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RESEARCH REPORT

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Electrodiagnostic methods to verify Guillain-Barré syndrome subtypes in Istanbul: A prospective multicenter study

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Abstract

Background and Aims: This study aimed to identify the clinical characteristics and electrodiagnostic subtypes of Guillain-Barré syndrome (GBS) in Istanbul.

Methods: Patients with GBS were prospectively recruited between April 2019 and March 2022 and two electrodiagnostic examinations were performed on each patient. The criteria of Ho et al., Hadden et al., Rajabally et al., and Uncini et al. were compared for the differentiation of demyelinating and axonal subtypes, and their relations with anti-ganglioside antibodies were analyzed.

Results: One hundred seventy-seven patients were included, 69 before the coronavirus disease 2019 pandemic (April 2019–February 2020) and 108 during the pandemic (March 2020–March 2022), without substantial changes in monthly frequencies. As compared with the criteria of Uncini et al., demyelinating GBS subtype diagnosis was more frequent according to the Ho et al. and Hadden et al. criteria (95/162, 58.6% vs. 110/174, 63.2% and 121/174, 69.5%, respectively), and less frequent according to Rajabally et al.'s criteria (76/174, 43.7%). Fourteen patients' diagnoses made using Rajabally et al.'s criteria were shifted to the other subtype with the second electrodiagnostic examination. Of the 106 analyzed patients, 22 had immunoglobulin G anti-ganglioside antibodies (14 with the axonal subtype). They had less frequent sensory symptoms (54.5% vs. 83.1%, $p = 0.009$), a more frequent history of previous gastroenteritis (54.5% vs. 22.9%, $p = 0.007$), and a more severe disease as compared with those without antibodies.

Interpretation: Serial electrodiagnostic examinations are more helpful for accurate subtype diagnosis of GBS because of the dynamic pathophysiology of the disease. We observed no significant increase in GBS frequency during the pandemic in this metropolis.

KEYWORDS

anti-ganglioside antibodies, diagnostic criteria, electrodiagnosis, Guillain-Barré syndrome, serial examinations

1 | INTRODUCTION

Guillain-Barré syndrome (GBS) is the most common immune-mediated acute paralytic neuropathy, characterized by symmetrical arm and leg weakness, decreased deep tendon reflexes, and ascending sensory symptoms. The incidence of GBS is estimated at 100 000 cases/year worldwide and the frequency of its pathologic and electrodiagnostic subtypes is reported differently in various countries.[1,2]

GBS has two main subtypes: acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and axonal GBS. The axonal forms mainly comprise acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN). The differentiation of the subtypes has been largely based on electrodiagnostic criteria defined by, in chronologic order, Ho et al., Hadden et al., Rajabally et al., and Uncini et al.[3–6] In the past two decades, patients with immunoglobulin G (IgG) anti-GM1 antibody-associated AMAN with rapid resolution of conduction block, called reversible conduction failure (RCF), have been reported.[7–11] Consequently, Uncini et al. recommended serial electrodiagnostic testing to increase the accuracy of identifying RCF and length-dependent conduction failure (LDCF). However, Rajabally et al., suggested that one single electrodiagnostic study might suffice by using more strict criteria.[5,11–13]

The distribution of GBS subtypes has been reported from many parts of the world, and the AMAN subtype has been published with a rate of 5%–17% in Europe and 22%–78% in Asian countries.[14–18] However, the epidemiology of GBS subtypes has not yet been explored in Turkey. Istanbul, the 13th most populous city in the world and largest in Turkey, which received massive immigration over decades from all regions of the country, may be considered a good sampling area for reflecting the population characteristics of the whole of Turkey.

The main aims of this prospective study were to (a) identify the clinical characteristics and electrodiagnostic subtypes of patients with GBS in Istanbul, (b) compare different electrodiagnostic criteria for subtype analysis, (c) determine the correlation of electrodiagnostic classifications with serum anti-ganglioside antibodies, and (d) emphasize the significance of serial electrodiagnostic examinations.

Almost 1 year after the commencement of the study, the coronavirus disease 2019 (COVID-19) pandemic emerged and the first case in Turkey was officially announced in March 2020. To identify the effect of the pandemic, we decided to analyze patients encountered in the pre-pandemic and pandemic periods separately.

2 | METHODS AND MATERIALS

2.1 | Patients

Patients aged 18 years and older, who had acute-subacute onset progressive muscle weakness and/or sensory symptoms and were admitted to 13 tertiary centers in Istanbul between April 2019 and March 2022 were included in the study. Patients were classified according to the Brighton criteria.[19] The pre-pandemic period included patients admitted between April 2019 and February 2020 and the pandemic period included those diagnosed between March 2020 and March 2022. Demographic data elicited in the first (March 2020–March 2021) and second (April 2021–March 2022) years of the pandemic were analyzed separately as early and late pandemic periods.

The exclusion criteria were the diagnosis of GBS mimicking conditions such as transverse myelitis, acute myopathy, critical illness neuromyopathy, acute-onset chronic inflammatory demyelinating polyneuropathy, or any other acute neuropathy (Figure 1).

The patients' symptoms were questioned, and their neurologic examinations were performed twice by a physician in each center, first in the 21 days after the onset of symptoms, and the second between the 4th and 6th weeks. The sensory, motor, autonomic and respiratory, cranial neuropathy, and ataxia symptom and sign categories were labelled as positive if the patient had ≥1 symptom and/or signs that fell into any of these categories (Table S1). Cerebrospinal fluid (CSF) lymphocyte count and protein levels were noted if available. The clinical aspects of the patients were rated using the Medical Research Council (MRC) sum score, Hughes functional scale, and the Erasmus GBS score at the first examination.[20–22]

The local ethics committee of the Istanbul Faculty of Medicine approved the study (Date: 02.08.2019, Number: 2019/179) and all participants provided written informed consent.

2.2 | Electrodiagnostic testing

Each patient underwent two electrodiagnostic examinations; the first one in the 21 days after the beginning of the symptoms and the second between the 4th and 6th weeks of the illness. Sensory nerve conduction studies (NCS), motor NCS, and F-wave studies were conducted in one upper and one lower extremity. In the upper extremity, median and ulnar sensory and motor NCS were performed. For median and ulnar sensory NCS, antidromic or orthodromic techniques from a distance of 13 and 11 cm between recording and stimulating electrodes, respectively, were performed according to the routine protocols of the contributing laboratories. In the lower extremity, tibial and peroneal motor, superficial peroneal, and sural sensory NCS were conducted. Superficial peroneal and sural sensory responses were recorded antidromically from a distance of 12 and 14 cm between recording and stimulating electrodes, respectively. The stimulation and recording sites for the motor NCS were as follows: median nerve, wrist and elbow, abductor pollicis brevis muscle; ulnar nerve, wrist, below the elbow, above the elbow, and axilla, abductor digiti minimi muscle; tibial nerve, ankle and popliteal fossa, abductor hallucis muscle; peroneal nerve, ankle and fibular head, extensor digitorum brevis muscle. Twenty F-waves were recorded from the relevant muscles by stimulating the ulnar, median, and tibial nerves at the wrist/ankle levels. Values outside the normal reference limits of each laboratory for a specific examination were considered abnormal. Sural-sparing was determined when abnormal median and/or ulnar sensory nerve action potential (SNAP) amplitudes were present along with a normal sural NCS.[23,24]

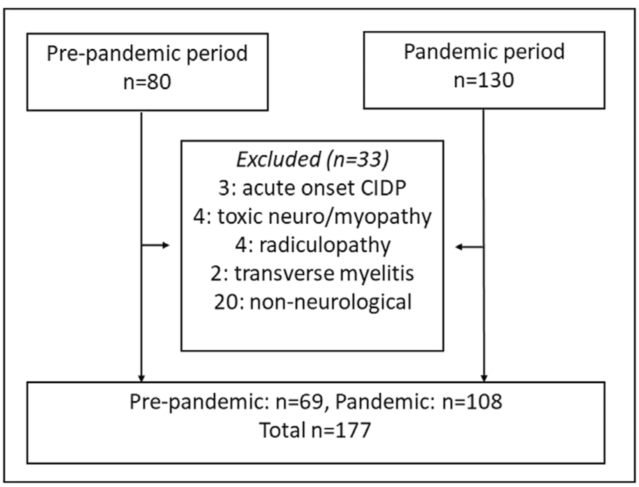

FIGURE 1 Flowchart of the study. CIDP, chronic inflammatory demyelinating polyneuropathy.

The data were then printed by the electrophysiologist who performed the study. The printouts consisted of tables including the values of distal latencies, negative peak durations, and base-to-peak amplitudes of the compound muscle action potentials, peak-to-peak and base-to-peak amplitudes of SNAPs, conduction velocities, minimal F-wave latencies, and F-wave persistence. The recordings of all electrodiagnostic examinations were evaluated by the same investigator (NGS). In each patient, GBS subtypes (demyelinating, axonal, equivocal, and inexcitable) were classified according to all four criteria (Table S2).[3–6] The classification using the criteria set by Uncini et al., was made by considering the findings elicited in both the first and second examinations.[6] Accordingly, the patients who could not be examined with a second electrodiagnostic study were not evaluated using those criteria, except for those diagnosed as having a demyelinating subtype or inexcitable/equivocal study in the first examination. RCF and LDCF were also defined by the criteria of Uncini et al.[25]

2.3 | Anti-ganglioside antibody tests

Sera were collected venously before the initiation of immune treatment, then transferred to the laboratory (Istanbul University, Aziz Sancar Experimental Medicine Research Institute), and stored in a -80°C freezer until use. IgG antibodies against GM1, GM2, GM3, GD1a, GD1b, GT1b, and GQ1b gangliosides in sera were determined using an immunoblotting kit as per the manufacturer's recommendations (Euroimmun, Anti-Gangliosides Profile 2 [IgG], DL1130-1601-2G). Positive results were also confirmed using Homemade ELISA.

2.4 | Statistical analysis

Statistical analyses were performed using the SPSS version 21.0 software package (IBM, Armonk, New York). The Mann–Whitney U test was used to compare continuous variables and the Chi-square (χ^2) test

TABLE 1 General clinical features GBS patients.

	All GBS ($n = 177$)	Anti-ganglioside antibodies (+) ($n = 22$)	Anti-ganglioside antibodies (−) ($n = 84$)[†]	p
Age, years, mean ± SD	51.8 ± 17.2	49.1 ± 17.8	50.0 ± 17.8	0.767
Sex (F/M), n	72/105	6 (45.2)	38 (54.8)	0.151
Symptom onset to admission, days, mean ± SD	9.4 ± 6.1	9.0 ± 5.4	8.8 ± 6.4	0.540
Clinical features[†]				
Sensory symptoms/signs, n (%)[‡]	133 (75.6)	12 (54.5)	69 (83.1)	**0.009**
Distal hypoesthesia	111 (83.5)	10 (83.3)	61 (88.4)	
Asymmetric hypoesthesia	2 (1.5)	0 (0)	1 (1.4)	
Others (sensory ataxia, sensory symptoms/signs in upper extremities)	9 (6.8)	0 (0)	3 (4.3)	
Not recorded	12 (9.0)	2 (16.7)	5 (7.2)	
Motor symptoms/signs, n (%)[§]	156 (88.6)	22 (100)	72 (86.7)	0.115
Distal dominant weakness	67 (43.0)	14 (63.6)	37 (51.4)	
Distal/proximal weakness	57 (36.5)	6 (27.3)	23 (31.9)	
Proximal dominant weakness	32 (20.5)	2 (9.1)	12 (16.7)	
Cranial neuropathy (bulbar, facial diplegia, and paresis), n (%)	61(34.7)	4 (18.2)	33 (39.8)	0.079
Ophthalmoparesis, n (%)	16 (9.1)	3 (13.6)	3 (3.6)	0.105
Autonomous symptoms/signs, n (%)	24 (13.6)	3 (13.6)	8 (9.6)	0.695
Ataxia, n (%)	30 (17.0)	4 (18.2)	12 (14.5)	0.740
Respiratory symptoms[¤], n (%)	17 (9.7)	1 (4.5)	9 (10.8)	0.684
MRC sum score, mean ± SD	48.5 ± 11.7	45.7 ± 13.1	49.5 ± 12.3	0.126
Hughes score, mean ± SD	2.9 ± 1.2	3.3 ± 1.0	2.7 ± 1.3	**0.041**
Deep tendon reflexes				
Hypo/areflexia[¶], n (%)	164 (93.2)	19 (86.4)	73 (88.0)	1.000
Normal deep tendon reflexes, n (%)	7 (4.0)	3 (13.6)	4 (4.8)	0.155
Hyperreflexia[¶], n (%)	7 (4.0)	0 (0)	6 (7.2)	0.339
Erasmus GBS outcome score, mean ± SD	3.6 ± 1.4	4.1 ± 1.5	3.3 ± 1.4	**0.042**
Antecedent incident ($n = 175$*), n (%)	130 (74.3)	10 (45.5)	55 (66.3)	0.088
Antecedent incident type ($n = 142$**), n (%)				-
URTI	66 (46.5)	3 (17.6)	35 (54.7)	
SARS-CoV-2/other	24/42	1/2	12/23	
Gastroenteritis	45 (31.7)	12 (70.6)	19 (29.7)	
Other (vaccination, surgery)	31 (21.8)	2(11.8)	10 (15.6)	
Gastroenteritis history, n (%)	-	12 (54.5)	19 (22.9)	**0.007**
Comorbidities, n (%)	57 (32.2)	24 (30.0)	8 (38.1)	0.599
DM	19 (10.7)			
HT	21 (11.9)			
Others	27 (15.3)			
Second examination time (day) mean ± SD	32.2 ± 10.7	32.9 ± 12.1	32.5 ± 9.6	0.947
Symptom onset to LP (days) mean ± SD, ($n = 145$)	9.4 ± 6.2	9.0 ± 6.3	9.0 ± 4.8	0.635
CSF protein levels (mg/dL) mean ± SD ($n = 153$)	111.1 ± 87.3	70.7 ± 47.1	107.5 ± 82.0	**0.038**
CSF leukocyte levels (cells/μL) mean ± SD ($n = 145$)	4.4 ± 12.5	3.4 ± 9.3	4.2 ± 10.3	0.486
≤5, n (%)	123 (84.8)	17 (83.9)	56 (82.4)	
5–50, n (%)	19 (13.1)	2 (10.5)	11 (16.2)	
>50, n (%)	3 (2.1)	0 (0)	1 (1.5)	

(Continues)

TABLE 1 (Continued)

	All GBS ($n = 177$)	Anti-ganglioside antibodies (+) ($n = 22$)	Anti-ganglioside antibodies (−) ($n = 84$)[†]	p
Symptom onset to nadir (days) mean ± SD	13.5 ± 7.9	11.8 ± 5.3	13.7 ± 6.2	0.426
Treatment ($n = 159$[¶]), n (%)				0.969
IVIg	136 (85.5)	18 (85.7)	67 (85.9)	
PE	6 (3.8)	0 (0)	2 (2.6)	
IVIg + PE	9 (5.7)	1 (4.8)	4 (5.1)	
IVIg + CS	1 (0.6)	0 (0)	1 (1.3)	
No treatment	7 (4.4)	2 (9.5)	4 (5.1)	
ICU admission[≈], n (%)	11 (6.2)	1 (4.5)[≈]	6 (7.1)[≈]	-
Death, n (%)	2 (1.1)	0 (0)	2 (2.4)	-
EDX subtype according to the criteria of Uncini et al.,[6] n (%)***				**0.001**
Demyelinating		3 (15.0)	48 (59.3)	
Axonal		14 (70.0)	25 (30.9)	
Equivocal		2 (10.0)	8 (9.9)	
Inexcitable		1 (5.0)	0 (0)	

Note: Bold denotes $p < 0.05$.
Abbreviations: CS, corticosteroids; CSF, cerebrospinal fluid; DM, diabetes mellitus; F, female; GBS, Guillain-Barré Syndrome; HT, hypertension; ICU, intensive care unit; IVIg, interavenous immunoglobulin; M, male; MRC, medical research council; PE, plasmapheresis; SD; standard deviation; URTI, upper respiratory tract infection.
[†]One patient's clinical data could not be obtained because of ICU admission.
[‡]Patients with sensory symptoms and/or signs in either first or second examination. One patient had both distal and asymmetric hypoesthesia.
[§]Patients with motor signs in either first or second examination.
[¤]Respiratory symptoms consist of difficulty breathing and shortness of breath.
[¶]Two patients had both hyperreflexia and hipo/areflexia.
*Three patients' data of antecedent events and 18 patients' data of treatment could not be obtained.
**Twelve patients had two antecedent events.
***Two patients with and three without anti-ganglioside antibodies could not be classified because of the single electrodiagnostic test.
[≈]Among 11 patients who were admitted to ICU, anti-ganglioside antibodies could be analyzed in seven.

was used to compare categorical variables between the pre-pandemic and pandemic groups and patients with and without anti-ganglioside antibodies. $p \leq 0.05$ was accepted as the limit of significance.

3 | RESULTS

3.1 | Patients

One hundred seventy-seven patients with GBS, 108 of whom were admitted during the pandemic period, were included. One patient's clinical data were not available because of the pandemic conditions. Among 176 patients, diagnostic certainty in 101 was classified as level 1, 52 as level 2, and nine as level 3 according to the Brighton criteria. Fourteen patients could not be classified using those criteria because of the presence of hyperreflexia in four, hyperreflexia and pleocytosis more than 50/μL in one, normoactive reflexes in seven, and pleocytosis more than 50/μL in two. These three patients with more than 50 cells/μL in CSF analyses were diagnosed as having GBS after the exclusion of other possible diagnoses such as infectious and neoplastic polyradiculoneuropathies.

When clinical features were assessed (Table 1), the majority of the patients presented with motor (156/176, 88.6%) and sensory (133/176, 75.6%) symptoms and/or signs. Twelve (6.8%) patients had asymmetric weakness. Although most patients had hypo/areflexia (164/176, 93.2%), seven (4.0%) had hyperreflexia in their neurologic examination (Table S3).

The frequency of GBS in the pre-pandemic period (April 2019–February 2020) was 6.3 patients per month, whereas it was 4.3 patients per month during the pandemic (March 2020–March 2022), representing a slight overall decrease. However, when the pandemic period was analyzed in two consecutive episodes, the frequency was 3.5 per month during the early period between March 2020 and March 2021, which was less than that recorded before the pandemic, and 5.3 patients per month during the late pandemic period, between April 2021 and March 2022, showing a value quite similar to that recorded before the pandemic.

3.2 | Electrodiagnostic tests

Electrodiagnostic tests could not be performed in three patients because of intensive care unit (ICU) admission and second tests could not be performed in 30 patients because of ICU admission, restrictions caused by the pandemic, and/or death.

When compared with the criteria by Uncini et al., GBS subtypes were classified more frequently as demyelinating according to Ho et al. and Hadden et al. (95/162, 58.6% vs. 110/174, 63.2% and 121/174, 69.5%, respectively), but less frequently as demyelinating according to Rajabally et al. (76/174, 43.7%, Table 2).[3–6] According to the criteria by Uncini et al.,[6] the RCF pattern was found in 63.5% (33/52), and LDCF was observed in 17.3% (9/52) of the patients with the axonal subtypes.

The effects of the COVID-19 pandemic on the frequency of GBS subtypes according to Uncini et al.[6] are presented in Table 3. Although the demyelinating subtype seemed to be higher in the first year of the pandemic, the results showed no statistically significant difference between the pre-pandemic and pandemic periods.

In this study, we preferred to perform serial electrodiagnostic examinations. Accordingly, the electrodiagnostic subtypes were classified using the criteria of Rajabally et al. for the data elicited both in the first and second tests (Table 4), and the results were compared with the final diagnoses reached using the criteria of Uncini et al.[5,6] GBS subtypes of 14 patients classified using the criteria of Rajabally et al. in the first test shifted to the other subtype with the same criteria set after the second electrodiagnostic test and became concordant with the electrodiagnosis made using Uncini et al.'s criteria.[5,6]

Among 45 patients with the sural-sparing pattern in the first test, 41 (91.1%) were diagnosed as having the demyelinating subtype according to the criteria of Uncini et al.[6] The remainder was classified as axonal ($n = 1$), equivocal ($n = 2$), and inexcitable ($n = 1$).

3.3 | Anti-ganglioside antibody tests

We collected serum samples from 106 of 177 patients, and 20.8% (22/106) of them were positive for IgG antibodies against GM1, GM2,

TABLE 2 Subtype classifications made by four sets of criteria.

Subtypes	Ho et al.[4] ($n = 174$), n (%)[†]	Hadden et al.[3] ($n = 174$), n (%)[†]	Rajabally et al.[5] ($n = 174$), n (%)[†]	Uncini et al.[6] ($n = 162$), n (%)[‡]
Demyelinating	110 (63.2)	121 (69.5)	76 (43.7)	95 (58.6)
Axonal	33 (19)	27 (15.5)	67 (38.5)	52 (32.1)[§]
Equivocal	31 (17.8)	25 (14.4)	30 (17.2)	14 (8.6)
Inexcitable	-	1 (0.6)	1 (0.6)	1 (0.6)

[†]These classifications were performed according to the first electrodiagnostic tests.
[‡]Among 30 patients with only one study, 16 with a demyelinating electrodiagnostic study, one with inexcitable nerves, and the other with equivocal findings in the first study were classified accordingly. The remaining 12 cannot be grouped according to the criteria of Uncini et al. because of the absence of the second test.
[§]Ten patients were classified as acute motor and sensory axonal neuropathy.

TABLE 3 Comparison of the electrodiagnostic subtypes in the pre-pandemic and pandemic periods (diagnosed by using the criteria of Uncini et al.[6]).

Subtypes	Pre-pandemic[†] ($n = 65$), n (%)	Early pandemic[†] (1st year) ($n = 40$), n (%)	Late pandemic[†] (2nd year) ($n = 57$), n (%)	p*
Demyelinating	34 (52.3)	29 (72.5)	32 (56.1)	0.378
Axonal	25 (38.5)	8 (20.0)	19 (33.3)	
Equivocal	6 (9.2)	3 (7.5)	5 (8.8)	
Inexcitable	0 (0)	0 (0)	1 (1.8)	

[†]Pre-pandemic period includes patients admitted during the period between April 2019 and February 2020, early pandemic period includes those between March 2020 and March 2021, and late pandemic period includes those between April 2021 and March 2022; excluding the patients with one electrodiagnostic test except those presenting demyelinating features or having inexcitable nerves or equivocal study in the first test.
*χ^2 test.

TABLE 4 Patients, whose subtype diagnoses, made according to the criteria by Rajabally et al.[5] in the first study, were changed by the second test.

Number of patients	Rajabally et al.,[5] 1st EDX	Rajabally et al.,[5] 2nd EDX	Uncini et al.[6]
6 patients	Axonal	Demyelinating	Demyelinating
1 patient	Demyelinating	Axonal	Axonal
3 patients	Equivocal	Demyelinating	Demyelinating
4 patients	Equivocal	Axonal	Axonal

Abbreviation: EDX, electrodiagnosis.

GM3, GD1a, GD1b, GT1b, or GQ1b gangliosides. The patients with anti-ganglioside antibodies had fewer sensory signs and/or symptoms (54.5% vs. 83.1%, $p = 0.009$), a more frequent history of gastroenteritis (54.5% vs. 22.9%, $p = 0.007$), and a more severe disease based on Hughes and Erasmus GBS outcome scores (3.3 ± 1.0 vs. 2.7 ± 1.3, $p = 0.041$ and 4.1 ± 1.5 vs. 3.3 ± 1.4, $p = 0.042$) as compared with those who were negative for the antibodies (Table 1). Among the patients with IgG anti-ganglioside antibodies, the most frequent subtype was axonal, showing a statistically significant difference when compared with those without antibodies (70.0% vs. 30.9%) using Uncini et al.'s criteria[6] ($p = 0.001$) (Table 1).

The most frequently found antibody was anti-GM1 (18/22, 81.8%). Among the patients who were anti-GM1 positive, 13 (72.2%) were classified as axonal, three were demyelinating, one was inexcitable, and the other was equivocal. Seven patients were positive for only anti-GM1 antibodies (six axonal and one demyelinating), two were positive for anti-GM1 and anti-GM2 (one axonal and one inexcitable), and eight were positive for anti-GM1 and anti-GD1b (five axonal, two demyelinating and one equivocal). One patient was anti-GM1 and anti-GT1b positive (axonal), one was anti-GM3 (axonal), one was anti-GM3 and anti-GD1b (unclassified using the criteria of Uncini et al. because of a single EDX test, axonal using the criteria of Rajabally et al.[5,6]) and two were anti-GQ1b positive (one equivocal and one unclassified because of a single test-equivocal using the criteria of Rajabally et al.[5,6]).

Among the 33 patients with RCF and nine with LDCF, 26 and seven, respectively, were analyzed for anti-ganglioside antibodies. Ten patients with RCF (38.5%) and four patients with LDCF (57.1%) were positive for anti-ganglioside antibodies, which was anti-GM1 in all with RCF and three with LDCF. One patient with LCFD was positive for anti-GM3 antibodies.

4 | DISCUSSION

During the last three decades, there have been some essential developments in the understanding of the pathophysiology of GBS.[2,11,26] In AMAN and AMSAN, anti-ganglioside antibodies that are produced as a response to the molecular mimicry between the gangliosides and the lipo-oligosaccharides on the surface antigens of the infectious agent, mainly *Campylobacter jejuni*, trigger a complement-mediated process, which begins at the nodes of Ranvier and paranodal region leading to the disruption of conduction.[27–29] This pathologic process can be detected electrophysiologically in its early stages as RCF, which may either reverse and restore the conduction or progress toward axonal degeneration during the course of the illness.[11,13,26,30,31] New electrodiagnostic criteria sets have been suggested for making use of RCF in categorizing the subtypes of GBS.[6,13,32] Using these criteria, the incidence of AMAN and AMSAN were found to be higher in Western countries than were earlier reported; however, still less than in some Eastern countries.[1,2] In this multicenter study, we found that the most frequent subtype was AIDP in Istanbul, representing 59% of the patients, followed by axonal subtypes with 32%. The axonal subtypes were found to be more frequent than most of those reported from Western countries (5–17%).[1,2] In a recent retrospective study from Italy, Benedetti et al. reported the incidence of axonal GBS as 35%, similar to our cohort.[33] However, patients with axonal GBS in that study predominated in Western rural areas of Italy and the authors could not determine the genetic or environmental factors responsible for this finding.[33]

In the present study, we preferred to evaluate patients through serial electrodiagnostic studies for more accurate subtype classification because of the dynamic nature of the pathophysiology of GBS and chose the criteria of Uncini et al.[6] as the primary criteria. In addition to allowing the opportunity to evaluate the patients at two different times during the early period of the disease, the criteria also provided the lowest number of equivocal cases. In our study, when two electrodiagnostic tests were assessed using the criteria by Rajabally et al., the subtype diagnoses of 14 patients were changed, and their final diagnoses were the same as those classified using the criteria of Uncini et al.[5,6] Subtype change from demyelinating to axonal may be considered to be related to secondary axonal degeneration in AIDP after a serious disease process. However, in the only patient whose electrodiagnosis changed to axonal from demyelinating, the second test revealed the presence of RCF, which was not compatible with serious demyelinating damage. On the other hand, the patients who changed from axonal to demyelinating subtypes probably reflect the rate of misdiagnosis in the first study. Furthermore, through serial electrodiagnostic tests, some patients could be diagnosed as having demyelinating or axonal GBS despite not being diagnosed with their first examination (equivocal cases). Although the misdiagnosis rate in our cohort (8.0%, [14/174]) with a single electrodiagnostic study might be considered acceptable, we believe that accurate classification through repeated electrodiagnostic tests is important in understanding the pathophysiology and prognosis of the disease and may also have future implications from the standpoint of potential new and diverse treatments. We only evaluated the criteria of Rajabally et al. in the analysis of the second electrodiagnostic examinations, not the more historic Ho et al. and Hadden et al. criteria, because they do not include assessments of RCF and LDCF and recommend that electrodiagnostic tests be performed within 2 weeks after symptom onset.[3–5]

Sural-sparing is one of the most specific findings in distinguishing GBS from its mimics, and incorporating sural-sparing has been reported to improve the specificity of GBS diagnosis.[34,35] It was seen mostly in demyelinating subtypes of GBS in our cohort, similar to previous studies.[23,34]

It is known that anti-ganglioside antibodies mostly relate to axonal pathology.[36] In our study, 70% of the patients with anti-ganglioside antibodies were classified as axonal, similar to previous reports.[17,28,29,36–38] Our findings support the relationship of anti-ganglioside antibodies with AMAN and gastroenteritis, similar to previous studies from Japan, Bangladesh, and Korea, implying the association between *Campylobacter jejuni*-related gastroenteritis, AMAN, and anti-ganglioside antibodies.[8,17,27–29] However, serologic studies for *Campylobacter jejuni* infections could not be performed in this study.

The most common anti-ganglioside antibodies found in our cohort were anti-GM1 antibodies. Anti-GM1 antibodies were related to the axonal subtype in 72% of the patients. In addition, anti-GM1 antibodies were detected in nearly all patients with anti-ganglioside antibodies showing RCF and LDCF electrophysiologically. These findings were similar to previous reports.[8,17,28,29,36–38] Besides anti-GM1 antibodies, anti-GD1a was also found to be associated with axonal pathology previously[8,17,27,36,39]; however, anti-GD1a was not detected in any of our patients. Previous studies suggested anti-GD1a was related to poor outcomes, seen mostly in children, and with a history of *Campylobacter jejuni* gastroenteritis.[37,39,40] In our cohort, all patients were adults, and the proportion of patients needing ICU treatment and mechanical ventilation was low. Anti-GD1b antibodies, which were found to be related to AMAN,[25,36,39] were the second most common anti-ganglioside antibodies in this study and were mostly associated with axonal GBS.

Different diagnostic criteria, different types of antecedent infections in diverse periods, and different hygiene and dietary habits may all play roles in the vast range of axonal GBS incidences worldwide. Likewise, during the COVID-19 pandemic, several reports have been published to identify the relationship between COVID-19 and GBS.[41–48] Cases of GBS have been reported to have increased during the COVID-19 period in some of these studies,[42,43,47,48] but not in others.[44,45] Our prospective study began before and coincided with the COVID-19 pandemic. The monthly GBS cases during the pre-pandemic and late-pandemic periods seem to be similar; however, their rate declined during the early phase of the pandemic. One of the probable reasons for this decline was the pandemic restrictions in that era, which limited referrals to the tertiary neurology centers that participated in the study. Although the electrodiagnostic subtypes showed no differences between the three periods, there was a slightly higher frequency of demyelinating subtype during the early pandemic period without reaching statistical significance. Studies from Western countries showed an association between COVID-19 and the demyelinating GBS subtype as well as some other clinical features such as facial paralysis and poor prognosis.[41–43,45–48] Therefore, we are presently conducting a detailed analysis of the clinical features of COVID-19 infection-related GBS cases included in this present study. In addition, although the introduction of COVID-19 as a new antecedent event into the population and the absence of any increase in the frequency of GBS in our study seem to be contradictory at the first glance, it could be the result of possible decreases in the number of other infectious events, for example, upper respiratory tract and gastrointestinal infections in the same period due to the restriction of close personal contact and eating out habits. Finally, the logistic difficulties caused by the pandemic also led to some missing clinical, electrodiagnostic, and serologic data in our cohort, which stood as a limitation in our study.

A small part of the patients with GBS may present with brisk reflexes and asymmetrical clinical findings. In a systematic review conducted between 1993 and 2019, hyperreflexia was mostly associated with the axonal subtype, antecedent diarrhea, and anti-ganglioside antibodies, but rarely with AIDP, which was similar to our observation.[49] In previous studies, GBS showing asymmetric weakness was rarely reported.[14,50–52] Although the cause of asymmetric involvement is not clearly explained in GBS, the variations in the blood-nerve barrier, body position, the difference in the use of extremities, and asymmetric distribution of gangliosides within the nervous system have been accused previously.[50,53]

The ICU admission and death rate was relatively low in our group, probably because some more severe cases could be directly referred from the secondary centers to ICUs instead of the tertiary neurology departments. This may have reduced the ratio of severe cases and is a major limitation of the present study. Axonal loss either in demyelinating or axonal subtype might be a good predictor in long-term prognosis of GBS. However, as a limitation, the follow-up visits after 6 weeks of symptom onset were not registered in the present study. In addition, needle electromyography to reveal axonal loss was not performed in the second electrodiagnostic test of all patients.

In conclusion, although the diagnosis of GBS can be made using a single EDX study, serial electrodiagnostic tests are better for accurate GBS subtype diagnosis because of the dynamic course of the disease process. This study revealed no evidence showing an increase in GBS incidence during the COVID-19 pandemic and the frequency of the axonal subtype was 32.1% in Istanbul.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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