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REVIEW ARTICLE

Miller Fisher syndrome associated with COVID-19: an up-to-date systematic review

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Abstract

Recently, during the pandemic infection of the novel SARS-CoV-2, some cases of Miller Fisher syndrome (MFS) have been reported. We want to summarize the main features of patients with MFS and COVID-19. A PubMed search was performed on 8 October to identify references reporting cases with MFS associated with COVID-19 from the first report of COVID-19 to 8 October 2020 using the following keywords: "Miller Fisher syndrome" AND "COVID-19" OR "SARS-CoV-2". A systematic review from the first report of coronavirus disease 2019 (COVID-19) to 8 October 2020 revealed 7 cases with Miller Fisher syndrome (MFS) associated with COVID-19. The 7 cases came from 5 countries but most of these patients were from Europe (85.7%), especially Spain. There are 5 cases of MFS diagnosed after the laboratory confirmation of SARS-CoV-2 infection. The mean onset time of MFS-associated neurological symptoms was 14.75 days after the diagnosis of COVID-19. However, the two remaining cases presented initially with MFS-associated neurological symptoms followed by the diagnosis of COVID-19. The most common symptoms of COVID-19-associated MFS were perioral paresthesias (57.1%), ataxia (57.1%), blurred vision (42.9), ophthalmoplegia (42.9), and generalized areflexia (42.9). However, more cohort and case-control studies are required to establish the epidemiological linkage.

Keywords COVID-19 · SARS-CoV-2 · Miller Fisher syndrome · MFS

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome (SARS)-like coronavirus 2 (SARS-CoV-2), has quickly spread across the world and become as a global health emergency (Boehmer et al. 2020; Dirlikov et al. 2020; Grantz et al. 2020). The most common symptoms of COVID-19 include cough, fatigue, myalgia, sputum production, and shortness of breath, indicating that SARS-CoV-2 mainly affects the respiratory system and results in acute respiratory illness (Hauguel-Moreau et al. 2020; Munro and Faust 2020; Nie et al. 2020; Puccioni-Sohler et al. 2020). Recently, neurological symptoms of COVID-19 have been increasingly reported, with the spectrum ranging from temporary loss of smell and taste to potentially life-threatening encephalopathy and acute cerebrovascular disease (Ahmed et al. 2020; Iadecola et al. 2020; Liotta et al. 2020; Rifino et al. 2020). More recently, there have been sporadic case reports on development of Miller Fisher syndrome (MFS) in patients with COVID-19 (Fernández-Domínguez et al. 2020; Gutiérrez-Ortiz et al. 2020; Lantos et al. 2020; Manganotti et al. 2020; Ray 2020; Reyes-Bueno et al. 2020; Senel et al. 2020). Nevertheless, the epidemiological linkage between these two diseases remains unclear.

MFS is a rare variant of Guillain-Barré syndrome (GBS), an autoimmune disease of the peripheral nervous system (Al Othman et al. 2019; Gómez et al. 2019; Hsueh et al. 2020).

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MFS is characterized symptomatically by ophthalmoplegia, ataxia, and areflexia and biochemically by elevated cerebrospinal fluid (CSF) protein concentration and the presence of autoantibody against ganglioside GQ1b, which is abundant in the paranodal region at the nodes of Ranvier along myelinated axons (Arányi et al. 2012; Heckmann and Dütsch 2012; Teener 2012). Both axonal injury and demyelination might take part in the pathogenesis of MFS (Scelsa and Herskovitz 2000).

As of 8 October 2020, over 36 million patients have been diagnosed of COVID-19, causing more than 1,005,000 deaths worldwide. Given the heightened concern over the possible linkage between COVID-19 and MFS, the objective of the present study is to systematically review case reports on COVID-19-associated MFS, including the electrophysiological and clinical phenotypes. We also aim to identify the temporal relationship between COVID-19 and MFS so as to infer whether post-infective and/or parainfective pathogenic mechanism is at work.

Methods

A PubMed search was performed on 8 October to identify references reporting cases with MFS associated with COVID-19 from the first report of COVID-19 to 8 October 2020 using the following keywords: "Miller Fisher syndrome" AND "COVID-19" OR "SARS-CoV-2". Full-text references in English were collated and analyzed and detailed information of each patient were collected. Data were extracted from each report according to a pre-defined template. Clinical characteristics were retrieved as the number of patients in whom the variable was present as the numerator and the total number of reported cases as the denominator: n/N (%). If clinical features were reported at multiple time points, data representing the full disease course were presented. Continuous variables (age, time between the onset of infectious and neuropathic symptoms) were expressed as medians. Certainty of GBS and MFS diagnosis was assessed, on the basis of the reported findings, by the Brighton Collaboration GBS Working Group criteria. A level 1 diagnosis based on Brighton criteria indicates the highest degree of diagnostic certainty supported by nerve conduction studies and the presence of albuminocytological dissociation in CSF. A level 2 diagnosis was supported by either a CSF white-cell count of less than 50 cells/μl (with or without an elevated protein level) or nerve conduction studies consistent with the polyneuropathy patterns described for GBS and MFS if the CSF is unavailable. A level 3 diagnosis is based on clinical features without support from nerve conduction or CSF studies. A diagnostic classification was also employed to categorize the different GBS and MFS presentations. This systematic review was conducted in accordance with, wherever applicable, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.

Results

A total of 7 case studies reporting on 7 individual patients with COVID-19-associated MFS were identified. The clinical, imaging, and laboratory findings and demographic data of these 7 cases are summarized in Table 1 and Table 2. The majority of cases were men (57.1%) with a median age of 55 years. The first case, a man who came from Madrid, Spain, was published online on 17 Apr 2020. Overall, cases were from 5 countries but most of these patients were from Europe (85.7%) and especially from Spain (42.9%).

Five (71.4%) cases presented to the hospital due to the COVID-19 symptoms and then developed neurological symptoms consistent with MFS. The two remaining cases (28.6%) were presented to the hospital due to neurological symptoms. The diagnosis of COVID-19 was made by quantitative RT-PCR for SARS-CoV-2 in nasopharyngeal swab in 6 cases (85.7%) and by serology positive for antibodies against SARS-CoV-2 in 1 case (14.3%). The diagnosis of COVID-19 was made before the onset of MFS in 5 cases (71.4%) and during hospitalization for MFS in the two remaining cases (28.6%).

The most common symptoms of COVID-19 in these 7 patients were fever (71.4%) and cough (42.9%). Other symptoms of COVID-19 included headache, bilateral pneumonia, taste alteration, chills, myalgia, heavy night sweat, weight loss, and diarrhea. The temporal relationship between the onset of MFS and COVID-19 symptoms in 3 cases (42.9%) was not reported. The median onset time of the neurological symptoms related to MFS was 14.75 days after the diagnosis of COVID-19 in the remaining 4 cases. The symptoms of COVID-19 clinically resolved before onset of MFS in 2 cases (28.6%).

The most common symptoms of COVID-19-assocaited MFS were perioral paresthesias (57.1%), ataxia (57.1%), blurred vision (42.9), ophthalmoplegia (42.9), generalized areflexia (42.9), and other neurological features. Some of these patients (42.9%) have electrodiagnostic features of F-wave delay. The examination of CSF was done in 6 (85.7%) cases and showed an albuminocytological dissociation in 5 out of 6 (83.3%) patients at which SARS-CoV-2 RNA could not be detected in 3 patients. Antiganglioside antibodies were detected in 5 cases (71.4%) and specific anti-GD1b IgG in 1 case (20%). MRI of the head was carried out in 3 cases (42.9%), among which one patient showed high-resolution imaging of the orbits and retro-orbital region with hyperintense signal of the left cranial nerve III. All cases were given intravenous immunoglobulins and eventually recovered.

Table 1 Demographic, geographical, clinical, and laboratory features of patients with Miller Fisher syndrome (MFS)

	Number (%)
Number of patients	7
Age: years, median (IQR) (range)	55, 51 (36–74)
Gender: males:females	4 (57.1):3 (42.9)
Country	
Spain	3 (42.9)
Italy	1
UK	1
New York	1
Germany	1
Diagnosis of SARS-CoV-2 infection	
Nasopharyngeal swab positive	6 (85.7)
Serology positive	1 (14.3)
Presenting symptoms of COVID-19	
Fever	5 (71.4%)
Cough	3 (42.9%)
Headache	1 (14.3)
Bilateral pneumonia	1 (14.3)
Taste alteration	1 (14.3)
Chills	1 (14.3)
Myalgia	1 (14.3)
Heavy night sweat	1 (14.3)
Weight loss	1 (14.3)
Diarrhea	1 (14.3)
Relationship between onset of COVID-19 and MFS symptoms	
Not reported	3
MFS as presenting feature	2
Time interval between onset of COVID-19 and MFS in 4 patients: days, median (IQR) (range)	14.75, 15, (5–24)
COVID-19 clinically resolved before MFS	2

Discussion

Recently, the neurological symptoms of COVID-19 were increasingly reported (Edén et al. 2020; Guadarrama-Ortiz et al. 2020). There are multiple case studies reporting on the association between COVID-19 and MFS. In this systematic review, based on these case reports, we learned about the clinical characteristic of COVID-19 patients developing. However, whether COVID-19 is indeed epidemiologically linked to MFS awaits confirmation by large cohort studies. Given that the COVID-19 is still spreading quickly, more research would be needed to investigate how COVID-19 could impact on the nervous system. Moreover, if COVID-19 really increases the risk for MFS, it is crucial to understand the underlying mechanism. MFS is a rare neurological disorder that is considered to be a variant of GBS (Abu-Rumeileh et al. 2020; Mayer et al. 2020; Verboon et al. 2019). The incidence of GBS is about 1–2 per 1,000, 000 of adults and about 0.4–1.4 per 100,000 of children (Melone et al. 2020; Stojanov et al. 2020). To this end, several infectious diseases, including infection with Zika virus, cytomegalovirus, human immunodeficiency virus, Epstein–Barr virus, and *Campylobacter jejuni*, have shown epidemiological linkage to GBS (Brito Ferreira et al. 2020; De Sanctis et al. 2020; Dyachenko et al. 2018; Korinthenberg and Sejvar 2020; Leung et al. 2020). Until now, no child with COVID-19-associated MFS has been reported.

Until now, there are only 7 reported patients with COVID-19-associated MFS. It is therefore impossible to draw a conclusion as to whether post-infective and/or parainfective pathogenic mechanism is at work. Pathologically, it is plausible that SARS-CoV-2 might directly induce neuropathogenic effect due to the widespread expression of ACE2 (host receptor for SARS-CoV-2) in the nervous system. Alternatively, deregulated immune response upon SARS-CoV-2 infection might underlie

Table 2 Clinical and laboratory features of patients with Miller Fisher syndrome (MFS) with SARS-CoV-2 infection

	Number (%)
Total number of patients	7
Neurological features	
Perioral paresthesias	1, 4, 5, 7
Absent deep tendon reflexes in the upper and lower limbs	1
Right fascicular oculomotor palsy	1
Ataxia	1, 3, 4, 6
Progressive gait impairment	2
Blurred vision	2, 5, 7
Diplopia and facial paresthesia	3
Ophthalmoplegia	3, 4, 6
Left upper arm cerebellar dysmetria	3
Generalized areflexia	3, 4, 6
Lower facial defects	3
Hypoesthesia	3
Maxillary branch of the face	3
Unstableness	6
Weakness	7
Electrodiagnosis	
No done	1, 3, 4, 5
F-wave delay	2, 6, 7
Antiganglioside antibodies	
Not done	4, 5
Negative	1, 2, 3, 6, 7
GD1b (1gG)	1,
GD1b (1gG) negative	2, 3, 5, 6
MRI	
Not done	1, 2, 6, 7
Normal	3, 4
High-resolution imaging of the orbits and retro-orbital region	5
Hyperintense signal of the left cranial nerve (CN) III	5
Immunotherapy	
IV	1, 2
IVIG	3, 4, 5, 6, 7
CSF	
Not done	5
Normal	1
Albuminocytological dissociation	
Increased protein level	2,3, 4, 6, 7
RT-PCR for SARS-CoV-2 negative	1,2, 6
Follow-up	
Recovery	1,2, 3, 4, 5, 6, 7

COVID-19-associated MFS. Particularly, increasing amount of evidence has illustrated that SARS-CoV-2 can induce severe immune and inflammatory reaction that leads to tissue damage. Thus, targeting the inflammatory cascade, for example, with corticosteroids, might be effective against COVID-19-associated MFS.

Conclusion

There are sporadic reports on patients with concurrent diagnosis of COVID-19 and MFS, suggesting a possible link between these two diseases. However, more cohort and case-control studies are required to confirm the

epidemiological linkage. Nevertheless, it is important for physicians to pay more attention to the neurological manifestations of COVID-19.

Authors' contributions Conceptualization: all authors; methodology, formal analysis, and investigation: Zheng Li, Xingye Li, Jianxiong Shen; writing—original draft preparation: Zheng Li and Xingye Li; writing—review and editing: Matthew T.V. Chan, William Ka Kei Wu

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest related to the content of this article.

Ethical standard For the present study, no authorization to an Ethics Committee was asked, because the original reports, nor this work, provided any personal information of the patients.

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