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Guillain–Barré syndrome and its variants during COVID-19 pandemic: a retrospective study in Iran

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Abstract

Background Guillain-Barre syndrome (GBS) is a rare neurologic disorder with potential associations with viral triggers. This study aimed to investigate the incidence of GBS and its variants during COVID-19 pandemic in patients admitted to Kerman Shafa Hospital within 2020–2023.

Methods This was retrospective cross-sectional analysis of GBS cases reported during the COVID-19 pandemic in Shafa Hospital -Kerman during 2020–2023. to explore the incidence rate of GBS and, the association between demographic variables, the history of COVID-19 infection and vaccination within one month of GBS diagnosis, and the clinical outcomes. Data were analyzed using the SPSS 26 software.

Results A total of 87 patients with GBS were reported between 2020 and 2023, of whom 75.9% were men and the average age of the patients was 43.62 ± 20.85 years. The most common variants included AIDP (56.3%) and AMAN (24.1%). Overall, 21.8% of patients had a history of COVID-19 infection in the past month and 19.5% had positive COVID-19 PCR test. There was no significant association between the distributions of disease variants with other variables except year. The incidence rate of GBS in the population covered by Kerman University of Medical Sciences was estimated to be 1.33 cases per 100,000 person-year.

Conclusion Our study suggests that the overall incidence rate and clinical outcomes of GBS remained relatively consistent with pre-pandemic levels. Further research is needed to elucidate the complex relationship between GBS, COVID-19, and vaccination and to explore potential risk factors for severe outcomes in GBS patients.

Keywords Guillain-Barre syndrome, COVID-19, Kerman, Iran

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Introduction

Coronavirus disease 2019, abbreviated as COVID-19, was observed as pneumonia with clinical symptoms similar to viral pneumonia for the first time in December 2019 in a region called Wuhan in China [1]. This disease spread to different regions of the world in a short period. Nowadays, it is known as one of the most widespread and deadly pandemics caused by infectious diseases worldwide [2, 3]. The COVID-19 disease is caused by the SARS-CoV-2 virus from the category of coronaviruses. The primary way of its transmission is through respiratory droplets, although oral and fecal transmission has also been reported [4]. Based on the statistics of the World Health Organization, more than 750 million confirmed cases of the COVID-19 disease have been reported worldwide. The death rate due to this disease has been more than 6 million and eight hundred thousand people [5].

Statistics in Iran also suggest that the number of confirmed cases of the disease has been more than 7 million and five hundred thousand people and more than 144,000 people have lost their lives due to this disease [6]. Guillain-Barre' syndrome (GBS) is an acute, inflammatory, immune-mediated polyradiculoneuropathy characterized by symptoms such as paresthesia and progressive, symmetrical, and ascending muscle weakness and can be associated with hyporeflexia and areflexia [7]. The rate of this disease in the USA and Europe has been estimated to be 0.81 and 1.89 cases per 100,000 person-years [8]. Some studies in Iran have also reported a rate of 0.69 cases per 100,000 person-years [9].

GBS can be classified into axonal and demyelinating forms. Autoimmune Peripheral Neuropathies (APN) occur when the immune system loses tolerance to critical antigenic sites on the myelin, axons, nodes of Ranvier, or ganglionic neurons. Current evidence suggests that in APN, the autoimmune response is primarily driven by antibodies targeting myelin antigens. This process is further facilitated by autoreactive T cells and macrophages that infiltrate the myelin sheath, axonal membranes, or nodes of Ranvier [10].

In acute motor axonal neuropathy (AMAN), specific gangliosides, such as GM1 and GD1a, are targeted at nodal structures, ventral roots, and nerve terminals. This leads to complement-mediated axonal conduction block due to the loss of voltage-gated sodium channels and paranodal detachment, which can be reversible with treatment, resulting in prompt clinical recovery. In contrast, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) involves antigenic targets located within the myelin sheath. The activation of the complement system results in the formation of a membrane attack complex that contributes to myelin destruction. This distinction between AMAN and AIDP is crucial for

understanding the underlying mechanisms of these neuropathies and guiding appropriate therapeutic interventions [11].

Studies indicate that GBS is one of the neurological diseases that may occur or worsen with the infection with COVID-19 or the injection of the COVID-19 vaccine [12, 13]. Numerous studies indicate an association between the infection of COVID-19 and the vaccination of COVID-19 and the occurrence of GBS ([14, 15], and [16]). Since no study has been conducted in this area in Kerman, the present study evaluates the frequency of GBS and its variants in the COVID-19 pandemic in patients who were referred to Shafa Hospital in Kerman from 2020 to 2023.

Methods

The present descriptive and cross-sectional study was conducted on patients with GBS during the COVID-19 pandemic between 2020 and 2023 in Shafa Hospital in Kerman city. Their medical records were reviewed in this regard. The inclusion criteria of the study included the clinical records of patients who were hospitalized at Shafa Medical Center between the beginning of March 2020 (during the outbreak of the COVID-19 pandemic in Iran) and the end of March 2023 with the diagnosis of GBS based on ICD-10 coding. Exclusion criteria included the absence of diagnostic and clinical findings of GBS or the diagnosis of other disorders following COVID-19, including acute disease myopathy or polyneuropathy. GBS was diagnosed based on Brighton criteria and its variants were diagnosed based on the electrophysiological criteria of demyelinating and axonal polyneuropathy in EMG-NCV ([17–19], and [20]).

After obtaining the code of ethics from the Ethics Committee of Kerman University of Medical Sciences and obtaining permission to access the archives of Shafa Hospital, the clinical records were examined by the researchers of the project. According to the findings of the patient's medical record, data related to the patient's age, gender, season, and year of hospitalization, hospitalization coincides with the peak of COVID-19, history of COVID-19, and other infections or COVID-19 vaccination (one month before the appearance of the symptoms related to GBS), involvement pattern, disease variant, cerebrospinal fluid protein, hospitalization in ICU, type of treatment, PCR test result of COVID-19, and final outcome (recovery, discharge, and death) were recorded in the data collection form. In case of defects in the primary variables of the study, the data were completed by telephone follow-up. Then, the collected data were statistically analyzed to investigate the frequency of GBS cases during the COVID-19 pandemic and to describe the demographic and clinical characteristics of these patients. The data were statistically analyzed in SPSS-26

Table 1 Demographic characteristics (N=87)

Variable	group	frequency	Percent
Gender	Female	21	24.13%
	male	66	75.86%
Clinical features	Symmetrical generalize	52	59.77%
	Non symmetrical generalize	11	12.64%
	Paraparesis	16	18.39%
	Ataxia-areflexia-ophthalmoplegia	2	2.29%
	Facial diplegia & distal limb paresthesia	6	6.89%
EDX Study	AIDP	49	56.32%
	AMAN	21	24.13%
	AMSAN	15	17.24%
	MFS	2	2.29%
Vaccine exposure	Sinopharm	8	9.19%
	Barekat	1	1.14%
	AstraZeneca	1	1.14%
Year	1398(march2020)	3	3.44%
	1399(april2020-march2021)	27	31.03%
	1400(april2021-march2022)	27	31.03%
	1401(april2022-march2023)	30	34.48%
Season	Spring	22	25.28%
	Summer	22	25.28%
	Autumn	19	21.83%
	Winter	24	27.58%
Covid-19 PCR	Positive	17	19.54%
	negative	70	80.45%
Recent infection	Covid-19	19	21.83%
	Gastroenteritis	14	16.09%
	Respiratory	7	8.04%
ICU admission	Skin rash	1	1.14%
	Yes	13	14.94%
Me- chanical ventilation	No	74	85.05%
	Yes	10	11.49%
Outcome	No	77	88.50%
	Discharge	84	96.55%
Treatment	In-hospital mortality	3	3.44%
	Plasma exchange	50	57.47%
	IVIG	37	42.52%
Hospital- ization at the peak of covid-19	Yes	51	58.62%
	no	36	41.37%

Software. To describe the qualitative data, percentage and frequency indices were used, and to describe the quantitative data, the mean and standard deviation indices were used. Ethical approval for this study was obtained from the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1402.005). This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all participants or their legal guardians.

Table 2 Mean and standard deviation of variables

Variable	Mean $\pm$ SD	Minimum	Maximum
Age(Year)	43.62 $\pm$ 20.848	10	88
CSF Protein	88.11 $\pm$ 52.669	12	201
Distance from covid-19 or vaccine (Day)	16.25 $\pm$ 8.258	2	30
Distance from other infection (Day)	8.55 $\pm$ 4.009	2	20

Table 3 Age distribution of GBS

Age	Gender	Chi-square	P-VALUE
	female/male	1.116	0.99
10–19	3/9		
20–29	3/14		
30–39	3/9		
40–49	4/8		
50–59	3/10		
60–69	3/8		
70–79	1/4		
80–89	1/4		

Results

In this study, 87 patients with GBS, including 21 female subjects and 66 male subjects, were studied. Among 87 hospitalized patients, 54 cases belonged to the population covered by Kerman University of Medical Sciences and 33 cases belonged to other cities of the Kerman province. Nineteen cases had a history of recent infection with COVID-19 and 22 cases had a history of other infections (14 cases of gastroenteritis, 7 cases of respiratory infection, and 1 case of skin rash). (Table 1)

Based on the pattern of involvement, Symmetrical generalize (59.8%), paraparesia (18.4%), and non-Symmetrical generalize (12.6%) and based on variants, AIDP (56.3%) and AMAN (24.1%) were the most frequent findings. (Table 1)

The mean and standard deviation of the age of the patients in the study was 43.62 ± 20.8 and ranged from 10 to 88 years. The mean and standard deviation of the interval between the occurrence of GBS and the time of infection with COVID-19 or vaccination was 16.25 ± 8.2 days, and the mean interval from other infections was 8.55 ± 4.009 . The mean CSF Protein of the patients was 88.11 ± 52.6 mg/dl with a minimum of 12 and a maximum of 201. (Table 2)

The highest frequency of GBS was observed in male subjects aged 20–29 years. However, no significant relationship was observed between gender and different age groups ($P > 0.05$). (Table 3).

During the study period, 3 people in 1398(March 2020), 27 in 1399(April 2020–March 2021), 27 in 1400(April 2021–March 2022), and 30 in 1401 (April 2022–March 2023) were hospitalized with a definite diagnosis of GBS in 4 variants of AIDP, AMAN, AMSAN and miller

Table 4 year, season of involvement and some variables in GBS

	AIDP	AMAN	AMSAN	MFS	Chi-square	P-value
Year						
1398(march2020)	2	0	0	1	19.597	0.02
1399(april2020-march2021)	14	5	8	0		
1400(april2021-march2022)	15	8	4	0		
1401(april2022-march2023)	18	8	3	1		
Season						
Spring	12	7	3	0	8.974	0.44
Summer	12	5	5	0		
Autumn	11	3	5	0		
Winter	14	6	2	2		
ICU admission						
Positive	7	4	2	0	0.677	0.87
Negative	42	17	13	2		
Recent covid infection						
Positive	12	4	3	2	0.886	0.82
Negative	37	17	12	0		

fisher. The results indicated that there is a significant relationship between the variants and the year. Also, the distribution of the frequency of the patients was different in recent years, and most cases were observed in 2022($p < 0.05$). (Table 4)

Based on the season, 22 cases were hospitalized in spring, 22 cases in summer, 19 cases in autumn, and 24 cases in winter. No significant relationship was observed between the variables and the season of hospitalization ($P > 0.05$). There was no significant relationship between the variables and recent infection with COVID-19 ($P > 0.05$). Out of 87 hospitalized patients, 13 were hospitalized in ICU, 10 were intubated and mechanically ventilated, and 3 died. There was no significant relationship between the variables and hospitalization in ICU. (Table 4).

Based on the chi-square test, the frequency of death ($P = 0.624$), the need for hospitalization in ICU ($P = 0.398$), and the need for intubation ($P = 0.140$) were not significantly different in the patients with GBS with a recent history of COVID-19 and the patients without a history of COVID-19 infection. Additionally, the frequency of death ($P = 0.540$), the need for hospitalization in ICU ($P = 0.268$), and the need for intubation ($P = 0.083$) were not significantly different in the patients with GBS with positive PCR test and negative PCR test. Moreover, the frequency of death ($P = 0.525$), the need for hospitalization in the ICU ($P = 0.159$), and the need for intubation ($P = 0.226$) were not significantly different in the patients with GBS with a history of recent COVID-19 vaccination and the patients without a recent history of COVID-19 vaccination.

Discussion

This study was conducted in the area of Kerman University of Medical Sciences, which includes the cities of Kerman, Shahr-e-Babak, Baft, Zarand, Bardsir, Kuhbanan, Rabor, Orzuiyeh and Raver. The population of Kerman province is estimated to be 3,164,718 people in 2022, but the population covered by the health care services of Kerman University of Medical Sciences is slightly more than 1,399,000 people. During three years (2020–2022), 87 cases of Guillan-Barre' (GBS) syndrome have been reported in the registry of this disease in Shafa Medical Center affiliated to Kerman University of Medical Sciences. The annual incidence of this can be estimated at 1.33 people per 100,000. Unfortunately, we do not have the rate of occurrence of this disease in the previous years, so that we can't report with full confidence the increase or decrease of this disease, considering that during this period we were under one of the most severe epidemic crises of a viral infection (corona virus type 2019 = Covid 19). But many studies have been done in other regions of Iran that we can make a comparison, In Kashan province of Iran (northwest), the incidence rate has been estimated at 2.11 per 100,000 [21]. In the population under 15 years of age, two studies have been conducted, one in Iran and the other in Kerman-Iran, and the incidence rates were 1.72 and 0.96 per 100,000, respectively [22, 23]. The global annual incidence is between 1.1 and 1.8 per 100,000 [24]. Another study that reviewed 72 articles found the annual incidence to be 1.73 to 4.30 per 100,000 people [25]. According to the reports before the covid-19 pandemic, there is no increase in the incidence of GBS in the area covered by the health care services of Kerman University of Medical Sciences. This finding exists while we know that in 70% of cases before the syndrome occurs, there is a viral infection, especially the

upper respiratory or digestive system [26–28]. In a study conducted in Shiraz, Iran, a significant increase in GBS was reported after the influenza pandemic [29]. Also, other studies have confirmed the increase in the incidence of GBS after influenza [30, 31]. A similar situation was also observed in northern Iran, no significant difference between the incidence of GBS cases before and during the pandemic was observed [32].

In our study, men suffered from this syndrome more than women, the ratio of men to women is 3 to 1. This finding is also seen in most studies. In the study of west-central Iran by Mazaheri et al. (2007), the male to female ratio was reported to be 2.4 to 1 [33]. In the research conducted by Bostani et al. (2019) in northeast Iran, the ratio was found to be 78% to 22% [34]. In Rahimi Jaber's (2013) study, while the proportion is still higher in men, it is lower overall, with a male to female ratio of 55.6 to 44.4 [35].

The prevalence of male-to-female involvement is also seen in children, in the study of Ebrahimi et al. (2014), boys were involved more than girls [23]. The study of Tonkabani et al. (2021) also showed that boys were involved more than girls [22]. This is different from most autoimmune diseases, which are usually more common in women. We do not have a clear reason for this finding.

Guillain-Barre' syndrome can be seen in several forms. In our study, the most common form is AIDP, which accounts for more than 56% of cases, and the next category is form AMAN, which accounts for more than 24% cases (Table 1). In most of the reports, the number of types of GBSs is about the same. The most common form of acute inflammatory demyelinating polyneuropathy (AIDP), followed by pure motor form is acute motor axonal neuropathy [36–38]. Conversely, the opposite results were obtained in the northern Iran found that most patients with Guillain-Barré Syndrome (GBS) during the COVID-19 pandemic were diagnosed with Acute Motor and Sensory Axonal Neuropathy (AMSAN), accounting for 71.4% of cases. Although AMSAN was the predominant subtype during this period, its occurrence was twice as high as in the pre-pandemic phase; however, the overall distribution of GBS subtypes between the two periods did not show a statistically significant difference ($P = 0.42$) [32]. This difference in the subtype of Guillain Barre in this study can be due to the difference in the climate of the two regions as well as the large difference between the number of cases of the two studies.

In this study the patients who had a history of covid-19 in one month before the onset of the syndrome did not have a significant increase compared to people who do not have this history. (Table 4)

Other studies have not been able to show a significant relationship between suffering from covid-19 before the syndrome. In addition, we had no reason for it; we

assumed that because of lockdown, the chances of other infections such as *Campylobacter* Jejuni and respiratory viruses that cause GBS decreased. Therefore, more studies are needed to confirm or deny the correlation between COVID-19 and GBS.

Also, there was no significant difference between the different forms of the syndrome in people who had a history of Covid-19 up to a month ago and people who did not have this history [21, 36, 39, 40].

In our study, the average age of the patients is 43.62 ± 62.84 year. There was no significant difference in the age of patients with the syndrome in people who had a history of covid-19 in the previous month compared to people who did not have this history. This finding is consistent with other reports. It can be concluded that the infection of covid has not had a significant impact [37, 41, 42].

It seems that the incidence of Guillain-Barré syndrome (GBS) has seasonal trends depending on weather as well as environmental and demographic factors such as upper respiratory tract (URI) and gastrointestinal (GI) infections as recent triggers, which might be higher in special weather conditions [43]. In our study, there was no significant difference in the incidence of the GBS in different seasons of the year (Table 4). In the reports, no clear relationship has been found with the incidence of the GBS in different seasons of the year. This contrasts with other studies in Iran, which identified the highest occurrences in winter and the lowest in summer, respectively [43].

Conclusion

Our study suggests that the overall incidence rate and clinical outcomes of GBS remained relatively consistent with pre-pandemic levels. Further research is needed to elucidate the complex relationship between GBS, COVID-19, and vaccination and to explore potential risk factors for severe outcomes in GBS patients.

Limitation

our limitations in this study are: non-referral of mild cases of patients who did not refer or were considered under the title of fatigue. Another point that is noteworthy is the presence of a lot off mild facial nerve palsy that was seen after the injection of vaccination against Covid-19. They referred to outpatient clinics and were not recorded anywhere.

Abbreviations

GBS	Guillan barre syndrome
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
Aman	Acute motor axonal neuropathy
AMSAN	acute motor and sensory axonal neuropathy
MFS	miller fisher syndrome
Covid_19	Corona virus disease 2019
ICU	Intensive care unit
PCR	Polymerase chain reaction

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Authors' contributions

MAP: wrote the proposal and the manuscript. SEN: wrote the proposal, collected data, analyzed data, and wrote the manuscript. HAEM: wrote the proposal, analyzed data, and wrote the manuscript, and corresponding author. MKH: analyzed data, and wrote the manuscript. All authors read and approved the manuscript.

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Data availability

The data generated during the current study are not publicly available. The data are available from the corresponding author on a reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all participants or their legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

This study was approved by the Ethics Committee of Afzalipour Hospital, Kerman University of Medical Sciences, approval ID; IR.KMU.AH.REC.1402.005. Written informed consent has been obtained from all the participants and for individuals younger than 16, consent to participate was obtained from their parents or legal guardians.

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