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Case report of ocular myasthenia gravis

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Abstract
Myasthenia gravis is a rare type of autoimmune disease wherein the post-synaptic acetylcholine receptors at skeletal muscle's neuromuscular junctions are destroyed by antibodies. The clinical presentation includes a specific distribution of motoric deficit with no involvement of sensory deficit that gets diminished with rest and usually worsens with excessive use. Hereby, we report a case of a man 35-year-old who presented with bilateral ptosis and diplopia to an ophthalmology outpatient department. Response to ice pack test was positive. Repetitive nerve stimulation demonstrated >15% decremental response. The patient was timely diagnosed and received necessary treatment that showed clinical improvement.

Keywords: Ocular myasthenia gravis, ptosis, diplopia, neuromuscular junction, acetylcholine receptor antibody

Introduction
Myasthenia gravis (MG) is a multifaceted autoimmune condition marked by fatigue, variable muscle weakness and primarily impacting the neuromuscular junction [1]. It is based on postsynaptic membrane pathology, often associated with thymoma and accompanied with bulbar and limb weakness [2]. In about 85% of individuals with generalized myasthenia gravis, autoantibodies target the nicotinic acetylcholine receptor (AchR) [3, 4]. For the remaining 15%, other autoantibodies are present, specifically against lipoprotein receptor-related protein 4 (LRP4) or muscle-specific kinase (MuSK) [5, 6].
Approximately 85% of MG patients presenting with only ocular signs and symptoms may develop systemic MG within two years of presentation [2]. Among these most commonly presenting symptoms such as fluctuating ptosis, diplopia, and orbicularis muscle weakness are usually seen 15-50% of cases, the acute management of MG is critical to prevent life-threatening complications [9, 10].
The present case study focused on Ocular Myasthenia Gravis (OMG) a relatively common subtype of MG in which the weakness is limited to ocular and bulbar muscles, which may lead to significant visual disability [7, 8]. Patient clinical examinations are important for the accurate diagnosis and treatment plan of OMG patients [1]. The following features were assessed to find clinical features.

Clinical Features
OMG typically manifests with diplopia or ptosis due to paralysis of the eye muscles. A defining characteristic of the disease is its hallmark variability and fatigability, which can be readily detected during clinical investigation. Ptosis may present unilaterally or bilaterally, with the upper eyelid elevator muscle displaying increased fatigability during sustained upgaze [11]. A notable phenomenon, enhanced ptosis or the "curtain effect," occurs when lifting one eyelid causes the contralateral eyelid to develop or worsen ptosis. This is elucidated by Hering's law of equal innervation, where yoke muscles receive equal stimulation. Another distinctive clinical sign is "Cogan's lid twitch," After sustained downward gaze, the upper eyelid briefly shoots upward, appearing to "twitch" and exposing the upper limbus before settling back to its resting position [12]. This sign is highly specific (99%) and moderately sensitive (75%) for diagnosing OMG, with a false positive rate of just 1%, accredited to muscle fatigue, and rapid recovery [13, 14].
Another variation of this sign is the "forced eyelid closure test", where the patient is instructed to tightly shut their eyes for 5-10 seconds before opening them and fixating on a target in the primary position. A positive test is indicated by an upward overshoot of the eyelid followed by a downward drift. Gerling *et al*. found this test to be highly effective, with a sensitivity of 94% and a specificity of 91% for diagnosing OMG [14].

Orbicularis weakness, resulting in partial eyelid closure known as the "Peek-sign," is another distinctive marker of OMG. In OMG, ophthalmoplegia can mimic various ocular motility disorders, such as cranial nerve palsy, thyroid eye disease, chronic progressive external ophthalmoplegia, decompensated phorias, and internuclear ophthalmoplegia. Testing pupillary function is useful, as the pupils are not affected in myasthenia [14].

A careful clinical investigation can reveal inconsistency in orthoptic dimensions, helping to distinguish OMG from other ocular motility ailments. Patients may exhibit intrasaccadic fatigue, marked by a decrease in saccadic velocity during prolonged saccades. In OMG, ocular deviation is typically incomitant, meaning it varies with different gaze positions. This contrasts with comitant deviation, which is consistent across all gaze directions and suggests congenital phorias or central causes such as brain stem or cerebellar lesions. However, approximately 25% of OMG cases exhibit comitant deviations or transitions between comitant and incomitant deviations [15, 16].

Clinical and Pharmacological Diagnosis

The ice test involves filling surgical gloves with crushed ice and keeping it over the ptotic eyelid (or both eyelids in cases of bilateral ptosis) for 2 minutes. A positive test is indicated by a clear improvement in the ptosis. This test boasts a 90% sensitivity and 100% specificity for OMG, making it highly reliable for ptosis but less sensitive for ophthalmoplegia. Earlier, the edrophonium (cholinesterase inhibitor) test was commonly used to diagnose OMG, but recently, it has been replaced by few newer diagnostic methods. The edrophonium test has a low sensitivity of 60% for OMG and lacks specificity, as false positives can occur in conditions like brain stem glioma, multiple sclerosis, pituitary tumors, Guillain-Barre syndrome, and ischemic cranial neuropathy [17-19].

Current Treatment for OMG

The primary medical treatments for OMG include cholinesterase inhibitors like oral corticosteroids, pyridostigmine and immunosuppressive agents of second-line treatment such as cyclosporine, mycophenolate mofetil, azathioprine, cyclophosphamide, and tacrolimus. Oral steroids are frequently prescribed for diplopia or ptosis with diplopia when cholinesterase inhibitors prove ineffective. Advances in the treatment of MG have introduced new biological agents targeting complement pathways, FcRn receptors, and B-cell antigens, offering rapid and targeted immunotherapies despite challenges related to cost and infection risks. Additionally, the exchange of plasma, intravenous immunoglobulins, as well as eculizumab and rituximab, which are types of biologic monoclonal antibody therapies are employed [20, 21].

Surgical interventions, including thymectomy, ptosis repair, and strabismus surgery, are considered for cases where ptosis and diplopia have stabilized. Surgical interventions, like eyelid suspension, address impairments resistant to medical treatment. Azathioprine and mycophenolate mofetil, steroid-sparing agents, offer safe and well-tolerated alternatives to steroids. The exploration of new therapies, such as rozanolixizumab and zilucoplan, shows promise in improving patient outcomes by targeting specific pathogenic mechanisms and enhancing therapeutic options. Electrodiagnostic evaluations further underscore the importance of precise diagnostics in differentiating MG from other similar disorders, aiding in tailored treatment approaches. These therapeutic strategies are tailored to the individual patient's response and the severity of the condition, ensuring an optimal balance between efficacy and side effect management [14, 22, 23].

As per the largest hospital-based studies on myasthenia gravis from 841 Indian patients, MG was found to be more common in males (M: F of 2.70:1) with a single peak of age at onset (males sixth to seventh decade; females third decade). Two hundred and twenty-two (26.31%) patients had ocular MG and 616 (73.68%) had generalized myasthenia [3].

Most of the MG patients first present with extraocular symptoms (diplopia and/or ptosis), and clinical symptoms in about 15% of the cases remain restricted to only the extraocular muscles (ocular myasthenia gravis [OMG]) [24]. Approximately 85% of MG patients presenting with only ocular signs and symptoms may develop systemic MG within two years of presentation [25]. Patient's history and clinical examination are very important for the accurate diagnosis of OMG patients, since the supportive serologic or electrodiagnostic studies could be frequently nondiagnostic. [1].

Description of Case

A 35-year-old male patient presents with history of gradual onset progressive drooping of bilateral eyes and diplopia for 8 months. The patient reported positive history of diurnal fluctuations.

He denied other ocular symptoms including anisocoria, vision loss and denied systemic symptoms including muscle pain, generalized weakness of extremities or trunk, no dysarthria, no pain, no tingling, nor difficulty of breath. No reported history of sensory symptoms. Patient denied any difficulty in chewing hard food or any difficulty in deglutition or speech abnormality.

A Cogan's lid twitch along with eyelid curtaining were observed. The pupils, Visual acuity (VA) as well as visual fields, slit lamp and fundus exam were noted to be unremarkable.

On exam, extraocular movements were restricted in all directions along with mild bilateral facial weakness. (Figure 1). The fatiguability test was positive in bilateral eye lids, levator palpebrae superioris being affected (Figure 1). The ice pack was performed with positive response with the significant improvement after 5 minutes of ice pack application raising suspicion for diagnosis of MG. (Figure 2).

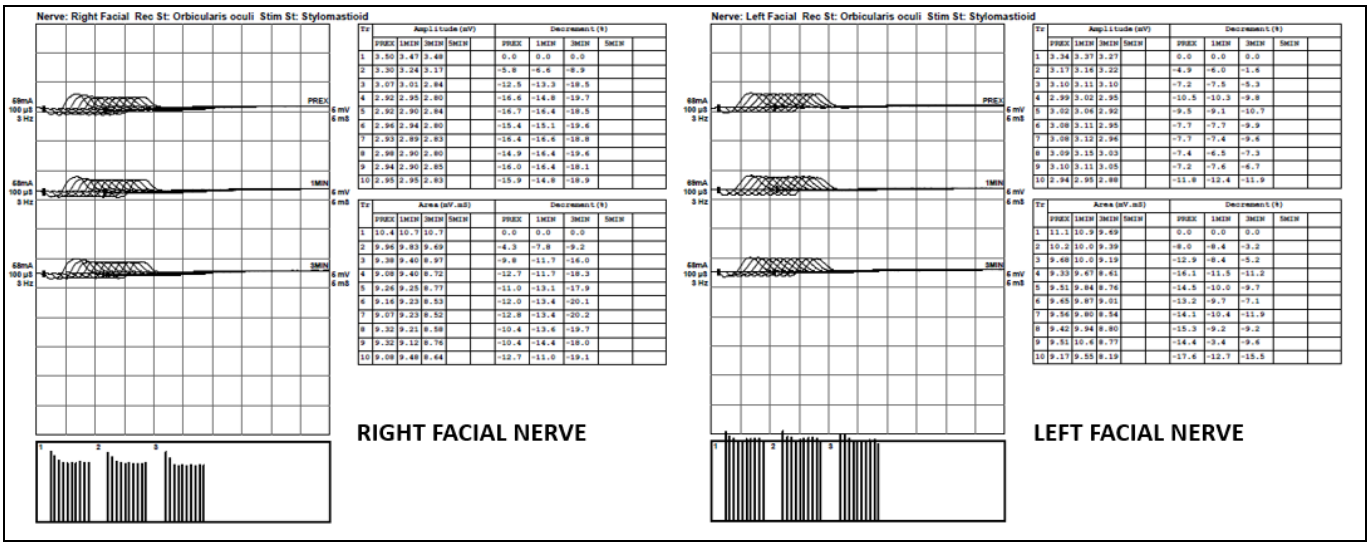
Fig 1: Restricted extraocular movements in all directions

Fig 2: A: Bilateral ptosis in primary gaze, pre-ice pack test, B: Post-ice pack test. Ptosis of both eyes improved

Repetitive Nerve Stimulation (RNS) Testing was performed. After 1 min of rapid eye blink, followed by 3 Hz slow repetitive nerve stimulation test of both facial nerves resulted in progressive decline in the compound muscle action potential (CMAP) response (decremental >15%) with improvement just after 10 seconds of brief exercise, suggestive of neuromuscular junction disorder likely Myasthenia gravis that is to be correlated clinically. (Table 1)

On general examination, clinical weakness or fatiguability in upper as well as lower limbs not observed. All Deep tendon reflex were normal with normal sensory examination.

Table 1: Repetitive nerve stimulation (RNS) testing



The treatment was initiated with prednisolone 20 mg per day along with Azathioprine 50 mg once in a day with a plan to up titrate the dose 10 mg per week to look for optimal response followed by alternate day regimen to be planned. Patient was asked to review with liver function tests and complete blood count indices. Results & further clinical progress?

Discussion

Myasthenia gravis is an autoimmune disease affecting neuromuscular junctions and characterized by fatigue and fluctuating weakness of skeletal muscles [2].

As per the largest hospital-based studies on myasthenia gravis from 841 Indian patients, MG was found to be more common in males (M: F of 2.70:1) with a single peak of age at onset (males sixth to seventh decade; females third decade). Two hundred and twenty-two (26.31%) patients had ocular MG and 616 (73.68%) had generalized myasthenia [26]. Most of the MG patients first present with extraocular symptoms (diplopia and/or ptosis), and clinical symptoms in about 15% of the cases remain restricted to only the extraocular muscles (ocular myasthenia gravis [OMG]) [22].

The presence of triad of ptosis, oculomotor paresis, and orbicularis oculi weakness shall raise suspicion for the purely ocular form of MG [29]. About more than 50% of patients with MG initially present with isolated ptosis, diplopia, or both together, with no clinical signs or symptoms of any muscular weakness elsewhere.[28] This leads to weakness of skeletal muscles which can be variable and fatigable, and often presents with ptosis and/or diplopia, with about 60% of patients presenting with ocular features at onset, and thus it may be brought initially to eye care practitioners. Approximately 15% of patients have ocular myasthenia gravis (OMG), where symptoms are confined to this distribution [26].

Characteristic findings including fatigable ptosis and Cogan's lid twitch sign can be identified during the clinical examination [22] Cogan's lid twitch is characterized by overshooting of the eyelid with ptosis when patient can sustain downgaze and saccades back to neutral gaze, and eyelid curtaining, present when one eyelid is manually elevated which results into enhanced ptosis of the contra eyelid. Both these findings, when present together, are highly suggestive of MG [27].

If any of the symptoms such as pain, proptosis, perception loss or pupillary involvement are noticed, then an alternate diagnosis other than MG can be considered [27].

Further investigations that could be ordered to confirm the diagnosis of OMG include simple in-clinic procedures such as the ice test, and checking for serum autoantibodies, as well as electrophysiological testing *viz*. repetitive nerve stimulation (RNS) or single-fiber electromyography [4]. Single-fiber electromyography (SFEMG) is useful

electrophysiological diagnostic test for OMG patients, especially in cases of autoantibody sero-negativity. It also helps to predict severity of disease, with more jitter correlating with more severe disease [28].

The management of ocular myasthenia gravis includes non-pharmacological options, pyridostigmine, corticosteroids, other immunosuppressive agents, and thymectomy.

Acetylcholinesterase inhibitors can increase the duration of action of the neurotransmitter to provide symptomatic improvement, without modifying the long-term immunologic disease activity [28]. Acetylcholinesterase inhibitors do not directly influence the natural course of the disease (36% of OMG patients that were treated with pyridostigmine but not steroids were observed to have developed generalized MG within 2 years) [29]. Immunosuppressive therapy can be considered in all MG patients irrespective of serum AChR-Abs are detectable or not and are indicated in cases when AChE inhibitors are intolerable/ineffective [31]. Corticosteroids are immune modulating agents which are most widely used in MG patients. Corticosteroids mainly act through anti-inflammatory properties, to result into an additional reduction in cytokine expression, lymphocyte differentiation and proliferation, and increase in muscle AChR synthesis [30].

Conflict of Interest

Not available

Financial Support

Not available

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