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Myasthenia Gravis: Types, Diagnosis and Treatment

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ABSTRACT

The classic autoimmune disease, myasthenia gravis (MG), is brought on by certain autoantibodies at the neuromuscular junction. A classic illustration of an antibody-mediated autoimmune illness is MG. Autoantibodies against the acetylcholine receptors are present in the majority of MG patients (AChRs). Muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (Lrp4), and agrin are among the less frequently found autoantibodies. The downregulation, destruction, functional blockage, or disruption of AChR clustering in the postsynaptic membrane are all ways in which these autoantibodies interfere with cholinergic transmission between nerve terminals and muscle fibres. Fatigable muscle weakness, which may affect the ocular, bulbar, respiratory, and limb muscles, is the primary clinical symptom of MG. Depending on the autoantibody's kind and whether a thymoma is present, there are different clinical symptoms. By changing the immune homeostasis processes that stop the onset of autoimmune disorders like MG, a number of medications, including immune checkpoint inhibitors, penicillamine, tyrosine kinase inhibitors, and interferons, may cause de novo MG.

Keywords: myasthenia, gravis, diagnosis, treatment

INTRODUCTION

An autoimmune condition called myasthenia gravis affects the neuromuscular junction. Ocular symptoms will occur in the majority of myasthenia gravis patients at some time during the course of the disease, frequently as the earliest manifestation.[1]

Depending on how severely the striated muscles are affected, this condition manifests differently in each patient. Ocular symptoms, such as ptosis and diplopia, are the most prevalent type of symptom in people with myasthenia gravis. Excessive weariness has been documented in individuals with this disease as a result of frequent exercise, and these symptoms typically appear at the end of the day and after activities like watching TV or driving.[2]

Ocular myasthenia gravis (OMG), which affects about 40% of patients at the time of presentation and ultimately 15% of all myasthenia gravis patients, is diagnosed when the disease is limited to the ocular muscles.[3,4] The majority of patients who initially exhibit only ocular symptoms will eventually develop systemic symptoms,[5] but if the condition is still exclusively ocular after two years, there is a 90% likelihood that generalization will never take place .Similar to the generalized form, the distribution of OMG is bimodal in women between the ages of 30 and 60 and unimodal in men with a peak at around 70. However, both variations can manifest themselves at almost any age, from early childhood to old life.[6]

Ocular myasthenia gravis (OMG) is a localized type of MG (e.g., binding, blocking, modulating AChR antibodies). But many OMG patients lack detectable AChR antibodies (i.e., seronegative MG). Commonly, OMG affects one or more extra

ocular muscles, causing painless ptosis and/or diplopia in the eyes. The estimated incidence ranges from 0.04 to 5 per 100,000 per year for all forms of MG, while the estimated prevalence ranges from 0.5 to 12.5 per 100,000 per year.[7]

History of Myasthenia Gravis

The first authors to discuss MG were Thomas Willis (1672) and Samuel Wilks (1877), as well as their European contemporaries Erb and Goldflam.[8] German physician Jolly first coined the term "Myasthenia Gravis (MG) pseudo-paralytica" in 1895. Since MG symptoms were similar to those of curare poisoning, Mary Walker treated a case of MG using physostigmine (a cholinesterase inhibitor) in 1934, making MG treatment viable. This episode is known as "The miracle at St. Alfege's." [1,2]The pathogenesis of MG was further expanded independently by Simpson and Nastuck, and Patrick and Lindstrom (1973) demonstrated that rabbits inoculated with pure muscle-like acetylcholine (Ach) receptors exhibited symptoms similar to those of MG.[9]

Subtypes of MG & Their Clinical Manifestations

1. MG Due to Antibodies against AChR (AChR-MG)

Two -subunits and one each of β-, δ-, and γ-subunit (embryonic type) or -subunit (adult type) make up the heteropentamer nicotinic AChR, which is arranged around a central pore.[10] About 80% of MG patients have antibodies against the AChR. The AChR -subunits are targeted by at least half of the AChR autoantibodies.[11]

The main clinical symptom of MG is fatigable muscle weakness, which gets worse with activity and gets better with rest. Double vision and ptosis are the most typical ocular presenting signs. Most patients will experience diplopia and/or ptosis at some point throughout their illness. Additionally, after two years following the commencement of the disease, up to 80% of individuals with ocular onset would go on to acquire widespread symptoms.[12] Bulbar muscles are frequently affected as well, which causes face and jaw paralysis as well as flaccid dysarthria and dysphagia. Additionally, axial weakness may be observed, with neck flexion weakness typically being more prevalent than neck extension weakness.[13]

2. MuSK Antibody-Associated MG (MuSK-MG)

AChRs in the neuromuscular junction cluster because of the membrane protein MuSK. Agrin, which is produced from the presynaptic terminal, interacts with Lrp4 and causes the Lrp4/MuSK complex to become reoriented. This causes MuSK to become activated by phosphorylation. AChRs cluster when phosphorylated MuSK initiates a downstream signaling pathway.[14]

Around 7–10% of all MG patients and up to 40% of generalized MG patients who are seronegative for AChR Abs have antibodies against MuSK. Up to 85% of MuSK positive individuals are female, indicating a gender bias.[15]

MuSK antibodies are primarily IgG4 subclass antibodies. They are weak inducers of cell-mediated cytotoxicity and do not fix complement.[16] The Agrin-Lrp4-MuSK-Dok-7 signaling pathway is disrupted when MuSK antibodies attach to the protein's Ig-like domain and prevent it from being phosphorylated, which has a pathogenic effect on the neuromuscular junction. Muscle-intrinsic MuSK activator Dok-7 is necessary for synaptogenesis.[17]

Clinical Manifestations Young people are the most commonly impacted by MuSK-MG, which is more common in patients of African heritage and those who live close to the equator in European and Asian countries.[18] not environmental circumstances, but likely a genetic predisposition, is the cause of this. The cranial and bulbar muscles are most commonly affected by muscular weakness. Bulbar weakness, which is frequently accompanied by neck and respiratory dysfunction, is a presenting symptom in

over 40% of patients.[19] there is tongue atrophy in certain patients. Diplopia and/or ptosis are seen in about 30% of patients. Although limb weakness is not always present, when it does, it frequently manifests as a significant atrophy of the muscles. Strength variations during the day are less frequent.[20]

3. Double-Seronegative Generalized MG

AChR and MuSK antibody tests revealed negative results for this diverse group of patients. Patients who had previously been identified as double-negative by more popular serologic assays may have lower titers of these antibodies, according to cell-based assays.[21]

Clinical Signs and Symptoms

In terms of the distribution of muscular weakness, severity, and response to treatment, these patients typically exhibit characteristics similar to those who are positive for AChR antibodies.[22]

4. Pediatric MG

According to a meta-analysis of epidemiological data, there are between 1 and 5 instances of JMG per million person-years.[23] Ocular cases make for 16–38% of all JMG cases. Pre-pubertal children are more likely to have ocular JMG, whereas post-pubertal adolescents are more likely to have generalized MG.[27] Similar to adult-onset MG, AChR Ab, MuSK, and Lrp4 are the most often found pathogenic antibodies in JMG.[24]

Clinical Features-

Transient neonatal MG, which develops in 10-15% of infants born to moms with MG due to the passive transmission of maternal antibodies in gestation, is distinct from JMG. While neonatal MG typically resolves on its own over a period of weeks to months, the affected infants may also have extraocular muscle weakness, generalized hypotonia, and respiratory distress which calls for the use of respiratory support, neostigmine treatment, and in more severe cases, plasma exchange.[25]

Diagnosing Ocular Myasthenia Gravis

Sleep test

This test evaluates how OMG symptoms improve following a period of rest. For roughly 30 minutes, the patient is instructed to sleep or relax with his or her eyes closed. The patient is checked before the test, and any ptosis or ocular motility abnormalities are assessed. When ptosis or ophthalmoparesis disappears within 30 minutes of sleep, it is possible to confirm the diagnosis of myasthenia. Additional assurance is provided by the myasthenic symptoms returning within the next 30 to 5 minutes.

Ice test

The Ice test is a straightforward but reliable clinical examination that can be used to support the MG diagnosis. For 2 to 5 minutes (depending on the severity of the patient's ophthalmoparesis or ptosis), an ice pack is applied to the patient's closed eyelids.[26]

Although there are no set rules for how to interpret this test,[27] it is typically deemed positive when the upper eyelid elevates by at least 2 mm after being exposed to ice.[33] Cooling may decrease anticholinesterase (AChE) activity, which increases the amount of ACh that is available at the neuro-muscular junction .[28]

The ice test combined with the sleep test is very sensitive for MG and causes a bigger shift in lid position than rest alone.[29]

Pharmacological Testing and Laboratory Investigations

Edrophonium testing

A short-acting acetylcholinesterase inhibitor called edrophonium works by boosting the quantity of acetylcholine that is readily available in the synaptic cleft. It is administered intravenously at a starting dose of 2 mg, and after 10–30 seconds, it starts to work. Additional doses of 2-4 mg are

injected up to a maximum total dose of 10 mg[30] if there is no action after 45–60 seconds.

Despite the fact that the test can enhance ptosis and ocular motility, edrophonium commonly causes perspiration, nausea, fasciculations, and salivation. At a low rate of 0.16 percent, serious negative consequences such as hypotension and bradycardia have been seen.[31]

Edrophonium testing is still an effective test when used in appropriate clinical settings, despite the fact that it is gradually being replaced by alternative less intrusive modalities due to drug accessibility issues and worries about major side effects.[32]

Neostigmine test

For diagnostic testing, neostigmine, a longer-acting AChE, is replacing edrophonium more frequently. Although the response may be noticed as early as 15 minutes after an intramuscular injection, the peak effect is reached at about 30 minutes. The impact could continue for several hours. Adults often take 1.5 milligrammes of the medication intramuscularly in the deltoid muscle. Neostigmine has a longer duration of action than edrophonium, which makes it better suited for in-depth and protracted tests of ocular motility, diplopia, and etc.[26]

Autoantibodies

Seropositivity to the AChR antibodies or, less frequently, to other NMJ proteins such as anti-muscle specific tyrosine kinase (MuSK) and LDL-associated receptor related protein IV can be used to confirm the diagnosis of OMG (LRP4). OMG is very selective for finding higher AChR antibody levels in the appropriate clinical scenario.[33]

Acetylcholine receptors antibodies

The three available tests for AChR antibodies are binding, blocking, and modifying, with the binding antibody being the most common and biologically significant.[33] The latter attaches to the AChR's extracellular domains and causes the receptors to internalize and cross-link, impairing signal transmission.[34]

This antibody is mostly seen in both systemic and ocular myasthenia gravis. A number greater than 1.0 nmol/l is regarded to confirm the diagnosis of myasthenia gravis, while normal values range from 0.3 to 0.5 nmol/l amongst laboratories.[35]

LDL-related receptor-related protein 4 antibodies

Through the activation of MuSK during the development of the NMJ, LRP4 forms a complex with agrin and encourages AChR clustering and differentiation on the postsynaptic membrane. It is believed that LRP4 antibodies hinder the maintenance of NMJs. They are detected in 7–33% of myasthenia gravis patients who are seronegative to AChR and MuSK antibodies.[36] are seen in 1-5% of all myasthenia gravis patients [54], and are more frequently observed in female patients.

MuSK Antibodies (MuSKAbs)

An anchoring protein called MuSK has an intracellular domain with tyrosine kinase activity, a transmembrane domain, and an extracellular domain (42). Three immunoglobulin-like regions (Ig1, Ig2, and Ig3) plus a frizzled domain make up the extracellular domain. The MuSK protein is essential for maintaining the NMJ structure and is essential for the AChR clustering process.[27]

Ristocetin Induced Platelet Aggregation test is a highly specific assay that can find the MuSK antibodies. The finding of MuSKAbs in the patient's serum supports the MG clinical diagnosis.

The 125I-bungarotoxin labeledMuSK antigen in solution is inaccessible to some conformation-dependent MuSKAbs, though. Contrarily, it has been reported that the MuSK cell-based assay (MuSK-CBAs; HEK293 cells transfected with MuSK recombinant antigen) has higher sensitivity (6–10%) as a result of the added detection of conformation-dependent MuSK Abs.[37]

ELISA technique can also be used to detect MuSKAbs, but they must undergo thorough testing before being used in ordinary clinical practice.[38]

Electrophysiologic studies

Research on repetitive nerve stimulation

Surface electrodes are used to record the compound muscle action potential (CMAP) after electrically stimulating the study nerve 6–10 times at 2–3 Hz (slow rate) with a supramaximal stimulus.[39] The fourth or fifth response in a series of low-frequency RNS often reveals a significant reduction (>10%) in muscle action potential amplitude in MG, whereas the amplitude is constant in healthy persons.[40] It is possible for myopathies, motor neuron disorders, and the Lambert-Eaton myasthenic syndrome to exhibit a decreasing response to RNS.

Single-fiber electromyography

The most accurate diagnostic procedure for identifying aberrant neuromuscular transmission is single-fiber electromyography. In SFEMG, a customized concentric needle with a 25 mm recording area and a 500 Hz high-frequency filter captures individual muscle fiber action potentials produced by the same motor neuron. The time from stimulus to response varies when potentials induced by nerve stimulation are recorded with an SFEMG electrode. This variation, known as the neuromuscular jitter, is mostly brought on by changes in how long it takes end plate potentials at the NMJ to cross the AP threshold.[40]

TREATMENT

1. Medications that Enhance Neuromuscular Transmission

A myasthenic patient was treated for the first time with physostigmine, an acetylcholinesterase (AChE) inhibitor, in 1934; pyridostigmine bromide (PB) replaced it in 1954. The initial course of treatment for MG is oral AChE inhibitors.

Due to their brief half-life, AChE inhibitors are beneficial in the short term. AChE inhibitors should be taken into consideration as the first-line treatment for MG, especially for mild cases, according to European guidelines.[41] They may also be used as a supplement to other forms of treatment for people with more serious illnesses. The most widely used AChE inhibitor is PB, which has a 30-minute onset, a 2-hour peak, and a 3- to 4-hour duration of action; PB is offered as:

○The most often used formulation is an oral standard tablet, dose 60 mg.

○A 180 mg sustained-release medication that is typically recommended at bedtime for individuals who experience symptoms in the middle of the night or early in the morning. Although it has been suggested, sustained-release PB has not yet undergone a thorough investigation.

○A syrup (12 mg/mL) for children, individuals who need nasogastric feeding, and, very occasionally, people who have adverse responses to medicine excipients.

PB is also offered as 2-mL ampules with a 5 mg/ml concentration for intramuscular or intravenous delivery.[42]

2. Immunomodulating therapies interfering with autoantibody effects on NMJ

The following are examples of both established and novel medicines that can affect the immune pathogenetic mechanisms of MG:

1. Steroids;
2. Immunosuppressants;
3. Immunomodulating agents;
4. Biological and cellular therapies.

Prednisone is the most often utilized steroid in the treatment of MG because of its strong immunosuppressive effect, minimal anti-edemigen activity, and half-life that is suitable for an alternate-day schedule. For the treatment of widespread MG, the starting dose is 1 mg/kg/day.[28]

Osteoporosis, cataract, diabetes mellitus, hypertension, gastrointestinal discomfort, glaucoma, weight

gain, and skin conditions are side effects of prolonged corticosteroids.

Immunosuppressants

Several immunosuppressive medications are used to treat MG, including azathioprine (AZA), cyclosporin A (CyA), methotrexate, mycophenolate mofetil (MMF), and tacrolimus (FK506). Typically, it takes longer than it does to achieve a clinical benefit with these medications than it does with steroids, sometimes up to several months. They are frequently combined with corticosteroids as "steroid-sparing agents" or used as standalone medications, as an alternative to steroids in people for whom it is contraindicated, or both.

Thymectomy

In order to maximize the likelihood of remission or improvement, thymectomy is advised for non-thymomatous patients with widespread MG who have cholinergic antibodies and are younger than 60 years old. Thymectomy is required for patients with thymoma.[41]

New treatment options

The need for new, effective therapies that combine adequate efficacy, a reduction in side effects, and the use of therapeutic schedules optimized for chronic immunosuppression is the main driver of innovation in the treatment of MG. Another important factor is the use of medications with higher specificities that target only the crucial immunopathological steps from AChR sensitization to autoantibody production.

Rituximab

Rituximab is a humanized monoclonal antibody to CD20 that produces extended B-cell depletion and has been used to treat refractory MG. It is approved for the treatment of adult B-cell lymphoma. There are a few small case series that have been treated for both MG with and without thymoma. Rituximab offers optimistic prospects for treating MG.[43]

Etanercept

In a prospective pilot study using etanercept for corticosteroid-dependent autoimmune MG, 70% of patients who finished the study reported increased muscular strength and a decreased need for corticosteroids. The levels of plasmaL-6, TNF, and interferon were found to be directly correlated with the patients' post-treatment clinical scores.[44]

A complement inhibitor was recently administered to experimental MG rats, and the results showed a reduction in both disease severity and complement deposition at neuromuscular end-plates. These findings are highly intriguing for future human applications.

Cellular therapy

Another approach for targeted immunotherapy in MG may be provided by the manipulation of professional antigen-presenting cells (dendritic cells) by AChR proteins or peptides or by the mobilization of regulatory T cells specific for specific antigens. These therapeutic modalities have been shown to be successful in preventing the induction of or treating Experimental Autoimmune Myasthenia Gravis.[45]

Specific anti-AChR removal

The basis for a targeted elimination of anti-AChR antibodies was the expression of the extracellular domains (ECD) of the various AChR subunits using molecular biology methods. These recombinant ECDs were in fact attached to insoluble carriers that were employed to immune absorb antibodies from MG patients. The technique was effective enough to remove pathogenic components from MG serum and depleted anti-AChR antibodies, demonstrating its viability.[46]

CONCLUSION

MG affects all age groups but is more common in younger women and older men. There is a lot of variation in the incidence and prevalence rates of MG by geographic area, with the latter mainly attributable to increased awareness and advancements in the diagnosis of the condition. The clinical suspicion might be supported by a variety of clinical signs and laboratory tests. To boost

the diagnostic sensitivity, new detectable antibodies like anti-MuSK and single-fiber electromyography should be included in the algorithm. Immunosuppression is frequently necessary for the treatment of OMG, but it can usually be accomplished with a minimal incidence of systemic side effects. The method will need to be scaled up in order to go through rigorous clinical trials and to maximize the effectiveness of antibody elimination.

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REFERENCES

1. Kerty E, Elsais A, Argov Z, Gilhus NE. EFNS/ENS guidelines for the treatment of ocular myasthenia gravis. Eur J Neurol 2014; 21:687–693.
2. Shield TW, editor. General thoracic surgery, 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010. pp. 2323–64.
3. Gilhus N, Myasthenia gravis. N Engl J Med 2016; 375:2570–2581.
4. Gilhus N, Skeie GO, Romi F. Myasthenia gravis - autoantibody characteristics and their implications for therapy. Neurology 2016; 12:259–26
5. Evoli A, Tonali E, Bartoccioni M, Monaco ML. Ocular myasthenia: diagnostic and therapeutic problems. Acta NeurolScand 1988; 77:31–35.
6. Paragallo JH, Bitrian E, Kupersmith M, et al. Relationship between age, gender, and race in patients presenting with myasthenia gravis with only ocular manifestations. J Neuroophthalmol 2016; 36:29–32.
7. Vaphiades MS, Bhatti Lesser RL. Ocular myasthenia gravis. CurrOpinOphthamol 2012; 23:537-42.
8. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: Past, present, and future. J Clin Invest 2006; 116:2843-54.
9. López-Cano M, Ponseti-Bosch JM, Espin-Basany E, Sánchez-García JL, Armengol-Carrasco M. Clinical and pathologic predictors of outcome in thymoma-associated myasthenia gravis. Ann ThoracSurg2003; 76:1643-9.
10. Albuquerque E.X., Pereira E.F.R., Alkondon M., Rogers S.W. Mammalian Nicotinic Acetylcholine Receptors: From Structure to Function. *Physiol. Rev.* 2009; 89:73–120. doi: 10.1152/physrev.00015.2008.
11. . Tzartos S.J., Barkas T., Cung M.T., Mamalaki A., Marraud M., Orlewski P., Papanastasiou D., Sakarellos C., Sakarellos-Daitsiotis M., Tsantili P., et al. Anatomy of the Antigenic Structure of a Large Membrane Autoantigen, the Muscle-Type Nicotinic Acetylcholine Receptor. *Immunol. Rev.* 1998; 163:89–120. doi: 10.1111
12. Oosterhuis H.J. The Natural Course of Myasthenia Gravis: A Long Term Follow up Study. *J. Neurol. Neurosurg. Psychiatry.* 1989; 52:1121–1127.
13. Hong Y.-H., Kwon S.-B., Kim B.-J., Kim B.J., Kim S.H., Kim J.K., Park K.-S., Park K.-J., Sung J.-J., Sohn E.H., et al. Prognosis of Ocular Myasthenia in Korea: A Retrospective Multicenter Analysis of 202 Patients. *J. Neurol. Sci.* 2008; 273:10–14.
14. Gilhus N.E. Myasthenia Gravis. *N. Engl. J. Med.* 2016; 375:2570–2581. doi: 10.1056/NEJMra1602678.
15. Kim N., Stiegler A.L., Cameron T.O., Hallock P.T., Gomez A.M., Huang J.H., Hubbard S.R., Dustin M.L., Burden S.J. Lrp4 Is a Receptor for Agrin and Forms a Complex with MuSK. *Cell.* 2008; 135:334–342. doi: 10.1016
16. Guptill J.T., Sanders D.B., Evoli A. Anti-Musk Antibody Myasthenia Gravis: Clinical Findings and Response to Treatment in Two Large Cohorts. *Muscle Nerve.* 2011; 44:36–40. doi: 10.1002/mus.22006.
17. Plomp J.J., Huijbers M.G., van der Maarel S.M., Verschuuren J.J. Pathogenic IgG4 Subclass Autoantibodies in MuSK Myasthenia Gravis: MuSK Myasthenia Gravis IgG4. *Ann. N. Y. Acad. Sci.* 2012; 1275:114–122.
18. Okada K., Inoue A., Okada M., Murata Y., Kakuta S., Jigami T., Kubo S., Shiraishi H., Eguchi K., Motomura M., et al.

The Muscle Protein Dok-7 Is Essential for Neuromuscular Synaptogenesis. *Science.* 2006; 312:1802–1805.
19. Gilhus N.E. Myasthenia Gravis. *N. Engl. J. Med.* 2016; 375:2570–2581.
20. Gilhus N.E., Verschuuren J.J. Myasthenia Gravis: Subgroup Classification and Therapeutic Strategies. *Lancet Neurol.* 2015; 14:1023–1036.
21. Pasnoor M., Wolfe G.I., Nations S., Trivedi J., Barohn R.J., Herbelin L., McVey A., Dimachkie M., Kissel J., Walsh R., et al. Clinical Findings in MuSK-Antibody Positive Myasthenia Gravis: A U.S. Experience. *Muscle Nerve.* 2010; 41:370–374.
22. Cortés-Vicente E., Gallardo E., Martínez M.Á., Díaz-Manera J., Querol L., Rojas-García R., Illa I. Clinical Characteristics of Patients with Double-Seronegative Myasthenia Gravis and Antibodies to Cortactin. *Jama Neurol.* 2016; 73:1099.
23. Higuchi O., Hamuro J., Motomura M., Yamanashi Y. Autoantibodies to Low-Density Lipoprotein Receptor-Related Protein 4 in Myasthenia Gravis. *Ann. Neurol.* 2011; 69:418–422.
24. Parr J.R., Jayawant S. Childhood Myasthenia: Clinical Subtypes and Practical Management. *Dev. Med. Child. Neurol.* 2007; 49:629–635.
25. Barraud C., Desguerre I., Barnerias C., Gitiaux C., Boulay C., Chabrol B. Clinical Features and Evolution of Juvenile Myasthenia Gravis in a French Cohort. *Muscle Nerve.* 2018;57:603–609.
26. Namba T., Brown S.B., Grob D. Neonatal Myasthenia Gravis: Report of Two Cases and Review of the Literature. *Pediatrics.* 1970;45:488–504.
27. (Grigg J. Extraocular muscles: Relationship of structure and function to disease. Aust N Z J Ophthalmol1999; 27:369-70.
28. Sethi KD, Rivner MH, Swift TR. Ice pack test for myasthenia gravis. Neurology 1987; 37:1383-5.
29. Kubis KC, Danesh-Meyer HV, Savino PJ, Sergott RC. The ice test versus the rest test in myasthenia gravis. Ophthalmology 2000; 107:1995-8.
30. Al-Haidar M, Benatar M, Kaminski H. Ocular myasthenia. Neurol Clin 2018; 36:241–251.
31. Ing EB, Ing SY, Ing T, et al. The complication rate of edrophonium testing for suspected myasthenia gravis. Can J Ophthalmol 2000; 35:141–144.
32. Pasnoor M, Dimachkie MM, Farmakidis C, Barohn RJ. Diagnosis of myasthenia gravis. Neurol Clin 2018; 36:261–274.
33. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 2009; 8:475–490.
34. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 2015; 14:1023–1036.
35. Zhang B, Tzartos JS, Belimezi M, et al. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol 2012; 69:445–451.
36. Kupersmith MJ, Latkany R, Homel P. Development of generalized disease at 2 years in patients with ocular myasthenia gravis. Arch Neurol2003;60:243-8.
37. Grob D, Arsura EL, Brunner NG, Namba T. The course of myasthenia gravis and therapies affecting outcome. Ann N Y Acad Sci 1987;505:472-99.
38. Keane JR. Vertical diplopia. Semin Neurol1986;6:147-54.
39. Juel VC, Massey JM. Myasthenia gravis. Orphanet J Rare Dis 2007;2:44.
40. Ozdemir C, Young RR. The results to be expected from electrical testing in the diagnosis of myasthenia gravis. Ann N Y Acad Sci 1976;274:203-22.
41. Gilhus N.E. Myasthenia Gravis. *N. Engl. J. Med.* 2016;375:2570–2581. doi: 10.1056/NEJMra1602678.
42. Gilhus N.E., Verschuuren J.J. Myasthenia Gravis: Subgroup Classification and Therapeutic Strategies. *Lancet Neurol.* 2015;14:1023–1036. doi: 10.1016/S1474-4422(15)00145-3.
43. Gilbert ME, de Sousa EA, Savino PJ. Ocular myasthenia gravis treat- ment: the case against prednisone therapy and

thymectomy. Arch Neurol. 2007;64(12): 1790–1792.
44. Rowin J, Meriggioli MN, Tuzun E, Leurgans S, Christadoss P. Etanercept treatment in corticosteroid-dependent myasthenia gravis. Neurology. 2004;63(12): 2390–2392.
45. Sheng JR, Li LC, Ganesh BB, Prabhakar BS, Meriggioli MN. Regu- latory T cells induced by M-CSF suppress ongoing experimental myasthenia gravis. Clin Immunol. 2008;128(2):172–180.
46. Tzartos S, Bitzopoulou K, Gavra I, et al. Antigen-specific apheresis of pathogenic autoantibodies from myasthenia gravis sera. Ann N YAcad Sci. 2008;1132:291–299.

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