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COVID-19 presenting with ophthalmoparesis from cranial nerve palsy

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Neurological complications of COVID-19 are not well described. We report two patients who were diagnosed with COVID-19 after presenting with diplopia and ophthalmoparesis.

Case 1:

A 36-year-old man with a history of infantile strabismus presented with left ptosis, diplopia and bilateral distal leg paresthesias. He reported subjective fever, cough and myalgias which had developed 4 days earlier and resolved before presentation. Exam was notable for left mydriasis, mild ptosis and limited depression and adduction, consistent with a partial left oculomotor palsy. Abduction was limited bilaterally consistent with bilateral abducens palsies (Figure A). Lower extremity hyporeflexia and hypesthesia, and gait ataxia were noted. WBC was $2.9 \times 10^3/\mu\text{L}$ with absolute lymphocyte count $0.9 \times 10^3/\mu\text{L}$. Nasal swab for SARS-CoV-2 PCR was positive. MRI revealed enhancement, T2 hyperintensity and enlargement of the left oculomotor nerve (Figure B-D). Chest radiograph was unremarkable. The next day, there was worsening left ptosis, complete loss of depression and horizontal eye movements on the left, and loss of abduction on the right. The patient received intravenous immunoglobulin (2g/kg over three days) to treat presumed Miller Fisher Syndrome, and hydroxychloroquine for COVID-19 (600mg twice a day for one day, followed by 400mg daily for four days). Deficits improved partially before discharge three days after admission. A ganglioside antibody panel was negative.

Case 2:

A 71-year-old woman with hypertension presented with painless diplopia on waking two days prior and could not abduct her right eye (Figure E). Visual acuity, pupils and funduscopy were normal. She reported cough and fever for several days. She was sent to the emergency room, where she was febrile and hypoxemic. WBC was $9.2 \times 10^3/\mu\text{L}$ with absolute lymphocyte count $0.5 \times 10^3/\mu\text{L}$. Lumbar puncture was normal with opening pressure 16cm H₂O. MRI showed enhancement of the optic nerve sheaths and posterior Tenon capsules (Figure F-G). Chest radiograph revealed bilateral airspace opacities (Figure H) and nasal PCR for SARS-CoV-2 was positive. Her COVID-19 pneumonia was treated with hydroxychloroquine (dosing as above). Her abduction palsy did not improve significantly before discharge

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on room air after a 6-day admission. She reported gradual improvement of diplopia when contacted by phone 2 weeks after discharge.

Discussion: We describe two patients who developed cranial neuropathies within days of respiratory symptoms related to SARS-CoV-2 infection and were found to have abnormal perineural or cranial nerve findings on MRI. To reduce the risk of transmission, work-up was limited to the essential studies needed to determine management.

In a retrospective review of 214 patients with COVID-19 in Wuhan, China, 36.5% had neurological symptoms¹, which were more common in patients with severe disease. Most were non-specific symptoms common in viral infections such as headache and dizziness, but 5.7% presented with acute cerebrovascular disease. The occurrence of hypogeusia and anosmia suggests olfactory bulb involvement, which has been proposed as a mechanism of entry into the nervous system². COVID-19 encephalitis with positive SARS-CoV-2 PCR in the CSF³ and acute necrotizing brainstem encephalopathy⁴ have been reported. CNS manifestations were more prevalent in patients with lymphopenia¹, as seen in our patients. CNS entry of SARS-CoV-2 may depend on viral interaction with membrane-bound ACE2 receptor⁵, which is expressed not only in nasal and oral mucosa but also in the nervous system², and SARS-CoV-2 appears to have a 10-20 fold higher affinity than SARS-CoV for the ACE2 receptor⁵. Notably, neither patient had a history of ACE inhibitor use.

The combination of ophthalmoparesis, leg paresthesia and areflexia in our first case suggested an acute demyelinating inflammatory polyneuropathy secondary to a virus-mediated immune response, similar to other reports⁶. However, the occurrence of neurological symptoms within a few days of disease onset led to consideration of direct infection. In our second case, although radiological evidence of abducens nerve involvement was lacking, the presence of optic nerve sheath enhancement of the involved eye could reflect viral leptomeningeal invasion, though these findings are non-specific⁷. Given her risk factors and the painless nature of the diplopia, the differential includes an ischemic process. In both cases, neurologic

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symptoms could be unrelated to SARS-CoV-2 infection. Nonetheless, in the setting of the COVID-19 pandemic, the occurrence of cranial neuropathies should prompt consideration of SARS-CoV-2 infection in patients with even mild symptoms and signs of COVID-19. Hydroxychloroquine was used in both cases per institutional practice, though whether clinical benefit was conferred is not known. Further studies are needed to understand the natural history and prognostic significance of cranial neuropathies in SARS-CoV-2 infection and to determine the best treatment.

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Appendix 1. Author Contributions

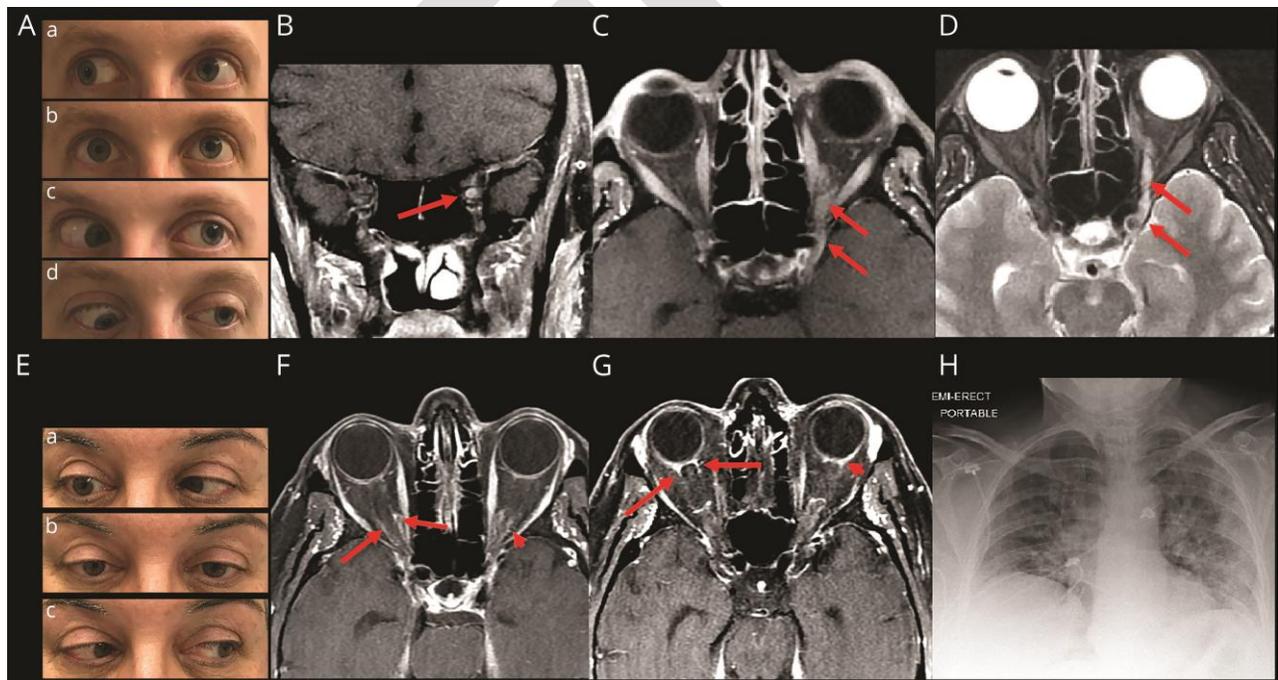
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Figure: Eye movements and radiological findings in two patients with COVID-19 and ophthalmoparesis

Motility examination of patient 1 (A) revealed limitation of left eye adduction (A.a) and depression (A.d). A subtle left eye hypertropia was observed in primary gaze (A.b), which worsened in left gaze (A.c). Enhancement of the left oculomotor nerve (arrows) can be seen on coronal (B) and axial (C) T1 fat-saturated post-contrast MRI. Enlargement and hyperintense signal of the left oculomotor nerve is demonstrated (arrows) on axial T2 fat-saturated MRI sequence (D). Motility examination of patient 2 (E) revealed 40% abduction of the right eye consistent with a right abducens palsy (E.a), and an esotropia in primary gaze (E.b). Enhancement of the perineural sheaths without involvement of the optic nerve substance was seen in the right eye (arrows) and left eye (arrowhead) on axial T1 fat-saturated post-contrast MR sequence (F). Enhancement of Tenon's capsule was seen OD (arrows) and OS (arrowhead) on axial T1 fat-saturated post-contrast MRI (G). Chest X-ray revealed multifocal pneumonia (H).



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