



Myasthenia gravis

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Myasthenia gravis (MG) is an autoimmune antibody-mediated disorder which causes fluctuating weakness in ocular, bulbar and limb skeletal muscles. There are two major clinical types of MG. Ocular MG (OMG) affects extra ocular muscles associated with eye movement and eyelid function and generalized MG results in muscle weakness throughout the body. Patients with OMG have painless fluctuating extra ocular muscles weakness, diplopia and ptosis accompanied by normal visual acuity and pupillary function. Frequently, patients with OMG develop generalized MG over 24 months. Pure OMG is more often earlier in onset (<45 years) than generalized MG. It can also occur as part of an immune-genetic disorder or paraneoplastic syndrome related to thymus tumors. Diagnosis is based on clinical manifestations, laboratory findings, electrophysiological evaluation and pharmacologic tests. Therapeutic strategies for MG consist of symptom relieving medications (e.g., acetylcholine esterase inhibitors), immunosuppressive agents, and surgical intervention (e.g., thymectomy).

Keywords: Myasthenia gravis (MG); autoimmune disorder; neuro-ophthalmology

Received: 09 April 2018; Accepted: 06 May 2018; Published: 15 May 2018.

doi: 10.21037/aes.2018.05.02

View this article at: <http://dx.doi.org/10.21037/aes.2018.05.02>

Myasthenia gravis (MG) as an autoimmune disorder characterized by deposition of antibodies in the neuromuscular junction (NMJ), and weakness of skeletal and extraocular muscles. MG is classified as either ocular or generalized forms based on the locations of involved muscles, types of autoantibodies, the age of onset and thymus abnormalities (1). Immunoglobulin (Ig) G1 and IgG3 antibodies are deposited in NMJ in most MG cases (2). These two immunoglobulins bind to acetylcholine receptors in postsynaptic membrane and cause complement-mediated damage (3). Eighty-five percent of patients with the generalized form of MG have antibodies to the acetylcholine receptor but these antibodies (AChR-Ab) are found in only 50% of those with purely ocular MG (2). In cases without acetylcholine receptor antibodies, antibodies against muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (LRP4) and agrin

may be present (4). In an individual patient the AchR and MuSK antibodies do not occur together but in some cases LRP4 and agrin antibodies are presented with AchR and MuSK antibodies in single patient (5). MuSK related-MG mostly occurs in younger age and female patients and it is also responsible in 70% of seronegative cases (no detectable AChR antibodies) (6,7).

In general, the incidence of MG is 0.04 to 5/100,000 person per year and the prevalence of MG is 0.5 to 12.5/100,000 person per year (8). It affects all ages, genders and ethnicity with a male dominant pattern in OMG. Epidemiological studies have reported the risk of developing MG in first grade relatives or siblings to be about 4.5% which shows a strong genetic background (9,10). Both incidence and prevalence of MG are increasing, especially in older patients (11,12). Pediatric MG may also present with a variety of ocular motility abnormalities or blepharoptosis.

As in adults, early diagnosis should be considered to reduce MG related complications such as bulbar and respiratory muscles weakness which could be life threatening (3,13).

Clinical presentation

The primary presentation of MG in more than 80% of cases are ocular symptoms (ptosis and/or diplopia), although other muscle involvement can cause dysphagia, dysarthria, difficulty in chewing food, change in voice, extremity weakness and dyspnea (14). One hallmark of MG is cyclic relapse, remission and crises of symptoms (1), including muscle fatigability and fluctuating weakness (15). The weakness gets worse with repetitive muscle usage and improves with rest and cold temperature. Difficulties with swallowing and respiration occur in severe cases of MG; producing myasthenic crisis. The severity of MG varies from one case to another and even within an individual (14). Patients with OMG often develop the generalized form of MG in the first 2 years of disease; prednisolone may delay or prevent the onset of generalized form of MG and also can control the ocular symptoms (16,17). Also other autoimmune comorbidities such as Graves' disease, antibody positive thyroid disease and also thymus hyperplasia may increase the risk for MG generalization in the first six months of disease (18). In ocular form of MG with MUSK antibodies, chronic ocular muscle paresis is common and conjugated gaze limitation is related to low functional disabilities (19).

The symptoms of ocular MG include any combination of ptosis, diplopia and trouble focusing or each of them as an isolated finding due to fluctuating weakness of extraocular muscles (14). Pupillary reaction, sensory function and visual acuity all are normal in MG (20). Ptosis can be either unilateral or bilateral, and may fatigue with sustained upward gaze (14). OMG can mimic any painless ophthalmoplegia with or without ptosis (21). Diplopia is a common symptom because weakened extraocular muscle causes misalignment of the eyes. The lid elevation after vertical saccade of downward gaze, named Cogan's lid twitch, can be seen in ocular form of MG (22). Hypermetric saccade, jerky eye movement, inter-saccadic fatigue and gaze-evoked nystagmus can be seen in OMG (22).

The differential diagnosis of MG could include all supra, inter and infra nuclear efferent system disorders, ocular motor cranial nerve palsy (without pupil involvement), Lambert Eaton, Thyroid ophthalmoplegia, Kearns-Sayre disease, chronic and progressive external ophthalmoplegia,

and levator dehiscence (14,20). Furthermore, in patients with double vision and concurrent thyroid related orbitopathy, the co-existing of MG should be considered especially if exotropia is present (23).

Diagnosis

Diagnosis of MG generally begins with a physician assessing the symptoms and performing a physical examination, laboratory, imaging, pharmacology and physiological testing (24). ACHR-Ab is required to confirm a diagnosis of MG; however, for patients with ocular MG, blood tests have high false negative results (up to 50%) (15). In 80% to 90% of cases with generalized form of MG, the circulatory autoantibodies are detected (24). Worsening ptosis in sustained upward gaze is pathognomonic for OMG (14). The "sleep" test is conducted by having the patient close their eyes for a period of 30 minutes and observing transient improvement or resolution of ptosis immediately after the eyes are open. Improvement after rest can be used for MG diagnosis confirmation (1). The ice test may be used to differentiate myasthenic ptosis from non-myasthenic causes. The ice test as an easy, economic and specific test in which an ice pack is placed on a ptotic eyelid for 2 minutes. Improvement in ptosis of greater than 1 mm is highly sensitive and specific for OMG. One caveat is that if there is complete ptosis, the ice test is often negative (20). Edrophonium chloride and or neostigmine inhibit acetylcholinesterase and thus reversal of ptosis and/or ophthalmoplegia after administration confirms the diagnosis of MG. Administration of these drugs should be considered with caution in cases of heart disease and beta blocker or digoxin usage due to cardiovascular adverse effect. These invasive tests with potentially critical side effect are increasingly being replaced by fatigue, rest and ice tests (14).

Recently, the novel "forced eyelid closure test" (FECT) for diagnosis of ocular form of MG has been introduced. It is an easy test with 94% sensitivity and 91% specificity (25). In this screening test, patients were asked to squeeze their eyelids for a short time (5–10 seconds), open and fixate at the first position. The upward eyelids overshoot reported as a positive FECT (25).

Electromyography (EMG) and single fiber EMG are the most accurate methods to diagnose MG especially in seronegative cases, as they measure the electrical responses of muscles from stimulation to the nerves. Decrease in compound muscle action potential in stimulated nerves is

shown in MG patients (26). There is high specificity and low sensitivity of repetitive nerve stimulation owing to minimal muscle involvement in ocular MG (24). Single fiber EMG has higher sensitivity than repetitive stimulation of nerves. The single fiber EMG abnormalities have been reported in up to 99% of patients with MG (14).

Despite the variety of tests available for MG, diagnosis can still be difficult. Neuroimaging is recommended for suspected cases of OMG if a definitive diagnosis cannot be made because OMG can mimic so many other causes of ophthalmoplegia and ptosis (14).

Treatment

OMG is usually co-managed by neurology and ophthalmology. Treatment should be individualized based on symptoms at the time of presentation, disease severity, and age (15,27,28). There are four main treatment options for ocular MG: short course based on symptom relief, long term immunomodulation, rapid immunomodulation, and surgery (5,29). Most clinicians begin with pyridostigmine (Mestinon) to inhibit acetylcholinesterase. Side effects of pyridostigmine including diarrhea, abdominal cramps, nausea, and vomiting occur at variable dosages and thus dosage is usually gradually increased based on side effects and treatment effects. Patients with MuSK antibody related-MG may require higher dosage of pyridostigmine (5). In myasthenic crisis, intravenous administration of pyridostigmine may be used (30). Corticosteroids are often used alone or in combination with pyridostigmine in low and moderate doses to control the immune response. The long-term corticosteroid side effects such as osteoporosis, diabetes, high blood pressure, sleep disturbance, and emotional changes limits their role in chronic management (5). The "Efficacy of Prednisone for the Treatment of Ocular Myasthenia" clinical trial which was done to assess the risk and safety of corticosteroid therapy suggests there is a beneficial effect of low dose treatment on prevention of ocular to generalized MG progression (31). Other immunosuppressive treatments include azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, rituximab and cyclophosphamide (*Table 1*).

Other than symptomatic relief, Wong and associates reported a 30% reduction of ocular MG progression to generalized form after early immunosuppressant therapy (40).

Plasma exchange, intravenous Ig and plasmapheresis are applied for rapid immunomodulation in unstable and refractory MG cases with disabling symptoms.

Intravenous immunoglobulins (IVIg) including polyclonal immunoglobulins suppress inflammation via Fab or Fc fragments (5). It should be administered in dosage of 0.4 g/kg per day for 5 consecutive days or 1 g/kg per day for 2 days. IVIG can be helpful during myasthenic crisis to reduce the period of mechanical ventilation. Complications include allergic/anaphylactic reactions, pulmonary edema due to fluid overload, headache, viral hepatitis and aseptic meningitis (5). In addition, plasmapheresis has therapeutic effects based on the mechanism of removing the circulatory, pathogenic immune factors and autoantibodies. It could be applied in refractory cases for stabilization prior to thymectomy and/or high dose corticosteroid pulse therapy (41).

There are several medications which should be avoided in myasthenic patients regarding exacerbation or unmasking MG including Telithromycin, a new ketolide antibiotic (42); Fluoroquinolones (43,44); Streptomycin (45); Quinidine (46) and hydroxychloroquine (47) and beta-blockers.

A new pathway treatment in MG may be the Agrin-LRP4-MUSK signaling cascade. Agrin interacts with LRP4 to activate the MuSK tyrosine kinase receptor. MuSK and LRP4 prepare complex network of interacting proteins which is necessary for AChR clustering. Agrin-LRP4-MuSK signaling cascade drives acetylcholine receptors and secure signal transduction in the NMJ (48). Another new treatment is Eculizumab (humanized monoclonal antibodies) which inhibits the complement system in AChR antibody positive patients. Eculizumab should be applied as a 35 min intravenous infusion (each 30 mL vial contains 300 mg of eculizumab). It may be a valuable emerging therapy in AChR antibody positive adults MG or refractory generalized MG (49). More experiments should be done to figure out the tolerability, appropriate period of treatment, long term efficacy and complications.

The role of thymus and thymic B cells in anti-acetylcholine receptor antibodies production in MG has been clearly reported and thus thymectomy may have beneficial effect (*Table 2*) (1,11,52,64-66). Mediastinal imaging should be obtained to rule out thymoma. Thymectomy should be done if thymoma is present and even if not, should be considered in cases of medication intolerance, insufficient treatment effect and severe complications of first line treatment (5,31).

Although the treatment goal in OMG is symptomatic relief, sometimes ptosis and/or ophthalmoplegia are refractory. Local treatments for ptosis can include eyelid crutches or surgery if the ptosis is fairly stable (54,67). Occlusion of one eye can be used in the short term for

Table 1 Immunotherapy in myasthenia gravis

Name	Sample size	Type of study	Treatment	Conclusion
Tindall <i>et al.</i> , 1993 (32)	39	Clinical therapeutic trial	Cyclosporine A	Continuous steroid dosage reduction-35% discontinued cyclosporine A due to side effect
Heckmann <i>et al.</i> , 2011 (33)	31	Single-blinded trial	Methotrexate versus azathioprine	Methotrexate was the great choice of steroid sparing-similar to azathioprine in efficacy and tolerability
Hehir <i>et al.</i> , 2010 (34)	102 patients	Randomized, controlled trial	Mycophenolate mofetil	Improve AChR-positive MG with mycophenolate mofetil and prednisone-prednisone dosage reduction
Muscle Study Group, 2008 (35)	80 patients	Double-blind controlled trials	Mycophenolate mofetil with prednisone	No differences between mycophenolate mofetil with prednisone 20 mg/day and prednisone 20 mg/day alone
Sanders <i>et al.</i> , 2008 (36)	176 patients	Phase III, randomized trial	Mycophenolate mofetil	Mycophenolate mofetil was not superior to placebo
Yoshikawa <i>et al.</i> , 2011 (37)	80 patients	Randomized, double-blind, placebo-controlled	Tacrolimus	Good steroid sparing agent
Benatar <i>et al.</i> , 2006 (38)		Updated review	Corticosteroids and azathioprine	Probable effect of corticosteroids and azathioprine in reducing the risk of progression to GMG
Nagane <i>et al.</i> , 2010 (39)	28 patients	Prospective open trial	Cyclosporine micro emulsion	Improved the MG severity, decreasing steroid dosage—no adverse effect was reported

MG, myasthenia gravis.

Table 2 Thymectomy in myasthenia gravis

Name	Year	Type of study	Sample size	Conclusion
Nakamura <i>et al.</i> (50)	1996	Retrospective Study	22 patients	Is effective in OMG if done during 12 months of symptoms
Liu <i>et al.</i> (51)	2011	Retrospective Study	115 patients	58.2% of patients showed the improvement in ocular symptoms
Wolfe <i>et al.</i> (52)	2016	Randomized trial	126 patients	Improving clinical outcomes after thymectomy
Cea <i>et al.</i> (53)	2013	Review article of randomized controlled trials		No clinical trial with meaningful report of the thymectomy's efficacy until 2013
Kerty <i>et al.</i> (54)	2014	Review article		Thymectomy may modify the symptoms of ocular MG
Yuan <i>et al.</i> (55)	2007	Retrospective paired cohort study	48 patients	Good prognosis and therapeutic option for increase probability of remission in seronegative MG patients after thymectomy
Guillermo <i>et al.</i> (56)	2004	Retrospective, descriptive, comparative	71 patients	Better prognosis in seronegative MG patients after thymectomy
Jaretzki <i>et al.</i> (57)	1988	Prospective cohort	95 patients	Good prognosis of generalized MG after thymectomy
Uzawa <i>et al.</i> (58)	2015	Retrospective Study	39 patients	Beneficial effect in generalized late onset of MG and thymic hyperplasia
Liu <i>et al.</i> (59)	2016	Retrospective Study	31 patients	Thymectomy is the effective treatment for MG patients with history of crises
Kaufman <i>et al.</i> (60)	2016	Retrospective review of a prospectively maintained database	317 patients	Long term stable remission with long term follow up after thymectomy in patients with MG
Bak <i>et al.</i> (61)	2016	Retrospective Study	345 patients	Thymectomy combined with immunotherapy was reported as a satisfactory treatment with long term remission rate
Keijzers <i>et al.</i> (62)	2015	Retrospective Study	85 patients	No significant difference in the remission rate of patients with or without anti-AChR antibodies after thymectomy
Yu <i>et al.</i> (63)	2015	Retrospective Study	306 patients	Satisfactory remission rate with both extended thymectomy and immunotherapy

MG, myasthenia gravis; OMG, ocular MG.

diplopia. If the ocular misalignment is fairly stable, prism glasses can be considered. If the misalignment is very stable, strabismus surgery can be considered (67). Although strabismus surgery can be helpful, some complications including worsening diplopia and exposure keratopathy have been reported (67-69).

Summary

MG can mimic most ocular motility disorders and will be encountered by every ophthalmologist. One must be aware of its systemic manifestations and usually co-manage with a neurologist. Diagnosis can be difficult as there is no test that absolutely rules out this condition. Thus, one must be aware of the various tests described and on occasion trust their clinical judgement. It is often successfully treated with one or more of the methods described above.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/aes.2018.05.02

Cite this article as: Jabbehdari S, Golnik KC. Myasthenia gravis. *Ann Eye Sci* 2018;3:23.