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Research Paper: Guillain-Barre Syndrome and COVID-19 Vaccine: A Report of Nine Patients

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ABSTRACT

Introduction: Guillain-Barre Syndrome (GBS) is an autoimmune acute inflammatory demyelinating polyneuropathy usually elicited by an upper respiratory tract infection. Several studies reported GBS associated with Coronavirus Disease 2019 (COVID-19) infection. In this study, we described nine GBS patients following the COVID-19 vaccine.

Methods: In this study, nine patients were introduced from six referral centers for neuromuscular disorders in Iran between April 8 and June 20, 2021. Four patients received the Sputnik V, three patients received the Sinopharm, and two cases received the AstraZeneca vaccine. All patients were diagnosed with GBS evidenced by nerve conduction studies and/or cerebrospinal fluid analysis.

Results: The median age of the patients was 54.22 years (ranged 26-87 years), and seven patients were male. The patients were treated with Intravenous Immunoglobulin (IVIg) or Plasma Exchange (PLEX). All patients were discharged with some improvements.

Conclusion: The link between the COVID-19 vaccine and GBS is not well understood. Given the prevalence of GBS over the population, this association may be coincidental; therefore, more studies are needed to investigate a causal relationship.

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Highlights

- Guillain-Barre elicited by an infection of the upper respiratory and gastrointestinal tract.
- Guillain-Barre Syndrome has been reported associated with post COVID-19 infection.
- Recently, Guillain-Barre Syndrome has been reported accompanying with COVID-19 vaccines.
- Nine patients with Guillain-Barre Syndrome have been revealed following COVID-19 vaccines in Iran.

Plain Language Summary

With the onset of the COVID-19 pandemic in Wuhan-China at the end of 2019, research studies to find medications for treatment and vaccines to prevent infection began. COVID-19 Vaccination became available after one year globally, and Vaccination was started in February 2021 in Iran. Vaccines may have various side effects in rare cases, including neurological disorders. Guillain-Barre syndrome (GBS) strongly correlates with different infectious agents, including COVID-19. It has also been described after polio, hepatitis B, rabies, and influenza vaccines in 2 days to 6 weeks. Several studies have reported the association of GBS with the COVID-19 vaccine. Herein, we report nine cases of GBS after receiving the first dose of vector-based and inactivated COVID-19 vaccine 4-37 days after Vaccination. The link between the COVID-19 vaccine and GBS is not well understood, but possible mechanisms such as epitopes cross-reaction have been implicated. Although this does not establish a causal association, it requires all patients vaccinated for COVID-19 with neurological problems.

1. Introduction

Guillain-Barre Syndrome (GBS) is an autoimmune acute inflammatory demyelinating polyneuropathy usually elicited by an upper respiratory or gastrointestinal tract infection in two-thirds of patients (Govoni & Granieri, 2001; Hughes & Rees, 1997). The mean annual incidence rate in Iran has been reported 2.11/100 000 populations and men were more affected than women (Arami, Yazdchi & Khandaghi, 2006). The most commonly recognized infection include campylobacter, cytomegalovirus, Epstein-Barr virus, mycoplasma pneumonia, Influenza-like illness, HIV, and Zika virus (Ansari et al., 2018; Bardage et al., 2011; Cao-Lormeau et al., 2016). Moreover, evidence exists that coronavirus disease 2019 (COVID-19) is possibly linked to GBS development. In April 2020, the first case of GBS in a patient with COVID-19 was reported in Iran (Karimi & Sedaghat, 2020; Sedaghat & Karimi, 2020). Subsequently, some researchers have identified GBS associated with COVID-19 infection (Li et al., 2020; Okhovat et al., 2020). There are currently several types of vaccines against COVID-19, including inactivated virus, protein-based vaccines, viral vector vaccines, and mRNA vaccine, which some of them have been approved by the WHO emergency use listing, Food and Drugs Administration (FDA), and European Medicines Agency (EMA) (Cavaleri, Enzmann, Straus, & Cooke, 2021; Coronavirus » Vaccination Information from Other Organisations, n.d.). In previous studies, the association of vaccines, including influenza, hepatitis B, polio, tetanus, meningococcus, rabies, and adenovirus vaccine with GBS has been reported (Chen, Zhang, Chu, Xu, & Ma, 2020; McNeil et al., 2019; Perez-Vilar et al., 2021). Recently, several studies have reported the association between GBS and COVID-19 after receiving Pfizer, Oxford/AstraZeneca, and Johnson & Johnson COVID-19 vaccines (Allen et al., n.d.; Márquez Loza et al., 2021; Patel, Khurram, Lakhani, & Quirk, 2021; Waheed, Bayas, Hindi, Rizvi, & Espinosa, 2021). Herein, we described nine GBS patients after receiving the first or second dose of the COVID-19 vaccine in the absence of any other triggering factors.

2. Methods

In this study, nine patients were introduced from four referral centers for neuromuscular disorders in Iran between April 8 and June 20, 2021. Four patients had received Sputnik V, two patients had received the Sinopharm, and one patient had received the AstraZeneca vaccine. According to clinical examination, laboratory tests, including CSF analysis and electrodiagnostic (EDX) study, all patients were diagnosed with GBS. Reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19 was performed for all patients and it was negative. We evaluated the patients using the Medical Research Council Score (MRC) and GBS Disability

Scale (GDS) before and after treatment. The study was in accordance with the ethical standards of the Tehran University of Medical Sciences Research Committee and the Helsinki Declaration (IR.TUMS.MEDICINE.REC.1400.275).

3. Results

The median age of the patients was 54.22±21.34 years (range, 26-87 years), and seven patients were male. After receiving the vaccine, the mean duration of onset of symptoms was 14±9.79 days (range, 4-37 days). Five patients were treated with intravenous immunoglobulin (IVIg), and four received plasma exchange (PLEX). The demographic data and outcome of nine patients with GBS after receiving the COVID-19 vaccine are summarized in Table 1. In addition, the history, neurological examination, and paraclinical information for each patient are described below.

Patient 1

This 38-year-old male patient that was previously healthy presented with right peripheral facial palsy after two weeks of receiving the Sputnik V COVID-19 vaccine. He complained of fatigue and myalgia after the injection of the vaccine. Two days later, the left side of the face was also involved, along with headache and paresthesia in the distal of the upper limbs. No respiratory or Gastrointestinal (GI) problems were reported before the onset of the disease. On admission, he was conscious, and his vital signs were normal; Blood Pressure (BP) was 130/80 mm Hg, pulse rate (PR) was 115 beats/min, respiratory rate (RR) was 19 breaths/min, and body temperature (T) was 36.3 °C). The neurological examination revealed bilateral facial palsy [House–Brackmann (HB) grade 4] without the involvement of other cranial nerves. The muscle strength in all four limbs showed the Medical Research Council (MRC) scale of 5/5. He had generalized areflexia with normal sensory examinations. In terms of laboratory findings, the blood chemistry study was within normal range, and viral markers, including Varicella-Zoster Virus (VZV), Cytomegalovirus (CMV), human inflammatory virus (HIV), hepatitis B, and C were negative. A lumbar puncture was performed on the third day of admission, indicating a protein level of 220 mg/dl (15-45 mg/dl); white cell count was 10 with 60% lymphocytes. Cervical and brain Magnetic Resonance Imaging (MRI) showed a normal finding except for mild protrusion of the C5-C6 intervertebral disc. The EDX test was performed nine days after the disease onset and showed normal motor and sensory conduction studies and F-wave latencies. Blink reflex showed prolonged latency in bilateral R1 and R2. The patient was treated with PLEX 2.5 liter every other day to replace 20% human serum albumin in saline. The facial paresis showed a significant improvement.

Patient 2

A 38-year-old man with no medical or travel history was admitted to our hospital due to 5-day history of ascending progressive and symmetric paresthesia in hands and feet. Fourteen days before admission, he received the first dose of the Sputnik V COVID-19 vaccine and after that, the patient developed a low-grade fever and sore throat. After six days, the patient developed bilateral facial weakness and lower limb weakness. He was admitted to the Intensive Care Unit (ICU) due to autonomic symptoms and rapid disease progression. On admission, the patient was afebrile (36°C), and vital signs were as follows: BP: 130/80 mm Hg, PR: 115 beats/min, RR: 19 breaths/min, and oxygen saturation: 98% at room air. He was conscious and had no cardiorespiratory disorders. The neurological examination demonstrated bilateral facial palsy (HB grade 4) and mild decreased light touch sensation and proprioception in the lower limbs, distal to the ankle joints. The muscle strength examination showed weakness in all four limbs with an MRC of 4/5 in proximal and distal of the upper extremities, 2/5 in proximal, and 3/5 in distal of the lower extremities. The Deep Tendon Reflexes (DTRs) were generally absent. Cervical and brain MRI only showed a few nonspecific T2- hyperintensities in the brain white matter. Lumbosacral MRI with gadolinium demonstrated cauda equina nerve roots enhancement (Figure 1). EDX study was performed on day five and demonstrated decreased sensory nerve action potentials (SNAPs) amplitude with slowing conduction velocities (CV). Motor studies showed slowing of CV with temporal dispersion and conduction block in bilateral tibial nerves. These findings were in favor of an acute demyelinating sensorimotor polyneuropathy. Chest computed tomography (CT) scan during admission was normal, with no evidence of COVID-19 pneumonitis. CSF analysis revealed a protein level of 180 mg/dl (15–45) and a white cell count of 10 with 100% lymphocytes. He was treated with PLEX. The patient did not need mechanical ventilation during hospitalization. He had moderate bilateral facial paresis at discharge, and muscle strength showed an MRC score of 4/5 in the upper limbs and 3/5 in the lower limbs. He was visited after two weeks, and the muscle strength in the upper limbs was 5 and in the lower limbs was 4.

Patient 3

An 87-year-old man with a history of ischemic heart disease (IHD) and diabetes Mellitus (DM) was admitted to the hospital with progressive upper and lower limbs weakness four days after receiving the first dose of Sinopharm COVID-19 vaccine. The patient reported mild myalgia after receiving his vaccination. On admission, the patient was alert, and vital signs were as follows: BP: 130/75, HR: 60, RR: 16 breaths/min, T: 36.3 °C, and O2 saturation: 97% at room air. Neurological examination showed no cranial nerve involvement. Motor examination revealed hypotonia in bilateral upper and lower extremities with an MRC of 1/5 in both proximal and distal limbs. The sensory study showed a decrease in pinprick sensation in bilateral lower extremities up to the knees. The patient had generalized areflexia. Routine lab tests were normal except for blood sugar of 250 mg/dl. CSF analysis showed protein of 133 mg/dl and WBC of 0. Brain MRI showed mild diffuse cortical atrophy and evidence of ischemic microvascular changes in the deep white matter without restriction in diffusion-weighted imaging (DWI). EDX study after seven days of disease onset showed unobtainable SNAPs with severely decreased amplitude in the upper limbs CMAPs and conduction slowing. Lower limbs CMAPs were unobtainable. The patient was treated with IVIG (2g/kg) over five days starting on the second day of admission. He did not show any signs of respiratory compromise, and after receiving five days of IVIG, the muscle strength showed an MRC score of 2/5 in proximal of the upper and lower limbs and 3/5 in distal of the upper limbs. The patient received physiotherapy during his stay in the hospital and was referred to a rehabilitation center after discharge.

Patient 4

A 52-year-old man with a history of hypothyroidism was admitted to the hospital with progressive weakness of the upper and lower limbs starting 12 days ago. The first symptom was paresthesia of the lips and one-third of the anterior tongue, which was started three weeks after receiving of Sputnik V COVID-19 vaccine. Four days later, paresthesia developed in the distal upper and lower extremities, accompanied by gait disorder and weakness of the lower limbs. On admission, the patient was alert and afebrile, and vital signs were normal. Neurological examination showed no cranial nerve involvement. Motor examination revealed an MRC of 4/5 in the upper limbs and 3/5 in the lower extremities with generalized areflexia. Sensory examination indicated a decrease in pinprick sensation in the bilateral distal of the upper and lower extremities. Routine lab tests were normal, and CSF protein was 165 mg/dl. EDX study after one week showed decreased amplitude in all tested SNAPs and lower limbs CMAPs with slowing of CV. Brain and cervical MRI were normal. The patient was treated with IVIG (2g/kg) for five days. On the third day after receiving IVIG, muscle strength improved, and gradually, the patient could walk without assistance.

Patient 5

A 48-year-old woman was admitted to the hospital with progressive weakness of the upper and lower limbs starting four days ago. She had received Sputnik V COVID-19 vaccine 17 days preceding the onset of the symptoms. After the vaccine injection, the patient complained of fever, myalgia, headache, and vomiting. At hospitalization, the patient had a generalized weakness with bulbar symptoms, dyspnea, and autonomic disorder. She was intubated due to respiratory distress and was admitted to the ICU. She was awake and obeyed from comments. The vital signs were as follows: BP: 120/90, HR:110, RR: 28 breaths/min, T: 36.3 °C, and O2 saturation: 95% at room air. Cranial nerves examination showed bilateral asymmetric facial weakness. The limb and neck muscle strength was severely reduced with an MRC score of 1/5 in proximal and distal of the upper and lower limbs and flexion and extension of the neck. The DTRs were absent, and position sensation was impaired in the distal limbs.

Blood culture, viral markers, and COVID-19 oropharyngeal polymerase chain reaction (PCR) were negative. GBS was probably diagnosed based on clinical symptoms and neurological examination, and therefore, the patient was administered with PLEX. After one session of PLEX, the patient developed hypotension, elevated serum troponin, and ECG changes in favor of an acute coronary attack. Cardiac counseling was given, and the patient was treated with aspirin, Plavix, and atorvastatin. PLEX was discontinued, and the patient received IVIG at a dose of 2g/kg (160g) for five days. After three weeks, she had no improvement, and IVIG (125 g) was injected again. After two weeks, the patient was weaned from the ventilator and was discharged to a rehabilitation center.

Patient 6

A 26-year-old woman with unremarkable history was admitted to the hospital due to progressive paresthesia and weakness of the limbs. She received the second dose of Sinopharm COVID-19 vaccine two weeks before the onset of symptoms. On neurological exam, she was found tetraparesis as follows: MRC score of 3/5 in distal

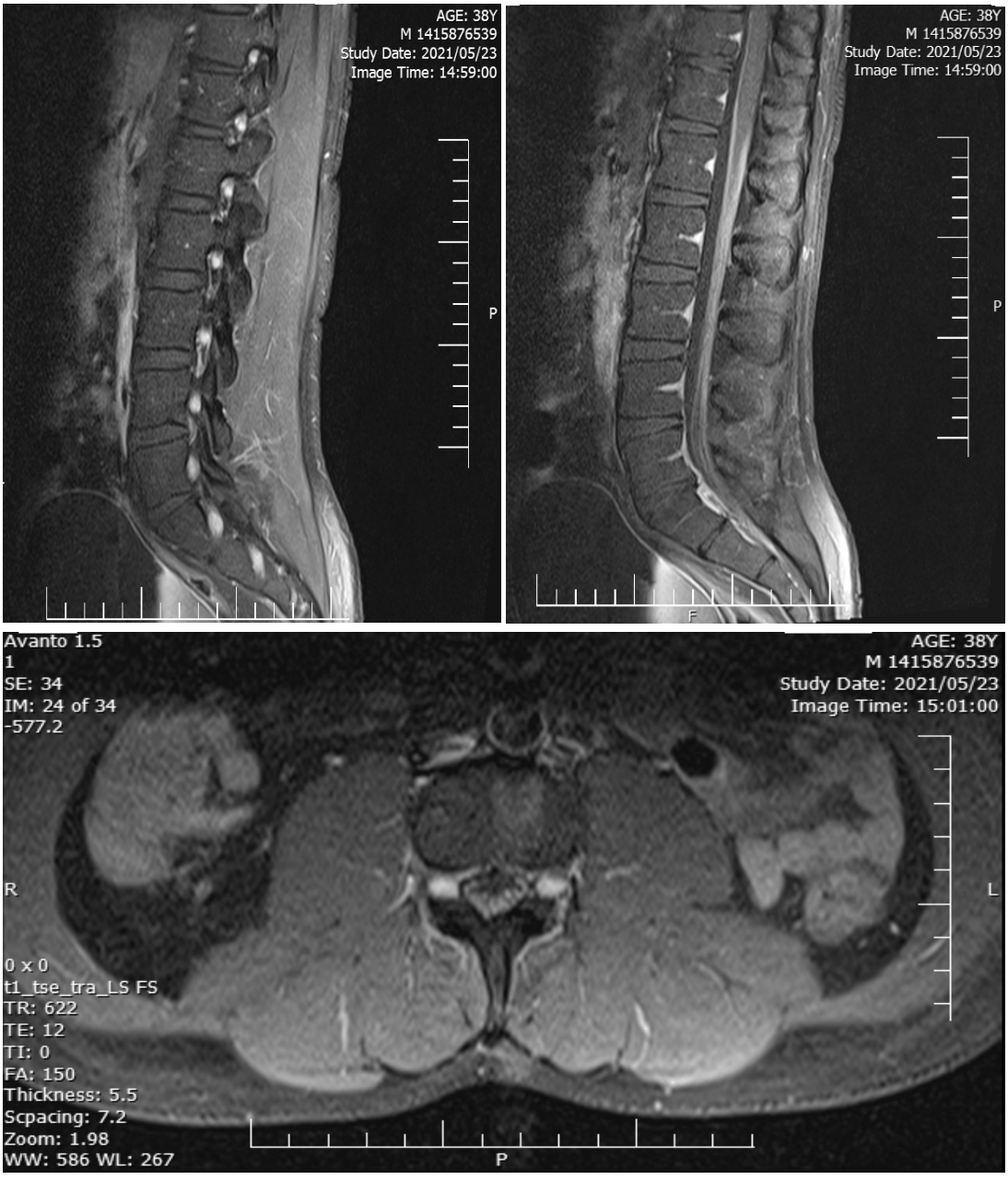

Figure 1. Lumbosacral magnetic Resonance Imaging (MRI) with contrast

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Sagittal and coronal T1-weighted post-contrast MRI revealed enhancement of cauda equine nerve roots suggestive of Guillain-Barre Syndrome.

of the lower limbs, 4/5 in proximal of lower and distal of the upper limbs, and 5/5 in proximal of the upper limbs. DTRs were generally absent. No objective sensory loss nor bowel or bladder dysfunction was observed. EDX study and lumbar puncture were performed on the third day after the onset of the disease. It revealed normal indices of motor and sensory NCSs, except prolonged F waves and the absence of H waves. CSF analysis showed a normal pattern. Based on the findings mentioned above and the diagnosis of GBS, she received IVIG (2g/kg) for five days. The muscle strength improved at the time of discharge.

Patient 7

A 44-year-old man was referred with paresthesia and weakness in the lower limbs starting one day ago. He had received the first dose of the AstraZeneca COVID-19 vaccine about five weeks before the onset of symptoms. In past medical history, the patient had mild to moderate

Table 1. Demographic data and clinical findings of nine patients with GBS following COVID-19 vaccine

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	patient 9
Sex	M	M	M	M	F	F	M	M	M
Age (year)	38	38	87	52	48	26	44	76	79
Comorbidities	No	No	IHD, DM	Hypothyroid	HTN	No	HTN	No	HTN, CABG
Type of Vaccines	Sputnik V	Sputnik V	Sinopharm	Sputnik V	Sputnik V	Sinopharm	AstraZeneca	Sinopharm	AstraZeneca
Time to onset of sym., days	14	8	4	21	17	37	14	14	7
COVID-19 PCR	Negative	Negative	Negative	Unknown	Negative	Unknown	Unknown	Negative	Negative
EDX finding	abnormal BR	AIDP	AMSAN	AIDP	not performed	AIDP	AMSAN	AMAN	AMSAN
CSF protein, mg/dl	220	180	133	165	not performed	NL	100	55	not performed
Treatment	PLEX	PLEX	IVIg	IVIg	PLEX-IVIg	IVIg	IVIg	PLEX	PLEX
Outcome	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	On admission
GDS pre-treatment	1	4	4	4	5	3	4	4	3
GDS post-treatment	1	3	4	3	4	2	4	3	on admission

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M: Male; F: Female; IHD: Ischemic Heart Disease; DM; Diabetics Mellitus; HTN: Hypertension; AIDP: Acute Inflammatory Demyelinating Polyradiculopathy; AMSAN: Acute Motor-Sensory Axonal Polyneuropathy; PLEX: Plasma Exchange; IVIg: Intravenous Immunoglobulin. GDS: GBS Disability Score. Dc: Discharge; BR: Blink Reflex.

COVID-19 infection about five months ago and HTN crisis (BP: 210/120 mm/hg) one day ago, managed by IV furosemide and oral captopril. On neurological exam, he could not walk and was flaccid tetraparesis with an MRC score of 2/5 in the upper and lower limbs. CSF analysis showed high protein without cells according to the diagnosis of GBS. The patient was treated with IVIG (2g/kg) for five days. On day five of admission, bilateral facial palsy appeared. A couple of days after starting IVIG, the progression of weakness reached the plateau. No respiratory involvement happened during the disease. EDX study was performed about three weeks after beginning symptoms and found a pronounced reduction in CMAPs' amplitude with mildly reduced SNAPs, except for sural nerve (i.e., Sural sparing). The patient was discharged and was referred to the rehabilitation center. After ten days of discharge, muscle strength improved (MRC score 3/5).

Patient 8

A 76-year-old male with no relevant past medical history complained of ascending weakness in the upper and lower limbs starting four days ago. He was not able to walk from two days ago. The patient had received a first dose of the Sinopharm COVID-19 vaccine 14 days before the beginning of symptoms. On examination, cranial nerves were normal. Muscles strength revealed an MRC of 4/5 in the upper limbs and 2/5 in the lower limbs with generalized areflexia and without apparent sensory deficits. The routine laboratory tests were normal. CSF analysis revealed a mildly elevated protein (55 mg/dl). The electrophysiological assessment was performed six days after clinical presentations, which demonstrated a pattern of Acute Motor Axonal Neuropathy (AMAN) variant of GBS. The patient received five sessions of PLEX and was referred to a rehabilitation center after discharge.

Patient 9

A 79-year-old male patient with a history of HTN and CABG was referred to the hospital with dysphagia and

weakness of the upper and lower limbs starting seven days ago. He had received the first dose of the AstraZeneca COVID-19 vaccine the week before the onset of symptoms. On admission, the patient was afebrile and vital signs were normal. The neurological examination demonstrated bilateral facial palsy (HB grade 4), and muscles strength was an MRC of 4/5 in proximal and distal of the upper extremities and 4/5+ in the lower extremities. DTRs were generally absent. Biochemistry lab tests were normal. The electrophysiological assessment was performed seven days after clinical symptoms, which demonstrated declined amplitude in SNAPs and CMAPs studies compatible with the AMSAN variant of GBS. The patient is currently hospitalized receiving PLEX.

4. Discussion

In this case report, we described nine patients with GBS associated with the COVID-19 vaccine. Our patients had clinical manifestations compatible with GBS that occurred at different intervals after vaccination. Although previous studies have reported GBS association with COVID-19, at present, there is no conclusive evidence showing a significant increase in the risk of GBS in patients with COVID-19 infection (Karimi & Sedaghat, 2020; Okhovat et al., 2020; Sedaghat & Karimi, 2020). Several studies have reported the temporal association of GBS with vaccination (Bardage et al., 2011; Cao-Lormeau et al., 2016). Nevertheless, Chen and et al. found no evidence of the association of vaccines with an increased risk of GBS among pediatric and adult populations, especially with the influenza vaccine (Chen et al., 2020). Recently, a co-occurrence of GBS with various COVID-19 vaccines has been reported (Allen et al., 2021; Márquez Loza et al., 2021; Patel, Khurram, Lakhani, & Quirk, 2021; Waheed et al., 2021). Likewise, we described a temporal link between receiving Sputnik, Sinopharm, and AstraZeneca COVID-19 vaccines and GBS onset 4-37 days after vaccine injection. The most common adverse events of COVID-19 vaccines were a flu-like complaint, injection site reactions, headache, and asthenia that most of them were mild and self-limiting and did not require any treatment (Logunov et al., 2020; Xia et al., 2020). Also, in the phase 3 trial of the Sputnik V vaccine, in the vaccine group, the mortality rate of <0.1% has been reported, which was not related to the vaccine. In trials of COVID-19 vaccines, GBS has not been reported as a side effect of the vaccine. In comparison, complications, disability, and GBS have been reported following infection with COVID-19 much more (Karimi & Sedaghat, 2020; Okhovat et al., 2020; Sedaghat & Karimi, 2020).

Given that COVID-19 is a pandemic disease involving over one hundred million people and developed over two million deaths to date, vaccination against this virus has become one of the most important strategic plans of any country. Several mechanisms may be involved in the association of autoimmune diseases after vaccination, such as 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 (Vadalà, Poddighe, Laurino, & Palmieri, 2017). So far, no extensive epidemiological studies have been performed to determine the increased risk of the COVID-19 vaccine and the development of GBS. However, since GBS is a debilitating disease, further studies on the safety of the COVID-19 vaccine should be performed to determine whether GBS association with the vaccine is coincidental or causal.

5. Conclusion

Herein, we reported nine cases of GBS after receiving the first dose of vector-based and inactivated COVID-19 vaccine 4-37 days after vaccination. The link between the COVID-19 vaccine and GBS is not well understood, but a possible mechanism with epitopes cross-reaction has been implicated. Given the prevalence of GBS in the general population, this association may be coincidental. Therefore, more studies are needed to investigate a causal relationship. However, the value of COVID-19 vaccines in preventing disease and decreasing morbidity and mortality needs to be deliberated compared to the possible risk of GBS.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Tehran University of Medical Sciences Research Committee (Code: IR.TUMS.MEDICINE. REC.1400.275.)

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declare no conflicts of interests.

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