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REVIEW

Guillain-Barré syndrome in association with COVID-19 vaccination: a systematic review

Meysam Abolmaali[1,3] · Fatemeh Rezania[2] · Arman Karimi Behnagh[3] · Negin Mahmoudi Hamidabad[3] · Ali Gorji[1,4,5] · Zahra Mirzaasgari[1,6]

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Abstract

Since the beginning of worldwide vaccination against coronavirus disease 2019 (COVID-19), studies have reported a possible association between vaccination and Guillain-Barré syndrome (GBS). In this regard, we conducted a systematic review assessing different demographic, clinical, and neurophysiological aspects of patients with GBS following immunization with COVID-19 vaccines. A comprehensive search of PubMed, Web of Science, Scopus, and Google Scholar was performed. Articles in English between January 2020 and November 2021 were included. Data on demographics, clinical characteristics, vaccines information, treatment approaches, and outcomes were extracted. The data of a total of 88 patients out of 41 studies was included. The mean age of patients was 58.7 ± 16.6 years and 55 cases (62.5%) were male. AstraZeneca was the most-reported vaccine associated with GBS with 52 cases (59.1%) followed by Pfizer with 20 cases (22.7%). GBS occurred after the first dose of vaccination in 70 cases (79.5%). The mean time interval between vaccination and symptom onset was 13.9 ± 7.4 days. Limb weakness (47.7%), sensory disturbance (38.6%), and facial weakness (27.3%) were the most common reported symptoms, respectively. Albuminocytologic dissociation was seen in 65% of patients who underwent lumbar puncture ($n = 65$). Acute inflammatory demyelinating polyradiculopathy was the most common GBS subtype, which was reported in 38 patients (43.2%). While one-fifth of patients underwent intubation ($n = 17$), a favorable outcome was achieved in the majority of subjects ($n = 46$, 63%). Overall, a small rise in GBS incidence, following various COVID-19 vaccines, was observed. Notably, 85% of affected individuals experienced at least a partial recovery.

Keywords Guillain-Barré syndrome · Vaccination · COVID-19 · SARS-COV-2

Introduction

Guillain-Barré syndrome (GBS) is an autoimmune disease. In the majority of cases, the individual is affected by an infection or other immunological stimulants that results in an aberrant autoimmune response. The aberrated immunologic response targets the peripheral nerves and their spinal roots leading to a progressive neuropathic weakness [1, 2].

Typically, GBS is a monophasic disease and the disease onset often arises shortly (< 1 month) after an upper respiratory or gastrointestinal tract infection, usually without relapse. Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus, mycoplasma pneumonia, influenza-like illness, HIV, and Zika virus are the most common infections reported to precede the onset of GBS [3]. Notably, the association of coronavirus disease 2019 (COVID-19) and different types of neuropathies, such as GBS, has been repeatedly described in the literature in recent years.

✉ Zahra Mirzaasgari
mirzaasgari@gmail.com

1 Shefa Neuroscience Research Center, Khatam Alanbia Hospital, Tehran, Iran

2 Clinical Neurosciences, St. Vincent's Hospital Melbourne, Melbourne, VIC, Australia

3 School of Medicine, Iran University of Medical Sciences, Tehran, Iran

4 Epilepsy Research Center, Department of Neurosurgery, Westfälische Wilhelms-Universitat Münster, Munster, Germany

5 Neuroscience Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

6 Department of Neurology, Firoozgar Hospital, University of Medical Sciences, Tehran 15937-48711, Iran

COVID-19-associated GBS was first brought to the attention of the medical community after a series of 5 patients who had GBS after the onset of COVID-19 was reported in Italy in early 2020 [4]. Since there has been a growing body of evidence introducing COVID-19 as a new infection that can cause GBS [4–6].

On the other hand, GBS has also been described following immunization with various vaccines, but not limited to Semple rabies vaccine and various types of influenza A virus vaccines [7, 8]. The potential link between influenza vaccine and GBS was noted during the H1N1influeza vaccination campaign in 1976 where the increased risk was estimated roughly at one additional case of GBS for every 100,000 people who had been vaccinated [9]. The subsequent studies during 1992–2004 in USA and Canada confirmed this observation [10, 11]. Further multinational investigations revealed that influenza vaccines, both adjuvant or un-adjuvant forms, could increase the risk of GBS following vaccination [12–15].

Following the COVID-19 pandemic, several groups attempted to design effective vaccines against the virus. In late 2020, the first trials of vaccines showed promising results. Since the beginning of immunization with COVID-19 vaccines, some studies have implicated the association between the COVID-19 vaccine and GBS. In February 2021, Waheed et al. described the first case of GBS following immunization with BNT162b2 mRNA (Pfizer) vaccine [16]. More recently, several cases of GBS were reported following Pfizer, Oxford-AstraZeneca (AZV), and Johnson & Johnson (J&J) COVID-19 vaccines [17–20]. Since the beginning of the COVID-19 vaccination program, there have been databases designed to record all the COVID-19-related adverse events. The UK National Immunization Management System database revealed an increased risk of GBS following the first dose of ChAdOx1nCoV-19 (AZV) [21]. However, this risk was not higher than the risk of GBS following COVID-19 infection [21]. The US Vaccine Adverse Event Reporting System, which is a passive reporting system, showed a small but statistically significant risk of GBS associated with Ad26.COV2.S (J&J) COVID-19 vaccine [22]. Here, we systematically review the current literature regarding the risk of GBS after COVID-19 vaccination.

Method and materials

This study was conducted by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [23], a well-known tool to increase the transparency of reporting systematic reviews. To find relevant studies, we performed a comprehensive search in PubMed, Web of Science, and Scopus, as well as a manual search in Google Scholar to find relevant studies. The search query of each source was provided as supplementary materials; nonetheless, we used the following keywords: Guillain-Barré syndrome, COVID-19, SARS-COV-2, Vaccine. We included articles in English between January 2020 and November 2021. All published or pre-published studies that had data regarding the association of COVID-19 and neurological defects, especially GBS in adults who received vaccination against COVID-19, were considered eligible for inclusion regardless of vaccine type (Fig. 1). We also examined large-scale population-based cohort studies, case series, and case reports providing practical details regarding GBS incidence after COVID-19 vaccination.

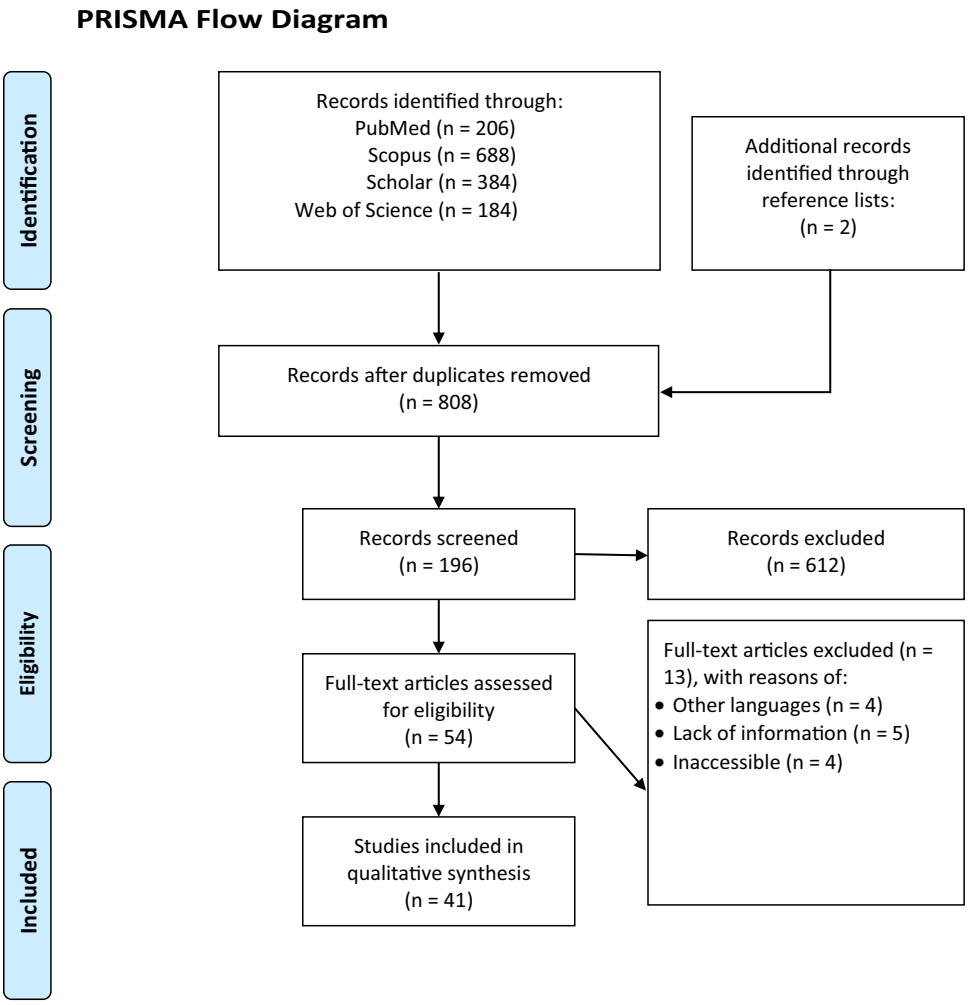
After retrieving the relevant studies, two reviewers (M.A. and N.M.H.) independently extracted the data from the included studies. The extracted data included general information (author, year, geographic area, study design), demographics data (including age and gender), clinical data (vaccine type, vaccine dose number (first vs. second), the time interval between injection and symptom onset, presenting signs and symptoms, GBS subtype), electrophysiological findings, laboratory data (cerebrospinal fluid analysis, anti-ganglioside antibodies), treatment approaches, need for intubation, and clinical outcome. We classified patients' outcomes into three categories (favorable, partial recovery, and poor). The patients who were discharged with no complications were categorized as "favorable" (complete recovery), those who recovered but needed assistance and further rehabilitation were listed as "partial recovery," and patients who remained bedridden and intubated were classified as "poor" outcome. Moreover, the level of diagnostic certainty was evaluated via Brighton criteria for each case [24]. Due to the qualitative and summative nature of this review and significant variations in study designs and reporting of findings, a meta-analysis and statistical calculations were not performed.

Results

In this study, a total of 88 cases of COVID-19 vaccine–associated GBS were included from 41 studies in 17 countries. Two patients had a previous history of GBS [25, 26]. Five patients received the influenza vaccine in addition to the COVID-19 vaccination [27, 28]. The patients' age ranged between 14 and 90 years and the mean age was 58.7 ± 16.6 years. The majority of the cases were male (62.5%). The demographic and clinical characteristics are shown in Table 1.

AZV was the most-reported vaccine with 52 cases (59.1%) and Pfizer was the second most-reported vaccine with 20 cases (22.7%). Each of the J&J, Sputnik V, Sinopharm, Moderna, and Sinovac vaccines was reported in 5, 4, 3, 2, and 1 patients, respectively. Most of the cases

Fig. 1 PRISMA flow diagram



occurred after the administration of the first dose (79.5%). The mean latency period from vaccination to the onset of the symptoms was 13.9 ± 7.4 days. Limb weakness was the most common symptom reported in 42 patients (47.7%). The sensory disturbance occurred in 34 patients (38.6%). Facial weakness was reported in 24 patients (27.3%). Incidence of bulbar weakness and ophthalmoplegia was 11.4% (10 patients) and 8% (7 patients), respectively. Only one patient suffered sphincter disturbance. Sixty-five patients underwent lumbar puncture. Albuminocytologic dissociation was shown in 65% of the patients. Anti-Ganglioside antibodies including anti-GQ1b, anti-GQ2b, anti-GM1, anti-GM2, anti-GM3, anti-GM4, anti-titin, and anti-sulfatide antibodies were found in 18% of patients who were tested for (5 out of 28).

The most common GBS subtype was acute inflammatory demyelinating polyradiculopathy reported in 38 patients (43.2%). Bifacial weakness with paresthesia (BFP) was the second most common subtype of GBS with an incidence of 15.9% (14 cases). Unspecified classic sensory-motor GBS was reported in 11 patients (12.5%). Acute motor-sensory axonal neuropathy and acute motor axonal neuropathy were reported in 9 (10.2%) and 4 (4.5%) cases, respectively. Other rare subtypes were paraparetic GBS in 4 cases, Miller Fisher syndrome (MFS) in 3 cases, MFS-GBS overlap in 2 cases, pure sensory GBS in 2 subjects, and pure motor GBS in one patient. Patients were divided into four levels based on The Brighton Collaboration definitions with 41 cases in level 1 (46.6%), 24 in level 2 (27.3%), 4 in level 3 (4.5%), and 19 cases in level 4 (21.6%).

The most frequent treatment used as the first-line therapy was intravenous immunoglobulin (IVIG) ($n = 61$, 69.3%). Plasmapheresis (PLEX) was performed in 13.6% of the cases ($n = 12$, four cases received PLEX solely, seven received PLEX following IVIG, and one case received PLEX prior to IVIG). Six patients have received corticosteroids (6.8%) while 3 patients were managed conservatively (3.4%). Almost one-fifth of patients were intubated ($n = 17$). The majority of the patients experienced favorable outcomes ($n = 46$, 6%) and roughly 22% of the patients had partial improvement ($n = 16$). Poor outcome was reported in 10

Table 1 Demographics and clinical characteristics of cases with GBS after COVID-19 vaccination ($n = 88$)

No	Authors	Country	Age/sex	Vaccine/dose	Onset time (day)	GBS subtype	Electrophysiologic finding	Albuminocytological dissociation	Ganglioside Ab	MRI	Brighton collaboration level	Treatment	Intubation	Outcome
1	Abičić et al. [29]	Croatia	24/F	Pfizer/1	18	MFS		NR	+(anti GQ1b)	NP	4	- Prednisolone, IVIg	–	CR
2	Allen et al. [30]	UK	54/M	AZV/1	16	BFP	See below[a]	+	–	See below[c]	4	- Prednisolone	–	CR
			20/M	AZV/1	26	BFP	See below[b]	+	– –	Normal	4		–	CR
			57/M	AZV/1	21	BFP	Normal	+	–	Normal	4	- Prednisolone	–	CR
			55/M	AZV/1	29	BFP	NT	+		Rt facial nerve enhancement	4	- IVIg - Conservative	–	CR
3	Aomar-Millán et al. [17]	Spain	77/M	Pfizer/1	3	AMSAN	AMSAN	–	–	NP	2	- IVIg, PLEX	–	CR
4	Azam et al. [31]	UK	67/M	AZV/1	15	AIDP	AIDP	+	–	Bilateral enhancement in facial nerves	1	- IVIg	–	NR
5	Bax et al. [32]	Italy	90/M	Pfizer/2	3	AMSAN	AMSAN	+	+[d]	NP	2	- IVIg	–	CR
			51/F	AZV/1	10	AIDP	AIDP		–	NP	1	- IVIg	–	CR
6	Bonifacio et al. [33]	UK	66/M	AZV/1	17	BFP	Demyelinating	+	–	See below[c]	4	- IVIg		CR
			43/M	AZV/1	17	BFP		+	–	See below[c]	4	- IVIg		PR
			51/M	AZV/1	14	BFP	Demyelinating	+	+/GM3	See below[c]	4	- NR		CR
			71/F	AZV/1	15	BFP		+	–	Normal	1	- NR		CR
			53/M	AZV/1	14	BFP	Demyelinating Demyelinating NT	+	NT	NP	4	- NR		CR
7	Bouattour et al. [34]	Tunisia	67/M	Pfizer/1	7	AIDP	AIDP	+	–	NP	1	- IVIg	–	CR
8	Dang et al. [35]	Australia	63/M	AZV/1	14	MF&GBS overlap		+	–	Bilateral enhancement of CNVII and III	3	- IVIg	–	PR
9	da Silva et al. [36]	Brazil	62/F	AZV/1	18	Classic SM	NT	+	NR	NP	2	- IVIg	–	CR

Table 1 (continued)

No	Authors	Country	Age/sex	Vaccine/dose	Onset time (day)	GBS subtype	Electro-physiologic finding	Albumino-cytological dissociation	Ganglioside Ab	MRI	Brighton collaboration level	Treatment	Intubation	Outcome
10	Finsterer et al. [26]	Austria	32/M	Vector based/1	8	AIDP	AIDP	+	NR	Non-specific bilateral white matter hyperintensity	1	- IVIg	–	PR
11	García-Grimshaw et al. [27]	Mexico	33/M	Pfizer/1	28	AIDP	AIDP	+	NR	NR	1	- IVIg	–	CR
			25/M	Pfizer/1	12	AIDP	AIDP	+	NR	NR	1	- IVIg	–	PR
			53/F	Pfizer/1	6	AMAN	AMAN	–	NR	NR	2	- IVIg	+	Poor
			72/M	Pfizer/1	4	AMAN	AMAN	NT	NR	NR	2	- IVIg	–	PR
			31/M	Pfizer/1	11	AIDP	AIDP	NT	NR	NR	2	- IVIg	–	PR
			67/F	Pfizer/1	4	AMAN	AMAN	–	NR	NR	2	- IVIg	+	Dead
			81/F	Pfizer/1	3	AIDP	AIDP	+	NR	NR	1	- IVIg	–	PR
12	Hasan et al. [37]	UK	62/F	AZV/1	11	AIDP	AIDP	+	NR	Normal	1	- IVIg	+	Poor
13	Hughes et al. [38]	USA	65/M	Pfizer/1	2	AIDP	AIDP	+	NR	Normal	1	- IVIg	–	CR
14	Introna et al. [39]	Italy	62/M	AZV/1	10	AIDP	AMSAN	+	+/GM1	Normal	1	- IVIg	–	PR
15	Jain et al. [20]	USA	65/F	J & J	19	BFP	NT	+	–	Normal	4	- IVIg, PLEX	–	CR
16	James et al. [19]	India	60/M	AZV/1	11	AMSAN	AMSAN	+	NT	-Normal	1	- IVIg	–	CR
			66/M	AZV/1	12	AIDP	AIDP	+	NT	-Nonspecific[e]	1	- IVIg, IVMP	–	CR
			54/F	AZV/1	13	AIDP	AIDP	NT	–	-Normal	2	- IVIg, IVMP	–	CR
17	Kanabar et al. [40]	UK	61/F	AZV/1	10	AIDP	AIDP	+	NR	NP	1	- IVIg	–	CR
			56/M	AZV/1		AIDP	AIDP	+	NR	NP	1	- IVIg	–	CR
18	Karimi et al. [41]	Iran	38/M	Sputnik V	14	BFP	Prolong R1 and R2 latency	+	NR	-Normal	4	- PLEX	–	CR
			38/M	Sputnik V/1	8	AIDP		+	NR	-Normal	1	- PLEX	–	PR
			87/M	Sinopharm/1	4	AIDP		+	NR	-Normal	1	- IVIg	–	PR
			52/M	Sputnik V	21	AIDP	AIDP	+	NR	-Normal	1	- IVIg	–	CR
			48/F	Sputnik V	17	Classic SM	AIDP	NT	NR	-NP	3	- IVIg, PLEX	+	PR
			26/F	Sinopharm/2	37	AIDP	AIDP	_	NR	-NP	2		–	CR
			44/M	AZV/1	14	AMSAN	NT	+	NR	-NP	1	- IVIg	–	CR
			76/M	Sinopharm/1	14	AMAN	AIDP	+	NR	-NP	2	- IVIg	–	CR
			79/M	AZV/1	7	AMSAN	AMSAN AMAN AMSAN	NT	NR	-NP	2	- PLEX - PLEX		PR
19	Ling et al. [25]	Canada	63/M	AZV/1	12	AIDP	AIDP	+	NT	Normal	1	- IVIg, PLEX	–	PR

Table 1 (continued)

No	Authors	Country	Age/sex	Vaccine/dose	Onset time (day)	GBS subtype	Electrophysiologic finding	Albuminocytological dissociation	Ganglioside Ab	MRI	Brighton collaboration level	Treatment	Intubation	Outcome
20	Loza et al. [42]	USA	60/F	J&J	10	MFS and classic overlap	Absent F waves and H reflex	+	−	Cauda equina enhancement	1	- IVIg	−	CR
21	Malamud et al. [43]	USA	14/M	Pfizer/2	30	AIDP	AIDP	+	NR	NP	1	- IVIg	−	CR
22	Maramottom et al. [44]	India	43/F	AZV/1	10	AIDP	AIDP	+	NT	NP	1	- IVIg	+	CR
			67/F	AZV/1	14	AMSAN	AMSAN	+	−	Normal	1	- IVIg, PLEX	+	Poor
			53/F	AZV/1	12	AIDP	AIDP	+	−	Normal	1		+	Poor
			68/F	AZV/1	14	AIDP	AIDP	+	−	Normal	1	- IVIg	+	Poor
			70/M	AZV/1	11	AIDP	AIDP	NT	NT	NP	2	- IVIg	+	Poor
			69/F	AZV/1	12	AIDP	AIDP	NT	NT	NP	2	- IVIg	−	Poor
			69/F	AZV/1	13	AIDP	AIDP	+	NT	NP	1	- IVIg, PLEX - IVIg	+	Poor
23	Masuccio et al. [45]	Italy	80/M	Moderna/2	44	AIDP	AIDP	+	−	Normal	1	- IVIg	−	CR
25	Matarneh et al. [46]	Qatar	61/M	Moderna/2	4	Pure motor	Demyelinating motor neuropathy	+	NT	NR	4	- IVIg	−	CR
27	McKean et al. [47]	Malta	48/M	AZV/1	10	AIDP	AIDP	+	−	Normal	1	- IVIg, Prednisolone	−	CR
26	Michaelson et al. [48]	USA	78/M	Pfizer/2	14	MFS	MFS	+	Equivocal	Normal	4	- IVIg	−	CR
27	Min et al. [49]	Korea	58/M	AZV/1	15	Sensory GBS	See below[f]	+	−	Normal	4	- Gabapentin	−	CR
			37/F	AZV/1	18	Sensory GBS	Normal	NT			4	- Gabapentin, Duloxetine, Tramadol		CR
28	Morehouse et al. [50]	USA	49/F	J&J	5	Classic SM	NT	−	NT	Small punctate foci	3	- IVIg, PLEX	+	Poor
29	Nasuelli et al. [51]	Italy	59/M	AZV/1	10	AIDP	AIDP	+	−	Normal	1	- IVIg	−	CR
30	Nishiguchi et al. [52]	Japan	71/M	Pfizer/1	18	MFS	MFS	+	−	Normal	4	- IVIg	−	CR
31	Ogbebor et al. [53]	USA	86/F	Pfizer/1	1	Paraparetic	NT	+	NT	Normal	2	- IVIg	−	CR

Table 1 (continued)

No	Authors	Country	Age/sex	Vaccine/dose	Onset time (day)	GBS subtype	Electro-physiologic finding	Albumino-cytological dissociation	Ganglioside Ab	MRI	Brighton collaboration level	Treatment	Intubation	Outcome
32	Oo et al. [28]	Australia	51/M	AZV/1	14	AIDP	AIDP	+	NT	NR	1	- IVIg,	+	Poor
			65/F	AZV/1	7	AIDP	AIDP	+	−	Nonspecific[g]	1	PLEX	+	PR
			66/M	AZV/1	21	AIDP	AIDP	+	NT	NR	1	- IVIg - IVIg	−	CR
33	Osowicki et al. [54]	Australia	75/F	AZV/1	17	AIDP	AIDP	NR	NR	NR	1	- NR	NR	NR
			77/F	AZV/1	17	AIDP	AIDP	NR	NR	NR	1	- NR	NR	NR
			57/F	AZV/1	13	AIDP	AIDP	NR	NR	NR	1	- NR	NR	NR
			57/M	AZV/1	12	Paraparetic	NR	NR	NR	NR	2	- NR	NR	NR
			52/F	AZV/1	20	BFP	NR	NR	NR	NR	4	- NR	NR	NR
			54/M	AZV/1	10	AIDP	AIDP	NR	NR	NR	1	- NR	NR	NR
			80/F	AZV/1	21	Paraparetic	NR	NR	NR	NR	2	- NR	NR	NR
			72/M	AZV/1	14	Classic	NR	NR	NR	NR	3	- NR	NR	NR
			59/M	AZV/1	25	Classic	NR	NR	NR	NR	4	- NR	NR	NR
			69/M	AZV/1	16	Classic	NR	NR	NR	NR	2	- NR	NR	NR
			72/F	AZV/1	11	Classic	NR	NR	NR	NR	2	- NR	NR	NR
			66/M	AZV/1	11	Classic	NR	NR	NR	NR	1	- NR	NR	NR
			63/M	AZV/1	14	Classic	NR	NR	NR	NR	2	- NR	NR	NR
			70/M	AZV/1	14	AMSAN	AMSAN	NR	NR	NR	1	- NR	NR	NR
34	Patel et al. [55]	UK	37/M	AZV/1	14	Classic SM	Patchy attenuation of motor response	+	NT	Prominent ventral Cauda equina nerve root enhance-ment	2	- IVIg	−	CR
35	Prasad et al. [56]	USA	41/M	J&J	15	BFP	demyelinat-ing	+		Normal	1	- IVIg	−	PR
36	Razok et al. [57]	Qatar	73/M	Pfizer/2	16	Paraparetic	Absent bilateral H reflex	+	NR	Bilateral lumbar nerve root enhance-ment	1	- IVIg	−	CR

Table 1 (continued)

No	Authors	Country	Age/sex	Vaccine/dose	Onset time (day)	GBS subtype	Electro-physiologic finding	Albumino-cytological dissociation	Ganglioside Ab	MRI	Brighton collaboration level	Treatment	Intubation	Outcome
37	Rossetti et al. [58]	USA	38/M	J&J	30	BFP		+	NR	Focal bilateral enhancement of the internal auditory canal, fundi and cisternal segments of the trigeminal nerves	4	- IVIg	–	CR
38	Scendoni et al. [59]	Italy	82/F	Pfizer/2	14	AIDP	AIDP	+	+[h]	NP	1	- IVIg	–	PR
39	Trimboli et al. [60]	Italy	25/F	Pfizer/2	8	AIDP	AIDP	–	NR	NP	2	- IVIg	–	CR
40	Tutar et al. [61]	Turkey	76/M	CoronaVac/2	8	AMSAN	AMSAN	–	–	Normal	2	- IVIg	–	CR
41	Waheed et al. [16]	USA	82/F	Pfizer/1	14	Classic SM	NT	+	NT	Cauda equina nerve root enhancement	2	- IVIg	–	PR

GBS, Guillain–Barré syndrome; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; *MRI*, magnetic resonance imaging; *AZV*, AstraZeneca vaccine; *J&J*, Johnson & Johnson; *NR*, not reported; *NT*, not tested; *NP*, not performed; *AIDP*, acute inflammatory demyelinating polyradiculopathy; *AMAN*, acute motor axonal neuropathy; *AMSAN*, acute motor-sensory axonal neuropathy; *BFP*, bifacial weakness with paresthesia; *MFS*, Miller Fisher syndrome; *IVIg*, intravenous immunoglobulin; *PLEX*, plasmapheresis; *CR*, complete recovery; *PR*, partial recovery; *SM*, sensory-motor; *rt*, right; *lt*, left; *SNAP*, sensory nerve action potential; *CMAP*, compound muscle action potential; *IVMP*, intravenous methylprednisolone; *CN*, cranial nerve. [a]Decreased facial CMAP amplitude, denervation in facial muscles. [b]Denervation in facial muscles. [c]Bilateral enhancement in facial nerves. [d]Anti-GQ1b, anti-titin. [e]Tiny hyperintensity in Rt anterolateral spinal cord. [f]Decreased Rt/Lt sural SNAP amplitude, temporal dispersion in Lt, and absent Rt peroneal CMAP. [g]Nonspecific white matter hyperintensities. [h]Anti-sulfatide, anti- GM2, anti-GM4

cases (~ 14%) and one person died due to GBS complications (1.1%; Table 2).

Discussion

Here, we characterized 88 patients who developed GBS following the administration of the COVID-19 vaccine. The majority of cases occurred after receiving a vector-based vaccine with the AZV vaccine being the most reported. The motor deficit was the most common finding among patients who received the AZV vaccine. The latency between vaccination and the onset of neurological symptoms was highly variable (2–30 days; 13.9 ± 7.41 days). The severity of the complications ranged from mild symptoms to severe life-threatening conditions. Thirteen patients required mechanical ventilation. While the favorable outcome was achieved in most cases, some patients had partial recovery and poor outcomes such as unconsciousness and prolonged mechanical ventilation via tracheostomy. A favorable prognosis with a high chance of response to IVIG therapy was in line with our own experience, i.e., we recently reported three cases of post-COVID-19 vaccination GBS of acute motor axonal neuropathy subtype with a considerable short-term recovery in response to treatment with IVIG suggestive for a temporal association between GBS incidence and COVID-19 vaccination [62].

Notably, a high proportion of patients with BFP variant was reported with COVID-19 vaccine–associated GBS, compared to previous studies of non-vaccine-associated GBS. In the current study, the BFP variant was seen in 15.9% of patients while it generally constitutes less than 5% in GBS cases [63].

General pain and weakness were reported to be the most common adverse events of the AZV COVID-19 vaccine in a recently published large-scale phase III study. Interestingly, only two patients who received the vaccine have shown nervous system disorders, i.e., one patient developed chronic inflammatory demyelinating polyradiculoneuropathy and the other suffered from hypoesthesia [64]. The Pfizer vaccine ranked second for COVID-19 vaccine–associated GBS in our study while no neurological adverse events were described in the phase III study [65]. Another interesting notion was that the majority of GBS cases occurred after the second dose of the Pfizer vaccine which was in contrast to the other observations.

In earlier studies, a higher incidence of GBS was observed among those vaccinated with AZV compared to the general population [21, 66] while this was not the case in Pfizer-vaccinated individuals. In a self-controlled case study using the English national immunization database of COVID-19 vaccination, a total of 187 cases of GBS (out of more than 32 million subjects) have been observed during 1–28 days following vaccination with the first dose of either AZV or Pfizer vaccines (incidence ~ 0.6 cases per 100,000 first dose vaccination). No association was found between the Pfizer vaccine and the risk of GBS in this period. However, an increased risk of GBS was found after AZV vaccination (IRR, 2.04; 95% CI: 1.60–2.60). Nevertheless, the risk of GBS was substantially higher within 28 days of a positive COVID-19 test (IRR, 5.25; 95% CI: 3.00–9.18) [21].

In an interim analysis of surveillance data of COVID-19 vaccines, Hanson et al. compared the adjusted rate ratio (RR) of GBS incidence in the other vector-based vaccine (J&J) vs. mRNA vaccines (Pfizer, Moderna) during the 1–21 days post-vaccination period. The adjusted RR (adjusted for age, sex, race/ethnicity, and calendar day) of GBS following J&J vs. mRNA vaccines was 20.56 showing a significantly higher risk for J&J recipients compared to mRNA vaccines with 15.5 excess GBS cases per million J&J vaccines (95% CI: 6.94–64.66, $P < 0.001$) [67].

Very rarely central nervous system autoimmune diseases were also described in association with the COVID-19 vaccine [68]. Different potential mechanisms can be suggested for the possible association of autoimmune diseases after vaccination. This may include the similarity of vaccine epitopes with myelin or axon epitopes and triggering cellular and humoral immune responses, degradation of axon or myelin membranes due to direct exposure of vaccine virus or vaccine-related products, and chances of genetic predisposition [69]. The presence of a temporal association between vaccination and GBS is by no means adequate evidence for a causal relationship between the two, however suggestive of one. Regardless, a wide range of time intervals between the vaccination and the occurrence of GBS symptoms (3 h to 39 days) seen in this study again suggests a complex multifactorial relationship rather than a direct link between the two.

Conclusion

GBS is a rare neurologic disease and a few cases of GBS have been reported worldwide in association with vaccination against COVID-19. The available data is insufficient to determine the precise pathophysiology behind this observation. In this review, we provided a summary of current evidence on clinical and neurophysiological characteristics of post-COVID-19 vaccination GBS. This information helps physicians in early diagnosis and appropriate management of this rare type of GBS and enables them to have an evidence-based discussion with patients, particularly when dealing with vaccine hesitancy. Furthermore, our data add to the growing body of evidence suggestive of an association between various COVID-19 vaccines and the occurrence of GBS. Nonetheless, the benefits of vaccines against

Table 2 Summary of types of vaccine injections and related clinical findings

Variable			Total cases
Sex (%)	Female	33 (37.5)	88
	Male	55 (62.5)	
Age, years, mean ± SD		57.80 ± 16.59	
Vaccine name (%)	AstraZeneca	52 (59.1)	88
	Pfizer & BioNTech	20 (22.7)	
	Moderna	2 (2.3)	
	Johnson & Johnson	5 (5.7)	
	Sputnik	4 (4.5)	
	Sinopharm	3 (3.4)	
	SinoVac	1 (1.1)	
	Unknown vector-based	1 (1.1)	
Vaccination dose	First	70 (79.5)	88
	Second	10 (11.4)	
Latency period, days, mean ± SD (from vaccination to symptom onset)		13.90 ± 7.41	87
Symptoms (%)	Facial weakness	24 (27.3)	88
	Limb weakness	42 (47.7)	
	Bulbar palsy	10 (11.4)	
	Ophthalmoplegia	7 (8)	
	Sensory disturbances	34 (38.6)	
	Sphincter weakness	1 (1.1)	
CSF protein (%)	Elevated	57 (87.7)	65
	Normal	8 (12.3)	
Ganglioside antibody (%)	Positive	5 (17.9)	28
	Negative	23 (82.1)	
GBS subtype (%)	AIDP	38 (43.2)	88
	AMAN	4 (4.5)	
	AMSAN	9 (10.2)	
	BFP	14 (15.9)	
	Paraparetic	4 (4.5)	
	MFS-GBS overlap syndrome	2 (2.2)	
	Pure motor	1 (1.1)	
	Pure sensory	2 (2.3)	
	Unspecified classic sensory-motor	11 (12.5)	
	Miller Fisher Syndrome	3 (3.4)	
Treatment (%)	IVIg	61 (69.3)	88
	Glucocorticoids	6 (6.8)	
	Plasmapheresis	12 (13.6)	
	Conservative	3 (3.4)	
Intubation (%)	Yes	17 (25.4)	67
	No	50 (74.6)	
Outcome (%)	Favorable	46 (63)	73
	Partial improvement	16 (21.9)	
	Poor	10 (13.7)	
	Death	1 (1.4)	
Brighton collaboration level (%)	1	41 (46.6)	88
	2	24 (27.3)	
	3	4 (4.5)	
	4	19 (21.6)	

CSF, cerebrospinal fluid; *GBS*, Guillain–Barre syndrome; *AIDP*, acute inflammatory demyelinating polyradiculopathy; *AMAN*, acute motor axonal neuropathy; *AMSAN*, acute motor-sensory axonal neuropathy; *BFP*, bifacial weakness with paresthesia; *MFS*, Miller Fisher syndrome; *IVIg*, intravenous immune globulin

COVID-19 certainly outweigh the potential risk of GBS with a prognosis that proved to be favorable in the majority of cases.

Author contribution All authors contributed to the study conception and design. Material preparation, data extraction, and assessment were performed by Meysam Abolmaali, Arman Karimi Behnagh, and Negin Mahmoudi Hamidabad. The first draft of the manuscript was written equally by Zahra Mirzaasgari, Meysam Abolmaali, Arman Karimi Behnagh, and Negin Mahmoudi Hamidabad and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

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