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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.[1] There is evidence of MFS being preceded by infections similar to those preceding GBS.[2] Cases of MFS[3,4] 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

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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[3-14] were assessed for eligibility, resulting in the exclusion of 3 studies.[6,7,14] Two additional studies[15,16] were identified from the reference lists, and finally 11 studies[3-5,8-13,15,16] 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,[5,10,11] 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%),[3,4,8,9,12,13,15,16] 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%), ophthalmoparesis/diplopia (82%), sensory symptoms (73%), weakness of facial muscles (55%), and eyelid ptosis (36%). Magnetic resonance imaging was performed for nine patients,[4,5,8,10-13,15,16] but only one (11%) case[8] presented alterations, which were

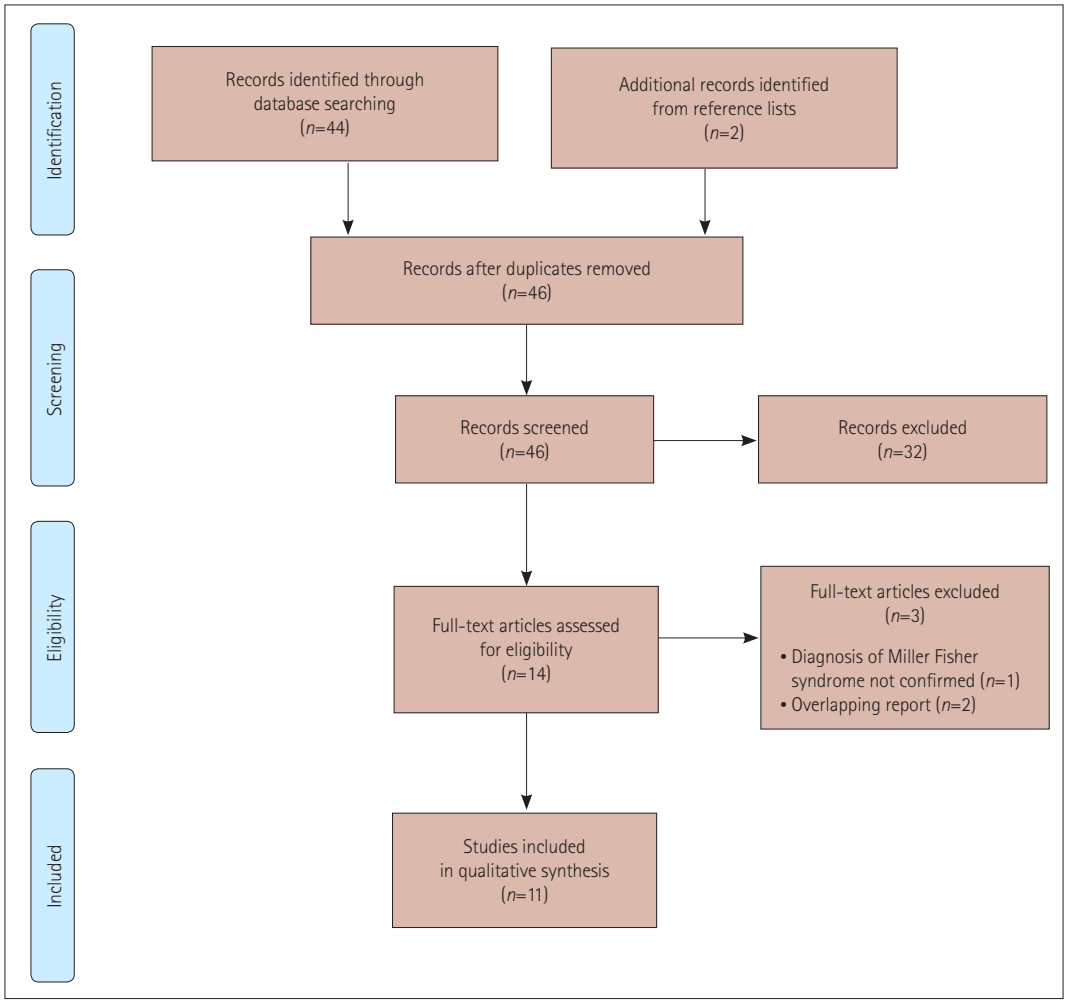

Fig. 1. Flow diagram of studies included in the systematic review.

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
Kopscik 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)
Ray[5]	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.

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[3] and anti-GQ1b[10] 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 patient[11] 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).

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 ptosis	4 (36.4)
Dysphonia/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.

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.[18] 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[22] and

encephalitis.[23] However, a postinfectious immune-mediated process has been speculated as the main mechanism of SARS-CoV-2-associated neuropathology.[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.[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[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.[31] Despite gangliosides being a possible target for IgG antibodies for patients exposed to viral infections,[2,30,32] the presence of anti-ganglioside antibodies in patients with MFS associated with 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 arginylglycylaspartic acid (RGD) are known to be involved in cell adhesion,[33] and RGD has been suggested as an alternative receptor for SARS-CoV-2.[34] We therefore hypothesized that different targets and immune-mediated mechanisms could be associated with the neuropathology 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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REFERENCES

1. Teener JW. Miller Fisher's syndrome. *Semin Neurol* 2012;32:512-516.
2. Koga M, Kishi M, Fukusako T, Ikuta N, Kato M, Kanda T. Antecedent infections in Fisher syndrome: sources of variation in clinical characteristics. *J Neurol* 2019;266:1655-1662.
3. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Mañas R, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* 2020;95:e601-e605.
4. Fernández-Domínguez J, Ameijide-Sanluis E, García-Cabo C, García-Rodríguez R, Mateos V. Miller-Fisher-like syndrome related to SARS-CoV-2 infection (COVID 19). *J Neurol* 2020;267:2495-2496.
5. Ray A. Miller Fisher syndrome and COVID-19: is there a link? *BMJ Case Rep* 2020;13:e236419.
6. Lantos JE, Strauss SB, Lin E. COVID-19-associated Miller Fisher syndrome: MRI findings. *AJNR Am J Neuroradiol* 2020;41:1184-1186.
7. Gogia B, Gil Guevara A, Rai PK, Fang X. A case of COVID-19 with multiple cranial neuropathies. *Int J Neurosci* 2020 Dec 30 [Epub]. Available from: https://doi.org/10.1080/00207454.2020.1869001.
8. Dinkin M, Gao V, Kahan J, Bobker S, Simonetto M, Wechsler P, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology* 2020;95:221-223.
9. Senel M, Abu-Rumeileh S, Michel D, Garibashvili T, Althaus K, Kassubek J, et al. Miller-Fisher syndrome after COVID-19: neurochemical markers as an early sign of nervous system involvement. *Eur J Neurol* 2020;27:2378-2380.
10. Kopscik MR, Giourgas BK, Presley BC. A case report of acute motor and

sensory polyneuropathy as the presenting symptom of SARS-CoV-2. *Clin Pract Cases Emerg Med* 2020;4:352-354.
11. Kajani S, Kajani R, Huang CW, Tran T, Liu AK. Miller Fisher syndrome in the COVID-19 era – a novel target antigen calls for novel treatment. *Cureus* 2021;13:e12424.
12. Reyes-Bueno JA, García-Trujillo L, Urbaneja P, Ciano-Petersen NL, Postigo-Pozo MJ, Martínez-Tomás C, et al. Miller-Fisher syndrome after SARS-CoV-2 infection. *Eur J Neurol* 2020;27:1759-1761.
13. Manganotti P, Pesavento V, Buoite Stella A, Bonzi L, Campagnolo E, Bellavita G, et al. Miller Fisher syndrome diagnosis and treatment in a patient with SARS-CoV-2. *J Neurovirol* 2020;26:605-606.
14. Garnero M, Del Sette M, Assini A, Beronio A, Capello E, Cabona C, et al. COVID-19-related and not related Guillain-Barré syndromes share the same management pitfalls during lock down: the experience of Liguria region in Italy. *J Neurol Sci* 2020;418:117114.
15. Rana S, Lima AA, Chandra R, Valeriano J, Desai T, Freiberg W, et al. Novel coronavirus (COVID-19)-associated Guillain-Barré syndrome: case report. *J Clin Neuromuscul Dis* 2020;21:240-242.
16. Assini A, Benedetti L, Di Maio S, Schirinzi E, Del Sette M. New clinical manifestation of COVID-19 related Guillain-Barrè syndrome highly responsive to intravenous immunoglobulins: two Italian cases. *Neurol Sci* 2020;41:1657-1658.
17. Favas TT, Dev P, Chaurasia RN, Chakravarty K, Mishra R, Joshi D, et al. Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. *Neurol Sci* 2020;41:3437-3470.
18. Gold DM, Galetta SL. Neuro-ophthalmologic complications of coronavirus disease 2019 (COVID-19). *Neurosci Lett* 2021;742:135531.
19. Chen R, Wang K, Yu J, Howard D, French L, Chen Z, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Front Neurol* 2021;11:573095.
20. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol* 2020;92:699-702.
21. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med* 2020;383:590-592.
22. Yousefi K, Poorbarat S, Abasi Z, Rahimi S, Khakshour A. Viral meningitis associated with COVID-19 in a 9-year-old child: a case report. *Pediatr Infect Dis J* 2021;40:e87-e98.
23. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020;94:55-58.
24. Hasan I, Saif-Ur-Rahman KM, Hayat S, Papri N, Jahan I, Azam R, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: a systematic review and individual participant data meta-analysis. *J Peripher Nerv Syst* 2020;25:335-343.
25. Hussain FS, Eldeeb MA, Blackmore D, Siddiqi ZA. Guillain Barré syndrome and COVID-19: possible role of the cytokine storm. *Autoimmun Rev* 2020;19:102681.
26. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. *Cell* 2020;183:16-27.
27. Bodro M, Compta Y, Llansó L, Esteller D, Doncel-Moriano A, Mesa A, et al. Increased CSF levels of IL-1β, IL-6, and ACE in SARS-CoV-2-associated encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e821.
28. Cutillo G, Saariaho AH, Meri S. Physiology of gangliosides and the role of antiganglioside antibodies in human diseases. *Cell Mol Immunol* 2020;17:313-322.
29. Spatola M, Du Pasquier R, Schluep M, Regeniter A. Serum and CSF GQ1b antibodies in isolated ophthalmologic syndromes. *Neurology* 2016;86:1780-1784.
30. Kusunoki S, Iwamori M, Chiba A, Hitoshi S, Arita M, Kanazawa I. GM1b is a new member of antigen for serum antibody in Guillain-Barré syndrome. *Neurology* 1996;47:237-242.
31. Yuki N, Sato S, Tsuji S, Ohsawa T, Miyatake T. Frequent presence of anti-GQ1b antibody in Fisher's syndrome. *Neurology* 1993;43:414-417.
32. Communal C, Filleron A, Baron-Joly S, Salet R, Tran TA. Pediatric Miller Fisher syndrome complicating an Epstein-Barr virus infection. *Pediatr Neurol* 2016;63:73-75.
33. Probstmeier R, Michels M, Franz T, Chan BM, Pesheva P. Tenascin-R interferes with integrin-dependent oligodendrocyte precursor cell adhesion by a ganglioside-mediated signalling mechanism. *Eur J Neurosci* 1999;11:2474-2488.
34. Dakal TC. SARS-CoV-2 attachment to host cells is possibly mediated via RGD-integrin interaction in a calcium-dependent manner and suggests pulmonary EDTA chelation therapy as a novel treatment for COVID 19. *Immunobiology* 2021;226:152021.