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## **Miller Fisher Syndrome and polyneuritis cranialis in COVID-19**

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## **Abstract**

**Objective:** To report two patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) who acutely presented 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, Madrid, Spain and from the University Hospital “12 de Octubre”, Madrid, Spain.

**Results:** The first patient was a 50-year-old man who presented with anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, albuminocytologic dissociation and positive testing for GD1b-IgG antibodies. Five days before, he had developed a cough, malaise, headache, low back pain, and a fever. The second patient was a 39-year-old man who presented with ageusia, bilateral abducens palsy, areflexia and albuminocytologic dissociation. Three days before, he had developed diarrhea, a low-grade fever, and a poor general condition. The oropharyngeal swab test for coronavirus disease 2019 (COVID-19) by qualitative real-time reverse-transcriptase–polymerase-chain-reaction assay was positive in both patients and negative in the cerebrospinal fluid. The first patient was treated with intravenous immunoglobulin and the second, with acetaminophen. Two weeks later, both patients made a complete neurological recovery, except for residual anosmia and ageusia in the first case.

**Conclusions:** Our two cases highlight the rare occurrence of Miller Fisher syndrome and polyneuritis cranialis during the COVID-2 pandemic. Neurological manifestations may occur because of an aberrant immune response to COVID-19. The full clinical spectrum of neurological symptoms in patients with COVID-19 remains to be characterized.

Coronavirus belongs to a family of single-stranded RNA viruses,<sup>1</sup> which includes the severe acute respiratory syndrome coronavirus (SARS-CoV)<sup>2</sup> and the Middle East respiratory syndrome coronavirus (MERS-CoV).<sup>3</sup> A new coronavirus, SARS-CoV-2, has rapidly spread 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 the coronavirus disease 2019 (COVID-19) ranges from asymptomatic infection to severe respiratory failure; fever, cough, fatigue, sputum production, shortness of breath, myalgias or arthralgias, and sore throat are among its most common manifestations.<sup>4</sup> Other less common features, such as gastrointestinal (e.g., diarrhea, nausea, and vomiting) or even neurological manifestations (e.g., headache) have also been reported. In addition, other neurological symptoms such as anosmia and ageusia are presented by many patients.<sup>5</sup> However, the knowledge of the clinical features and pathogenesis of COVID-19 still needs to be elucidated. Specifically, the exact nature and mechanism of COVID-19-induced neurological manifestations largely remains unknown. In this sense, different neurological complications have been reported with its predecessors. The SARS-CoV was occasionally associated with the development of different neurological manifestations including axonopathic polyneuropathy, myopathy, rhabdomyolysis and large artery ischemic stroke, among others.<sup>6</sup> During or after MERS-CoV treatment, Bickerstaff's encephalitis overlapping with Guillain-Barré syndrome, intensive-care-unit-acquired weakness, or other toxic or infectious neuropathies have been reported.<sup>7</sup>

We herein report two patients infected with SARS-CoV-2 who acutely presented

with Miller Fisher syndrome and polyneuritis cranialis, respectively

## **METHODS**

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

### ***Standard Protocol Approvals, Registrations, and Patient Consents***

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

### ***Data Availability***

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

## **RESULTS**

***Patient 1.*** A 50-year-old man was admitted to the emergency room of the University Hospital “12 de Octubre”, Madrid, because of a 2-day history of vertical diplopia, perioral paraesthesias and gait instability. His past 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 the presence of 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 of 98%). Pulmonary and cardiac auscultation and abdominal examination were also unremarkable.

The neurological examination revealed that cognitive function and language were intact. He 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 and heel-to-shin tests. Muscle stretch reflex examination revealed absent deep tendon reflexes in the upper and in the lower limbs. The plantar responses were flexor bilaterally. The neuro-ophthalmological 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. His 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.

The blood work-up revealed lymphopenia (1000 cells/ul) and elevated C-reactive protein (2.8 mg/dl). The antibodies to gangliosides (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and anti-sulfatide antibodies) in the serum were examined. He was only positive to the antibody GD1b-IgG. The patient's oropharyngeal swab test for COVID-19 by qualitative real-time reverse-transcriptase–polymerase-chain-reaction (rRT-PCR) assay was positive. The cerebrospinal fluid (CSF) examination revealed an opening pressure of 11 cm of H<sub>2</sub>O, white blood cell count = 0/μl, protein = 80 mg/dl, glucose = 62 mg/dl, with normal cytology, sterile cultures and negative serologies, including the rRT-PCR for COVID-19. Chest X-ray and head computerized tomography without contrast were normal.

He was treated with intravenously administered immunoglobulin 0.4 g/kg for 5 days starting on the fifth day of his neurological symptoms. The cranial neuropathies and the

ataxia improved significantly over the succeeding days and he was discharged home two weeks after admission, with a resolution of the neurological features, except for residual anosmia and ageusia.

**Patient 2.** A 39-year-old man was admitted to the emergency room of the University Hospital “Príncipe de Asturias”, Alcalá de Henares, Madrid because of acute onset diplopia. His past medical history was unremarkable. Three days before, 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 the presence of ageusia. On examination, his body temperature was 96.3°F, pulse 74, blood pressure 125/72 mmHg and basal oxygen saturation 98%. Respiratory, cardiovascular, and abdominal examinations were also normal. On neurological examination, the patient was conscious, alert and well oriented to time, place, and person. The neuro-ophthalmological examination revealed visual acuity of 20/25 in both eyes. The anterior poles, intraocular pressure, and the 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 neurological 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 (3100 cells/ul). The patient’s oropharyngeal swab test for COVID-19 by qualitative rRT-PCR assay was

positive. The CSF examination revealed an opening pressure of 10 cm H<sub>2</sub>O, white blood cell count = 2/ $\mu$ l (all monocytes), protein = 62 mg/dl, glucose = 50 mg/dl, with normal cytology, sterile cultures and negative serologies, including the rRT-PCR for COVID-19. Chest X-ray and head computerized tomography without contrast were normal.

The patient was discharged home and treated symptomatically with acetaminophen and telemedicine monitoring due to a complete hospital saturation with COVID-19 patients. The anti-ganglioside antibody profile could not be performed because of the aforementioned hospital saturation. At the next consultation, two weeks later, he had made a complete neurological 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 coronavirus may also be applicable for SARS-CoV-2. Specifically, the human receptor for SARS-Cov-2 may be angiotensin-converting enzyme 2 receptor, similar to that of SARS-CoV.<sup>8</sup> A growing body of evidence shows that neurotropism is one common feature of coronavirus.<sup>9</sup> Animal models show that SARS-CoV and MERS-CoV might enter the brain, possibly via the olfactory nerves, and thereafter rapidly spread to specific brain areas including the thalamus and brainstem.<sup>9</sup> This might explain the complaints of anosmia of many patients infected by SARS-Cov-2.<sup>5</sup> Furthermore, inflammatory or immune-associated-molecules, such as cytokines, that are detected in COVID-19 infected patients, may affect the taste buds and hence cause ageusia.<sup>10</sup> Notwithstanding, an understanding of the exact mechanism of coronavirus-induced neurological 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 one patient with COVID-19 infection who had a Miller Fisher syndrome as an unusual initial neurological manifestation. The second patient did not, however, have classic Miller Fisher syndrome, but polyneuritis cranialis (or isolated multiple cranial neuropathy) that spontaneously and rapidly improved. There are however incomplete forms of Miller Fisher, 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.<sup>11</sup> Nevertheless, polyneuritis cranialis may be a separate subtype altogether, which lies at the interface between Miller Fisher syndrome and Guillain-Barré syndrome.<sup>12</sup>

Miller Fisher syndrome has been shown to be preceded by infections similar to those preceding Guillain-Barré syndrome, suggesting a para- or postviral process. Haemophilus influenzae, Campylobacter jejuni and cytomegalovirus are the most common pathogens involved.<sup>13</sup> However, to the best of our knowledge, Miller Fisher syndrome has not been reported associated to the SARS-Cov-2. The occurrence of Miller Fisher syndrome and polyneuritis cranialis in these two patients with the SARS-CoV-2 infection could be simply coincidental. However, taking into account the temporal relationship, we feel that COVID-19 might have been responsible for the development of these two neurological 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.<sup>14</sup>

The pathogenesis of Miller Fisher syndrome and polyneuritis cranialis in a COVID-19 infection may include immune mechanisms or direct viral neuropathogenic effects. We think that the main mechanism was an aberrant immune response. First, in neither of our

two 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 pro-inflammatory cytokines that could be involved in the damage induced by SARS-Cov-2.<sup>15</sup> Third, serum GD1b-IgG antibodies can be detected in Miller Fisher syndrome,<sup>16</sup> and were positive in the first patient, supporting the hypothesis of immune-mediated injury rather than direct viral neurotropism. Most patients with Miller Fisher syndrome show GQ1b positivity; however, antibodies to GD1b have been associated with a faster recovery.<sup>16</sup> Finally, there was a significant recovery of the neurological deficit with the use of intravenous immunoglobulin therapy in the first patient. In this sense, immunotherapy with intravenous immunoglobulin could be used to neutralize the SARS-Cov-2 infection. However, its efficacy would be much better 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.<sup>17</sup>

We recognize that the main limitations of each one of the cases was the absence of electromyography and nerve conduction studies as well as magnetic resonance imaging (to detect nerve enhancement). The reason for this was the extreme circumstances in our hospitals at the peak of this pandemic.

In conclusion, we describe two patients with COVID-19 with Miller Fisher syndrome and polyneuritis cranialis, respectively, who had good outcomes. We suggest considering the presence of a COVID-19 infection in those patients with Miller Fisher syndrome or with polyneuritis cranialis in the setting of the current pandemic. Neurological manifestations may occur because of an aberrant immune response to COVID-19. At present, the full clinical spectrum of patients with COVID-19 with neurological symptoms remains to be characterized.

## APPENDIX 1. AUTHORS

Name	Location	Contribution
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Antonio Méndez, MD	Department of Neurology, University Hospital “12 de Octubre”, Madrid, Spain	Conception, organization and execution of the research project; writing of the first draft and the review and critique of the manuscript
Sara Rodrigo-Rey, MD	Department of Glaucoma and Neuro-Ophthalmology, University Hospital “Príncipe de Asturias”, Alcalá de Henares, Madrid, Spain	Conception and organization of the research project; review and critique of the manuscript
Eduardo San Pedro-	Department of Neurology,	Conception and

Murillo, MD	University Hospital "12 de Octubre", Madrid, Spain	organization of the research project; review and critique of the manuscript
Laura Bermejo-Guerrero, MD	Department of Neurology, University Hospital "12 de Octubre", Madrid, Spain	Conception and organization of the research project; review and critique of the manuscript
Ricardo Gordo-Mañas, MD	Department of Neurology, University Hospital "Príncipe de Asturias", Alcalá de Henares, Madrid, Spain	Conception and organization of the research project; review and critique of the manuscript
Fernando de Aragón-Gómez, MD	Department of Glaucoma and Neuro-Ophthalmology, University Hospital "Príncipe de Asturias", Alcalá de Henares, Madrid, Spain	Conception and organization of the research project; review and critique of the manuscript
Julián Benito-León, MD, PhD	Department of Neurology, University Hospital "12 de Octubre", Madrid, Spain; Centro de Investigación Biomédica en Red sobre Enfermedades	Conception, organization, and execution of the research project; writing of the manuscript first draft and the review and critique of the manuscript

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