

Miller Fisher syndrome and polyneuritis cranialis in COVID-19

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Abstract

Objective

To report 2 patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who presented acutely with Miller Fisher syndrome and polyneuritis cranialis, respectively.

Methods

Patient data were obtained from medical records from the University Hospital “Príncipe de Asturias,” Alcalá de Henares, and the University Hospital “12 de Octubre,” Madrid, Spain.

Results

A 50-year-old man presented with anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, albuminocytologic dissociation, and positive testing for anti-GD1b-immunoglobulin G antibody. Five days previously, he had developed a cough, malaise, headache, low back pain, and fever. A 39-year-old man presented with ageusia, bilateral abducens palsy, areflexia, and albuminocytologic dissociation. Three days previously, he had developed diarrhea, a low-grade fever, and poor general condition. Oropharyngeal swab test for SARS-CoV-2 by qualitative real-time reverse transcriptase PCR assay was positive in both patients and negative in the CSF. The first patient was treated with IV immunoglobulin and the second with acetaminophen. Two weeks later, both patients made a complete neurologic recovery, except for residual anosmia and ageusia in the first case.

Conclusions

Our 2 cases highlight the rare occurrence of Miller Fisher syndrome and polyneuritis cranialis during the coronavirus disease 2019 (COVID-19) pandemic. These neurologic manifestations may occur because of an aberrant immune response to COVID-19. The full clinical spectrum of neurologic symptoms in patients with COVID-19 remains to be characterized.

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Glossary

COVID-19 = coronavirus disease 2019; **IgG** = immunoglobulin G; **MERS-CoV** = Middle East respiratory syndrome coronavirus; **rRT-PCR** = real-time reverse transcriptase polymerase chain reaction; **SARS-CoV** = severe acute respiratory syndrome coronavirus.

Coronavirus belongs to a family of single-stranded RNA viruses,¹ which includes the severe acute respiratory syndrome coronavirus (SARS-CoV)² and the Middle East respiratory syndrome coronavirus (MERS-CoV).³ A new coronavirus, SARS-CoV-2, has spread rapidly throughout China and other countries, representing a global public health concern.

SARS-CoV-2 is a highly pathogenic virus, and the understanding of its epidemiology, natural history, transmission, clinical presentation, and therapeutics is currently evolving. The spectrum of coronavirus disease 2019 (COVID-19) ranges from asymptomatic infection to severe respiratory failure; fever, cough, fatigue, sputum production, shortness of breath, myalgias or arthralgias, sore throat, and chills are among its most common manifestations.⁴ Other features, such as gastrointestinal (e.g., diarrhea, nausea, and vomiting) or neurologic manifestations (e.g., headache), have also been reported.⁴ In addition, other neurologic symptoms such as anosmia and ageusia are presented by many patients.⁵ However, the clinical features and pathogenesis of COVID-19 need to be elucidated. Specifically, the exact nature and mechanism of COVID-19-induced neurologic manifestations remain largely unknown. Different neurologic complications have been reported with its predecessors. SARS-CoV was occasionally associated with the development of different neurologic manifestations including axonopathic polyneuropathy, myopathy, rhabdomyolysis, and large artery ischemic stroke, among others.⁶ During or after MERS-CoV treatment, Bickerstaff encephalitis overlapping with Guillain-Barré syndrome, intensive care unit–acquired weakness, or other toxic or infectious neuropathies have been reported.⁷

We report 2 patients infected with SARS-CoV-2 who presented acutely with Miller Fisher syndrome and polyneuritis cranialis, respectively.

Methods

Patient data were obtained from medical records from the University Hospital “12 de Octubre” and University Hospital “Príncipe de Asturias,” Alcalá de Henares, Madrid, Spain.

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from 2 patients participating in the study (consent for research).

Data availability

The data supporting the findings of this study are available within the article.

Patient 1

A 50-year-old man presented to the emergency department of the University Hospital “12 de Octubre,” Madrid, Spain, with a 2-day history of vertical diplopia, perioral paresthesias, and gait instability. His medical history was remarkable for bronchial asthma. Five days prior to his visit, he had developed a cough, malaise, headache, low back pain, and a fever. He did not report nausea, vomiting, sensory deficits, or urinary incontinence, but noted anosmia and ageusia. Except for a temperature of 99.9°F, his vital signs were normal (pulse 72, blood pressure 132/68 mm Hg, and basal oxygen saturation 98%). Pulmonary and cardiac auscultation and abdominal examination were unremarkable.

Neurologic examination revealed that cognitive function and language were intact. The patient complained of perioral paresthesias, but no facial weakness was observed. Strength and muscle tone were normal in all extremities, and no sensory deficits were detected. He had a broad-based ataxic gait. There was no dysmetria on finger-to-nose or heel-to-shin tests. Muscle stretch reflex examination revealed absent deep tendon reflexes in the upper and lower limbs. Plantar responses were flexor bilaterally. Neuro-ophthalmologic examination revealed visual acuity of 20/25 in both eyes. The anterior poles, intraocular pressure, and fundi were normal, and the optic nerves did not show disk edema. The patient’s pupils reacted briskly to light, without a relative afferent pupillary defect. There was no ptosis. He showed right hypertropia in all fields of gaze, severe limitations to the adduction and downgaze movements of his right eye, and left eye nystagmus on left gaze. All these findings were consistent with right internuclear ophthalmoparesis and right fascicular oculomotor palsy. No orbicularis weakness, variability, or fatigability was noted.

Blood workup revealed lymphopenia (1,000 cells/ μ L) and elevated C-reactive protein (2.8 mg/dL). Antibodies to gangliosides (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and antisulfatide antibodies) in the serum were examined. The patient was only positive for the anti-GD1b–immunoglobulin G (IgG) antibody. The patient’s oropharyngeal swab test for SARS-CoV-2 by qualitative real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assay was positive. CSF examination revealed an opening pressure of 11 cm H₂O, white blood cell count 0/ μ L, protein 80 mg/dL, and glucose 62 mg/dL, with normal cytology, sterile cultures, and negative serologies, including rRT-PCR for SARS-CoV-2. Chest X-ray and head CT without contrast were normal.

The patient was treated with IV immunoglobulin 0.4 g/kg for 5 days starting on the 5th day of his neurologic symptoms.

The cranial neuropathies and the ataxia improved substantially over the succeeding days and he was discharged home 2 weeks after admission, with a resolution of the neurologic features, except for residual anosmia and ageusia.

Patient 2

A 39-year-old man presented to the emergency department of the University Hospital “Príncipe de Asturias,” Alcalá de Henares, Madrid, Spain, because of acute onset of diplopia. His medical history was unremarkable. Three days previously, he had presented with diarrhea, a low-grade fever, and a generally poor condition, without any headache, respiratory symptoms, or dyspnea. He did not report nausea or vomiting but noted ageusia. On examination, his body temperature was 96.3°F, pulse 74, blood pressure 125/72 mm Hg, and basal oxygen saturation 98%. Respiratory, cardiovascular, and abdominal examinations were also normal. On neurologic examination, the patient was conscious, alert, and well-oriented to time, place, and person. The neuro-ophthalmologic examination revealed visual acuity of 20/25 in both eyes. The anterior poles, intraocular pressure, and fundi were normal without disk edema. His pupils were normal. He showed esotropia of 10 prism diopters at distance and 4 prism diopters at near, severe abduction deficits in both eyes, and fixation nystagmus, with the upper gaze more impaired, all consistent with bilateral abducens palsy. No orbicularis weakness, variability, or fatigability was noted. All deep tendon reflexes were absent; the remainder of the neurologic examination of limbs, including sensation, was normal. No gait instability or truncal ataxia was observed. Finger-to-nose and heel-to-shin tests showed no dysmetria or decomposition.

Routine blood tests as well as those for liver function, renal function, myocardial enzymes, and electrolytes, were normal, but leukopenia was present (3,100 cells/ μ L). The patient’s oropharyngeal swab test for SARS-CoV-2 by qualitative rRT-PCR assay was positive. The CSF examination revealed an opening pressure of 10 cm H₂O, white blood cell count 2/ μ L (all monocytes), protein 62 mg/dL, and glucose 50 mg/dL, with normal cytology, sterile cultures, and negative serologies, including the rRT-PCR for SARS-CoV-2. Chest X-ray and head CT without contrast were normal.

The patient was discharged home and treated symptomatically with acetaminophen and telemedicine monitoring because of complete hospital saturation with patients with COVID-19. The antiganglioside antibody profile could not be performed because of the aforementioned hospital saturation. At the next consultation, 2 weeks later, he had made a complete neurologic recovery with no ageusia, complete eye movements, and normal deep tendon reflexes.

Discussion

Coronaviruses, in general, share a similar viral structure, and the pathogenic mechanisms of other coronaviruses may also be applicable for SARS-CoV-2. The human receptor for SARS-CoV-2 may be angiotensin-converting enzyme 2 receptor,

similar to that of SARS-CoV.⁸ A growing body of evidence shows that neurotropism is a common feature of coronavirus infection.⁹ Animal models show that SARS-CoV and MERS-CoV might enter the brain, possibly via the olfactory nerves, and thereafter spread rapidly to specific brain areas including the thalamus and brainstem.⁹ This might explain the complaints of anosmia of many patients infected by SARS-Cov-2.⁵ Furthermore, inflammatory or immune-associated molecules, such as cytokines, which are detected in patients with COVID-19, may affect the taste buds and hence cause ageusia.¹⁰ An understanding of the exact mechanism of coronavirus-induced neurologic symptoms is in its infancy.

Miller Fisher syndrome is characterized by the acute onset of external ophthalmoplegia, ataxia, and loss of tendon reflexes. We have described 1 patient with SARS-CoV-2 infection who had a Miller Fisher syndrome as an unusual initial neurologic manifestation. The second patient did not have classic Miller Fisher syndrome, but polyneuritis cranialis (isolated multiple cranial neuropathy) that improved spontaneously and rapidly. There are incomplete forms of Miller Fisher syndrome, including acute ataxic neuropathy, which can be diagnosed in the absence of ophthalmoplegia, and acute ophthalmoparesis, which may occur in the absence of ataxia, as in this second patient.¹¹ Polyneuritis cranialis may be a separate subtype, which lies at the interface between Miller Fisher syndrome and Guillain-Barré syndrome.¹²

Miller Fisher syndrome has been shown to be preceded by infections similar to those preceding Guillain-Barré syndrome, suggesting a paraviral or postviral process. *Haemophilus influenzae*, *Campylobacter jejuni*, and cytomegalovirus are the most common pathogens involved.¹³ To our knowledge, Miller Fisher syndrome has not been reported associated with SARS-Cov-2. The occurrence of Miller Fisher syndrome and polyneuritis cranialis in these 2 patients with SARS-CoV-2 infection could be coincidental. However, taking into account the temporal relationship, COVID-19 might have been responsible for the development of these 2 neurologic pictures. Further supporting this hypothesis was the recent publication of a single case report suggesting a possible association between Guillain-Barré syndrome and SARS-CoV-2 infection.¹⁴

The pathogenesis of Miller Fisher syndrome and polyneuritis cranialis in SARS-Cov-2 infection may include immune mechanisms or direct viral neuropathogenic effects. The main mechanism may be an aberrant immune response. First, in neither of our 2 patients did we detect SARS-Cov-2 in the CSF, suggesting that virus may not be directly encephalogenic. Second, patients infected with SARS-Cov-2 may show increased levels of plasma proinflammatory cytokines that could be involved in the damage induced by SARS-Cov-2.¹⁵ Third, serum anti-GD1b-IgG antibody can be detected in Miller Fisher syndrome,¹⁶ and was positive in the first patient, supporting the hypothesis of immune-mediated injury rather than direct viral neurotropism. Most patients with Miller Fisher syndrome show anti-GQ1b positivity; however, antibodies to GD1b have been associated with a faster recovery.¹⁶ Finally, there was a significant recovery of the neurologic deficit with the use of IV immunoglobulin in the first patient. In this sense,

immunotherapy with IV immunoglobulin could be used to neutralize the SARS-Cov-2 infection. Its efficacy would be much improved if the immune IgG antibodies were collected from patients who have recovered from SARS-Cov-2 infection in the surrounding area, in order to increase the chance of neutralizing the virus.¹⁷

The main limitation of each of the cases was the absence of electromyography and nerve conduction studies as well as MRI (to detect nerve enhancement). The reason for this was the extreme circumstances in our hospitals at the peak of this pandemic.

We describe 2 patients with COVID-19 with Miller Fisher syndrome and polyneuritis cranialis who had good outcomes. We suggest considering the presence of SARS-CoV-2 infection in patients with Miller Fisher syndrome or with polyneuritis cranialis in the setting of the current pandemic. These neurologic manifestations may occur because of an aberrant immune response to SARS-CoV-2. The full clinical spectrum of patients with COVID-19 with neurologic symptoms remains to be characterized.

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Disclosure

C. Gutiérrez-Ortiz, A. Méndez-Guerrero, S. Rodrigo-Rey, E. San Pedro-Murillo, L. Bermejo-Guerrero, R. Gordo-Mañas, and F. de Aragón-Gómez report no relevant disclosures. J. Benito-León is supported by the NIH (National Institute of Neurological Disorders and Stroke #R01 NS39422), European Commission (grant ICT-2011-287739, NeuroTREMOR), the Ministry of Economy and Competitiveness (grant RTC-2015-3967-1, NetMD—platform for the tracking of movement disorder), and the Spanish Health Research Agency (grants FIS PI12/01602 and FIS PI16/00451). Go to Neurology.org/N for full disclosures.

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Appendix (continued)

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