Miller Fisher syndrome following COVID-19 vaccines: A scoping review

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Background and Purpose: Miller Fisher syndrome (MFS), a variant of Guillain–Barré Syndrome (GBS), could be underestimated in evaluations of its adverse events (AEs) following COVID-19 vaccination. We aimed to identify and characterize MFS following COVID-19 vaccination.

Materials and Methods: Relevant studies reported on during the COVID-19 pandemic were included in the MEDLINE, Embase, and other databases.

Results: Nine cases of MFS following COVID-19 vaccination from various regions were included. Unlike MFS following COVID-19 infection, patients with MFS following COVID-19 vaccination frequently presented with anti-GQ1b antibody positivity (44%, 4/9). Unlike GBS following COVID-19 vaccination, only two of nine (22%) cases of MFS following COVID-19 vaccination had developed after viral-vector-related vaccine administration.

Conclusions: Miller Fisher syndrome following COVID-19 vaccination seems to have a different pathophysiology from MFS following COVID-19 infection and GBS following COVID-19 vaccination. This neurological syndrome with a rare incidence and difficulty in diagnosis should be considered an AE of COVID-19 vaccination.

KEYWORDS adverse effects, COVID-19 vaccine, Guillain–Barré syndrome, miller Fisher syndrome, systematic review

INTRODUCTION

The swine influenza vaccine program in the US (A/New Jersey/1976/H1N1) has resulted in Guillain–Barré syndrome (GBS) being considered a frequent adverse event (AE) following vaccination. Given that GBS is well-known acute immune-mediated peripheral neuropathy, vaccination is an important antecedent immunological event related to the pathogenesis of GBS.

Since Miller Fisher syndrome (MFS) was described and suspected as a variant of GBS, it has now been well characterized by ophthalmoplegia, ataxia, and areflexia. In addition to other atypical GBS variants, MFS is one of the representative variants of GBS that presents with cranial nerve involvement without definite motor weakness in the limbs.

GBS has historically been investigated as an AE following vaccination. Nevertheless, the incidence of MFS and other localized GBS variants could be underestimated because of their atypical or minor symptoms following vaccination. Recent population-based studies from the US and UK could only analyze GBS codes and could not analyze MFS or other variants among their cohorts.

This study systematically reviewed and focused on MFS occurrence following COVID-19 vaccination. This approach was aimed at identifying the demographic and clinical characterization of MFS following COVID-19 vaccination.
MATERIALS AND METHODS

Data sources and study selection

On May 30, 2022, we identified relevant studies through electronic medical subject headings and keyword searches of MEDLINE (PubMed) and Embase using the following terms, without language or publication date restrictions: “Guillain-Barré Syndrome,” “Miller-Fisher syndrome,” “variant,” “cranial nerve diseases,” “ophthalmoplegia,” “oculomotor motility disorder,” “ataxia,” “COVID-19,” “SARS-CoV-2,” “COVID-19 vaccines,” “ChAdOx1 nCoV-19,” “AstraZeneca vaccine,” “2019-nCoV vaccine mRNA-1273,” “Moderna vaccine,” “BNT162 vaccine,” “Pfizer and BioNTech vaccine,” “Baiya SARS-CoV-2 VAX COVID-19 vaccine,” “Sinovac COVID-19 vaccine,” “Ad26Cov1,” and “Johnson and Johnson vaccine.” The reference lists of the selected articles were systematically reviewed for other potentially relevant citations.

Final enrollment of studies and data extraction

Two researchers (J.E.K. and B.A.Y.) independently curated titles and abstracts. In case of disagreement, consensus on the articles to screen the full texts of was reached through discussion. The same researchers then independently screened full-text articles for inclusion or exclusion, following the same procedure. We designed a data extraction form to collect age (in years), sex, comorbidities, type of vaccine administrated (Astra Zeneca, Moderna, Pfizer, or other type), vaccine dose (first or second), preceding infection (upper respiratory infection, diarrhea, or other), interval between vaccination and initial symptoms (in days), initial subjective symptoms, presence of typical and atypical MFS features (ophthalmoplegia, ataxia, or other), cerebrospinal fluid (albuminocytological [A/C] dissociation), nerve conduction study findings, and antiganglioside antibodies assay results.

Three authors (J.E.K., B.A.Y., and J.S.B.) used the data extracted from eligible studies, with discrepancies resolved through discussion. The following exclusion criteria were applied: (1) unclear MFS definition due to lack of clinical or laboratory information, (2) insufficient differential diagnosis from MFS-mimicking diseases such as idiopathic granulomatous neuropathies of other causes, or (3) ophthalmoplegic GBS of the classic phenotype with subtle findings of oculomotor findings without anti-GQ1b positivity. The final inclusion of studies was based on the agreement of all the reviewers.

Standard protocol approval, registration, and patient consent

This systematic review was based on bibliometric data without animal or human data, and so it was not necessary to obtain ethical approval.

RESULTS

The search process identified 37 potential articles. After removing duplicates, 12 articles were reviewed for inclusion. Of these, two were excluded because one reported ophthalmoplegic GBS and the other was about cranial dominant GBS, which is not compatible with MFS diagnosis. Ten articles were finally enrolled in this systematic review, with one case among these also being excluded from the analyses. Despite the authors diagnosing MFS, we could not find any clinical or laboratory findings that supported it. We also searched articles that cited any of or were references of the initially included studies. This resulted in nine articles finally being analyzed for this review. A flow diagram illustrating the full search process is shown in Figure 1.

Table 1 lists a summary of the finally included articles. All the articles were case reports except for one case series. The nine analyzed articles comprised five from Asia (three from Japan, one from South Korea, and one from Pakistan) and the rest from the USA, Croatia, Belgium, and Australia (one case each).

Table 2 lists the demographic, clinical, and laboratory characteristics of nine cases of MFS following COVID-19 vaccination. The median age was 65 years (age range 24–85 years). All but one of the cases were male. The vaccine types were as follows: Pfizer (6/9 cases, 67%), AstraZeneca (2/9, 22%), and Sinovac (2/9, 22%). Three cases had diabetes mellitus, and two had a history of ophthalmoplegia with other etiologies (one for diabetic ophthalmoplegia and one for orbital pseudotumor). Two cases were diagnosed as acute ophthalmoplegia (AO) with anti-GQ1b antibody positivity and the rest were classic MFS. All of the available cases (8/9) presented with A/C dissociation. Four cases had serum positivity for anti-GQ1b antibody. During the disease course, two cases presented a syndrome possibly overlapping between GBS and MFS, and one presented respiratory involvement.

DISCUSSION

This scoping review found that MFS following COVID-19 vaccination has been rare but has been reported among various vaccine types in various countries. The phenotype of MFS also varied, with cases manifesting with classic MFS and partial MFS (i.e., AO). Three cases even presented additional manifestations such as limb weakness (MFS/GBS overlap syndrome) and respiratory involvement. Regardless of its rarity, this review identified that most cases were male and presented with A/C dissociation.

Most GBS cases following vaccination have been related to a viral vector vaccine such as the AstraZeneca or Janssen vaccine. However, our review found that only two of nine cases of MFS were related to a viral vector vaccine (AstraZeneca), and that the rest had developed after either mRNA or inactivated virus vaccination (Pfizer and Sinovac). This finding suggests that MFS following COVID-19 vaccination has a different immune mechanism to GBS following COVID-19 infection.
One possible hypothesis was based on the unique patterns of invasion and immunogenesis in the COVID-19 virus. Since earlier stages of the COVID-19 pandemic, a loss of smell and taste has been widely identified among patients. Gutiérrez-Ortiz et al. documented two patients who tested positive for COVID-19 who presented with areflexia, oculomotor palsy, and ataxia who also reported anosmia and ageusia. They were subsequently diagnosed with MFS and multiple cranial neuropathy. These cases suggest that MFS following COVID infection has a somewhat different mechanism from sporadic MFS following COVID-19 vaccination. In another aspect, some study that analyzed MFS following COVID-19 infection indicated that anti-GQ1b antibody positivity was less common than in our review; however, our analysis revealed positivity for that antibody in 44% (4/9) of cases. Frequent antiganglioside antibody positivity in MFS following COVID-19 vaccination can be explained in two ways. First, sporadic MFS might be incidentally included in MFS following COVID-19 vaccination. Any possible antecedent event might have occurred at the interval between vaccination and the initial onset of MFS symptoms (i.e., fever, myalgia, diarrhea). Second, vaccination may induce GQ1b or GT1a ganglioside antibody production via a molecular mimicry mechanism. Nearly 30 years after swine flu vaccination, one study found that mice immunized with the influenza vaccine developed anti-GM1 antibodies, which can support the molecular mimicry between vaccine-induced factors and antiganglioside antibodies.

Despite the recent availability of vaccines, it is presumed that 70–80% of the population have active immunity through infection or vaccines, thereby breaking down the disease chain.
TABLE 2 Demographic, clinical, and laboratory characteristics of patients with Miller Fisher syndrome following COVID-19 vaccination

| Case no. | Age (years) | Sex | Vaccine type | Dose | Comorbidities | Preceding infection | Interval between vaccination and initial symptoms (days) | Initial subjective symptoms | Ophthalmoplegia | Ataxia | Other findings | A/C dissociation | NCS findings | Antiganglioside antibodies |
|----------|-------------|-----|--------------|------|---------------|---------------------|--------------------------------------------------------|-----------------------------|----------------|--------|---------------|----------------|-------------|--------------------------|
| [1]      | 65          | M   | Pfizer       | Second | DM, glaucoma  | None                | 17                        | Diplopia                     | +              | −       | −             | +               | Normal      | Anti-GQ1b (+)             |
| [2]      | 71          | M   | Pfizer       | First and second | DM, diabetic ophthalmoplegia (7 years ago) | None | 26 (first), 5 (second) | Ptosis, ophthalmoplegia | + | − | − | + | Normal |
| [3]      | 78          | M   | Pfizer       | Second | COVID-19, inflammatory pseudotumor | NA | 42 (first), 14 (second) | Gait ataxia, paresthesia of the hands | + | + | Paresthesia, respiratory involvement | + | NA | Anti-GQ1b (borderline) |
| [4]      | 63          | M   | AZ           | First | − | None | 14 | Facial diplegia | + | + | Overlap syndrome | + | Axonal neuropathy | − |
| [5]      | 65          | M   | Pfizer       | First | DM | None | 35 | Diplopia, ataxia | + | + | − | + | NA | − |
| [6]      | 84          | F   | AZ           | First | HT | None | 8 | Ptosis, diplopia, ataxia | + | + | − | + | Normal | Anti-GQ1b (+) |
| [7]      | 53          | M   | Sinovac      | First | HT | None | 8 | Diplopia, ataxia | + | + | Overlap syndrome (quadripareisis) | + | Demyelinating neuropathy | NA |
| [8]      | 24          | M   | Pfizer       | First | − | Diarrhea | 18 | Diplopia | + | − | − | + | Normal | + |
| [9]      | 30          | M   | Pfizer       | Second | − | Cough | 7 | Diplopia, dizziness | + | + | − | NA | Normal | Anti-GQ1 (+), anti-GT1a (+) |

Abbreviations: AO, acute ophthalmoplegia; A/C, albuminocytological; AZ, AstraZeneca; DM, diabetes mellitus; F, female; M, male; NA, not available; NCS, nerve conduction study.
of the effective periods of COVID-19 vaccinations also mandate the administration of regular doses or booster shots of the vaccine. This suggests that AEs following COVID-19 vaccination can continue and that clinicians should pay more attention to any neglected AEs after COVID-19 vaccination.

Miller Fisher syndrome is a rare and unique GBS variant characterized by ataxia, ophthalmoplegia, and areflexia. In most countries, it is impossible to distinguish atypical GBS variants from classic GBS due to the coding used in surveillance for vaccine safety. Recent nationwide studies of vaccine safety investigated the coding of GBS, which were confined to the recordings of hospital admissions and mortality. 4–6 MFS or other variants of GBS therefore appeared to be underestimated in surveillance systems for COVID-19 vaccination safety. Moreover, specific environments around the world during the COVID-19 pandemic may influence the healthcare delivery system and distort valid diagnoses and medical outcome registration.22

We should address several limitations of our analysis: first, because of different medical environment in centers of each case, it might exist a concern of diagnostic certainty—availability of neurology specialist or special testing such as antganglioside antibody assay. In addition, some of enrolled cases could be suspected as other atypical variant or overlapped spectrum of GBS rather than MFS. Finally, a causal link between vaccination and development of MFS could not be confirmed by observational studies which were included in this analysis.

Nevertheless, this scoping review highlights that a neurological disease with a rare incidence and difficult diagnosis should be considered as an AE of COVID-19 vaccination. Furthermore, there might be a possible underestimation of MFS in that mild cranial symptoms can be ignored or misdiagnosed as other focal neurological syndrome. Studies targeting its epidemiological and scientific features across the COVID-19 pandemic and endemic era can provide useful clues for the understanding of those diseases, such as GBS or MFS.

AUTHOR CONTRIBUTIONS
J.S.B. and J. K. K. designed the study. J.E.K., B.A.Y., and Y.H.K. conducted the data collection. J. S. B., J.E.K., and J. K. K. interpreted the data and wrote this manuscript. All of the authors reviewed the first manuscript draft, critically revised the manuscript, and read and approved the final version. The funders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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CONFLICT OF INTEREST
The authors have no potential conflicts of interest to disclose.

PEER REVIEW
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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL
This systematic review was not necessary to obtain ethical approval.

PATIENT CONSENT
This systematic review was not necessary to obtain patient consent.

REFERENCES
1. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol. 1979;110:105-123.
2. Wakerley BR, Uncini A, Yuki N. Guillain-Barré and Miller Fisher syndromes—new diagnostic classification. Nat Rev Neurol. 2014;10:537-544.
3. Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). N Engl J Med. 1956;255:57-65.
4. Patone M, Handunnetthi L, Saatci D, et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med. 2021;27:2144-2153.
5. Keh RYS, Scanlon S, Datta-Nemdharry P, et al. COVID-19 vaccination and Guillain-Barré syndrome: analyses using the National immunoglobulin database. Brain. 2022;awac067. Online ahead of print.
6. Frontera JA, Tamborska AA, Doheim MF, et al. Neurological events reported after COVID-19 vaccines: an analysis of VAERS. Ann Neurol. 2022;91:756-771.
7. Assiri SA, Althaqafi RMM, Alswat K, et al. Post COVID-19 vaccination-associated neurological complications. Neuropsychiatr Dis Treat. 2022;18:137-154.
8. Kubota T, Hasegawa T, Ikeda K, Aoki M. Case report: isolated, unilateral oculomotor palsy with anti-GQ1b antibody following COVID-19 vaccination. F1000Res. 2021;10:1142.
9. Nishiguchi Y, Matsuyama H, Maeda K, Shindo A, Tomimoto H. Miller Fisher syndrome following BNT162b2 mRNA coronavirus 2019 vaccination. BMC Neurol. 2021;21:452.
10. Michaelson NM, Lam T, Malhotra A, Schiff ND, MacGowan DJL. Miller Fisher syndrome presenting after a second dose of Pfizer-Biontech vaccination in a patient with resolved COVID-19: a case report. J Clin Neuromuscul Dis. 2021;23:113-115.
11. Dang YL, Bryson A. Miller-Fisher syndrome and Guillain-Barre syndrome overlap syndrome in a patient post Oxford-AstraZeneca SARS-CoV-2 vaccination. BMJ Case Rep. 2021;14:e246701.
12. Pierre-Yves Sansen EC, Weynants N, Glorieux P, Miller-Fisher syndrome following the first dose of Comirnaty (Pfizer COVID-19 vaccine). J Med Case Rep Case Series. 2021;43:1-3.
13. Kim JE, Min YG, Shin JY, et al. Guillain-Barré syndrome and variants following COVID-19 vaccination: report of 13 cases. Front Neurol. 2021;12:820723.
14. Siddiqi AR, Khan T, Tahir MJ, Asghar MS, Islam MS, Yousaf Z. Miller Fisher syndrome after COVID-19 vaccination: case report and review of literature. *Medicine (Baltimore)*. 2022;101:e29333.

15. Abičić A, Adamec I, Habek M. Miller Fisher syndrome following Pfizer COVID-19 vaccine. *Neural Sci*. 2022;43:1495-1497.

16. Yamakawa M, Nakahara K, Nakanishi T, Nomura T, Ueda M. Miller Fisher syndrome following vaccination against SARS-CoV-2. *Intern Med*. 2022;61:1067-1069.

17. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology*. 2020;95:e601-e605.

18. Senel M, Abu-Rumeileh S, Michel D, 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.

19. 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.

20. Nachamkin I, Shadomy SV, Moran AP, et al. Anti-ganglioside antibody induction by swine (a/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barré syndrome. *J Infect Dis*. 2008;198:226-233.

21. Anand P, Stahel VP. The safety of Covid-19 mRNA vaccines: a review. *Patient Saf Surg*. 2021;15:22.

22. Xu S, Hong V, Sy LS, et al. Changes in incidence rates of outcomes of interest in vaccine safety studies during the COVID-19 pandemic. *Vaccine*. 2022;40:3150-3158.

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