PEARLS & OY-STERS: FACIAL NERVE PALSY AS A NEUROLOGICAL MANIFESTATION OF COVID-19 INFECTION

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Pearls

- Coronavirus disease 2019 (COVID-19) has been associated with various neurological manifestations, including anosmia, acute ischemic stroke, Guillain-Barre syndrome, and encephalopathy.
- During the COVID-19 pandemic, physicians seeing patients with these neurological manifestations should consider COVID-19 as a differential diagnosis to prevent diagnostic delays and further transmission of disease.
- Cranial nerve involvement could potentially be associated with COVID-19.

Oy-ster

- When a patient presents with isolated facial nerve palsy, a careful neurological examination is required to rule out concomitant cranial nerve involvement (such as trigeminal nerve or vestibulocochlear nerve palsies), that would suggest alternative localisation sites.
- Facial nerve palsy is commonly due to, or associated with, a viral infection and should not be assumed to be idiopathic.
- Investigations such as cerebrospinal fluid analysis and magnetic resonance imaging can be helpful in evaluating for central nervous system infection, inflammation and other secondary causes.

In early March 2020, a previously well 27-year-old gentleman was directly admitted to the isolation ward of a tertiary healthcare center in Singapore with symptoms of myalgia, cough and fever for 4 days. His symptoms started the day after he returned from Spain. He also complained of a new left-sided throbbing headache with no associated photophobia or neck stiffness. On examination, he had mild bilateral conjunctival injection and respiratory examination was unremarkable. He did not have any focal neurological deficits. Chest radiography did not show any infiltrates and a nasopharyngeal swab returned positive for SARS-CoV-2 on real-time reverse-transcription–polymerase-chain-reaction (RT-PCR) assay.
On the third day of hospitalization (day 6 of illness), he developed left facial weakness, which was preceded by left retro-auricular pain and dysgeusia. Neurological exam revealed involvement of the left frontalis, orbicularis oculi, buccinator, and orbicularis oris, consistent with a left lower motor neuron type facial nerve palsy. Corneal reflex was present, and there was no hyperacusis. The rest of the neurological examination was unremarkable and his reflexes were normal. Kernig's and Brudzinski's signs were negative. There were no associated vesicles in the outer ear nor was there any parotid swelling. HIV screen was negative. Cerebrospinal fluid (CSF) analysis did not show any pleocytosis, and glucose and protein levels were normal. CSF PCR for herpes simplex virus, varicella zoster virus, Epstein-Barr virus and cytomegalovirus, and RT-PCR for SARS-CoV-2 were negative. Magnetic resonance imaging (MRI) of the brain showed enhancement of the left facial nerve. (Figure 1A). He was started on prednisone and valacyclovir for treatment of Bell’s palsy. Lopinavir/ritonavir was also initiated with the intention of reducing SARS-CoV-2 viral replication. His SARS-CoV-2 viral load was high during the early phase of illness (4-7 days from symptom onset) and decreased rapidly following the administration of lopinavir/ritonavir, becoming undetectable by the end of the second week (Figure 1B). No significant virologic rebound was observed. On review one week later, there was no significant change in the degree of his facial weakness, but his headache and retro-auricular pain improved.

**Discussion**

We are in the exponential phase of learning about COVID-19, an emerging infectious disease, which has caused an ongoing global pandemic. In a cohort of 214 Chinese patients, COVID-19 presents most commonly with fever in 88.7% and cough in 67.8% of patients, of which 5% required intensive care monitoring.¹ Neurological manifestations of COVID-19 have been reported in up to 36.4%.² Thus far, impairment of taste and smell, dizziness and headache have been reported as common symptoms in COVID-19 patients.²
Recently, reports of significant neurological associations have emerged, including increased incidences of Guillain-Barré syndrome, encephalopathy, and strokes. In an Italian cohort, Guillain-Barré syndrome has been reported in approximately 0.5% of COVID-19 patients, with the first symptoms of flaccid paralysis and facial diplegia occurring at 5-10 days after onset of acute respiratory symptoms. In Strasbourg, France, encephalopathic features were commonly seen in patients with severe COVID-19 who had acute respiratory distress syndrome, some of whom had MRI abnormalities including leptomeningeal enhancement, perfusion abnormalities, and ischemic stroke. A case of acute hemorrhagic necrotizing encephalopathy associated with COVID-19 infection has also been reported in Detroit, Michigan, and postulated to be due to intracranial cytokine storm, with MRI showing T2 FLAIR hyperintensities within the thalami and bilateral medial temporal lobes with rim enhancement post contrast. The incidence of stroke was 5.7% in COVID-19 patients with more severe respiratory symptoms in Wuhan, China. A case series from Spain described cranial nerve manifestations associated with COVID-19 in two patients, one of which had Miller Fisher syndrome and the other presenting with polineuritis cranialis. To our knowledge, isolated cranial neuropathies have yet to be described.

Facial nerve palsy can be associated with infections, most commonly herpes simplex virus, as well as varicella zoster and human immunodeficiency viruses, Lyme disease, and mycobacterium tuberculosis. Non-infectious causes include sarcoidosis and neoplasms. The exact pathogenesis of acute facial nerve palsy remains unclear, but in association with neurotropic herpesviruses (HSV and VZV), it is thought to be related to axonal spread and viral replication leading to inflammation and demyelination.

Coronaviruses are known to have a neuroinvasive propensity. Animal models show that SARS-CoV and MERS-CoV could potentially have a transcribial route to the brain, causing central nervous system manifestations. The mechanism underlying neurological symptoms in COVID-19 infection has yet to be clearly elucidated. Similar to the patients with Miller-Fisher syndrome and perineuritis cranialis described in Spain and those with Guillain-Barré syndrome described in Italy, our patient
developed an isolated facial nerve palsy during the early phase of his illness, on day 6.\textsuperscript{5,6} This may suggest a parainfectious phenomenon. Serum GD1b-IgG antibodies were also detected in the patient with Miller Fisher syndrome. In all of these cases with Guillain-Barré syndrome and Miller Fisher syndrome, SARS-CoV-2 was not detected in the CSF. As such, cranial neuropathies may be related to immune-mediated injury from pro-inflammatory cytokines rather than direct viral neutrophism.\textsuperscript{6}

Studies of viral dynamics show that viral loads are highest 1-2 days prior to symptom onset, decreases in a monotonic pattern with prolonged viral shedding hovering near the level of detection, resulting in RT-PCR results that vacillate between positive and negative.\textsuperscript{9} Lopinavir/ritonavir is a protease inhibitor combination approved for use in HIV-1 and has demonstrated in-vitro activity against SARS-CoV-2. A recent randomized trial conducted in China on COVID-19 patients with severe respiratory symptoms compared lopinavir/ritonavir, in addition to standard care, to standard care alone, and found no significant decrease in viral load or clinical benefit with lopinavir/ritonavir.\textsuperscript{10} However in this study, the frequency of RT-PCR testing was only every 4-7 days, and it has been proposed that daily sampling following antiviral treatment may have provided more detailed characterization of the viral load kinetics. More studies are needed to determine if there is a direct effect of lopinavir/ritonavir on viral load, if there is an indirect effect on the immune response or no effect on the natural course of the disease process. In our patient, we observed a declining trend in SARS-CoV-2 viral load (which is inversely related to the cycle threshold or Ct value) determined by daily nasopharyngeal swab samples after lopinavir/ritonavir was initiated.

This single case report only suggests a possible association between isolated cranial neuropathies and COVID-19. More cases are required to support causality. We are reporting this case to inform and alert physicians of the possibility of cranial nerve involvement in the presentation of COVID-19 patients.
### Appendix. Authors

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References


Figure. Neuroimaging and Viral Load of COVID-19 Patient with Facial Nerve Palsy
A: Contrast enhanced magnetic resonance of the brain showing enhancement of the left facial nerve
SARS-CoV-2 viral load correlated with clinical course and treatment.
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