DEPARTMENT OF OPHTHALMOLOGY

FACULTY OF MEDICINE PADJAJARAN UNIVERSITY

NATIONAL EYE CENTER CICENDO EYE HOSPITAL

BANDUNG

Case Report	:	Diagnostic Approach in Patient With Ocular Myasthenia Gravis in Office Setting
Presenter	:	Medissa
Supervisor	:	Bambang Setiohadji, MD

Has been reviewed and approved by

Supervisor of Neuro-Ophthalmology Unit

Bambang Setiohadji, MD

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DIAGNOSTIC APPROACH IN PATIENT WITH OCULAR MYASTHENIA GRAVIS IN OFFICE SETTING

Abstract
Introduction : *Myasthenia gravis (MG) is an autoimmune disease in which antibodies mediate damage and destruction of acetylcholine receptors in striated muscle. There is a female predominance overall. The diagnosis of ocular myasthenia gravis is based on the clinical history and examination, pharmacological testing, serologic testing and electrophysiology*
Purpose : *To report a case patient with ocular myasthenia gravis in both eyes.*
Case report : *patient, woman 33 years old came to neuro-opthalmology unit with chief complaint droopy eye lid on both eyes accompanied by double vision since 5 months ago. In ophthalmology examination, there is ocular movement deficit to all quadrant on both eyes. Inter palpebral fissure was 8mm on both eyes. Other examination for anterior and posterior segment within normal limit. Patient was performed another aexamination, such as ice pack test, cogan's lid twitch test, stare test and ocular muscle weakness test, and the result positive in all test. Patient was performed prostigmin test in neurology unit, and the result is positive. Patient was treated with pyridostigmine oral 3x60mg and artificial tears 4 gtt 1 on both eyes.*
Conclusion :
Myasthenia gravis (MG) is an autoimmune disease characterized by variable and fatigable weakness. Clinical assessment of myasthenia gravis is important in making diagnose, although there is no test is specific for ocular MG, and its diagnosis should not be based exclusively on any single test.
Key word : *ocular myasthenia gravis, myasthenia gravis*

I. Introduction

Myasthenia gravis (MG) is an autoimmune disease in which antibodies mediate damage and destruction of acetylcholine receptors in striated muscle. The resultant impairment of neuromuscular conduction causes weakness and fatigability of skeletal musculature. Autoimmune MG affects all races and ages, with an incidence of 4 to 5 per 100.000. There is a female predominance overall, but the sex predilection in age dependent, with women predominating among younger patient and men among those who are older at diagnosis. In about 60% to 70 % of patients, MG first or only affects the extraocular muscles, levator palpebrae superior, orbicularis oculi, or combination of these. The diagnosis of ocular myasthenia gravis is based on the clinical history and examination, pharmacological testing, serologic testing and electrophysiology.[1,2] This

case report present how to diagnose patient with ocular myasthenia gravis in office setting.

II. Case Report

A 33 years old women came to Cicendo Eye Hospital with a chief complaint droopy eye lid on both eyes accompanied by double vision since 5 months ago. The symptoms worsened during end of the day and often associated with physical exertion. There is no weakness in her both feet. History of medication to ophthalmologist before and patient was diagnose asthenopia. There is no other symptoms like fever, nausea, vomit, headache, dysphagia, hoarseness, dysarthria and dyphnea. There is no history of trauma. She denied history of systemic disease such as hypertension, diabetes mellitus, and dyslipidemia.

On general examination within normal limit. On ophthalmology examination, visual acuity was 0,63 on both eyes . Intra ocular pressure was 16 in both eyes. The eye position was orthotropia, there is ocular movement deficit in all quadrant for both eyes. Right eye (RE) -2 to superior and medial eye movement, and -1 in lateral and inferior eye movement. Left eye (LE) -2 in superior, lateral and medial eye movement, and -1 to inferior eye movement. There is no eye movement pain in both eyes. Anterior segment examination, there are ptosis on both eyes, interpalpebral fissure (IPF) both eyes 8mm with margin reflex distance (MRD)-1 2mm, MRD-2 6mm and levator palpebra function (LPF) 12mm. other anterior segment examination was within normal

limit. Amsler grid examination, contrast sensitivity and color vision test within normal limit. Posterior segment round papil clear border on both eyes.

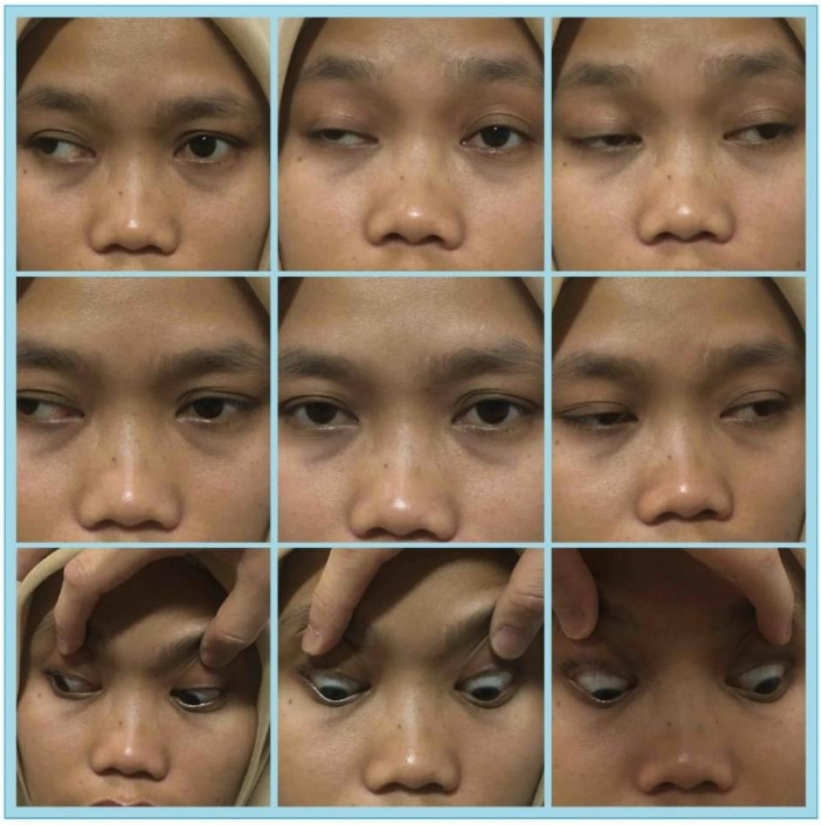

Figure 2.1 9 gaze positions
Source : Neuroophthalmology Unit Cicendo Eye Hospital

We performed another examination for the ptosis, such as ice test, using ice cube then applied to the eyes for 2 minutes. After 2 minutes the ice is removed and we measured IPF on both eyes 11mm, MRD-1 5mm, MRD-2 6mm. the IPF is greater after cooling, so we considered the test is positive in both eyes.

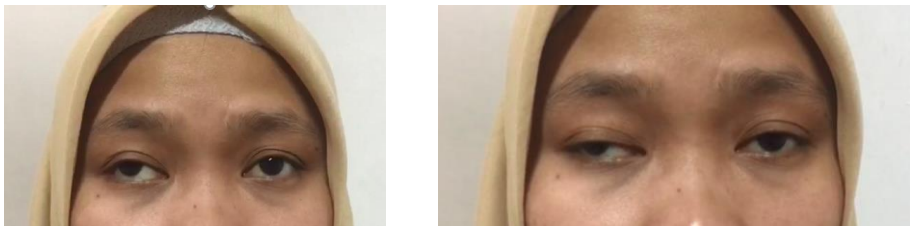

Figure 2.1 Fatigability test (stare test)
Source : Neuroophthalmology Unit Cicendo Eye Hospital

We performed orbicularis muscle weakness**,** patient forcefully shut the eyes while examiner manually attempts to open the eyelids against the forced lid closure. We performed Fatigability test (stare test), patient asked to look up without blinking at the examiners hand for 1-2 min, and there are lid fatigue on prolonged up gaze. We performed Cogan's lid twitch test, After prolonged down gaze refixation to the primary position results in overshooting of the upper lid on both eyes.

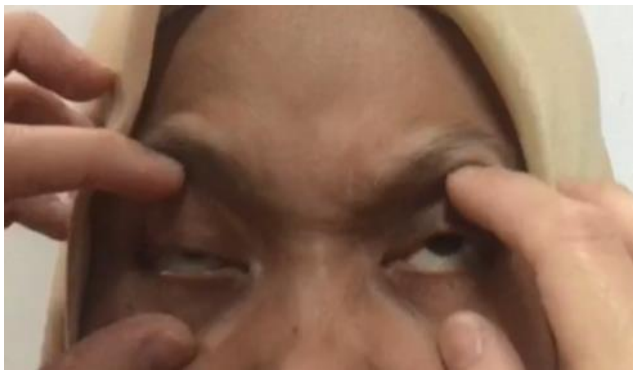

Figure 2.3 Orbicularis Muscle Weakness
Source : Neuroophthalmology Unit Cicendo Eye Hospital

Patient was diagnosed with ocular myasthenia gravis on both eyes and refractive error on both eyes. The patient was consult to Neurology Department in Hasan Sadikin Hospital for prostigmin test and the result is positif, than patient was treated with pyridostigmine oral 3x60mg and artificial tears 4x1 gtt on both eyes. Prognosis for this patient ad funciona is dubia ad bonam and for vitam is dubia.

Figure 2.4 Cogan Lid twitch test
Source : Neuroophthalmology Unit Cicendo Eye Hospital

III. Discussion

Myasthenia gravis is the rare clinical disease that results from impaired neuromuscular transmission at the synapse between the termination of the axon of the lower motor neuron and the muscle, at the motor end plate. Neuromuscular transmission depends on normal synthesis and release of acetylcholine into the gap substance of the synapse, and its uptake by healthy receptors on the muscle membrane. The main pathological abnormality in myasthenia gravis at the neuromuscular junction is the presence of auto-antibody attached to receptor sites on the post-synaptic membrane. This auto-antibody both degrades and blocks acetylcholine receptor sites, thus impairing neurotransmission across the synapse.[3,4]

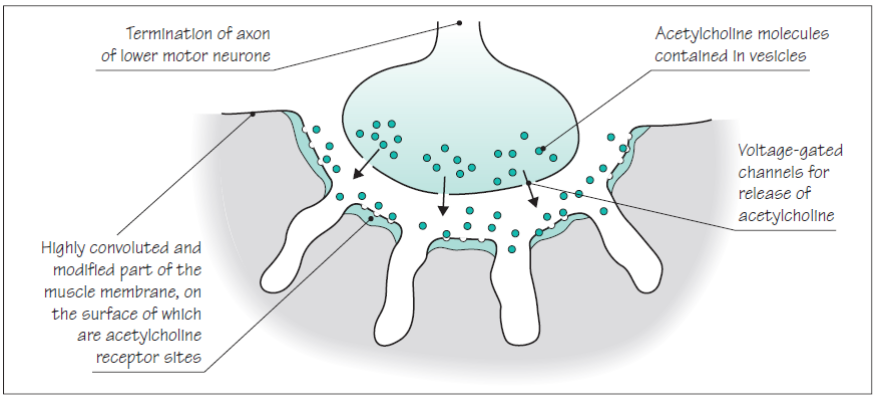

Figure 3.1 Diagram to show a motor end plate in skeletal muscle
Source : Wilkinson[4]

Myasthenia gravis (MG) is an autoimmune disease in which antibodies mediate damage and destruction of acetylcholine receptors in striated muscle, characterized by variable and fatigable weakness. There is abnormal weakness in some or all voluntary muscles. The most commonly affected muscles are the levator palpebrae superior, the extraocular muscles, the orbicularis oculi, triceps, quadriceps, and the tongue. Other voluntary muscles innervated by cranial nerves (facial, masticatory, pharyngeal, and laryngeal muscles) and cervical, pectoral girdle, and hip flexor muscles are also frequently affected. Symptoms may improve with rest. Most patient in MG incur neuro-ophthalmic abnormalities. Although the disease is usually a systemic disorder, one-half of affected patients have ocular symptoms. There is a female predominance overall, but the sex predilection in age dependent, with women predominating among younger patient and men among those who are older at diagnosis.[2,5,6]

Clinical signs and symptoms usually worsen in the evening and with the use of the eyes and may improve with rest. The most common sign of MG is unilateral or bilateral ptosis. The extent of ptosis tends vary, with eyelid more ptotic in the evening, after exertion, of after up gaze. Myasthenia gravis frequently causes diplopia. The diplopia may be variable, both during the day and form one day to another. Ptosis in MG may occur as an isolated sign or in association with extraocular muscle involvement, although the reason for this is unknown. In most cases, disturbances of ocular motility and alignment are associated with ptosis. There is no set pattern to the diplopia experienced by such patients or to the nature of extraocular muscle involvement. All degrees of ocular motor dysfunction, from apparent muscle involvement of a single isolated muscle to complete external opthalmoplegia. [5,6]

In this case, patient a women 33 years old came with chief complaint droopy eye lid on both eyes accompanied by double vision since 5 months ago. The symptoms worsened during end of the day and often associated with physical exertion. Ophthalmic examination showed Intra ocular pressure was 16 in both eyes. The eye position was orthotropia, there is ocular movement deficit in all quadrant for both eyes. Right eye (RE) -2 to superior and medial eye movement, and -1 in lateral and inferior

eye movement. Left eye (LE) -2 in superior, lateral and medial eye movement, and -1 to inferior eye movement. There is no eye movement pain in both eyes. Anterior segment examination, there are ptosis on both eyes, interpalpebral fissure (IPF) both eyes 8mm with margin reflex distance (MRD)-1 2mm, MRD-2 6mm and levator palpebra function (LPF) 12mm.

Systemic symptoms and signs extensors of the neck, trunk and limbs, dysphagia, hoarseness, dysarthria and dypnea. The patient not complained weakness in her both feet and there is no other symptoms like fever, nausea, vomit, headache, dysphagia, hoarseness, dysarthria and dyphnea.

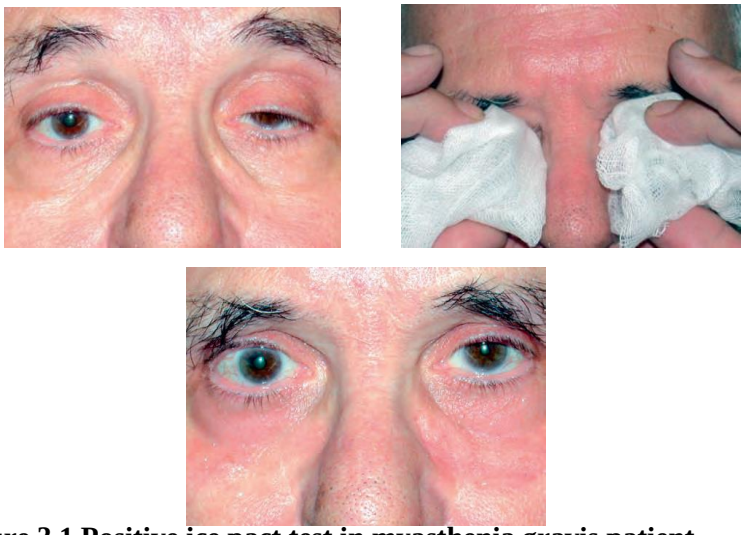

Figure 3.1 Positive ice pact test in myasthenia gravis patient
Source : Miller[6]

The diagnosis of MG is made clinically by identifying typical signs and symptoms, exam, pharmacologic testing, serologic testing and electrophysiology. The ice pack test is a test for an improvement after ice pack is placed on the ptotic eyelid for 2 minutes, as cold inhibits the breakdown of acetylcholine by acetylcholinesterase. It is around 75% sensitive but highly specific. In this patient we performed ice pack test, and showed improvement in ptosis eyes. Before the test, the IPF on both eyes were 8mm, meanwhile after the test, the IPF on both eyes were 11mm.[2,57]

Fatigability test (stare test) is the test when patient asked to look up without blinking at the examiners hand for 1-2 minutes. Lid fatigue and prolonged up gaze is perhaps the most frequently elicited signs. In this patient there are lid fatigue on prolonged up gaze on both eyes.[5,8 7]

Cogan lid twitch is another important sign that suggest MG. when patient's eyes are directed downward for 10 to 20 seconds and the patient then is instructed to make a vertical saccade back to primary position, the upper eyelid elevates and either slowly droop or else twitches several times before settling into a stable position. This sign is caused by the rapid recovery and easy fatigability of myasthenic muscle. In this patient we performed cogan's lid twitch test, and there is a overshooting of the upper lid on both eyes.[3,6]

Orbicularis oculi weakness is often present in patient with ocular MG and, if present, can be diagnostically crucial in differentiating MG from other causes of external ophthalmoplegia. The combination of ptosis, ocular motility disturbances, and weakness of orbicularis oculi is found in only a few disorders, including MG. Patients suspected of having MG therefore should have testing of orbicularis oculi strength by having the patient forcefully shut the eyes while examiner manually attempts to open the eyelids against the forced lid closure. This patient was performed ocular muscle weakness and the result is positive on both eyes.[2,6]

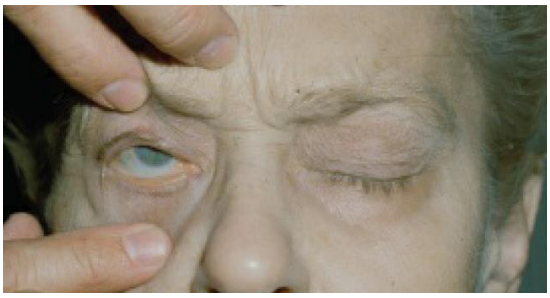

Figure 3.2 Orbicularis oculi weakness in patient with myasthenia gravis
Source : Miller[6]

Patients with MG-related ptosis often have worsening of ptosis on one side when the opposite eyelid is elevated and held in a fixed position. The explanation of this

"enhancement of ptosis" phenomenon is Hering law of equal innervation, which relates to the levator muscles as it does to the extraocular muscles.[5,6]

The "sleep test" may also be incorporated to demonstrate objective improvement in MG symptoms after rest. This test is based on the observation that when many patients with MG awaken in the morning, they have little or no ptosis or diplopia. However these manifestations appear or worsen during the day. The patient is kept in a quiet, darked room and instructed to close the eyes and rest for 30 minutes. The ptosis and ocular motility are quantified before and after the rest period. Most patient with MG show marked improvement in ptosis, ocular motor dysfunction, or both immediately upon awakening from sleep. The improvement lasts 2 to 5 minutes, following which ptosis and ophthalmoparesis recur. The sleep test is safe, moderately sensitive and specific way to con firm a presumptive diagnosis of MG.[2,6]

Pharmacologic test also needed to diagnose MG. the abnormal fatigability of skeletal muscles may be evaluated by observing or quantifying their strength before and after the injection of antichoinesterase agents. Anticholinesterase pharmacologic testing has a sensitivity of about 50% to 70% in MG.[6]

Edrophonium (Tensilon) test is needed because endrophonium chloride is a rapidly acting and quickly hydrolyzed anticholinesterase that competes with Ach for acetylcholinesterase and thus allows prolonged and repentitive action of Ach at the synapse. It commonly is used because of the rapid onset (≤30 sec) and short duration (about 5 min) of its effects. A total of 10 mg (1cc) of endrophonium is drawn up in a 3-cc syringe, 2mg of edrophonium is injected intravenously, and the patient is observed for improvement in ptosis, ocular alignment, rage of movement, or combination of these. If definite improvement occurs, the test is considered positive and is terminated. If no such changes occur within 30 seconds, the reminder of the dose (8mg) is injected as a single bolus. A positive endrophonium test usually, but not always, is indicative of MG. the sensitivity of the test in ocular MG ranges from 60% to 95%.[1,6]

Neostigmine (prostigmin) test is needed because of the transient nature of the ocular and systemic changes in muscle strength that occur following the administration of

edroponium, the neostigmine bromide (prostigmin) test remains an exceptionally valuable method of diagnosing MG. the longer duration of the effects of this drug is sufficient to permit careful assessment not only of eyelid position and strength, but also ocular motility and alignment. In adults with obvious ptosis and/or ophthalmoparesis, one mixes 0.6 mg of atropine sulfate with 1.5 mg of neostigmine in a 3-cc syringe and injects the mixture into a deltoid or gluteus muscle. A change in ocular motility and ptosis usually is apparent 30 to 45 minutes following the injection. The sensitivity of this test ranges from 70% to 94%. [6]

Specific autoantibody assays such as radioimmunoassay to detect Ach receptor antibodies is one of the standard diagnostic test for MG. Antibody testing supports a diagnosis of MG. testing is confounded by recent (within 48 hours) general anesthesia with muscle relaxants. Acetylcholine receptor (AChR) antibodies, present in around 90% of systemic cases but only 50-70% of ocular myasthenia. Anti-muscle-specific kinase (MuSK) antibodies are positive in 50% of those negative for AChR antibodies. In addition, anti-MuSK antibodies only very rarely are found in patients with ocular myasthenia. Thus, should a patient with a clinical diagnosis of ocular MG show no evidence of either antireceptor or anti-MuSK antibodies, the diagnosis should not necessarily be abandoned. Electrophysiologic testing might establish the diagnosis of MG. Electromyography (EMG) sometimes it is helpful to show that the amplitude of the compound muscle action potential, recorded by surface electrodes over a muscle, decrease on repetitive stimulation of the nerve to the muscle..[1,2,6]

Treatment for patient with ocular MG is an anticholinesterase agent such as pyridostigmine, which can be used alone in mild disease, but usually combined with steroid and other immunosuppressive treatment. Plasmapheresis and intravenous immunoglobulins are shorter-term measures to address acute illness. This patient was treated with pyridostigmine oral 3x60mg.[5,9]

Myasthenia gravis is a systemic disease with disastrous potential. Although purely ocular MG does exist, systemic MG will develop over the next 2 years in up to 85% of patients who present with ocular MG. Because MG patients may develop respiratory

and other life-threatening manifestations, it is prudent to manage their care in cooperation with neurologist. If ocular signs remain truly isolated for more than 2 years, the disease is likely to remain clinically ocular. Neverthless, late conversion to generalized MG is possible. Prognosis for this patient ad funcionam is dubia ad bonam and for vitam is dubia.[5,10]

IV. Conclusion

Myasthenia gravis (MG) is an autoimmune disease in which antibodies mediate damage and destruction of acetylcholine receptors in striated muscle, characterized by variable and fatigable weakness. There are a clinical assessment that physician can do in their office to diagnose ocular MG, such as stare test, orbicularis muscle weakness test, cogan's lid twitch test and ice pack test, but there is no test is specific for ocular MG, and its diagnosis should not be based exclusively on any single test. Patient with pure ocular MG must be warned of possibility of generalization of the disease process and should specifically be instructed to inform their physician immediately if symptoms such as dysphagia, respiratory involvement, or extremity weakness develop.

REFERENCE

1. Bowling B. Neuro-opthalmology. In : Kanski's Clinical Opthalmology. Eight Edition. Philadelphia : Elsevier Saunders; 2016. p 838-840.
2. Lee AG, Brazis PW. Ocular Myasthenia Gravis. In : Clinical Pathways in Neuro-Opthalmology. Editor : Gumpert E. Second Edition. New York : Thieme; 2003. p 337-348.
3. Ropper AH, Brown RH. Disease of spinal cord, peripheral nerve and muscle. In : Principles of neurology. Eight Edition. New York : McGraw-Hill; 2005. p1472-1474.
4. Wilkinson L, Lennox G. Motor neurone disease, peripheral neuropathy, myasthenia gravis and muscle disease. In : Essential Neurology. Fourth Edition. Massachusetts : Blackwell; 2005. p 164-166
5. American Academy of Ophthalmology. Selected Systemic Conditions With Neuro-ophthalmic Signs. In : Basic and Clinical Science Course. Section 5th : Neuro-Ophthalmology. San Francisco: American Academy of Ophthalmology; 2015-2016. p. 309-311
6. Miller NR, Subramanian PS, Patel VR. Disorders of Neuromuscular transmission. In : Clinical Neuro-Opthalmology The Essentials. Third Edition. Philadelphia: Wolters Kluwer; 2016. p 733-750.
7. Gandhi R, Karna M, Rao A, S KS. Myasthenia gravis. In Neuro-ophthalmology: Clinical Examination and Diagnosis. New Delhi: Jaypee brothers; 2006.p 310-312.
8. Agarwal A, Agarwal A. Ocular Myopathies. In : Manual of Neuro-ophthalmology. New Delhi: Jaypee brothers medical publisher; 2008. p 197-200.
9. Kidd D., et al. Blue books of neurology series : neuro-ophthalmology. Butterworth-Heinemann. Elsevier. 2008. P 316-18.
10. Nagia L, Lemos J, Abusamra K, Cornblath WT. Prognosis of Ocular Myasthenia Gravis. American Academy of Ophthalmology. 2015;122:1517-1521.