Myasthenia Gravis.

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ABSTRACT

Myasthenia Gravis (MG) is a relatively rare neurological disease that is associated with the loss of the acetylcholine receptors that initiate muscle contraction. This results in muscle weakness, which can be life threatening. MG results from antibody-mediated, T cell-dependent immunologic attack on the end-plate region of the postsynaptic membrane. Management must be individualized, and may include symptomatic treatment with cholinesterase inhibitors and immune modulation with corticosteroids, azathioprine, cyclosporine, and mycophenolate mofetil. Rapid, temporary improvement may be achieved for myasthenic crises and exacerbations with plasma exchange (PEX) or intravenous immunoglobulin (IVIg). Prognosis is good due to improved diagnostic testing, immunotherapy, and intensive care.

Keywords: Myasthenia gravis(MG), Weakness, Acetylcholine receptors(Ach Rs).

INTRODUCTION

MG remains one of the most challenging medical diagnoses due to its fluctuating character and to the similarity of its symptoms to those of other disorders. Although a formal clinical classification system and research standards have been established for MG[1], there are no widely accepted formal diagnostic criteria. The most important elements of diagnosis are history and clinical findings of fluctuating and fatigable weakness, particularly involving extra-ocular and bulbar muscles.

Muscular weakness and fatigability are the hallmarks of myasthenia gravis. They are caused by an antibody-mediated autoimmune attack directed against AchRs at neuromuscular junctions. There are several mechanisms by which the autoantibodies reduce the number of available AchRs at neuromuscular junctions. The molecular structure of nicotinic AchR is now well characterised and the receptor has been purified from a variety of sources, including human muscle. An experimental model of myasthenia gravis has been produced by immunisation of animals with AchRs. This has been of great help to understand the disease mechanisms. There have been significant advances in the diagnosis and treatment of myasthenia gravis. It used to be a very disabling and often fatal (and, hence, the name gravis) disease in the past. However, with modern immunotherapy the prognosis has been dramatically improved and nearly all patients are now able to lead full, productive lives.[2]

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PATHOPHYSIOLOGY

Autoimmune MG results from antibody-mediated, T-cell dependent immunologic attack on the postsynaptic membrane of the neuromuscular junction. Abnormal neuromuscular transmission and clinical weakness in MG result from the effects of antibodies that bind to various epitopes of the skeletal muscle endplate region. In most cases, antibodies bind to the main immunogenic region of the α-subunit of the AchR, though MG patients with antibodies to MuSK exhibit clinical weakness and electro-physiologic findings that are quite similar to MG patients with AChR antibodies. MuSK initiates aggregation of AChRs at the muscle endplate during development[3], but the function of MuSK in mature skeletal muscle and the pathophysiology of MG related to MuSK antibodies are currently unknown. In systemic MG, binding of antibody to the AChR initiates autoimmune attack on the endplate region. Subsequent damage to the postsynaptic membrane results in simplification of the normal, highly-infolded surface which is accompanied by reduced number and density of AChR.[4] The functional loss of AChRs reduces the probability of successful neuromuscular transmission following quantal release of acetylcholine by the motor nerve terminal, resulting in clinical weakness in striated muscles.

CLINICAL FEATURES [5,6]

The salient features of MG include double vision, drooping of eyelids, difficulties with speech and swallowing, neck weakness, weakness of shoulder and hip muscles leading to difficulties in raising arms or getting up from a chair. This may develop over months with relative exacerbations and remissions or may develop over a matter of days. The latter is easier to diagnose due to the rapidity and severity.

Typically, patients present with a history of weakness and fatigability of muscles on sustained or repeated activity that improves after rest. The symptoms vary from day to day and from hour to hour, typically increasing toward evening. The factors known to increase weakness include exertion, hot temperatures, infections, emotional upsets, certain drugs (aminoglycosides, phenytoin, local anaesthetics), surgery, menstruation, and pregnancy. The most commonly affected muscles in the decreasing order of frequency are: levator palpebrae superioris, extraocular muscles, proximal limb muscles, muscles of facial expression, and neck extensors. The external ocular muscles are affected initially in about 50% and eventually in 90% of cases. Ptosis (weakness of levator palpebrae superioris) is a common presenting feature. It is often fluctuating in nature.

The presence of an eyelid twitch response (Cogan's lid twitch) is characteristic of myasthenia gravis. When the patient's eyes are directed downward for 10–20 seconds and the patient is then instructed to make a vertical saccade back to primary position, the upper eyelid elevates and either slowly begins to droop or twitches many times before reaching a stable position. This phenomenon is caused by the rapid recovery and easy fatigability of myasthenia gravis. This test is not pathognomonic of myasthenia gravis as it can occur with the brain stem or ocular disorders. The ptosis improves after a period of sleep (the so-called "sleep test") or with application of the ice on the lid (the so-called "ice test").

There may also be a weakness of orbicularis oculi leading to difficulty in eye closure. The ocular palsies are often asymmetric and fluctuating, and can mimic various types of ophthalmoplegia, including internuclear ophthalmoplegia, ocular motor nerve palsies, or gaze palsies. Saccades are typically hypometric that begin with normal velocity but eventually show a decrease in velocity (intrasaccadic fatigue) and undershoot the target. The pupils are typically spared in the myasthenia gravis.

The face may appear expressionless. The mouth may be open and patient may have to support his/her jaw with a finger. When the patient attempts to smile, the face may take an appearance of a "snarl". This is due to the fact that the corners of the mouth are not drawn up and out while the levators expose the canines. The voice may have nasal character and nasal regurgitation may result from palatal weakness. Dysphonia may result from laryngeal weakness. Dysphagia is a common presentation due to the fatigue of muscles concerned chewing and swallowing. The voice becomes progressively softer during conversation. The weakness may remain confined to ocular muscles in about 10% of patients (ocular myasthenia), but in most cases, it progresses to involve other facial and limb muscles (generalised myasthenia).

The progression of weakness in myasthenia gravis usually occurs in a craniocaudal direction (as in Eaton-Lambert syndrome): ocular→ facial→ lower bulbar→ truncal→ limb muscles. The weakness of intercostal muscles and diaphragm leads to dyspnoea on exertion or at rest. The orthopnoea with rapid resolution on sitting up and diaphragmatic paradox are important clinical signs of neuromuscular breathlessness. Patient presenting with sudden breathlessness should be closely monitored with regular measurements of their forced vital capacity.

In severe cases (class V of modified Osserman's grading), patients may require intubation and mechanical ventilation. With the limb muscle involvement, fatigue on exertion becomes obvious to the patients. The deep tendon reflexes are normal or brisk and there are no objective sensory signs. Weakness may fluctuate from day to day or over long periods of time, making objective assessment difficult in some cases. Moreover, spontaneous remissions of variable periods are known particularly in the early stages, though complete remissions are rare.[7,8]

Congenital myasthenia syndrome(CMS) is a rare heterogeneous group of genetically determined disorders of neuromuscular transmission. The term 'congenital myasthenia' was coined by Bowman to describe an infant whose parents were normal but his myasthenic symptoms persisted in childhood.[9] CMS is not an autoimmune disorder with no response to immunomodulatory therapy. The clinical presentation varies from isolated ocular weakness to more serious bulbar and respiratory involvement. Typical features include, exercise induced weakness of skeletal muscle with hypotonia, respiratory distress or joint contractures, bilateral ptosis, ophthalmoparesis and facial weakness. CMS is misdiagnosed as myasthenia gravis, limb girdle or congenital muscular dystrophy, spinal muscular atrophy, neurometabolic disease, central hypotonia and congenital myopathy.[10] In a study conducted by SA Jagtap et al on CMS, it was found that ptosis is the commonest symptom at onset, in the absence of molecular diagnosis of CMS, with favourable response acetylcholinesterase inhibitor without exacerbations.[11]

DIAGNOSIS

Edrophonium Testing

Edrophonium chloride is an acetylcholinesterase inhibitor having rapid onset and short duration of action. It temporarily improves the safety factor of neuromuscular transmission and may elicit improved strength in patients with abnormal neuromuscular transmission. Edrophonium testing

is considered positive when unequivocal improvement in strength follows intravenous administration of edrophonium. Development of increased weakness may also suggest abnormal neuromuscular transmission. The main limitation of edrophonium testing includes selection of an objective muscle strength parameter for assessment. Hence, edrophonium testing is most useful in patients who have significant ptosis or restricted extraocular movements. The sensitivity of edrophonium testing has been estimated to be about 86% for ocular MG and 95% for generalized MG.[12] False positive edrophonium testing may occur in other neurological conditions including lower motor neuron disorders and brainstem tumors.[13,14]

Electrophysiology

The exhaustion of neuromuscular transmission due to a reduced number of functional
postsynaptic acetylcholine receptors can be demonstrated electro-physiologically by means of supramaximal electrical repetitive 3Hz stimulation (serial nerve stimulation) of, for example, the accessory nerve, or the facial nerve, with measurement of the myoelectric response in the corresponding muscles. A positive decrement (reduction in the amplitude/area by more than 15%/10%) is seen in up to 80% of patients with generalized MG and in less than 50% of patients with the ocular form.[15]

Serology[16]

The analysis of patient serum for pathologically raised titers of acetylcholine receptor antibodies using an immune precipitation test (acetylcholine receptor extracts from human amputated muscle) is the most specific tool in the diagnosis of MG6. Seronegative patients should be tested for antibodies against MuSK.

Imaging Investigations

Imaging of the thorax with CT or MRI to investigate the thymus is mandatory in all new cases of MG, and should be repeated at intervals of one to two years, even where the initial investigation was normal, to exclude incipient thymoma. Scintigraphy using indium-111-DTPA-D-phe-octreotide can be helpful in imaging the extent of growth of a thymoma by means of the somatostatin receptors expressed on the surface, even when there is considerably marked scarring following surgery.[17]

TREATMENT

Myasthenia gravis is currently treated with several therapeutic approaches with the aim to induce pharmacological remission and, when possible, complete stable remission.[18,19]

Anticholinesterases[20]

Acetylcholinesterase inhibitors slow the hydrolysis of acetylcholine at the neuromuscular junction and provide temporary improvement in strength in many patients with MG. However, there are no controlled clinical trials of these agents in MG. Acetyl cholinesterase inhibitors are a symptomatic therapy for MG and do not retard the underlying autoimmune attack on the neuromuscular junction. They are indicated in the patients who cannot receive immunosuppression, and adjunctive treatment for patients receiving immunotherapy with residual or refractory myasthenic weakness. Effective dosing of acetylcholinesterase inhibitors reduces myasthenic weakness, minimizes muscarinic medication side effects, and must be individualized to each patient's distribution of weakness and diurnal symptom fluctuation.

Adverse effects of acetylcholinesterase inhibitors relate to increased muscarinic activity and include nausea, vomiting, abdominal cramping, diarrhoea, diaphoresis, and increased lacrimation, salivation, and bronchial secretions.

Cholinergic crisis may develop with excessive dosing of acetylcholinesterase inhibitors in patients with more severe MG. In cholinergic crises, depolarization blockade at diseased neuromuscular junctions results in increased weakness, and increased muscarinic activity generates copious oropharyngeal and bronchial secretions that may obstruct the airway or be aspirated. Signs of cholinergic crisis include weakness indistinguishable from myasthenic weakness. Cholinergic crisis is treated with atropine.

Corticosteroids[21]

Corticosteroids are the most widely used immune modulating agents for MG. Although the mechanism of action in MG is unknown, corticosteroids have numerous effects on the immune system including reduction of cytokine production. Corticosteroids are often used as the initial immunotherapy in patients with ocular and generalized MG, particularly in patients with unsatisfactory responses to acetylcholinesterase inhibitors. These agents may produce rapid improvement in MG, but may produce significant dose dependent side effects and occasionally elicit transient and potentially serious myasthenic exacerbations within the first two weeks of treatment.

Usually therapy is started with a daily dose of 60-100 mg (1 mg/kg) to be tapered to an alternate day dose, which is sufficient to suppress myasthenic symptoms. The final maintenance dosage may vary between 5-60 mg on alternate days for a prolonged period of several years or longer. The effect usually starts after two to three weeks. An unexplained transient initial worsening of myasthenic symptoms may occur within 1 week after starting this therapy

in about 10% of the patients and necessitates hospitalization at the start of treatment.

The adverse effects of corticosteroids are mainly dose-dependent. They include: hypertension, fluid retention, weight gain, potassium loss, hyperlipidemia, diabetes mellitus, osteoporosis, gastric ulceration, cataracts, glaucoma, moon facies, obesity, acne, skin friability, juvenile growth suppression, and mood/personality changes. Individuals at particular risk for side effects include those who are diabetic or glucose intolerant, obese, hypertensive, osteoporotic or post-menopausal etc. An alternative immune modulator may be considered in such patients.

Immunomodulators[22,23]

Azathioprine is hepatically converted to 6-mercaptopurine, an active anti-metabolite that blocks nucleotide synthesis and T-lymphocyte proliferation. The dosage beingose of 2½-3 mg/kg body weight. Azathioprine is an effective agent for long-term immune modulation in MG as a steroid sparing drug or as initial immunotherapy. Compared to corticosteroids, azathioprine has a favourable side effect profile for long-term use. However, the typically long delay of four to eight months from beginning treatment with azathioprine to improved strength in MG is a significant liability to its usefulness, particularly in MG patients with progressive disease or functionally limiting symptoms. Side effects include dose dependent myelosuppression with macrocytic anemia, leukopenia, and thrombocytopenia, toxic hepatitis, and alopecia. Hypersensitivity pancreatitis represents a rare, but serious idiosyncratic reaction, and patients with sustained abdominal pain taking azathioprine should be screened with serum amylase and lipase assays. With long-term use, there is a small increased risk for lymphoma. Teratogenic effects of azathioprine are not obvious.[24]

Cyclosporine exerts an immunomodulatory effect by blocking interleukin-2 production and T lymphocyte proliferation. Although effective, the use of cyclosporine in

MG has been limited by its nephrotoxicity and numerous drug interactions. In view of this, cyclosporine is used in MG as a steroid-sparing agent or for refractory generalized disease. It is a possible alternative for steroids in a start dose 3- 5 mg/kg body weight. The effect starts after 2-4 weeks. Care-full monitoring for renal function is highly important. Further side effects are hypertension, hypertrichosis, headache, tremors, basal cell skin carcinomas and others. Another option is to add a low dose cyclosporine (2 mg/kg) to prednisolone and azathioprine in patients who do not sufficiently respond to this combination.[25]

Mycophenolate mofetil (MMF) is a relatively novel immune modulator that selectively inhibits T and B lymphocyte proliferation by blocking purine synthesis exclusively in lymphocytes. In human kidney transplant trials, MMF exhibited minimal toxicity. So MMF is used in MG both as a steroid-sparing agent and as initial immunotherapy in patients at risk for corticosteroid complications. Improved strength is observed within about two months after reaching a therapeutic dose of MMF.A significant improvement may be seen on an average after 12 weeks with a dosage of 2-3 grams (25 mg/kg) a day. In some small series a therapeutic effect is seen in 70% of the patients. Side effects are mainly gastro-intestinal (diarrhoea, abdominal pain) or bone marrow depression. A recent randomized trial in MG failed to show a significant corticosteroid-sparing effect when compared to placebo.[26]

Immunoglobulins[27]

The mechanism by which intravenous immunoglobulins exert their clinical effect in several autoimmune disorders is still unknown but several hypothesis have been proposed, including Fc receptor blockade of the reticuloendothelial system, modulation of the idiotypic anti-idiotypic network, enhancement of regulatory T-cells, inhibition of complement deposition, modulation of cytokines, growth factors and adhesion molecules, modulation of apoptosis and macrophages, and immune regulation of both B-cell and T-cell immune function.[28] The mechanism of action in myasthenia might be due to their influence on the idiotypic network, inhibition of complement deposition and an effect on T-cell immunoregulatory function.[29] Intravenous immunoglobulins are given intravenously, the dose usually being 400 mg/kg body weight for 3-5 days. The infusion is generally well tolerated but potential adverse events must always be taken into consideration. Patients may experience anaphylaxis and anaphylactoid reactions, mild reactions including headache, fever and rash; renal failure, stroke and possible myocardial infarction have also been reported. Anaphylaxis may occur in the IgA-deficient patient. Hematological complications include hemolitic anemia and intravascular hemolysis. Thromboembolic complications have also been reported and attention should be paid to the patient's general conditions and risk factors (older age, hyper-viscosity syndromes, underlying cardiovascular disorders, previous thromboembolic events). In patients at risk, high dose therapy should not be given in a short period of time, should be followed be adequate hydration, and higher daily doses should be avoided.

In MG, IVIg may provide short-term improvement in strength for MG exacerbations and crises, for surgical preparation in patients. Side effects include volume overload, particularly for patients with cardiomyopathy or valvular heart disease, solute-

induced renal failure, especially in patients with pre-existing renal insufficiency or diabetic nephropathy and idiosyncratic reactions such as fever, chills, nausea, vomiting, vascular headaches, and aseptic meningitis. High infusion rates may be associated with thrombosis and stroke. It is mandatory to screen for IgA deficiency, since IVIg preparations contain traces of IgA.

Imbach[30] reported the effect of intravenous immunoglobulins in children with idiopathic thrombocytopenic purpura, with dramatic increase of platelets after intravenous immunoglobulins infusion. Since that observation, the use of intravenous immunoglobulins has been extended to several neurological and non neurological autoimmune and inflammatory disorders.[31] Recently, the subcutaneous administration of intravenous immunoglobulins has been proposed. This route does not require a venous access and seems to be associated with fewer side effects. On the other hand, frequent administrations are needed because the volumes infused intravenously cannot be given by the subcutaneous route.[32]

Thymectomy[33]

Thymectomy has been widely performed in an effort to achieve medication-free remission in MG following Blalock's early observations of remissions following thymectomy in non-thymomatous MG. To date, there have been no prospective, randomized studies completed to assess the technique or effectiveness of thymectomy in non-thymomatous MG.

CONCLUSION

MG is an important autoimmune disease. It may be treated either medically or surgically. Diagnosis can be made from pharmacologic or serologic methods. The disease has many implications on pregnancy and anaesthesia etc. There are no conclusive studies regarding role of thymectomy in this condition.

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