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Neuroimmunology Reports 2 (2022) 100083

Contents lists available at ScienceDirect

Neuroimmunology Reports

journal homepage: www.elsevier.com/locate/nerep

Guillain-Barre syndrome following COVID-19 vaccination: a case report and an updated review.

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ARTICLE INFO

Keywords:
Guillain-Barre
Covid-19 vaccine
Vaccination

ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) has caused a pandemic that has recently affected every aspect of life. Fortunately, many vaccines with high safety and efficacy profiles were developed timely to face this pandemic. In a very short time, billions of people were vaccinated. In the meantime, a wide range of neurological syndromes are being reported. Guillain-Barré syndrome (GBS) which is a rare immune-mediated post-infectious peripheral neuropathy was reported after both the COVID-19 infection itself and many types of its vaccines.
Methods: We are reporting a case of post-AstraZeneca vaccine GBS and reviewing the literature of all reported post-COVID-19 vaccines GBS till July 2021.
Results: 29 adult patients were reported. Of them 58.6% were males. Their mean age is 58.2 years. The median time to clinical onset after vaccine administration was 13.2 days. 86.2% of patients had their symptoms following immunization with the 1st dose of AstraZeneca vector-based covid vaccine. Facial palsy was the most predominant single symptom in 75.8% of patients.
Conclusion: Guillain-Barré syndrome is a well-recognized but still rare adverse event following vaccination against COVID-19. Although preliminary data incriminates viral vector-based vaccines more than the other types, active post-vaccination surveillance and more powerful statistics are mandatory to reach a solid conclusion regarding the presence of a causal relation.

1. Introduction

Coronavirus disease "Covid-19" has recently caused a prevalent pandemic that has severely impacted the world's health and economic resources. Therefore, developing urgent vaccines has emerged as a necessity to alleviate such a burden. Since December 2020, millions of people have been immunized with different Covid vaccines. Despite the reported efficacy and the high safety profile of COVID-19 vaccines, their possible association with rare side effects is still being explored. Adverse events following immunization "AEFIs" with covid vaccines have been reported, through notifying The Vaccine Adverse Event Reporting System "VAERS" and The United States Centers for Disease Control and Prevention "The CDC", or by using the yellow card scheme in the Uk. Guillain-Barre syndrome, a rare neurological condition, is one of the earliest reported nervous system adverse events following covid-19 vaccination.

GBS "acute idiopathic polyneuritis, acute idiopathic polyradiculoneuritis or Landry's ascending paralysis" is an autoimmune disease reported to affect 1.1 to 1.8/100,000/year, and this incidence increases with age after 50 years from 1.7 to 3.3/100,000/year (McGrogan et al., 2009). Most GBS cases naturally occur after a viral upper respiratory tract infection, or less commonly a gastrointestinal infection. The critical significance of GBS is the possible fatal complications of respiratory failure, pneumonia, cardiac arrest, and autonomic dysfunction in some cases (van den Berg et al., 2013), and despite the self-limiting nature of the disease, early detection and treatment have proven vital to decrease hospital stay and thus prevent such lethal complications (Coll-Cantí et al., 2009, Harms, 2011, Klinov and Campellone, 2015).

Recently there were reports of GBS cases that followed infection with covid-19. Molecular mimicry, or "cross-reactivity", of glycolipid-like antigens on both neurons and viruses' cell membranes has been postulated as the main mechanism in these cases (Rahimi, 2020).

Cases of GBS were also reported to occur after vaccination, most famously influenza vaccine and swine flu vaccine in 1976. Recently, a CDC analysis revealed an increased risk of GBS following vaccination with Shingrix, a recombinant vaccine for Herpes Zoster (Tavares et al., 2019). However, it was later concluded that such occurrences were merely a coincidental temporal association and not a direct causality of the vac-

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https://doi.org/10.1016/j.nerep.2022.100083
Received 7 October 2021; Received in revised form 2 February 2022; Accepted 19 February 2022

Table 1
Motor nerves conduction studies.

Motor Nerves	Stim - Rec			Lat [ms]	Amp [mV]	CV [m/s]	Amp % [%]	Dist [m/s]
Femoral-Vastus	A.Lng.Canal	–	–	–	–	–		
Medialis-Left	B.Lng.Canal - A.Lng.Canal	12.7	0.3	–	–	–		
Femoral-Vastus	A.Lng.Canal	10.2	0.1	–	–	–		
Medialis-Right	B.Lng.Canal - A.Lng.Canal	–	–	–	–	–		
Median-APB-Right	Wrist - APB	5.8	2.1	–	–	–		
	Elbow - Wrist	10.9	1.3	39	-38.9	200		
Peroneal-EDB-Left	Ankle - EDB	5.3	0.2	–	–	–		
Peroneal-EDB-Right	Ankle - EDB	4.2	0.9	–	–	–		
Tibial-AH(Knee)-Left	Ankle - AH	9.5	-0.2	–	–	–		
	Knee - Ankle	21.5	0.3	29	–	350		
Tibial-AH(Knee)-Right	Ankle – AH	9.5	0.5	–	–	–		

cine. To confirm post-vaccination GBS, the absence of other etiologies and symptoms development within 6 weeks after immunization are both essential to the diagnosis (Park et al., 2016).

Here we describe a case of a young man who developed a severe form of GBS following immunization with AstraZeneca/Oxford vaccine and review other cases that followed covid-19 vaccines and were described in the literature.

1.1. Case presentation

A 29-year-old male patient with a previous history of asthma was seen on May 20th with a history of subacute onset of ascending bilateral weakness. The condition started 9 days before admission (May 11th) and that was 10 days after his first dose of Astrazeneca (1st of May). Before the presentation, he had received six sessions of plasma exchange with only minimal improvement.

Upon examination, the patient was fully conscious, alert, and responsive. His cranial nerve examination showed bilateral lower motor neuron facial weakness and associated dysphagia. Motor examination showed generalized hypotonia and areflexia in all limbs. The distribution of motor weakness was bilaterally symmetrical, proximal more than distal, and more profound on the lower limbs (grade 1/5) than the upper limbs (grade 3/5). Sensory examination revealed marked paraesthesia in lower limbs up to groin level bilaterally.

Nerve conduction studies were done on presentation. They showed features of axonal sensorimotor polyradiculoneuropathy (Table 1) with poor to unobtainable F waves(Figure 1). EMG revealed severe denervation potentials at rest. CSF aspirate was done, showing high albumin-cytologic dissociation (Table 2).

To exclude current or recent Covid-19 infection, a CT scan of the chest was done, which showed no signs of a viral infection, and a nasopharyngeal swab RT-PCR testing for COVID was negative on two occasions. After fulfilling the Brighton criteria for GBS (Fokke et al., 2014), and with no better explanation at hand, a diagnosis of post-vaccination GBS was made.

1.2. Treatment and follow-up

The patient was admitted to ICU for close monitoring; however, he did not require mechanical ventilation during his hospital stay. The patient was commenced on an urgent intense regimen of IVIG at a dose of 0.4/kg/day for six days. On the third day, he began to show improvement, more evident in his upper limbs motor power. After the sixth day, the muscle power assessment revealed full muscle power (5/5) in the upper limbs and improved power at 3/5 in his lower limbs. Two months later, after intense physiotherapy, he can stand without support, yet requires minimal assistance for walking.

Table 2
Laboratory investigations of the patient.

Test	Patient result	Normal range
CBC		
Hb:	13.7 g/dL	13.5:17.5
PLT:	298 × 103 /μL	140:400
WBCs:	7.72 x103 /μL	4-11
CRP	15.3	<5 mg\dL
Serum Sodium	138 mEq/L	135:155
Serum Potassium	4.3 mEq/L	3.6:5.3
Total Calcium	8.6 mg/dL	8.5:10.5
Ionized Calcium	4.5 mg/dL	4.5:5.2
Virology:		
HCV Ab	Negative	Negative
HIV Ab	Negative	Negative
HBsAg	Negative	Negative
CSF:		
WBC:	10 Cells/μL	Normal up to
MN (lymphocytes):	8 Cells/μL	5(Adult)
PMN (Neutrophils):	2 Cells/μL	Normal: Nil
RBCs:	4 Cells/μL	
Glucose	68 mg/dL	Normal: 40:70
Protein	383 mg/dL	Normal: 15:40
LDH	53 U/L	Normal: 10% of the blood level
Microbiology	Gram stain revealed no visible bacteria. Culture on blood and chocolate agar yielded no growth after 48 hours of incubation.	

1.3. Literature review

1.3.1. Patient selection and methodology

We performed an extensive search on Pubmed for Medline data to detect GBS cases that followed immunization with different covid vaccines, like our case, since December 2020, the date of first administered Covid vaccine dose. 14 published case reports and series with detailed information on 29 patients, including ours, were found between December 2020 to July 2021 (Allen et al., 2022, Patel et al., 2021, Maramattom et al., 2022, Azam, Khalil and Taha, 2021, Hasan et al., 2021, Kohli et al., 2021, James et al., 2021, Nasuelli et al., 2021, Bonifacio et al., 2021, Razok et al., 2021, Waheed et al., 2021, Márquez Loza et al., 2021, Koreen, 2021). All articles with sufficient data have been included in this literature review. Keywords used were “Guillain barre –Covid – vaccine –vaccination”.

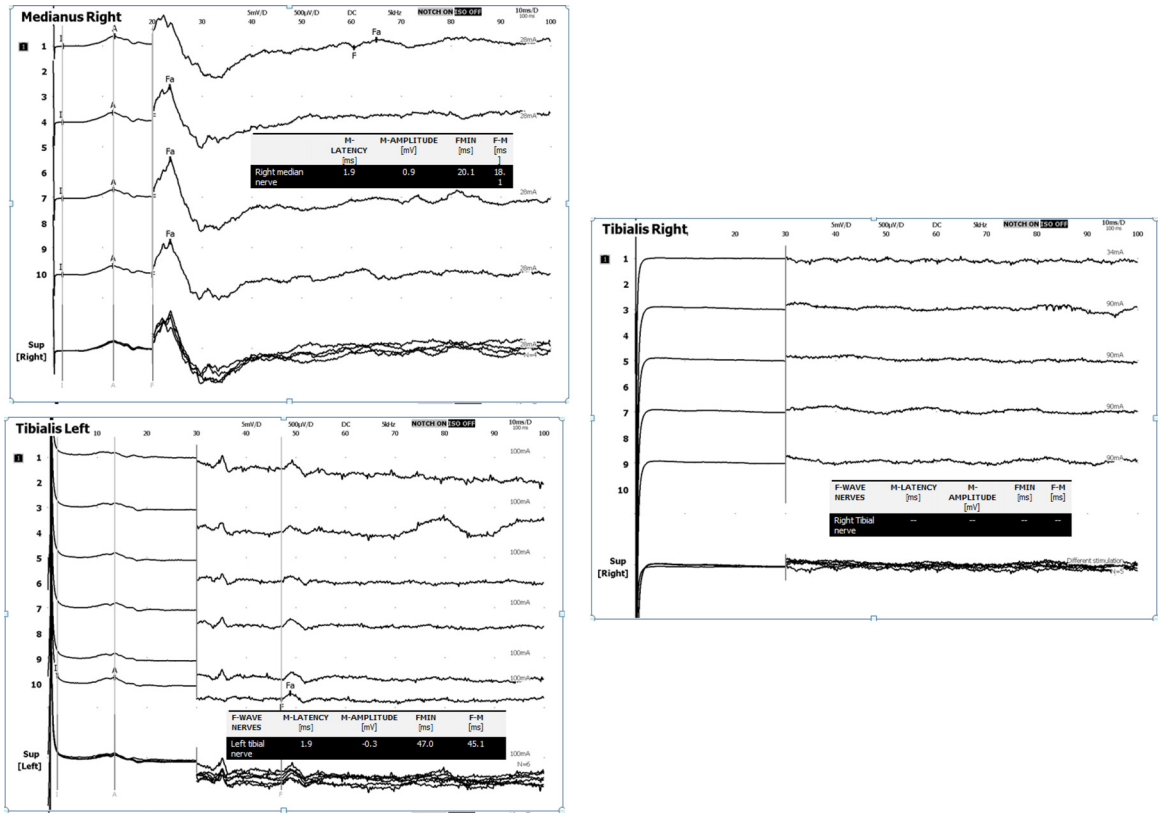

Fig. 1. F Wave latencies

*1.3.2. *Inclusion criteria*

All patients with symptoms onset within 6 weeks after immunization and no evidence of viral infection or other potential etiologies during this period (Park et al., 2016).

*1.3.3. *Exclusion criteria*

1-One patient had symptoms of GBS 40 days after receiving the first AstraZeneca dose, yet he had covid infection 15 days before symptoms' onset and thus was excluded from our literature review (Finsterer, 2021).

2-Cases that didn't follow the Brighton Criteria for GBS diagnosis were excluded (Fokke et al., 2014).

3- Cases that were not written in English were also excluded.

2. Results

The full results of the review are summarized and tabulated in Appendix 1 in supplementary material

2.1. Patient characteristics

29 adult patients were reported, and 58.6% of them were males. Their mean age is 58.2 years.65.5% of cases were reported in the age group of 50-69years (Table 3)The time to clinical onset after vaccine administration ranged from 7 to 29 days, with a median of 13.2 days.

Most patients, 86.2%, had their symptoms following immunization with the 1st dose of AstraZeneca vector-based covid vaccine (25 patients). Only two followed Pfizer vaccine doses (Razok et al., 2021, Waheed et al., 2021), and two more followed vaccination with Janssen vaccine (Márquez Loza et al., 2021, Koreen, 2021).

Table 3
The demographic characteristics of GBS' patients.

Age group	Total number	Males	Females
20-29	2	2	0
30-39	1	1	0
40-49	2	1	1
50-59	9	6	3
60-69	10	4	6
70-79	4	3	1
80-89	1	0	1
Age range	20-82	20-73	43-82
Mean age	58.2	54.7	63.1
Total	29 (100%)	17 (58.6%)	12 (41.4%)

2.2. Clinical presentation (Table 4)

22/29 patients (75.8%) had motor weakness, 17 patients had Quadriparesis with varying degrees, while five had LL weakness that ranged from only right hip flexor weakness "case 22" (Bonifacio et al., 2021)to paraparesis grade 2/5 "case 28" (Márquez Loza et al., 2021).

In seven patients, sensory examination manifested impaired sensation "paraesthesia, dysesthesia, numbness, etc," in all extremities with different presentations, while 10 patients had only LL sensory affection.

Cranial nerves involvement was reported in 25/29 patients (86.2%). Facial palsy was the most predominant single symptom in (22/29 patients) (75.8%), with 21 patients having bilateral lower motor neuron facial palsies and one patient with a unilateral affection (Koreen, 2021), which might suggest a predilection towards facial nerve involvement. Interestingly, all 22 patients received a vector-based vaccine.

12/29 patients had bulbar involvement, including a patient who had aspiration pneumonia for which he was intubated then had a tracheostomy "case 14" (Hasan et al., 2021).

Table 4
MRI findings of GBS' patients.

Case number as in Appendix 1	MRI modality and findings
Case 1 (Allen et al., 2022)	Brain with contrast: Facial nerve enhancement bilaterally
Case 2 (Allen et al., 2022)	Brain non-contrast: normal
Case 3 (Allen et al., 2022)	Brain non-contrast: normal
Case 4 (Allen et al., 2022)	Brain with contrast: Facial nerve enhancement bilaterally
Case 5 (Patel et al., 2021)	- Spine with contrast: Thickened cauda bilaterally, more at S1, T1 ventral caudal root contrast enhancement + Pial enhancement - Brain with contrast: normal
Case 7 (Maramattom et al., 2022)	Brain normal
Case 8 (Maramattom et al., 2022)	Brain normal
Case 9 (Maramattom et al., 2022)	Brain normal
Case 13 (Azam, Khalil and Taha, 2021)	Brain with contrast: Facial nerve enhancement bilaterally Cervical spinal cord normal
Case 17 (James et al., 2021)	Spinal cord normal
Case 18 (James et al., 2021)	C4-C5 level anterolateral hyperintensity
Case 19 (James et al., 2021)	Spinal cord normal
Case 20 (Nasuelli et al., 2021)	Brain and spinal cord with contrast: normal
Case 21 (Bonifacio et al., 2021)	Brain with contrast: Facial nerve enhancement bilaterally
Case 22 (Bonifacio et al., 2021)	Brain with contrast: Facial nerve enhancement bilaterally
Case 23 (Bonifacio et al., 2021)	Brain with contrast: Facial nerve enhancement bilaterally
Case 24 (Bonifacio et al., 2021)	Brain non-contrast: normal
Case 26 (Razok et al., 2021)	Spinal cord with contrast: bilateral nerve root enhancement in the lumbar region and the upper part of the cauda equine
Case 27 (Waheed et al., 2021)	Spine with contrast: enhancement of the cauda equine
Case 28 (Márquez Loza et al., 2021)	Spine with contrast: enhancement of the cauda equine
Case 29 (Koreen, 2021)	Brain and Spinal cord: normal

8 patients (27.5%) had signs of respiratory failure and seven of them were mechanically ventilated (Maramattom et al., 2022, Hasan et al., 2021, Kohli et al., 2021).

2.3. Investigations

24 patients underwent CSF analysis and all of them showed albumino-cytologic dissociation.

Protein levels in CSF ranged from 75 mg/dl (Maramattom et al., 2022) to 2,417 mg/dl (Allen et al., 2022) with a mean value of 410.8, and six patients had mild CSF pleocytosis.

Electrophysiological studies' results were reported in 25 of the patients. One patient was due to have NCS and EMG after the report submission (Razok et al., 2021). The studies were performed at different times in relation to the patients' clinical history, treatment onset, or follow-up.

Out of these 25 patients, Nerve conduction of the limbs showed normal conduction in 3 patients. 3 patients (12%), including ours, had primary axonal pathology (Maramattom et al., 2022, James et al., 2021). 18 patients (72%) had demyelinating neuropathies, with 16 of them (64% of total) having secondary axonal features. Full details on the electrophysiological data of each patient are found in Appendix 1.

MRI was performed in 21 patients (Table 5). Cauda equina enhancement was reported in four patients, while facial nerve showed enhancement in six patients who had facial diplegia.

Table 5
The clinical presentations of GBS' patients.

The clinical presentation	Number of patients (percentage)
Motor and sensory examination:	
Quadriparesis	17 (58.6%)
Only LLs weakness	5 (17.2%)
Sensory impairment in 4 limbs	7 (24.1%)
Sensory impairment in LLs	10 (34.4%)
Cranial Nerve affection:	25 (86.2%)
Facial diplegia	21 (72.4%)
Unilateral facial palsy "Right"	1 (3.4%)
Bulbar manifestations:	12 (41.3%)
Dysphagia	10 (34.4%)
Dysarthria or slurred speech	4 (13.7%)
Ocular movements affection:	4 (13.7%)
Total ophthalmoplegia	2 (6.9%)
Bilateral abducent palsies	1 (3.4%)
Unilateral abducent palsy "Right"	1 (3.4%)
Autonomic Dysfunction "Dysautonomia":	5 (17.2%)
Labile blood pressure	2 (6.9%)
Urinary retention	3 (10.3%)
SIADH and associated hyponatremia	1 (3.4%)
Respiratory failure	8 (27.5%)

2.4. Treatment and follow–up

IVIG was the mainstay treatment in 22 patients (75.8%) either alone, with plasma exchange (3 patients), or with IV pulse Methylprednisolone (2 patients) (James et al., 2021) in severe cases. Two patients, who had only facial diplegia with sensory symptoms, were treated with Oral Prednisolone alone (Allen et al., 2022).

Unfortunately, follow-up information was missing in many reports. However, complete resolution of all symptoms was stated in three patients (Maramattom et al., 2022, Razok et al., 2021, Waheed et al., 2021). Eight patients (27.5%) were mechanically ventilated, two of them were extubated, and one patient had tracheostomy (Hasan et al., 2021). The remaining five patients were still intubated when their respective case reports were submitted. The rest of the patients had a minor, partial, or near-complete recovery. Full details on patients' follow-up are found in Appendix 1.

3. Discussion

At the time of writing this review, late July 2021, there are more than one billion people who have been fully vaccinated, and more than 3.7 billion doses of vaccines have been administered (Tracking Coronavirus Vaccinations Around the World 2022). Different types of vaccines are being offered with different mechanisms of action ranging from modified mRNA vaccines, vector-based vaccines, inactivated COVID-19 virus vaccines, and recombinant protein subunits vaccines (Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process 2022).

Although the AstraZeneca vaccine was the most commonly reported triggering vaccine in this review, no data is available to reflect the total observed cases relative to the number of vaccinated individuals. Regarding the other two reported vaccines Janssen and Pfizer, in a recent meeting on the 22nd of July 2021, of the Advisory Committee on Immunization Practice of the centers for disease control and prevention (CDC), it was stated that GBS was reported at a higher rate than expected within the 42 days following the Janssen vaccine and not with other mRNA vaccines(Moderna and Pfizer-BioNTech). The reported cases were 98 cases after 12 million doses of the Janssen vaccine while the expected cases were only 19 (Daley, 2021). The rate of GBS cases per million doses administered was 8 for the Janssen vaccine in comparison to 1.21 and 1.05 for Moderna and Pfizer-BioNTech vaccines respectively (Alimchandani, 2021). This might raise the suspicion against the viral vector vaccine technology being more likely to trigger the condition. However, these reports were only concerned with U.S. COVID-19 vaccine products Janssen, Moderna, and Pfizer-BioNTech.

Post-vaccination Guillain Barre exhibits typical clinical presentations with a potential predilection for facial nerve involvement. However, this observation still needs more validation.

The same applies to electrophysiological investigations, where the majority of patients showed a demyelinating with a secondary axonal pattern of involvement. Additionally, IVIG and PLEX are the treatment modalities employed for managing the condition.

As well-known, corticosteroids are not among the treatment modalities approved for conventional GBS, especially alone. Eight large randomized clinical trials showed that treatment with steroids didn't significantly improve the outcome in GBS patients, and that patients treated with oral steroids even had non-significantly less improvement than non-treated patients (Hughes et al., 2007).

Although the response to treatment couldn't be judged based on the published reports, it is expected to follow the same pattern as the typical GBS, with the demyelinating pathology harboring a better prognosis than the axonal one.

In literature, GBS cases were reported after different types of vaccines (Souayah et al., 2009), but a solid correlation was not proven except for a few of them, most importantly, the influenza vaccine (De Wals et al., 2012, Perez-Vilar et al., 2019, Babazadeh et al., 2019). In comparison to the Korean study which investigated post-immunization GBS over 12 years (Park et al., 2016), the time course of post-COVID-19-vaccine interval and duration to the nadir of symptoms was more prolonged. Considering that the population of the Korean study was younger as most vaccines were given to school-aged individuals, this difference can be due to different ages rather than the type of vaccine.

The mechanism of post-vaccination GBS is thought to be similar to the post-infectious one, as a delayed immune-mediated reaction which is displayed through the activation of both CD4+ and CD8+ T-cells that cross-react to both a self-antigen in the nervous system and a viral antigen resulting in the clinical syndrome of either demyelinating or axonal GBS (Willison, Jacobs and van Doorn, 2016).GBS has been reported to occur after COVID-19 infection itself and this may suggest similar immunologic pathways to what is happening after the vaccination. A common step in the mechanism of action of COVID-19 vaccines is stimulating the production of the S glycoprotein, spike protein of the COVID-19 virus, to induce immunity against the virus. Subsequently, molecular mimicry between COVID-19 spike protein and a myelin protein is one of the suggested theories (Fantini et al., 2020). On the ground that more than 80% of the cases in this review occurred after the AstraZeneca vaccine and based on the CDC risk reports on the Janssen vaccine, investigating structural characteristics specific to these vaccines might generate further theories. Both AstraZeneca and Janssen vaccines are adenovirus vector-based. As the name implies, the ChAdOx1 vaccine (AstraZeneca) is one of the vaccines that utilize the chimpanzee adenovirus as a vector coding for the S glycoprotein of the COVID-19 virus. Adenovirus vector has been used in many vaccines due to its safety and high immunogenicity (Tatsis et al., 2006). At the same time, this could be another target of the molecular mimicry behind the post-vaccination GBS pathogenesis (Velikova and Georgiev, 2021). Furthermore, since GBS is a rare syndrome, host vulnerability is a key factor, which is determined by the human leukocyte antigen haplotype profile (HLA) (Gigli et al., 2020).

Recently, a large scale study, conducted on more than 32 million people, has linked the English national immunization Database for covid vaccination to the national data for mortality and hospital admissions. The same database has been linked to the same population to investigate the association with covid infection and the GBS incidence using positive SARS-COV-2 test as an indication for covid infection. The study concluded that the increased risk of GBS in the four weeks following covid infection "IRR 5.25" was significantly higher than the risk following covid vaccination with the first dose of AstraZeneca vaccine "IRR:2.32" and Pfizer- BioNTech vaccine "IRR:0.86". Another independent Scottish survey incorporated in the same cohort has found similar correlation between AstraZeneca vaccine administration and GBS incidence (IRR, 2.32 at 1–28 days). (Patone et al., 2021).

The combination of the massive vaccination, as well as the rarity of GBS, limits the degree of risk we can conclude from reviewing dispersed case reports in the literature. Nevertheless, it does highlight the importance of a more meticulous reporting system and post-vaccination surveillance to compare the number of observed GBS cases to the expected one for a certain type and size of the population.

4. Conclusion

Guillain-Barre syndrome is a well-recognized adverse event following vaccination against COVID-19. Preliminary data incriminates viral vector-based vaccines more than the other types. However, the withdrawal of solid conclusions is limited by the fact that this review is based on the few reported cases so far. Hopefully, as more people get vaccinated, confident data can be provided regarding the true incidence and risk factors of developing such a condition.

Disclosures

Authors have no disclosures to report that are applicable to this study.

Funding

No funding received.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nerep.2022.100083.

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