Ocular Myasthenia Gravis: A Review

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ABSTRACT
Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction of skeletal muscles. Patients affected with MG may present with ocular features or develop ocular involvement later in the course of the disease, known as ocular MG (OMG). OMG can mimic ptosis, committant and innominant strabismus, cranial nerve palsies, gaze palsies and internuclear ophthalmoplegia. Hence, it is important to establish a correct diagnosis and start appropriate treatment. This review focuses on the clinical features, diagnosis, and management of OMG.

KEY WORDS: Antibodies, electrophysiology, management of ocular myasthenia, ocular myasthenia gravis

INTRODUCTION
Myasthenia gravis (MG) is a disease of the neuromuscular junction characterized by defective transmission of pulses from the motor neuron to the skeletal muscle and subsequent muscle weakness.

Ocular MG (OMG) is defined as occurring in those patients who have myasthenic symptoms and signs restricted to extraocular muscles (EOMs) for at least 2 years.

Myasthenia may affect any age group; the average age of onset was 43 years, with a lower age of onset in women.[¹] OMG develops in a greater proportion of males than females, in contrast to generalized myasthenia, which affects women more often.[²]

Pathophysiology
MG is a B-cell mediated autoimmune disease, with antibodies directed against acetylcholine receptors (AChR), which block the receptors, cause faulty transmission of impulses and consequently cause muscle weakness.[³] The role of the various antibodies is detailed further in the section on investigations.

Clinical features
Generalized MG is characterized by skeletal muscle weakness, exacerbated by activity and improving with rest. It involves the limbs, respiratory, facial, and bulbar muscles.

OMG involves the extraocular muscles, levator palpebrae superioris, and orbicularis oculi.[³] Typically the pupil is not involved. Extraocular muscles are commonly affected as they are composed of twitch fibers which have a higher frequency of firing and develop tension faster. Extraocular muscles also have a distinct muscle allotype and fewer AChR.[⁴]

More than 50% patients of OMG present with ptosis and diplopia.[⁵] Multiple extraocular muscles may be involved which leads to variable presentation; typically the patient has limitation of ocular movement which is variable and does not fit into any specific pattern of strabismus.[³] About 50-80% of cases of ocular involvement go on to develop generalized myasthenia, 90% within first 2 years of onset of OMG.[⁴]

Myasthenia in the pediatric age-group merits particular attention. This includes transient neonatal myasthenia, congenital myasthenia, and juvenile myasthenia. Transient neonatal myasthenia results from transplacental transmission of maternal antibodies.[⁶] Congenital myasthenic syndromes are a heterogeneous group of heritable disorders of neuromuscular transmission, and present in childhood,
where the post-synaptic receptors are resistant to the action of ACh.\textsuperscript{[7,8]} Juvenile MG is an autoimmune disorder with antibody-mediated dysfunction of the neuromuscular junction (NMJ).\textsuperscript{[9]} The childhood myasthenia patients have predominantly ocular myasthenia (in 85-95\%), which rarely progresses to the generalized disease. The condition responds to steroids. Only rarely are there long-term neurological sequelae. However, a few patients develop amblyopia resulting from loss of binocularity.\textsuperscript{[10-12]}

Clinical symptoms and signs in OMG include the following:

**Eyelid signs**

- Ptosis can be variable, unilateral or bilateral, symmetric or asymmetric - History of diurnal variation is frequently elicited, with exacerbation of ptosis/ophthalmoplegia by the end of the day.
- Eyelid fatiguability test - The vertical palpebral fissure height is measured, the patient is asked to look in upgaze and sustain the position for 30 s. The palpebral fissure height is measured again at the end of this interval. A decrease in palpebral fissure height by 2 mm is considered significant.
- Cogan’s lid twitch sign - Patient is asked to look down for at least 15 s and then perform a saccade back to primary position. This leads to a quick upward movement followed by downward drift of upper lid.
- Peek sign - It is a sign of orbicularis oculi weakness. The patient is asked to keep his eyes shut. Eyelids tend to drift apart and underlying sclera can be seen, as though the patient is peeking through the nearly closed eyelids.
- If the ptosis is asymmetric or unilateral, manually elevating the worse affected eyelid will cause drooping of the other eyelid. This is described as “see-saw ptosis.” Lifting the ptotic lid decreases the need for nerve impulses for the levator. By Hering’s law, the stimulus to the contralateral eyelid decreases as well, which then manifests ptosis.

**EOMs**

- Patients present with binocular diplopia.\textsuperscript{[13]} The most common muscle to be affected in MG is medial rectus followed by superior rectus
- MG can mimic any type of strabismus (comitant or incomitant) with or without ptosis.\textsuperscript{[2]}

**Differential diagnosis**

Differential diagnoses of OMG include other causes of acquired ptosis and/or limitation of ocular movement, including aponeurotic ptosis, chronic progressive external ophthalmoplegia (CPEO), myotonic dystrophy, cranial nerve palsy, thyroid ophthalmopathy, and orbital myositis. Eaton-Lambert syndrome is a differential diagnosis for generalized MG; however, it very rarely involves ocular muscles.

Certain drugs and medications can also cause myasthenia-like manifestations. These include D-penicillamine, phenytoin, beta blockers, antibiotics such as aminoglycosides, chloroquine, cisplatinum and lithium.\textsuperscript{[14]}

**ASSOCIATED CONDITIONS**

Thymic tumors and certain autoimmune disorders are seen in association with myasthenia.\textsuperscript{[15]} More than 75 % of patients with AChR-antibody (AChR-Ab) positive myasthenia patients have thymic abnormalities. Thymic hyperplasia is the most common pathology reported. Thymic tumors are present in 15% patients and are usually non-invasive cortical thymomas. Autoimmune thyroid disease is seen in 3-8% of patients with myasthenia. Other associated autoimmune conditions are rheumatoid arthritis and systemic lupus erythematosus.

**Clinical tests**

**Sleep test**

Sleep test measures improvement in OMG signs and symptoms after a period of rest. The patient is asked to sleep or rest with eyes closed for 30 min. Resolution of ptosis or ophthalmoplegia after rest confirms myasthenia. Signs of myasthenia may reappear after 5 min, which further confirms the diagnosis.

**Ice test**

An ice pack is placed over patient’s eyelids, and improvement in ptosis or ocular motility defects is noted before and after the ice test. The ice pack needs to be placed for a period of 2-min for ptosis and 5 min for ophthalmoplegia.\textsuperscript{[3]}
Ice test is said to be positive if the upper eyelid elevates by at least 2 mm after applying the ice pack.\[3\]

The rationale of ice test is based on the physiologic principle of improved neuromuscular transmission at reduced temperatures. Application of ice reduces anticholinesterase activity, which increases the amount of ACh available at the neuromuscular junction and leads to increased action of ACh and improvement of symptoms.\[16,17\]

The sensitivity of ice test has been shown to be 77-89% in various studies while the specificity has been seen to be 98-100%.\[18,19\] The positive predictive value of the ice test has been 100%.\[19\]

The clinical tests are more likely to yield results when there is a clinically manifest ptosis. However, they may be negative in very severe or long-standing disease, where the ptosis has become “fixed” and lost its variability.

**Pharmacologic and electrophysiologic tests**

The diagnosis is of myasthenia is based on the clinical features, the benefit of administering cholinesterase inhibitors, the detection of specific autoantibodies (anti-AChR, anti-muscle specific tyrosine kinase [MuSK] or anti-lipoprotein related protein 4 [LRP4]), and significant decrement evidenced by electrophysiological tests including repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG).

**Pharmacologic tests**

Administration of ACh esterase inhibitors will increase the availability of ACh at the neuromuscular junction, and overcome the neuromuscular transmission block, thereby improving the patient’s signs and symptoms. This principle is the basis of edrophonium test and neostigmine test.

Edrophonium (Tensilon) is a short-acting acetylcholinesterase inhibitor, and acts within minutes. The palpebral fissure height is measured, and 2 mg (0.2 ml) of edrophonium injected intravenously. The patient is observed for 60 s for any improvement. If improvement is seen, the test is positive, else another 8 mg is injected. The patient has to be monitored for the side effects of bradycardia, bronchoconstriction, or syncope; resuscitation measures, including atropine sulfate injection, should be available. The minor side effects are fasciculations, nausea, and perspiration; these are indications of the action of the drug on the patient, and can help avoid false negatives.

Neostigmine has similar effects but is slower acting. Atropine is administered simultaneously with neostigmine. The patient has to be observed 45-60 min for a positive outcome.

**Electrophysiologic testing**

RNS studies and SFEMG are the recommended electrophysiological tests for MG.\[20\]

**RNS**

RNS is the most frequently performed electrodiagnostic test for MG. It is performed by placing the recording electrode over the endplate region of a muscle and stimulating the motor nerve to that muscle. The nerve is electrically stimulated 6-10 times at 2-3 Hz and the compound muscle action potential amplitude (CMAP) is recorded from the electrodes over the muscles. In patients with ocular myasthenia, the orbicularis oculi is studied.

The change in amplitude with RNS is evaluated at rest and can also be done post-exercise. Post-exercise (for 30-60 s) evaluation increases the sensitivity of the test by 5-10%. There is no change in CMAP in normal muscles, whereas a progressive decline (\(>10\%\)) in the amplitude with the first four to five stimuli is seen in MG (a decremental response).\[21,22\] To maximize the sensitivity, the muscles tested should be warm, and acetylcholinesterase inhibitors should be withheld for 12 h before the study.

The sensitivity of RNS is \(>70\%\) in case of generalized MG.\[23\] In OMG, the test shows 15-45% sensitivity and 90% specificity.\[24,25\] The RNS test is not specific to MG, it is also seen in Lambert Eaton myasthenic syndrome, motor neuron diseases, and myopathies.

**SFEMG**

SFEMG identifies abnormal neuromuscular transmission by measuring temporal variability in the firing of adjacent motor nerve fibers from
a single motor unit, phenomenon called “jitter.” The latency from stimulus to response varies in a different group of muscles. The fluctuations in the time taken by the end plate potentials at NMJ to reach the action potential threshold produces this variation - called the neuromuscular jitter.[26] Any disorder, such as MG, that reduces the safety factor of transmission at the NMJ will produce increased jitter. SFEMG is more sensitive than RNS and may identify electrophysiologic abnormalities in clinically normal muscles. It is less widely available, and more technically demanding than RNS.

SFEMG requires a specialized concentric needle, which records individual muscle fiber action potentials. A recording surface of 25 μ diameter and a 500 Hz high-frequency filter ensure recording of the individual muscle fiber action potential. The nerve is stimulated and the potentials elicited are recorded with an SFEMG electrode.

In OMG the sensitivity of SFEMG is 80-90% in facial muscles, over 95% in orbicularis oculi and superior rectus levator complex.[27-29]

Abnormal jitter is not specific for myasthenia. A standard EMG examination helps differentiate it from the abnormal jitter seen in other neuromuscular disorders such as motor neuron disease, polymyositis, peripheral neuropathy, and Lambert Eaton myasthenic syndrome. However, SFEMG may not clearly distinguish between CPEO from OMG.

Serologic testing

In myasthenia autoantibodies are described against the AChR-Ab. Recently, other targets have been described such as the MuSK protein or the LRP4.

Demonstration of AChR-Ab or MuSK-Ab antibodies confirms the diagnosis of MG.[15,30] Patients with positive AChR-Ab or MuSK-Ab assays are classified as seropositive MG (SPMG).

Anti-AChR antibodies have been demonstrated in as many as 80-99% of patients with generalized myasthenia and 30-77% of patients with OMG.[13,31,32]

Serologic testing for AChR-Ab is done before initiating the immune modulating therapy, as therapy can sometimes lead to apparent seronegativity.[33] A patient may also become seropositive after 6-12 months of initial clinical presentation.[34] AChR-Ab titers correlated poorly with disease severity of patients. A low-titer or even antibody-negative patient may have more severe clinical disease than a patient with high titers. However, in an individual patient, the titers tend to fall with successful immunotherapy and clinical improvement, and the patient may become seronegative.[33] Nearly all patients (98-100%) with MG and thymoma are seropositive for these antibodies.[35,36]

MUSK-AB

Antibodies to the MuSK that mediates agrin-dependent AChR clustering and NMJ formation during development. It is present in 38-50% of those with generalized MG who are AChR-Ab negative.[37-39] MuSK-Ab positive MG may have a different cause and pathologic mechanism than AChR-Ab positive disease.[38,40] It is not commonly present in patients with ocular myasthenia but has been detected in a few cases.[41,42]

Clinical features of patients with AChR-Ab negative and MuSK positive myasthenia are slightly different with female preponderance, any age of onset, oculobulbar form with diplopia, ptosis, dysarthria, restricted myopathic form, no thymic pathology, and poor responsiveness to acetylcholinesterase inhibitors. They usually show a good response to plasma exchange and immunosuppression.[39,43-46]

MuSk-Abs are not routinely evaluated. They are useful in cases not responding to the usual medications or patients who are AChR-Ab negative.

Patients who test negative for both these antibodies have seronegative MG. They have a clinical profile and electrophysiological tests similar to the seropositive patients but are more likely to have purely ocular disease and generally have a better outcome after treatment.[39]

Treatment

The treatment of ocular MG is aimed at relieving the symptoms of ptosis and diplopia, as well as preventing the development of generalized MG
symptoms. Treatment options include symptomatic and immunomodulatory treatment of myasthenia, thymectomy, and corrective treatments for ptosis and strabismus.

**Pharmacotherapy in myasthenia**

Acetylcholinesterase inhibitors are the agents of the first choice in the treatment of myasthenia. They retard the degradation of ACh that occurs by enzymatic hydrolysis in the NMJ, prolonging the life of ACh, and leading to a variable improvement in strength of muscle.\(^{[47]}\)

Pyridostigmine is the most commonly used drug. No randomized trials have studied the efficacy of anticholinesterase agents in OMG.\(^{[48]}\) Pyridostigmine treatment alone rarely (6.9%) results in resolution of ocular symptoms, particularly diplopia.\(^{[49]}\) Pyridostigmine has a rapid onset of action (15-30 min) with peak action at about 2 h, and its effects last for 3-4 h, sometimes longer. In adults and adolescent, the initial dose is 30 mg 3 times a day, titrated based on the clinical response and side effects. A maximum dose of 120 mg every 4 h can be given. Most adult patients respond to 60-90 mg every 6 h. Few patients need a dose every 3 h to maintain symptomatic benefit. Minimum effective dose of pyridostigmine for relief of symptoms should be used in patients with longstanding disease and low risk of generalization.

**IMMUNOSUPPRESSIVE AGENTS**

Immunosuppression is usually necessary to achieve remission of ptosis or ophthalmoparesis. Only about 10% of patients with OMG achieve spontaneous remission without corticosteroids. Ocular symptoms are more likely to resolve with corticosteroids than with pyridostigmine alone (70% vs. 29%).\(^{[48-50]}\) Apart from the symptomatic relief, studies also suggest that corticosteroids reduce the progression to generalized MG.\(^{[49,51,52]}\) The treatment may reduce the incidence of generalized MG, delay its onset, or mask its symptoms.\(^{[48,51-53]}\)

There is no single recommended dosing regimen. Alternate-day dosing is preferred. Prednisone is started with lower doses and gradually increased over 3-4 weeks, as some patients may have unrecognized generalized MG. Maximum daily doses of 0.5-1 mg/kg of prednisone are often needed for several weeks (occasionally months) in order to maintain benefit. Patients who are started on a high dose of oral prednisolone should be monitored monthly, as there can be worsening of symptoms or even myasthenic crisis in up to 15% patients.\(^{[54]}\) This neurological worsening is less common in patients with OMG compared to generalized MG.

After initial resolution and stabilization, steroids are then tapered. Low maintenance dose (5-10 mg every other day) are often effective in OMG, but response is highly variable. The decision to use corticosteroids in OMG should be made after weighing the severity of symptoms, the efficacy of non-pharmacologic measures and the possible side effects of the steroids.

**STEROID SPARING AGENTS**

Patients who do not tolerate or do not respond to prednisone require second-line immunosuppressants like azathioprine (AZA), mycophenolate mofetil (MMF), and cyclosporine. AZA is the most commonly used drug. The side effects of these drugs limit their use in older age group and isolated OMG, but they may be necessary to control the symptoms.

AZA is used as monotherapy or in conjunction with prednisone; the latter is then tapered off. Combined therapy reduces failures, improves remission rates, and decreases side effects.\(^{[55]}\) Observational studies also suggest that AZA reduces the risk of progression to generalized MG.\(^{[52,53]}\)

AZA is initially started at a dose of 50 mg daily for 2-4 weeks. If it is tolerated well then the dose can be increased by 50 mg increments every 2-4 weeks to a maintenance dose of 2-3 mg/kg total body weight. Progressive fall in AChR-Ab titers along with clinical response is delayed more than 6 months with AZA alone. Continuous administration for 2-3 years is required to achieve the full effect.\(^{[3,56]}\)

Risks and benefits of treatment should be evaluated before starting therapy with AZA. The side effects of AZA include flu-like illness, hepatotoxicity, leukopenia, pancreatitis, and teratogenicity.

Cyclosporine A is considered the next line in patients who are intolerant of steroids and/or AZA. It has a
faster onset of action compared to AZA, as early as 1-2 months after initiating therapy. The initial dose of 5 mg/kg/day in two to three divided doses is started and is modified on the basis of serum creatinine levels and clinical response. Improvement in muscle strength and a reduction in AChR-Ab titers have been reported with cyclosporine. Clinical response is seen in up to 90% of the patients with cyclosporine. However, multiple adverse effects make it the less favored option.[57]

MMF selectively inhibits lymphocyte proliferation by blocking purine synthesis exclusively in lymphocytes. It is the second line therapy after AZA, due to its favorable side effect profile and lesser treatment failures. It has been used both as a steroid sparing agent and as immunotherapy.[58]

NON-PHARMACOLOGICAL MANAGEMENT

Crutch glasses or lid adhesive devices can temporarily aid in the treatment while awaiting a response to acetylcholinesterase inhibitors or immunosuppressive therapy. Lubricating eye drops must be used along with these to prevent corneal dryness and exposure keratopathy.

Diplopia can be avoided using an eye patch, opaque contact lens, or occlusion of an eyeglass lens. However, these interventions have the disadvantage of loss of depth perception. In patients with a stable diplopia, use of prism lenses offers another non-pharmacologic alternative.

Thymectomy has been performed in younger adults to improve non-paraneoplastic MG. However, controlled prospective studies on the benefit of this surgical procedure are still lacking.[59]

Surgical management of blepharoptosis and strabismus

Surgery is an accepted modality for patients with blepharoptosis in OMG refractory to medical therapy. Multiple techniques have been attempted, including levator resection and frontalis sling using various materials.[60,61] A frontalis sling with a material such as silicone is advocated, along with planned under-correction. Some patients develop lagophthalmos, but incidence of exposure keratopathy is low and long-term safety is good.[62] Since a fine balance has to be achieved between avoiding excessive lagophthalmos and elevating the lid height sufficiently to allow unobstructed vision, re-surgeries may be required. The flexible and easily adjustable the sling material contributes to the safety of the procedure. Overall, the safety of the procedure is high, and patient satisfaction index is very high.[63-66]

In patients who exhibit stable diplopia, strabismus can be corrected surgically. A conservative approach is considered in the case of strabismus surgery as well. Based on the natural history of myasthenia, it is known to have a more stable course 3 years after initial onset.[67] Surgical corrections should be done at least 3 years of the onset of disease and deficits have been stable for at least 1 year. Surgical correction of strabismus has been reported to have 5-6 months of stability.[68]

CONCLUSION

OMG is commonly misdiagnosed. Correct clinical assessment and appropriate investigations can confirm the diagnosis. Although it is a subset of generalized myasthenia, there are features unique to ocular myasthenia. A team management by the ophthalmologist and the neurologist gives the best outcome for the patient.

REFERENCES

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