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EARLY PREDICTORS OF SEVERE DISABILITY IN GUILLAIN–BARRÉ SYNDROME

GUİLLAİN-BARRÉ SENDROMUNDA AĞIR ÖZÜRLÜLÜĞÜN ERKEN BELİRTEÇLERİ

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Öz

Amaç

Guillain-Barré sendromu (GBS), ihmal edilemez morbidite ve mortaliteye sahip otoimmün nörolojik bir hastalıktır. Bu çalışma, GBS hastalarında ağır engelliliğin erken belirteçleri olarak farklı hasta özelliklerini ve laboratuvar bulgularını değerlendirmeyi amaçladı.

Gereç ve Yöntem

1 Ocak 2018 ile 31 Aralık 2021 tarihleri arasında GBS tanısı alan 121 hastanın tıbbi kayıtlarını retrospektif olarak inceledik. Demografik özellikler, başvuru şikayetleri, ek hastalıklar, geçirilmiş enfeksiyon öyküsü, nörolojik muayene bulguları, 1. gün ve 1. ay sonu GBS Disabilite Skorları (GDS), serolojik ve beyin omurilik sıvısı (BOS) incelemesi laboratuvar parametreleri, elektromiyonörografi sonuçları, GBS alt tipleri, tedaviler, tedaviye bağlı komplikasyonlar ve prognozlar kaydedildi.

Bulgular

121 hastanın ortanca yaşı 58'di (20-87) (n = 73 erkek, %60). Ortalama GDS başvuruda 3 ve birinci ayın sonunda 2 idi. Serum C-reaktif protein (CRP) ve BOS protein seviyeleri yüksek, D vitamini seviyeleri düşüktü. İleri yaş, kraniyal sinir tutulumu, enfeksiyon öyküsü, yoğun bakım ünitesine (YBÜ) yatış, mekanik ventilasyon (MV) ihtiyacı, komplikasyon varlığı, yüksek plazma CRP düzeyleri, nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLO) GBS hastalarında 1. gün ve 1. ayın sonunda ciddi engellilik ile anlamlı şekilde ilişkiliydi.

Sonuç

GBS hastalarında ciddi engelliliği tahmin edebilecek çok sayıda özellik belirledik.

Anahtar Kelimeler: Biyobelirteçler, Guillain-Barré disabilite skoru, Guillain-Barré sendromu, Hughes skoru, Özürlülük belirteçleri

Abstract

Objective

Guillain-Barré syndrome (GBS) is an autoimmune neurological disorder with non-negligible morbidity and mortality. This study aimed to evaluate different patient characteristics and laboratory findings as early predictors of severe disability in GBS patients.

Material and Method

We retrospectively reviewed the medical records of 121 patients diagnosed with GBS between January

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1, 2018, and December 31, 2021. Data regarding demographic characteristics, presenting complaints, co-morbidities, previous infection history, neurological examination findings, GBS Disability Scores (GDS) on the 1st day and by the end of the first month, laboratory parameters of serological and cerebrospinal fluid (CSF) examination, electromyoneurography results, GBS subtypes, treatments, treatment-related complications, and prognoses were recorded.

Results
The median age of the 121 patients was 58 (20–87) years (n = 73 males, 60%). The average GDS was 3 on admission and 2 at the end of the first month. The serum C-reactive protein (CRP) and CSF protein levels were raised, while vitamin D levels were reduced. Advanced age, cranial nerve involvement, history of infection, admission to the intensive care unit (ICU), need for mechanical ventilation (MV), presence of complications, high plasma CRP levels, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLO) were significantly associated with severe disability in GBS patients at day 1 and at the end of the first month.

Conclusion
We identified multiple characteristics that can predict severe disability in GBS patients.

Keywords: Biomarkers, Guillain–Barré disability score, Guillain–Barré syndrome, Hughes score, Predictors of disability

Introduction

Guillain–Barre syndrome (GBS), an autoimmune disorder of the peripheral nervous system, develops following an infection and typically manifests as an ascending and rapidly progressing paralysis with or without sensory and autonomic dysfunction (1). The annual incidence of GBS is estimated at 1–2 cases per 100,000 people (2). Males are predominantly more affected than females; although the incidence increases with age, all age groups can be targeted (3). Most patients have a history of upper respiratory tract or gastrointestinal tract infection prior to the onset of symptoms, of which Campylobacter jejuni gastroenteritis is the most commonly identified infection (4, 5). Since there is ample evidence for an infective aetiology, the pathogenesis of GBS presumably involves the production of autoantibodies or recruitment of inflammatory cells on the surface of the myelin sheath or the node of Ranvier resulting in transient blocking of signal transmission (6, 7).

GBS is categorised into several variants based on the underlying pathology, clinical presentation, and neurophysiological features (8). The most common subtypes is acute inflammatory demyelinating polyradiculoneuropathy (AIDP); other presentations include acute axonal motor neuropathy (AMAN), acute motor sensory axonal polyneuropathy (AMSAN), Miller–Fisher syndrome (MFS), and Bickerstaff brainstem encephalitis (BBE) (9, 10). In general, intravenous immunoglobulins (IVIg) and plasma exchange (PE) are frequently used for the treatment of GBS (11).

Within the first year of the disease, although the mortality rate is roughly 4% (12), severe persistent disability is observed in 14% of patients. Muscular weakness, persistent pain, and the need for professional intervention develop in about 40% of patients. Older age, greater disability/weaker muscles at admission, short interval between symptom onset and admission, preceding diarrhoea, autonomic dysfunction, the need for mechanical ventilation (MV), and absent/low amplitude compound muscle action potentials are unanimously accepted as factors that negatively affect the disease course in GBS (12-14). At the same time, biomarkers associated with prognosis and the clinical outcome of GBS are gaining significant attention. Decreased levels of albumin (one of the acute phase proteins), bilirubin, uric acid (UA), thyroid-stimulating hormone (TSH), and sodium (hyponatremia), as well as elevated levels of certain novel inflammatory markers [neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and C-reactive protein (CRP)], liver enzymes, and cerebrospinal fluid (CSF) proteins have been found to be associated with worse prognosis in GBS (15-20).

Determining the predictors associated with severe disability in GBS may be beneficial for physicians when treating and managing the disease process. Therefore, this study aimed to evaluate the effect of the patient's demographic characteristics, clinical findings, and serum and CSF laboratory tests on the prognosis of GBS on their GBS disability score (GDS) at day 1 and during the first month of the disease.

Materıal and Method

In this retrospective study, we reviewed the medical records of 324 patients diagnosed with GBS and followed up at Ankara City Hospital between January 1, 2018, and December 31, 2021. Patients for whom detailed clinical history and neurological examination findings at the time of admission and in the first month, results of serological tests, CSF laboratory tests, and electromyography were available were included in the study. Patients were excluded if they had any functional limitations due to a previous illness, another neurological disease (stroke, neurodegenerative diseases such as multiple sclerosis, Parkinson's, or Alzheimer's, neuromuscular disease, plexopathy, radiculopathy, or polyneuropathy), comorbidities such as hypertension or diabetes, autoimmune disease, history of vasculitis, thyroid disease, heart failure, liver disease, renal disease, smoking, alcoholism, trauma, or local and systemic infection (such as COVID-19). A total of 121 patients who met these criteria were included in the study, and 203 patients were excluded. The following data were extracted from the records of the included patients: demographic details (age, gender), complaints at admission, comorbidities, drug, smoking, or alcohol use, antecedent infections (signs of respiratory tract infection or gastrointestinal tract infection, particularly diarrhoea), neurological examination findings (including cranial nerve involvement), GDS at day 1 and in the first month, laboratory results for serum and CSF examination, electromyoneurography (EMNG) results, GBS subtype, requirement for MV, complications related to GBS (autonomic dysfunction-related complications, such as cardiovascular, hydroelectrolytic disorders, or encephalopathy), treatments (IVIg, PE, or IVIg + PE) and treatment-related complications (catheter-related infection, deep vein thrombosis, allergic reaction) and prognoses of the patients.

Venous blood sample results obtained from all patients within the first 24 hours of admission were evaluated for the following laboratory parameters: complete blood count (total leukocyte count, neutrophils, lymphocytes, monocytes, NLR, haemoglobin, platelets, and PLR), erythrocyte sedimentation rate (ESR), CRP levels, glucose, urea, UA, creatinine (Cr), albumin (Alb), total protein, creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), direct bilirubin (Dbil), indirect bilirubin (Ibil), total bilirubin (Tbil), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low density lipoprotein (VLDL), triglycerides (TG), sodium (Na), potassium (K), magnesium (Mg), calcium (Ca), TSH, free T3 and T4 levels, folic acid, vitamin B12 (cobalamin), and vitamin D (calciferol). CSF analysis included estimation of protein, Na, chloride (Cl), and Alb levels. Abnormal results were determined based on the laboratory reference values used at our hospital.

A diagnosis of GBS was made based on international diagnostic criteria (21). All patients were classified into GBS subtypes – AIDP, AMAN, AMSAN, MFS, or unclassified—according to their clinical and electrophysiological findings. The severity of disability related to GBS was graded based on the GDS. GDS was first described by Hughes et al. in 1978; it scores the patient's disability level between 0–6 (22, 23) (Table 1).

Data Analysis

The correlation between abnormal laboratory test values and other patient data (age, gender, antecedent infections, cranial nerve involvement, hospitalization in the ICU, need for MV support, complications, and GDS score at admission and in the first month) was examined.

Table 1 Guillain-Barré syndrome disability scale (23).

Score	Description
0	A healthy state
1	Minor symptoms and capable of running
2	Minor symptoms and capable of running
3	Able to walk 10m or more without assistance but unable to run
4	Able to walk 10m across an open space with help
5	Bedridden or chairbound
6	Death

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 26.0., Armonk, NY: IBM Corp.). Mean, standard deviation, frequency, median, and minimum–maximum (range) values were used to describe the variables. The Mann–Whitney U test was used to evaluate two non-parametric groups, and Spearman's correlation coefficient was used to examine the correlation between two numerical variables. A p-value <0.05 was considered statistically significant.

Ethical Approval

The ethics committee of Ankara City Hospital provided ethical approval for the study (dated: 20/10/2021; approval number: E1-21-2077). The study was carried out according to the principles of the Declaration of Helsinki.

Results

Descriptive Data of GBS Patients

The median age of the 121 patients was 58 (20-87) years; 60% of the patients (n = 73) were males. Weakness in the limbs (n = 81, 67%) was the most common presenting complaint, followed by sensory disturbance (n = 27, 22.3%), difficulty with facial muscle movements, including speaking (n = 5, 4.1%), and difficulty with chewing or swallowing (n = 3, 2.5%); other complaints were double vision, severe pain, and inability to walk (n = 5, 4.1%). Cranial nerve involvement during neurological examination was detected in 31.4% of patients (n = 38), 21.5% of patients (n = 26) had respiratory system (RS) infection, and 18.2% (n = 22) had a history of gastrointestinal system (GIS) infection. EMG data were available for 118 out of 121 patients; based on the electrophysiological examination, 51.2% (n = 62) patients were diagnosed with AIDP, 15.7% (n = 19) with AMSAN, 11.6% (n = 14) with AMAN, 1.7% (n = 2) with MFS, and 17.4% (n = 21) of patients were unclassified. More than one-quarter (33%, n = 40) of the patients required ICU admission, and 9.9% (n = 12) of the patients required MV support.

When the laboratory data were examined, serum CRP and CSF protein levels were raised and serum vitamin D levels were reduced compared to the reference values. Regarding the treatment for GBS, 81% (n = 98) of the patients were treated with IVIg, 11.6% (n = 14) with PE, and 7.4% (n = 9) with a combination of IVIg and PE. Unfortunately, 5.8% (n = 7) of the patients died within the first month.

Early Disability Predictors for GBS

The median GDS on the first day of admission was 3. The distribution of GDS at the time of admission was 5 in 2.5% (n = 3) patients, 4 in 25.6% (n = 31),

Table 2 Predictors of severe GBS.

	GDSs 1_{st} day p (rs)*	GDSs 1_{st} month p (rs)*
Age	0.028 (0.201)	0.001 (0.309)
Gender	0.164	0.104
Cranial nerve involvement	0.035	0.018
Previous infection history	0.669	0.289
ICU admission	<0.001	<0.001
Need for MV support	<0.001	<0.001
Complications	<0.001	<0.001
CRP	<0.001 (0.301)	0.036 (0.195)
Vitamin D levels	0.680 (-0.059)	0.594 (0.76)
High CSF protein	0.392 (0.98)	0.794 (-0.30)
NLR	<0.001 (0.358)	<0.001 (0.355)
PLR	0.001 (0.310)	0.011 (0.233)

3 in 28.9% (n = 35), 2 in 25.6% (n = 31), 1 in 15.7% (n = 19), and 0 in 1.6% (n = 2). On the other hand, the median GDS was reduced to 2 by the end of the first month. The most common disability scores by the end of the first month were 1 and 2 in 29.8% (n = 36) patients each, followed by 4 in 15.7% (n = 19), 3 in 12.4% (n = 15), 6 in 5.8% (n = 7), 0 in 5% (n = 6), and 5 in 1.7% (n = 2).

Lastly, higher age, cranial nerve involvement, presence of antecedent infections, hospitalization in the ICU, need for MV support, occurrence of complications, high plasma CRP levels, NLR, and PLR were significantly correlated with worse disability in GBS patients both on the first day and at the end of the first month ($p < 0.05$) (Table 2).

Discussion

Although associated with minimal mortality, GBS can result in severe disability. Various clinical and laboratory factors may carry predictive value for prognosticating the extent of disability; therefore, early identification of factors that may cause severe disability can help reduce morbidity and mortality and contribute to the disease management process. However, only a few studies have assessed the severity of GBS and its associated factors. In this study, we found that age, presence of antecedent infections, need for ICU admission and MV support, complications, plasma CRP levels, NLR, and PLR were significantly correlated with worse disability in the acute phase of GBS.

The International Guillain-Barré Syndrome Outcome Study pointed out that the median age of GBS patients was 51 years and a male-to-female ratio of 1.5, with the number of patients peaking between 50–69 years of age (24). Unlike other autoimmune diseases, the risk of GBS is higher in males than in females, and there is a 20% increase in incidence with every 10-year increase in age (3). Furthermore, many studies evaluating GBS outcomes have shown that older age is associated with worse prognoses (13, 24, 25). In our study, the mean age of the patients was 58 years, and the male-female ratio was 1.5, which concurs with previous reports. While there was no statistically significant relationship between gender and the development of disability early in the disease course, our results confirm that early severe disability is associated with older age.

Epidemiological data establishing infection as an aetiology of GBS are still ill-defined (3); however, approximately half of the patients reportedly have a history of infection (15, 26). Many infections are associated with GBS, the most common being *Campylobacter jejuni* gastroenteritis (5, 27-29). Several reports suggest that the presence of antecedent infections, especially those leading to diarrhoea, is associated with worse short-term outcomes of severe GBS (12, 24, 30). In our study, approximately 40% of the patients had a history of antecedent infection, which was significantly associated with early worse disability.

Additionally, cranial nerve involvement during neurologic examination was observed in 38 patients (31.4%), and was associated with early worse disability. Tunç A. reported a comparable rate of cranial nerve involvement (27%) in GBS patients, which was significantly correlated with worse early disability (15). Furthermore, cranial nerve involvement is high in GBS patients who require MV support (17), which is strongly related to the short-term outcomes of any serious disease (12). Respiratory failure is seen in about 30% of GBS patients; consequently, these patients need MV (31, 32). Therefore, patients with severe GBS require close monitoring, even outside the ICU, to determine the need for ventilation assistance and to prevent respiratory insufficiency. In our study, 33% of the patients needed ICU admission and 9.9% of patients needed MV support on the first day of hospital admission, and both factors were closely associated with worse early disability.

Treatment-or autonomic dysfunction-related complications are frequently observed in GBS, the most common being cardiovascular involvement as a consequence of autonomic dysfunction, which is seen in two-thirds of these patients (33, 34). Therefore, the treating clinician must be able to recognise and manage the complications to reduce mortality and morbidity in GBS patients (34). In our study, complications were detected in 15.7% of the patients, which was significantly associated with the early development of severe disability.

It is known that inflammation is a significant factor in the aetiopathogenesis of GBS (9, 31, 35). In our study, GBS patients had raised plasma CRP levels, NLR, and PLR, which are well-known inflammatory markers; these factors were significantly correlated with early worse disability, which has also been reported by other studies (15, 36, 37). It is known that the increase in inflammation triggered by autoimmune conditions, such as GBS, may cause increased production of CRP levels (38). Although the CRP response has no specificity in terms of diagnosing a disease, elevated values may contribute significantly to the prognosis

and clinical management of the disease. On the other hand, some studies have highlighted the role of NLR and PLR as novel biomarkers for the presence of inflammation (39-41). There is evidence suggesting increased values for these biomarkers in certain neurological diseases, such as multiple sclerosis, stroke, and Becket's disease (42-44). By detecting the presence of neutrophils, leukocytes, and T lymphocytes, the probability of pure macrophage-associated demyelination in spinal root sections (45) was considered, which emphasises the importance of lymphocytes and neutrophils in the pathogenesis of GBS. Accordingly, studies have reported that NLR and PLR are potential inflammatory biomarkers in GBS patients (37, 46), with a possible role in disease prognostication (16), as observed in our study.

However, our study has some limitations. The most important of these is that it was designed retrospectively and did not include a healthy control group. Other limitations were that it was a single-center study with a small sample size, included different GBS subtypes, patients did not receive a standard treatment, prognoses follow-up was limited to one month, different pro-inflammatory cytokines (TNF-a, IFN-g, IL-1b and IL-6) were not studied, laboratory parameters of serological and CSF examinations were not repeated after admission.

In conclusion, recognising the risk factors that may result in severe disability in the early stages of GBS can guide clinicians in devising an effective treatment plan. This study consistently highlights the negative impact of older age, cranial nerve involvement, the presence of antecedent infections, the need for ICU admission and MV support, treatment-related complications, high plasma CRP levels, NLR, and PLR on the development of severe disability in early GBS.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The ethics committee of Ankara City Hospital provided ethical approval for the study (dated: 20/10/2021; approval number: E1-21-2077). The study was carried out according to the principles of the Declaration of Helsinki.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study

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Availability of Data and Materials
Data available on request from the authors.

Authors Contributions
ÜG: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

BG: Investigation; Data curation; Methodology; Resources.

ŞB: Conceptualization; Writing-review & editing.

GK: Writing-review & editing.

Editorial
Although GK, one of the authors of the article, is editorial board member of the journal, he has not taken part in any stage of the publication processes of this article.

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