Myasthenia Gravis

Myasthenia Gravis is an autoimmune disease which results in muscle fatigability and weakness throughout the day. Symptoms improve with rest. Its main symptoms, which the ophthalmologist may encounter, are ptosis, diplopia, variable extra-ocular muscle palsies or incomitant strabismus, and external ophthalmoplegia. This disease is managed medically.

Disease Entity

Myasthenia Gravis ICD-9 code: without acute exacerbation 358.00; with acute exacerbation 358.01

Disease

Myasthenia Gravis (MG) is an autoimmune disease in which antibodies destroy neuromuscular connections resulting in muscle weakness and fatigability. MG affects voluntary muscles of the body, but the muscles and motor nerves are intact. Smaller muscles tend to be affected first, larger muscles become affected as the disease progresses. Ocular MG affects only the ocular muscles. Systemic MG affects the ocular muscles (often the presenting sign) and other voluntary muscles. Approximately 85% of patients presenting with only ocular signs and symptoms of MG will develop systemic MG within 2 years of presentation.

Etiology

MG is an acquired autoimmune disease. It is not inherited. However, congenital MG is a rare, nonimmune inheritable disorder. For more information on congenital myasthenia gravis, please visit the category ***Pediatric Ophthalmology*** under the article ***Congenital Myasthenia Gravis***.

Risk Factors

There are no known risk factors for acquired MG. Aggravating factors, such as pregnancy, emotional stress, infections, excessive alcohol, UV light, extreme temperatures, thyroid disease and certain medications may worsen the disease and have been linked to myasthenic crises.

Pathophysiology

Antibodies directed against acetylcholine (ACh) receptor sites at the post-synaptic neuromuscular junction (NMJ) are attacked, destroyed and ultimately decrease in numbers by approximately 66%. These antibodies cause ACh receptor blockade, complement mediated membrane damage, and accelerate the degradation of the ACh, thereby reducing its effect on the NMJ. The amount of ACh released from the pre-synaptic terminal is normal, but because the number of receptors is reduced, the amplitude of endplate potentials at the NMJ may be too low to trigger an action potential. The

muscles become weak due to impaired transmission. This muscular weakness increases with sustained muscle activation, giving rise to increased fatigability with use, and improvement of symptoms with rest.

Normally, with sustained muscle activation, smaller amounts of ACh is released with each successive impulse, but transmission is not affected and muscular strength is maintained. In MG, the reduced amount of ACh released with sustained muscle activation results in further impairment of the NMJ transmission. This is the basis of muscle fatigability and the electrophysiologic decrement seen in MG.

Diagnosis

The definitive diagnosis of MG, either systemic or ocular, is made through various clinical, pharmacological and serologic tests.

History

The patient presents with complaints of fluctuating fatigability, worsening muscle weakness in the evening and/or with prolong use, and significant improvement with rest.

The disease has a bimodal pattern, having an early peak in the second and third decade, and a late peak in the sixth to eighth decade. The early peak shows a female predominance, approximately 3:1, and an association with HLA-B8, HLA-DR3, and HLA-DR1, the latter being more specific for ocular MG. Interestingly, the late peak features a male predominance and an association with HLA-B27 and HLA-DR2.

Physical examination

The physical exam will vary depending on which muscles are affected. Variable muscular weakness and fatigability are a consistent finding.

Signs

The most common presenting signs are ocular. Of these, the most common sign is ptosis. Initially ptosis may present as unilateral, frequently shifting from one eye to the other, to eventually involve bilateral upper lids. Cogan lid twitch, and demonstration of Hering's law of equal innervation are typical of myasthenic ptosis. The Cogan lid twitch is elicited by having the patient look in downgaze, followed with upgaze. As the affected eye saccades up, the upper lid overshoots. Hering's law of equal innervation states that the reciprocal eye muscle of each eye are innervated equally. As such, manual elevation of the more ptotic eyelid decreases the muscle strength required to keep the lid elevated, and so the contralateral levator palpebrae superioris relaxes and causes worsening ptosis. However, Hering's law can also be seen in other types of ptosis as well.

Other common ocular signs are incomitant strabismus, external opthalmoplegia, mimicking motor cranial nerve palsies. The pupils are never involved in MG. Systemic signs include variable muscle weakness and fatigability of the muscles of mastication, facial expression, speech, neck extensors, proximal limb muscles, and respiratory muscles late in the disease.

Symptoms

The main symptom is variable muscle weakness and fatigability, which worsens throughout the day, culminating in the evening. The most commonly affected muscles are the levator palpebrae superioris, extra-ocular muscles, orbicularis oculi, muscles involved in facial expressions, mastication, speech, neck extensor muscles, and proximal limb muscles (triceps, deltoid, iliopsoas). The most common presenting symptoms are also found to be ocular. More than 50% of MG patients present with ptosis, incommitant strabismus, or/and external ophthalmoplegia. These are usually bilateral and asymmetric. Progression of symptoms is insidious over weeks to months. Ophthalmoparesis is common in MG. The EOMs are small muscle in which a small amount of muscle weakness becomes symptomatic compared with the bigger limb muscles. EOMs are 80% single innervated twitch fibers with a high firing frequency. This increases their sensitivity to fatigue. Of all the EOMs, the medial rectus (MR) is commonly affected. Involvement of the MR results in poor adduction and incomittant strabismus.

Clinical diagnosis

One should have a high suspicion for MG when a patient's history and main signs and symptoms suggest variable muscle weakness and fatigability that worsens in the evening or with prolonged use, and improves with rest. The definitive diagnosis is made through various clinical, pharmacological and serologic tests.

Diagnostic Tests

1. Edrophonium (Tensilon) Test:

Edrophonium chloride inhibits acetylcholinesterase, thereby prolonging the presence of acetylcholine at the neuromuscular junction. This results in enhanced muscle strength. This test is only useful in patients with objective, measurable findings on physical exam, like ptosis or a tropia. In ptosis, a positive test is the elevation of eyelids in 2-5 minutes post adminstration of Tensilon. A negative response is no improvement within 3 minutes. Compared to other diagnostic tests, the Tensilon test has a relatively low sensitivity, approximately 60% for MG. False positive results occur in patients with Lambert-Eaton Myasthenic Syndrome (LEMS), Amyothrophic Lateral Sclerosis (ALS), and localized intracranial mass lesions. Edrophonium chloride can cause overactivation of the parasympathetic system, and cause unwanted side effects like fainting, dizziness, involuntary defecation, severe bradycardia, apnea, and even cardiac arrest. It is important to always have atropine at hand if such side effects should occur.

2. Repetitive Nerve Stimulation (RNS) Testing:

This is the most frequently used electrodiagnostic test for MG, with specificity of 95%. The nerve to be studied is electrically stimulated six to ten times at 2 to 3 Hertz. Compound muscle action potential (CMAP) is recorded via surface electrodes placed on the muscle in question. A positive test is the progressive decline in CMAP amplitudes within the first 4-5 stimuli. RNS testing is positive in

approximately 75% of patients with generalized MG, but is positive in only 50% of patients with ocular MG. False positive are seen in LEMS, ALS and polyomyositis.

3. Single Fiber EMG:

The single fiber EMG is highly sensitive for ocular myasthenia, with a sensitivity of 88-99%. This is a good diagnostic test for congenital myasthenia gravis.

4. Sleep Test:

The sleep test is a simple clinical test. The patient is asked to note if there is marked improvement in symptoms upon awakening. This can be done in the office if the patient is very sleepy!

5. Ice Test:

This is also a simple diagnostic test that can be done in the clinic. It is highly sensitive and specific for MG. The ice test is useful for ptosis. An ice pack is applied to the affected upper eyelid for 2-5 minutes. A positive test is the improvement of ptosis by > 2mm or more. This transient improvement in ptosis is due to the cold decreasing the acetylcholinesterase break-down of acetylcholine at the neuromuscular junction. More acetylcholine collects in the junction and therefore increases the muscle contraction. Prolonged cooling, however, can potentially decrease muscle contractility and result in a false negative result.

Laboratory tests

1. Serum anti-ACh Receptor Antibody Titer:

This assay measures three different anti-ACh receptor antibodies found in MG: binding antibodies, blocking antibodies, and modulating antibodies. Binding antibodies are present in 85- 90% of systemic MG patients, and 50% of ocular MG patients. When binding antibodies are negative, blocking and modulating antibodies are then tested.

Although this test is relatively sensitive and specific for MG, 10% to 15% of patients with systemic MG will test negative, as will 30% to 50% of patients with ocular MG. False positives occur in patients with immune liver disorders, thymoma without MG, LEMS, those with primary lung cancer and in a small percentage of older individuals.

2. Serum anti-Muscle-Specific Kinase Antibody Titer:

MuSk assays are used when anti-ACh receptor antibody titers are negative but the clinician has a strong clinical suspicion for MG.

Differential diagnosis

The differential diagnosis for MG is vast. Due to its variability in presenting symptoms, MG can mimick many diseases. It is important to remember that the presence of pupillary abnormalites excludes the diagnosis of MG.

Lambert-Eaton Myasthenic Syndrome (LEMS) can be thought of as the opposite of MG. The clinical features in LEMS include proximal muscle weakness and hyporeflexia with ***improvement of symptoms*** with repeated muscle stimulation. LEMS is caused by antibodies directed against ***presynaptic*** calcium channels. It is associated with small cell lung carcinoma.

Since ptosis is the most common presenting symptom in MG, it is important to go through its differential diagnosis. Ptosis is defined as margin to reflex diameter 1 (MRD 1) of less than 2mm or an asymmetry of more than 2mm between eyes. Normal palpebral fissure (PF) vertical length is about 9mm, a ptotic lid has a PF < 9mm. Myasthenia gravis with ptosis has an extensive differential diagnosis. This includes: an intracranial lesion, tumor, pituitary adenoma, aneurysm, fascicular lesion of CN 3, evolving CN 3 palsy, post-viral neuropathy, thyroid disorders*, migraines, meningitis, Horner's syndrome, levator aponeurosis, chronic progressive external ophthalmoplegia (CPEO), and developmental myopathy of the levator palpebrae superioris muscle.

Diplopia is another common symptom. A variable pattern of diplopia without pupillary involvement should bring MG to the top of your differential list.

* Thyroid eye disease occurs in conjunction with MG in up to 5% of patients.

Management

Medical therapy

Medical therapy includes acetylcholinesterase inhibitors, pyridostigmine (Mestinon), oral steroids, and immunomodulators. These drugs have no effect on the underlying disease process, they are purely to help manage symptoms.

Acetylcholinesterase inhibitors reduce the hydrolysis of ACh by the enzyme acetylcholinesterase at the synaptic cleft. By inhibiting the hydrolysis of ACh, the ACh released from the presynaptic cleft remains at the NMJ longer, giving the muscle a longer period of activation. Pysidostigmine is a long acting cholinesterase inhibitor used to treat ocular MG. Oral steroids are used adjunctly. Immunomodulators are reserved for refractory cases.

Surgery

Surgical removal of the thymus gland is recommended for the treatment of symptomatic MG. Approximately 66% of MG patients have thymic hyperplasia (thymomas) with germinal center formation, and 10% of patients have a thymic tumor. Within this lymphoid tissue, B-cells interact with helper T-cells to produce the anti-ACh receptor antibodies. As such, symptoms of MG generally improve after thymectomy.The role of thymectomy in purely ocular myasthenia is debatable, but it may play a small role in the management of symptoms.

Complications

Complications in MG arise late in the disease when larger muscle groups become involved. Dysphagia and dyspnea should raise red flags as these two symptoms may lead to respiratory compromise and ultimately death.

Myasthenic crises are exacerbation of symptoms cause be an aggravating factor. Myasthenic crises can be life-threatening. Aggravating factors include pregnancy, emotional stress, infections, excessive alcohol, UV light, extreme temperatures, thyroid disease and certain medications. Medications such as chloroquine, quinidine, procainamide, prednisone, lithium, phenytoin, cisplatin, magnesium, statins, beta-blocker, calcium channel blockers, Botox, polymyxin, and aminoglycosides have been known to precipitate dormant MG and to trigger myasthenic crises.

Prognosis

The prognosis for MG, whether ocular or systemic, is generally fair as long as symptoms are well controlled and there is no disease progression to involve larger muscle groups such as respiratory muscles and muscles involved with the action of swallowing. Remember, 85% of patients who initially present with ocular MG will go on to develop systemic MG within 2 years of diagnosis.

Additional Resources

- Boyd K, DeAngelis KD. Myasthenia Gravis. American Academy of Ophthalmology. EyeSmart® Eye health. https://www.aao.org/eye-health/diseases/myasthenia-gravis-list. Accessed March 19, 2019.

References

1. Neuro-Ophthalmology, Section 5. Basic and Clinical Science Course, AAO, 2009-2010.

2. Miller NR & Newman MJ. The Essentials: Walsh & Hoyt's Clinical Neuro-Ophthalmology. 5th edition. Lippincott:1999.

Source: https://eyewiki.org/Myasthenia_Gravis