

# Ocular Myasthenia

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**Summary.** Myasthenia gravis is a chronic autoimmune neuromuscular disorder typically presenting with variable skeletal muscle fatigue. The most prevalent initial manifestation of myasthenia is ocular myasthenia. Approximately 50% of all myasthenia cases begin with the weakening of the eye muscles that generally presents as diplopia and/or ptosis. However, about 60% of these cases progress to a generalized type within the first 2 years. The diagnosis of ocular myasthenia is often difficult but is collectively confirmed by clinical evaluation and laboratory results.

Clinical manifestations, diagnostic approach, relevance, and therapeutic options are discussed in this article.

**Keywords:** myasthenia, ocular myasthenia, autoimmune, clinical characteristics, diagnosis, treatment.

## INTRODUCTION

Myasthenia gravis (MG) is a chronic autoantibody mediated disease with a prevalence of 78-188/million people in Europe [1–5]. This autoimmune disease is well-characterized at the effector stage with three autoantigens in roughly 90-95% of the clinical cases. The most common target in 80-85% of MG patients is the acetylcholine receptor (AChR), followed by muscle-specific tyrosine kinase (MuSK) or low-density lipoprotein receptor 4 (LRP4) [6–8]. This interaction in the postsynaptic neuromuscular junction causes a disruption of neurotransmission that results in weakness and fatigability of the muscles [6, 7]. Based on clinical characteristics, Myasthenia Gravis Foundation of America (MGFA) divides MG into 2 main types: generalized myasthenia gravis (GMG, II, III, IV, and V classes) and ocular myasthenia gravis (OMG, I class) [9]. Ocular myasthenia is the most common localized manifestation of myasthenia, typically presenting as double vision (diplopia) and/or droopy eyelids (ptosis). More than half of patients initially experience weakness of the eye muscles before the development of a

generalized form, and up to 20% have isolated ocular myasthenia [10–12]. The generalization of OMG remains a controversial subject as the findings of several studies range from 18% to 80% [10–15]. However, many studies indicate that in most patients the generalization of the disease occurs within the first 2 years [13, 16, 17].

Up to 25% of patients suffering from ocular muscle weakness are reported not to be diagnosed with MG due to clinical variations of ocular myasthenia and difficult differential diagnosis [16]. Therefore, it is very important to perform a thorough clinical examination in order to prevent common diagnostic mistakes [18].

This article will provide an update on main clinical manifestations, diagnostic strategies, and treatment options for ocular myasthenia.

## EPIDEMIOLOGY

Myasthenia gravis remains a rare disorder but the prevalence has been gradually rising due to the elderly population, better diagnostics, increased life expectancy, and improved therapeutic approaches. Population-based epidemiological analysis performed by Hendricks TM et al. has shown that an overall incidence of MG is 2.2 per 100 000/year and the incidence of OMG is 1.13 per 100 000/year, but in various other studies the incidence rates of MG vary from 0.3 to 3 per 100 000/year [11,

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19–21]. Myasthenia gravis can affect both males and females and has no race preference [11, 17, 19, 22]. In OMG, there was noticed a minor male predominance compared to a slight female predominance in GMG [11, 15, 23]. In women, the onset of the disease is earlier and bimodal, around 30 and 60 years old, while in men it has one age peak, around 70 years old [17, 19]. Although Yu and his colleagues show an age peak between 60–80 years for both sexes [24]. According to a systematic review of population-based epidemiological studies in myasthenia gravis by Carr et al., mortality rates due to myasthenia crisis vary from 0.06 to 0.89 cases per million people [21]. However, myasthenia gravis can occur/manifest at any period of life and have a different course and outcomes [15, 23].

## **PATHOPHYSIOLOGY**

Neuromuscular transmission is induced by the flow of calcium to the motor nerve through P/Q-type calcium channels and the release of acetylcholine (ACh) from the synaptic vesicles into the synaptic cleft. ACh then binds to AChR on the postsynaptic membrane and causes depolarisation of the muscle membrane and muscle contraction [18, 22]. Several pathogenic antibodies attack different elements of the neuromuscular junction, and problems in the synaptic transmission at the level of the junction between the motor nerve endings and the muscle in MG are identified [18]. Autoantibodies against AChRs are the most frequently detected antibodies in patients with GMG (85–90% of all cases) although they are much less present in OMG (around 50%). However, it is considered that acetylcholine receptor antibody testing is less sensitive in OMG than in generalized MG [25]. AChR-antibodies block ACh and AChR binding site, activate complement factors, and destruct the postsynaptic membrane by increasing the degradation of the AChRs [18, 22]. A smaller part of autoantibodies is directed towards muscle-specific receptor tyrosine kinase. These antibodies may be present in 70% of AChR-Ab seronegative MG patients but not in AChR-Ab seropositive MG patients, but they are rarely present in isolated ocular myasthenia [26, 27]. Recent studies indicate that low-density lipoprotein receptor-related protein 4 is another important target for autoantibodies in MG patients. However, data is still controversial. There are few studies analysing LRP4 in MG patients. Zhang et al. found LRP4 autoantibodies to be present in 9.2% of double seronegative MG patients [28]. Meanwhile, Pevzner et al. discovered the same autoantibodies present in 50% of double seronegative MG patients [29]. Further data with greater number of patients and various populations should be collected in order to better understand the etiology and pathology of LRP4 antibody positive MG.

It was found that 3.8–7.1% of patients with MG have a family history of the disease [30, 31]. Numerous studies have shown that genetic factors might play an important

role in the development of MG [8, 30–36]. The human leucocyte antigen (*HLA*) alleles, protein tyrosine phosphatase non-receptor type 22 (*PTPN22*), cytotoxic T lymphocyte antigen 4 (*CTLA-4*), *TNFAIP3*-interacting protein 1 (*TNIP1*), and forkhead box P3 (*FOXP3*) were proven to be associated with MG [8, 32–34, 36]. It is also reported that the *TNFSRF11A* locus increases susceptibility to MG among older people. MicroRNAs are also proven to play an important role in the pathogenesis of MG [35–37].

## **CLINICAL ASPECTS**

Ocular myasthenia is limited to the weakness of extraocular, levator palpebrae superioris, and orbicularis oculi muscles, which in about 80% of patients presents as diplopia and/or ptosis. In myasthenia, the pupils are always normal [38, 39]. It is common for symptoms to worsen throughout the day and improve after rest. Examination of multiple gaze directions for about 30–60 seconds is essential as ptosis and extraocular movements can fluctuate during examination [18].

### **Eyelid symptoms**

Ptosis is a very common symptom [38]. It is typically painless, fluctuating, unilateral, bilateral or alternating; if bilateral, it is often asymmetric, but may be absent [40]. Ptosis of one lid can be detected if the examiner raises the contralateral lid (Herring's law); the sign is triggered by bilateral and equal innervation. If the patient's gaze is held upward for a prolonged period of time, ptosis may also be enhanced [38]. The Cogan's lid twitch is another characteristic sign; patients are guided to look down for 10 seconds and then immediately move their eyes up to the original position. The upper eyelid twitches upwards briefly before moving into the ptotic position [18, 40]. Orbicularis weakness is also frequently noticed in OMG; therefore, the function of the orbicularis oculi muscle should be assessed. When the patient closes the eyelids with force, the so called "peek sign" may appear – the lids separate leading to sclera exposure [17, 40]. Incomplete blinking can cause pain and tearing. 21% of patients with ocular myasthenia may have dry eyes syndrome [39].

### **Extraocular muscles symptoms**

Ophthalmoplegia may involve a single extraocular muscle (EOM) or may impair any combination of EOMs [18]. Although many patterns of EOMs weakness might be present, the medial rectus, inferior rectus, and superior oblique muscles are most frequently affected [16]. Diplopia is very common among patients with OMG because even a slight weakness of the EOMs can be symptomatic [23]. According to Roh et al. study results, diplopia is present in 93% of OMG patients [39]. However, diplopia may be present but not related with eye movement deficiency.

Hypermetric saccades, intersaccadic fatigue, reduction in the saccadic velocity, gaze evoked nystagmus, and incomitant strabismus are less common symptoms in myasthenic patients [38].

## RISK FACTORS FOR THE DEVELOPMENT OF GENERALIZED MYASTHENIA GRAVIS

Various authors indicate that 60% of patients with only ocular onset eventually develop a generalized form within the first 2 years [13, 15, 17]. Some studies show that the generalization process depends on several risk factors, and the conversion rate to GMG is around 20%. However, all of these studies included steroid therapy which may modify the risk of generalization [10, 14, 41, 42]. It was found that bilateral ptosis, older age at onset, the presence of thymoma, as well as the presence of AChR-antibodies, and high levels of seropositivity are risk factors for the conversion of OMG to GMG [7, 9, 11, 14, 41–43]. The role of gender is still controversial in the prognosis of ocular myasthenia, but one cohort study has shown that females tend more often to develop GMG than men, because of the *HLA-DR3* and *B8* gene-alleles genetics [14, 44]. Positive or abnormal single-fiber electromyography (sfEMG) is also considered to increase the risk of transforming to GMG [11].

## DIFFERENTIAL DIAGNOSIS

There are many neuromuscular junction and neurological disorders that can imitate the symptoms of OMG, so a differential diagnosis is necessary to identify a specific impairment. Graves ophthalmopathy results in abnormal movement of the eyes due to the constrictive ophthalmopathy but no signs of ptosis. Constrictive ophthalmopathy can rarely resemble paresis of the superior oblique eye muscle [45]. Inabilities of eye movement, ptosis, and diplopia may indicate stroke, nerve palsies, and Horner's syndrome initiation [46]. Myotonic dystrophy (MD) should also be excluded with its symptoms such as ptosis, external ophthalmoplegia, and bilateral optic nerve atrophy. Differential diagnosis includes genetic testing for the presence of expanded cytosine-thymine-guanine repeat in the myotonic dystrophy protein kinase gene, muscle biopsy, and electromyography [47]. Botulism can mimic ocular myasthenia due to blurred or double vision and drooping eyelids. Botulism is usually verified by clinical neurological examination, detection of botulinum toxin in the serum and/or feces of patients [48]. Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disease that should also be considered. Pure ocular weakness is uncommon as an initial presentation of LEMS and includes less ocular, more proximal limb weakness. Of the eye symptoms in LEMS, ptosis and diplopia are most characteristic.

The diagnosis is clarified by using serology (radio-immunoassay test) – finding antibodies against P/Q sub-type voltage gated calcium channel. Electromyography can show low muscle action potential at rest and a decremental response at low rate repetitive nerve stimulation (RNS) [49].

## DIAGNOSIS

### Ice test

During this test, an ice pack is placed on the ptotic eye for 2-5 minutes. Elevation of the upper eyelid by 2 millimeters or more can be considered as a positive result for ocular myasthenia. According to Chatzistefanou et al., sensitivity and specificity of the ice pack test was found to be 76.9% and 98.3% respectively [50].

### 30 minutes rest test

Before the test, it is necessary to evaluate eye movements and the position of the eyelids. The patient should rest for 30 minutes with his eyes closed. After rest, improvement of ptosis or eye movements could be observed in ocular myasthenia [51].

### Edrophonium test

Edrophonium is a short-acting acetylcholinesterase (AChE) inhibitor that works by increasing the amount of available acetylcholine in the synaptic junction. It is injected intravenously at initial dose of 2 mg and has its onset of action after 10-30 seconds. Edrophonium prevents the peak of ACh by competitively inhibiting AChE in the neuromuscular junction. As a positive test result, ptosis and eye movement deficiency are relieved [52].

### Neostigmine test

Neostigmine is a longer acting AChE inhibitor. The peak effect is achieved at about 30 minutes after an intramuscular injection, although the response may be seen within 15 minutes. The duration of effect may last for several hours. The usual dose for adults is 2.5 mg/mL [53].

### Blood test for antibodies

The diagnosis of OMG can be confirmed by seropositivity to AChR antibodies or, less often, to other proteins of neuromuscular junction, including antibodies against MuSK and LRP4 [54, 55]. AChR antibody testing is the most common and specific immunologic way to clarify OMG diagnosis, but approximately 50% of patients do not have antibodies against AChRs and are seronegative [25]. Approximately 10% of patients with myasthenia gravis will have negative serologic testing for AChRs, anti-MuSK, and LRP4. It is known that patients can have other

autoantibodies, such as titin, agrin, collagen Q, and coarctin, but these antibodies are not routinely tested, and their utility in diagnosing myasthenia gravis is unclear [56, 57].

### Electrophysiological tests

Repetitive nerve stimulation and single-fiber electromyography are two basic electrophysiological tests used for MG and OMG diagnosis. RNS shows the efficacy of neuromuscular transmission. RNS is performed by stimulating the nerve at a frequency of 2-3 Hz. 10% and higher decrement is common for MG. In the absence of a decrement, exercises can be used to induce the exhaustion of muscles and document the decrement. The test is abnormal in approximately 75% of patients with MG and 50% of patients with OMG [58].

### Thymus gland evaluation

Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest should be done to detect thymoma. Thymoma is found in approximately 15% of all MG cases [59].

## TREATMENT

Treatment is aimed to alleviate symptoms, extend remission periods, and delay/avoid the generalization process. Any treatment measure, single or combination of drugs, should be selected individually [60].

### Nonpharmacological treatment

Nonpharmacological treatment is reasonable to relieve symptoms of OMG (diplopia). One-eye patching, customized prisms may be also helpful for patients not responding to medical therapy [18].

### Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors are the first line treatment with pyridostigmine as the primary option. Pyridostigmine is a safe, fast-acting medication with a recommended starting dose of 30 mg three to four times a day, which can be increased up to 150 mg four times a day if necessary. If satisfactory results are achieved, no other drugs are prescribed. Pyridostigmine is sometimes only partially effective for ophthalmoplegia, therefore, other treatment options may be necessary [17].

### Corticosteroids

Prednisone is used as a second therapy option for OMG if pyridostigmine fails [61]. Initially, prednisone is started at low doses and gradually increased until the symptoms resolve; a dosage of 20 mg daily is usually sufficient [17].

Several studies suggest that early corticosteroid therapy could prevent the generalization of OMG [60, 62]. However, further studies are needed to determine whether immunosuppression reduces the risk of conversion of OMG to GMG.

### Steroid-sparing agents

When prednisone is ineffective or intolerable, or the patient has severe coexisting conditions (i.e., elderly diabetics with osteoporosis), azathioprine and mycophenolate mofetil are typically offered [17, 61]. These medications can be additionally added for patients who require higher dosages of steroids or are at high risk of complications caused by steroids [18, 60]. Tacrolimus and cyclosporine are more often used for patients with GMG and only in rare cases of OMG [40].

The dose of azathioprine is determined by the weight of the patient and is usually 2.5-3 mg/kg. In general, azathioprine is a well tolerated medication, however, its therapeutic effect frequently occurs after 3-10 months of continuous therapy [17]. Complete blood count, liver function, and thiopurine methyltransferase activity should be monitored regularly to prevent life-threatening side effects such as thrombocytopenia, leukopenia, hepatotoxicity, and neoplasia [17, 18]. Mycophenolate mofetil is administered at a standard dose of 1000 mg twice a day. It has minor side effects but complete blood count needs to be monthly tracked [61].

### Surgical treatment

Thymectomy is inevitably performed in the presence of thymoma and should be considered for nonthymomatous patients when other medical therapies fail and patients are AChR antibodies seropositive [17]. Blepharoplasty can be performed to improve the quality of life of patients with fixed and treatment-resistant ptosis lasting at least 2 years [40, 63]. Strabismus surgery may be recommended for patients with stable diplopia and stable ocular alignment for at least 6 months, confirmed by an ophthalmologist [61].

## RESEARCH AT THE HOSPITAL OF LITHUANIAN UNIVERSITY OF HEALTH SCIENCES KAUNO KLINIKOS

Our study performed at the Hospital of Lithuanian University of Health Sciences Kauno Klinikos analysed 140 cases of myasthenia gravis. MG was diagnosed in 55 (39.3%) men and 85 (60.7%) women. The mean age of men was 63.42 years, and the mean age of women was 58.40 years. Ocular myasthenia was diagnosed in 32 (22.9%) cases, but the generalized type of myasthenia dominated – 108 (77.1%) cases. In addition, it is noteworthy that many cases were well controlled: exacerbations were diagnosed once per year in 124 (88.6%) cases, 1-2 times per year in

13 (9.3%) cases, 3-4 times per year in 2 (1.4%) cases, more than 5 times per year only in 1 (0.7%) patient, and myasthenic crisis was present only in 5 (3.5%) cases. In our study, only 10 (7%) patients had eye movement deficiency, but diplopia occurred in as many as 50 (35.7%) cases [64].

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## AKIŲ MIASTENIJA

### Santrauka

Miastenija yra lėtinė autoimuninė neuroraumeninė liga, kuri gali pasireikšti patologiniu raumenų silpnumu ir nuovargiu. Apie 50 % visų pacientų liga gali prasidėti akių miastenija: akių raumenų silpnumu, kuris pasireiškia dvejinimusi ir (ar) vokų užkirtimu – ptoze. Ši miastenijos forma per pirmuosius dvejus metus apie 60 % atvejų gali pereiti į generalizuotą ligos formą. Todėl yra svarbu laiku diagnozuoti akių miasteniją, remiantis klinikiniu ištyrimu ir laboratoriniais duomenimis, kad būtų paskirtas gydymas, kuris sumažintų ligos simptomus.

Šiame straipsnyje apžvelgiama akių miastenijos klinikinis pasireiškimas, diagnostinių metodų ypatumai ir svarba bei terapinės galimybės.

**Raktažodžiai:** miastenija, akių miastenija, autoimuninė, klinika, diagnostika, gydymas.

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