Miller Fisher Syndrome in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A Systematic Review

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**Background and Purpose** Miller Fisher syndrome (MFS) is a subtype of Guillain-Barré syndrome characterized by the triad of ophthalmoparesis, areflexia, and ataxia. Although cases of MFS have been associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, no studies have synthesized the clinical characteristics of patients with this condition.

**Methods** In this rapid systematic review, we searched the PubMed database to identify studies on MFS associated with SARS-CoV-2 infection.

**Results** This review identified 11 cases, of whom 3 were hospitalized with motor and/or sensory polyneuropathy as the first sign of SARS-CoV-2 infection. SARS-CoV-2 RNA was not detected in analyses of cerebrospinal fluid, suggesting a mechanism of immune-mediated injury rather than direct viral neurotropism. However, antiganglioside antibodies were found in only two of the nine patients tested. It is possible that target antigens other than gangliosides are involved in MFS associated with SARS-CoV-2 infection.

**Conclusions** The present patients exhibited clinical improvement after being treated with intravenous immunoglobulin. Although rare, patients with SARS-CoV-2 infection may present neurological symptoms suggestive of MFS. Early recognition of the MFS clinical triad is essential for the timely initiation of treatment.

**Keywords** coronavirus disease 2019; severe acute respiratory syndrome coronavirus 2; Guillain-Barré syndrome; Miller Fisher syndrome.

INTRODUCTION

Miller Fisher syndrome (MFS) is recognized as a rare variant of Guillain-Barré syndrome (GBS) and defined by the acute onset of the triad of ophthalmoparesis, areflexia, and ataxia. There is evidence of MFS being preceded by infections similar to those preceding GBS. Cases of MFS have recently been linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which is the causal agent of coronavirus disease 2019 (COVID-19), but no studies have synthesized the characteristics of patients with this condition, which is critical for clinical practice. Here we systematically describe the clinical features of MFS in patients with COVID-19.

METHODS

In this rapid systematic review, we searched the PubMed database to identify studies of cases of MFS associated with SARS-CoV-2 infection. We included studies provided clinical...
data and information on neurological examinations, cerebrospinal fluid (CSF) analyses, and antiganglioside antibody tests. We excluded cases in which SARS-CoV-2 infection was not confirmed using a polymerase chain reaction test.

Reports were screened in two stages: 1) screening of titles and Abstracts, followed by 2) the retrieval and screening of full-text articles. PubMed was searched from January 1, 2020 up to January 30, 2021, without language restrictions. The reference lists for all eligible studies and reviews were also evaluated to identify additional studies for inclusion. We used the following search strategy for primary studies: (“Miller Fisher Syndrome” [MeSH] OR “Fisher Syndrome” OR “Miller-Fisher”) AND (LitCGeneral [Filter]). Data were extracted from publications by two authors and cross-checked for accuracy. The results were collated in a descriptive manner.

RESULTS

After screening 44 titles and Abstracts, 12 full-text articles were assessed for eligibility, resulting in the exclusion of 3 studies. Two additional studies were identified from the reference lists, and finally 11 studies with case-report designs were included in this review (Fig. 1). The patients were aged from 31 to 74 years (median 51 years) and most of them were male (n=8, 73%). In three (27%) cases, patients were hospitalized with acute motor or sensory polyneuropathy as the first sign of SARS-CoV-2 infection. Two of these patients presented paresthesia without motor weakness, and the third reported upper-limb weakness without sensory symptoms. In the remaining cases (75%), neurological manifestations were reported up to 3 weeks after typical COVID-19 symptoms (Table 1).

The most common neurological feature was hyporeflexia or areflexia (100%), followed by ataxia (91%), ophthalmoplegia/diplopia (82%), sensory symptoms (73%), weakness of facial muscles (55%), and eyelid ptosis (36%). Magnetic resonance imaging was performed for nine patients, but only one (11%) case presented alterations, which were...
characterized by enhanced T2-weighted hyperintensity and enlargement of the oculomotor nerve. Neurophysiological studies were performed in five patients,4,9,12,15,16 with acute inflammatory demyelinating polyneuropathy diagnosed in four (80%) of them.9,12,15,16 CSF investigations were described for nine patients,3-5,9-13,16 which revealed albuminocytological dissociation in most cases (78%).3-5,9,11-13 The CSF analyses did not produce any positive results for SARS-CoV-2 RNA. A ganglioside antibody panel was explored for nine patients,3,4,8-13,16 with the presence of anti-GD1b and anti-GQ1b found in only two (22%) cases. Ten (91%) patients were treated with intravenous immunoglobulin (IVIg), which resulted in clinical improvement in nine patients; the tenth patient11 died of ventricular arrhythmia as manifestation of dysautonomia 2 weeks after the onset of neurological manifestations. One patient did not receive any pharmacological treatment (Table 2).

DISCUSSION

Neurological manifestations are common in COVID-19 and they may represent the only disease symptom.17 There is a potential association between SARS-CoV-2 infection and neurological symptoms, but the underlying biological mechanisms remain poorly defined.14 It was recently found that angiotensin-converting enzyme 2 may be expressed in neurons, astrocytes, oligodendrocytes, and the olfactory bulb, which is critical for SARS-CoV-2 cellular tropism in humans.19 There is increasing evidence of the neuroinvasivity of SARS-CoV-2 in postmortem examinations,20,21 and the viral RNA detection in CSF samples from patients with meningitis and

Table 1. COVID-19 symptoms and the onset of neurological manifestations in patients with Miller Fisher syndrome

| Study                      | Country | Age (yr) | Sex | COVID-19 symptoms               | Onset of neurological manifestations                                      |
|----------------------------|---------|----------|-----|---------------------------------|----------------------------------------------------------------------------|
| Kopschik et al.10          | USA     | 31       | M   | None                            | No respiratory symptoms; neurological symptoms were the first sign of SARS-CoV-2 infection |
| Kajani et al.11            | USA     | 50       | M   | None                            | No respiratory symptoms; neurological symptoms were the first sign of SARS-CoV-2 infection |
| Manganotti et al.13        | Italy   | 50       | F   | Fever, cough, dyspnea, and ageusia | 2 weeks after respiratory symptoms (10 days)                               |
| Rana et al.15              | USA     | 54       | M   | Fever, chills, odynophagia, rhinorrhea, and dyspnea | 2 weeks after respiratory symptoms (14 days)                               |
| Assini et al.16            | Italy   | 55       | M   | Fever, cough, anosmia, and ageusia | 3 weeks after respiratory symptoms (20 days)                               |
| Dinkin et al.8             | USA     | 36       | M   | Fever and cough                  | During the first week of respiratory symptoms (4 days)                     |
| Fernández-Domínguez et al.4| Spain   | 74       | F   | Bilateral pneumonia             | 2 weeks after respiratory symptoms (12–15 days)                           |
| Senel et al.9              | Germany | 61       | M   | Fever and mild breathing difficulties | 3 weeks after respiratory symptoms (20 days)                               |
| Reyes-Bueno et al.12       | Spain   | 51       | F   | Cough, odynophagia, and diarrhea  | 2 weeks after respiratory symptoms (15 days)                               |
| Gutiérrez-Ortiz et al.3    | Spain   | 50       | M   | Cough, headache, musculoskeletal pain, fever, anosmia, and ageusia | During the first week of respiratory symptoms (7 days)                     |
| Ray5                       | UK      | 63       | M   | Fever                            | No respiratory symptoms; neurological symptoms were the first sign of SARS-CoV-2 infection |

COVID-19, coronavirus disease 2019; F, female; M, male; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Clinical, laboratory, and neuroimaging findings for patients with Miller Fisher syndrome

| Neurological complication | Value (n=11) |
|---------------------------|--------------|
| Hyporeflexia/areflexia    | 11 (100.0)   |
| Ataxia                    | 10 (90.9)    |
| Extraocular muscle paresis| 9 (81.8)     |
| Diplopia                  | 9 (81.8)     |
| Sensory symptoms          | 8 (72.7)     |
| Weakness of facial muscles| 6 (54.5)     |
| Eyelid prossis            | 4 (36.4)     |
| Dysphasia/dysarthria      | 3 (27.3)     |
| Autonomic dysfunction     | 3 (27.3)     |
| Motor weakness            | 3 (27.3)     |
| Nystagmus                 | 2 (18.2)     |
| Tongue deviation          | 2 (18.2)     |
| Dysphagia                 | 2 (18.2)     |
| MRI alterations* (n=9)    | 1 (11.1)     |
| AIDP pattern in NPS (n=5) | 4 (80.0)     |
| Albuminocytological dissociation in the CSF analysis (n=9) | 7 (77.8) |
| Positivity for SARS-CoV-2 RNA in CSF (n=5) | 0 (0.0) |
| Presence of antiganglioside antibodies (n=9) | 2 (22.2) |
| Treatment with IVIg       | 10 (90.9)    |
| Death                     | 1 (9.1)      |

Data are presented as n (%).

*Enhanced T2-weighted hyperintensity and enlargement of the oculomotor nerve; †One neurophysiological study showed a slight F-wave delay in the upper limbs, without peripheral demyelination or axonal damage. AIDP, acute inflammatory demyelinating polyneuropathy; CSF, cerebrospinal fluid; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging; NPS, neurophysiological study; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
encephalitis.\textsuperscript{23} However, a postinfectious immune-mediated process has been speculated as the main mechanism of SARS-CoV-2-associated neuropahtology.\textsuperscript{24}

Most of the patients with MFS in this study presented albuminocytological dissociation (CSF with total white cell count <10 cells/μL and protein above the normal laboratory range). SARS-CoV-2 RNA was not detected in the CSF, suggesting a mechanism of immune-mediated injury rather than direct viral neurotropism. There is emerging evidence that immune-mediated inflammatory mechanisms is associated with the development of neurological disorders in patients with COVID-19 due to the increased release of cytokines and chemokines, including IL-1, IL-6, IL-17, IL-22, and TNF-α.\textsuperscript{25–27}

These observations have important clinical implications for the treatment of MFS associated with COVID-19. In clinical practice, patients with MFS exhibit good clinical outcomes when treated with IVIg and plasma exchange. This systematic review found no difference in the prognosis between anti-GQ1b-positive and -negative patients, with almost all of them presenting at least partial improvement during the first 2 weeks of treatment, which supports the immune-mediated injury mechanism. One patient who was negative for anti-GQ1b showed initial improvement on the second day of IVIg but died a few days later due to ventricular arrhythmia. Only one patient did not receive any pharmacological treatment, which was due to their MFS symptoms being considered mild.

Moreover, the presence of antibodies against gangliosides—a classical feature found in patients with non-COVID-19 MFS—\textsuperscript{28–30}—does not seem to be a useful diagnostic marker for MFS associated with COVID-19. Anti-GQ1b antibody has been reported to be present in 81% of patients with MFS.\textsuperscript{31} Despite gangliosides being a possible target for IgG antibodies for patients exposed to viral infections,\textsuperscript{2,30,32} the presence of anti-ganglioside antibodies in patients with MFS exposed to SARS-CoV-2 infection seems to be uncommon. In MFS patients who are positive for anti-GQ1b antibodies, there is a possibility of cross-reaction with other gangliosides such as GT1a, GD1b, and GD3. GD3 and arginyln-glycylaspartic acid (RGD) are known to be involved in cell adhesion,\textsuperscript{33} and RGD has been suggested as an alternative receptor for SARS-CoV-2.\textsuperscript{34} We therefore hypothesized that different targets and immune-mediated mechanisms could be associated with the neuropahtology of these patients.

In conclusion, this study has synthesized the published literature on MFS in patients with SARS-CoV-2 infection. Although rare, patients with COVID-19 may present neurological symptoms suggestive of MFS. SARS-CoV-2 RNA was not detected in the CSF analyses. The presence of antibodies against gangliosides was uncommon, and almost all patients exhibited good clinical outcomes after treatment with IVIg.

**Availability of Data and Material**

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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