Intermittent Diplopia and Ptosis as Presenting Signs of Seropositive Ocular Myasthenia Gravis Following COVID-19 Infection

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Abstract

A 65-year-old man presented to the eye clinic with non-specific blurry vision, mild intermittent horizontal diplopia and subtle intermittent left upper eyelid ptosis following an untreated COVID-19 infection three weeks prior. Ocular findings were variable and inconsistent over the course of two examinations. Intermittent ptosis and diplopia, followed by the development of poor balance and shortness of breath, led to acetylcholine receptor antibody testing, which provided a positive result. The patient was diagnosed with postinfectious seropositive myasthenia gravis and successfully treated with pyridostigmine and prednisone. In this case report, eye care providers are alerted to the possibility of new-onset myasthenia gravis following recent COVID-19 infection.

KEYWORDS:
eye, COVID-19, myasthenia gravis, ptosis, diplopia

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease in which autoantibodies destroy neuromuscular connections resulting in weakness and fatigability of skeletal muscles, which worsens with activity and improves with rest. Presenting symptoms of this condition may include intermittent and variable ptosis and/or diplopia[1] due to weakness and fatigability of the levator palpebrae superioris, orbicularis oculi, and oculomotor muscles.[2] When symptoms are localized to the ocular area, the condition is diagnosed as ocular myasthenia gravis. Within two years of presentation, approximately 50-60% of patients with ocular myasthenia gravis may develop potentially life-threatening generalized MG, exhibiting widespread weakness and fatiguability of the body's skeletal muscles.[3] Symptoms of generalized MG may include dyspnea, dysphagia, dysarthria, and weakness in the neck and extremities.[4] While timely diagnosis is important,[5] work-up for MG is typically considered non-emergent unless dyspnea or dysphagia is present.[6] MG can occur at any age but tends to impact women younger than 40 and men over 50.[7] Patients with known MG may suffer exacerbations due to infections or the use of certain medications. Infections may precipitate MG in patients with predisposing factors such as the presence of certain genetic markers, the presence of acetylcholine receptor antibodies in the absence of a myasthenia gravis diagnosis, or the presence of thymic abnormalities.[8] There is growing evidence that COVID-19 infection can lead to the development of autoimmune-related manifestations.[9] In this case report, eye care providers are alerted to the possibility of new-onset myasthenia gravis following recent COVID-19 infection.

CASE REPORT

A 65-year-old male presented for examination reporting non-specific blurry vision, mild intermittent horizontal diplopia, and poor balance following an untreated COVID-19 infection three weeks prior. Ocular history included refractive error and bilateral dermatochalasis. Medical history included osteoarthritis for which he was treated with oxycodone 5 mg/acetamino-

phen 325 mg as needed every eight hours and chronic osteomyelitis of the left ankle for which he was treated with sulfamethoxazole 800/trimethoprim 160 mg twice a day. The family medical history was unremarkable. Best corrected distance visual acuity was 20/25 in the right eye and 20/20 in the left. The results of all preliminary testing, including pupil testing, cover test, extraocular motility, gross visual fields, and intraocular pressures were normal in both eyes. Diplopia could not be elicited during examination. Anterior segment findings were significant for bilateral keratoconjunctivitis sicca and asymmetric dermatochalasis suspicious for mild left ptosis. Marginal reflex distance-1 was 4 mm in the right eye and 1 mm in the left eye. Dilated fundus examination was unremarkable in both eyes. Due to inconclusive results, the patient was asked to return in two weeks to monitor symptoms.

Between the first and second visits to the optometry clinic, magnetic resonance imaging of the brain and angiography of the head and neck were ordered as part of a stroke work-up by the primary care physician due to poor balance; neither revealed significant findings. Additional testing by the physician included thyroid-stimulating hormone, free T4, complete blood count with differential, glucose, C-reactive protein, rapid plasma reagin, antinuclear antibody, human immunodeficiency virus, and erythrocyte sedimentation rate (ESR); all gave normal results except for slightly elevated ESR.

On return to the optometry clinic, the patient reported continued intermittent diplopia. Best corrected distance visual acuity was 20/20 in each eye. Cover test revealed a slight hypertropia in the right eye. There was no apparent ptosis. The results of all other preliminary testing were normal. The patient was treated with a four base-down Fresnel prism over the right eye which alleviated diplopia in office but elicited a variable response over the next several days. Two weeks later, the patient was called by the optometry clinic for a telephone follow-up visit. He mentioned that he had recently been evaluated by his primary care physician for acute-onset shortness of breath. Due to suspicion of myasthenia gravis, acetylcholine receptor antibody (AChR) testing was ordered by the optometrist, and a neurology consult was placed by the primary care physician. A positive AChR result helped secure the diagnosis of seropositive myasthenia gravis. Computed tomography imaging of the chest was negative for thymic abnormalities.

The neurology clinic initiated treatment with 30 mg pyridostigmine, an acetylcholinesterase inhibitor, three times daily, which improved, but failed to completely alleviate, symptoms. Due to persistent symptoms, the dosage of pyridostigmine was increased to 60 mg three times daily with pyridostigmine timespan 180 mg for use each night at bedtime. Prednisone 10 mg once daily was also added to the treatment regimen. The patient's symptoms improved with the above treatment and at the six-month optometry follow-up he reported no further episodes of diplopia, shortness of breath, or difficulty swallowing or chewing. Examination revealed no ptosis or diplopia and treatment with Fresnel prism was no longer required. The patient continues to be monitored by the optometry, primary care, and neurology clinics for stability.

DISCUSSION

Myasthenia gravis is a diagnostic challenge due to non-specific signs and symptoms.[2] Ptosis in ocular myasthenia gravis and generalized MG may be unilateral or bilateral and is often asymmetric. It can be distinct from other causes in its variability and fatigability. Fatigue tests of the levator can be performed by having the patient look up for 30-60 seconds and then return to primary gaze. The clinician observes for lid lag or worsening of the ptosis, known as Pseudo Von Graphe's sign. Cogan's lid twitch is frequently noted in MG and occurs when the patient looks down for 15 seconds and then fixates on a target in primary gaze. A positive result occurs when the upper eyelid overshoots and elevates excessively before returning to a ptotic state, due to the fatigability and recovery of the muscle. Diplopia in OMG and MG may also be variable, worsening throughout the day or worsening on exertion and can mimic any eye movement disorder or complete external ophthalmoplegia.[6]

Disorders that are likely to be confused with ocular MG also involve weakness of both the eyelids and extraocular muscles, producing diplopia and ptosis. Thyroid ophthalmopathy restricts eye movements due to the enlargement of extraocular muscles and may cause proptosis, lid retraction, lid lag and periorbital edema. While ptosis is not a typical feature, it can be a presenting sign of thyroid eye disease.[10] Chronic progressive external ophthalmoplegia, myotonic dystrophy and oculopharyngeal dystrophy are also conditions that can mimic MG. These disorders are typically slowly progressive while MG usually has an acute presentation.[11] MG can also mimic any pupil-sparing ophthalmoplegia.[6] Tumors and aneurysms can impair the function of the third, fourth, and sixth cranial nerves. Multiple motor cranial neuropathies, such as those produced by meningitis or Miller-Fisher syndrome may also produce eye movement abnormalities that may be confused with MG. MRI and serologic testing can help clarify the diagnosis.[12]

Serologic testing for myasthenia gravis primarily includes acetylcholine receptor antibody testing followed by muscle-specific kinase antibody testing if the former is negative. Positive acetylcholine receptor antibody testing is considered to be diagnostic for myasthenia gravis but a negative result warrants further muscle-specific kinase antibody testing. A positive muscle-specific kinase antibody test is also considered to be diagnostic for myasthenia gravis.[6,13] Approximately 85% of myasthenia gravis patients are seropositive for AChR antibodies and approximately 40% of myasthenia gravis patients who are seronegative for AChR antibodies are seropositive for MuSK antibodies.[14] Approximately 85% of myasthenia patients have thymic abnormalities,[15] and 15% of these have a diagnosis of thymoma.[16]

Acetylcholinesterase inhibitors, which function to prevent the breakdown of acetylcholine at the neuromuscular junction, are considered to be first-line treatments for MG.[6] Immunosuppressive agents, such as corticosteroids, are often used in conjunction with acetylcholinesterase inhibitors to help prevent further damage to acetylcholine receptors and may be used short- or long-term depending on the need. In addition to corticosteroids, other long-term immunosuppressive agent options include Azathioprine, cyclosporine A, mycophenolate mofetil, cyclophosphamide, rituximab, tacrolimus, methotrexate, and etanercept. Short-term immunosuppressant options include intravenous immunoglobulin therapy and plasmapheresis. Patients with thymoma also require thymectomy.[6] If visual symptoms persist, supportive therapy such as head positioning and ocular occlusion may be performed. Persistent ptosis may improve with botulinum toxin injections or may require surgical repair.[6]

Infections have long been considered potential causative factors in the development of autoimmune disease. Specifically, emergence of myasthenia gravis weeks to months[17] following viral infection has been previously associated with Epstein-Barr virus, Polio virus, cytomegalovirus, Human Papillomavirus,[16] Varicella zoster, West Nile virus, Zika virus, Dengue virus,[8] and more recently, COVID-19,[18,19] although causality is difficult to prove.[16] COVID-19 is believed to exhibit inflammatory immune responses similar to those in autoinflammatory and autoimmune conditions[20] and to limit both innate and adaptive immune responses.[21] Depending on environmental and genetic factors,[22] this can lead to disrupted self-tolerance and eventual autoimmune response and disease.[20]

Angiotensin-converting enzyme 2 (ACE-2) receptors in the alveolar epithelial cells of the respiratory tract have been identified as the primary cellular point of entry for COVID-19.[22] Binding of COVID-19 to the host ACE-2 receptors results in dysregulation of angiotensin II signaling[23] and causes a significant inflammatory cascade. Autoantibodies form due to inflammatory injury and lead to impaired self-tolerance.[18] Due to the pathogenesis of COVID-19, therapies targeted directly at COVID-19 may be recommended earlier in the course of disease, along with immunosuppressive and anti-inflammatory therapies later in the course of the disease.[24]

Several mechanisms have been proposed to cause loss of self-tolerance, including molecular mimicry, epitope spreading, bystander activation, and viral persistence. Molecular mimicry between antibodies to COVID-19 and host proteins can cause damage to AChR and MuSk receptors at the postsynaptic membrane.[8,18] The latency period between COVID-19 infection and the development of MG favors this hypothesis.[25] Epitope spreading refers to an autoimmune response to endogenous epitopes, rather than antigenic epitopes, following infectious or inflammatory insult that results in damage to the postsynaptic membrane.[26] Bystander activation involves the autoactivation of lymphocytes not specific to the viral antigen with resulting damage to the postsynaptic membrane.[27] Additionally, it is hypothesized that persistent viral infection in the thymus, due to the infiltration of viral protein into the protein sequences of the cells of the postsynaptic membrane, results in damage to the postsynaptic membrane. In these cases, the prolonged presence of antigenic antibodies can be measured in serum titers.[28]

CONCLUSION

COVID-19 can cause immune dysregulation and trigger autoimmune disorders in susceptible individuals. Though the emergence of myasthenia gravis weeks to months following a COVID-19 diagnosis is rare, eye care providers should be aware of this possibility to ensure prompt diagnosis and treatment. ●

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