


# COVID-19 Induced Miller Fisher Syndrome Presenting With Autonomic Dysfunction: A Unique Case Report and Review of Literature

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## Abstract

A plethora of neurological manifestations are associated with the 2019 coronavirus infectious disease (COVID-19). We hereby report the first case of a patient infected with SARS-CoV-2 who acutely presented with autonomic dysfunction preceding the onset of complete clinical picture of Miller Fisher syndrome. She was finally diagnosed to be a case of anti-ganglioside antibody positive post-COVID-19 Miller Fisher syndrome with dysautonomia and treated with intravenous immunoglobulin with an excellent response. We also discuss the plausible pathogenic mechanisms of COVID-19 induced Miller Fisher syndrome and furnish a review of the post-COVID-19 Miller Fisher syndrome cases reported.

## Keywords

Autonomic dysfunction, COVID-19, Miller Fisher syndrome (MFS), SARS-CoV-2

## Introduction

A plethora of neurological manifestations are associated with the 2019 coronavirus infectious disease (COVID-19).<sup>1</sup> Apart from central nervous system manifestations, Guillain–Barré syndrome and its variants are considered as the most common peripheral nervous system disorders in COVID-19.<sup>2–4</sup> Dysautonomia has also been reported as an emerging complication of COVID-19.<sup>4</sup> Amidst the spectrum of Guillain–Barré syndrome, only a few cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced Miller Fisher syndrome (MFS) have been reported.<sup>3,5–14</sup> On the other hand, autonomic dysfunction preceding the development of full blown MFS is exceedingly rare,<sup>15</sup> unlike other variants of Guillain–Barré syndrome.

We hereby report a unique case of a patient infected with SARS-CoV-2 who acutely presented with autonomic dysfunction. She was finally diagnosed to be a case of anti-ganglioside antibody positive post-COVID-19 MFS with dysautonomia and treated with intravenous immunoglobulin with an excellent response. We have also discussed the plausible pathogenic mechanisms of COVID-19 induced MFS and furnish a review of literature of the post-COVID-19 MFS cases reported.

## Case Presentation

A 55-year-old woman presented to the emergency department with history of intermittent extreme dizziness, excessive dryness of mouth, squeezing sensation in central chest, recent-

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onset constipation and excessive sweating, for last six days. This was followed by sudden onset unsteadiness of gait, double vision, and “pins and needles” sensation over bilateral fingertips, distal legs and circumoral areas. Her past medical history was unremarkable except that 15 days prior to admission, she had suffered from COVID-19, but as the symptoms had been mild, she was advised to stay in vigilant home isolation without any specific therapy. General systemic examination was remarkable for slight nasal intonation, tachycardia (108 bpm) and arterial hypertension (supine blood pressure was 178/92 mm of Hg) and postural hypotension (blood pressure after standing from supine position for 3 minutes was 136/74 mm of Hg and heart rate was 114 bpm). Respiratory rate and room-air oxygen saturation were normal. Emergency electrocardiographic monitoring revealed absence of respiratory sinus arrhythmia without any signs of ischemic changes or high degree atrio-ventricular block. Urgent cardiac troponins tested by kit were negative. Neurological examination revealed normal cognitive functions, hyposmia, bilateral symmetrical abducens palsy, generalized areflexia, broad-based ataxic gait, and autonomic dysfunction as demonstrated by Valsalva manoeuvre (Valsalva ratio <1.2), absence of reflex blood pressure changes, abnormally decreased heart rate variability with respiration (5 bpm) and posture change (30:15 ratio <1), inadequate rise of blood pressure, nearly fixed heart rate during isometric handgrip exercise and abnormal bedside thermoregulatory sweat testing. Motor strength, sensory system and most of cerebellar functions (except broad-based ataxic gait) were normal. Visual acuity, pupillary reflexes, color perception, intraocular pressures and fundoscopic examination were otherwise normal. No ptosis, orbicularis weakness or diurnal variations were noted. Signs of meningeal irritation were absent.

Complete blood cell count revealed neutrophilic leucocytosis and lymphopenia. Thyroid, hepatic and renal function tests were normal. Pre-prandial and post-prandial plasma glucose levels were also normal. Serologies for hepatitis B, C, HIV (1, 2), *Campylobacter jejuni*, Cytomegalovirus, *Haemophilus influenzae* and Epstein Barr virus were all negative. Cerebrospinal fluid analysis revealed albuminocytologic dissociation (white blood cell count = 3/ $\mu$ l and protein = 245 mg/dl). Serum ganglioside antibody profile by immunoblot method revealed positive results for anti-GQ-1b-IgG and anti-GD-1b-IgG. Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain and spinal cord as well as computed tomography scan of the thorax revealed no abnormalities. The electromyography study of both abductor pollicis brevis, adductor digiti minimi, first dorsal interosseous, extensor digitorum communis, biceps brachii, triceps brachii, deltoids, extensor digitorum brevis, tibialis anterior, medial gastrocnemius, rectus femoris and vastus medialis was normal. Sensory and motor nerve conduction studies, F waves, and H reflexes were otherwise normal. In addition, on repetitive stimulation, no decremental or incremental response was observed.

Based on the Brighton criteria,<sup>16</sup> the diagnosis of MFS was established with level 1 of diagnostic certainty. She was treated with intravenous immunoglobulin 0.4 g/kg/day for five days on the third day of hospital stay. The cranial neuropathies and the ataxia improved significantly over the succeeding days and she was discharged home three weeks after admission, with a resolution of the neurological features, except generalized hyporeflexia.

## Discussion

Modern medicine is facing the evolution of COVID-19 over one year and has acquainted with several neurological conditions involving the entire cranio-spinal axis,<sup>1</sup> caused by a primary respiratory pathogen. Spectrum of neurological disorders encompass central,<sup>1,17</sup> peripheral<sup>2-4</sup> and autonomic nervous systems.<sup>4</sup> To date, nearly 80 cases of Guillain-Barré syndrome spectrum have been reported.<sup>2</sup> Among these, MFS has been expectedly reported on rare occasions (Table 1).<sup>3,5-14</sup> In the six out of 12 reported cases, including the current one, the neurological symptoms started two weeks after the onset of first symptoms of COVID-19 and in the remaining, the gap was typically less than five days.<sup>3,5-13</sup> Most the patients responded favourably to intravenous immunoglobulin with minimal or no persisting neurological deficits.<sup>3,5-13</sup> Only one patient died unexpectedly.<sup>14</sup> Classical albuminocytologic dissociation in cerebrospinal fluid analysis was found in seven out of 12 cases, meanwhile in the rest of them, three had normal findings and, in two cases, it was not reported.<sup>3,5-14</sup> Contrast-enhanced neuroimaging was available in 10 out of 12 cases,<sup>5,6,8-11,13,14</sup> in three patients, cranial, peripheral nerve root or radicular thickening, suggestive of leptomeningeal invasion by the virus or immune mediated radiculitis, was found.<sup>5,9,10</sup> Search for viral RNA in cerebrospinal fluid was reported only in five out of 12 cases and those conveyed negative results,<sup>3,11,12,14</sup> but one which was positive.<sup>13</sup> Eleven out of 12 patients were tested for anti-ganglioside antibodies,<sup>3,5,6,8-14</sup> of whom five had a positive result, including the current case.<sup>3,5,10,13</sup>

The pathogenesis of MFS following SARS-CoV-2 infection may be either mediated by neurotropism or by aberrant immune mediated injury, the latter being the most likely. Specifically, there are several pieces of evidence to support an aberrant immune mediated injury. First, the gap between the onset of first COVID-19 symptoms and the first neurological symptoms was in most cases more than two weeks, which may be suggestive of a post-infectious autoimmune process. Second, as seen in most cases of previously reported COVID-19 induced Guillain-Barré syndrome spectrum,<sup>2</sup> the cerebrospinal fluid was devoid of virus itself or its RNA, similarly to the cases of MFS.<sup>3,11,12,14</sup> This suggests that there is no intrathecal viral replication or direct neuroinvasion. Third, spectrum of Guillain-Barré syndrome, that also includes MFS, is a prototype for post-infectious immune-mediated neuropathy with known infectious triggers (i.e., *Campylobacter jejuni*, enterovirus, hepatitis virus, Zika virus, *Haemophilus influenzae*,

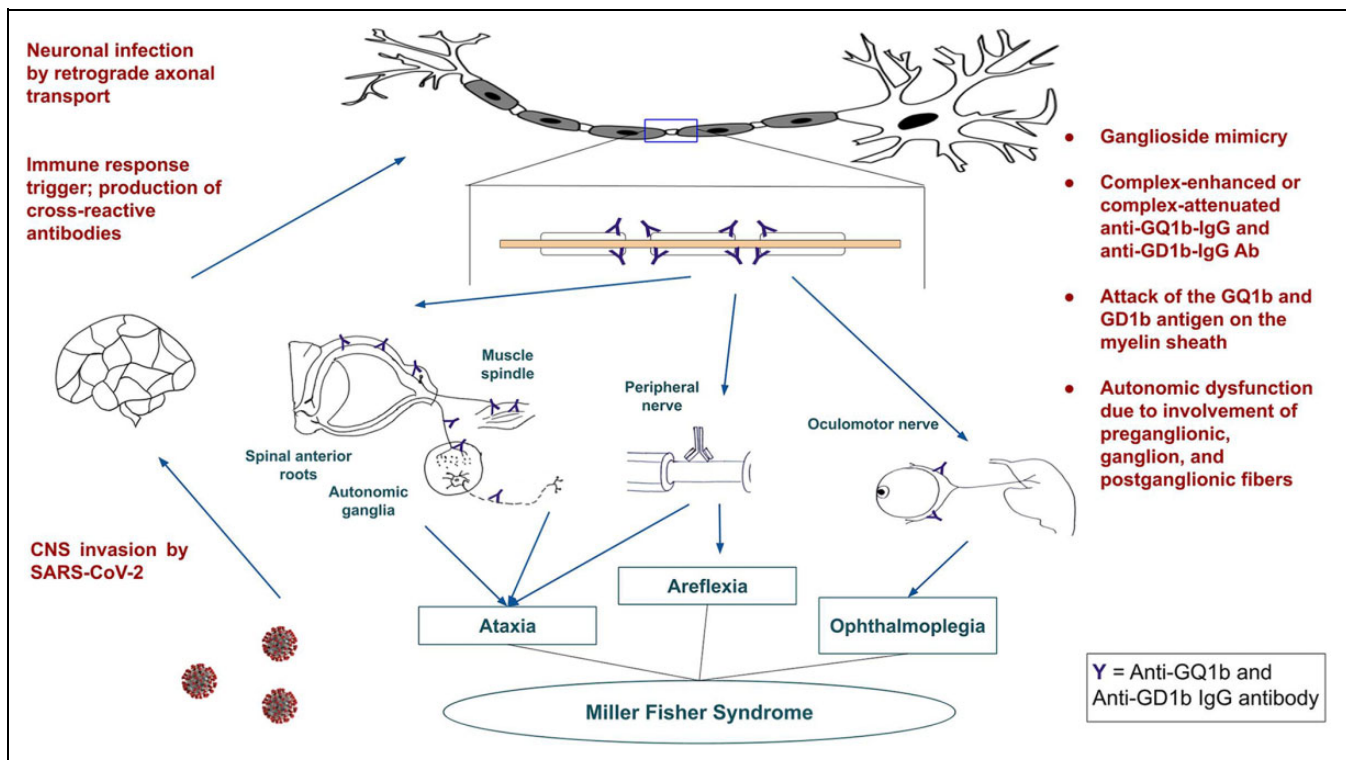
**Table 1.** Clinical Profile of Reported Patients With Post-COVID-19 Miller Fisher Syndrome.

| Author(s) | Age/<br>sex | Neurological findings  | Gap from the<br>COVID-19<br>onset (in days) | EMG/Nerve<br>conduction studies                        | Neuroimaging  | SARS-CoV-2<br>in cerebrospinal<br>fluid | Anti-ganglioside<br>antibody testing | Specific therapy              | Outcome                                  |
|-----------|-------------|--|---|--|---|---|--------------------------------------|-------------------------------|--|
| 3         | 50/M        | Anosmia, ageusia,<br>internuclear<br>ophthalmoparesis,<br>right fascicular<br>oculomotor palsy<br>ataxia and areflexia   | 5   | Not reported   | Normal unenhanced CT<br>scan of the brain   | Negative                                | Positive (anti-<br>GD1b-IgG)         | Intravenous<br>immunoglobulin | Resolution<br>within two<br>weeks        |
| 5         | 36/M        | Left eye drooping, blurry<br>vision, reduced<br>sensation, paresthesia<br>in both legs to all<br>modalities below knee<br>level, partial left third<br>nerve, bilateral sixth<br>nerve palsy and<br>areflexia  | 4   | Not reported   | Enlargement and T2<br>hyperintensity, and<br>enhancement of the<br>affected third cranial<br>nerve from the<br>cavernous sinus<br>through the orbit on<br>MRI | Not reported                            | Positive                             | Intravenous<br>immunoglobulin | Resolution after<br>one week             |
| 6         | 51/F        | Intense root-type pain in<br>all four limbs, dorsal<br>and lumbar back pain,<br>weakness in her lower<br>limbs, double<br>binocular vision (left<br>sixth cranial nerve<br>palsy), bilateral facial<br>paresis, symmetrical<br>paraparesis, global<br>areflexia and<br>autonomic dysfunction | 15  | Guillain-Barre type<br>demyelinating<br>polyneuropathy | Normal  | Not reported                            | Negative                             | Intravenous<br>immunoglobulin | Progressive<br>improvement               |
| 7         | 63/M        | Perioral and fingertips<br>paresthesias, diplopia,<br>divergent squint,<br>areflexia and ataxic gait   | 1   | Not reported   | Not reported  | Not reported                            | Not reported                         | Intravenous<br>immunoglobulin | Self-limiting<br>illness                 |
| 8         | 50/F        | Ataxia, ophthalmoplegia,<br>left upper arm<br>cerebellar dysmetria,<br>generalized areflexia,<br>mild lower facial<br>defects and mild<br>hypoesthesia over face   | 16  | Not reported   | Normal  | Not reported                            | Negative                             | Intravenous<br>immunoglobulin | Complete<br>resolution<br>within 14 days |

(continued)

Table 1. (continued)

| Author(s)    | Age/<br>sex | Neurological findings   | Gap from the<br>COVID-19<br>onset (in days) | EMG/Nerve<br>conduction studies    | Neuroimaging  | SARS-CoV-2<br>in cerebrospinal<br>fluid | Anti-ganglioside<br>antibody testing | Specific therapy  | Outcome   |
|--------------|-------------|---|---|------------------------------------|---|---|--------------------------------------|---|---|
| 9            | 36/M        | Partial left oculomotor palsy, bilateral abducens palsies, lower limbs hyporeflexia, hypoesthesia and gait ataxia | 4   | Not reported                       | Enhancement and T2-hyperintensity and enlargement of the left oculomotor nerve on MRI | Not reported                            | Negative                             | Intravenous immunoglobulin                                      | Partially complete resolution   |
| 10           | 45/M        | Ataxia, ophthalmoplegia, areflexia and tetraparesis   | 16  | Not reported                       | Intrathecal caudal-equina enhancement on MRI  | Not reported                            | Positive                             | Intravenous immunoglobulin                                      | During report writing still needed respiratory support. Partially improvement of neurological picture |
| 11           | 74/F        | Lower limbs areflexia with patent gait ataxia   | 15  | Slight F-wave delay in upper limbs | Normal MRI  | Negative                                | Negative                             | Intravenous immunoglobulin                                      | Improved  |
| 12           | 61/M        | Ophthalmoplegia, generalized areflexia and sensory ataxia   | 20  | F-wave was not detectable          | Not reported  | Negative                                | Negative                             | Intravenous immunoglobulin                                      | Improved  |
| 13           | 31/F        | Ophthalmoplegia, ataxia, areflexia and dysmetria  | 3   | Not reported                       | Normal  | Positive                                | Positive                             | Convalescent plasma, tocilizumab and intravenous immunoglobulin | Mild improvement  |
| 14           | 50/M        | Dysmetria, dysidiadochokinesia and absent upper limbs reflexes  | 1   | Not performed                      | Normal  | Negative                                | Negative                             | Intravenous immunoglobulin                                      | Some improvement, before developing ventricular arrhythmia and cardiac arrest unexpectedly.           |
| Current case | 55/F        | Dysautonomia, ataxia, ophthalmoplegia, areflexia, and paresthesias involving perioral areas and fingers/toes      | 15  | Normal                             | Normal MRI  | Not reported                            | Positive                             | Intravenous immunoglobulin                                      | Complete resolution, except generalized hyporeflexia  |



**Figure 1.** Proposed pathogenic pathway for the development of Miller Fisher syndrome in COVID-19.

H1N1 virus, West Nile virus, SARS-CoV, and MERS-CoV, among others).<sup>18</sup> Fourth, in a few cases of post-COVID-19 MFS, antibodies against ganglioside comprising of disialosyl moiety (i.e., GQ-1b, GD-1b and GT-1b) were detected.<sup>3,5,10,13</sup> Fifth, apart from ACE-2 receptors, there is robust evidence that SARS-CoV-2 also uses sialic-acid containing gangliosides/glycoproteins on cell surfaces.<sup>19</sup> Hence, cross-reactivity and molecular mimicry between SARS-CoV-2 antigenic (spike proteins) epitopes and carbohydrate moieties of surface cranial nerve glycoproteins may bring about immune-driven neuropathy in COVID-19 induced MFS.<sup>19</sup> Finally, last but not the least, dramatic response to intravenous immunoglobulin in all cases of MFS points towards an underlying immune driven process. On the other hand, direct neurotropism as a pathogenic process did not lie far behind. First, unlike rapidly reversible anosmia/hyposmia and ageusia/dysgeusia following viral infection to non-neural olfactory epithelial cells, in COVID-19 patients, anosmia/hyposmia tends to persist longer, implying this to be a result of viral neurotropism targeting olfactory neurons.<sup>20</sup> Second, gaining access to the olfactory bulb and later to the brainstem cranial nuclei may ensue in COVID-19 similarly to SARS-CoV infection in animal models.<sup>20</sup> Specifically, SARS-CoV can also enter the central nervous system via retrograde axonal transport through branches of trigeminal and glossopharyngeal nerves widely spread in oro-nasal cavity, corneal plexus and peripheral nerves.<sup>20</sup> The finding of enhancement and thickening of cranial nerve roots and peripheral nerve radicles in three cases of SARS-CoV-2 induced MFS

further supports this notion.<sup>5,9,10</sup> Theoretically, in the upcoming years, direct viral neurotropism might also catch attention as an additional pathogenic mechanism for SARS-CoV-2 induced MFS.

Figure 1 shows our proposed pathogenic pathway for the development of MFS in COVID-19. SARS-CoV-2 could gain entry to the central nervous system through retrograde axonal transport. Thereafter, it could affect the myelin sheath through ganglioside mimicry. The antibodies formed could be either complex-enhanced or complex-attenuated anti-GQ1b-IgG or anti-GD1b-IgG antibodies acting against the GQ1b and GD1b antigens in the myelin sheath. This in turn may cause the characteristic triad of areflexia, ataxia and ophthalmoplegia in MFS.

The main limitation of our case was that we could not search for viral RNA of SARS-CoV-2 in cerebrospinal fluid because of the extreme circumstances in our hospitals at this pandemic.

## Conclusions

Surveillance is needed to detect and manage COVID-19 associated immune-driven disorders. For cases of likely SARS-CoV-2 induced MFS, anti-ganglioside antibodies, along with targeted high-resolution contrast enhancing MRI, should be done to muster more information regarding natural history and pathogenesis of the disease. To improve outcome, facilitate early recovery and lessen the hospital stay, intravenous immunoglobulin should be initiated as soon as possible. Our case adds to the tally of novel cases of post-SARS-CoV-2 infection



related neurological manifestations as well as to the exceedingly rare list of cases in whom frank autonomic dysfunction preceded the fully developed clinical triad of MFS.

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### Authors' Note

Written informed consent was obtained from the patient participating in the study (consent for research). Informed written consent was obtained from the patient involved in this study.


### Declaration of Conflicting Interests


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