



Evaluation of Factors Associated with the Clinical Course and Prognosis of Patients with Guillain-Barre Syndrome

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Abstract

Aim: This study aims to investigate the clinical, laboratory, electrophysiological, and demographic characteristics of patients with Guillain-Barre Syndrome (GBS) who were admitted to our clinic and underwent treatment and the factors contributing to the prognosis at discharge.

Materials and Methods: The study included 138 patients admitted to our clinic for treatment between January 2013 and December 2017, whose patient records were reviewed retrospectively. The Hughes scores, demographic characteristics, and clinical and laboratory data of the patients at admission and discharge were recorded.

Results: The study sample comprised 61 female (44.2%) and 77 male (55.8%) patients with a mean age of 58.1 years. In evaluations of the Hughes scores at admission and discharge, 117 patients were considered to have a good prognosis and 21 patients to have a poor prognosis at discharge. In the poor prognosis group, advanced age ($p=0.028$), being in the acute motor axonal neuropathy (AMAN) subtype ($p=0.001$), development of sepsis ($p=0.007$), need for mechanical ventilation ($p<0.001$), high Hughes scores on admission ($p<0.001$), extended hospitalization ($p=0.030$), increased WBC count ($p=0.033$), presence of hyponatremia ($p<0.001$), abnormal liver function test ($p=0.08$) were higher than the good prognosis group.

Conclusion: Early identification of GBS patients who may have a poor prognosis and rapid application of appropriate treatment methods are essential in creating positive effects on the clinical course and prognosis in this patient group.

Keywords: Guillain-Barré syndrome, prognostic factors, clinical course

INTRODUCTION

Guillain-Barré Syndrome (GBS) is an inflammatory disease of the peripheral nervous system and is the most common cause of acute flaccid paralysis. The reported global incidence is 1-2 per 100.000 (1). GBS is more common in males than females, and the incidence increases with age (1). Up to 60% of patients have an infectious event history. The most important triggers are diarrhea caused by *Campylobacter* (*C.*) *jejuni* and upper respiratory tract infections (2). The pathophysiology of the disease involves severe immune mechanisms, including cellular and humoral immunity, complement deposition, proinflammatory cytokines, and other inflammatory mediators (3).

During the disease, neurological symptoms that are typically sensory start with or before weakness. Most patients experience paresthesias, such as burning and prickling in the hands and feet. Characteristically, the symptoms are highly symmetrical and often progressive. Deep tendon reflexes (DTRs) may be preserved in the early

period but are absent in up to 90% of cases, and weakness usually starts in the lower extremity and spreads upward. Manifestations of autonomic nervous system involvement may accompany the disease. Cranial neuropathy is observed in some cases, while respiratory distress and the need for respiratory support occurs in 20–30% of patients (4). Patients with GBS reach maximum disability in two weeks, while the disease enters a plateau phase after the initial progressive phase that can last from days to weeks or even months (5).

The diagnosis of GBS is based on patient history, neurological examination findings, electrophysiological findings, and cerebrospinal fluid (CSF) studies (6). Electrophysiological studies are of great importance in differentiating between the disease subtypes, such as acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and acute inflammatory demyelinating polyneuropathy (AIDP) (6).

GBS is a monophasic disease with an expected relapse

CITATION

Baydemir R, Kurt Gok D. Evaluation of Factors Associated With the Clinical Course and Prognosis of Patients With Guillain-Barre Syndrome. *Med Records*. 2023;5(1):47-52. DOI: 10.37990/medr.1150691

Received: 27.07.2022 **Accepted:** 24.8.2022 **Published:** 17.11.2022

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in only 2–5% of cases. Poor prognostic factors that negatively affect the clinical course include subtypes with axonal involvement, accompanying diabetes mellitus (DM), hypertension (HT), rapid progression in the early period, early respiratory depression, and the need for mechanical ventilation (MV), hyponatremia, hypoalbuminemia, elevated leukocyte (WBC) counts, abnormal liver function tests (LFTs) and acute kidney injury (AKI) (7,8).

The early identification of predictive factors that may result in poor prognosis would enable more effective and aggressive treatment in the early stages of the disease when nerve dysfunction is potentially reversible.

The present study assesses the clinical, laboratory, and electrodiagnostic findings of patients followed up for GBS and evaluates the prognostic factors based on the Hughes scores determined at discharge.

MATERIAL AND METHOD

Included in the study were 138 patients (61 female, 77 male) admitted to our clinic for treatment between January 2013 and December 2017. Patient records were reviewed retrospectively, and the age at admission, sex, presenting complaints, pre-disease status, CSF findings, examination findings, electrophysiological study results, and treatment protocols of all patients were recorded.

GBS was diagnosed according to the Electroneuromyographic (ENMG) examination defined by Asbury and Cornblath (9). The GBS subtypes and variants were differentiated and classified as AIDP, AMAN, AMSAN, and Miller-Fisher Syndrome (MFS). Inclusion criteria were new-onset symmetrical sensory loss and/or weakness and reduced or absent deep tendon reflexes. Patients with clearly defined sensory level loss, accompanying DM, rheumatic disease, toxic substance use or exposure, lesions identified on magnetic resonance imaging that may cause the clinical picture, and other known muscle diseases or neurological diseases were excluded from the study.

The patients' GBS disability scores (Hughes scores) were calculated at admission and discharge and defined as Grade 0: Normal; Grade 1: Minor symptoms, capable of running; Grade 2: Able to walk 10 m without support; Grade 3: Able to walk 10 m with support; Grade 4: Confined to bed or chair-bound; Grade 5: Requiring assisted ventilation for any part of the day; Grade 6: Death. Grade 2 and below were classified as good prognosis, and Grade 3 and above as poor prognosis (10).

Factors that may be effective in terms of prognosis were retrospectively reviewed. These were; age, gender, previous infection or vaccination, subtypes according to EMG findings, treatment modality, presence of complications, need for a mechanical ventilator, CSF protein level, presence of cranial nerve involvement, presence of facial

paralysis, Hughes score at admission, serum glucose level at hospitalization, duration of hospitalization, WBC count, serum albumin level and presence of hypoalbuminemia (hypoalbuminemia defined as serum albumin level lower than 3.4g/dL), presence of hyponatremia (defined as serum sodium level lower than 135 mmol/L), and presence of abnormal liver or renal function test [defined as abnormal aspartate aminotransferase-alanine aminotransferase (AST-ALT) and abnormal blood urea nitrogen-creatinine (BUN-Cr) levels].

The study was approved by the Clinical Research Local Ethics Committee of Erciyes University (No: 2018/41). Due to the study's retrospective design, informed consent was not obtained.

Statistical Analysis

All statistical analyses were made in IBM SPSS Statistics (Version 26.0. Armonk, NY: IBM Corp.). Data were presented as the number of patients, percentage, mean, median, and standard deviation. The normality of the data was analyzed with a Shapiro-Wilk test. Parametric tests were used for normally distributed data, and non-parametric tests were used for non-normally distributed data. The significance of the difference between categorical variables was assessed with Chi-square and Fisher's exact tests. A p-value of <0.05 was considered statistically significant.

RESULTS

The study sample of 138 patients admitted with Guillain-Barré Syndrome included 61 (44.2%) females and 77 (55.8%) males, with a mean age of 58.1±19.7 years. The clinical characteristics and demographic data of the patients are presented in Table 1.

There was no statistically significant difference in the seasonal distribution of the patients. 61 (44.2%) patients had a history of disease prior to the event. There was a history of upper respiratory tract infections (URTIs) in 25 (18.1%) patients, gastroenteritis in 24 (17.3%) patients, urinary tract infections (UTIs) in six (4.3%) patients, surgery in three (2.1%) patients, vaccination in two (1.4%) patients, and Herpes zoster in one (0.7%) patient.

All patients underwent an ENMG examination during their hospital stay, revealing AIDP in 83 (60.1%) patients, AMAN in 23 (16.7%) patients, AMSAN in 28 (20.3%) patients, and MFS in four (2.9%) patients.

All patients underwent a lumbar puncture (LP), and the cerebrospinal fluid (CSF) studies revealed a mean CSF protein value of 108 mg/dL (20-692) in the patients. Intravenous immunoglobulin (IVIG) alone was administered to 59 (42.8%) patients, plasma exchange (PD) alone to 42 (30.4%) patients, IVIG followed by PD to 22 patients (15.9%), PD followed by IVIG to seven (4.4%) patients. In contrast, eight patients received no treatment as the symptomatology included only sensory symptoms.

Table 1. Main demographic and clinical characteristics of the patients

Variables	N (%)
Age (years, mean \pm SD)	58.1 \pm 19.7
Sex	
Female	61 (44.2)
Male	77 (55.8)
Seasonal distribution Spring	
Spring	36 (26.1)
Summer	39 (28.3)
Fall	26 (18.8)
Winter	37 (26.8)
Previous disease or event	
Surgery	3 (2.1)
Vaccination	2 (1.4)
URTI	25 (18.1)
Gastroenteritis	24 (17.3)
UTI	6 (4.3)
Herpes zoster	1 (0.07)
ENMG findings	
AIDP	83 (60.1)
AMAN	23 (16.7)
AMSAN	28 (20.3)
MFS	4 (2.9)
Treatment	
IVIG	59 (42.8)
PE	42 (26.6)
PE+IVIG	7 (5.1)
IVIG+PE	22 (15.9)
No treatment	8 (5.8)
Complications	
AKI	1 (0.7)
Ileus	1 (0.7)
Pneumonia	1 (0.7)
Infection	8 (6)
Sepsis	2 (0.7)
Pancreatitis	1 (0.7)
Need for MV	15 (10.9)
CSF protein, median (min-max)	108 (20-692)
Cranial nerve involvement	17 (12.3)
Facial paralysis	12 (8.8)
Mortality	10 (7.2)

N: Number, SD: Standard deviation, URTI: Upper respiratory tract infection, UTI: Urinary tract infection, ENMG: Electroneuromyography, AIDP: Acute inflammatory demyelinating polyneuropathy, AMAN: Acute motor axonal neuropathy, AMSAN: Acute motor and sensory axonal neuropathy, MFS: Miller-Fisher syndrome, IVIG: Intravenous immunoglobulin, PE: Plasma exchange, AKI: Acute kidney injury, MV: Mechanical ventilation, CSF: Cerebrospinal fluid

Table 2. Factors affecting the prognosis of patients according to the Hughes scores at discharge

Variables	Good prognosis (Hughes score \leq 2 N=117)	Poor prognosis (Hughes score $>$ 2)N=21	p value
Age (years, mean \pm SD)	57.7 \pm 20.2	65.8 \pm 14.1	0.028
Sex			0.732
Female	51 (43.6)	10 (47.6)	
Male	66 (56.4)	11 (52.4)	
Seasonal distribution			0.323
Spring	29 (24.8)	7 (33.3)	
Summer	34 (29.1)	5 (23.8)	
Fall	20 (17.1)	6 (28.6)	
Winter	34 (29.1)	3 (14.3)	
Previous event or disease			0.231
No previous disease or event	62(53.9)	12 (60.0)	
Surgery	2 (1.7)	1 (5.0)	
Vaccination	1 (0.9)	1 (5.0)	
URTI	20 (17.4)	5 (25.0)	
Gastroenteritis	23 (20.0)	1 (5.0)	
UTI	6 (5.1)	0	
Herpes zoster	1 (0.9)	0	
ENMG findings			
AIDP	78 (66.7)	5 (23.8)	0.001
AMAN	14 (12.5)	9 (42.9)	0.001
AMSAN	22 (18.8)	6 (28.6)	0.80
MFS	3 (2.6)	1 (4.8)	0.95
Treatment			
IVIG	56 (47.9)	1 (14.3)	0.08
PE	34 (29.1)	8 (38.1)	0.96
PE+IVIG	4 (3.4)	3 (14.3)	0.35
IVIG+PE	17(14.5)	5(23.8)	0.88
No treatment	6 (5.1)	2 (9.5)	0.96
Complications			
No	110 (94)	14 (66.7)	0.03
Sepsis	0 (0)	2 (9.6)	0.07
Pneumonia	0 (0)	1 (4.8)	0.45
Infection	6 (5.1)	2 (9.5)	1.00
AKI	0 (0)	1 (4.8)	0.45
Pancreatitis	1(0.9)	0 (0)	1.00
Ileus	0 (0)	1 (4.8)	0.45
Need for MV	3 (2.6)	12 (57.1)	<0.001
CSF protein	104.8 (132.8)	140.9 (171.9)	0.430
Cranial nerve involvement	14 (12.1)	3 (15.0)	0.714
Facial paralysis	11 (9.4)	1 (4.8)	0.487
Hughes score at admission	2.1 (0.9)	3.6 (0.5)	<0.001
Serum glucose, median (min-max)	80 (48-301)	105.5 (47-329)	0.057
Length of hospital stay (days)	15.8 (9.9)	22 (19.5)	0.030
WBC count	9.9 (7.8)	14.7 (15.1)	0.033
Albumin	4.1 (3.0)	4.8 (5.3)	0.462
Hyponatremia	4 (3.4)	9 (42.9)	<0.001
Abnormal liver function tests	7 (6)	5 (23.8)	0.08
Abnormal kidney function tests	0 (0)	1 (4.8)	0.152

SD: Standard deviation, URTI: Upper respiratory tract infection, UTI, Urinary tract infection, ENMG: Electroneuromyography, AIDP: Acute inflammatory demyelinating polyneuropathy, AMAN: Acute motor axonal neuropathy, AMSAN: Acute motor and sensory axonal neuropathy, MFS: Miller-Fisher syndrome, IVIG: Intravenous immunoglobulin, PE: Plasma exchange, AKI: Acute kidney injury, MV: Mechanical ventilation, CSF: Cerebrospinal fluid, WBC: White blood cell count (p-value, in bold those statistically significant)

A need for mechanical ventilation (MV) developed in approximately 10.9% of the patients at follow-up, and among these, ten died (6 male, 4 female) while five were discharged. The patients who developed ileus and AKI as complications died. At admission, complications included infections, pneumonia, sepsis, ileus, pancreatitis, and acute kidney injury.

The Hughes scores were assessed at admission and discharge, and the factors affecting the scores at discharge were analyzed. Accordingly, 117 patients were considered to have a good prognosis and 21 patients to have a poor prognosis. In terms of prognosis, the groups were divided into two as good and bad prognosis. Accordingly, there was no difference between the groups in terms of gender, seasonal distribution, previous events or disease history, CSF protein, cranial nerve involvement, presence of facial paralysis, serum glucose level, serum albumin value, and kidney function tests ($p>0.05$).

Presence of hyponatremia ($p<0.001$), presence of abnormal liver function test ($p=0.08$), need for a mechanical ventilator ($p<0.001$), presence of sepsis among complications ($p=0.07$), presence of AMAN subtype in EMG ($p=0.001$), high Hughes score at admission ($p<0.001$), advanced WBC count ($p=0.033$), extended hospital stay ($p=0.030$) and advanced age ($p=0.028$) were detected more frequently in the poor prognosis group.

The parameters that differ in the groups with good and bad prognosis according to the Hughes score results are shown in Table 2.

DISCUSSION

The present study identified in the poor prognosis group at discharge, advanced age, being in the AMAN group according to EMG findings, development of sepsis, need for mechanical ventilation, high Hughes scores at admission, extended hospital stay, increased WBC count, presence of hyponatremia, and abnormal liver function test were higher than the good prognosis group. Concerning the sex distribution of the study patients, the male sex was diagnosed with GBS 1.3 times more frequently, which is consistent with the literature, although sex did not affect the Hughes score at discharge (1,11,12). Previous studies have emphasized the negative effects of the female sex on long-term prognosis, especially in terms of functional independence (13,14). In the evaluation of prognosis at discharge in the present study, the effects on functional prognosis could differ in the long-term prospective follow-up of the patients.

Most patients in the study presented during the spring and summer, although there are conflicting data in the literature on this subject. While some studies found the autumn and winter months to be riskier, others reported spring and summer to be riskier (15,16). Studies have attributed this to the incidence of *C. jejuni* or influenza virus, which varies by season and even months. It has been suggested that the seasonal distribution changes because *C. jejuni* is mainly

seen in summer and autumn, and influenza in winter, both in our country and worldwide (17-19). Similar studies in our country have reported higher admissions in the summer season (20,21). The present study found no significant relationship between the admission season and prognosis at discharge, and similarly, Çetiner et al. reported that the season did not affect the 3-month prognosis (20).

In this study, 44.2% of patients had a triggering event, such as vaccination or infection, prior to the disease, with the majority of these events being URTIs and gastroenteritis. Our study did not find a significant relationship between any previous event in terms of prognosis. In previous studies, URTIs and gastroenteritis have also been reported as preceding events in the etiology. However, none of the preceding events identified in our study had a positive or negative effect on prognosis at discharge (1,22). Cetiner et al., on the other hand, associated gastroenteritis with a poor prognosis, while another study reported adverse effects on a 6-month prognosis in those with a history of diarrhea (20,23).

In our country, the most common GBS subtype is AIDP, and this was the case also in the patient population in the present study (20,24). While some publications report no difference in prognosis between the subtypes or a greater need for mechanical ventilation in the early period in the demyelinating subtype, others report the axonal subtype to be associated with a more severe course and a poorer prognosis (20,21,25,26). In our study, we found a statistically significantly higher rate of AIDP variant in the good prognosis group and AMAN variant in the poor prognosis group.

Most of our patients were administered IVIG treatment alone or in combination with PD, while around 5.8% were followed up without treatment as their complaints were limited to isolated sensory symptoms. All of these untreated patients with mild sensory complaints had a good prognosis. Examining the effects of IVIG, PD, and combined PD-IVIG treatments on prognosis revealed that those who received IVIG treatment had a better prognosis than those who received plasmapheresis and combined plasmapheresis-IVIG treatments. In our clinic, the first-choice treatment for all patients admitted with GBS is IVIG if there are no contraindications, and plasma exchange is administered to those who cannot receive IVIG. Plasmapheresis is also used in patients with a severe disease course who do not benefit from IVIG alone. This is attributed to the better disease course observed in patients receiving IVIG compared to PD alone or IVIG combined with PD. Previous studies have stated that none of these two treatment options is superior to the other and that steroids are ineffective (27).

Various complications developed in 13 of the 138 patients in the present study, the most common of which were infections of various types (such as urinary tract infections, catheter site infections, etc.). Among the patients who developed complications, two with ileus and AKI died, while sepsis, on the other hand, had a negative effect on

prognosis at discharge. Two people who developed sepsis were also in the poor prognosis group. The absence of any complication in the clinical course was found to be quite high in the good prognosis group. The need for MV was identified as a negative prognostic factor in the present study, consistent with the literature (28). A prolonged hospital stay may also predispose to the development of complications. In addition, patients who needed MV and required intensive care unit admission stayed in the hospital for longer durations. So a prolonged hospital stay was identified as a poor prognostic factor in our study.

There was no significant effect of CSF protein levels, serum glucose levels, facial paralysis, or other cranial nerve involvement on prognosis. At the same time, an elevated WBC count was higher in the poor prognosis group, supporting similar studies in the literature (7,29). The absence of a relationship between hospitalization serum glucose values and prognosis groups in our study was interpreted as the fact that we did not include diabetic patients. A high Hughes score at admission also suggested a poor prognosis at discharge, and the clinical course was also poor in patients with severe disease onset and primarily motor symptoms (20,21).

There was one patient with an abnormal kidney function test, and acute kidney injury developed in that patient. This patient, who developed acute renal failure, later died. No abnormality was detected in other patients. No significant difference between the group was found when serum albumin values were compared. However, hyponatremia and increased liver function tests were significantly higher in the poor prognosis group. Hyponatremia increased liver and kidney function tests, and low albumin values have been associated with poor prognosis (7).

One of the limitations of our study is the evaluation of patients only according to their prognosis at discharge due to the retrospective study design. At the same time, the long-term follow-up would have provided more valuable information, especially regarding long-term motor prognosis. Furthermore, our study only assessed prognosis according to the Hughes scale and did not use other functional scales. Another limitation is the low number of patients. More extensive and prospective studies are needed of this issue are required.

CONCLUSION

In conclusion, the GBS patient series in the present study mainly consisted of those with AIDP, with the demyelinating subtype being predominant, which is in line with the literature. The parameters associated with poor prognosis at discharge were identified as the need for MV, prolonged hospital stay duration, elevated WBC count, hyponatremia, elevated liver function tests, presence of sepsis, and advanced age.

Financial disclosures: *The authors received no support from any financial institution or organization for this study.*

Conflict of Interest: *The authors declare that they have no*

competing interest.

Ethical approval: *The study was approved by the Clinical Research Local Ethics Committee of Erciyes University (No: 2018/41).*

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