Superior Divisional Palsy of the Oculomotor Nerve as a Presenting Sign of SARS-CoV-2 (COVID-19)

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Abstract
Although COVID is a predominantly respiratory disease, recent studies demonstrate variable and atypical presentations with multiorgan involvement. Neurological manifestations involving cranial nerves and the peripheral nervous system are more frequently being described. Although mechanisms are still under investigation, several studies demonstrate the neuroinvasive potential of COVID via angiotensin-converting enzyme 2 (ACE2) receptor interactions and postulate this mechanism to be the route of COVID central nervous system (CNS) infection. We present the rare case of a purely superior divisional palsy of the left oculomotor nerve in a 46-year-old woman with no medical history in the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, confirmed by magnetic resonance imaging (MRI) findings of asymmetrical thickening and enhancement of the left oculomotor nerve. With this report, we hope to increase clinical suspicion for oculomotor nerve palsies as a manifestation of SARS-CoV-2 infection and also to inspire further studies investigating neurological manifestations of COVID.

Keywords
Oculomotor nerve palsy, diplopia, cranial nerve, neurology, COVID

Introduction
A cluster of pneumonia cases originating in Wuhan, China, in late 2019 led to the discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since being recognized by the World Health Organization (WHO) as a public health emergency and declared a pandemic on February 2020, the virus has claimed more than 1.9 million lives worldwide.¹ COVID is predominantly a respiratory disease and typically presents with fever, cough, shortness of breath, myalgia, and fatigue.² Recent studies, however, demonstrate multiorgan system involvement with variable and atypical manifestations of disease.³ Here, we report the rare case of a woman with divisional palsy of the left oculomotor nerve as a presenting sign of SARS-CoV-2 infection.

Case Presentation
A 46-year-old woman with no medical history of headache, diabetes, and hypertension presented to the emergency department with headache, diplopia, and drooping of the left eyelid ongoing for 4 days. The headache was bifrontal, constant, and gradually progressive, without photophobia or phonophobia. In addition, the patient complained that her headache was worse with movement and was associated with a pulsatile buzzing in her right ear. Two days after developing the headache, the patient noticed drooping of her left eyelid and diplopia while looking upward and to the right. On review of systems, the patient denied eye pain, redness, neck stiffness, hearing or balance impairment, fever, chills, cough, or shortness of breath. She had no focal weakness, sensory loss, or slurring of speech. Incidentally, she reported recent exposure to a co-worker who tested COVID positive.

On examination, vitals were stable (heart rate [HR] 85, blood pressure [BP] 135/64, respiratory rate [RR] 22, temperature 37.5°C, SpO₂ 100% on room air). Ophthalmological examination was as follows: visual acuity—right eye 20/30, left eye 20/25, partial ptosis of left eyelid; extra-ocular...
motility examination revealed left eye partial limitation of upward gaze, with exotropia on upward gaze. Left eye adduction, infraflection, and abduction movement were normal. The examination of the right eye was unremarkable. Both pupils were symmetric and reactive to light and accommodation. The remainder of her examination, including a cardiac, respiratory, and neurological examination, was unremarkable.

Initial laboratory workup revealed increased C-reactive protein (CRP) 3.53 mg/dL, normal ferritin, and D-dimer level. Her vitamin B12, HbA1c, syphilis, and HIV screen were within normal limits. Her thyroid function test showed normal thyroid-stimulating hormone (TSH) level, and all 3 (binding, blocking, and modulating) anti-acetylcholine receptor antibodies were negative. Real-time polymerase chain reaction (RT-PCR) nasopharyngeal swab was positive for COVID, and the patient was admitted for further neuroophthalmological workup. Radiographic workup, including a computed tomography (CT) head and CT brain angiogram, was without a localizing lesion or aneurysm. Further imaging with magnetic resonance imaging (MRI) of the brain and orbit revealed asymmetrical thickening and enhancement of the left oculomotor nerve in the region of Meckel’s cave and orbital apex—suspicious for possible nerve sheath tumor or neuritis (Figure 1). Lumbar puncture with cerebrospinal fluid (CSF) analysis was unrevealing (clear, glucose 52 mg/dL, protein 28 mg/dL, red blood cells [RBCs] 24/μL, white blood cells [WBCs] 2/μL with 100% lymphocytes).

The patient’s hospital course continued with only symptomatic management of her headache. By day 2, both her diplopia and headache began to improve, and by day 4, she was able to be discharged with neurology follow-up and repeat MRI brain and orbit in 3 months.

Nine days after discharge, the patient was seen at a posthospital clinic where she reported her ptosis and diplopia were largely resolved. She still had complaints of pulsatile tinnitus in her right ear for which she was referred to ENT, and an audiogram done was normal.

Discussion

We present the case of a patient with acute onset superior divisional palsy of the left oculomotor nerve without pupillary involvement in the setting of SARS-CoV-2 infection. Anatomically, third cranial nerve (CN III) divides into superior and inferior divisions in the anterior cavernous sinus and superior orbital fissure. This anatomy, combined with the topographical arrangement of nerve fibers in the cisternal portion and midbrain, largely determines how a patient presents clinically. Although superior divisional oculomotor nerve palsies often occur secondary to internal carotid artery aneurysms, case reports describe posterior communicating aneurysms, superior cerebellar artery aneurysms,4 and brain stem infarctions affecting the intra-axial course of CN III as causing similar presentations.5 Partial oculomotor nerve palsy as an isolated manifestation of COVID infection is infrequently described in literature.

Early in the pandemic, the SARS-CoV-2 virus was recognized for a broad range of respiratory symptoms that spanned from mild flu symptoms to severe and fatal respiratory distress.2 With time, COVID was found to have multiorgan disease manifestations.3,6-8 The pathophysiology of SARS-CoV-2 infection involves an S1 spike protein. Using this protein, the virus is able to interact with host angiotensin-converting enzyme 2 (ACE2) receptors, facilitating cell membrane attachment and invasion of host cells.9 The distribution and concentration of the ACE2 receptor in

Figure 1. MRI Brain and Orbits showing asymmetrical thickening and enhancement of the left oculomotor nerve.
different organs explain the variability of disease and frequency of lung involvement, as pulmonary tissues have high expression of ACE2 receptors. More recently, literature has shown ACE2 receptors to be ubiquitously expressed in the cell body of neurons, axons, and dendrites. Given the asymmetrical thickening and enhancement of the left oculomotor nerve seen on our patient’s MRI in the setting of active COVID infection, we suspected a COVID-induced neuritis caused her presentation.

Neurological manifestations were reported in 36.4% of patients diagnosed with COVID-19 in a study conducted in Wuhan, China. Among the participants, 24.8% had central nervous system (CNS) manifestations (e.g., dizziness, headache, cerebrovascular accident [CVA], ataxia, seizure), 8.9% had cranial and peripheral nervous system manifestations (e.g., taste, smell, and vision impairment and neuropathy), and 10.7% had skeletal muscle manifestations. Such studies demonstrate the neuroinvasive potential of COVID via ACE2 receptor interaction and raise suspicion that SARS-CoV-2 directly infects the CNS via systemic circulation and pathways across the ethmoid bone’s cribriform plate. Vonck et al postulated that SARS-CoV-2 enters the brain via the Vagus nerve as it has a direct connection to the pulmonary system and respiratory tract. This conclusion was recognized after COVID-19-positive study participants presented with vagal nerve involvement and cardiorespiratory dysfunction of the brainstem.

Several studies, including case series and case reports, have mentioned cranial nerves (e.g., facial, hypoglossal, oculomotor, and abducens nerves) involvement in SARS-CoV-2 infection. Loss of sense of smell is likely due to involvement of the olfactory bulb during its passage to the CNS and might suggest early CNS involvement. Ophthalmological manifestations ranging from conjunctivitis to vision impairment and palsy of the oculomotor and abducens nerves have been reported. Previous case reports describe complete and partial oculomotor nerve paralysis, whereas our case is an example of pure superior divisional palsy of the oculomotor nerve. A retrospective study examining neuroimaging of COVID-19 patients reported cranial nerve involvement in 10% of the study cohort.

The MRIs of patients with oculomotor nerve involvement in studies by Belghmaidi and Wei were unremarkable. Contrarily, a case report by Dinkin mentioned nerve enhancement, T2 hyperintensity, and enlargement of the oculomotor nerve and closely resembles what was seen on our patient’s MRI. Our case differed from the case presented by Wei et al, in that their patient, in addition to oculomotor nerve involvement, later developed respiratory failure leading to death by day 12 of admission. Similar to our case, Belghmaidi et al presented a patient with oculomotor nerve involvement who completely recovered by day 6 of admission without other systemic manifestations. While our patient had significant improvement by day 4, she had persistent tinnitus in her right ear without hearing impairment weeks after infection. While the cause of our patient’s tinnitus is unclear, Guittion reports that tinnitus may occur secondary to increased neuronal excitability as a result of enhanced synaptic transmissions. It is reasonable to assume that the mechanism of her tinnitus occurred in the setting of a viral polynneuritis, as a consequence of COVID. This however needs to be investigated further.

Conclusion
Although respiratory manifestations of SARS-CoV-2 infection are the most common, neurological manifestations are more frequently being recognized as signs of infection. With this report, we hope to increase clinical suspicion for oculomotor nerve palsies as a manifestation of SARS-CoV-2 infection. In addition, we hope to inspire further studies investigating neurological manifestations of SARS-CoV-2, as doing so will lead to early identification, prevention of unnecessary workup, and reduced health care expenditure.

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Our institution does not require ethical approval for reporting individual cases. Our institution does not require ethical approval for reporting individual cases or case series.

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Consent to Participate
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