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Myasthenia Gravis

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Introduction

Background

Myasthenia gravis (MG) is an acquired autoimmune disorder characterized clinically by weakness of skeletal muscles and fatigability on exertion. Thomas Willis reported the first clinical description in 1672.

Pathophysiology

The antibodies in myasthenia gravis are directed toward the acetylcholine receptor (AChR) at the neuromuscular junction (NMJ) of skeletal muscles.

In 1960, Strauss demonstrated the presence of antibodies to muscle striations in serum of patients suffering from myasthenia gravis, implicating autoimmunity as the pathophysiological process.[1] Patrick and Lindstrom established the autoimmune origin of the disease when rabbits they immunized with the *Torpedo californica* AChR became myasthenic.[2]

To understand myasthenia gravis, familiarity with normal anatomy and functioning of NMJ is necessary. The nerve terminal of the motor nerve enlarges at its end, which is called the bouton terminale (terminal bulb). It lies within a groove or indentation along the muscle fiber. The presynaptic membrane (nerve membrane), postsynaptic membrane (muscle membrane), and synaptic cleft (space between the 2 membranes) together constitute the NMJ.

The presynaptic terminal contains vesicles filled with acetylcholine (ACh). On arrival of a nerve action potential, the contents of these vesicles are released into the synaptic cleft in a calcium-dependent manner. The released ACh molecules diffuse across the synapse and bind to the AChRs on the postsynaptic membrane.

AChR is a ligand-gated sodium channel that opens briefly upon binding ACh. This allows entry of sodium ions into the interior of the muscle cell, which results in partial depolarization of the postsynaptic membrane and generation of an excitatory postsynaptic potential (EPSP). If the number of open sodium channels reaches threshold, a self-propagating muscle action potential is generated in the postsynaptic membrane.

ACh molecules are hydrolyzed by the enzyme acetylcholinesterase (AChE), which is abundantly present at the neuromuscular junction. The surface area of the postsynaptic membrane is increased by infolding of the membrane adjacent to the nerve terminal (see Image 1). This enables the NMJ to utilize fully the ACh released. AChRs are present in small quantities over most of the muscle membrane surface but are concentrated heavily at the tips of the NMJs.

Adult AChR consists of 5 subunits (2 alpha, and 1 each of beta, gamma, and delta), each of which is a membrane-spanning protein molecule. Homology of AChR subunits exists among different species, which suggests that these encoding genes have evolved from a common ancestral gene. The subunits are arranged in a circular fashion, forming a central opening that functions as an ion channel (see Image 2). When an ACh molecule binds to the AChR, the AChR undergoes a 3-dimensional conformational change that opens the channel and results in increased sodium conductance.

Immunogenic mechanisms play important roles in the pathophysiology of myasthenia gravis. Supporting clinical observations include the presence of associated autoimmune disorders in patients suffering from myasthenia gravis (eg, autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis). Moreover, infants born to myasthenic mothers can develop a transient myasthenia-like syndrome. Patients with myasthenia gravis will have a therapeutic response to various immunomodulating therapies including plasmapheresis, corticosteroids, intravenous immunoglobulin (IVIg), other immunosuppressants, and thymectomy.

Anti-AChR antibody is found in approximately 80-90% of patients with myasthenia gravis. Experimental observations supporting an autoimmune etiology of myasthenia gravis include the following: Induction of a myasthenia-like syndrome in mice by injecting a large quantity of immunoglobulin G (IgG) from myasthenia gravis patients (ie, passive transfer experiments); demonstration of IgG and complement at the postsynaptic membrane in patients with myasthenia gravis; and induction of a myasthenia-like syndrome in rabbits immunized against AChR by injecting them with AChR isolated from *T californica.*

The exact mechanism of loss of immunologic tolerance to AChR, a self antigen, is not understood. Myasthenia gravis can be considered a B cell–mediated disease, as antibodies (a B cell product) against AChR are responsible for the disease. However, the importance of T cells in pathogenesis of myasthenia gravis is becoming increasingly apparent. The thymus is the central organ in T cell–mediated immunity, and thymic abnormalities such as thymic hyperplasia or thymoma are well recognized in myasthenic patients.

Antibody response in myasthenia gravis is polyclonal. In an individual patient, antibodies are composed of different subclasses of IgG. In

most instances, 1 antibody is directed against the main immunogenic region (MIR) on the alpha subunit. The alpha subunit is also the site of ACh binding, though the binding site for ACh is not the same as the MIR. Binding of AChR antibodies to AChR results in impairment of neuromuscular transmission in several ways, including the following: cross-linking 2 adjacent AChR by anti-AChR antibody, accelerating internalization and degradation of AChR molecules; causing complement-mediated destruction of junctional folds of the postsynaptic membrane; blocking the binding of ACh to AChR; and decreasing the number of AChRs at the NMJ by damaging the junctional folds on the postsynaptic membrane, with resultant decrease in available surface area for insertion of newly synthesized AChRs.

Patients without anti-AChR antibodies are recognized as seronegative myasthenia gravis (SNMG). Many of these patients with SNMG have antibodies against muscle-specific kinase (MuSK). MuSK plays a critical role in postsynaptic differentiation and clustering of acetyl choline receptors. The patients with anti-MuSK antibodies are predominantly female, and respiratory and bulbar muscles are frequently involved. Another group has reported patients having prominent neck, shoulder, and respiratory weakness.[3, 4]

Frequency

United States

Myasthenia gravis is uncommon. Estimated annual incidence is 2 per 1,000,000.

Mortality/Morbidity

Recent advances in treatment and care of critically ill patients have resulted in marked decrease in the mortality rate. The rate is now 3-4%, with principal risk factors being age older than 40 years, short history of severe disease, and thymoma. Previously, the mortality rate was as high as 30-40%.

Sex

The female-to-male ratio is said classically to be 6:4, but as the population has aged, the incidence is now equal in males and females.

Age

Myasthenia gravis presents at any age. Female incidence peaks in the third decade of life, whereas male incidence peaks in the sixth or seventh decade. Mean age of onset is 28 years in females and 42 years in males.

Transient neonatal myasthenia gravis occurs in infants of myasthenic mothers who acquire anti-AChR antibodies via placental transfer of IgG. Some of these infants may suffer from transient neonatal myasthenia due to effects of these antibodies.

Most of the infants born to myasthenic mothers possess anti-AChR antibodies at birth, yet only 10-20% develop neonatal myasthenia gravis. This may be due to protective effects of alpha fetoprotein, which inhibits binding of anti-AChR antibody to AChR. High maternal serum levels of AChR antibody may increase the chance of neonatal myasthenia gravis; thus, lowering the maternal serum titer during the antenatal period by plasmapheresis may be useful.

Clinical

History

Myasthenia gravis is characterized by fluctuating weakness increased by exertion. Weakness increases during the day and improves with rest. Presentation and progression vary.

- Extraocular muscle (EOM) weakness or ptosis is present initially in 50% of patients and occurs during the course of illness in 90%. Bulbar muscle weakness is also common, along with weakness of head extension and flexion.
    - Weakness may involve limb musculature with myopathiclike proximal weakness greater than distal muscle weakness.
    - Isolated limb muscle weakness as the presenting symptom is rare and occurs in fewer than 10% of patients.
- Patients progress from mild to more severe disease over weeks to months. Weakness tends to spread from the ocular to facial to bulbar muscles and then to truncal and limb muscles.[5]
    - On the other hand, symptoms may remain limited to the EOM and eyelid muscles for years.
    - Rarely, patients with severe, generalized weakness may not have associated ocular muscle weakness.
    - The disease remains ocular in only 16% of patients. About 87% of patients generalize within 13 months after onset.
    - In patients with generalized disease, the interval from onset to maximal weakness is less than 36 months in 83% of patients.
- Intercurrent illness or medication can exacerbate weakness, quickly precipitating a myasthenic crisis and rapid respiratory compromise.
- Spontaneous remissions are rare. Long and complete remissions are even less common. Most remissions with treatment occur during the first 3 years of disease.

- The Medical Scientific Advisory Board (MSAB) of the Myasthenia Gravis Foundation of America (MGFA) formed a Task Force in May 1997 to address the need for universally accepted classifications, grading systems, and methods of analysis for patients undergoing therapy and for use in therapeutic research trials. Thus, MGFA Clinical Classification was created.[6]
    - Class I
        - Any ocular muscle weakness
        - May have weakness of eye closure
        - All other muscle strength is normal
    - Class II
        - Mild weakness affecting other than ocular muscles
        - May also have ocular muscle weakness of any severity
    - Class IIa
        - Predominantly affecting limb, axial muscles, or both
        - May also have lesser involvement of oropharyngeal muscles
    - Class IIb
        - Predominantly affecting oropharyngeal, respiratory muscles, or both
        - May also have lesser or equal involvement of limb, axial muscles, or both
    - Class III
        - Moderate weakness affecting other than ocular muscles
        - May also have ocular muscle weakness of any severity
    - Class IIIa
        - Predominantly affecting limb, axial muscles, or both
        - May also have lesser involvement of oropharyngeal muscles
    - Class IIIb
        - Predominantly affecting oropharyngeal, respiratory muscles, or both
        - May also have lesser or equal involvement of limb, axial muscles, or both
    - Class IV
        - Severe weakness affecting other than ocular muscles
        - May also have ocular muscle weakness of any severity
    - Class IVa
        - Predominantly affecting limb and/or axial muscles
        - May also have lesser involvement of oropharyngeal muscles
    - Class IVb
        - Predominantly affecting oropharyngeal, respiratory muscles, or both
        - May also have lesser or equal involvement of limb, axial muscles, or both
    - Class V
        - Defined by intubation, with or without mechanical ventilation, except when used during routine postoperative management.
        - The use of a feeding tube without intubation places the patient in class IVb.

Physical

Variability in weakness can be significant and clearly demonstrable findings may be absent during examination. This may result in misdiagnosis (eg, functional disorder).

The physician must determine strength carefully in various muscles and muscle groups to document severity and extent of the disease and to monitor the benefit of treatment.

Another important aspect of the physical examination is to recognize a patient in whom imminent respiratory failure is imminent. Difficulty breathing necessitates urgent/emergent evaluation and treatment.

- Weakness can be present in a variety of different muscles and is usually proximal and symmetric.
- Sensory examination and deep tendon reflexes are normal.
- Facial muscle weakness
    - Weakness of the facial muscles is almost always present.
    - Bilateral facial muscle weakness produces a mask-like face with ptosis and a horizontal smile.
    - The eyebrows are furrowed to compensate for ptosis, and the sclerae below the limbi may be exposed secondary to weak lower lids.
    - Mild proptosis due to EOM weakness also may be present.

- Bulbar muscle weakness
  - Weakness of palatal muscles can result in a nasal twang to the voice and nasal regurgitation of food and especially liquids.
  - Chewing may become difficult.
  - Severe jaw weakness may cause the jaw to hang open (the patient may sit with a hand on the chin for support).
  - Swallowing may become difficult and aspiration may occur with fluids, giving rise to coughing or choking while drinking.
  - Weakness of neck muscles is common and neck flexors usually are affected more severely than neck extensors.
- Limb muscle weakness
  - Certain limb muscles are involved more commonly than others (eg, upper limb muscles are more likely to be involved than lower limb muscles).
  - In the upper limbs, deltoids and extensors of the wrist and fingers are affected most. Triceps are more likely to be affected than biceps. In the lower extremities, commonly involved muscles include hip flexors, quadriceps, and hamstrings, with involvement of foot dorsiflexors or plantar flexors less common.
- Respiratory muscle weakness
  - Such weakness may produce acute respiratory failure. This is a true neuromuscular emergency, and immediate intubation may be necessary. Weakness of the intercostal muscles and the diaphragm may result in carbon dioxide retention due to hypoventilation.
  - Weak pharyngeal muscles may collapse the upper airway. Careful monitoring of respiratory status is necessary in the acute phase of myasthenia gravis.
    - Negative inspiratory force (NIF), vital capacity (VC), and tidal volume must be monitored carefully.
    - Relying on pulse oximetry to monitor respiratory status can be dangerous.
    - During the initial phase of neuromuscular hypoventilation, carbon dioxide is retained but arterial blood oxygenation is maintained. This can lull the physician into a false sense of security regarding a patient's respiratory status.
- Ocular muscle weakness
  - Typically, EOM weakness is asymmetric. The weakness usually affects more than 1 EOM and is not limited to muscles innervated by a single cranial nerve. This is an important diagnostic clue.
  - The weakness of lateral and medial recti may produce a pseudointernuclear ophthalmoplegia, described as limited adduction of 1 eye, with nystagmus of the abducting eye on attempted lateral gaze.
  - The nystagmus becomes coarser on sustained lateral gaze as the medial rectus of the abducting eye fatigues.
- Eyelid weakness results in ptosis. Patients may furrow their foreheads, using the frontalis muscle to compensate for this weakness. A sustained upgaze exacerbates the ptosis while closing the eyes for a short period improves it.
- Evidence of other coexisting autoimmune diseases
  - Myasthenia gravis is an autoimmune disorder, and other autoimmune diseases occur more frequently in patients with myasthenia gravis than in the general population.
  - Some autoimmune diseases that occur at higher frequency in patients with myasthenia gravis are hyperthyroidism, rheumatoid arthritis, scleroderma, and lupus.
  - A thorough skin and joint examination may help diagnose any of these coexisting diseases.
  - Tachycardia or exophthalmos point to possible hyperthyroidism, which may be present in up to 10-15% of patients with myasthenia gravis. This is important because in patients with hyperthyroidism, weakness may not improve with treatment of myasthenia gravis alone.

Causes

- Myasthenia gravis is idiopathic in most patients.
- Penicillamine is known to induce various autoimmune disorders, including myasthenia gravis.
- AChR antibodies are present in about 90% of patients developing myasthenia gravis secondary to penicillamine exposure.
- Even in patients who do not develop clinical myasthenia, antibodies can be demonstrated in some cases.
- Various drugs can exacerbate symptoms of myasthenia gravis.
  - Antibiotics (eg, aminoglycosides, ciprofloxacin, erythromycin, ampicillin)
  - Beta-adrenergic receptor blocking agents (eg, propranolol, oxprenolol)
  - Lithium

- Magnesium
- Procainamide
- Verapamil
- Quinidine
- Chloroquine
- Prednisone
- Timolol (ie, a topical beta-blocking agent used for glaucoma)
- Anticholinergics (eg, trihexyphenidyl)

- Neuromuscular blocking agents, including vecuronium and curare, should be used cautiously in myasthenics to avoid prolonged neuromuscular blockade.

Differential Diagnoses

Amyotrophic Lateral Sclerosis
Basilar Artery Thrombosis
Brainstem Gliomas
Cavernous Sinus Syndromes
Dermatomyositis/Polymyositis
Lambert-Eaton Myasthenic Syndrome
Multiple Sclerosis
Sarcoidosis and Neuropathy
Thyroid Disease
Tolosa-Hunt Syndrome

Other Problems to Be Considered

Botulism
Brainstem syndromes
Compressive lesions of cranial nerves
Congenital myasthenic syndromes
Mitochondrial cytopathies
Mitochondrial myopathies with or without external ophthalmoplegia
Neurasthenia
Oculopharyngeal muscular dystrophy

Workup

Laboratory Studies

- Anti-acetylcholine receptor antibody
  - This test is reliable for diagnosing autoimmune myasthenia gravis. The result of the test for the anti-AChR antibody (Ab) is positive in 74% of patients.
    - Results are positive in about 80% of patients with generalized myasthenia and in 50% of those with pure ocular myasthenia.
    - Thus, the anti-AChR Ab test result is frequently negative in patients with only ocular myasthenia gravis.
  - False-positive anti-AChR Ab test results have been reported in cases of thymoma without myasthenia gravis and in patients with Lambert-Eaton myasthenic syndrome, small cell lung cancer, rheumatoid arthritis treated with penicillamine, and in 1-3% of the population older than 70 years.
  - Tindall reported AChR Ab results and their mean Ab titers in a group of patients with myasthenia gravis as shown in Table 1.[7]

- Table 1: Prevalence and Titers of AChR Ab in Patients with Myasthenia Gravis

Osserman Class	Mean Antibody Titer ($\times 10^{-9}$ M)	Percent Positive
R	0.79	24
I	2.17	55
IIA	49.8	80
IIB	57.9	100
III	78.5	100

IV	205.3	89

Classification: R = remission, I = ocular only, IIA = mild generalized, IIB = moderate generalized, III = acute severe, IV = chronic severe.

- A trend in these data suggests that the Ab titer is higher in more severe disease, although titer is not predictive of severity in an individual patient. Change in AChR Ab titer correlates with long-term improvement induced by prednisone or azathioprine. The same changes are not observed consistently in patients who undergo thymectomy. However, this is not consistent and serial antibody titer by itself is not reliable, and thus serial Ab titers by themselves are not useful clinically to judge a patient's response.

- Antistriated muscle (anti-SM) Ab is another important test in patients with myasthenia gravis.
  - It is present in about 84% of patients with thymoma who are younger than 40 years and less often in patients without thymoma.
  - Thus its presence should prompt a search for thymoma in patients younger than 40 years.
  - In individuals older than 40 years, anti-SM Ab can be present without thymoma.
- Thyroid function tests should be done to evaluate for coexistent thyroid disease.
- Anti-MuSK antibody: About half of the patients who are AChR-ab negative (seronegative myasthenia gravis) may be positive for anti–muscle-specific kinase (MuSK) antibodies. They may represent a distinct group of autoimmune myasthenia gravis, as they show some characteristics as a group that are different from AChR-positive patients.[8]
- Antistriational antibodies
  - Serum from some patients with myasthenia gravis possesses antibodies that bind in a cross-striational pattern to skeletal and heart muscle tissue sections. These antibodies react with epitopes on the muscle protein titin and ryanodine receptors (RyR). Almost all patients with thymoma and myasthenia gravis and half of the late-onset myasthenia gravis patients (onset $\geq$50 y) exhibit an antibody profile with a broad striational antibody response. Striational antibodies are rarely found in AChR Ab negative patients. These antibodies can be used as prognostic determinants in myasthenia gravis; as in all subgroups of myasthenia gravis, higher titers of these antibodies are associated with more severe disease.[9]
  - As it is often associated with thymoma in young patients with myasthenia gravis, the presence of titin/RyR antibodies should arouse strong suspicion of thymoma in a young patient with myasthenia gravis.

Imaging Studies

- Chest radiograph
  - Plain anteroposterior and lateral views may identify a thymoma as an anterior mediastinal mass.
  - A negative chest radiograph does not rule out a smaller thymoma, in which case a chest CT scan is required.
- Chest CT scan is mandatory to identify thymoma in all cases of myasthenia gravis. This is especially true in older individuals.
- MRI of the brain and orbits should not be obtained routinely. It is helpful when the diagnosis of myasthenia gravis is not established and to rule out other causes of cranial nerve deficits. MRI can evaluate for intraorbital or intracranial lesions, basal meningeal pathology, or multiple sclerosis.

Procedures

- Electrodiagnostic studies can demonstrate a defect of neuromuscular transmission in 2 ways.
  - The first is by repetitive stimulation of a muscle at 2-3 Hz, also known as repetitive nerve stimulation (RNS).
  - The second is by performing single-fiber electromyography (SFEMG) and evaluating neuromuscular block, jitter, and fiber density.
  - SFEMG is more sensitive than RNS in myasthenia gravis. However, SFEMG is technically more difficult and much more dependent on the experience and skill of the testing physician.
  - Thus RNS is the most frequently performed neurophysiological test of neuromuscular transmission.
- Single-fiber electromyography: A concentric needle electrode or other monopolar and bipolar needle electrodes record single motor unit potentials, but cannot discriminate individual muscle fibers within the motor unit.
  - The single-fiber needle, which has a small recording surface, allows recording from individual muscle fibers.
  - It can determine jitter (ie, variability of the interpotential interval between 2 or more single muscle fibers of the same motor unit) and fiber density (ie, number of single-fiber action potentials within recording radius of the needle).
  - The following findings are suggestive of NMF transmission defect: increased jitter (with or without impulse blocking) and

normal fiber density.

- Examination of a weak muscle by SFEMG is more useful than RNS in demonstrating abnormal neuromuscular transmission. In generalized myasthenia gravis, results of SFEMG of the extensor digiti communis (EDC) are abnormal in 87% of patients. Examination of a second muscle raises the sensitivity to 99%.
- In ocular myasthenia gravis, examination of the frontalis muscle is more useful than examination of the EDC, since frontalis findings are abnormal in almost 100% of patients; only approximately 60% of EDC findings are abnormal.
- Treatment with AChR inhibitors does not normalize SFEMG.
- SFEMG findings are abnormal in almost 100% of patients, while RNS findings are abnormal in only 44-65%.

- Repetitive nerve stimulation (RNS): During low-frequency RNS (1-5 Hz), the locally available ACh becomes depleted at all NMJs, and less is available for immediate release. This results in smaller EPSPs.
  - In patients without myasthenia gravis, all EPSPs exceed the threshold to generate an action potential (ie, safety factor). No change in the summated compound muscle action potential (CMAP) is noted.
  - In patients with myasthenia gravis, the number of AChRs is reduced, lowering the safety factor. During RNS, some EPSPs may not reach threshold and no action potential is generated. This results in the decrement in the amplitude of the CMAP.
  - In patients with myasthenia gravis, this decremental response usually has a maximum decrement at the fourth or fifth response and then a tendency toward repair (see Image 3).
  - Any decrement over 10% is considered abnormal.
  - Patients with myasthenia gravis rarely have a decremental response in a clinically normal muscle. Thus, testing a proximal weak muscle gives a better yield than testing a technically easier unaffected distal muscle. Testing a facial muscle (orbicularis oculi) is useful since most patients suffer from eyelid weakness or ptosis.
  - The most common employed stimulation rate is 3 Hz.
  - Several factors can affect RNS results.
    - Lower temperature increases the amplitude of the CMAPs. Patients with myasthenia gravis may report clinically significant improvement in cold temperatures. Typically they report worsening of ptosis in bright sunlight or on a warm day. Therefore maintaining a constant and perhaps higher-than-ambient temperature during RNS testing is important to bring out abnormalities of NMJ function. Temperature of skin overlying the tested muscle should be at least 34°C.
    - Administration of AChE inhibitors prior to the testing may mask the abnormality and should be avoided for at least 1 day prior to testing (even longer for long-acting agents).
  - Posttetanic potentiation and posttetanic exhaustion
    - A tetanic contraction of muscle is followed by 2 distinct phases: for the first 2 minutes after tetanic contraction, posttetanic potentiation occurs; this is followed by posttetanic exhaustion, which lasts an additional 15 minutes.
    - During posttetanic potentiation, accumulation of calcium inside the terminal axon causes enhanced mobilization and release of ACh, which overcomes the reduced number of AChR at the NMJ and results in larger EPSPs with additional recruitment of muscle fibers, resulting in a larger CMAP.
    - In myasthenia gravis, this potentiation may normalize RNS.
    - In the posttetanic exhaustion phase, the NMJ is less excitable and even fewer EPSPs reach threshold. Thus, some patients with an equivocal abnormality on RNS during resting phase may show clear-cut abnormality during the posttetanic exhaustion phase.
    - Tetanic contraction of the muscle can be achieved by electrical stimulation of the nerve at a rate of 50 per second lasting for 20-30 seconds. However, this is painful. Voluntary contraction of the muscle for 10 seconds at the maximum force can achieve the same goal without discomfort and is preferred.

- Pharmacological testing (edrophonium or Tensilon test) for the diagnosis of myasthenia gravis
  - In patients with myasthenia gravis, the number of AChR at the NMJ is low. This results in a decreased number of interactions between ACh and its receptor. ACh released from motor nerve terminals is metabolized by AChE.
  - Pharmacological inhibition of AChE increases ACh concentration at the NMJ, improving the chance for interactions between ACh and its receptor. Edrophonium (Tensilon) is a short-acting AChE inhibitor that improves muscle weakness in patients with myasthenia gravis.
  - Evaluate weakness (eg, ptosis, partial or complete ophthalmoplegia, and forced hand grip) before and after administration of Tensilon. Blinding of both the examiner and the patient increases the validity of the test.
  - Sinus bradycardia due to excessive cholinergic stimulation of the heart is a serious complication. An ampule of atropine should be available at the bedside or in the clinic room while performing the test.
  - To perform the test, a test dose of 0.1 mL of 10 mg/mL edrophonium solution is administered. If no response and no untoward effects are noted, remainder of the drug (0.9 mL) is injected.
  - While interpreting this test, it is important to remember that these drugs can improve weakness in diseases other than myasthenia gravis, such as amyotrophic lateral sclerosis, poliomyelitis, and some peripheral neuropathies.

Histologic Findings

Lymphofollicular hyperplasia of thymic medulla occurs in 65% of patients with myasthenia gravis; thymoma, in 15%.

Treatment

Medical Care

- Even though no rigorously tested treatment trials have been reported and no clear consensus exists on treatment strategies, myasthenia gravis is one of the most treatable neurologic disorders. Several factors (eg, severity, distribution, rapidity of disease progression) should be considered before initiating or changing therapy. Immunomodulation can be achieved by various medications, such as commonly used corticosteroids. Other medications that are used to treat more difficult cases include azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide, and rituximab. However, the effectiveness of many of these medications are far from proven and caution should be advised against use of them lightly.[10, 11, 12]
- AChE inhibitors and immunomodulating therapies are the mainstays of treatment. In the mild form of the disease, AChE inhibitors are used initially. Most patients with generalized myasthenia gravis require additional immunomodulating therapy.
- Plasmapheresis and thymectomy are important modalities for treating myasthenia gravis. They are not traditional medical immunomodulating therapies, but they function by modifying the immune system.
- Plasmapheresis or plasma exchange
    - Plasma exchange (PE) is an effective treatment for myasthenia gravis, especially in preparation for surgery or as short-term management of an exacerbation. Improvement in strength may help to achieve rapid postoperative recovery and to shorten the period of assisted ventilation.
    - Weakness improves within days, but the improvement lasts only 6-8 weeks.
    - PE usually is used as an adjunct to other immunomodulatory therapies and as a tool for crisis management.
    - Long-term regular PE on a weekly or monthly basis can be used if other treatments cannot control the disease.
    - Complications of PE are limited primarily to complications of intravenous access (eg, central line placement), but also include less commonly hypotension and coagulation disorders.
    - PE is thought to act by removing circulating humoral factors (ie, AChR Ab and immune complexes).

Surgical Care

- Thymectomy
    - This is an important treatment option in myasthenia gravis, especially if a thymoma is present.
    - It has been proposed as a first-line therapy in most patients with generalized myasthenia.
    - The beneficial effect of thymectomy was reported as early as the 1930s and 1940s in a variety of case reports and small series.
    - Even though no controlled trial to assess the efficacy of thymectomy in myasthenia gravis has been reported, thymectomy has become the standard of care and should be done in all patients with thymoma and in patients aged 10-55 years without thymoma but with generalized myasthenia gravis.
    - Thymectomy may induce remission. This occurs more frequently in young patients with a short duration of disease, hyperplastic thymus, and high antibody titer.
    - Remission rate increases with time: at 7-10 years after surgery, it reaches 40-60% in all categories of patients except those with thymoma.

Consultations

Coordinate care with the primary care physician.

Diet

- Patients with myasthenia gravis may experience difficulty chewing and swallowing because of oropharyngeal weakness. It may be difficult for the patient to chew meat or vegetables because of masticatory muscle weakness.
- If dysphagia develops, it is usually most severe for thin liquids because of weakness of pharyngeal muscles. To avoid nasal regurgitation or frank aspiration, liquids should be thickened.

Activity

Educate patients about the fluctuating nature of weakness and exercise-induced fatigability. Patients should be as active as possible but should rest frequently and avoid sustained physical activity.

Medication

AChE inhibitors are considered to be the basic treatment of myasthenia gravis. Long-term corticosteroid therapy and immunosuppressive drugs are also effective.

Anticholinesterase inhibitors

These agents inhibit AChE, raising the concentration of ACh at the NMJ and increasing the chance of activating the AChR. Any medication that increases the activity of the AChR can have an effect on myasthenia gravis.

Pyridostigmine bromide (Mestinon)

An intermediate-acting agent, preferred in clinical use to shorter-acting neostigmine bromide (Prostigmin) or longer-acting ambenonium chloride (Mytelase). Starts working in 30-60 min; effects last 3-6 h.
Also available as time span tablet, whose effects last 2.5 times longer. Time span form useful adjunct to regular pyridostigmine for nighttime control of myasthenic symptoms. Absorption and bioavailability of timespan vary among subjects. It should be used only at bedtime, and patients need close monitoring for cholinergic adverse effects.
Individualize dose because myasthenia gravis does not affect all skeletal muscles similarly, all symptoms may not be controlled without producing adverse effects.
In critically ill or postoperative patients, administer IV.
In US, available in 3 forms: 60 mg scored tab, 180 mg time span tab, and 60 mg/5 mL syrup.

Dosing

Adult

Adjust dose to needs of individual patient
60-960 mg/d PO in divided doses
2 mg IV/IM q2-3h or 1/30th PO dose; IV form best given as IV drip, infusing 1/30th of total daily dose over 24 h; avoid IM route if possible because of erratic absorption

Pediatric

7 mg/kg/d PO in divided doses

Interactions

Increases effects of depolarizing neuromuscular blockers; increases toxicity of edrophonium

Contraindications

Documented hypersensitivity, peritonitis, mechanical obstruction of GI or GU tract

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Overdose may cause cholinergic crisis, which may be fatal; IV atropine should be readily available to treat cholinergic reactions
Use cautiously in patients with bronchial asthma and those receiving a cardiac glycoside; adverse effects stem from dose-related, excessive stimulation of muscarinic AChR and include excessive salivation, abdominal cramps, diarrhea, blurring of vision, and flushing; adverse GI effects are common and can be controlled by anticholinergic drugs preferentially affecting muscarinic AChR, such as diphenoxylate hydrochloride (Lomotil) and atropine sulfate

Neostigmine (Prostigmin)

This short-acting AChE inhibitor is available in PO form (15 mg tab) and form suitable for IV/IM/SC administration. Half-life is 45-60 min.
Poorly absorbed from GI tract, should be used only if pyridostigmine unavailable.
Individualize dose for all patients.

Dosing

Adult

15 mg/dose PO q3-4h

0.5-2.5 mg IV/IM/SC q1-3h or 1/30th PO dose; not to exceed 10 mg/d

Pediatric

2 mg/kg/d PO divided q3-4h
0.01-0.04 mg/kg IV/IM/SC q2-4h or 1/30th PO dose

Interactions

Muscarinic effects antagonized by atropine; increases effects of neuromuscular agents; pyridostigmine may decrease response to nondepolarizing neuromuscular blockers

Contraindications

Documented hypersensitivity to drug or bromides; peritonitis, mechanical obstruction of GI or GU tract

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Use caution in patients with asthma, bradycardia, hyperthyroidism, cardiac arrhythmias, or peptic ulcer; AChE insensitivity can develop for brief or prolonged periods

Immunomodulatory therapy

Myasthenia gravis is an autoimmune disease, and immunomodulatory therapies have been used for these disorders since introduction of steroids. Although no rigorous clinical trials have established the efficacy of immunomodulatory therapies in myasthenia gravis, several uncontrolled trials and retrospective studies support use of such therapies. The therapies used in myasthenia gravis include prednisone, azathioprine, IVIg, plasmapheresis, and cyclosporine.

Prednisone (Deltasone, Sterapred, Orasone)

Corticosteroids were among first immunomodulating agents used to treat myasthenia gravis and still are used frequently and effectively. Prednisone is most commonly used corticosteroid in US. Typically used in moderate or severe cases that do not respond adequately to AChE inhibitors and thymectomy. Long-term treatment with corticosteroids is effective and may induce remission or cause marked to moderate improvement in most patients.
Significant improvement, which may be associated with decreased Ab titer, usually occurs in 1-4 mo.
Alternate-day regimen may minimize adverse effects. Trial of steroid withdrawal may be attempted, but most patients on long-term corticosteroid therapy relapse and require re-institution of steroids.

Dosing

Adult

No single regimen accepted for corticosteroid treatment of myasthenia gravis; some regimens start with low dose and increase gradually; others, use high dose initially to achieve quicker response
No consensus exists on dosing schedule among physicians using initial low-dose regimen
Authors use starting dose of 15 mg/d PO, increasing by 5 mg q2-3d until satisfactory clinical response achieved or maximum dose of 50-60 mg/d reached; taper should begin after 3-6 mo of treatment and documented response
Starting with high doses (20-30 mg/d PO, increasing by 5-10 mg q2-3d to maximum 60 mg/d) may improve weakness more rapidly; some start with 60-80 mg/d and others 100 mg qod
Initial deterioration in weakness before improvement is common and serious concern within first 3 wk; this potential complication warrants initiation of high doses in supervised setting

Pediatric

4-5 mg/m^2/d PO; alternative: 1-2 mg/kg PO qd; taper over several mo as symptoms resolve

Interactions

Clearance may be decreased by estrogens; with concurrent digoxin, may increase digitalis toxicity secondary to hypokalemia; metabolism may be increased by phenobarbital, phenytoin, and rifampin (consider increasing maintenance dose); patients taking concurrent diuretics should be monitored for hypokalemia

Contraindications

Documented hypersensitivity; systemic viral, fungal, or tubercular infections

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Long-term use may predispose patients to various problems, including hyperglycemia; manifestations of latent diabetes mellitus; nonketotic hyperosmolar state; osteoporosis; avascular necrosis of the hip; peptic/gastric ulcer disease; GI bleeding; cataracts; glaucoma; steroid myopathy; cushingoid appearance; weight gain; suppression of pituitary-hypothalamic axis; growth suppression in children; water retention, which may precipitate congestive heart failure and hypertension; hypokalemia; unmasking of latent infections (such as TB or herpes zoster), predisposition to fungal and parasitic infection, and increased susceptibility to opportunistic infections
Due to suppressed pituitary-hypothalamic axis, additional steroid dosing may be necessary at times of stress (eg, systemic infections or surgery)

Azathioprine (Imuran)

Second most commonly used immunosuppressive medication in myasthenia gravis, reserved for steroid failure or unacceptable effects from prolonged steroid use. Can be used for steroid-sparing effects to lower steroid dose. One drawback is that onset of action is 6-12 mo.

Dosing

Adult

1 mg/kg/d PO initial dose; increase gradually to desired effect, usually 2-3 mg/kg/d qd; may be divided ac if adverse GI effects are bothersome
Some experts advocate dose increases until RBC MCV >100 fL; do not increase dose if patient develops leukopenia

Pediatric

Maintenance: 1-2 mg/kg/d PO

Interactions

Toxicity increased by allopurinol; concurrent ACE inhibitors may induce severe leukopenia; may increase plasma levels of methotrexate metabolite; may decrease effects of anticoagulants; may decrease cyclosporine plasma levels

Contraindications

Documented hypersensitivity, severe flulike reaction to drug (20-30%), inability to tolerate medication, pregnancy or nursing

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Monitor CBC regularly for development of leukopenia, thrombocytopenia, or macrocytic anemia; rarely causes hepatotoxicity, but 2- to 3-fold elevation of hepatic enzymes common (decrease dose should this occur); may increase risk of serious infections and neoplasia

Immune globulin intravenous (Gamimune, Gammagard, Sandoglobulin)

High-dose IVIg successfully treats myasthenia gravis. Like plasma exchange, has rapid onset of action, but effects last only short time. Best used in crisis management (eg, myasthenic crisis and perioperative period).

Dosing

Adult

2 g/kg slow IV infusion over 2-5 d

Pediatric

Administer as in adults

Interactions

None reported

Contraindications

Allergy to immunoglobulins, IgA deficiency, presence of antibodies to IgA, renal insufficiency or renal artery stenosis (ie, increased risk of

renal failure)

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Check serum IgA before administering; use IgA-depleted product (G-Gard-SD); may increase serum viscosity and thromboembolic events; watch for fluid overload or hypotension; carefully and frequently monitor vital signs during and immediately after administration; headaches frequent during or after infusion; rarely, aseptic meningitis may develop; flulike syndrome may occur

Cyclosporine A (Neoral, Sandimmune)

Fungal peptide with potent immunosuppressive activity. Has been shown effective in patients with myasthenia gravis in prospective, double-blind, placebo-controlled clinical trial. Does have some significant adverse effects, which usually preclude its use as first-line immunosuppressive therapy. However, in patients who are at high risk for adverse steroid effects, CsA can be used as initial therapy. Onset of action within a few wk to mo, similar to that of prednisone.

Dosing

Adult

Clinical and immunological effects correlate with serum concentration; dose usually adjusted to achieve trough serum level of 100-200 ng/mL (as determined by HPLC)
4-10 mg/kg/d PO divided bid/tid has been used

Pediatric

Administer as in adults

Interactions

Several drugs may act synergistically to enhance nephrotoxicity of CsA, including gentamicin, tobramycin, vancomycin, amphotericin B, ketoconazole, melphalan, diclofenac, cimetidine, ranitidine, trimethoprim with sulfamethoxazole, and azapropazone
CsA metabolized by liver microsomal enzymes; concurrent diltiazem, verapamil, nicardipine, ketoconazole, fluconazole, or itraconazole may increase serum level of CsA, while phenytoin, phenobarbital, carbamazepine, and rifampin may decrease serum level

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Two most significant adverse effects are hypertension, which is easily treated with antihypertensive medication; more important is nephrotoxicity—careful monitoring of renal function mandatory
Like azathioprine, CsA can lower blood counts, predispose to opportunistic infections, and may increase incidence of malignancy in patients on long-term therapy

Cyclophosphamide (Cytoxan, Neosar)

Alkylating agent that interferes with cell proliferation. More effective against B cell compared to T cells, making it a good choice in an antibody-mediated disease such as myasthenia gravis. Because of potential for serious side effects, usually reserved for more severe cases where more routinely used immunotherapy has failed due to lack of efficacy or intolerable side effects.

Dosing

Adult

Variable dosages used

Standard oral dosages used in clinical trials include 1-2 mg/kg/d in one series and 3-5 mg/kg/d in another; some patients treated with 200-250 mg IV for 5 d; IV doses ranging from 350-1000 g/m^2 administered

Pediatric

Not established

Interactions

Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects; may potentiate doxorubicin-induced cardiotoxicity; may reduce digoxin serum levels and antimicrobial effects of quinolones; toxicity may increase with chloramphenicol; may increase effect of anticoagulants; coadministration with high doses of phenobarbital may increase leukopenic activity; thiazide diuretics may prolong cyclophosphamide-induced leukopenia; coadministration with succinylcholine may increase neuromuscular blockade by inhibiting cholinesterase activity

Contraindications

Documented hypersensitivity; preexisting bone marrow depression

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Regularly examine hematologic profile (particularly neutrophils and platelets) to monitor for hematopoietic suppression; regularly examine urine for RBCs, which may precede hemorrhagic cystitis

Mycophenolate mofetil (CellCept, Myfortic)

Inhibitor of de novo purine synthesis by blocking the enzyme inosine monophosphate dehydrogenase. Very effective against proliferative lymphocytes, which do not make use of purine salvage pathway.

Dosing

Adult

1-3 g PO qd or divided bid

Pediatric

No data available on pediatric patients with myasthenia gravis
Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, recommended dose of CellCept oral suspension is 600 mg/m^2 bid

Interactions

In combination with either acyclovir or ganciclovir may result in higher levels for both interacting drugs due to competition for renal tubular excretion; aluminum/magnesium present in some antacids, and cholestyramine containing products may decrease absorption, reducing levels (do not administer together); probenecid may increase levels of mycophenolate; salicylates and azathioprine may increase toxicity; may decrease levonorgestrel AUC; may decrease live-virus vaccine immune response; when administered in combination with theophylline may increase free fraction levels of theophylline

Contraindications

Documented hypersensitivity to drug or components

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Increases risk for infection (monitor blood count); severe renal impairment (CrCl <25 mL/min) may have increased adverse effects due to increase free MPA; caution in active peptic ulcer disease; incidence of malignancies and lymphoma consistent with that reported for other immunosuppressants (0.9%); commonly causes constipation, nausea, diarrhea, urinary tract infection, and nasopharyngitis; rare reports include interstitial lung disorders, colitis, pancreatitis, intestinal perforation, GI hemorrhage, gastric ulcers, duodenal ulcers, and ileus; do not chew, crush, or cut Myfortic tab

Follow-up

Further Outpatient Care

- Patients with myasthenia gravis require close follow-up care in cooperation with the primary care physician.
- Myasthenia gravis is a chronic disease that may worsen acutely over days or weeks (and on rare occasions, over hours).
- Treatment requires scheduled reevaluation and a close doctor/patient relationship.

Inpatient & Outpatient Medications

See Medication.

Complications

- Respiratory failure may occur if respiratory muscle weakness is severe.
- Dysphagia due to pharyngeal muscle weakness may occur and may lead to aspiration pneumonia.
- Complications secondary to drug treatment: Long-term immunomodulating therapies may predispose patients with myasthenia gravis to various complications.
    - Long-term steroid use may cause or aggravate osteoporosis, cataracts, hyperglycemia, weight gain, avascular necrosis of hip, hypertension, and other complications.
    - Long-term steroid use increases the risk of gastritis or peptic ulcer disease. Patients on such therapy also should take an H2 blocker or antacid.
    - Some complications are common to any immunomodulating therapy, especially if the patient is on more than 1 agent. These would include infections such as tuberculosis, systemic fungal infections, and *Pneumocystis carinii* pneumonia.
    - Risk of lymphoproliferative malignancies may be increased with chronic immunosuppression.
    - Immunosuppressive drugs may have teratogenic effects.

Prognosis

- Untreated myasthenia gravis carries a mortality rate of 25-31%. With current treatment (especially pertaining to acute exacerbations), the mortality rate has declined to approximately 4%.
- The disease frequently presents (40%) with only ocular symptoms. However, the EOM almost always are involved within the first year. In patients with only ocular involvement at onset, only 16% remain ocular exclusively at the end of 2 years.
- In patients with generalized weakness, the nadir of maximal weakness usually is reached within the first 3 years of the disease. Half of the disease-related mortality also occurs during this time period. Those who survive the first 3 years of disease usually achieve a steady state or improve. Worsening of disease is uncommon after 3 years.
- Important risk factors for poor prognosis include age older than 40 years, a short history of progressive disease, and thymoma.

Patient Education

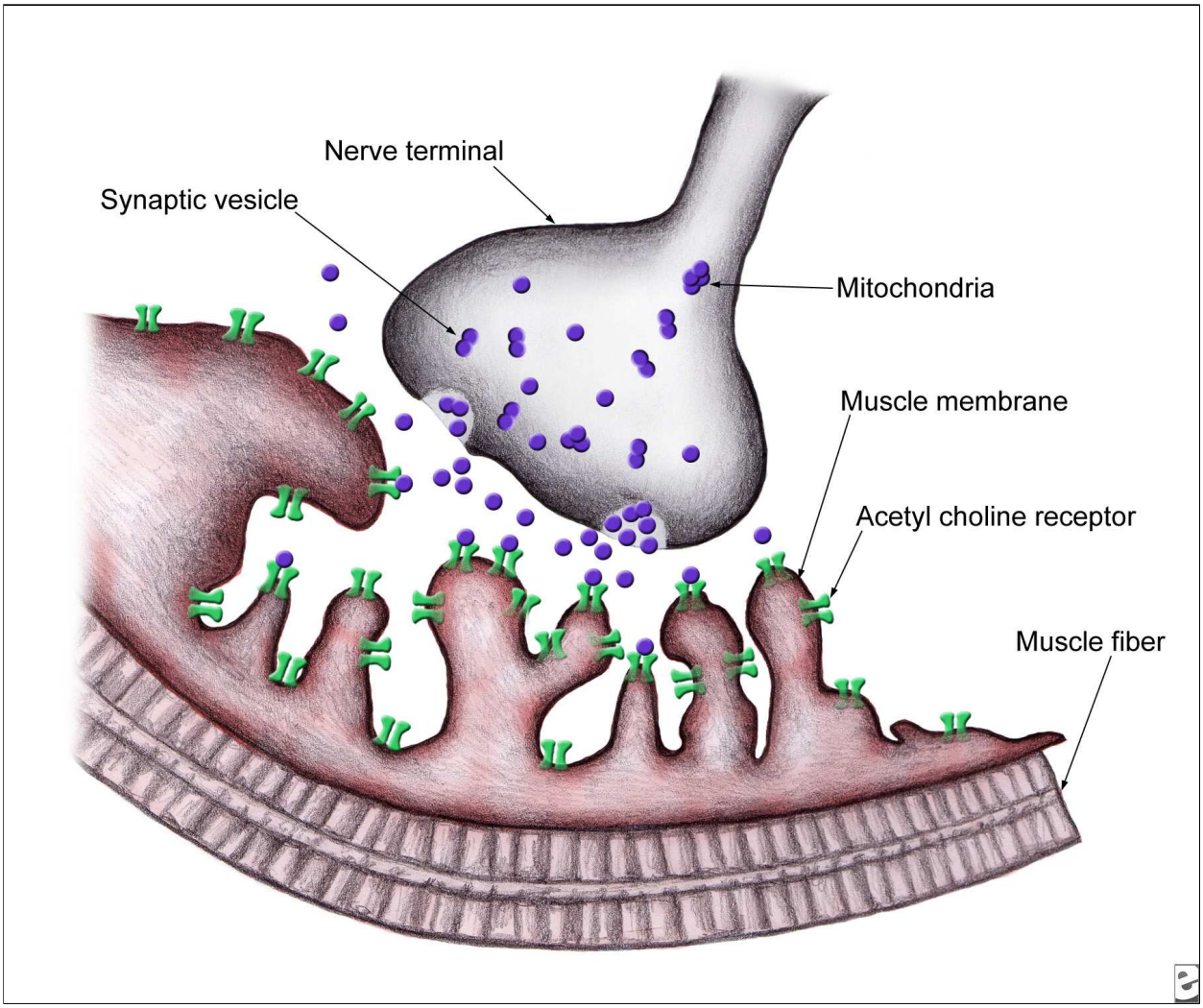
- Educate patients to recognize impending respiratory crisis.
    - Intercurrent infection may worsen symptoms of myasthenia gravis temporarily.
    - Mild exacerbation of weakness is possible in hot weather.
- Risk of congenital deformity (arthrogryposis multiplex) is increased in offspring of women with severe myasthenia gravis.
    - Neonates born to women with myasthenia gravis need to be monitored for respiratory failure for 1-2 weeks after birth.
    - Certain immunosuppressant drugs have teratogenic potential.
    - Discuss these aspects with women in reproductive years prior to beginning therapy with these drugs.
- Certain medications such as the aminoglycosides, ciprofloxacin, chloroquine, procaine, lithium, phenytoin, beta-blockers, procainamide, and quinidine may exacerbate symptoms of myasthenia gravis. Many other drugs have been associated only rarely with exacerbation of myasthenia gravis.
- Medications that induce the hepatic microsomal cytochrome P-450 system (eg, corticosteroids) may render oral contraceptives less effective.
- Statins may cause worsening of myasthenia without regard to type of myasthenia gravis or brand of statin. Worsening of weakness can occur independently of myalgic syndrome and usually involves oculobulbar symptoms within 1-16 weeks of onset of statin treatment.[13]

Miscellaneous

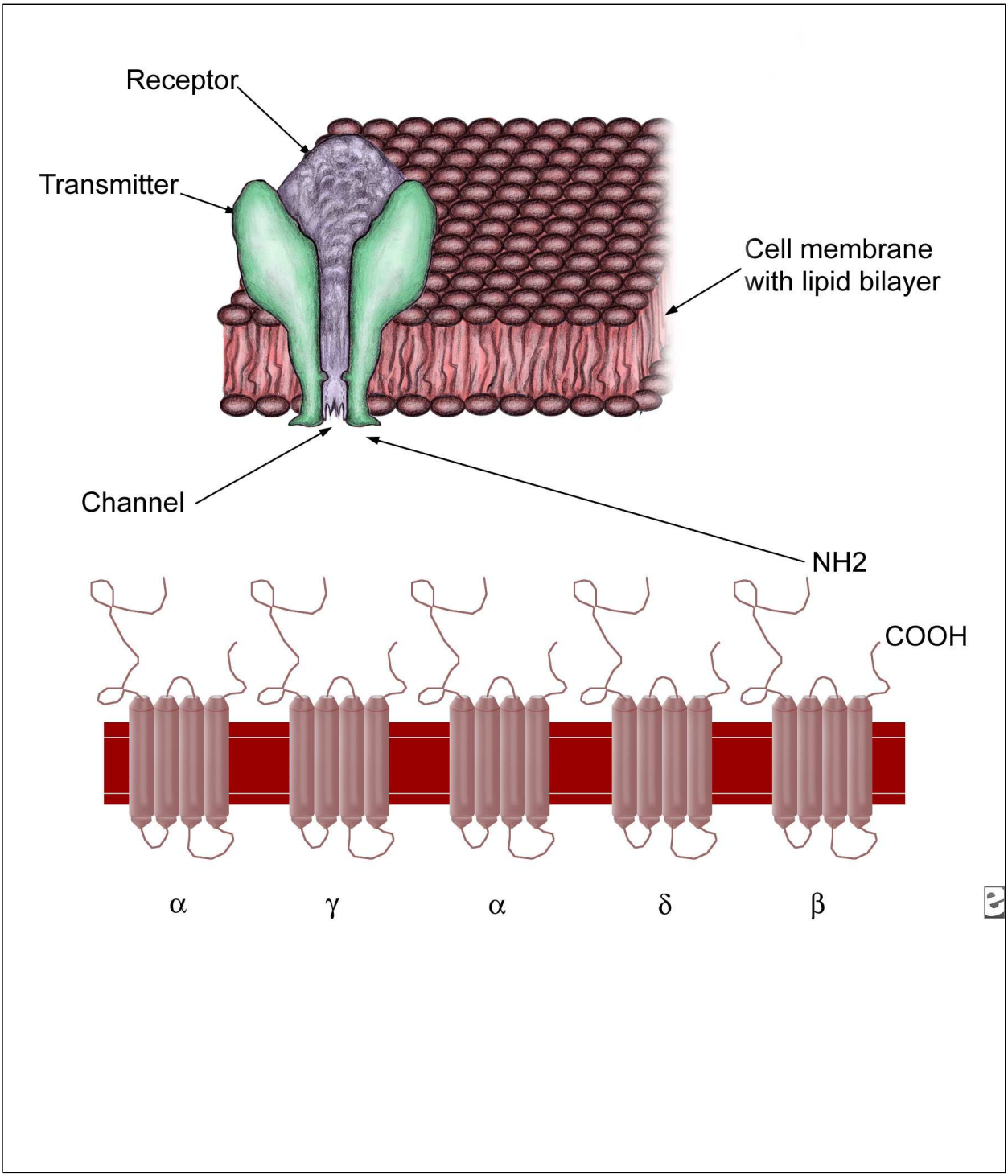
Medicolegal Pitfalls

- Rapid respiratory failure may occur if the patient is not monitored properly. Patients should be watched very carefully, especially during exacerbation, by measuring negative inspiratory force (NIF) and vital capacity (VC).
- Transient neonatal MG occurs in 10-30% of neonates born to myasthenic mothers. It may occur any time during the first 7-10 days of life, and infants should be monitored closely for any signs of respiratory distress.

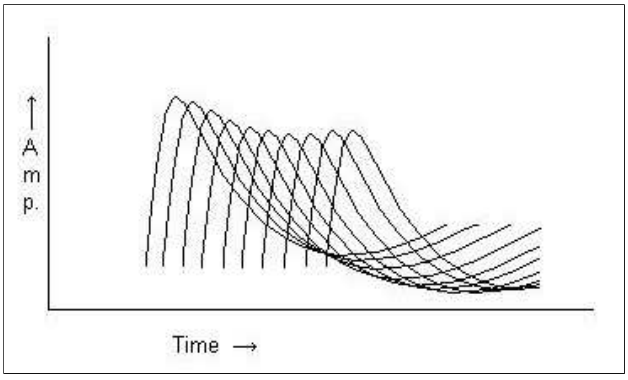
Multimedia



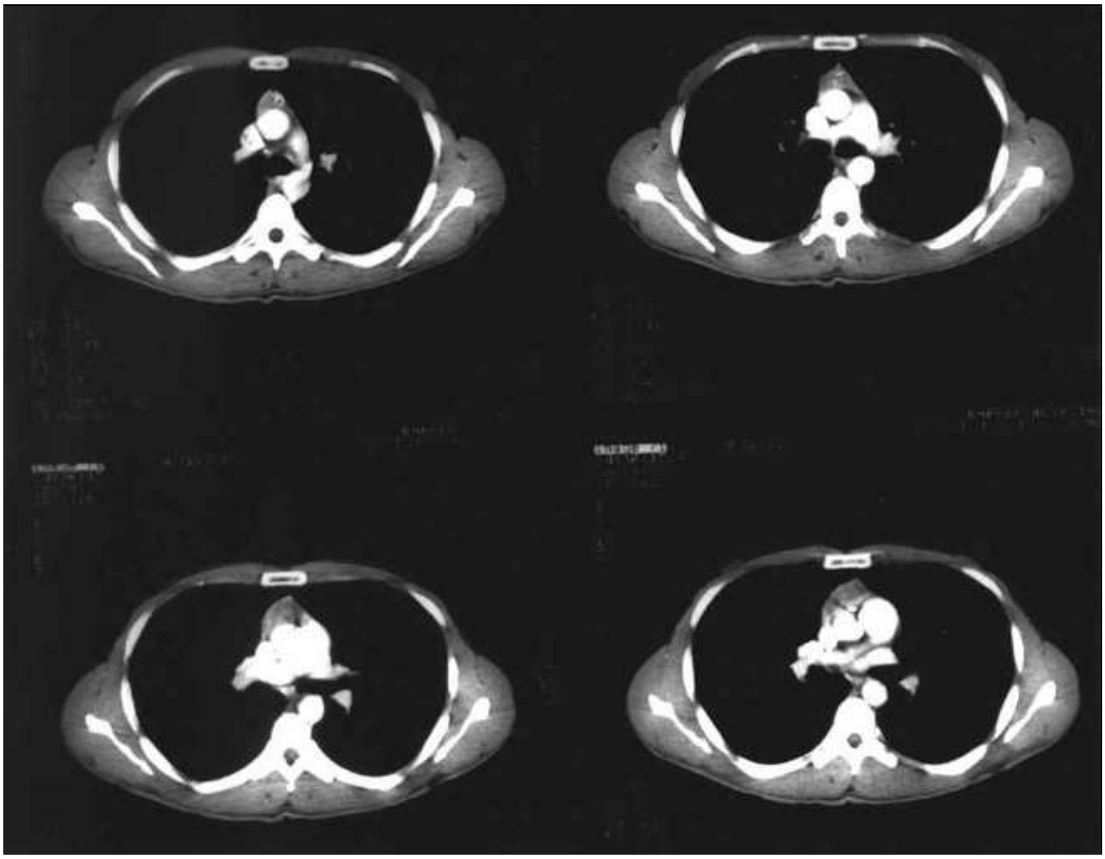
Media file 1: Normal neuromuscular junction showing a presynaptic terminal with a motor nerve ending in an enlargement (bouton terminale): Synaptic cleft and postsynaptic membrane with multiple folds and embedded with several acetylcholine receptors.



Media file 2: Acetylcholine receptor. Note 5 subunits, each with 4 membrane-spanning domains forming a rosette with a central opening. The central opening acts as an ion channel.



Media file 3: A typical recording of compound muscle action potentials with repetitive nerve stimulation at low frequency in a patient with myasthenia gravis. Note the gradual decline in the amplitude of the compound muscle action potential with slight improvement after the fifth or sixth potential.



Media file 4: CT scan of chest showing an anterior mediastinal mass (thymoma) in a patient with myasthenia gravis.

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Keywords

myasthenia gravis, autoimmune neuromuscular disease, skeletal muscle weakness, fatigability on exertion, muscle weakness, acetylcholine receptor, AChR, seronegative myasthenia gravis, SNMG, muscle-specific kinase, MuSK, MG

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