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A RARE CASE OF TRIPLE-NEGATIVE OCULAR MYASTHENIA PRESENTING AS PUPILLARY SPARING THIRD CRANIAL NERVE PALSY.

General Medicine

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ABSTRACT

Ocular Myasthenia Gravis (OMG) is a localised autoimmune disorder characterised by fatigable weakness of extraocular muscles, typically presenting with ptosis and diplopia. While most cases are associated with autoantibodies against acetylcholine receptor (AchR), muscle-specific kinase (MuSK), or low-density lipoprotein receptor-related protein 4 (LRP4), a subset of patients remains seronegative, complicating diagnosis. We report a case of a 48-year-old woman who presented with a 20-day history of right-sided ptosis and horizontal diplopia. Neurological examination revealed complete third cranial nerve palsy with pupillary sparing. Brain and orbital MRI with contrast and a comprehensive metabolic and autoimmune workup were unremarkable. Initially managed as possible vasculitic neuropathy with intravenous methylprednisolone, she showed partial improvement. On further evaluation, the presence of diurnal variation in symptoms, a positive ice-pack test, and Cogan's lid twitch sign raised clinical suspicion for ocular myasthenia. Serologic testing for AchR, MuSK, and LRP4 antibodies was negative. A diagnosis of seronegative ocular myasthenia gravis was established based on clinical features. The patient was treated with pyridostigmine and a tapering course of oral corticosteroids, resulting in marked improvement in ptosis and diplopia within two weeks.

KEYWORDS

Seronegative Myasthenia Gravis, Ocular Myasthenia, Third Nerve Palsy, Ice-Pack Test

BACKGROUND

Ocular myasthenia gravis (OMG) is a neuromuscular disease caused by autoantibodies against post-synaptic proteins at the neuromuscular junction. Diagnosis involves clinical evaluation and serological tests for acetylcholine receptor (AchR), muscle-specific tyrosine kinase (MuSK), and low-density lipoprotein receptor-related protein 4 (LPR4) antibodies. Other autoantibodies, like cortactin and agrin, have uncertain diagnostic value. Diagnostic tools such as the ice-pack test and single-fibre electromyography are also useful. Treatment typically includes cholinesterase inhibitors and steroids for ophthalmoplegia, with additional options like antimetabolites and biological agents. It can also present as pupillary-sparing ophthalmoplegia in a seronegative form, where patients lack detectable antibodies against acetylcholine receptors (AChR) or muscle-specific kinase (MuSK). This subtype is particularly challenging to diagnose and treat due to the absence of these common biomarkers. Patients typically experience muscle weakness primarily affecting the eye muscles, leading to symptoms such as ptosis and diplopia. Despite the absence of AChR and MuSK antibodies, the disease mechanism still involves impaired neuromuscular transmission, necessitating a tailored approach to diagnosis and management. (Heckmann & Nel, 2018)

Case Presentation

A 48-year-old female, without any known comorbidities or prior hospitalisations, presented to the outpatient department of AIIMS with complaints of drooping of the right eyelid and horizontal double vision for the past 20 days. There was no history of headache, facial pain, altered sensorium, trauma, fever, or other focal neurological deficits. On detailed neurological examination, she was found to have a complete right-sided oculomotor nerve palsy. This manifested as profound ptosis, impaired adduction, elevation, and depression of the right eye, with the globe deviated “down and out” in primary gaze. Importantly, the right pupil was spared, round and reactive to light. There was no evidence of proptosis, periorbital oedema, chemosis, or conjunctival congestion. Visual acuity and fundoscopic examination were within normal limits.

Initial diagnostic workup focused on identifying common causes of third nerve palsy. Laboratory investigations were within normal range, including fasting blood glucose, HbA1c, thyroid function tests, and serum vasculitis markers. An urgent MRI of the brain and orbits with contrast was performed to evaluate for ischemic, compressive, inflammatory, or vascular pathology. The imaging revealed no abnormalities involving the midbrain, oculomotor nerve fascicles, cavernous sinus, or extraocular muscles. There was no evidence of aneurysm, infarct, thrombosis, mass lesion, or demyelinating plaques. Given the subacute course and absence of radiological findings, a presumptive diagnosis of vasculitic neuropathy was considered, and the patient was initiated on high-dose intravenous methylprednisolone (1 g/day for 3 days).

Following corticosteroid therapy, she reported partial subjective improvement in ptosis (approximately 20%), although her diplopia persisted. This partial and delayed response, along with negative imaging, effectively ruled out conditions like cavernous sinus thrombosis or compressive lesions. On re-evaluating her history more closely, she recalled that her symptoms—particularly the ptosis and diplopia—tended to worsen as the day progressed, a detail that raised suspicion for a neuromuscular junction disorder. Bedside testing for ocular myasthenia was then undertaken. The ice pack test yielded positive results, with notable transient improvement in ptosis after application of ice over the affected eyelid. Additionally, Cogan's lid twitch sign was positive. Serologic testing for acetylcholine receptor (AChR) antibodies, low-density lipoprotein receptor-related protein 4 (LPR4) antibodies and muscle-specific kinase (MuSK) antibodies was subsequently ordered and returned negative, ruling out seropositive myasthenia.

Based on the classical clinical presentation, diurnal variability, positive response to the ice pack test, and absence of alternative structural or systemic causes, a diagnosis of ophthalmoplegic seronegative myasthenia gravis (OMSG) was established. The patient was commenced on pyridostigmine (30 mg twice daily) along with a tapering course of oral corticosteroids. Over the next four days of inpatient observation, she exhibited significant clinical improvement in both ptosis and diplopia. She was discharged in stable condition with instructions to continue medications and attend regular follow-ups. Two weeks post-discharge, a contrast-enhanced CT scan of the thorax was performed to evaluate for underlying thymic pathology, including thymoma; the results were unremarkable.

Notably, during her follow-up visit, she reported a recurrence of ocular symptoms on the day she inadvertently missed a single dose of

pyridostigmine, further corroborating the diagnosis of a cholinergic deficit at the neuromuscular junction.

Figure 1 Shows Right ptosis with Pupillary sparing oculomotor palsy (Day 2 of IV MPS)

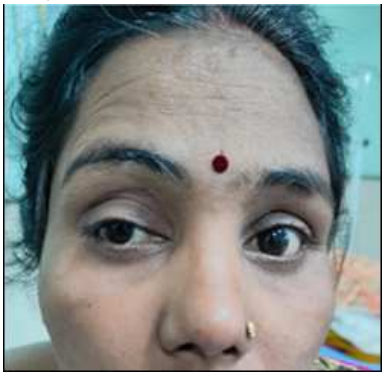

Figure 2 Shows improved ptosis after ice-pack application (Day 2 of IV MPS)

Figure 3 Improving ptosis on day 4 of pyridostigmine. Impaired right medial rectus function seen.

Figure 4 Shows complete ptosis resolution on day 14 of pyridostigmine therapy

Investigations

At the time of admission, the patient's complete blood count revealed a hemoglobin level of 13 g/dL, total leukocyte counts of 4700/cumm, and platelet count of 4.7 lakh/cumm. Random blood sugar was 90 mg/dL and HbA1c was 4.8%, effectively ruling out diabetes mellitus. Thyroid function was within normal limits, with a TSH level of 2 IU/L. Contrast-enhanced MRI of the brain showed no abnormalities involving the midbrain, oculomotor fascicles, or cavernous sinus, and there was no evidence of infarct, mass lesion, demyelination, or aneurysm. Chest X-ray and contrast-enhanced CT of the thorax revealed no signs of thymic enlargement or mediastinal pathology. A comprehensive myasthenia gravis antibody panel was negative for anti-acetylcholine receptor (AchR), anti-muscle-specific kinase (MuSK), and anti-LRP4 antibodies. Based on clinical findings and bedside tests such as a positive ice-pack test and Cogan's lid twitch, a diagnosis of seronegative ocular myasthenia gravis was made. Following initiation of pyridostigmine and a low dose tapering regimen of oral corticosteroids, the patient exhibited complete resolution of ptosis within 14 days.

Treatment

Oral Pyridostigmine 60 mg daily continued, along with 20 mg daily prednisolone, tapered over 4 weeks.

Follow-up And Outcomes

Repeated examination after 2 weeks was suggestive of ptosis resolution. The patient was advised monthly follow-up.

DISCUSSION

Myasthenia gravis (MG) is an autoimmune disorder causing fatigue and variable muscle weakness, primarily affecting ocular muscles. Symptoms include diplopia from eye muscle weakness, ptosis, and occasional dry eyes. Ptosis tends to be asymmetric, with fluctuating severity that can shift between eyes over time. In a prospective cohort, 82% of MG patients initially exhibited ocular symptoms. 10–20% initially experience weakness in limbs. Ocular muscle susceptibility in MG may be due to neuromuscular junction differences: fewer AChRs, smaller motor units, higher innervation rates, and limited complement regulation. (de Meel et al., n.d.) Autoantibodies are undetected in 50% of patients with ocular myasthenia gravis (OMG), contrasting with a higher positivity rate of 80% observed in generalized myasthenia gravis (GMG). (Kim & Oh, 2021) Most cases of ophthalmoplegic myasthenia gravis (OP-MG) involve IgG1 and IgG3 antibodies targeting acetylcholine receptors (AChR), activating complement and causing muscle damage. However, OP-MG also includes cases with IgG4 antibodies against MuSK-MG, which activate complement less effectively. Instances of this sub-phenotype have also been observed in triple seronegative MG. This diversity suggests complex pathogenic mechanisms beyond complement-mediated damage. (Heckmann & Nel, 2018) "Cogan's lid twitch" is a specific sign for OMG diagnosis, with 99% specificity and 75% sensitivity. The ice test, which involves placing ice over the ptotic eyelid for 2 minutes, is 90% sensitive and 100% specific. Although AChR antibody testing is highly sensitive in GMG (80-90%), it is less sensitive in OMG (40-70%). Anti-MuSK antibodies are less common in pure OMG. In double-seronegative MG, LRP4 antibodies are tested, with positivity ranging from 2-50%. Repetitive nerve stimulation (RNS) is abnormal in 30-50% of OMG cases, making it a less valuable diagnostic tool. Single-fibre electromyography (SFEMG) is useful for diagnosing OMG, especially when clinical suspicion is high. SFEMG has a sensitivity of 79% and a specificity of 80%. Medical treatments include cholinesterase inhibitors (pyridostigmine), oral steroids, and second-line immunosuppressive agents. Surgical treatments involve thymectomy, ptosis repair, or strabismus surgery. Pyridostigmine is effective for ptosis but less so for diplopia. Steroids, particularly oral prednisone, are used when cholinesterase inhibitors are ineffective. (Behbehani, 2023) Tests such as the ice pack test and attention to diurnal variation remain invaluable in clinical decision-making. Early initiation of appropriate therapy can lead to dramatic functional recovery in such patients.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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