

Guillain-Barré Syndrome and Its Variants: Clinical Course and Prognostic Factors

Guillain-Barré Sendromu ve Varyantları: Klinik Seyir ve Prognostik Faktörler

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ABSTRACT

Introduction: We aimed to analyze the frequency, clinical characteristics, medical treatment options and final functional status of Guillain-Barré syndrome (GBS) and its variants in a population from a tertiary hospital setting.

Methods: All medical records of patients with acute inflammatory polyneuropathy between the years of 1998–2013 were retrospectively screened. Demographic, clinical and laboratory information, treatment options and the rate of recovery of the patients were gathered.

Results: A total of 183 patients met the study criteria. Subtypes were typical demyelinating form (n=102, 79.1%), acute motor sensory axonal variant (n=11, 8.5%), acute motor axonal variant (n=10, 7.8%), Miller-Fisher syndrome (n=5, 3.9%), and pure sensory subtype (n=1,

0.8%). Remaining patients had the diagnosis of acute-onset chronic inflammatory demyelinating polyneuropathy. The data of treatment option were available for 70 patients. Most of the patients received intravenous immunoglobulin (IVIg) treatment or the combination of IVIg and methylprednisolone. One patient died, there was no improvement in eight patients and rest showed improvement with varying degrees.

Conclusions: We did not observe major change of recovery between different treatment options, however, most of the patients using methylprednisolone required IVIg because of inadequate response.

Keywords: Guillain-Barré syndrome, intravenous immunoglobulin, prognosis

ÖZ

Amaç: Üçüncü basamak hastaneye başvuran popülasyonda, Guillain-Barré sendromu (GBS) ve varyantlarının, sıklık, klinik özellikleri, tıbbi tedavi seçenekleri ve son fonksiyonel durumlarını incelemeyi amaçladık.

Yöntem: 1998–2013 yılları arasında akut enflamatuvar polinöropati tanısı alan tüm hastaların tıbbi kayıtları retrospektif olarak tarandı. Demografik, klinik ve laboratuvar bilgileri, tedavi seçenekleri ve düzelleme oranları toplandı.

Sonuçlar: Toplam 183 hasta çalışma kriterlerini karşıladı. Altıtip, tipik demiyelinizan form (n=102, %79,1), akut motor duysal aksonal formu (n=11, %8,5), akut motor aksonal formu (n=10, %7,8), Miller-Fisher sendromu (n=5, %3,9), saf duysal tip (n=1, %0,8) şeklindeydi. Diğer

hastalarda tanı, kronik enflamatuvar demiyelinizan polinöropati idi. Tedavi bilgilerine 70 hastada ulaşılabilirdi. Hastaların çoğu intravenöz immunoglobulin (IVIg) veya IVIg ve metilprednizolon kullanmıştı. Bir hasta ölmüş, sekiz hastada iyileşme olmamıştı ve diğerlerinde farklı derecelerde iyileşme olmuştu.

Yorum: Farklı tedavi seçenekleri arasında fark görülmemiş olmakla birlikte metilprednizolon kullanan hastalarda yetersiz yanıt nedeniyle IVIg gereksinimi dikkat çekti.

Anahtar Kelimeler: Guillain-Barré sendromu, intravenöz immunoglobulin, prognoz

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INTRODUCTION

Polyneuropathy is classified as acute according to the duration between the onset of symptoms and maximal impairment which lasts up to 4 weeks (1). The acute polyneuropathies may arise in association with various causes which may be listed as immune-mediated, vasculitic, infectious, metabolic, toxic or paraneoplastic causes (2). The typical immune-mediated inflammatory picture which is Guillain-Barré syndrome (GBS) involves the ascending paralysis clinically, demyelinating features like prolonged latencies and significantly reduced conduction velocities electrophysiologically and albumino-cytological dissociation in the cerebrospinal fluid (CSF) analysis (3). However, there are

increasing numbers of GBS variants. The diagnosis of acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered when a patient who was thought to have Guillain-Barré syndrome deteriorates again after 8 weeks from the onset or when deterioration occurs three times or more (4).

Our clinical impression suggests the treatment options included predominantly high-dose methylprednisolone in GBS in the 1980's and early 1990's whereas it has largely been replaced by intravenous immunoglobulin (IVIg) in the last 20 years in our clinical practice and in the world as well.

Our aim was to analyze the frequency and characteristics of GBS and its variants, medical treatment options and final functional status in a population from a tertiary hospital setting from Turkey.

METHODS

All medical records of patients who were treated in our inpatient clinic between the years of 1998–2013 were retrospectively screened. All patients with the diagnosis of acute inflammatory polyneuropathy were included in the study. The inclusion criteria were as follows:

- i. Clinical symptoms and signs attributed to polyneuropathy like progressive weakness and/or numbness, and
- ii. The acute onset of complaints and progression of these complaints maximally up to four weeks.

Patients with diabetes mellitus were not excluded, however, any patients with typical features of neuropathy attributed to the diabetes mellitus were not included. Patients with neurotoxic drug or alcohol use were also excluded.

Information regarding age, gender, precipitating factors, season in which the complaints presented, GBS subtype, presence of pain, involvement of cranial nerves, autonomic dysfunction, involvement of respiratory system, recurrence, duration between the onset of symptoms, treatment of choice in the acute period and the improvement of the patients were gathered. GBS subtype was determined according to the published electrophysiological criteria (5). The recurrence was defined as having two or more episodes that fulfilled the National Institute of Neurological Disorders and Stroke (NINDS) criteria for GBS (6) with either a minimum interval of more than four months between the episodes if the patient did not recover completely, or more than two months when there was a complete or near complete recovery (7) whereas acute-onset CIDP was defined when the patient had rapidly progressive weakness, with a nadir of 8 weeks from the onset of the disease, and had a following chronic course (4). CSF findings and timing of investigation were included when available. The last functional status of patients was also explored via phone calls at the time of study. The GBS disability scale was used to determine the functional status (8, 9). Recovery was defined as one-point improvement of GBS disability scale.

All patients underwent the standardized electrophysiological examinations in accordance with the methods for precautions of safety, measurements and electrode placement (10).

All clinical, electrophysiology and laboratory investigations were done after informed consent of patients or relatives. As this was a retrospective analysis, no informed consent or ethical approval was obtained for patient enrollment. Retrospective analysis of medical recordings was performed according to the Helsinki declaration.

Statistical analysis

Data analyses were performed using the SPSS 11.5 software statistical

package (SPSS Inc., Chicago, IL, USA). Comparisons were made by t-test when distributed homogeneously and by Mann-Whitney U when distributed heterogeneously for quantitative data and by chi-square test for qualitative data. Descriptive statistical methods were used for calculation of mean values, standard deviation, percentages and frequency distribution. Pearson correlation analysis was performed to analyze the relationship between rate of recovery and clinical characteristics; $p < 0.05$ was considered statistically significant.

RESULTS

In the study period, a total of 299 patients were hospitalized with the diagnosis of polyneuropathy and 183 patients had acute presentation. More than half (62.8%, $n=115$) of the patients were male. After the diagnostic work-up and follow-up, the diagnosis of 54 (29.5%) patients were acute-onset CIDP. The remaining 129 (70.5%) patients were diagnosed GBS and its variants.

Subtypes were typical acute inflammatory demyelinating polyradiculoneuropathy (AIDP, $n=102$, 79.1%), acute motor sensory axonal neuropathy (AMSAN, $n=11$, 8.5%), acute motor axonal neuropathy (AMAN, $n=10$, 7.8%), Miller-Fisher syndrome (MFS, $n=5$, 3.9%), pure sensory subtype ($n=1$, 0.8%).

Male gender was predominant in acute-onset CIDP group (68.5%, $n=37$). The mean age of patients within the GBS spectrum group (43.11 ± 20.35) was found to be lower than that of the acute-onset CIDP group (57.85 ± 13.08) without significant difference ($p=0.660$). Also, the mean ages of GBS spectrum subtypes did not differ significantly ($p=0.382$) (see Table 1).

Regarding clinical findings in GBS group, one patient had pure ataxia, and two patients had pure total ophthalmoparesis whereas one patient had paresthesia with hypoactive deep tendon reflexes. All remaining patients had flask paraparesis or quadriparesis with hypoactive or absent deep tendon reflexes. None of the patients had total loss of muscle strength. Cranial nerve involvement, sensory findings or ataxia accompanied in some of these patients. Pain was the most frequent complaint with the ratio of 73% and 33.3% had cranial nerve involvement like ophthalmoparesis, peripheral facial paralysis, ptosis or dysphonia. Autonomic dysfunction and respiratory system involvement was observed in 11.1% and 16.6% of patients (Table 2).

Pain was equal in all GBS spectrum subtypes ($p=0.645$). Following MFS, the second highest ratio of cranial nerve involvement was seen in typical GBS and the frequency of cranial involvement was significantly higher in these two subtypes compared to AMAN and AMSAN ($p=0.025$). Although it was not significant, the highest ratio of autonomic dysfunction was observed in AMSAN type (33.3%, $n=3$) ($p=0.171$). Respiratory system involvement was not statistically different among groups ($p=0.903$), again it was found higher in AMSAN type (33.3%, $n=3$) than the other subtypes.

Table 1. The distribution of gender and mean age among Guillain-Barré syndrome subtypes

	GBS n=129	Acute onset CIDP n=54	GBS subtypes				
			AIDP n=102	AMSAN n=11	AMAN n=10	MFS n=5	Pure sensory type n=1
Gender, n (%)							
Male	78 (60.5)	37 (68.5)	64 (62.7)	5 (45.4)	7 (70)	1 (20)	1 (100)
Female	51 (39.5)	17 (31.5)	38 (37.3)	6 (54.6)	3 (30)	4 (80)	-
Mean age, years	43.1 ± 20.3	57.8 ± 13.1	40.9 ± 22.3	42.7 ± 11.6	54.7 ± 16.9	38.6 ± 17.2	34

GBS, Guillain-Barré syndrome; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMSAN, acute motor sensory axonal neuropathy; AMAN, acute motor axonal neuropathy; MFS, Miller-Fisher syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy.

Diagnosis was supported by electromyography and the mean time from onset to electrophysiological studies was 23.7 days.

CSF analysis was carried out in 81 patients. Lumbar puncture was performed in the first week of complaints in most of the patients (97.5%, n=79). Elevation of CSF protein was the most frequent finding (53.1%, n=43). Only one patient had CSF leucocyte count over 10/mL. Rest of the patients had normal CSF analysis.

The data related to the presence of triggering factor was noted in 85 patients out of 129 patients (Table 2). Of these, 43.5% (n=37) had precipitating factor. The most frequent precipitating factor was upper respiratory tract infection (URTI) (67.5%, n=25), one had preceding tonsillectomy. Ten patients reported diarrhea, one of these patients had both upper respiratory tract infection and diarrhea. The presence or type of precipitating factor did not differ significantly among subtypes of GBS spectrum (p=0.405). In one patient, GBS developed during pregnancy.

The seasonal variation of the disease was known in 92 patients of the GBS spectrum group. The most frequent presentation was in spring (38%, n=35), followed by winter (23.9%, n=22), summer (22.9%, n=21) and autumn (15.2%, n=14).

The mean time period between the onset of symptoms and the treatment was found to be 12.7±8.6 days. Out of all patients, the data of treatment option were available for 70 patients (Table 2). Most of the patients (64.3%, n=45) received IVIg treatment. The second most frequent treatment option (15.75%, n=11) was the combination of IVIg and high-dose intravenous steroid. Five patients were treated only with high-dose intravenous steroid which was almost always preceded by the use of IVIg. Data of recovery were available for 64 patients. The duration between the onset of complaints and phone calls to obtain data about recovery was between 1–4 years and the mean duration was 1.8±1.3 years. Of those, 65.6% (n=45) showed more than 50% recovery. One patient died because of respiratory complications. In eight patients, no improvement was noted. Rest of the patients showed less than 50% of recovery (% 21.8, n=14). However, they were all able to walk without assistance (GBS disability scale 2). There were no patients requiring assisted ventilation after discharge from the hospital. Regarding recovery, involvement of respiratory system and functional status at onset were correlating factors (p=0.007). Other parameters like the age, gender, GBS subtype, presence

of pain, cranial nerve involvement, autonomic dysfunction, precipitating factor, the time period up to treatment or treatment options were not found to be related with the recovery.

DISCUSSION

Clinical and laboratory findings of our study did not show a major deviation from what was reported in the literature:

- i. The most frequent type was AIDP followed by, with descending order, acute motor sensory axonal, acute motor axonal, MFS, pure sensory type;
- ii. After motor or sensory loss, pain was the most frequent complaint;
- iii. Cranial nerve involvement was rare in AMAN and AMSAN;
- iv. CSF analysis may be normal or may include up to 10 leukocytes;
- v. Rate of recovery correlated with respiratory involvement and functional status at onset.

However, there were also somewhat controversial results especially regarding the rate of recovery. There were similar recovery rates between different subtypes and different treatment options.

The statement of “acute immune-mediated or inflammatory polyneuropathy” primarily connotes GBS to the clinician. However, the term GBS actually encompasses a broad spectrum of neuropathies including the typical demyelinating type and other variants which are AMAN, AMSAN, MFS along with other rarer subtypes like acute sensory neuropathy (ASN), acute pandysautonomia, oropharyngeal and other regional variants and Fisher/GBS overlap syndrome (11). Among subtypes, the basic common feature is the rapid progression whereas diversity results from the pathophysiology and/or clinical/regional features involved. Accordingly, the target for the typical variant is myelin whereas it is axon for AMAN and AMSAN subtypes. As an example of regional/clinical variant, MFS presents with its typical triad consisting of areflexia, ataxia, and ophthalmoplegia whereas in acute sensory neuropathy, primarily sensory involvement is responsible for the clinical picture (12). Proportion of AIDP and axonal forms to total GBS may vary between different countries. AMAN was reported to be more frequent in eastern Asian countries. Our figure represents an intermediate one between Europe and Asia (13), probably correlating with geographical location. Interestingly, one study from the eastern part of Turkey reported a very high ratio of axonal forms (14) compared to our study suggesting that regional differences even occur within a country. This difference may originate from the antecedent events. Epidemiological differences and climate may be the major underlying factors in this striking difference. The presence of an antecedent upper respiratory or gastrointestinal infection ratio reaches up to two thirds of cases. *Campylobacter jejuni* is the major responsible agent in especially reports from Asia (15). However, diarrhea was quite uncommon among our patients which may account for low frequency of axonal forms.

The diagnosis of GBS depends on clinical findings. Muscular weakness and hypoactive deep tendon reflexes dominated in our patient population probably because of the retrospective design and inclusion criteria of our study. The reason for relatively mild to moderate muscular weakness and absence of severe bulbar involvement was probably the result of exclusion of patients requiring intensive care. Laboratory, especially neurophysiological examination has a supportive and a discriminative role. Another laboratory tool is CSF analysis which is supportive for the diagnosis if there is protein elevation without pleocytosis (11). Normal results may originate from several reasons such as the analyzing the CSF in the inappropriate time period or the results may also normal in some of the variant forms.

Table 2. The clinical features of all Guillain-Barré syndrome patients

Demography	GBS group
Symptoms of antecedent infection	
None	48/85 (56.5%)
Upper respiratory tract infection	25/85 (29.5%)
Diarrhea	10/85 (11.8%)
Tonsillectomy	1/85 (1.1%)
Upper respiratory tract infection+ diarrhea	1/85 (1.1%)
Cranial nerve involvement	73%
Pain	33.3%
Autonomic dysfunction	11.1%
Respiratory involvement	16.6%
Treatment	
Plasma exchange	0
IVIg	45/70 (64.3%)
IVIg and methylprednisolone	11/70 (15.8%)
Methylprednisolone	5/70 (7.1%)
No treatment	9/70 (12.8%)
Outcome	
Walking without assistance	59/64 (87.4%)
Death	1/64 (1.5%)

GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin

In addition to supportive treatment, there is also disease modifying treatment options such as plasma exchange and IVIg which are implicated as effective when compared to intravenous high-dose corticosteroid treatment. The classical knowledge is that oral steroids slow the recovery, intravenous methylprednisolone does not produce an effect whereas IVIg hastens recovery. However, none of the treatment options changes the long-term outcome or mortality (16, 17). Parameters like severity on admission, axonal involvement, severity at nadir, latency to nadir, having an age over 40 or 50 years, longer duration of the plateau phase, and antecedent gastroenteritis are considered to be associated with a worse recovery (18). Mortality was found to be related to older age and disability during recovery phase (19). The first immunomodulatory treatment was steroid for GBS after 1950 s whereas the first use of IVIg was reported in 1992. The patient population in our study included a heterogeneous group who were admitted between 1998 and 2013. The choice of treatment for GBS has substantially changed on behalf of IVIg in the last two decades. Cochrane reviews in 2001 and 2006 demonstrated that there were only limited number of patients and no adequate trials to determine whether IVIg was more beneficial than placebo (20). Evidence suggested that intravenous methylprednisolone alone does not produce significant benefit or harm (17). Recently, moderate quality evidence exists showing that, especially in severe disease, IVIg started within two weeks from onset hastens recovery as much as plasmapheresis (20). However, steroids were more widely used till 2005 due to unavailability of IVIg or technical problems regarding plasmapheresis which is also true for our patient population. Our results suggest that long-term recovery does not change according to the different treatment options whereas, in the short-term most patients using steroids also required IVIg probably because of an inadequate response. However, we should keep in mind that IVIg is now the efficient choice of treatment with the evidence level A according to EAN guideline.

There are certain limitations of the study largely originating from its retrospective observational nature. We were strict about the diagnostic criteria and excluded some of the patients using follow-up data. Sejvar and colleagues previously reported guidelines for data analysis and collection studies in GBS (21). According to this study, number of patients with certain clinical and electrodiagnostic features should be reported in a study of GBS. Limited access of some findings prevented more detailed presentation and more certain conclusions. There were no patients who were referred for the plasmapheresis in the study period. The reason was probably related to technical unavailability at that time period.

In conclusion, our results represent a long period with changing treatment options from steroids to IVIg. Although we did not observe major change of recovery between different treatment options, most of the patients using methylprednisolone required IVIg because of inadequate response in the short period.

Ethics Committee Approval: Retrospective analysis of medical recordings were performed according to Helsinki declaration.

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