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ORIGINAL ARTICLE

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 identified 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

1 | INTRODUCTION

The swine influenza vaccine program in the US (A/New Jersey/1976/H1N1)[1] 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.[2]

Since Miller Fisher syndrome (MFS) was described and suspected as a variant of GBS,[3] 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.[2]

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.[4–6]

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.

Jee-Eun Kim and Byeol-A Yoon contributed equally to this work.

2 | MATERIALS AND METHODS

2.1 | 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," "Ad26COVS1," and "Johnson and Johnson vaccine." The reference lists of the selected articles were systematically reviewed for other potentially relevant citations.

2.2 | 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 (AstraZeneca, 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 cranial 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.

2.3 | 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.

3 | 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.[7] 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.[8–16] 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 were anti-GQ1b antibody. During the disease course, two cases presented a syndrome possibly overlapping between GBS and MFS, and one presented respiratory involvement.

4 | 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.[4–6] 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.

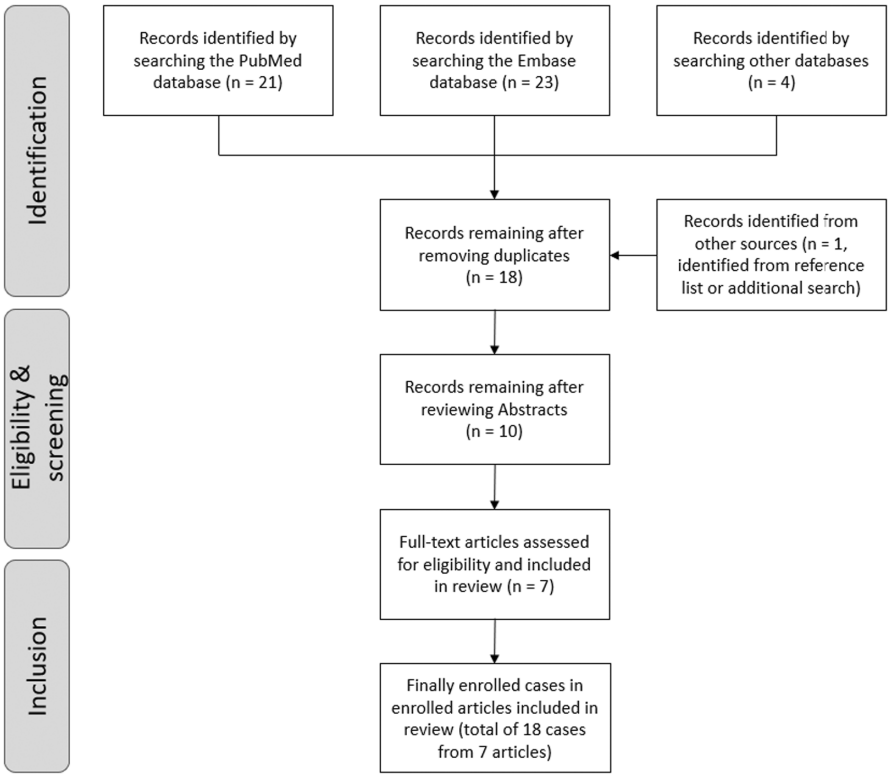

FIGURE 1 Flow diagram demonstrating the inclusion/exclusion process for studies included in the final analyses

TABLE 1 Summary of enrolled studies

First author. Reference	Country	Journal	Publication year	Study type	No. of patients	Case no.
Kubota[8]	Japan	F1000Research	2021	Case report	1	[1]
Nishiguchi[9]	Japan	BMC Neurology	2021	Case report	1	[2]
Michaelson[10]	USA	Journal of Clinical Neuromuscular Disease	2021	Case report	1	[3]
Dang[11]	Australia	BMJ Case Reports	2021	Case report	1	[4]
Sansen[12]	Belgium	Journal of Medical Case Reports and Case Series	2021	Case report	1	[5]
Kim[13]	Korea	Frontiers in Neurology	2022	Case series	1 of 13	[6]
Siddiqi[14]	Pakistan	Medicine	2022	Case report	1	[7]
Abičić[15]	Croatia	Neurological Science	2022	Case report	1	[8]
Yamakawa[16]	Japan	Internal Medicine	2022	Case report	1	[9]

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 COIVD-19 who presented with areflexia, oculomotor palsy, and ataxia who also reported anosmia and ageusia.[17] 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[18,19]; 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.[20]

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.[21] The duration

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 (quadriparesis)	+	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 antiganglioside 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.

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