Review Article

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MYASTHENIA GRAVIS – A REVIEW

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Myasthenia gravis (MG) is a neuromuscular disorder that causes weakness in the skeletal muscles, which are the muscles your body uses for movement. It occurs when communication between nerve cells and muscles becomes impaired. This impairment prevents crucial muscle contractions from occurring, resulting in muscle weakness. According to the Myasthenia Gravis Foundation of America, MG is the most common primary disorder of neuromuscular transmission. It's a relatively rare condition that affects between 14 and 20 out of every 100,000 people in the United States.

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is a relatively rare autoimmune disorder in which antibodies form against acetylcholine nicotinic postsynaptic receptors at the neuromuscular junction of skeletal muscles [1, 2].MG is sometimes identified, as having an ocular and generalized form, although one is not exclusive of the other and the ocular form is considered an initial, milder form of illness that progresses to the more severe generalized form in most but not all patients.

SIGNS AND SYMPTOMS

The presentation of MG has the following charact eristics:

- ✓ The usual initial complaint is a specific muscle weakness rather than generalized weakness.
- ✓ Extraocular muscle weakness or ptosis is present initially in 50% of patients and occurs during the course of illness in 90%.
- ✓ The disease remains exclusively ocular in only 16% of patients.
- ✓ Rarely, patients have generalized weakness without ocular muscle weakness.
- ✓ Bulbar muscle weakness is also common, along with weakness of head extension and flexion Limb weakness may be more severe proximally than distally.
- ✓ Isolated limb muscle weakness is the presenting symptom in fewer than 10% of patients.[6]
- ✓ Weakness is typically least severe in the morning and worsens as the day progresses.
- ✓ Weakness is increased by exertion and alleviated by rest. Weakness progresses from mild to more severe over weeks or months, with exacerbations and remissions.
- ✓ Weakness tends to spread from the ocular to facial to bulbar muscles and then to truncal and limb muscles.
- ✓ About 87% of patients have generalized disease within 13 months after onset.
- ✓ Less often, symptoms may remain limited to the extraocular and eyelid muscle.[5]

THE FOLLOWING FACTORS MAY TRIGG ER OR WORSEN EXACERBATIONS:

- ✓ Bright sunlight Surgery
- ✓ Immunization
- ✓ Emotional stress
- ✓ Menstruation

  Intercurrent illness (eg, viral infection)
- ✓ Medication (eg, aminoglycosides, ciprofloxacin, chloroquine, procaine, lithium, phenytoin, beta blockers, procainamide, statins). [8]

CAUSES OF MYASTHENIA GRAVIS

- ✓ Myasthenia gravis is caused by a problem with the transmission of nerve signals to the muscles.
- ✓ It's an autoimmune condition, which means the body's immune system (specific antibodies) attacks its own tissues.[8]

NERVE SIGNALS

- ✓ Nerve signals travel down the nerves and stimulate the nerve endings to release a chemical substance called acetylcholine.
- ✓ When acetylcholine comes into contact with specific receptors on the muscle membrane, the receptors are activated and cause the muscles to contract (tighten).
- ✓ However, in myasthenia gravis the immune system produces antibodies (proteins) that block or damage the muscle acetylcholine

receptors, which prevents the muscles contracting.
- ✓ The disruption between your nerves and muscles means your muscles become weak and easily tired.

THE THYMUS GLAND
- ✓ It's not fully understood why some people's immune systems produce antibodies that act against the muscle receptors.
- ✓ However, it's thought the thymus gland, which is part of the immune system, may be linked to the production of the antibodies.
- ✓ During infancy, the thymus gland is large and gradually increases in size before getting smaller during adulthood.[10,11]

THE MYASTHENIA GRAVIS FOUNDATIO N OF AMERICA CLINICAL CLASSIFICAT ION DIVIDES MG INTO 5 MAIN CLASSES AND SEVERAL SU BCLASSES[3] :

- ✓ Class I: Any ocular muscle weakness; may hav e weakness of eye closure; all other muscle strength is normal.
- ✓ Class II: Mild weakness affecting other than o cular 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 mus cles.
- ✓ Class IIb: Predominantly affecting oropharyng eal, respiratory muscles, or both; may also have lesser or equal involveme nt of limb, axial muscles, or both.
- ✓ Class III: Moderate weakness affecting other t han 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 mus cles.[18]
- ✓ Class IIIb: Predominantly affecting oropharyn geal, respiratory muscles, or both; may also have lesser or equal involveme nt 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, axial muscles, or both; may also have lesser involvement of oropharyngeal mus cles
- ✓ Class IVb: Predominantly affecting oropharyn geal, respiratory muscles, or both; may also have lesser or equal involveme nt of limb, axial muscles, or both; use of a feeding tube without intubation
- ✓ Class V: Defined by the need for intubation, w ith or without mechanical ventilation, except when used during routine p ostoperative management s for years.[15,18,20]

DIAGNOSING MYASTHENIA GRAVIS

The process of diagnosing myasthenia gravis can take a long time because muscle weakness is a common symptom of many different conditions.Your GP will look at your medical history and symptoms. They may suspect myasthenia gravis if your eye movements are impaired or if you have muscle weakness but you're still able to feel things. Around half of people with myasthenia gravis initially develop symptoms of double vision or eyelid droop, with more than 90% of people developing these symptoms at some point during the illness. [13,15]

You may be referred to a neurologist (specialist in nervous system disorders), who will carry out some tests to help confirm the diagnosis.

TESTS

A number of tests can be used to help diagnose myasthenia gravis.

BLOOD TEST

A special type of blood test can be used to detect the antibodies (proteins) that block or damage the muscle receptors.

Most people with myasthenia gravis have an abnormally high number of acetylcholine receptor antibodies.

The antibody blood tests are quite specific, which means they're almost never detected in patients who don't have myasthenia gravis.

However, in people whose symptoms are limited to the eyes, (ocular myasthenia), high levels of antibodies may only be detected in around half of cases

A small amount people with myasthenia gravis may test negative for acetylcholine receptor antibodies but have anti-MuSK antibodies insteaad[19]

NERVE CONDUCTION TESTS

Electromyography is a procedure that can be used to identify communication problems between the nerves and muscles. It involves inserting a needle electrode through the skin into the muscle.

This produces an electrical recording of the muscle activity. If you have myasthenia gravis, your muscles won't respond well to nerve stimulation. [17]

Repeated nerve stimulation can be used to test for muscle fatigue. In myasthenia gravis, the transmission of signals between the nerve and muscle declines during repeated stimulation.

Single-fibre EMG is the most sensitive electrical test for detecting disruption of the signal between the nerve ending and the muscle membrane (as in myasthenia gravis). It usually involves taking a recording from a very small needle in one of the muscles around the eye, forehead, or sometimes in the forearm.

EDROPHONIUM TEST

An edrophonium test involves having an injection of a type of medication called edrophonium chloride. Edrophonium chloride prevents the substance acetylcholine from being broken down, which temporarily increases the amount of acetylcholine around the muscle.

In people with myasthenia gravis, the increased amount of acetylcholine produces a sudden but temporary improvement in muscle power. However, this won't usually occur in people with other causes of muscle weakness. [22]

There are significant side effects associated with the edrophonium test, such as heart rate and breathing problems, that may occur during the investigation. For this reason, the test is rarely performed.

This test should only be considered if myasthenia gravis is still suspected despite negative blood and electrical tests. If performed, the test should only be carried out by experienced neurology doctors in specialist centres with resuscitation equipment available

TREATING MYASTHENIA GRAVIS

Treatment for myasthenia gravis can significantly improve symptoms of muscle weakness and many people with the condition are able to lead a relatively normal life. However, severe or chronic symptoms frequently require long-term treatment.

If symptoms are mild, many people find that getting plenty of rest helps improve their symptoms without the need for additional treatment.

MEDICATION

Medicines such as pyridostigmine, an acetylcholinesterase inhibitor, prevent the breakdown of acetylcholine, an important chemical that helps the muscles contract (tighten).

These medicines tend to work best in mild myasthenia gravis. They can improve muscle contractions and strength in affected muscles. They're often used if the initial symptoms aren't too severe but pyridostigmine isn't a suitable long-term treatment for most people.

However, they can cause side effects, such as stomach cramps, muscle twitching, diarrhoea and nausea. Other medications may be prescribed to counteract these side effects.

If initial treatment with pyridostigmine isn't effective, or only suitable for temporary use, then steroid tablets, such as prednisolone, are used at a low dose. The dose can be increased gradually over time and is usually kept at a high dose for several months until remission is achieved.

Immunosuppressant medication may be prescribed if remission isn't achieved or the high dose of prednisolone isn't suitable. This is usually azathioprine, mycophenolate or methotrexate. These are used to help achieve remission so the prednisolone dose can be reduced and eventually stopped.

Your blood will have to be regularly monitored when taking immunosuppressants, which may take at least a year to take full effect

If long-term remission is achieved over time (usually years), it may be possible to stop all immunosuppressant medication. [22,23,24]

Thymectomy

In some cases of myasthenia gravis, surgery to remove the thymus gland (a thymectomy) may be recommended.

In some studies, thymectomy has been shown to improve the symptoms of people who don't have

tumours (thymomas) on their thymus gland. The improvement often happens within the first few months, although continued benefit may be seen for up to two years after surgery. Nowadays, the thymus gland is usually removed using keyhole surgery.

The current recommendations for people under 45 years old, with general symptoms of myasthenia gravis, no thymomas and have had the illness for less than two years, thymectomy gives:

● A 25% chance of remission

● A 50% chance of improvement of symptoms, still requiring long-term immunosuppression

● A 25% chance of no benefit

A thymectomy often has little effect on the symptoms of myasthenia gravis for people with thymomas. However, removal is often recommended to avoid complications caused by the tumour spreading in the chest[23,24]

PLASMAPHERESIS AND IMMUNOGLOBULIN THERAPY

Plasmapheresis or intravenous immunoglobulin therapy may be needed in very severe cases of myasthenia gravis, where a person's muscle weakness is causing life-threatening breathing or swallowing problems. [22]

These treatments are given in hospital and involve:

● Plasmapheresis – your blood is circulated through a machine that removes the plasma containing some of the harmful antibodies.[23]

● Intravenous immunoglobulin therapy – injections of normal immunoglobulin, taken from healthy donated blood, that temporarily change the way your immune system operates.

Both treatments can improve the symptoms of myasthenia gravis, but the benefits usually only last a few weeks. They aren't suitable as long-term treatments for myasthenia gravis, and are usually only used to treat people who are seriously ill.[21.20]

✓ The antiacetylcholine receptor (AChR) antibody test for diagnosing MG has the following characteristics:
High specificity (up to 100% [4])Positive in as many as 90% of patients who have generalized MG Positive in only 50-70% of patients who have purely ocular MG [25]

✓ False-positive anti-AChR antibody test results have been reported in patients with the following:
Thymoma without MG
Lambert Eaton myasthenic syndrome
Small cell lung cancer
Rheumatoid arthritis treated with penicillamine1-3% of the population older than 70 years [24]

✓ Assays for the following antibodies may also be useful:
Anti-MuSK antibody (present in about half of patients with negative results for anti-AChR antibody)
Anti-lipoprotein-related protein 4 (LRP4) antibody
✓ Anti-agrin antibody
Antistriational antibody (present in almost all patients with thymoma and MG, as well as in half of MG patients with onset of MG at 50 years or older)[22].

AYURVEDA ON MYASTHENIA GRAVIS

The pathogenesis similar to MG is in disease conditions Amavata, Sanayughat vata, sanayu-mansa-ghat vata, kaphaavritavyanavayu & the name of disease with similar clinical presentation is Khanja, Urustambha & by following the line of treatmentdocumented in these conditions MG can be treated with Ayurveda based herbal medicines , the increased Acetylene choline-receptor- anti-bodies start coming after a treatment of 45 to 60 days & improvement in muscles strength can also be noticed 30-45days treatment.

At Vedanta Ayurveda personalized herbal formulations in two combinations are prepare based on the nature, state, bala of disease & diseased –1.Amahara-to reverse the disease process, 2.Medhya rasayana-to improve the neural activities[23,24].

MANEGMENT

With recent advances in understanding the various underlying antibodies that cause myasthenia gravis and differences in how they present clinically and respond to various

therapies, it is suggested that patients with myasthenia gravis should be classified into subgroups. Subgroups based on serum antibodies and clinical features may include early-onset, late-onset, and patients with thymoma, MuSK, LRP4, antibody-negative, and ocular forms of myasthenia gravis.[25]

Therapy for MG includes the following:

Anticholinesterase (AchE) inhibitor
Immunomodulating agentsIntravenous immune globulin (IVIg) Plasmapheresis Thymectomy [25]
AchE inhibitors
Initial treatment for mild MG Pyridostigmine is used for maintenance therapy [26, 27] Neostigmine is generally used only when pyridostigmine is unavailable Corticosteroid therapy provides a short-term benefit Azathioprine, usually after a dose of corticosteroids, is the mainstay of therapy for difficult cases.Cyclosporine A and occasionally methotrexate and cyclophosphamide are used for severe cases[27]
IVIg
Moderate or severe MG worsening into crisis (no value in mild disease) [28] Elderly patients. Patients with complex comorbid diseases (eg, acute respiratory failure) [29] Patients with severe weakness poorly controlled with other agents .[28,29]
Plasmapheresis
Generally reserved for myasthenic crisis and refra ctory cases
Also effective in preparation for surgery
Improvement is noted in a couple of days, but does not last for more than 2 months Can be used long-term on a regular weekly or monthly basis can be used if other treatments cannot control the disease [29]
Thymectomy
The standard of care for all patients with thymom a and for patients aged 1055 years without thymo ma but with generalized MG.

Proposed as a first line therapy in most patients with generalized myasthenia In ocular MG, should be delayed at least 2 years to allow for spontaneous remission Not recommended in patients with antibodies to muscle specific kinase (MuSK) Controversial in prepubescent patients and, to a lesser extent, patients older than 55 years.[29,30]

PATHOPHYSIOLOGY

With every nerve impulse, the amount of ACh released by the presynaptic motor neuron normally decreases because of a temporary depletion of the presynaptic ACh stores (a phenomenon referred to as presynaptic rundown).

In MG, there is a reduction in the number of AChRs available at the muscle endplate and flattening of the postsynaptic folds. Consequently, even if a normal amount of ACh is released, fewer endplate potentials will be produced, and they may fall below the threshold value for generation of an action potential. The end result of this process is inefficient neuromuscular transmission. [32,33,34]

Inefficient neuromuscular transmission together with the normally present presynaptic rundown phenomenon results in a progressive decrease in the amount of muscle fibers being activated by successive nerve fiber impulses. This explains the fatigability seen in MG patients.

Patients become symptomatic once the number of AChRs is reduced to approximately 30% of normal. The cholinergic receptors of smooth and cardiac muscle have a different antigenicity than skeletal muscle and usually are not affected by the disease.

The decrease in the number of postsynaptic AChRs is believed to be due to an autoimmune process whereby anti-AChR antibodies are produced and block the target receptors, cause an increase the turnover of the receptors, and damage the postsynaptic membrane in a complement mediated manner. [37]

Clinical observations support the idea that immunogenic mechanisms play important roles in the pathophysiology of MG. Such observations include the presence of associated autoimmune disorders (eg, autoimmune thyroiditis, systemic lupus erythematosus [SLE], and rheumatoid arthritis [RA]) in patients with MG. [38]

Moreover, infants born to myasthenic mothers can develop a transient myasthenialike syndrome. Patients with MG 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 MG. Experimental observations supporting an autoimmune etiology of MG include the following:

• Induction of a myasthenialike syndrome in mice by injecting a large quantity of immunoglobulin G (IgG) from MG patients (ie, passive transfer experiments.)

• Demonstration of IgG and complement at the postsynaptic membrane in patients with MG.

• Induction of a myasthenialike syndrome in rabbits immunized against AChR by injecting them with AChR isolated from Torpedo californica (the Pacific electric ray).[33,34]

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