific antibodies have not been identified. A new antibody, muscle-specific tyrosine-kinase (anti-MuSK), has recently been identified.

Defects in neuromuscular junction transmission can be detected by electrodiagnostic testing. The normal response to repetitive stimulation of a motor nerve is an unchanging response from the muscle. However, in MG there will be a characteristic decrement of the response with the third stimulus at 3 Hz stimulation frequency.



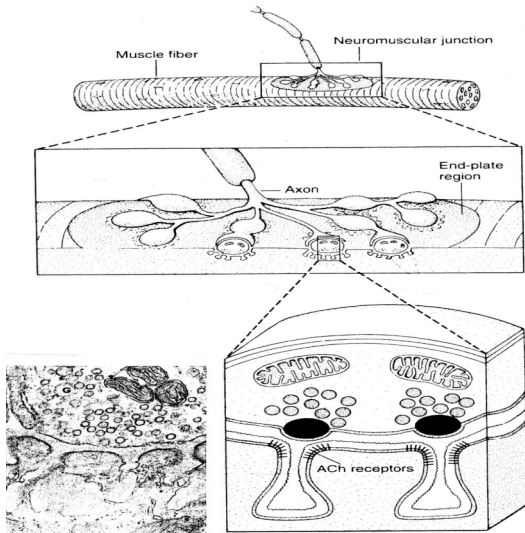
Decremental muscle response to 3Hz nerve stimulation (response amplitude drops with successive stimuli). Normal response would show no decrement.

The most sensitive test for a defect in neuromuscular junction transmission is single fiber EMG measurement of jitter. Normal neuromuscular transmission has a small degree of variability (normal jitter) measured in microseconds. With mild defects in transmission, which may not be apparent with repetitive stimulation testing, the degree of transmission variability will be excessive (abnormal jitter). Jitter is abnormal in 95% of weak muscles when weakness is due to MG.



Jitter measurements. Superimposed traces showing normal (NL) and abnormal (ABNL) jitter with impulse blocking.

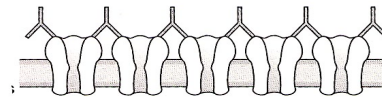
Pathogenesis: Every muscle fiber receives a terminal nerve branch at the neuromuscular junction where the nerve electrical impulse is transmitted to the muscle fiber. Every muscle has hundreds of thousands of muscle fibers and neuromuscular junctions.



Montague showing presynaptic nerve and terminal arborization forming a neuromuscular endplate region. Enlarged figure on right shows presynaptic terminal with vesicles containing acetylcholine (ACh) positioned over post synaptic folds with acetylcholine receptors. Electron micrograph on left shows similar structures.

The defect in neuromuscular junction transmission in seropositive MG is due to antibodies that recognize some portion of the acetylcholine receptor or surrounding membrane and cause complement-mediated

destruction of the receptor. This represents a failure of the immune system to recognize “self”, and thus the antibodies mount an attack on “self”. This failure in recognition is felt to involve the thymus gland, however the exact role of thymus gland is not clear. The pathogenesis for seronegative MG is less clear, but likely involves similar issues, although the thymus may not be involved.



Antibodies (upside-down “Y”) attached to acetylcholine receptors.

Treatment: Treatment falls into several categories. Pyridostigmine (Mestinon®) inhibits the enzyme acetylcholinesterase that rapidly hydrolyzes acetylcholine after it interacts with the receptor, resulting in more acetylcholine available to enhance interaction with the reduced number of receptors.

Immunosuppressive or immunomodulating drugs reduce the production of antibodies (seropositive MG) or inhibit other immunologic mechanisms (seronegative MG). Drugs include corticosteroids (prednisone),

Azathioprine (Imuran®) and mycophenolate mofetil (Cell-Sept®). Prednisone is the first choice, and is given in high dose (60 mg/day) for one month and slowly tapered to a low dose. Azathioprine and mycophenylate modafinil are steroid-sparing drugs. Intravenous immune globulin (IVIG) likely has a number of actions on the immune system, and is a second choice drug.

Plasmapheresis separates the cellular fraction of blood from plasma, and discarding the plasma reduces the concentration of circulating antibodies (seropositive MG) or other circulating factors (seronegative MG). However, antibodies and factors are renewed, and the effects of plasmapheresis are relatively short lived, and immunosuppressive and modulating drugs are usually given concurrently.

The role of removing the thymus (thymectomy) is controversial. If the thymus is enlarged or looks as if there is a tumor it should be removed (thymectomy). If it is of normal size removing it is not a surgical cure, and most patients require ongoing pharmacologic treatment.

Management: MG is a manageable disease. The spectrum and severity of symptoms varies markedly among patients as does their management strategies. Most patients require long-term immunosuppressive medication with the goal of the lowest dose. Markedly weak patients may not return to full strength, while mildly affective patients may return to relatively normal activity. Respiratory failure is rare, but is a concern in patients with brittle MG.