Ocular myasthenia gravis

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Abstract

Myasthenia gravis is primarily an autoimmune disorder of neuromuscular junction at the skeletal muscles. The hallmark is fatigability and variability in muscle weakness. It has a diverse presentation because of the variation in the extent of muscles involved. Most often ophthalmologists are the first to diagnose it, as systemic myasthenia may have ocular involvement either at the onset or later in the course of the disease. This review article highlights the presentation, differential diagnosis, investigations, and treatment of ocular myasthenia.

Keywords : Myasthenia, acetylcholine, neuromuscular junction, antibody.

Introduction

Ocular Myasthenia gravis (OMG) is a localized form of generalised myasthenia in which antibodies directed against acetylcholine receptors destroy or bind the acetylcholine receptors at neuromuscular junction.

Ocular muscles are involved in around 95% of patients during the course of the disease, whereas 40–90% of generalised myasthenia may initially present with droop and diplopia and around 50-80% of ocular myasthenia may eventually progress to general myasthenia.1 Ocular Myasthenia Gravis (OMG) may affect any age and sex, age distribution is bimodal, women are afflicted more in their mid 20s whereas men show their peak at around 40s.

Pathophysiology

Neuromuscular junction is the site of connection between a nerve terminal and a muscle. When action potential generates, there is release of acetylcholine (a neurotransmitter) from the nerve terminal which then binds to the Ach(nicotinic) receptors at the post synaptic membrane of striated muscle which then initiates the muscle contraction. In myasthenia antibodies are directed against acetylcholine receptors and decrease the available receptors by blocking or complement mediated membrane damage thereby decreasing the signal transduction. Acetylcholine receptor antibodies are present in around 90% generalized myasthenia and 50-70% of ocular myasthenia3. Extraocular muscles are the most susceptible to it as they have a high frequency of synaptic firing with fewer number of acetylcholine receptors. Moreover they are at constant tension in maintaining gaze in a particular direction. Hallmark of OMG is variability in muscle weakness and fatigability. Most common presentation is diplopia and ptosis. The pupillary fibres are devoid of nicotinic acetylcholine receptors, and thus pupils are unaffected in myasthenia gravis3.

Presentation

Majority of patients present with pupil sparing ocular motility disorder with ptosis either at presentation or during course of disease. Around 20% may remain purely ocular, rest may progress to generalized form and chances of progression are high in 2 years from the onset.

Ptosis is one the most common presentations of OMG (Figure 1a). It is due to the involvement of levator palpebrae superioris. Ptosis worsens as the day progresses, or after repeated or sustained use of muscle throughout the day. Patient typically feels better after a period of rest. One should always rule out OMG in a case of acquired ptosis.

Ptosis can be unilateral or asymmetrical bilateral. Important clinical signs in favour of myasthenia are “Cogans lid twitch sign” in which there is overshooting of lid as patient is instructed to look downwards for at least 15 seconds and then gaze upwards to primary gaze. Test is considered positive when there is overshoot followed by downward drift.
of the lid. This is not specific for myasthenia, as it may be seen in thyroid eye disease.

Other clinical sign due to the lid involvement is “see saw ptosis or enhanced ptosis” in case of bilateral ptosis which is elicited by first asking patient to look upwards, ptosis will worsen after prolonged upgaze and now one of the lid is elevated manually, there will be worsening of ptosis or enhancement of ptosis in contralateral eye. This can be explained by Herring's law of equal innervations. This test helps to differentiate from other causes of bilateral ptosis like nuclear third nerve palsy, myotonic dystrophy. There is decreased tone in orbicularis oculi muscle which can be elicited by an attempt to open the eyes manually by the examiner after patient is being asked to forcefully close the eyes. There is lack of inhibition due to decreased orbicularis tone. The lids may fall apart even without forceful opening and there is peeking of underlying sclera. This sign is called “peek sign”.

Extraocular involvement can vary from single muscle to multiple muscles. Ocular myasthenia is a big masquerader and may mimic supranuclear, internuclear, or infranuclear cranial nerve palsies. It may mimic any cranial nerve palsy which is pupil sparing. Thus OMG should be kept as a differential of unilateral/bilateral/painless ophthalmoplegia sparing pupil with or without ptosis.

**Diagnosis and tests**

Myaesthesia is a clinical diagnosis which is complemented by clinical, serological and electrophysiological tests.

**Clinical Tests**

Common bed side tests are fatigue test, ice test and sleep test.

- **Fatigue Test**

  There is worsening of ptosis or extraocular muscle impairment after a period of sustained upward gaze and on voluntary contraction of antagonist orbicularis muscle there is temporary recovery of ptosis.

- **Ice and Sleep Test**

  Improvement in symptoms especially ptosis with cooling is the basis of ice test. Lowering the temperature decreases the activity of acetylcholinesterase at neuromuscular junction thereby increasing the available acetylcholine molecules for muscle contractions. There is improvement of around 2mm droop after keeping ice pack over lids for around 3 to 5 minutes (Figure 1 b). Ice test is a simple bed side test with sensitivity and specificity of 80-100% in OMG. Golkin et al concluded that the sensitivity of the Ice test is less in complete ptosis but its reliability can be compared with edrophonium test. Positive sleep test is improvement in ptosis after 30 mins of rest.

![Fig. 1: (a) At presentation  (b) After ice test  (c) Tensilon test](image)

- **Edrophonium Test**

  Edrophonium is a short acting, quickly hydrolyzed anticholinesterase. It competitively inhibits the enzyme acetylcholinesterase thereby increasing the acetylcholine. It has a rapid onset of action (30 seconds) with short duration (<5 minutes). It is of particular use in cases where we have evident ptosis. The dose of edrophonium is 0.15mg/kg in children and total dose is no more than 10 mg in adults. After noticing and documenting the position of eyelids, test dose 2mg of tensilon is injected intravenously. Patient is observed for any improvement in ptosis, also watch out for idiosyncratic cholinergic side effects. If there is no side effect with the test dose, incremental dose of 3-4 mg is injected after 2 minutes. If there is no positive response after 1 minute rest of the dose is given in incremental dose.

  Tensilon test should be done under proper observation and monitoring of vitals. Atropine sulphate (0.4-0.6mg) should be available immediately, some even premedicate by injecting 0.4mg atropine subcutaneously. Positive tensilon test is suggestive of myasthenia but not pathognomonic, some patients with intracranial lesions may show positive response. The sensitivity of tensilon test is 95% in generalized myasthenia gravis (GMG) and 86% in OMG. (Figure 1 c)

- **Prostigmine and Neostigmine Test**

  Neostigmine is a longer acting anticholinesterase,
permitting the proper evaluation of improvement in ocular motility. It is of special use in patients with diplopia without ptosis, in children who are not too cooperative for evaluation. Mix of 0.6mg of atropine with 1.5mg of prostigmine is injected in one of the deltoid muscles. The onset of action is 15 mins and effect is most obvious 30 minutes after injection.

**Electrophysiological Tests**

- **Rapid nerve stimulation test (RNS)**
  Supramaximal electric stimuli are delivered to proximal and facial muscles repetitively (6-8 times) at lower frequencies (2-3 hertz) and amplitude of the compound action potential is noted. In myasthenia there is characteristic decremental response (usually more than than 10 %) after 3rd or 4th stimuli. Sensitivity of RNS is 70-80% in GMG and 50% in OMG. The response is also subjective to the type of muscle excited. Moreover, it is not specific for myasthenia as we may get decremental response in other Neuromuscular disorders.

- **Single fibre electromyography (SFEMG)**
  It is the most sensitive test for neuromuscular disorders. Two muscle fibres innervated by single axon are stimulated with a special concentric needle electrode with a recording surface. SFEMG studies the adjacent action potentials from same motor unit. The latency between the potentials is noted. The variation in the time interval between two action potentials is called jitter. SFEMG records this jitter. This jitter is also not specific of myasthenia and can be seen in other neuromuscular disorders.

**Serological Tests**

- **Acetylcholine receptor antibody test**
  It measures the IgM and IgG antibodies to Ach receptors. It is highly specific of myasthenia with increased sensitivity for generalized myasthenia (around 80%) as against 50% for OMG. The absolute titres may also help in prognosticating the progression from ocular to generalized myasthenia. Changes in antibody titres correlate with disease severity. Patients with negative acetylcholine receptor antibody test are seronegative patients. Of these patients, 30% have antibodies against muscle specific kinase (anti MuSK Ab). Anti Musk antibodies are particularly helpful in cases with strong clinical suspicion who are seronegative along with negative tensilon test.

**Imaging Tests**

Patients with positive ice test and positive response to tensilon test may not require neuroimaging. Atypical cases should undergo neuroimaging to rule any intracranial pathology. Confirmed cases of myasthenia should undergo CT mediastinum to rule out thymoma. About 15% of myasthenia patients have thymoma and one half of the thymoma patients develop myasthenia gravis.

**Treatment**

Goal of therapy in myasthenia is to relieve patient symptomatically, reduce the acetylcholine receptor antibodies and induce remission, prevent progression to generalized myasthenia, and avoid the long term side effects of treatment.

Modulation of neuromuscular transmission

Acetylcholine esterase inhibitors: They remain the first line treatment to relieve patient symptomatically. The aim is to increase the duration of neurotransmission for muscle contraction.

Pyridostigmine bromide:

Pyridostigmine (mestinone) is initially given at 30mg twice daily to four times daily and may be increased to a maximum of 1500mg daily. Studies have shown that pyridostigmine given alone does not help in remission of disease. It has good effect on ptosis but diplopia and ocular motility does not improve much with pyridostigmine.

Immunosuppressive therapy

- **Long term immunosuppression**
  Oral corticosteroids in low or moderate dose relieve patients of diplopia. The response can start within days and maximum benefit can be achieved in weeks. There are two common approaches of steroid therapy-high dose/rapid induction regime or low dose/slow titration regimen. High dose therapy carries the risk of exacerbation of myasthenia crisis. After remission, dose is gradually tapered after 4-6 weeks and shifted to alternate day regime. In low dose regimen, 10mg is given and gradually increased by 10mg every week till maximum dose of 1mg/kg which is maintained for 6-12 weeks and then tapered gradually.
  Steroids induce remission in 85% of OMG and decrease the progression from OMG to
GMG. Common side effects of long term steroid use are obesity, hirsutism, osteoporosis, hypertension and increased risk of opportunistic infections.

**Steroid sparing agents**

- Azathioprine- It is a purine antagonist and interferes with T and B cell proliferation. It has been used either as an adjunct to steroid or as monotherapy. Randomized controlled trial of the adjunct therapy has shown increased remission, lower relapse, decrease in antibody titre and low steroid maintenance dose at the end of 3 years of follow up. \(^{15}\)
  Initial dose is 50mg/day which is increased by 50mg every week till maximum of 2-3mg/kg/day in two to three divided doses. Initial response is delayed (more than 6 months) which peaks by 2 to 3 years.
  Potential side effects are hepatotoxicity and bone marrow suppression. Blood counts and liver function tests should be done bi-weekly for the first 2 months after initiating treatment and monthly thereafter. Dose is reduced if count falls below 4000/mm^3^ and therapy should be discontinued if it is below 3000/mm^3^, \(^{16}\)
- Mycophenolate mofetil- It blocks purine synthesis and has been used widely in organ transplant patients. Initial dose is 500-1000mg / day which is titrated over weeks to maximum dose of 1.5gm twice daily. Effects are seen earlier than AZA, it has favourable side effect profile. Randomized trials have shown no added benefit of combination of mycophenolate with steroids over steroids alone. \(^{17}\)
  Other immunosuppressive agents which have been studied and tried are Methotrexate, Cyclosporine A, Tacrolimus, Cyclophosphamide. Although results are encouraging with these steroid sparing agents but one has to be cautious about the risk benefit ratio of the treatment.
  - Short term immunomodulation
  - IVIG and plasmapheresis
  High doses of immunoglobinulin (IVIG) and plasma exchange represent short-term treatments, are indicated in severe cases of GMG, myasthenia crisis, preoperatively to prepare patients for thymectomy. These therapies are usually not indicated for patients with pure ocular myasthenia gravis. \(^{18}\)

**Thymectomy**

Thymectomy is indicated in thymomatosus myasthenia gravis, in patients early in the course of their disease and those younger than 60 years of age. Studies have even shown remission and improvement in generalized myasthenia without documented thymic enlargement. It is not indicated in ocular myasthenia. \(^{19}\)

**Supportive therapy**

It includes measures to elevate the lid using crutch glasses, and lid surgery if ptosis has been stable for long. Small ocular deviations and diplopia can be managed with prisms, strabismus surgery can be done in ocular alignment which is stable for 6 months.

**Paediatric Myasthenia**

It includes neonatal, congenital and juvenile myasthenia. The etiopathogenesis of all three types is different. Neonatal myasthenia is a temporary myasthenia due to transplacental transmission of antibodies from a MG mother. Congenital myasthenia presents at birth and persists life long, it is due to genetic defect at neuromuscular junction which is not responsive to anticholine esterases. \(^{20}\)

Juvenile myasthenia gravis is a rare condition of childhood and prepuberty with antibodies against Ach receptors. It is usually ocular and has good remission rates\(^{20,21}\). (figure 2 a and b)

![Fig. 2(a) At presentation](image1.png) ![Fig. 2(b) After tensilon test](image2.png)

**Conclusion**

Ocular myasthenia is a masquerader and can present as variable, unilateral or asymmetrical bilateral, pupil sparing painless ophthalmoplegia with or without ptosis. The diagnosis is supported by clinical bed side tests, serological, and various electrophysiological tests. Anticholine esterases give symptomatic relief but do not help in remission or preventing progression of OMG to GMG. Oral corticosteroids alone or along with other immunosuppressive agents help in remission of disease and conversion to generalized myasthenia. Surgery for ptosis and diplopia can be
considered if there is no response with medical therapy and the measurements are stable for at least 6 months.

References


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