

Ocular Manifestations of Myasthenia Gravis

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1. Introduction

Myasthenia Gravis (MG) is presently an incurable antibody-mediated autoimmune disorder characterized by generalized voluntary skeletal muscle weakness. Literally translated from its Latin and Greek etymological roots, myasthenia gravis means, "grave muscle weakness."

The cause of the weakness is due to a defect at the level of the neuromuscular junction in which autoimmune antibodies block the receptors responsible for initiating muscular contraction. The neurotransmitter that is subject to this competitive inhibition is acetylcholine (ACh). The muscles commonly affected include those of the neck, limbs and chest cavity with regards to breathing. The muscles of the eye, including those responsible for eye movements, as well as those involved with swallowing, chewing, and speaking, are most notably affected. Muscle weaknesses involving the eye produce symptoms of blurred vision, variable diplopia, and ptosis. Colavito et al. noted that nonstriated ocular muscles can also be involved in MG. They cautioned that when patients with myasthenia present with complaints of asthenopia and blur, resulting from accommodative dysfunction and vergence insufficiency, the underlying systemic disease process may be missed. Ptosis is defined as an abnormal eyelid "drooping" beyond the normal 1-2 mm of the upper limbus of the cornea.

Since the process in which the muscular weakness manifests is a result of competitive inhibition, the weakness observed is transient and improves with periods of rest. Likewise, muscular weakness increases during periods of increased or prolonged physical activity.

Even though MG is an antibody-mediated autoimmune disease, a reported 15% of patients with systemic or generalized MG have no detectable antibodies to acetylcholine receptors (i.e., they have "seronegative" MG). Seronegative MG is common in children; 40% of cases present before the age of 10 years.

It is estimated that 85-90% of all reported MG cases, whether seropositive or seronegative, present with ocular symptoms. Additionally, it has been reported that 20-50% of all cases of MG are purely ocular. Ocular myasthenia is considered a distinct diagnosis from generalized MG. Although there is evidence of ocular MG progressing to generalized MG, it has been reported that those with purely ocular symptoms for a period of 1-3 years have a greatly reduced chance of progressing on to generalized MG. Furthermore, a reported estimate of 55% of all cases of ocular MG are seropositive.

Two reasons have been suggested to explain the high proportion of MG cases that present with ophthalmic manifestations. The first is the susceptibility of ocular muscles to the disease process. The second reason is that ocular involvement in MG is relatively easy to recognize compared to that of other muscle groups. The exact reasoning why is unknown, but the following four reasons are hypothesized to contribute in part or in whole: First, even the slightest extraocular muscle (EOM) weakness will sufficiently misalign the visual axis to produce symptoms of diplopia. This is in contrast to an affected muscle in a limb, where an individual would not notice minute reductions in muscle-generated forces most likely.⁷ Moreover, the ocular motor system relies primarily on visual feedback, not so much on proprioceptive mechanisms, thereby making its ability to adapt swiftly to asymmetric or variable weakness more limited compared to an extremity muscle. Second, the high firing frequencies of ocular motor neurons might contribute to neuromuscular transmission fatigue. No other motor neuron in the body exhibits the rate of firing frequency of the ocular motor neurons. It is estimated ocular motor neurons fire at a frequency exceeding up to 600 Hz during saccades. Motor neurons found elsewhere in the body rarely exceed a firing frequency of 100 Hz. Therefore, any disruption in the ability of these ocular neurons to maintain a high firing rate would cause a decrease in effectiveness and appropriate output. Myasthenia gravis produces this kind of disruption. Third, several anatomic and physiologic properties of EOM fibers make them more susceptible to neuromuscular transmission blockade. EOM nerve fibers possess anatomical characteristics that possibly make them more susceptible to neuromuscular transmission block. The fibers of the EOMs have less prominent synaptic folds, and the conclusion is drawn that there are fewer ACh receptors and sodium channels on the postsynaptic membrane. Much has been previously documented in that the mean quantal content (in other words, the average number of vesicles released during a synaptic event) of ocular motor neurons is lower than motor neurons innervating other muscles. Fourth is the preferential immunologic targeting of EOM synapses. This theory remains purely speculative, but it has been observed that the sera from some MG patients bind only to multi-innervated fibers' synapses, and the use of EOM as a source of ACh receptors for ACh antibody assays leads to higher rates of autoantibody detection, which suggests that EOMs have unique antigenic targets.

Treatment for systemic or generalized MG includes a wide variety of options, but remains primarily systemic medication. First line therapy typically consists of an acetylcholinesterase inhibitor like pyridostigmine bromide (Mestinon). Although it must be noted that pyridostigmine bromide has rather variable results in pure OMG with an approximate effectiveness ratio of 1 to 2. Another option is immunosuppressant therapy such as prednisolone, cyclosporine, azathioprine, methotrexate and mycophenolate mofetil (Cellcept). Yet again, it must be noted with regards to pure OMG, it is suggested there is not sufficient evidence to warrant the routine use of immunosuppressant therapy (i.e. corticosteroids). More drastic measures attempted in the past include systemic oral medications, plasmapheresis (a.k.a. plasma exchange) and IVIG injections. Plasmapheresis is the removal of antibodies from the blood. An IVIG injection is a sterile solution of plasma proteins containing IgG antibodies from pooled human plasma. Although the mechanism of action is unknown, it is thought to down-regulate the production of antibodies. The preparation contains no less than 90% immunoglobulin consisting of all the IgG substances and trace amount of IgA and IgM. However, this treatment is usually reserved for patients

demonstrating dysphagia with an associated high risk of aspiration and those who are unable to ambulate without assistance. Although slower-acting than plasma exchange, the response is similar and offers advantages when therapeutic plasmapheresis is not available or when vascular access is problematic. Significant improvement is seen in patients whose therapy consist of an initial dose of 400 mg/kg/d for 5 days and followed by maintenance with 400 mg/kg once monthly. Furthermore, it has been noted that with regards to a similarly treated disease, Guillian-Epstein Barr Syndrome, IVIG treatment in many ways is considered to be the more effective successor to plasmapheresis.

Thymectomy, the surgical removal of the thymus gland, is also an effective and accepted treatment for generalized MG; however, while effective, it is controversial as a treatment measure in pure OMG. Recent theories suggest thymectomies could be performed on early presentations of OMG to prevent and/or slow the disease progression and immunosuppressive therapy only if proven necessary. Thymectomies are often performed on young individuals in the early stages of MG regardless of the presence of a tumor.⁸ As related to generalized MG and post-surgical improvement, it has been shown both the grade of follicular hyperplasia and density of T-cell subsets in the middle part of the thymus (space between the superior and inferior horns) had a significant correlation with the level of improvement of MG after thymectomy.

Additionally, if there is found to be thyroid involvement, a thyroidectomy is a viable treatment option.

Treatment for ocular MG specifically may include all the aforementioned options because a report 50-60% of individuals who present with purely ocular MG will eventually progress and develop generalize MG. Nevertheless, ocular MG treatments consist of both surgical and non-surgical treatments. Surgical options for myogenic ptosis are ptosis repair surgery, blepharoplasty, and frontalis suspension for which a Tutoplast sling can be utilized, external levator advancement, and tarsomyectomy. A non-surgical option is Botulinum Toxin Type A (Botox) injection to temporarily treat myogenic ptosis.

The first line of treatment should be a refraction in order to achieve the patient's best corrected visual acuity (BCVA). Assessment of accommodation and vergence testing should also be considered. As for diplopia, standard treatments such as occlusion and prisms are commonly employed. However, with prisms, the practitioner must keep in mind the variability of the disease's manifestations, thereby making it possible for the angle of deviation to fluctuate.

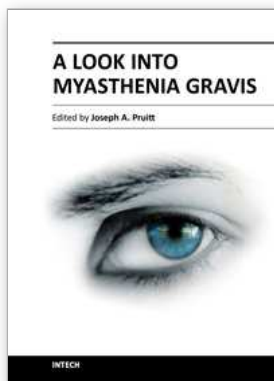
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