

Isolated Abducens Nerve Palsy in a Patient With COVID-19

A Case Report and Literature Review

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Introduction: The pandemic of coronavirus disease 2019 (COVID-19) stands as a major global health and social burden. As cases are growing, several other symptoms, besides the typical respiratory ones, are emerging. The involvement of the nervous system is increasingly recognized with manifestations ranging from hyposmia to meningoencephalitis and cranial neuropathies.

Case Report: We report the case of a 41-year-old female patient who presented to the emergency department complaining of diplopia and headache over the last 2 days. She denied any medical history, as well as any other neurological or respiratory symptom. A detailed neurological and ophthalmological examination revealed a limitation to the abduction of the right eye due to palsy of the right lateral rectus muscle causing painless, horizontal diplopia in the right gaze. The computed tomography of the brain was normal. Based on the detected lymphopenia, she was tested for COVID-19 and was positive. The cerebrospinal fluid analysis showed no abnormalities, while also a repeated head computed tomography was similarly normal. The patient received no specialized medical treatment, and after 6 days, she was discharged home having a minimal degree of persistent diplopia. Two weeks later, brain magnetic resonance imaging was performed that was similarly unrevealing.

Conclusions: Isolated abducens nerve palsy can be the only presenting symptom in COVID-19. Although several pathophysiological mechanisms have been proposed, the exact nature of this manifestation has not been clarified yet. Vigilance is required by neurologists to detect and manage patients with such subtle clinical presentations.

Key Words: COVID-19, SARS-CoV-2, abducens nerve palsy, cranial neuropathy

(The Neurologist 2022;27:139–142)

The global pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) accounts to date for > 140 million cases and 3 million deaths worldwide.¹ Although it typically affects the respiratory system producing symptoms ranging from cough to severe pneumonia and acute respiratory distress syndrome, it can implicate several other organ systems including the peripheral and central nervous system. According to 2 observational studies,^{2,3}

neurological manifestations can be present in 36.4% and 57.4%, respectively, of hospitalized patients with COVID-19, while their prevalence is higher in patients with severe infection.² The spectrum of neurological disorders that can manifest ranges from mild symptoms, such as hyposmia, hypogeusia, headache, and myalgia to more severe ones, such as encephalopathy, meningoencephalitis, cerebrovascular disease, acute disseminated encephalomyelitis, Guillain-Barré syndrome, and cranial neuropathies.^{4,5} We herein expand on the current literature of neurological complications by presenting a case of a young woman with isolated abducens nerve palsy in the setting of COVID-19.

CASE REPORT

A 41-year-old white female patient presented in the emergency department of our hospital complaining of headache, unresolved with common analgesics, and double vision over the last 2 days. She was otherwise healthy with a normal body mass index, reporting no known medical history, such as diabetes, hypertension, hypercholesterolemia, or skull trauma, and no drug abuse apart from tobacco smoking. She denied any other neurological symptoms, such as hyposmia, hypogeusia, weakness, paresthesias, and gait disturbance, as well as any respiratory symptom. In the emergency department, she was afebrile and had normal vital signs with an oxygen saturation rate of 99%. The physical examination was otherwise entirely normal and only revealed a limitation to the abduction of the right eye due to palsy of the right lateral rectus muscle causing painless, binocular, horizontal diplopia in the right gaze. The ophthalmology consultation verified this finding and also assessed the visual acuity, color vision, and both fundi as normal. The emergent computed tomography (CT) of the brain did not reveal any acute pathology, such as ischemia or hemorrhage. However, her routine blood tests demonstrated markedly low white blood cell count ($2.8 \times 10^9/L$) along with lymphopenia ($0.6 \times 10^9/L$). Following this, a rapid antigen test and a reverse transcription-polymerase chain reaction molecular test for SARS-CoV-2 from a nasopharyngeal swab were performed both of which came out positive, and hence the patient was admitted to the hospital for further evaluation and management.

During her hospital stay, the patient developed no other symptom, remained afebrile with excellent respiratory function, and received no medical treatment except for acetaminophen for headache relief. A complete blood workup revealed a normal lipid profile, thyroid function, coagulation profile, and thrombophilia testing. From the second day on, the function of the lateral rectus muscle improved significantly along with the diplopia. Nevertheless, we proceeded to a lumbar puncture that showed no abnormalities from the cerebrospinal fluid (CSF) analysis (cell count: $2/mm^3$, red blood cells: $40/mm^3$, protein: 19.10 mg/dL , glucose: 67 mg/dL , lactate dehydrogenase: 15 IU/L). Also, the reverse transcription-polymerase chain reaction of CSF for SARS-CoV-2 and other viruses, including influenza A and B, herpes simplex virus type I and II, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, and West Nile virus, was negative. Due to the unavailability of magnetic resonance imaging scan at the time, a repeated head CT and CT cerebral venography were performed

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The authors declare no conflict of interest.

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ISSN: 2331-2637/22/2703-0139

DOI: 10.1097/NRL.0000000000000382

TABLE 1. Patients With Isolated Abducens Nerve Palsy in the Setting of COVID-19*

References	Age (y)/ Sex	Medical History	Presentation of Diplopia	Accompanying Symptoms/Syndromes	Imaging Findings on Brain MRI	Possible Pathophysiological Mechanisms	Treatment Administered	Duration of Diplopia	Outcome
Dinkin et al ⁶	71/F	Hypertension	Painless right abducens nerve palsy	Pneumonia with fever, cough, and hypoxemia	T1-enhanced optic nerve sheaths and posterior Tenon capsules	Viral leptomenigeal invasion; ischemic process	Hydroxychloroquine	3 wk at least	Gradual improvement after 3 wk
Falcone et al ⁷	32/M	Unremarkable	Painless left abducens nerve palsy	Upper respiratory illness symptoms progressing to acute hypoxemic respiratory failure	T2 hyperintense atrophic left lateral rectus muscle	Lateral rectus muscle denervation through a direct or indirect virally mediated insult along the path of the abducens nerve	Hydroxychloroquine	5 wk at least	No improvement after 5 wk
Greer et al ⁸	43/F	Migraines, well-controlled hypertension	Left abducens nerve palsy	Fever, respiratory symptoms, fatigue, lightheadedness	Unrevealing	Viral leptomenigeal invasion; hypertensive episode in the state of acute viral illness	NR	NR	NR
	52/M	Well-controlled hypertension	Left abducens nerve palsy	Fever, anosmia, ageusia, sense of imbalance, myalgias, fatigue, severe headache	Not performed	Viral leptomenigeal invasion; hypertensive episode in the state of acute viral illness	None	2 wk	Full recovery
Gutiérrez-Ortiz et al ⁹	39/M	Unremarkable	Bilateral abducens nerve palsy	Diarrhea, fever, ageusia, absent deep tendon reflexes	Not performed	Polyneuritis cranialis	Acetaminophen	2 wk	Full recovery
This case	41/F	Unremarkable	Painless right abducens nerve palsy	Headache	Unrevealing	Thrombotic microvascular injury	Acetaminophen	4 wk	Full recovery

*We searched MEDLINE via PubMed from inception to May 5, 2021, using relevant free-text and controlled vocabulary terms and without imposing any restrictions regarding language or publication status. COVID-19 indicates coronavirus disease 2019; F, female; M, male; MRI, magnetic resonance imaging; NR, not reported.

that were free of any pathologic findings. In addition, the chest x-ray and CT scan were also normal. After 4 more days, the ocular movement dysfunction was fully resolved, and the patient was discharged home to quarantine having only a minimal degree of diplopia. Two weeks later, and while a nondebilitating diplopia in the right horizontal gaze insisted, a gadolinium-enhanced brain magnetic resonance imaging was performed and, similarly, did not reveal any pathologic sign regarding the cranial nerves, brainstem, orbits, or brain parenchyma. The patient was contacted by phone 1 week later, 1 month in total since the onset of the symptom, reporting that the diplopia had been completely resolved.

DISCUSSION

We report the case of a patient with acute, painless, isolated palsy of the right sixth cranial nerve in the setting of SARS-CoV-2 infection. Abducens nerve palsy is the commonest ocular motor palsy and can be caused by a variety of disorders including vascular, demyelinating, and neoplastic disorders. However, no clinical, laboratory, or imaging sign suggestive of an underlying pathology was found indicating that COVID-19 might have triggered the transient abducens nerve palsy in this case. Since the literature on the neuro-ophthalmological complications of COVID-19 is growing, similar cases of patients with systemic illness, respiratory symptoms, and either unilateral or bilateral abducens nerve palsy have been described^{6–9} (Table 1). However, to our knowledge, this is the first case of abducens nerve palsy in the setting of SARS-CoV-2 infection without any sign of systemic or respiratory illness.

Although the exact mechanisms leading to nervous system involvement in COVID-19 have not been fully clarified yet, several potential pathophysiological pathways have been proposed. First, hypoxemia, prevalent in patients with SARS-CoV-2 infection, seems to act in a similar manner to other metabolic derangements leading to neuronal and astrocytic injury and causing ischemic damage.¹⁰ However, such mechanism is more relevant in cases of encephalopathy, hence is unrelated to our patient who was also nonhypoxicemic. Furthermore, the viral spike proteins utilize and bind to the endothelial cell receptor angiotensin-converting enzyme 2 (ACE2), which converts angiotensin II to angiotensin-(1-7). The latter has vasodilator, antiproliferative, antifibrotic, and antithrombotic properties, and its downregulation is associated with a prothrombotic state.¹¹ This may be relevant in our case since the presence of headache in the setting of diplopia can be a result of microvascular damage, as seen in ischemic cranial nerve palsies.¹² Not only that, but also the binding to ACE2 receptor, present in the epithelial cells of the nasal mucosa, olfactory nerve, and endothelial and arterial smooth muscle cells in the brain, provides a direct route of SARS-CoV-2 into the central nervous system by disrupting the blood-brain barrier.¹³ However, apart from the trans-synaptic invasion, there seems to be a hematogenous pathway, as well. Indeed, according to Zheng et al,¹⁴ in up to 41% of cases of COVID-19, there is some evidence of hematological dissemination. This fact is also supported by the rise in the concentration of plasma biomarkers indicative of astrocytic and intra-axonal neuronal injury, such as the glial fibrillary acidic protein and the neurofilament light chain protein.^{15,16} In addition, the dysregulated immune system responds by releasing proinflammatory cytokines, such as interleukin-6, interleukin-1 β , and tumor necrosis factor, which mediate microglial activation and, hence, brain injury, disrupt the blood-brain barrier facilitating the virus spread into the central nervous system, and also, along with the complement activation, lead to a prothrombotic state, thereby increasing the risk of thrombotic microvascular injury.^{17–20} Finally, the role of gangliosides and their associated antibodies as mediators of

Miller Fisher syndrome has been highlighted because of the viral spike proteins affinity not only to ACE2 receptors but also to gangliosides on cell surfaces. This binding can potentially induce cross-reactivity between SARS-CoV-2 spike-bearing gangliosides and peripheral nerve glycolipids.²¹ Although we did not test for antiganglioside antibodies and an immune-mediated neuropathy cannot be ruled out, the lack of symptoms of ataxia and areflexia and the normal CSF analysis make the diagnosis of a Guillain-Barré syndrome variant unlikely.

CONCLUSIONS

Abducens nerve palsy can be the only presenting symptom in patients with COVID-19. Although the full spectrum of neurological complications of the disease has not been revealed yet, the still-growing number of cases is going to provide a more thorough insight into the subject and the underlying pathophysiological mechanisms. Until then, vigilance is required by medical professionals to detect patients with such subtle clinical presentation, pursue a diagnostic assessment with the appropriate laboratory tests and imaging modalities, and potentially provide treatment according to the most probable underlying pathophysiological mechanism.

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