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Assessment of the relationship between COVID -19 and Guillain Barre syndrome: a single center pandemic experience

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Abstract

Background & Objective: This study aimed to determine the relationship between COVID-19 infection/ vaccination and Guillain-Barré syndrome (GBS) and to compare clinical characteristics and functional outcomes between COVID-19-related and non-COVID-19 GBS patients. *Method:* The medical files of the patients who sought treatment with the diagnosis of GBS between March 2020 and July 2022 were retrospectively analyzed. The patients were divided into groups as COVID-19-related GBS (C-GBS) and non-COVID-19 GBS (NC-GBS). Demographic and clinical characteristics, neurological examination findings, treatment protocols, and outcomes, including functional status, ambulation level, independence in daily living activities, and anxiety-depression levels of the patients with GBS, were recorded. *Results:* A total of 25 patients were included in the study. GBS was found to be associated with COVID-19 in 9 (36%) patients. Among them, 5 (20%) patients developed GBS after COVID-19 infection and 4 (16%) after the COVID-19 vaccine. The latency between COVID-19 infection and the onset of GBS ranged from 7 to 60 days, and the latency between vaccination and the onset of GBS ranged from 3 to 60 days. The clinical presentation and features, disease severity, and electrodiagnostic patterns of C-GBS patients were similar to NC-GBS patients. Also, there was no significant difference between patients with C-GBS and NC-GBS regarding functional status, ambulation level, functional independence in daily activities, and anxiety-depression levels.
Conclusion: GBS is not uncommon in COVID-19. In this study, 20% of GBS cases admitted to our hospital during the pandemic seem to be associated with COVID-19 infection and 16% with COVID-19 vaccination. However, clinical features and functional outcomes of C-GBS and NC-GBS cases are similar.

Keywords: Guillain Barre syndrome, COVID-19, SARS-CoV-2, neurological manifestation, functional outcome

INTRODUCTION

Various viral outbreaks have been reported over the past two decades; severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), H1N1 influenza, Zika, and Ebola virus.[1] In late 2019, the World Health Organization (WHO) declared the novel coronavirus, and on 11 March 2020, WHO announced COVID-19 as a pandemic.[2] This new coronavirus infection was observed to be very similar to SARS-CoV. For example, both use angiotensin-converting enzyme 2 (ACE2) as a functional receptor in human tissues, and both have spike proteins. Therefore, this virus is also named SARS-CoV-2.[3,4] COVID-19 is mainly a respiratory infection but is also associated with various neurological symptoms like SARS-CoV and MERS-CoV.[5] It has been reported that more than 90% of COVID-19 patients report at least one subjective neurological symptom. Therefore, it is essential to determine the subsequent neurological effects of the disease.[6] SARS-CoV-2 is considered a potentially neuroinvasive virus, and central and peripheral nervous system involvement can

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be seen.[4] Central nervous system involvement due to COVID-19 infection has been reported as headache, dizziness, impaired consciousness, acute cerebrovascular accident, encephalopathy, seizures, ataxia, and peripheral nervous system involvements as anosmia, ageusia, visual impairment, Guillain-Barré syndrome (GBS).[3]

GBS is an acute, generalized inflammatory polyradiculoneuropathy that may result in severe paralysis. Approximately one-third of patients develop respiratory failure that requires admission to the intensive care unit (ICU) and ventilation. The mortality rate in GBS cases is 3-5%, and about two-thirds of the patients develop permanent disability.[7] GBS has been reported in numerous viral infections. *Campylobacter jejuni*, Epstein-Barr virus, influenza, or cytomegalovirus are the most well-known pathogens responsible for most GBS cases.[5] There is also an association with other conditions, such as vaccinations, surgeries, drugs, and malignancies.[7] In the recent, Zika virus outbreak in Latin America, increased cases of GBS were reported.[8] GBS associated with COVID-19 is recently reported in numerous case reports and reviews. Most of these reports are focused on the clinical and electrodiagnostic features of the disease, but they cannot establish functional improvement and outcomes for the patients. Therefore, in this study, we aimed to evaluate the relationship between COVID-19 infection/vaccination and GBS in terms of clinical features and findings, treatment protocols, and outcomes, including functional status, ambulation level, independence in daily living activities, and anxiety-depression levels.

METHOD

Study design and patients

This study was a single-center retrospective study of patients diagnosed with GBS who applied to the Health Science University, Ankara Diskapi Yildirim Beyazit Training and Research Hospital, between March 2020 and July 2022. We screened the medical records of all GBS patients admitted to the Neurology or Physical Medicine and Rehabilitation Clinic during this period. Inclusion criteria accepted as all GBS patients whose diagnosis confirmed with Brighton criteria during the pandemic. COVID-19 diagnosis confirmed by nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR) tests. Serum Ig M and Ig G antibodies for other infectious agents including hepatitis B and C viruses, human immunodeficiency virus (HIV), cytomegalovirus (CMV), Ebstein-Barr virus (EBV), herpes simplex virus tip 1 and 2 (HSV-1, HSV-2), and varicella zoster virus (VZV), and the PCR tests of influenza A, influenza B, and respiratory syncytial virus (RSV) were also screened. Patients were ruled out of the study if they had i) other neurological manifestations such as myopathy, toxic polyneuropathy, myasthenia gravis, botulism, critical illness neuropathy, and myopathy; ii) missing clinical data. The records of 43 patients were accessed, patients who met the exclusion criteria were excluded from the study, and 25 patients were included. The data of the patients were analyzed from the patient files. Three patients died during the illness. 22 surviving patients were called for a control examination. They underwent a neurological evaluation after signing informed consent, and their functional status, independence levels in daily living activities, and anxiety and depression levels were evaluated. The study was performed under the Declaration of Helsinki, and local ethics committee approval was obtained for the study.

Demographic and clinical characteristics

The patients' demographic and clinical characteristics, including age, gender, body mass index (BMI), educational level, and comorbidities, were recorded. COVID-19 symptoms (fever, cough, dyspnea, myalgia, anosmia, ageusia), the results of nasopharyngeal SARS-CoV-2 RT-PCR tests, treatment agents (favipiravir, tocilizumab, anakinra), treatment place (home, hospital, intensive care unit), treatment time (days), need of respiratory support and mechanical ventilation were recorded. The GBS onset symptoms (tingling, numbness, limb weakness), antecedent events (upper respiratory infection, diarrhea), clinical variants (pure motor, sensory-motor, Miller Fisher syndrome, cervical-brachial variant), electrophysiological subtypes (acute inflammatory demyelinating polyneuropathy [AIDP], acute motor axonal neuropathy [AMAN], acute motor sensory axonal neuropathy [AMSAN]), and cerebrospinal fluid (CSF) analysis (electrolytes, glucose, protein, albuminocytological dissociation, cell account), neurological symptoms (limb weakness, paresthesia, or pain, bulbar symptoms), neurological examination findings (muscle strength according to Medical Council Research, hypo/areflexia, sensory abnormalities, facial asymmetry, bulbar weakness, mechanical ventilation), treatment protocol (intravenous immunoglobulin [IVIG], plasmapheresis) were recorded.

Functional status

The Hughes functional grading scale (HFGS) was used to evaluate disease severity which Hughes *et al*. developed.[9] Scoring ranges from 0 to 6 (stage 0; healthy, stage 1; has mild symptoms and can run stage 2; can walk 10 meters (m) without support but cannot run, stage 3; can walk 10 m with a person's support or a walker, stage 4; wheelchair or bedridden, stage 5; needs a mechanical ventilator, stage 6; death).

Functional independence in daily living activities

The functional independent measure (FIM) was used to evaluate patients' functional independence in daily activities. FIM analyzes two critical components of disability; motor and cognitive functions. FIM motor assessment; focuses on three functional areas self-care, sphincter control, and mobilization (a total of 13 activities—7 points for each). The Turkish reliability and validity studies were performed by Kucukdeveci *et al*.[10]

Ambulation level

The functional ambulation scale (FAS) was used to determine the ambulation levels of the patients. Although this scale was first developed to classify ambulation levels in post-stroke cases, in general, it is also used in neurological rehabilitation cases. Cases are classified between 0 and 5, and higher scores indicate a better level of functional ambulation.

Anxiety and depression

Beck's depression and anxiety scale was used to evaluate the depression and anxiety levels of the patients. Both of them were developed by Beck et al. The Beck depression scale consists of 21 questions, and the scoring ranges from 0 to 3 for each answer. The Turkish adaptation studies were conducted by Hisli *et al*.[11] Beck anxiety scale consists of 21 questions, the questions are scored between 0-3, and the total score determines the severity of anxiety symptoms. The Turkish adaptation studies were performed by Ulusoy *et al*.[12]

Statistical analysis

Statistical Package for Social Science (SPSS) version 20.0 software (IBM Corporation, Chicago, IL) was used to perform all statistical analyses. The normality of continuous variables was evaluated using the Shapiro-Wilks test. Categorical variables and other discrete and continuous variables were represented in percentage number and median (min-max), respectively, while variables with normal distribution were represented in mean±standard deviation (SD). The Pearson chi-square and Fisher's exact tests were used to compare the categorical variables. Continuous and non-parametric variables were compared using the Mann-Whitney U test. The paired samples t-test and Wilcoxon test were used to compare paired variables. Mortality and survival rates of the patients were generated by the Kaplan–Meier method and verified by the log-rank (Cox–Mantel). A p-value of less than 0.05 was found statistically significant.

RESULTS

We screened the records of a total of 43 patients. Among them, ten patients were diagnosed with GBS before March 2020, two patients were referred to another hospital, and six patients had incomplete records. Therefore, these patients were excluded from the study. Twenty-five patients were included in the final analysis. The flow chart of the study design is shown in Figure 1. The study population consisted of 56.5% women and 48% men. The population's median age was 60.5 years (7.0-78.0). The demographic characteristics of the patients according to the groups are shown in detail in Table 1. GBS was associated with COVID-19 in 9 (36%) patients. Among them, 5 patients thought that GBS was associated with COVID-19 infection, and 4 patients were associated with the COVID-19 vaccine (m-RNA-based vaccine). The latency between COVID-19 infection and onset of GBS ranged from 7 to 60 days, and the latency between vaccination and onset of GBS ranged from 3 to 60 days. Flu symptoms were significantly higher in the C-GBS group than in the NC-GBS group ($p<0.05$). The clinical characteristics of patients in both groups were summarized in Table 2. Of all the 25 cases, 60% (n = 15) were of AIDP variant, 20% (n = 5) AMAN variant, 16% (n = 4) AMSAN variant, 4% (n = 1) cervico-brachial variant. All patients received IVIG, and 6 (24%) received plasma-pheresis plus IVIG. GBS features of the patients are given in detail in Table 3. COVID-19 features of patients in the C-GBS group are given in Table 4. Three patients died during the illness of severe respiratory insufficiency. The overall mortality rate was 12% (3/25). This rate was 22.2% in the C-GBS group and 6.25% in the NC-GBS group. The mean time from diagnosis to death

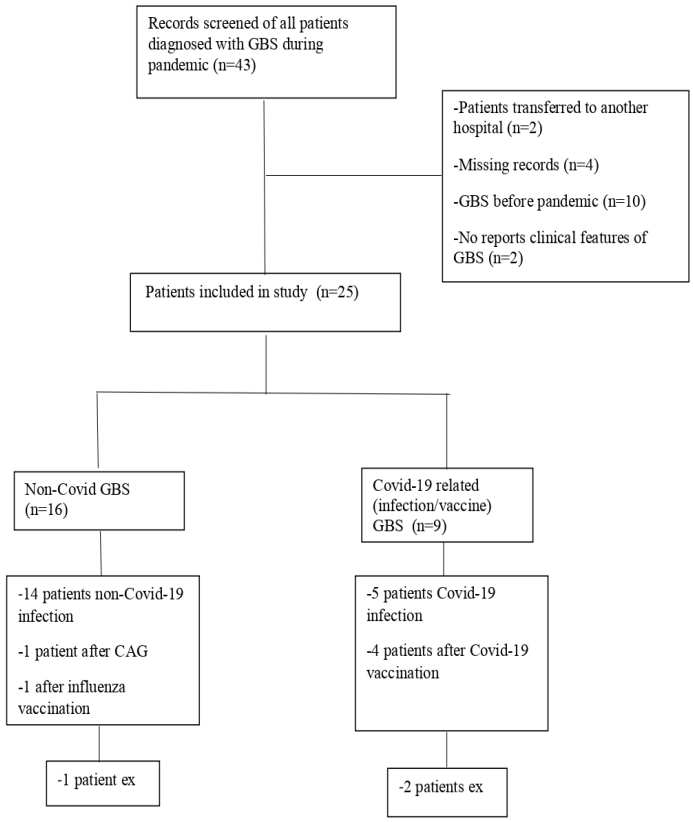

Figure 1. The flow chart of the study design

Table 1: Demographic and anthropometric characteristics of patients

Variables	C-GBS (n=9)	NC-GBS (n=16)	P-value
Age (years), med (min-max)	66 (48-78)	58.5 (7-74)	0.094
BMI (kg/cm²), mean±SD	28.83±3.93	26.29±5.16	0.369
Gender, n (%)			
Female	5 (38.5)	8 (61.5)	
Male	4 (33.3)	8 (66.7)	0.560
Education level, n (%)			
Unschooled	0 (0)	1 (100)	
Primary school	7 (46.7)	8 (53.3)	
High school	1 (14.3)	6 (85.7)	
University	0 (0)	2 (100)	
Comorbidities, n (%)			
Hypertension	2 (25)	6 (75)	0.661
Diabetes mellitus	3 (50)	3 (50)	0.630
Coronary heart disease	2 (40)	3 (60)	1.000
Chronic obstructive pulmonary disease	1 (50)	1 (50)	1.000
Thyroid dysfunction	2 (66.7)	1 (33.3)	0.530
Malignancy	2 (66.7)	1 (33.3)	0.530
Smoking habits, n (%)			
Smoker	2 (33.3)	4 (66.7)	
Non-smoker	7 (36.8)	12 (63.2)	1.000

Values are mean±SD (standard deviation), median (min-max) or percentage (n,%), C-GBS: COVID-19-related Guillain Barre syndrome, NC-GBS: Non-COVID-19 Guillain Barre syndrome, BMI: Body mass index

Table 2: Symptomatology and clinical findings of GBS patients

Clinical features	C-GBS (n=9)	NC-GBS (n=16)	P-value
Symptoms preceding neurological symptoms			
Flu symptoms	4 (80)	1 (20)	**0.040**
Diarrhea	1 (12.5)	7 (87.5)	0.182
Neurologic symptoms, n (%)			
Paresthesia or dysesthesia	6 (27.3)	16 (72.7)	0.231
Limb weakness	5 (27.8)	13 (72.2)	0.565
Acendan progression	8 (36.4)	14 (63.6)	1.000
Bulbar symptoms	0 (0)	1 (100)	0.653
Neuropathic pain	7 (33.3)	14 (66.7)	1.000
Fatigue	7 (36.8)	12 (63.2)	0.523
Neurological examination findings,			
Muscle strength (MRC), med (min-max)			
Proximal upper extremities	4.5 (2-5)	5 (2-5)	0.469
Distal upper extremities	4.5 (4-5)	5 (3-5)	0.276
Proximal lower extremities	2.87±1.45	3.82±1.13	0.328
Distal lower extremities	2.37±1.13	2.94±1.14	0.570
Deep tendon reflex abnormalities, n (%)			
Hyporeflexia	4 (40)	6 (60)	0.667
Areflexia	4 (26.7)	11 (73.3)	0.667
Sensory abnormalities, n (%)	6 (27.3)	16 (72.7)	0.231
Facial asymmetry, n (%)	1 (25)	3 (75)	1.000
Bulbar weakness, n (%)	0 (0)	1 (100)	1.000
Mechanical ventilation, n (%)	3 (75)	1 (25)	0.116
Intensive care unit, n (%)	3 (60)	2 (40)	0.312

Values are mean±SD (standard deviation), median (minimum-maximum) or percentage (n,%) *p values are statistically significant ($p < 0.05$) are shown in bold. C-GBS: COVID-19-related Guillain Barre syndrome, NC-GBS: Non-COVID-19 Guillain Barre syndrome

was 17±3.21 days. Disease-related characteristics and outcomes of C-GBS patients are shown in Table 5. The mean time from admission to control examinations of the surviving patients was 12.8±1.57 months (range, 6-24 months). HFGS scores at the admission and control examinations were similar between the two groups (p=0.770 and p=0.477, respectively). While HFGS scores of the NC-GBS group determined at admission were significantly higher than control examination scores ($p<0.05$), no significant difference was observed between HFGS scores at admission and control examinations in the C-GBS group (p=0.204). FAS levels were significantly higher than the control examination levels in both groups at admission (p=0.016 and p=0.001), and there was no significant difference between the groups (p=0.899 and p=0.118). FIM motor and total scores of the NC-GBS patients were higher than those with C-GBS, but the difference was not statistically significant (p=0.294 and p=0.280, respectively). FIM motor and total scores were significantly higher at admission than control examination scores in both groups (p=0.001 and $p<0.001$, respectively). Although not statistically significant, as seen in Table 6, patients with C-GBS had higher Beck anxiety and depression scores than patients with NC-GBS (p=0.410 and p=0.325, respectively).

DISCUSSION

C-GBS has been reported recently in several case reports and reviews, but this relationship continues to be discussed. In this study, 20% of GBS cases admitted to our hospital during the first two years of the pandemic seem to be associated with COVID-19 infection and 16% with COVID-19 vaccination. However, clinical and electrophysiological features, treatment protocols,

Table 3: GBS disease-related features

GBS features	C-GBS (n=9)	NC-GBS (n=16)	P-value
GBS etiology, n (%)			
COVID-19 infection	5 (55.6)	0 (0)	
Other infectious agents	0 (0)	14 (87.5)	
COVID-19 vaccination	4 (44.4)	0 (0)	
Influenza vaccination	0 (0)	1 (6.25)	
After coronary angiography	0 (0)	1 (6.25)	
Cerebrospinal fluid			
Glucose (mg/dl), mean±SD	73.87±10,2	67.41±11.39	0.832
Potasium, mean±SD	2.90±0,20	3.03±0.25	0.615
Clor, med (min-max)	123 (120-132)	122 (110-131)	0.252
Protein (mg/dl), mean±SD	135.87±53.66	132.14±83.73	0.140
Pleocytosis (mm^3), n (%)	1 (33.3)	2 (67.3)	1.000
Bacteria, n (%)	0 (0)	0 (0)	
Albuminocytologic dissociation, n (%)	8 (36.4)	14 (63.6)	1.000
Electroneuromyography			
Demyelinating polyneuropathy	7 (41.2)	10 (58.8)	
Axonal polyneuropathy	2 (25)	6 (75)	0.661
GBS subtype, n (%)			
AIDP	7 (77.8)	8 (50)	
AMAN	1 (11.1)	4 (25)	
AMSAN	1 (11.1)	3 (18.8)	
Pharyngeal-cervico-brachial variant	0 (0)	1 (6.3)	
GBS treatment, n (%)			
IVIG	7 (36.8)	12 (63.2)	
IVIG+plasmapheresis	2 (33.3)	4 (66.7)	1.000
Mechanical ventilation, n (%)	3 (75)	1 (25)	0.116
Intensive care unit, n (%)	3 (60)	2 (40)	0.312
Death, n (%)	2 (66.7)	1 (33.3)	0.530
Rehabilitation need, n (%)	4 (22.2)	14 (77.8)	0.077
Time of rehabilitation, med (min-max)	1 (0-2)	1 (0-2)	0.458
Rehabilitation period (days), med (min-max)	30 (0-40)	30 (0-60)	0.264

Values are mean±SD (standard deviation), median (minimum-maximum), or percentage (n,%). C-GBS: COVID-19-related Guillain Barre syndrome, NC-GBS: Non-COVID-19 Guillain Barre syndrome. AIDP: Acute inflammatory demyelinating polyneuropathy, AMAN: Acute motor axonal neuropathy, AMSAN: Acute motor sensory axonal neuropathy, IVIG: Intravenous immunoglobulin

and clinical outcomes, including functional status, ambulation levels, independence levels in daily living activities, and anxiety-depression levels, were similar in C-GBS cases and NC-GBS cases.

Numerous case reports and reviews indicate that SARS-CoV-2 is associated with GBS and some other neurological disorders and that COVID-19 causes an increase in GBS cases. However, there are also studies stating the opposite.[3-5,13] Casess *et al*. noted that they did not notice a significant increase in GBS cases in their academic centers, suggesting that GBS is rarely associated with COVID-19.[5] Toscana *et al*. reported an incidence of 0.42% for GBS, which was not higher than the general population in their study of 1,200 patients presenting with SARS-CoV-2 in the first year of the pandemic.[14] Sriwasta *et al*. noticed interestingly in recent studies that GBS is one of the most common neurological manifestations of the peripheral nervous system in COVID-19 patients.[15] In this study, 20% of GBS cases admitted to our hospital in the first two years of the pandemic seem to be associated with COVID-19 infection. As this is a single-center study, the number of patients is limited. However, we think that this rate cannot be a coincidence.

The pathogenesis of GBS induced by SARS-CoV-2 is still unclear, but some hypotheses exist. One of them is the cross-reaction between the ACE-2 receptor, which mediates the binding of SARS-CoV-2 to cell surfaces, and the viral spike protein

Table 4: COVID-19-related clinical features of patients with GBS who developed following COVID-19 infection

COVID-19-related clinical features	Post-COVID- 19 İnfection GBS (n=5)
Symptoms, n (%)	
Fever	4 (80)
Cough	5 (100)
Myalgia	5 (100)
Anosmia	3 (60)
Agnosia	3 (60)
Headache	4 (80)
Diarrhea	1 (20)
Dyspnea	2 (40)
Nasopharyngeal SARS-CoV-2 RT-PCR test, n (%)	5 (100)
Positive	5 (100)
Negative	0 (0)
Pulmonary imaging, n (%)	
Pneumonia	2 (40)
Normal	3 (60)
Treatment place, n (%)	
Home	2 (40)
Hospital	1 (20)
Intensive care unit	2 (40)
Treatment agents, n (%)	6 (31,6)
Favipiravir	5 (100)
Tocilizumab	0 (0)
Anakinra	1 (20)
Pulse steroid	2 (40)
Moxifloxacin	3 (60)
LMWH	3 (60)
Treatment time (days), med (min-max)	10 (5-40)
Mechanical ventilation, n (%)	2 (50)
Intensive care unit, n (%)	2 (50)

Values are median (minimum-maximum) or percentage (n,%).
RT- PCR: Reverse transcription-polymerase chain reaction, LMWH: Low molecular weight heparin

that binds to gangliosides. It has been considered that this cross-reaction develops between spike protein-associated gangliosides of SARS-CoV-2 and peripheral nerve gangliosides due to molecular similarity.[15,16] Another mechanism that causes peripheral nerve damage is T-cell activation and inducing the release of inflammatory mediators by macrophages.[14,15] Comprehensive studies are needed to clarify these mechanisms.

Caress *et al*. reviewed that the mean time to onset neurological symptoms was 11 ± 6.5 days (range 3-28) from the onset of COVID-19.[5] The latency between COVID-19 infection and onset of GBS ranged from 7 to 60 days (mean 25.4±21.34) in this study. This latency period was longer than reported in the literature. In this study, two patients developed GBS when they were hospitalized for treatment of COVID-19 infection. During the illness, they were intubated in the ICU for four weeks due to severe respiratory failure. Weakness in the extremities was noticed after the patients were extubated. One patient had a COVID-19 infection two months ago and was treated at home. To identify a triggering infectious agent, serum Ig M and Ig G antibodies for hepatitis B and C viruses, HIV, CMV, EBV, HSV-1, HSV-2, VZV, and respiratory system rapid virus test panel which is including SARS-CoV-2 RT-PCR, Influenza A, Influenza B, and RSV-PCR were screened, but all were negative. Since no infectious agents triggering GBS appeared, it was thought to be associated with COVID-19 disease. He died 15 days after being diagnosed with GBS. For the reasons mentioned above, the latency time may be longer than the times reported in the literature. In two patients, GBS symptoms started 7-10 days

Table 5: Clinical characteristics of COVID-19-related (infection/vaccination) GBS patients

Clinical features	**Post-COVID-19 Infection GBS (n=5)**					**Post-COVID- 19 Vaccination GBS (n=4)**			
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 1	Case 2	Case 3	Case 4
Age	78	57	70	48	66	66	61	73	66
Gender	Male	Female	Female	Female	Male	Male	Female	Female	Male
Comor-bidities	Vertigo	Hip dysplasia	DM	Hypo-thyroi-dism	HT	DM, CAD, Crohn Prostate ca op	ILD	Hypo-thyroidism Asthma	HT, DM, head and neck tm
Smoking	-	-	-	-	-	-	-	-	-
The time between COVID-19 inf/vac-GBS (days)	7	30	10	20	60	28 (first dose Biontech Phizer)	60 (first dose Biontech Phizer)	3 (second dose Biontech Phizer)	45 (first dose Biontech Phizer)
RT-PCR	+	+	+	+ (Delta mutant)	+	-	-	-	-
Hospitaliza-tion time for COVID-19	7	45	-	40	-	-	-	-	-
GBS subtype	AIDP	AMAN	AIDP	AMSAN	AIDP	AIDP	AIDP	AIDP	AIDP
CSF protein	69	188	150	209	33	149	134	112	110
ACD	+	+	+	+	+	+	+	+	+
Treatment	IVIG	IVIG	IVIG	IVIG	IVIG+-PE	IVIG	IVIG	IVIG	IVIG+ PE
MV	-	+	-	+	+	-	-	-	+
ICU	-	+	-	+	+	-	-	-	+
Ambulation	Walking alone	Walking with walker	Walking with canes	Walking with crutches	Ex	Walking alone	Walking alone	Walking with cane	Ex
HFGS admission	3	3	3	3	4	3	4	3	4
HFGS control	1	1	2	2	6	1	2	2	6
FAS admission	1	0	1	0	0	3	0	1	0
FAS control	4	2	3	3	-	5	4	4	-
FIM-motor admission	52	28	57	34	32	63	42	52	35
FIM-motor control	69	75	76	68	-	84	88	77	-
Beck-anxiety	10	20	21	17	-	11	17	15	-
Beck-depression	8	12	14	3	-	6	12	12	-
Rehabil.	-	+	-	+	-	-	+	+	-

GBS: Guillian Barre syndrome, inf: infection, vac: vaccination, dissoc: dissociation, CSF: cerebrospinal fluid, ACD: albuminocitological dissociation, MV: mechanical ventilation, ICU: intensive care unit, HGFS: Hughes functional grading scale, FAS: functional ambulating scale, FIM: functional independence measure, Rehabil: rehabilitation, DM: diabetes mellitus, HT: hypertension, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, ILD: interstitial lung disease, AİDP: acute inflammatory demyelinating polyneuropathy, AMAN: acute motor axonal neuropathy, PE: plasma exchange

Table 6: Functional outcome measures

Functional tests	C-GBS (n=9)	NC-GBS (n=16)	P**
HFGS, med (min-max)			
Admission	3 (3-4)	3 (2-4)	0.770
Control examination	2 (1-6)	2 (1-6)	0.477
P*	0.204	**0.005***	
FAS, med (min-max)			
Admission	1 (0-3)	0 (0-3)	0.899
Control examination	3 (2-5)	3 (1-5)	0.118
P*	**0.016***	**0.001***	
FIM-Motor, mean±SD			
Admission	46.71±12.72	49.60±10,43	0.294
Control examination	81.71±12.72	84.6±10.43	0.280
P*	**0.001***	**<0.001***	
FIM-Total, mean±SD			
Admission	81.71±12.72	84.6±10.43	0.294
Control examination	111.71±7.29	104.4±9.22	0.280
*P**	**0.001***	**<0.001***	
Beck (control examination)			
Depression, mean±SD	9.57±3,99	7.93±3,23	0.325
Anxiety, mean±SD	15.85±4,18	13.53±5,97	0.410

Values are mean±SD (standard deviation) or median (minimum-maximum). P- values are statistically significant ($p < 0.05$) are shown in bold. P*: intra-group analysis P**: inter-group analysis. C-GBS: COVID-19-related Guillain Barre syndrome, NC-GBS: Non-COVID-19 Guillain Barre syndrome, HFGS: Hughes functional grading scale, FAS: functional ambulation scale, FIM: functional independence measure.

after COVID-19 infection, as in other studies.[5,13,17]

The clinical presentation, progress, and disease severity of GBS are variable.[15] Limb paresthesias and weakness were the most common symptoms on presentation in this study, consistent with similar studies.[5,14,17] Patients experience varying degrees of limb weakness during the disease. Most cases show a mild clinical course and recovery with a good response to standard therapy with IVIG or plasmapheresis. But some cases also show poor prognosis. About 30% of GBS patients had poor outcomes due to respiratory failure.[18] Caress *et al*. reported that more than a third of patients with GBS following COVID-19 need mechanical ventilation.[5] Although non-significant, a greater proportion of C-GBS patients (33.4%) were needed for mechanical ventilation and stay in the ICU compared to NC-GBS patients (6.25%) in this study (p=0.116). This is not a very unexpected result considering the co-existing lung disease in patients with COVID-19. Arguments also support that COVID-19 is a triggering factor for rapidly progressing neuropathy.[19] Varying degrees of recovery was observed in 22 patients (88%), and three patients (12%) had a fatal outcome. In this study, mortality rates were higher in the C-GBS patients (25%) than in the NC-GBS patients (5.9%). However, due to the limited number of patients, the difference in mortality rates of the two groups was not statistically significant (p=0.530). Sriwasta et al. reported a fatality rate of 11% in their study.[15] As respiratory failure can be a common symptom in both GBS and SARS-CoV-2 understanding the severity and mortality outcomes of peripheral nervous system disorders associated with COVID-19 is vital, particularly GBS.

As with all vaccines, some side effects can be seen after SARS-CoV-2 vaccines. They are usually mild or moderate but sometimes severe such as GBS.[20] In this study, GBS developed in 4 patients that it was thought to be associated with the SARS-CoV-2 vaccine. All of them were m-RNA-based vaccines. The age of the patients ranged between 61-73 years. Half of them were males, and half were females. GBS developed after the first dose of the vaccine in three patients and after the second dose in one patient. However, the patient who developed GBS after the second dose reported that she complained of numbness and tingling in the hands and feet after the first dose of the SARS-CoV-2 vaccine. Three days after the second dose of vaccine, numbness and weakness started in the legs, and GBS was diagnosed. In another patient, GBS symptoms began four weeks after the first dose. In a review,

Finsterer et al. reported that the latency period between vaccination and the onset of GBS ranged from 3 hours to 39 days.[21] In our study, the latent periods between vaccination and the onset of GBS in two patients were similar to the time intervals described in this review. GBS developed in a patient 60 days after this study's first dose of the SARS-CoV-2 vaccine. The patient had no history of any other vaccination, upper respiratory infection, or gastrointestinal infection. The serum Ig M and Ig G antibodies for hepatitis B and C viruses, HIV, CMV, EBV, HSV-1, HSV-2, and VZV were all negative. Although the etiology was not certain in this case, it was assumed to be associated with the SARS-CoV-2 vaccine since no other trigger could be identified. The other patient in our study was diagnosed with GBS 45 days after the first vaccination dose. The patient had been operated on for a head and neck tumor two years ago. He also had hypertension and diabetes mellitus. The serum Ig M and Ig G antibodies for hepatitis B and C viruses, HIV, CMV, EBV, HSV-1, HSV-2, VZV, as well as SARS-CoV-2 RT-PCR, Influenza A, Influenza B, and RSV-PCR were all negative. Since GBS could not be associated with another triggering infectious agent or event in this patient, it was assumed to be associated with the COVID-19 vaccine. The patient died 12 days after being diagnosed with GBS. Most GBS cases reported in the literature associated with the vaccine were seen after the first vaccination dose.[21] In our study, 3 (75%) of the vaccine-related C-GBS cases developed after the first dose, and 1 (25%) after the second dose.

The diagnosis of GBS is based on detailed history and neurological examination of patients. Electrophysiological studies and CSF analysis help confirm the diagnosis and exclude other diseases.[22] High CSF protein level is a biomarker determining the severity and extent of the disease and is frequently used in diagnosing GBS.[23] Although not significant, the mean CSF total protein levels were higher in patients in the C-GBS group than the NC-GBS patients (135.87±53.66 vs. 132.14±83.73) in this study (p=0.140). Albuminocytological dissociation is another important biomarker in GBS that was found in 22 patients (88%), of which 8 had C-GBS (100%) and 14 had NC-GBS (82.3%). The most common GBS variant associated with COVID-19 was AIDP (75%) in this study, and the demyelinating polyneuropathy (77.8%) was the most frequent electrodiagnostic pattern, consistent with the other studies.[18] Different electrodiagnostic patterns have also been reported with COVID-19.[5]

RT-PCR nasopharyngeal swabs and serological antibody tests are generally used to diagnose SARS-CoV-2 infection.[24] In this study, all patients in the C-GBS group underwent nasopharyngeal RT-PCR testing to confirm the diagnosis. RT-PCR testing was positive during COVID-19 infection in patients who developed GBS after COVID-19 infection. GBS developed in two patients in this study while they were hospitalized due to SARS-CoV-2 infection. In these patients, RT-PCR testing was positive when they got GBS. The test results were negative when they were diagnosed with GBS in patients who developed GBS after the COVID-19 vaccine. PCR testing for SARS-CoV-2 in the CSF was unavailable in our laboratory; therefore, it had not been performed. In most cases reported in the literature, the RT-PCR test was negative in the CSF.[15,17,22] This is an indication of the role of immune mechanisms in the pathophysiology of the disease. Araújo *et al*. recently reported the first case of positive SARS-CoV-2 RNA in CSF analysis in a pediatric GBS patient.[25]

IVIG or plasma exchange are often used for GBS treatment.[26] Both IVIG and COVID-19 are known to predispose to thrombotic events.[27] In our study, IVIG treatment was used all of the cases. Three patients also received plasmapheresis. No thromboembolic complication was noted. More comprehensive and multi-center studies are needed to determine which treatment method should be preferred in cases of C-GBS. There is still no specific treatment for COVID-19. In our study, treatment agents included antivirals (5/5, 100%), antibiotics (3/5, 60%), IL-1 blockers (1/5, 20%), and pulse steroid (2/5, 40%).

This study reports the functional outcomes of patients at least six months after symptom onset (min-max 6-24 months). The control examinations evaluated muscle strength, HFGS, FAS, FIM, and Beck anxiety and depression scale scores. We determined the functional status of the patients using the HFGS. The HFGS is a disability scale that evaluates the clinical outcomes of GBS patients, primarily through walking.[28] HFGS scores at the admission and control examinations were similar between the two groups in this study (p=0.770 and p=0.477). In a study by Yevgi., HFGS scores were significantly higher in the C-GBS patients than in NC-GBS patients both at admission and discharge.[22] This result may lead to the conclusion that the worse prognosis in C-GBS patients. In a review by Finsterer and Scorza with 220 patients, it was reported that the clinical characteristics and treatment of patients

with C-GBS and NC-GBS were not different. However, the outcome parameters of C-GBS were worse compared to NC-GBS patients.[17]

Contrary to the studies mentioned above, Masuccio et al. reported that C-GBS appeared to have a better clinical outcome than NC-GBS.[29] In our study, functional recovery was similar between C-GBS pad NC-GBS patients. We used FAS to determine the ambulation levels of the patients. Five patients in the C-GBS group and 8 patients in the NC-GBS group had an admission FAS grade of 0, so they could not ambulate. At the control examination, 2 patients were walking independently (FAS grade 5), 4 patients were walking independently on flat ground (FAS grade 4), 8 patients were walking under supervision (FAS grade 3), 8 patients were walking with the assistance of one person (FAS grade1-2). FAS scores were significantly higher at admission than control examination scores in both groups, but no significance was obtained between the groups (p=0.899 and p=0.118). Khan et al. reported that most of survivors (75%) could walk independently.[30]

In our study, the GBS survivors showed a good functional recovery (motor FIM score 81.71±12.72 vs. 84.6±10.43) as in other studies.[31,32] Bernsen *et al*. reported that although 90% of GBS survivors achieved a full functional recovery, 27% had to make significant changes in their work, hobbies, or social activities.[33] Distal motor weakness, sensory impairment, and psychological problems can result in persistent disability. Patients with residual neurological deficits (motor and sensory) reported minimal change in their physical status.[30] In a study conducted with 90 Dutch patients one year after GBS, it was reported that 32% of the patients changed their jobs due to GBS, 30% did not work at home as before, and 52% changed their leisure time activities.[34]

In the C-GBS group evaluated during the control examinations, the mean Beck depression and anxiety scale scores of the patients were 9.57±3.99 and 15.85±4.18, respectively. In the NC-GBS group, these scores were 7.93±3.23 and 13.53±5.97, respectively. Although the Beck anxiety and depression scores of the C-GBS patients were higher than those of NC-GBS patients, the difference was not statistically significant (p=0.410 and p=0.325, respectively). The patients in both groups had a minimum level of depression and a moderate level of anxiety. Khan et al. reported moderate to extreme levels of depression (18%), anxiety (22%), and stress (17%) compared with the normative Australian population (13%).[30] COVID-19 causes psychological, respiratory, and physical dysfunction in affected patients.[35] In some cases, patients had to stay bedridden in ICUs for extended periods. The significant reduction in social interactions due to home quarantine and isolation negatively affects patients.[36] For this reason, it may be why anxiety and depression scores are higher in cases of C-GBS.

Our study has several strengths. Our study differs from other studies evaluating functional outcomes, including functional status, ambulation level, independence in daily activities, and anxiety-depression levels. This study has several limitations. First, it is a single-center study. Due to the limited number of patients, although parameters such as mortality rates or mechanical ventilation rates between the two groups were different, statistical analysis could not yield significant results. Including more patients from more cities in Turkey or other countries would be better to obtain more precise results. Second, two patients in the C-GBS group had a longer latency time (60 days) between COVID-19 infection/vaccination and the onset of GBS. Third, in the control examinations, the time (range, 6-24 months) elapsed since the GBS onset of the patients was different from each other.

In conclusion, GBS is not uncommon in COVID-19. C-GBS appears to share many of the clinical features and functional outcomes of classical post-infectious GBS. However, more comprehensive and multi-center studies are needed to clarify these issues.

DISCLOSURE

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