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Clinical short communication

COVID-19 vaccine-related Guillain-Barré syndrome in the Liguria region of Italy: A multicenter case series

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ABSTRACT

Background and purpose: Guillain-Barré-Syndrome (GBS) can follow COVID-19 vaccination, with clinical and paraclinical features still to be precisely assessed. We describe a cohort of patients who developed GBS after vaccination with different types of COVID-19 vaccines.

Methods: Patients with post-COVID-19 vaccination GBS, admitted to the six hospitals that cover the whole Liguria Region, Northwestern Italy, from February 1st to October 30th 2021, were included. Clinical, demographic, and paraclinical data were retrospectively collected.

Results: Among the 13 patients with post-COVID-19 vaccination GBS (9 males; mean age, 64 year), 5 were vaccinated with Oxford-AstraZeneca, 7 with Pfizer-BioNTech, and one with Moderna. Mean time between vaccination and GBS onset was 11.5 days. Ten patients developed GBS after the first vaccination dose, 3 after the second dose. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) was the predominant GBS variant, mainly characterized by sensory involvement. Bilateral seventh cranial nerve involvement followed AstraZeneca vaccination in two cases. Three patients presented treatment-related fluctuations, and 4 mild symptoms that delayed treatments and negatively affected prognosis. Prognosis was poor (GBS-disability score, $\geq$3) in 5/13 patients, with a disability rate of 3/13.

Conclusions: Our findings confirm that most post-COVID-19 vaccination GBS belong to the AIDP subtype, and occur after the first vaccine dose. Treatment-related fluctuations, and diagnosis-delaying, mild symptoms at onset are clinical features that affect prognosis and deserve particular consideration.

1. Introduction

Guillain-Barré Syndrome (GBS) is a rare immune-mediated disorder of the peripheral nerves and nerve roots, usually presenting with different degrees of weakness, sensory abnormalities and autonomic dysfunction [1]. Infections of the respiratory and gastrointestinal tracts can typically precede GBS, and SARS-CoV-2 has revealed as one of the many infectious agents associated with the disease [2]. COVID-19 vaccination campaign is effective in reducing the risk of severe disease. Efforts in such vaccination, and the hope for a pancoronavirus vaccine, can make pandemic of SARS-CoV-2, its new variants, or any future cousins under control a realistic expectation [3]. The vaccination is also expected to limit SARS-CoV-2 infection long-term sequelae, including those affecting the nervous system. GBS is one of the

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neurological adverse events that can associate with both SARS-CoV-2 infection and vaccination reviewed in [4]. Large well-designed epidemiologic studies cast doubt upon associations between COVID-19 and GBS [5], and between COVID-19 vaccination and GBS [6]. Frequency of neurological complications after SARS-CoV-2 infection, including GBS, is much higher than after COVID vaccination [7]. However, information on the clinical and paraclinical features of post-COVID-19 vaccine GBS can be useful for optimal management of single cases and for health system-related purposes.

We report on a case-series of 13 patients who developed GBS after being vaccinated with different COVID-19 vaccines, and who were admitted to the hospital network that covers a highly populated region of Northwestern Italy.

2. Patients and methods

2.1. Study design and methods

In Italy, as well as in most countries of the European Union, a mass vaccination campaign against SARS-CoV-2 started in December 2020. Patients with GBS admitted to the six hospitals that cover the whole Liguria region, North-western Italy, from February 1st 2021, to October 30th 2021, were included in this study.

Epidemiologic data about the vaccination campaign in the Liguria Region were obtained [8].

The patients, who fulfilled the diagnostic criteria for GBS [9], were enrolled if the syndrome occurred within six weeks after COVID-19 vaccination [10], and they resulted negative to nasopharyngeal swab PCR tests for COVID-19. Clinical, demographic, and paraclinic data were retrospectively collected.

To properly distinguish acute inflammatory demyelinating polyradiculoneuropathy (AIDP) from acute motor and motor-sensory axonal neuropathy (AMAN-AMSAN), the Hadden criteria [11] were applied on the second electrodiagnostic study [12], when available.

Degree of disability was assessed by the GBS Disability Score (GBS-DS) [13], and muscle strength measured by the Medical Research Council Muscle Score (MRC-MS) [14] on 12 muscles at the first neurological examination (T0), and at the last neurological evaluation (T1). GBS-DS ≥ 3 were considered predictors of poor prognosis. Treatment-related fluctuations of symptoms were also considered [15], and, if necessary, adequately treated (Table 2).

Laboratory tests included extensive microbiological and autoimmune screening, complete cerebrospinal fluid (CSF) analysis, including the search for oligoclonal IgG bands, serum ganglioside antibody determinations with both ELISA (GM1, GQ1b, GD1b IgG and IgM; Bühlmann, Switzerland) and immunoblot (GM1/2/3/4, GD1a/b, GD2/3, GT1a/b, GQ1b, and sulfatides IgG and IgM; Alifax, Italy). Recent infections were excluded by testing for: *Cytomegalovirus*, *Herpes simplex virus-1/2*, *Haemophilus influenzae* and *Mycoplasma pneumoniae* IgM, *Campylobacter jejuni* IgM/IgA, *Epstein-Barr virus* capsid antigen (VCA) IgM.

Finally, using the IGOS registry [16] and medical and electronic records from the Liguria Region's hospitals discharge data (ICD-9 code, 357.0), we also gathered information on the GBS cases unrelated to COVID-19 vaccine that occurred in the same timeframe considered by this study.

2.2. Ethics

The study was approved by the local Ethics Committees, and all subjects gave their consent to use anonymized data.

3. Results

In the period covered by this study, 1,115,509 inhabitants (72.7% of the Ligurian population) received a first dose of COVID-19 vaccine, 1,062,010 a second dose, and 37,457 a booster dose. The percentages of the first doses and second doses, subdivided by type of vaccine, were, respectively: Janssen 2.93% (no second dose), Moderna 12.99 and 13.42%, Pfizer 68.15 and 72.88%, and AstraZeneca 15.93 and 13.70%.

Tables 1 and 2 summarize clinical, demographic, and paraclinical features of the 13 patients with post-COVID-19 vaccination GBS (9 males; mean age at onset, 64.1 years; age range, 18–89; 11 with AIDP, 2 with AMSAN). Five patients were vaccinated with ChAdOx1 nCov-19 (Oxford-AstraZeneca), 7 with BNT162b2 (Pfizer-BioNTech), and one with mRNA1273 (Moderna). None of them reported infectious episodes during the month before the onset of GBS symptoms and recent infections that more commonly precede GBS were reasonably excluded by negative serology results.

The onset of GBS symptoms occurred in 10 patients after the first vaccine dose, and in 3 after the second dose of Pfizer-BioNTech vaccine. GBS apart, only common and mild adverse events following immunization were reported (Table 1).

The mean time between vaccination and GBS onset was 11.5 days (range, 4–21). All the patients but one with a pure ataxic form developed the classic sensorimotor form of GBS, with cranial nerve involvement in 4, and ataxia in 2 (Table 2). Only one patient developed autonomic dysfunction. Notably, four patients were hospitalized >45 days (mean time, 79 days; range, 60–90) after the onset of symptoms, which were particularly mild (#10–13, Table 1). They suffered from distal paresthesia of lower limbs with balance disturbances starting an average of 9 days after vaccination, and progressively worsening over a month, with heavy motor disability (Table 2). Their polyneuropathy was demyelinating. Clinical pictures subsequently improved progressively without therapy, and stabilized, but the patients did not fully recover. This led to late therapeutic attempts with IVIg in two of them, without clinical improvements. In these patients, the temporal correlation with the vaccine, the achievement of the nadir during the first 4 weeks from the onset of symptoms, the spontaneously improving disease course, the failure of the late therapeutic attempt with IVIg, and the lack of subsequent relapses led us to achieve a final diagnosis of GBS, and to exclude acute CIDP.

CSF findings were characterized by high total protein concentrations in 7 patients. In two of them, lymphomonocyte counts were above the reference value (Table 2). Extensive microbiological analysis, which included serology for HIV and *Borrelia burgdorferi*, namely the two infectious agents typically associated with pleocytosis in GBS, was negative. Alternative causes of pleocytosis in the two patients were excluded with dorso-lumbar MRI too. Ganglioside antibodies were negative.

As for disease severity, Table 2 reports the MRC-MSs and GBS-DSs calculated at baseline and follow-ups, assessed after a mean time of 57 days (range, 16–113). Poor prognosis (GBS-DS ≥ 3) occurred in 5/13 (38.4%) of the patients, with mortality rate of 15.4% (2/13), and disability rate of 23,1% (3/13).

Ten patients were treated with intravenous immunoglobulins (IVIg; 0.4 g/kg for 5 days). Infusions were stopped in one at the fourth day due to pulmonary thromboembolism. One patient underwent plasma-exchange, whereas two patients improved without treatment. After initial post-therapy improvements, GBS worsened in three patients over two months after onset (treatment-related fluctuation) [15]. Therefore, one patient was treated with a further course of IVIg, one with plasma-exchange followed by IVIg, and one improved without therapy (Table 2). Re-treatments were unsuccessful, as one patient died, and another did not substantially improve.

Finally, Table 3 shows the features of the 17 GBS cases unrelated to COVID-19 vaccine that occurred during the same period covered by this study. By comparing the two groups, there was no difference in age at onset, gender prevalence, prognosis, and mortality rate (Table 4). Conversely, in the COVID-19 vaccine-unrelated GBS patients, the antecedent infectious events ($p = 0.001$), and the AMSAN-AMAN subtype ($p = 0.025$) were more frequent.

Table 1
Clinical, demographic, and vaccine-related features of the 13 patients with post-COVID-19 vaccination Guillain-Barrè syndrome.

Pt #	Sex, Age (yrs)	Comorbidity	Vaccine type	AEFI	Vaccine to onset (days)	Onset to hospital (days)	Onset to therapy (days)	Back pain	Deep tendon reflexes	Sensory symptoms	Ataxia	Cranial nerves	Dys-autonomia	Respiratory failure
1	M, 68	None	OAZ 1st dose	Muscle pain	12	20	21	Yes	Areflexia, UL & LL	Distal paresthesia, LL	No	Bifacial paresis	No	No
2	F, 71	Diabetes, hypertension	PBT 1st dose	Asthenia	10	12	19	Yes	Hypo-reflexia, UL & LL	Distal paresthesia, UL & LL	No	3rd & 6th paresis	No	No
3	F, 40	None	PBT 2nd dose	Muscle pain	4	4	5	No	Areflexia, LL	None	No	7th & 9th paresis	No	No
4	M, 89	Atrial fibrillation, chronic ischemic heart disease	Mod 1st dose	None	15	13	19	Yes	Areflexia, UL & LL	Paresthesia, hands & tongue	No	None	Unstable blood pressure	Yes
5	M, 65	Psoriasis	OAZ 1st dose	Headache	15	1	5	No	Hypo-reflexia, UL & LL	Distal paresthesia, LL	No	Bifacial paresis	No	Yes
6	M, 80	Atrial fibrillation, hypertension	PBT 2nd dose	None	21	7	8	No	Areflexia, LL	Distal paresthesia LL	No	None	No	No
7	F, 69	None	OAZ 1st dose	None	17	4	8	Yes	Hypo-reflexia, UL & LL	Distal paresthesia, UL & LL	No	None	No	No
8	M, 18	Type 1 diabetes	PBT 1st dose	None	12	2	4	No	Hypo-reflexia, UL; areflexia, LL	Distal paresthesia, LL	No	None	No	No
9	M, 57	Hypertension, obesity	PBT 1st dose	Fever	5	19	20	No	Areflexia, LL & UL	None	Yes	None	No	No
10	M, 64	None	OAZ 1st dose	Abdomino-pelvic rash	15	90	120	No	Areflexia, LL	Distal paresthesia, LL	No	None	No	No
11	M, 88	Type 2 diabetes, chronic ischemic heart disease	PBT 2nd dose	None	15	75	90	No	Hypo-reflexia, LL & UL	Distal paresthesia, LL	Yes	None	No	No
12	F, 73	None	OAZ 1st dose	None	5	90	NA	No	Hypo-reflexia, UL; areflexi, LL	Distal paresthesia, UL & LL	No	None	No	No
13	M, 51	None	PBT 1st dose	None	4	60	NA	No	Hypo-reflexia, UL; areflexia, LL	Distal paresthesia, UL & LL	Yes	None	No	No

Pt, patient; yrs., years; F, female; M, male; OAZ, Oxford-Astra-Zeneca; PBT, Pfizer-BioNTech; Mod, Moderna; AEFI, Adverse events following immunization; UL, upper limbs; LL, lower limbs; NA, not applicable (no therapy).

Table 2
Disease subtype, laboratory findings, and treatment-related features of the 13 patients with post-COVID-19 vaccination Guillain-Barré syndrome.

Pt #	Subtype	CSF Ly (cells/mm^3)*	CSF proteins (g/L)^	Therapy	TRF	TRF therapies	T1 (days from T0)	MRC-MS (T0 vs T1)	GBS-DS (T0 vs T1)
1	AIDP	15	1.67	IVIg	None	NA	60	43; 49	4; 1
2	AMSAN	2	1.63	IVIg	Yes	None	60	41; 48	4; 2
3	AIDP	3	2.92	IVIg	None	NA	60	51; 46	4; 2
4	AMSAN	0	1.20	IVIg	None	NA	16	35; 20	4; 6
5	AIDP	4	0.52	PEX	Yes	PEX, IVIg	90	42; 14	3; 6
6	AIDP	38	1.27	IVIg	None	NA	66	44; 56	4; 3
7	AIDP	0	0.41	IVIg	Yes	IVIg	113	46; 55	4; 3
8	AIDP	1	0.29	IVIg	None	NA	36	50; 60	3; 1
9	AIDP	1	0.80	IVIg	None	NA	30	54; 60	3; 1
10	AIDP	NP	NP	IVIg	None	NA	60	54; 54	2; 2
11	AIDP	3	1.83	IVIg	None	NA	60	60; 60	3; 3
12	AIDP	0	0.37	None	None	NA	60	58; 58	1; 1
13	AIDP	2	0.39	None	None	NA	30	58; 58	2; 2

Pt, patient; CSF, cerebrospinal fluid; Ly, lymphomonocytes; *reference range, < 5; ^reference range, < 0.52; AIDP, acute inflammatory demyelinating polyneuropathy; AMSAN, acute motor-sensory axonal neuropathy; GBS-DS, GBS-disability score; IVIg, intravenous immunoglobulins; MRC, medical research council muscle score; NP, lumbar puncture not performed; NA, not applicable; PEX, plasma exchange; T0, first neurological evaluation; T1, last follow-up neurological evaluation; TRF, treatment-related fluctuations.

Table 3
Clinical and demographic features of the 17 patients with COVID-19 vaccination-unrelated Guillain-Barrè syndrome.

Pt #	Sex, Age (years)	Antecedent events	GBS subtype	Therapy	TRF	Cranial Nerves	Ataxia	Dysautonomia	Respiratory failure	Months to last follow-up visit	GSB-DS (T0 vsT1)
1	F, 32	Influenza vaccination	AIDP	IVIg	No	No	No	No	No	3 months	2; 1
2	M, 55	*Campylobacter Jejuni* infection	AMAN	PEX, IVIg	No	Bifacial paresis, dysphagia, dysphonia	No	Hypotension	Yes	6 months	5; 6
3	M, 57	None	AIDP	PEX, IVIg,	No	Bifacial paresis	No	No	Yes	1 month	5; 6
4	F, 80	Fever	AIDP	PEX	No	No	Yes	No	No	14 months	2; 1
5	F, 28	CMV infection	normal ENG	IVIg	No	Bifacial paresis, perioral myokymies	No	No	No	5 months	1; 1
6	F, 62	None	AMSAN	PEX	No	Left 3rd nerve paresis, dysphonia, dysphagia	No	Acute urinary retention	Yes	1 month	5; 6
7	F,70	Bronchitis	AMSAN	IVIg	No	No	No	Acute urinary retention	Yes	12 months	3; 2
8	M, 58	None	AIDP	IVIg	No	No	No	No	No	4 months	4; 3
9	M, 52	SARS-CoV-2	AMAN	PEX, IVIg	No	Bifacial & left 6th nerve paresis	No	No	Yes	12 months	5; 3
10	M, 91	Gastroenteritis	AMAN	IVIg	No	No	No	No	No	5 months	4; 1
11	M, 80	Pneumonia	AMAN	IVIg	No	No	No	No	Yes	NA	5; NA
12	M, 59	Gastroenteritis	AMSAN	IVIg	No	5th nerve paresis, dysphagia, dysphonia	No	No	Yes	5 months	5; 1
13	M, 74	SARS-CoV-2	AMSAN	IVIg	No	No	No	No	No	10 months	4; 0
14	M, 75	None	AIDP	IVIg	Yes	No	Yes	No	No	2 months	2; 2
15	M, 86	Gastroenteritis	AMSAN	IVIg	No	No	No	No	No	5 months	4; 0
16	M, 45	None	AIDP	IVIg	No	Bifacial paresis	Yes	No	No	2 months	2; 1
17	M, 74	None	AIDP	PEX	No	No	Yes	No	No	3 months	4; 1

AIDP, Acute Inflammatory Demyelinating Polyneuropathy; AMAN, Acute Motor Axonal Neuropathy; AMSAN, Acute Motor and Sensory Axonal Neuropathy; CMV, Cytomegalovirus; ENG, electroneurography; GBS, Guillain-Barré syndrome; GBS-DS, Guillain-Barré Syndrome Disability Score; IVIg, intravenous immunoglobulins; NA, not available; PEX, plasma-exchange; Pt, patient; TRF, treatment related fluctuations; T0, first neurological evaluation; T1, last follow-up neurological evaluation.

4. Discussion

We outlined the clinical features of thirteen post-COVID-19 vaccination GBS patients admitted to the hospital network of the Liguria Region, an area of about 1.5 million inhabitants, over a period that covers the mass vaccination campaign for COVID-19 in Italy.

The patients were mostly male, with mean age at onset older than that reported in other case series [4], but in Italy the vaccination campaign for young people started later, in the second half of 2021. The demyelinating type of GBS (AIDP) was more frequent than the axonal form, as previously reported [17,18], with the exception of the case series by Kim and colleagues [19], characterized by patients with a primary axonal subtype. A peculiarity of post-COVID-19 GBS is the common cranial nerve involvement [18,20,21], which occurred in 4/13 of our patients. Two of them, vaccinated with AstraZeneca vaccine, showed bilateral facial paresis, a finding already associated with this type of vaccine [17,18,20].

A particularly interesting feature of our case series is the predominance of sensory disturbances, which were overt in 11/13 patients, and only electrophysiologically documentable in the other two patients (#3 and #9). This is noteworthy also because we did not find AMAN cases, which, conversely, were the most frequent within a series of COVID-19 vaccine-unrelated GBS that we documented as occurring in the Liguria Region over the timeframe considered in this study. A higher frequency of antecedent infectious events characterized this GBS variant too (Table 4). A high frequency of sensory-predominant GBS forms has been

Table 4
Comparison of features between patients with COVID-19 vaccine-related and -unrelated Guillain-Barré syndrome.

Features		COVID-19 vaccine-related GBS	COVID-19 vaccine-unrelated GBS	*p*-value*
		(*n* = 13)	(*n* = 17)	
Male (%)		9 (69.2)	12 (70.6)	0.936
Mean age at onset (SD)		64.1 (19.4)	63.4 (17.8)	0.922
EDX subtype (%)	AIDP	11 (84.6)	7 (41.2)	**0.022**
	AMSAN-AMAN	2 (15.4)	9 (52.9)	**0.023**
	Normal ENoG	0	1 (5.9)	NA
Infectious antecedent (%)		0	10 (58.2)	**0.001**
Cranial nerves (%)		4 (30.7)	7 (41.2)	0.558
Ataxia (%)		3 (15.3)	4 (23.5)	0.97
Autonomic dysfunction (%)		1 (7.6)	3 (17.7)	0.427
TRF (%)		3 (23)	1 (14)	0.172
Therapy (%)	IVIg	10 (76.9)	11 (64.7)	0.132
	PEX	1 (7.6)	3 (17.6)	
	IVIg plus PEX	0	3 (17.6)	
	No therapy	2 (15.3)	0	
Mean GBS-DS at the last follow up (SD)		2.53 (1.71)	2.18 (2.07)	0.629
Mortality (%)		2 (15.4)	3 (17.6)	0.869

AIDP, Acute Inflammatory Demyelinating Polyneuropathy; AMAN, Acute Motor Axonal Neuropathy; AMSAN, Acute Motor and Sensory Axonal Neuropathy; EDX, electrodiagnostic; ENoG, electroneurography; GBS, Guillain-Barré syndrome; GBS-DS, Guillain Barré Syndrome Disability Score; IVIg, intravenous immunoglobulins; PEX, plasma-exchange; TRF, treatment related fluctuations; *paired *t*-test.

also reported by Min and colleagues, who described 13/15 patients with sensory symptoms, with the remaining two showing electrophysiologically documented sensory involvement [4].

In 5/13 (~40%) of our cases, GBS prognosis was poor. In comparison with the literature data (3–7% [1]), our mortality rate (2/13) was higher, but overestimation is more than likely. On the contrary, our percentage of patients with residual disability was superimposable to what expected [1]. Prognosis was initially good in 8/13 patients. However, in 4 of them post-vaccination GBS started with symptoms so mild that led to late diagnosis, late therapy, and, eventually, uncomplete recovery. The recognition of this insidious onset is thus important to start early treatments and favor complete recovery.

As an element of distinction, already described in only one case series of post-COVID-19 vaccination GBS [19], three patients showed early deterioration after initial improvements, or plateau phases (treatment-related fluctuation). This phenomenon suggests that in a part of post-COVID-19 vaccination GBS patients the immunologic mechanisms underlying disease activity could be less responsive to the effects of immunotherapy, thus requiring additional treatment. We found no difference in prognosis and mortality rate, when comparing the features of two groups with either COVID-19 vaccine related vs unrelated GBS that occurred in the Liguria Region during the same timeframe.

The study has some limitations. First, the observational retrospective nature of the study, and the relatively small sample size hinder in-depth analysis and definite conclusions. Second, previous data on GBS epidemiology in the Liguria Region were available for the lockdown period only (from February 15th to May 3rd 2020) [22], so it was impossible to assess whether, over an equivalent period, GBS cases increased following both COVID-19 vaccination, and SARS-CoV-2 infection. Third, in the Liguria Region the administration of Pfizer was prevalent over the other types of vaccines, so if one type (especially conventional vs mRNA-based vaccines) was more frequently involved in inducing GBS cannot be assessed.

5. Conclusions

Our findings on post-COVID-19 vaccination GBS confirm that most cases belong to the AIDP subtype and occur after the first vaccine dose, and that AstraZeneca-associated bilateral seventh cranial nerve involvement is not an uncommon manifestation. Particular features include a very high frequency of sensory involvement, and clinical manifestations, such as treatment-related fluctuations, and insidious diagnosis-delaying, mild symptoms at onset, that adversely affect prognosis and deserve prompt recognition. Overall, our data contribute to fill a gap in the current literature on post-COVID-19 vaccine adverse events.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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