Original Article

Guillain-Barre Syndrome Followed by Covid-19 Infection, Vaccination and Other Precipitating Factors during the Pandemic

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Abstract

Background and Aims: Guillain-Barré syndrome (GBS) is usually triggered by an infection. Vaccination is mentioned as a possible trigger in a small number of GBS cases. The aim of this study was to notice GBS distinctness provoked by various triggers during the COVID-19 pandemic. **Material and Methods:** A total of 109 GBS patients were divided into three groups, respectively: COVID-19 infection associated (19 patients), COVID-19 vaccination associated (16 patients) and precipitated by some other factors (74 patients). We compared the clinical, neurophysiological and laboratory characteristics of these three groups. **Results:** Neither were differences recorded in the age of the patients of these three groups at the time of illness, nor in the number of days from the precipitating factor to the onset of symptoms. There were no clinical differences between groups related to severity of the disease or patients' recovery. The only clinical difference was observed in relation to facial nerve bilateral affection because it was significantly higher in the post-vaccination group. According to neurophysiological findings, demyelinating form dominated in all three groups. **Conclusion:** Clinical characteristics, electrophysiological findings and laboratory characteristics did not differ significantly in Guillain-Barre syndrome followed by COVID-19 infection, vaccination and other precipitating factors during the pandemic. The bilateral involvement of facial nerves was significantly higher in the post-vaccination group. Most of these cases had a mild form of the disorder—distal paresthesias GBS variant.

Keywords: Associated, COVID-19 pandemic, Guillain-Barré syndrome, infection, vaccination

Introduction

Guillain-Barré syndrome (GBS) is usually triggered by respiratory or gastrointestinal infection.[1] Vaccines could play a role in triggering GBS hypothetically.[2,3] Although explicit association between the majority of vaccines and GBS has never been proven, it also cannot be definitely excluded. Vaccination as a hypothetical trigger in development of GBS is of great public concern because of potentially the life-threatening consequences of the disorder.

The aim of the study was to notice GBS features during the COVID-19 pandemic and to compare the characteristics of post-COVID-19 GBS, post-COVID-19 vaccination and GBS of some other origin.

Material and Methods

Data from electronic and paper medical records of patients with GBS during the COVID-19 pandemic from five tertiary health centres was selected retrospectively. The affected area covers two Western Balkans countries: Serbia without Kosovo and Montenegro with about 7 806 891 inhabitants (Serbian and Montenegro census 2011) during the COVID-19 pandemic period from January 2020 to April 2022. The approval from the local ethics committee is obtained (No 15/2021) and the date of the approval is 05/July/2021.

Using Brighton criteria clinical and neurophysiological assessment, a GBS diagnosis was made in all patients.[4,5]

Due to precipitating factors, the patients have been divided into three groups, respectively: COVID-19 infection associated, COVID-19 vaccination associated and precipitated by some other factor.

In each of these groups, the number of days from the precipitating factor to the first symptoms of the disease was

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calculated. Precipitating factors were considered relevant if they appeared within 3 days to 6 weeks before the appearance of the first symptoms of GBS.[6]

Immunization in the affected area began in January 2021. Four different COVID-19 vaccines were available: Pfizer/BioNTech, Sinopharm, Sputnik V and AstraZeneca. From November 2021, Moderna vaccine was also available. Choice of vaccine made by individuals. Coverage in adults was 54.1% for a primary series (58.0% received Sinopharm, 28.4% Pfizer/BioNTech, 9.5% Sputnik V, 4.1%, AstraZeneca, and 0.01% Moderna) and 32.7% for a booster dose (51.2% received Sinopharm, 39.6% Pfizer/BioNTech, 8.2% Sputnik V, 0.8% AstraZeneca, and 0.2% Moderna).[7]

The Hughes GBS disability scale was used to assess the functional status of patients with GBS—from 0 (absence of symptoms) to 6 (lethal outcome).[8] Functional disability assessment was carried out at nadir and on discharge from the medical records. Clinical improvement of GBS weakness was defined as a decrease in the Hughes score of at least one degree.

Due to possible rapid progression of the disease, it is recommended to perform electrophysiological studies "as soon as possible" in GBS patients. Electrophysiological studies were performed on our patients at very beginning of hospitalization, usually on the very first day.

A patient's neurophysiological form of the disease is categorized by Uncini[9] as: acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor and sensory axonal neuropathy and Miller Fisher syndrome.

In order to obtain a prompt diagnosis, a lumbar puncture was performed at the beginning of hospitalization, usually on the first day. According to the protein level of and number of cellular elements in cerebrospinal fluid (CSF), albuminocytologic dissociation was registered in the cerebrospinal fluid in some of our patients.

In order to question the possible differences in various variables, we conducted a series of Chi-Square tests and ANOVAs. In order to check possible correlations between various variables, we used Spearman and Pearson correlation coefficient.

This work had local Ethics Committee approval.

Results

Among 109 of our GBS patients, 19 GBS cases were COVID-19 infection triggered, 16 patients developed GBS after COVID-19 vaccination, while another 74 cases were precipitated by some other factor. There was no clear precipitating factor in the remaining 26 patients.

Patients with an infectious syndrome who tested positive for COVID-19 with antigen test and PCR test were considered diagnosed with COVID-19 infection. All patients from the group had milder form of COVID-19 infection and were treated at home.

Our patients received Sinopharm (Beijing), Pfizer/BioNTech, Oxford/AstraZeneca and Janssen (Johnson and Johnson) vaccines. First vaccination triggered 10 GBS cases; the second vaccination resulted in 4 patients with GBS and the third dose in 2 GBS cases [Figure 1].

Mean age at the onset of COVID-19 infection in the triggered GBS group was 48.74 ± 18.42 years, in the COVID-19 vaccination group it was 48.56 ± 19.94 years, and in patients triggered by some other factor it was 55.39 ± 14.63 years. There were no significant differences between these groups [Table 1].

The male to female ratio was 1.32:1 with no difference in the three groups.

COVID-19 infection preceded on average 14.05 ± 12.10 days before the first GBS symptoms, vaccination preceded 12.13 ± 9.29 days, while other provoking factors preceded on average 13.02 ± 11.65 days before the illness. There were no significant differences between groups in the number of days from precipitating factor to symptoms onset [Table 1].

A significant difference was not found in the number of days from onset to admission and from onset to nadir between all three groups of patients.

Comparing the disease severity of all three groups we concluded that there was no difference between groups in the Hughes scale at nadir. We noticed positive correlation between the age of our patients and severity of disease at nadir ($r = 0.194^*$, $P < 0.05$).

Patients' recovery was evaluated at discharge through Hughes scale decrease in comparison with Hughes scale at nadir and there was no significant difference between all three groups. None of our patients had withdrawal of all symptoms on discharge.

On mechanical ventilation were 9 patients: 2 post-COVID-19, 1 post-vaccination and 6 from the last group. According to

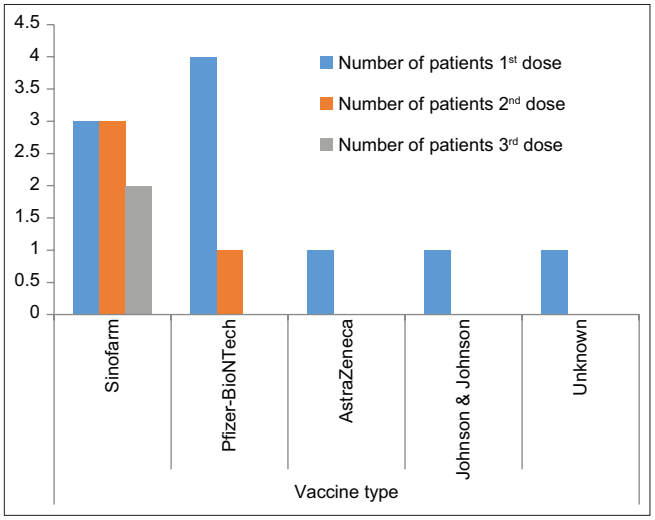

Figure 1: Number of GBS patients according to vaccine type and vaccine dose

Table 1: Basic statistical categories compared between three groups

	Post-COVID-19 group	Post-vaccinal group	Others	Statistic tests	Test results
Gender distribution (Male/Female)	8/11	9/7	45/29	Chi-Square test	x^2=2.160
Mean age at the symptoms' onset	48,74±18,42	48,56±19,94	55,39±14,63	ANOVA	F=2.063, P=0.132
Mean number of days from precipitating factor to the symptoms' onset	14,05±12,10	12,13±9,29	13,02±11,65	ANOVA	F=0.127, P=0.881
Mean number days of the symptoms' onset to hospital admission	8,68±6,07	7,69±4,54	8,99±10,19	ANOVA	F=0.138, P=0.871
Mean number days of the symptoms' onset to the peak of the disease	9,83±5,68	9,25±6,46	11,82±10,04	ANOVA	F=0.725, P=0.487
Hughes scale at the peak of the disease*	3,33±1,14	3,19±0,981	3,43±1,11	ANOVA	F=0.330, P=0.720
Hughes scale at the discharge*	2,71±1,21	2,62±1,03	2,94±1,21	ANOVA	F=0.618, P=0.541
Affection of facial nerve (unilateral/bilateral)	2/2	1/5	8/4	Chi-Square test	x^2=9.274
EMNG (demyelinating/axonal/undefined)	7/4/7	10/4/1	33/21/12	Chi-Square test	x^2=6.531
Number of days from symptoms' onset to lumbar puncture	9,63±5,68	9,43±4,70	11,82±9,56	ANOVA	F=0.807, P=0.449
Proteinorachie	1,45±1,05	1,14±0,95	1,31±0,98	ANOVA	F=0.382, P=0.684
WBC in CSF	1,50±1,37	2,83±3,07	3,29±5,01	ANOVA	F=1.702, P=0.347

*0-normal functional state; 1-able to run with minor signs and symptoms; 2-able to walk ≥10m without help, but does not run 3-walks 10m outdoors with help; 4-bed- or chair- bound; 5-requires assisted ventilation; 6-dead

the disease outcome, there were 3 deaths (no one from the post-COVID-19 and post-vaccination groups).

Facial nerve affection was registered in all three groups of GBS patients: 6 in the post-vaccination group (5 bilateral paresis and 1 unilateral), 4 in the post-COVID-19 group (2 bilateral paresis and 2 unilateral) and 12 in the last group (4 bilateral paresis and 8 unilateral) [Figure 2]. Bilateral affection of facial nerve was significantly higher in the post-vaccination group than in patients with other triggers ($X^2 = 8.889$, $P < 0.05$).

According to the electrophysiological findings, categorization was performed on the demyelinating and axonal form of GBS. The demyelinating form dominated in all three groups, without any difference between groups due to electrophysiological findings [Table 1]. There were none patients with clinical symptoms and electrophysiological findings for MFS among our presented patients.

Within 104 patients in our total cohort who had had a lumbar puncture performed, 95 patients (95.41%) had hyperproteinorachia. The number of days from symptoms' onset to the procedure was 11.07 ± 8.42 days. There was no significant difference between groups due to this data [Table 1].

There was no significant difference between groups of patients according to WBC number in CSF. We noticed significant inverse correlation between the CSF WBC number and the number of days from symptoms' onset to lumbar puncture (r = -0.219*, $P < 0.05$).

Patients were treated in the standard way with plasma exchange (PE) and intravenous immunoglobulin therapy (IVIg)

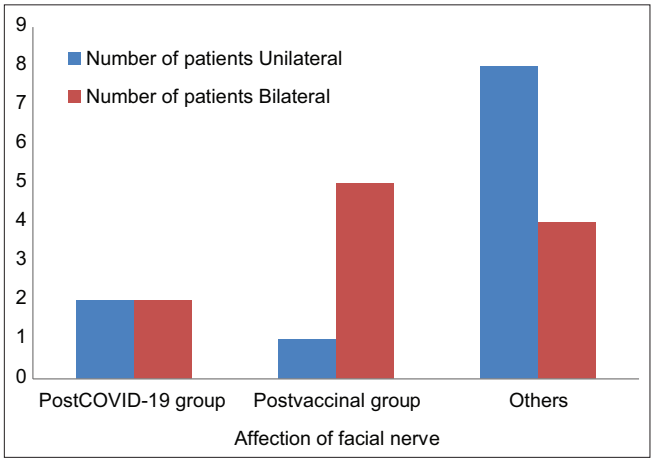

Figure 2: Number of GBS patients according to facial nerve affection

without significant difference between groups in the type of therapy [Table 1].

Discussion

The first reported case of GBS associated with COVID-19 infection was a 61-year-old woman from Wuhan.[10]

The concept of 'molecular mimicry' is considered responsible for GBS genesis and implies immune stimulation by pathogen or vaccine protein. According to previous studies, up to 70% of GBS cases were caused by infections, which corresponds to our data.[1] In our study, infection (COVID-19 or other infectious agents) was associated in 56.88% of the total number of our patients.

The third group our patients was COVID-19 vaccination triggered.

Because of only isolated case reports or very small clusters, GBS association with most types of vaccines is not so clear.[11] As the COVID-19 pandemic is the largest vaccination campaign in history with more than eight billion administered doses,[12] it seems interesting to single out GBS as a possible consequence of the vaccination. GBS after a COVID-19 vaccine was reported, for the first time, on February 2021, following a first dose of Pfizer COVID-19 vaccine.[13]

The aim of our study was not to indicate an increased risk of GBS in vaccinated patients, as that should be the task of future epidemiological studies, but to indicate the specifics of this type of GBS in order to facilitate its recognition and appropriate treatment.

Male gender was predominant in the total cohort of our patients, which was confirmed by previous studies from this region,[14] without any significant difference in gender between all three groups.

According to previous experience, the incidence of GBS increased after the age of 50.[1] The tendencies of increase in GBS incidence and the severity of disease in older age groups were present in our patients, although there was bimodal distribution of age in our total cohort: the lower peak at age 45-50 years and the higher one between 60 to 70, as found in previous studies from this region.[14]

Immune stimulation takes time in developing the first symptoms of GBS, which ranges between 3 days and 6 weeks.[6] Precipitating factors of all our patients occurred at an acceptable interval without differences between all three groups. In addition, the mean interval between COVID-19 infection and the onset of GBS among our patients is similar to the previous experience of other authors.[15]

Clinical characteristics in all three groups of our patients did not differ significantly. There were no significant differences in mean age, in recording time from the first symptoms to admission, disease severity at nadir, duration of hospitalizations or patients' recovery [Table 1]. Although the experiences of some studies indicate that post-COVID-19, GBS is a more severe in comparison with other post-infective GBS,[16] our study has not confirmed that.[17]

Significant clinical differences between groups were observed only in relation to the involvement of facial nerves. Facial nerve affection was registered in all three groups of our GBS patients, but bilateral affection was significantly higher in the post-vaccination GBS group. Similar experiences have been noted by other authors, who have concluded that the first dose of the AstraZeneca vaccine may be a risk factor for more commonly bifacial weakness and the distal paresthesias GBS variant[18] also seen in our post-vaccination group.

The concept of 'molecular mimicry' is considered responsible for GBS genesis and implies immune stimulation by pathogen or vaccine protein. It is possible that a part of vaccines is a provocative factor in the stimulation of antibodies that specifically bind to the facial nerve of vaccinated patients.

GBS associated with COVID-19 is usually manifested as an acute inflammatory demyelinating form of the disorder.[15,19] We had the same experiences in our cohort: demyelinating form dominated in all three GBS groups without significant difference between our groups of patients due to electrophysiological findings.

According to WBC number in CSF, there was no significant difference between groups of our patients. Previous studies had the same conclusion when considering post-COVID-19 and non-COVID-19 GBS patients.[16] We noticed significant inverse correlation between CSF WBC number and the number of days from symptoms onset to lumbar puncture. This result might indicate the possibility of involving intrathecal cellular immunity in the very early genesis of the disorder.

According to previous studies, post-vaccinal GBS developed much more frequently after the first dose of COVID-19 vaccine and less frequently after the second dose.[20,21] This was similar in our cohort: the first vaccination was the trigger in 10 GBS (3 Sinopharm, 4 Pfizer, 1 Johnson and Johnson, 1 Astra Zeneca, 1 unknown type of vaccine); the second vaccination in 4 patients (3 Sinopharm, 1 Pfizer). In our cohort, the third dose was the trigger in 2 GBS cases (both patients received the Sinopharm vaccine) [Figure 1].

Our patients were treated with IVIg therapy and PE in the standard way. There was no difference in the treatment strategy of our GBS patients in all three groups and it is in correlation with previous experiences.[16]

Conclusion

Clinical characteristics, electrophysiological findings and hyperproteinorachia in cerebrospinal fluid, did not differ significantly in Guillain-Barre syndrome followed by COVID-19 infection, vaccination and other precipitating factors during the pandemic.

Significant differences were observed only in relation to involvement of facial nerves—bilateral affection was significantly higher in the post-vaccination GBS group. Most of these cases had a mild form of the disorder—distal paresthesias GBS variant.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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