Ocular Myasthenia

Myasthenia gravis is a chronic neuromuscular disorder, characterized by weakness and fatigability of voluntary muscles. It particularly affects muscles innervated by cranial nerves, due to impaired synaptic transmission across the neuromuscular junction. Patients may display weakness of extra ocular, bulbar, and/or limb muscles. Weakness is exacerbated by repetitive or sustained contraction and transiently improved by rest or anticholinesterase medications. Ocular Myasthenia (OM) is a localized form of myasthenia clinically involving only the extra ocular, levator palpebrae superioris, and/or orbicularis oculi muscles.

Historical Perspective
The first report of a myasthenic patient in the literature is credited to Thomas Willis in 1672, though the nomenclature "myasthenia gravis" was not applied until over 200 years later10. In 1877, Wilks reported absence of brainstem disease on autopsy of a young woman with bulbar palsy (i.e., dysarthria, dysphagia), generalized weakness, strabismus, and respiratory paralysis, resulting in death. The postmortem examination was normal and the symptomatology was consistent with myasthenia. Jolly in 1895 introduced the term “myasthenia gravis pseudoparalytica” (from the Greek "mys" = muscle and "asthenia" = weakness, and Latin "gravis" = heavy or weighty). Jolly was the first to suggest physostigmine as possible treatment for this disease, as well as the first to demonstrate muscle fatigue following repeated faradic (electrical) stimulation (Jolly test). Mary Walker (1934) administered an injection of physostigmine to a patient with generalized myasthenia and observed a marked improvement in muscle strength. In 1935, Viets and Schwab described the use of intramuscular neostigmine (Prostigmin) for diagnosis of myasthenia.

Natural history
Autoimmune myasthenia affects all races and ages, with an incidence of 4 to 5 per 100,000. Incidence is age and sex dependent, peaking in young women and older men9. Fifty to eighty percent of patients presenting initially, with purely ocular symptoms and signs subsequently develop clinical generalized disease typically within two years1.

If myasthenia remains ocular for at least three years, then clinical generalized disease is unlikely to develop11. Ten to twenty percent of ocular myasthenics will spontaneously remit, either permanently or transiently, with relapse after one or more years. While corticosteroid treatment produces a higher incidence of remission and improvement, there is no evidence that anticholinesterase medications affect the ultimate course of disease. Age, sex, and pattern of onset are not helpful in predicting the eventual course of myasthenia12.

Physiology of Neuromuscular Transmission
Neuromuscular transmission is initiated by an action potential depolarizing the terminal membrane of the motor nerve axon. It elicits an increase in calcium permeability and release of acetyl choline (ACh) from specialized sites on the nerve terminal into the synaptic cleft. ACh molecules diffuse across the synaptic space, bind to their receptors, and depolarize the postsynaptic membrane.

The postsynaptic membrane is a convoluted structure, with ACh receptors (AChRs) located on the crests of the folds (about 1500 receptor sites per square micrometer) and acetyl cholinesterase in the clefts. Released ACh is rapidly eliminated from the synaptic space by simple diffusion and hydrolysis by acetyl cholinesterase, with neuromuscular transmission completed within milliseconds.

Spontaneous release of small quantities of ACh from single vesicles into the synaptic cleft results in localized, low-amplitude depolarizations of the motor endplate, called miniature endplate potentials (MEPP). Release of a large quantity of ACh from multiple vesicles elicits a larger depolarization, referred to as an endplate potential (EPP), which is usually sufficient to initiate muscle contraction. The amplitude of the EPP is proportionate to the amount of ACh released.
Normally there is a vast excess of both released Ach molecules and available postsynaptic AChRs in order to ensure optimal neuromuscular transmission. In addition, the amplitude of an EPP is four fold higher than that required to initiate muscle contraction. Thus, there is a safety factor, for neuromuscular transmission in normal EOM which prevents fatigue during repeated saccades. Any aberration that decreases the probability of interaction between ACh and its receptor, such as a reduction in the number of available AChRs in myasthenia reduces this “safety margin” and predisposes to failure of neuromuscular transmission, causing weakness and fatiguability.

Extraocular Muscle Physiology and Its Significance in Ocular Myasthenia

Extraocular muscles (EOM) fibers have extremely rapid contraction kinetics and high firing frequencies of twitch when compared to other skeletal muscles. The number of ACh receptors are less in EOM with lower quantities of ACh released. These factors may increase EOM susceptibility to fatigue, particularly in myasthenia.

Multi terminal fibers of EOM (those that receive multiple synapses per fiber) may be more vulnerable to weakness and fatigue than single-terminal fibers which are found in most other muscles. Muscles with a predominantly tonic innervation, such as the levator muscle, tend to fatigue more easily during the day than the extraocular muscles. Other factor that makes EOM weakness particularly symptomatic, is that even slight fatigue of an EOM may misalign the visual axes and cause diplopia.

Pathophysiology

Circulating AChR Abs have been well-documented in numerous studies of patients with myasthenia, and these antibodies have been found in up to 87% of myasthenic patients tested. Antibodies to each of the subunits of the ACh receptor molecule have been found.

Major Antibody-Mediated Mechanism in the Pathophysiology of Myasthenia
1. Cross-linking and internalization of ACh receptors (accelerated degradation)
2. Damage to ACh receptors and postsynaptic membrane (probably complement-mediated)
3. ACh receptor blockade

Other auto antibodies:- Multiple auto antibodies other than AChR Abs have been identified in patients with myasthenia. Antibodies against skeletal muscle have been found in almost all myasthenic patients with thymoma and in about 30% of myasthenics without thymoma. Studies have reported thyroglobulin antibodies, antinuclear antibodies, antimuscle immunoglobulins, and rheumatoid factor in patients with myasthenia.

Cell mediated immunity:- Changes in populations of lymphocytes in the thymus of myasthenics, including a lower percentage of T cells and a higher percentage of B cells than normal and possible alterations in their antigenic properties, have been observed.

Histopathology:- Histopathologic studies in myasthenia have demonstrated postsynaptic changes in most or all patients, including a 70-89% decrease in the number of AChRs per neuromuscular junction in myasthenics compared with normal controls. Findings include sparse, shallow folds and marked simplification of the post-synaptic membrane, with widening of the synaptic clefts in many cases.

Associated thymic disorders:- Both thymic hyperplasia and thymoma have been associated with myasthenia. Thymic hyperplasia, characterized by infiltration of the thymus with lymphocytes and plasma cells and formation of lymph follicles (germinal centers), is found in as many as 65-70s of all myasthenics, particularly in younger patients.

Clinical characteristics
Ptosis and extraocular muscle palsies with fluctuating
dioplia are the hallmark of the disease. These signs are present sometime in the course of the disease in over 90% of patients with MG, whereas ptosis and diplopia constitute the presenting complaints in 70% of myasthenic patients. If the weakness remains limited to extraocular muscles for 2 years, the chance of later dissemination is minimal.

Blepharoptosis is particularly suggestive of myasthenia if it is variable and worsens with fatigue or at the end of the day. Variability distinguishes this condition form others such as Horner’s syndrome or third cranial nerve dysfunction. Ptosis may be unilateral or bilateral, though often asymmetrical. Ptosis may be elicited or worsened on prolonged upgaze, which is the basis for the lid fatigue test. Goerlick et al. made a useful observation on a method of enhancing myasthenic ptosis. First, the patient is instructed to maintain upgaze. As ptosis comes about, the examiner passively elevates the more ptotic upper lid, and over the next few seconds the other eyelid progressively falls, to complete closure, sometimes with a few up and down oscillations. Cogan has labelled this phenomenon ‘see saw ptosis’. In a myasthenic with bilateral ptosis, manual elevation of one eyelid reduces the effort required to raise that eyelid. Less effort is thus exerted by the contralateral levator muscle, and that eyelid becomes more ptotic, according to Hering’s law.

Diplopia secondary to a paresis of the extraocular muscles is the second most frequent initial symptom. It usually, but not always, occurs with ptosis, and may mimic any disorder of eye movement, from paresis of an isolated eye muscle to a gaze palsy or complete external ophthalmoplegia. Muscles frequently involved are the medial rectus, inferior rectus and superior oblique, though any extraocular muscle may be affected. Paresis of upgaze is also common.

Special signs and symptoms in ocular myasthenia

Bells phenomenon:- Bells phenomenon of upward eye rotation on attempted eye closure may be absent in OM if the globe elevators are weak.

Cogan’s lid twitch:- Cogan’s lid twitch is a frequent finding in OM. If the eyes are rapidly returned to primary gaze from down gaze, the upper eyelid elevates excessively, i.e., a small overshoot occurs, and then either slowly becomes ptotic or twitches several times before returning to a fixed position. Cogan attributed this phenomenon to easy fatiguability and rapid recoverability of the myasthenic muscle.

Lid retraction:- In a patient with one eye myasthenic ptosis, the nervous system attempts to keep the eyes open by increasing the level of innervation to the ipsilateral and contralateral levator muscle (Herrings’ law). Non ptotic eye also receives increased innervation and rises above the normal level since it is less involved by the myasthenic process. If the ptotic eye is covered, the retraction of the other eye ceases and the lids fall to the normal position. Because now the normal eye is determining the level of innervation to the two lids. As soon as the ptotic eye is uncovered, it will be observed to be much lower than it was, when that eye was determining the lid innervation. This test distinguishes this type of ‘pseudo lid retraction’ (due to ptosis of the fellow eye) from true neurogenic lid retraction. True neurogenic lid retraction occurs in upper mid brain or diencephalon lesions (Collier’s sign). If the patient has true Collier’s sign, the retracted lid will not fall when either eye is covered.

Nystagmus:- Although isolated nystagmus is uncommon, it may be seen unilaterally or bilaterally in myasthenics without an apparent ophthalmoparesis. The diagnosis of myasthenic nystagmus may be confirmed by resolution of the nystagmus following intravenous edrophonium injection.

Orbicularis oculi:- Weakness of the orbicularis oculi is often found in myasthenics and is evaluated by the examiner attempting to open the eyes against forced eyelid closure. The “peek sign” is due to orbicularis fatigue during gentle eyelid closure causing one or both eyes to gradually open spontaneously, and the patient appears to “peek” at the examiner. Despite orbicularis weakness, corneal exposure is rarely a problem. However, these patients may occasionally complain of tearing due to an inadequate blink. Orbicularis fatigue may also cause lower eyelid ectropion occasionally, seen typically during the latter part of the day.

Pseudo inter nuclear ophthalmoplegia:- Failure of the adducting eye beyond the midline and and dissociated nystagmus of the abducting eye on attempted horizontal conjugate gaze constitutes the syndrome of inter nuclear ophthalmoplegia. In some myasthenic patients this constellation of eye movements has been reported. It is important to distinguish myasthenia from a brain stem lesion. Intravenous tension resolves this condition in myasthenia but not in brain stem lesion. In myasthenia dissociated nystagmus builds gradually in amplitude, where as the nystagmus in true INO is present at its full amplitude at the onset and does not vary thereafter.

Pupil involvement:- Although some degree of pupillary dysfunction can occur in patients with myasthenia, in most patients this dysfunction is not clinically significant. In
patients with nonspecific ocular motility disturbances and clinically normal pupillary responses, myasthenia should be strongly considered in the differential diagnosis. Conversely, when oculomotor disturbances occur in the setting of a dilated, poorly reactive pupil, myasthenia should not be considered a likely cause.

**Saccadic eye movements**- Eye movement recordings are useful in documenting the disorders of ocular motility. Four types of are found in myasthenic subjects: normometric, hypermetric, hypometric and glissade-like. Normometric, hypermetric and hypometric saccades had normal velocity for the actual size of eye movements. They differed in that normometric saccade reached the target, hypermetric ones overshot, and hypometric ones fell short. Glissade-like saccades had normal velocity at the beginning but decelerated toward the end of the movement.

Quiver (twitch like) eye movements are small amplitude saccades that are frequently hypermetric and have maximum velocities greater than normal due to a central compensatory adaptation that occurs in some myasthenics. It has been suggested that these quiver eye movements may be pathognomonic for myasthenia.

**Factors Influencing the Manifestations of Myasthenia**-
A wide variety of endogenous and exogenous factors may affect the signs and symptoms of myasthenia, often resulting in worsening or even onset of symptoms. These factors include temperature changes (worsening with heat, improvement with cold), fever, emotional stress, viral illness, surgery, menstruation, pregnancy, immunization, infection, thyroid dysfunction, and a variety of drugs.

**Diagnosis**
Ocular Myasthenia should be considered in any patient with ptosis and/or diplopia, particularly with variability and fatigability of muscle function. Symptoms tend to be worse at the end of the day. Exacerbation of muscle weakness after repetitive or sustained effort and improvement following rest are important features of this disease, as well as absence of pain, sensory loss, clinical pupillary involvement, or decreased vision. Old photographs are very helpful in documenting duration of blepharoptosis.

**Edrophonium and neostigmine tests**
The edrophonium (Tensilon) test has remained a first-line test for diagnosis of myasthenia since its introduction by Osserman and Kaplan in 1952. Edrophonium inhibits the enzyme acetyl cholinesterase and results in an increase in available ACh for the limited receptor population in myasthenia. Onset of action begins 30-60 seconds after intravenous injection. Since it is quickly inactivated by hydrolysis, the effects usually resolve within five minutes. It is given intravenously with blood pressure monitoring, and electrocardiographic monitoring, on occasion, when indicated. The dose of edrophonium chloride is 0.15 mg/kg in children and usually up to 10 mg in adults. For adults, a 1-2 mg test dose is injected intravenously to watch for a positive or idiosyncratic response. If eyelid function or ocular motility has not improved within one minute, then the remaining 8-9 mg of edrophonium is injected. If there is an improvement in muscle weakness, the test is recorded as positive and is concluded.

Neostigmine is a longer-duration anticholinesterase than edrophonium, permitting a lengthier evaluation of changes in ocular motility and eye alignment. Neostigmine is particularly useful in children and patients with minimal ocular manifestations.
Sleep test:- The patient is kept in a quiet, darkened room and instructed to close his eyes and rest for 30 minutes. The patient is photographed and ocular motility measurements are obtained before and after the rest. The test is considered positive if there is improvement in the ptosis and/or ocular motility disturbance following the rest. This test is especially useful in cases where an edrophonium test is technically difficult, e.g., poor venous access or in children, or in patients with relative medical contraindications to anticholinesterases (e.g., bradycardia or cardiac dysrhythmia).

Ice pack test:- Local cooling to eliminate ptosis in patients with suspected myasthenia is a rapid and simple test. The size of palpebral fissure is measured, and a surgical glove containing crushed ice is applied to more ptotic eye lid for 2 minutes. After 2 minutes the glove is removed and the size of palpebral fissure is again measured. The test is considered positive if the size of the palpebral fissure improves.

Electrophysiological studies
Repetitive Supramaximal Motor Nerve:- In myasthenia, a characteristic decrement (usually greater than 10%) in muscle action potential amplitude with repetitive stimulation is typically seen. The decrement generally begins with the second and typically plateaus by the fourth or fifth response.

Single-fiber Electromyography (SFEMG):- This test evaluates neuromuscular transmission in individual motor endplates. A single fiber electrode is placed into a muscle in a position where action potentials from two adjacent muscle fibers can be measured. The time interval between the firing of any two muscle fibers from the same motor unit displays variability called ‘jitter,’ which is minimal in normal patients. Defective neuromuscular transmission, as in myasthenia, causes increased temporal variability. SFEMG is more sensitive than RNS in the detection of myasthenia.

Anti acetylcholine receptor antibody assay
An elevated AChR Ab titer is diagnostic of myasthenia. With newer assays, AChR Abs have been demonstrated in up to 98-99% of patients with generalized myasthenia

Muscle biopsy
Muscle (motor point) biopsy, with quantitation of available AChRs by binding of radio labelled alpha-bungarotoxin, is considered highly sensitive and specific, though this test is technically difficult. Muscle biopsy may be extremely helpful in patients with borderline or absent AChR titers and equivocal electro diagnostic or pharmacologic test results. In addition to quantitation of AChRs, muscle biopsy provides opportunity for ultra structural analysis of the motor endplate.

If symptoms or signs are present that suggest a diagnosis other than myasthenia, MRI of the brain and orbits with contrast should be obtained.

Treatment
Treatment for myasthenia may be classified into two groups. The first group, symptom therapies, may reduce symptoms but do not alter the immunological process in myasthenia. Consequently they do not protect the patient from myasthenic crisis. The second group consists of immune therapies which may be used to alter the course of the autoimmune process and have the ability to prevent myasthenic crisis.

Symptom therapies
Acetylcholine Esterase Inhibitors
Inhibition of ACh esterase maximizes the availability of ACh to the remaining AChR molecules, contributing to successful postsynaptic membrane depolarization. However, continued immune attack on the neuromuscular junction eventually leads to sufficient loss of active AChR molecules resulting in an inadequate number of remaining AChR molecules to depolarize the postsynaptic membrane even when an excess of ACh is available. In these circumstances, inhibitors of ACh esterase will have little to no beneficial effect. Cholinesterase inhibitors should be used with caution in patients with bronchial asthma, cardiac dysrhythmia, pregnancy, lactation, and prostatic hypertrophy. Since
many patients with OM fail to note significant benefit from treatment with cholinesterase inhibitors alone, adjunctive immunotherapy is often necessary.

Side effects of cholinesterase inhibitors include abdominal pain and diarrhoea most commonly, due to cholinergic stimulation of the gastrointestinal tract which can be reduced by the use of oral atropine or belladonna containing compounds.

**Pyridostigmine (Mestinon):** Pyridostigmine is the most commonly used cholinesterase inhibitor. The duration of action is approximately 4 hours. Pyridostigmine is available in a 60 mg tablet, a 180 mg sustained-release tablet, and a liquid suspension (60 mg/5cc). A parenteral form (5 mg pyridostigmine bromide/cc) can be used to supplement oral doses or as a replacement for oral therapy. Therapy can be initiated at 30 mg p.o. t.i.d. and then increased as needed.

**Neostigmine (Prostigmin):** Neostigmine is available as neostigmine bromide in 15 mg tablets for oral use and as neostigmine methylsulfate for parenteral use in multiple concentrations. The duration of action of neostigmine is approximately 2-2.5 hours.

**Ambenonium:** Least frequently used for myasthenia, but it is occasionally used in patients who are intolerant to pyridostigmine or neostigmine.

**Immunotherapy**

Immunotherapy should be considered in all patients with myasthenia whether or not serum AChR Abs are detectable.

1. **Immunomodulators**
   a. **Corticosteroids:** They inhibit the release of immune cytokines such as interleukin-1 and -2, tumor necrosis factor and interferon-gamma which result in immunosuppression. In addition, corticosteroids influence the cell-mediated and humoral-mediated limbs of the immune system. In OM, 60 mg of prednisone is initiated. Once benefit is achieved, prednisone dosage can be slowly tapered to 20-30 mg (or less) on alternate days. Acute exacerbation of the myasthenic weakness on initiation of higher doses of oral corticosteroids has been reported frequently. These patients should be hospitalized for close monitoring during initial therapy. This initial worsening is attributed in part to an increase in AChR Ab titer, may be preventable by pre-treatment with intravenous gamma globulin.

   Prednisone may be replaced with long term therapies, such as azathioprine, in both generalized and ocular myasthenia.

   b. **Cyclosporin:** Cyclosporin inhibits the production of interleukin-2 and other immune cytokines, leading to moderate immune suppression. It is useful in patients who cannot tolerate prednisone. Cyclosporin is available as an oral solution (100 mg/ml), a soft gelatin capsule (25 mg or 100 mg), or an intravenous formulation. For a loading dose, 10-15 mg/kg may be used. 5-10 mg/kg/day is adequate to maintain serum levels between 100 and 500 mg/ml and achieve a good therapeutic response in myasthenia. Cyclosporin has a large number of adverse effects, generally the most problematic of which is its nephrotoxicity.

   c. **Tacrolimus (FK506)** is a calcineurin inhibitor just as cyclosporine. The drug inhibits the proliferation of activated T lymphocytes, but also acts on ryanodine receptor-mediated calcium release from sarcoplasmic reticulum in muscle cells. The drug has shown a beneficial effect in MG, and it represents an alternative second-choice drug for moderate to severe MG.

2. **Cytotoxic Therapy**

Azathioprine, a purine analog interfere with purine metabolism, eventually inhibits DNA and RNA synthesis. Azathioprine is available as a 50 mg tablet and in vials for intravenous use. Although the conventional dosage of azathioprine is 3-5 mg/kg. Complications of therapy are chemical hepatitis, bone marrow depression, stomatitis, gastrointestinal disturbances etc.

Mycophenolate mofetil is regarded as an alternative drug for mild MG. The drug has few and mild side effects and is easy to use both for patients and doctors.

Methotrexate should be used only when first-choice immunosuppressive drugs do not have sufficient effect. Methotrexate has a good and proven effect for other autoimmune disorders. It can be tried in selected MG patients with a marked functional deficit, because it is usually well tolerated.

3. **Humoral therapy**

**Plasmapheresis:** AChR Ab titers can be successfully decreased with plasmapheresis. Removal of one plasma volume (5% of the body weight in kilograms; 1.5-3 liters per exchange) will reduce antibody titers by 30-75% in the serum. Therefore, repeated exchanges over a short period of time are required to reduce the total IgG and AChR Ab titers significantly. Improvement is usually apparent 24-72 hours after treatment but may not be maximal until 1-2 weeks.
after a series of plasmaphereses. Complications include transient hypotension, cardiac arrhythmias, and, rarely, infections at the site of intravenous access.

**Intravenous Gamma Globulin:** Pooled human gamma globulin has been reported to be of transient benefit in myasthenia. Its mechanism of action is currently unknown. Most regimens involve administering intravenously 0.4 grams of pooled human gamma globulin per kilogram body weight followed by a repeat treatment daily for 3-5 days. These treatments may subsequently be followed by weekly or biweekly infusions to maintain effect.

**Monoclonal antibodies:** Rituximab is a chimaeric monoclonal antibody that targets B lymphocytes through its binding to the CD 20 molecule. MG is a prototype of an antibody-mediated autoimmune disease, and so rituximab and B-cell depletion are a very promising treatment alternative. Rituximab should be reserved for patients with severe MG, where treatment with prednisolone and at least two other standard immunosuppressive drugs has failed. For milder MG, the risk of progressive multifocal leucoencephalopathy and other potential long-term side effects probably outweigh its therapeutic potential.

**Coordinated Use of Immunotherapies**
Immunotherapy of myasthenia may be divided into an induction phase and a maintenance phase. In the induction phase, the immunotherapies used for major symptoms of myasthenia are those that have a rapid onset of effect, even though they may have significant toxicity with long term use. In maintenance therapy, the emphasis must be on therapies with acceptable long term toxicity.

**Thymectomy**
Although rarely used in ocular myasthenia, thymectomy is generally recommended for patients with generalized myasthenia. Multiple studies have shown an increased chance of remission for at least one to three years after thymectomy.

**Surgical correction**
In cases of burned out myasthenia, surgical correction of ptosis can be done after neurological evaluation. In some of our patients with bilateral severe ptosis we have done frontalis sling surgery.

**Future**
New and more selective immunoactive drugs are marketed worldwide. These drugs are established as first- or second-line treatment for an increasing number of autoimmune and inflammatory disorders, due to their proven superior clinical effect. As pathogenesis differs in MG subgroups, the immunoactive treatment needs to be individualised. Subgroups of MG will respond differently to various treatment alternatives. In the future, the detailed evaluation of each MG patient will hopefully have distinct therapeutic consequences, so that the treatment regime is tailored according to the specific autoimmune dysfunction.

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(Courtesy to Dr. Ani Sreedhar for clinical photographs)


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