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Clinical subtypes, seasonality, and short-term prognosis of Guillain-Barré syndrome in an Eastern city of Turkey

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Abstract

Background & Objective: This study aimed to analyze the frequency Guillain-Barré syndrome (GBS) subtypes and their relationship with clinical characteristics, seasonal variations and early prognosis in Van City, Turkey. *Methods:* Patients with GBS who were admitted between January 2007 and December 2017 and diagnosed with acute inflammatory demyelinating neuropathy (AIDP), acute motor axonal neuropathy (AMAN) or acute motor sensory axonal neuropathy (AMSAN) were reviewed. Demographics, season of clinical onset, history and type of preceding infection, the Hughes Disability Score (HDS) at admission and discharge were recorded. *Results:* Of a total 100 patients, 51% was diagnosed with AIDP, 25% with AMAN and the remaining 24% with AMSAN subtype. The most common seasonal onset was during the spring (34%), followed by the fall (30%). The history of gastroenteritis (GE) was present in 26% of the patients and these patients were more likely to have AMAN and AMSAN subtypes. HDS on admission and at discharge were significantly higher in patients with AMAN and AMSAN compared to those with AIDP ($p=0.003$ and $p<0.001$, respectively). The most important predictor of poor outcome at discharge was HDS on admission explaining between 50% and 80% of the total variance.
Conclusion: There is a high prevalence of AMAN and AMSAN subtypes in Eastern region of Turkey. The history of GE, which is also commonly found in patients with GBS in this region, is more likely detected in patients with AMAN and AMSAN subtypes. Finally, clinical severity on admission is the most important contributor to clinical outcome at discharge.

Keywords: Guillain-Barré syndrome, acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, seasonal variability, eastern Turkey, early prognosis

INTRODUCTION

Guillain–Barré syndrome (GBS) encompasses a group of clinical syndromes of acute polyradiculoneuropathy with an annual incidence of 1.1–1.8 cases per 100 000 worldwide.[1] Although the exact cause of GBS is still unclear, most of the patients presents a few weeks after a respiratory or gastrointestinal infection, or another immune stimulus that induces an aberrant autoimmune response to the peripheral nerves and their spinal roots.[2,3]

The typical clinical presentation of GBS is a rapidly progressive ascending motor weakness and hyporeflexia/areflexia. The severity and duration of disease is highly diverse in patients as some present with mild weakness while others with quadriplegia and some patients might need mechanical ventilation due to involvement of facial and bulbar muscles or autonomic disturbances.[4] The prognosis also ranges from recovery without any sequel to severe disability or death.[4,5]

Diagnosis of GBS depends on history and physical examination along with supportive findings on electrophysiological studies and cerebrospinal fluid (CSF) analysis.[6] GBS can be classified into at least 4 main types based on clinical and electrophysiological findings as following: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN) and Miller Fisher syndrome (MFS).[5]

Previous studies conducted in different countries have suggested that prevalence of GBS subtypes varies between different geographical

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regions as AIDP predominate in Europe and North America whereas AMAN is more frequent in Asian and South American countries.[7-9] The predominant subtype of GBS might even differ between different regions of the same country, as a study from China reported that AIDP subtype constitutes most of the cases in Southern China as opposed to Northern China where AMAN is the most frequent subtype in patients with GBS.[10] A recent international multicenter prospective study also demonstrated the major effect of geographical factors on disease subtypes, clinical severity, and outcome in patients with GBS.[11] Besides geographical differences, seasonal variability of GBS has also been examined in several studies with conflicting results.[12-16] In a meta-analysis including more than 10,000 patients with GBS worldwide showed increased incidence of GBS in winter than summer in particular geographical regions and concluded that the seasonality is likely to be related to regional variation in prodromal illnesses.[17]

Due to the lack of epidemiological reports, data on geographical and seasonal variabilities of GBS in Turkey is not clear. Besides, most of the GBS studies were performed in the western region of Turkey.[18-20] In this study, we aimed to investigate the frequency of subtypes and seasonal occurrence of the disease in Van city, located in Eastern Turkey. We also investigated factors affecting early prognosis in patients with GBS in this region of Turkey.

METHODS

In this study, we retrospectively reviewed patients with GBS who were admitted to the Neurology Department of the Yuzuncu Yil University in Van, Turkey between January 2007 and December 2017. The diagnosis of GBS was based on clinical symptoms and signs attributed to acute inflammatory polyneuropathy and supportive electrophysiological findings. Patients younger than 18 years/old and patients who had a clinical progression longer than 4 weeks were excluded from the study. Patients with Miller Fisher syndrome were not included into the study, either.

Demographics, any history of preceding infection or vaccination, the season in which the clinical symptoms started, detailed neurological examinations and cerebrospinal fluid examinations were reviewed. Functional disability was assessed using Hughes Disability Score (HDS)which is defined as following: 0) healthy state; 1) minor symptoms and capable of running; 2) able to walk 5 m or more without assistance but unable to run; 3) able to walk 5 m across an open space with help; 4) bedridden or chairbound; 5) requiring assisted ventilation for at least some part of the day; and 6) death.[21]A clinical fluctuation was previously defined as an improvement or stabilization longer than one week followed by secondary deterioration of at least one grade in the HDS.[22,23]A treatment-related fluctuation (TRF) was defined previously as a clinical fluctuation due to the transient effect of the treatment that usually occurs within 8 weeks after start of treatment.[22]

The studies of nerve conduction velocity were performed within 24-48 h of hospitalization in all cases of GBS. Needle EMG was also performed. At least one motor and one sensory nerve was tested on the upper and lower limbs. F response was recorded in all the extremities. Additionally, routine motor conduction studies were performed on the median, ulnar and tibial nerves using conventional procedures. Sensory nerve studies were performed on the median and sural nerves. The amplitude of the negative phase was measured for compound muscle action potentials and sensory nerve action potentials. In our study, NCS in patients with AIDP showed features of demyelination, including prolonged distal motor latency, decreased nerve conduction velocity, prolonged F-wave latency, increased temporal dispersion, and conduction blocks. The sural sensory potential was preserved. Features of axonal Guillain-Barré syndrome (AMAN and AMSAN) were decreased motor, sensory amplitudes, or both. AMSAN was defined as the presence of AMAN pattern in motor nerve studies with sensory nerve action potential amplitude reduction more than 50% of the normal in two or more sensory nerves. In 93 (93%) patients, the NCS showed evidence for the presence of a poly(radiculo)neuropathy and supported the diagnosis GBS. Patients were categorized into AIDP, AMAN and AMSAN subtypes based on previously proposed electrophysiological criteria. Abnormal NCS was equivocal in five patients (5%), and was reclassified as AMAN when serial NCS was performed. The fact that NCS was normal in the remaining only two (2%) patients, and did not recur can be explained by the late admission of most of the patients to the hospital and the late diagnosis of GBS in the patients.

The data on treatments that were given to the patients and on duration of hospitalization (in days) were gathered. HDS was also used at discharge to assess prognosis. Patients who had a HDS <3 on admission were considered to have a favorable clinical presentation and those who had HDS≥ 3 on admission were considered to have a

severe clinical presentation. On the other hand, patients who had a HDS <3 at discharge were considered to have a good outcome while those who had HDS≥ 3 at discharge were considered to have a poor outcome.

This study was performed with the approval of and in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The data was obtained from our hospital records retrospectively for the study.

Statistical analysis

The SPSS (Statistical Package for Social Sciences) for Mac Version 26 software and R statistical software (version 4.0.3) were used for statistical analyses. Categorical variables were presented as count (%) and comparisons between categorical variables were made by Pearson chi-square test. Continuous variables were presented as mean ±SD or median (IQR), as appropriate based on their distribution. The independent-samples *t* test or ANOVA was used for comparison of normally distributed continuous variables while the Mann-Whitney *U* test or Kruskal Wallis test for non-normally distributed variables. Finally, a model decomposition method was used to estimate the relative importance of potential predictors on the outcome. This method was proposed by Lindeman *et al*.[25] as implemented in the R package 'relaimpo' (version 2.2-3).[26] A *p* value less than 0.05 was considered statistically significant and all significance tests were 2 tailed.

RESULTS

In the study period, we identified a total of 100 patients who were diagnosed with GBS. Characteristics of the study cohort are presented in Table 1. The median (IQR) of age was 48

Table 1: Characteristics of the study population

Age, median (IQR)	48 (31-61)
Sex, male n (%)	67 (67)
History of preceding infection	
Upper respiratory tract infection, n (%)	41 (41)
Gastroenteritis, n (%)	26 (26)
Urinary tract infection, n (%)	2 (2)
No history of infection, n (%)	31 (31)
Season of the symptom onset	
Spring, n (%)	34 (34)
Fall, n (%)	30 (30)
Winter, n (%)	19 (19)
Summer, n (%)	17 (17)
HDS on admission	
0, n (%)	0 (0)
1, n (%)	0 (0)
2, n (%)	25 (25)
3, n (%)	36 (36)
4, n (%)	27 (27)
5, n (%)	12 (12)
GBS subtype	
AIDP, n (%)	51 (51)
AMAN, n (%)	25 (25)
AMSAN, n (%)	24 (24)
Immunotherapy	
IVIG only, n (%)	82 (82)
Plasmapheresis only, n (%)	5 (5)
IVIG + Plasmapheresis, n (%)	13 (13)
HDS at discharge	
0, n (%)	2 (2)
1, n (%)	42 (42)
2, n (%)	28 (28)
3, n (%)	16 (16)
4, n (%)	7 (7)
5, n (%)	0 (0)
6, n (%)	5 (5)

Table 2: Comparison of patient characteristics and GBS subtypes

	AIDP (n=51)	AMAN (n=25)	AMSAN (n=24)	P value
Age, median (IQR)	48 (28- 59.5)	51 (36-57)	43 (33.5-69.5)	0.843
Sex, male n (%)	38 (74.5)	16 (64)	13 (54.2)	0.203
Presence of precedinginfection, n (%)	35 (68.6)	19 (76)	15 (62.5)	0.592
Type of preceding infection (n=67)				
GE, n (%)	9 (25.7)	11 (61.1)	6 (42.9)	0.041
URTI, n (%)	16 (74.3)	7 (38.9)	8 (57.1)	
Season of the symptom onset				
Spring and summer, n (%)	29 (56.9)	14 (56)	8 (33.3)	0.139
Fall and winter, n (%)	22 (43.1)	11 (44)	16 (66.7)	
HDS on admission				
HDS ≥3	31 (60.8)	23 (92)	21 (87.5)	0.003
HDS<3	20 (39.2)	2 (8)	3 (12.5)	
Immunotherapy				
IVIG only, n (%)	47 (92.2)	16 (64)	19 (79.2)	0.010
Plasmapheresis ± IVIG, n (%)	4 (7.8)	9 (36)	5 (20.8)	
HDS on discharge				
HDS ≥3	5 (9.8)	11 (44)	12 (50)	<0.001
HDS<3	46 (90.2)	14 (56)	12 (50)	

(31-61) and 67% of the patients were male. Of all patients 74% were younger than 60 years old while the remaining 26% were ≥ 60 years old. In all patients, AIDP was found to be the most frequent subtype (51%), followed by AMAN (25 %) and AMSAN (24 %).

The symptom onset of GBS was mostly seen in the spring (34%) and the fall (30%) and less commonly in the winter (19%) and the summer (17%). Age (p=0.997), sex (p=0.724) or HDS on admission (p=0.909) did not differ between patients who had a symptom onset in the fall and winter period compared to those who had a symptom onset in the spring and summer period.

Sixty-nine (69%) of the patients had a history of preceding infection while 31% did not. The presence (vs. absence) of preceding infection was not associated with age (p=0.893), sex (p=0.137), the season of onset (p=0.443) or the HDS on admission (HDS ≥ 3 vs. HDS< 3) (p=0.105). Within the patients with history of gastroenteritis (GE) or upper respiratory tract infection (URTI) only (n=67), 27 out of 35 (77.1%) patients who had a symptom onset in the fall and winter period had history of URTI and 18 (22.9%) had history of GE while 18 out of 32 (56.3%) who had a symptom onset in the spring and summer period had a history of GE and14 (43.8%) had history of URTI (p=0.005). In other words, the rate of URTI was more common in the fall and winter period as compared to the spring and summer period while the rate of GE was more common in the spring and summer period than the fall and winter period. Age or sex did not differ between patients with history of GE and those with URTI (p=0.687 and p=0.326, respectively). On the other hand, the rate of having a HDS ≥ 3 on admission was significantly higher in patients with history of GE as compared to those with history of URTI (96.2 % vs. 68.3%, p=0.006).

The comparison of patient characteristics and GBS subtypes are presented in Table 2. Age, sex, seasonal onset, or presence of preceding infection were not associated with GBS subtypes (p>0.1 for all comparisons) but the history of URTI was significantly more common in patients with AIDP, while the history of GE was more common in patients with AMAN and AMSAN (p=0.041). Patients with AMAN and AMSAN more commonly demonstrated a HDS ≥3 on admission, were more commonly treated with plasmapheresis and had more commonly showed

HDS ≥3 at discharge than patients with AIDP. Duration of hospitalization was significantly longer in AMAN and AMSAN subtypes compared to AIDP subtype (p=0.005).

Overall, 72 of all patients had a good outcome (HBS<3) while the remaining 28 had a poor outcome (HBS≥3). The comparison of these groups is given in Table 3. Age did not differ between patients with poor outcome and those good outcomes (p=0.924), but male sex was significantly more common in those with good outcome compared to those with poor outcome (75% vs 46.4%, p=0.006). Seasonal onset or presence of preceding infection was not associated with outcome (p=0.748 and p=0.419). Patients with poor outcome more commonly had HDS≥3 on admission than those with good outcome (28% vs 0%, p<0.001). There were 18 patients who received plasmapheresis. 13 of these patients also received IVIG after PE while 5 patients did not. There were no differences in the type of initial treatment (IVIg, PE, or other) in severely affected patients with sensorimotor GBS vs the pure motor variant, or between demyelinating and axonal subtypes of GBS. However, patients with the axonal subtype (n = 11/49, 22.4%) were more often treated with multiple courses than patients with the demyelinating subtype (n = 2/51, 4%; p = 0.001). Previous studies have shown that TRFs may occur in up to 12 % of GBS patients[11]. In the current study, TRFs were reported in 13 (13%) patients, of whom were re-treated with PE followed by IVIG. A higher proportion of re-treated TRF patients was unable to walk independently and the treated group had more severe limb weakness around the time of the TRF, which indicates that the decision to start treatment in case of a TRF may depend on the severity of symptoms. Axonal GBS was associated with more severe limb weakness (indicated by higher HDS.) during the first 4 weeks as compared to demyelinating GBS. Patients with poor outcome more likely received plasmapheresis (either alone or in-combination) compared to IVIG alone while patients with good outcome more likely received IVIG alone as compared to plasmapheresis (either alone or in-combination) (p<0.001). Length of hospital stay was also longer in poor outcomes compared to those with good outcomes (p<0.001).

As mentioned before, patients with AMAN and AMSAN had more likely to have poor outcome as compared to patients with AIDP (p<0.001).

In a linear regression analysis including HDS at discharge as dependent variable and age, sex, season of symptom onset, presence of preceding infection, HDS on admission and GBS subtypes as independent variables, higher HDS on admission (ß =0.21, 95% CI 0.13-0.230, p<0.001) and presence of AMAN subtype (ß=0.13, 95% CI 0.03-0.22, p=0.009) were independently associated with higher HDS at discharge. Finally, HDS on admission explained between 50%-80%while GBS subtypes explained 15%-40% of the total variance in clinical outcome at discharge (Figure 1).

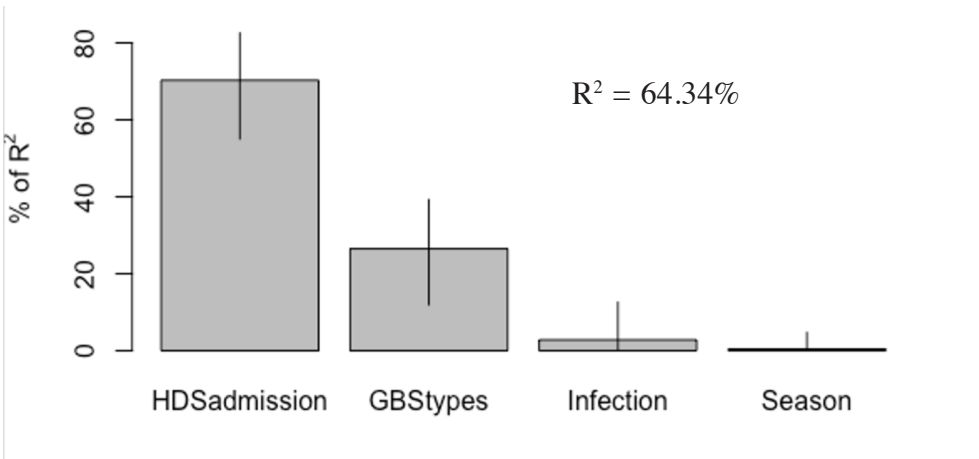

Figure 1. The model showing the contribution of HDS on admission, GBS subtypes, preceding infection and onset of season to the HDS on discharge. Lines represent 95% confidence intervals of the variance after bootstrapping.

DISCUSSION

In this study, we reported the prevalence of GBS subtypes, seasonal onset, presence and type of preceding infection, clinical severity on admission and discharge of patients with GBS admitted during a 10-year period in a single- center in the Eastern region of Turkey. The main findings of the study can be summarized as following: 1) The most frequent subtype was AIDP however this subtype constituted 51% of the patients while the AMAN was diagnosed in about one fourth and the AMSAN was diagnosed in the remaining one fourth of the subjects. 2) Most of the subjects were presented in the spring, followed by the fall season. 3) The prevalence of history of URTI was higher during fall and winter period and in patients with AIDP while history of GE was more common in patients presented during spring and summer period and in patients with AMAN and AMSAN. 4) Patients with AMAN and AMSAN had more severe clinical presentation, they were more likely treated with plasmapheresis and had poor functional outcome at discharge compared to patients with AIDP 5) The most important contributor of poor outcome was the clinical severity on admission, followed by having a subtype of AMAN or AMSAN.

The previous reports demonstrated that the rates of subtypes differ in different geographical areas as AIDP subtype is the most common type in Europe and North America while axonal variants are more common in Asia and South America.[7-9] Studies from Turkey that were conducted in western regions demonstrated that AIDP was also the most frequent type of GBS.[18,20] Compared to these reports, axonal subtypes were more common in our study results. Our study, to the best of our knowledge, is the first study investigated the prevalence of GBS subtypes in an Eastern region of Turkey, but our results are consistent with a previous study from the same region that found higher rates of AMAN subtypes in their study population that included pediatric patients mostly.[27] These results support the view that regional differences might occur within a country. *Campylobacter jejuni* has been reported as the major responsible agent in subjects from Asia.[28] The history of GE was quite common among our patients, and it was associated with axonal subtypes. A study conducted in Iran which is in the same area of the middle eastern region also demonstrated higher rates of AMAN and AMSAN subtypes and associated history of diarrhea prior to clinical onset.[29] Therefore, the higher rates of GE in Eastern Turkey and Middle Eastern countries might be the major underlying factor in higher rates of axonal subtypes. The spring was the most common season the patients presented as reported in a recent study from western region of Turkey but the rate of onset during the fall in our study was much more common than this report.[18] Overall, these variabilities in subtypes, type of infection and onset of season might be due to epidemiological, and geographical differences between western and eastern regions of the country.

Our study also showed more severe clinical presentation and poor functional outcome in patients with AMAN and AMSAN compared to AIDP subtype similar to previously published studies.[30,31] However, the most important contributor to poor functional outcome was clinical severity on admission in our patients. High disability on admission has been previously reported as a predictor of poor prognosis at 6 month.[32]

Although the treatment efficacy of IVIG and PE was largely demonstrated in patients with GBS unable to walk, our study showed that in current clinical practice, 75% of patients with mild disability were also treated. Previous studies have shown that the efficacy of a second course of IVIG is yet unknown. Although, about 12% of patients with GBS who have been treated with IVIG or plasma exchange deteriorate after initial improvement or stabilization—a phenomenon that is termed TRF.[11] These patients usually improve after retreatment with IVIg or plasma exchange, and although the efficacy of retreatment has never been demonstrated in a randomized controlled trial, this approach has become common practice. While the efficacy with PE followed by IVIG treatment practice is unproven, one may argue that IVIG and PE have different therapeutic targets and that if one treatment fails, the other might still be effective. However, a consequence of early secondary treatment with PE after IVIG is that IVIG is washed out and cannot further contribute to recovery.[33] On the basis of clinical experience, we and others advise retreatment with IVIG (2 g/kg over 5 days) in patients who develop TRF. These patients may have a prolonged autoimmune response that causes ongoing nerve damage, or functional blockade that requires prolonged treatment. Some patients experience multiple periods of deterioration or have a progression phase that exceeds 4 weeks. In these patients, the question often arises as to whether the diagnosis is still consistent with GBS, or the patient has chronic

inflammatory demyelinating polyneuropathy with acute onset. In a prospective study series, about 5% of patients initially diagnosed with GBS were eventually found to have acute onset chronic inflammatory demyelinating neuropathy.[22,34] The diagnosis of acute onset chronic inflammatory demyelinating neuropathy should especially be considered in patients initially diagnosed with GBS who have three or more periods with clinical deterioration, or when there is a new deterioration after 8 weeks from onset of weakness. These secondary deteriorations should be recognised because patients with Guillain-Barré syndrome with a TRF might improve after re-treatment, and patients with acute onset chronic inflammatory demyelinating neuropathy usually need chronic maintenance treatment with IVIG or a switch to corticosteroid treatment.

In conclusion, axonal types of GBS along with the history of gastrointestinal infection show a higher prevalence in Eastern region of Turkey and these patients had a more severe clinical presentation as well as poor prognosis. Finally, clinical severity on admission is the most important contributor to functional outcome at discharge

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