Clinical Variants and Evaluation of Clinical Severity of Guillain Barre Syndrome in a Tertiary Care Hospital of Nepal

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Abstract

Background

Guillain Barre Syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature. Our aim is to evaluate the grading of disability and outcome among different variants of GBS.

Methods

All consecutive patients recruited prospectively in the study were of age ≥16 years and were being admitted in department of Neurology of Tribhuvan University Teaching Hospital, Kathmandu, Nepal from 2016 March to 2017 February. All demographic, historical and clinical data were collected. Nerve conduction study, cerebrospinal fluid analysis along with clinical features were evaluated to assess the diagnostic certainty of Brighton Criteria. Overall disability sum score (ODSS) and GBS disability score were assessed in all patients. The study protocol was approved by the Institutional Review Boards.

Results

A total of 46 patients were included: male patients being predominant (70% vs 30%), mean age= 36.5±16.2, range = 16 - 80 years. Thirty-two patients (70%) were an axonal variant, acute motor axonal neuropathy being more common (18 patients), and 14 patients were acute motor and sensory axonal neuropathy. Fourteen patients (30%) were demyelinating type, out of which 11 patients had both motor and sensory features, and only 3 patients were pure motor demyelinating type. Axonal variants were found to have higher ODSS during nadir (p=0.024) and discharge(p=0.004), and also higher GBS disability score during nadir (p=0.012) and discharge (p=0.021). Acute motor axonal neuropathy (AMAN) had higher GBS disability score than acute inflammatory demyelinating polyneuropathy (AIDP) at nadir (p=0.034) and discharge (p=0.039).
Conclusions

Axonal neuropathy variants are predominant among the Nepalese population and are clinically severe than demyelinating variants. Further, prospective study of longer duration to include larger number of patients will be needed.

Background

Guillain-Barre syndrome (GBS) is an important cause of acute neuromuscular paralysis characterized by rapidly progressive, symmetric progressive weakness, ascending pattern and areflexia. GBS can be classified into different common variants: Acute inflammatory demyelinating polyneuropathy (AIDP), Acute motor axonal neuropathy (AMAN), Acute motor and sensory axonal neuropathy (AMSAN) and Miller Fisher Syndrome (MFS)[1]. In about 50-70% of patients, prodromal gastrointestinal or respiratory illness has been identified as trigger factors[2]. There can be involvement of cranial nerves and may even need respiratory support due to involvement of respiratory muscles[3].

Previous studies have shown that AIDP is reported as the most common variant in western countries, while in Asian countries like Japan, China and India, it comprises only 20-40% [2, 4]. Axonal variants were found to be clinically more severe than demyelinating variants in most of the studies[5, 6]. However, few studies found demyelinating variant were more severe, and some found no difference[7]. However, there are still few studies are available from Asian sub-continent evaluating the clinical severity of GBS. There is a distinct paucity of research on severity of GBS in Nepal. Given the aforementioned, the purpose of this study is to classify the GBS variants, describe their clinical and electrophysiological characteristics and evaluate clinical severity, disability and outcome among these variants. The abstract of this study has been presented in 31st international
congress of clinical neurophysiology, May 1-6, 2018, Washington DC, USA[8].

Methods

All consecutive patients selected for the study were being admitted in department of Neurology of Tribhuvan University Teaching Hospital, Kathmandu, Nepal between March 2016 to February 2017 were prospectively studied. Inclusion criteria were: Clinical manifestation with acute bilateral flaccid limb weakness and hyporeflexia or areflexia or cranial nerve palsy or precedent viral infection; Patient’s age >16 years; and nerve conduction study showing axonal or demyelinating neuropathy. Exclusion criteria was the diagnosis with peripheral neuropathy other than GBS. All demographic, historical and clinical data were collected. Nerve conduction study, cerebrospinal fluid analysis along with clinical features were evaluated to assess the diagnostic certainty of Brighton Criteria[9].

Clinical severity was described by Overall disability sum score (ODSS) and GBS disability score[10, 11]. Medical Research Council (MRC) grading was used to measure the muscle strength of each joints[12]. Symmetricity in weakness was defined as the absence of difference in weakness in major limb muscle groups between right and left side. Nadir was defined as highest overall disability score that the patient achieved during the disease course. In nerve conduction studies, median demyelination was reported if the distal motor latency was >4.8ms and velocity <45m/s (distal latency >5.3ms and conduction velocity <43m/s if the distal CMAP amplitude was <2.4mV). In case of ulnar demyelination, >4.0ms was taken standard distal latency, <46m/s was conduction velocity (>4.3ms distal latency and <44m/s conduction velocity if distal CMAP was <2.0mV)[13].

The statistical analysis included calculation of means, standard deviations, range,
frequencies and percentages. Means were compared by independent sample t-test. Comparison of means of ODSS and GBS Disability score of GBS variants were done by one-way Analysis of Variance (ANOVA) test with Bonferroni post-hoc analysis. Chi-square tests were used for the descriptive statistics. Statistical significance for all analyses was defined as P<0.05. All the statistical analysis was conducted using latest version of SPSS.

Results
Total 46 patients were included in the study, 32 male (69.6%) and 14 female (30.4%); mean age of population was 36.5±16.2 years, range = 16 years to 80 years as shown in Table 1. All of the GBS patients had limb weakness and the progression of limb weakness pattern was ascending in 41 patients (89.1%), 2 patients (4.3%) had descending pattern, and 3 patients (6.5%) had simultaneous pattern. Symmetricity and areflexia were found in all patients. Facial weakness was found in 26 patients (56.5%); 23 of them had bilateral weakness and 3 had mild unilateral weakness. Bulbar symptoms like slurring speech, dysphonia or dysphagia were present in 20 patients (43.4%). Neck muscles weakness with features of difficulty lifting or holding neck was present in 16 patients (34.8%). Sensory symptoms were present in 35 patients (76.1%). Dysautonomia was found in 19 patients (41.3%), 16 patients of them were of axonal type and only 3 were demyelinating type. Duration from symptoms onset to nadir was 10.7±4.2 days, range 3–22 days. Hospital presentation of patients after symptoms onset was 9.2±6.1 days. Total hospital admission days were 15.7±10.2 days, range 4-57 days. 32 patients (70%) were axonal type out of which 18 patients were AMAN and 14 patients were AMSAN. Fourteen patients (30%) were demyelinating type out of which 11 patients had both motor and sensory features, and only 3 patients were pure motor demyelinating type.

ODSS of GBS patients at nadir was 8.1±2.2 and discharge was 5.6±1.7. GBS disability
score at nadir was 3.6±0.9 and, 2.76±0.8 at discharge. No significant difference in ODSS and GBS disability scores was found between male and female patients (Table 1) and between younger (age < 40 years) and older age groups (age³ 40 years) (Table 2). Axonal variants have higher ODSS than demyelinating variant at nadir (8.5±2.2 vs 7.0±1.8; p=0.024) (Figure 1) and discharge (6.0±1.8 vs 4.7±1.1; p=0.004) (Figure 2). Axonal variants also have higher GBS disability score at nadir (3.8±0.9 vs 3.1±0.8; p=0.012) and discharge (2.9±0.8 vs 2.3±0.5; p=0.021) than demyelinating variant. Hospital admission duration of axonal variants was more than demyelinating variant, (17.3±11.3 vs 12.2±5.8 days, p=0.122). ANOVA post-hoc test among AMAN, AMSAN and AIDP showed no significant difference in ODSS was seen among these variants at nadir (Table 3). AMAN variant had higher GBS disability score than AIDP at nadir (p=0.034; Table 4). AMAN had higher ODSS (p=0.048; Table 5) and GBS disability score than AIDP at discharge (p=0.039; Table 6) whereas no significant difference in GBS disability score was seen among these variants at nadir.

Discussion

Our study showed men are more likely to have GBS than women which was consistent with most of the GBS studies[14-16]. GBS can affect people of all ages, but majority of patients were below the age of 40 years. Our result was similar to an Indian study showing high prevalence below 40 years and only few patients were above 50 years[17]. Similarly, a Northern Chinese study has also reported younger age-group GBS patients have higher incidence than elderly population[18]. In contrast to this, few studies reported the increase in incidence of GBS with age and rate is high among those are 50 years and above[19]. British studies has reported a bimodal peak of incidence among 2 age-groups 15-24 years and 65-74 years [20].
Histologically, GBS can be classified into two types of neuropathy: axonal and demyelinating. Neurophysiological study further can distinguish different patterns of axonal or demyelinating neuropathy. AIDP is reported as most common variants in western countries (80-90%) while 20-40% in Asian countries like Japan, China and India[21]. Our study results are consistent with most other Asian studies as demyelinating and axonal variants was 30% and 70% respectively[2, 5, 22]. Incidence of MFS is often less frequently reported in previous studies [23, 24], as no MFS patients were reported during our study period.

Typical clinical manifestations of GBS are: monophasic, rapidly progressive limb weakness with symmetricity, and absence or reduced tendon reflexes. Deep tendon reflexes have been reported to be preserved in some cases of AMAN variant [2]. All of the GBS patients of our study satisfied those typical clinical presentations except 1 patient of AMAN variant had preserved tendon reflexes during the emergency presentation in 48 hours, it got gradually reduced in next 48 hours. Most of our GBS patients had ascending pattern of weakness, but 2 patients (4.3%) had descending pattern, and 3 patients (6.5%) had simultaneous pattern of onset. An Indian study reported GBS patients had similar pattern of weakness with simultaneous involvement of upper and lower limbs was reported in 27.1% and descending pattern of weakness in 6.8% [15]. Facial palsy was seen in more than half of the GBS patients and bilateral weakness pattern was seen in most of them which was consistent with previous studies[25, 26]. Bulbar and neck muscles weakness were other important presenting features in our GBS patients and were also reported in previous studies[22, 25]. Although sensory symptoms are not usually disabling in GBS, it is one of the presenting complain in most patients[1]. Three-fourth of our patients had some sensory symptoms during admission. Dysautonomia, an important cause of death in
GBS and is commonly associated with patients of severe limb weakness or bulbar involvement [27, 28]. Axonal variants which are the severe form of GBS are likely to have more risk of having dysautonomia[29]. Similar to our finding, Dysautonomia is a common manifestation seen in GBS in other studies, but no specific correlation with axonal pattern has been studied [6, 30].

Increase in CSF protein is one of the important supportive factor for diagnosis of GBS. But only 50% patient might show some slight increase in 1st week, and subsequently protein elevation is seen after 1st week[6]. Since lumbar puncture was done in range of 5-15 days, 54% of CSF protein were in normal range. Some of the studies has reported up to 80-95% of CSF protein elevation in GBS patients[17, 31, 32]. A recent Iranian study has reported CSF protein elevation in 20% of their patient, but the duration of CSF analysis and disease onset has not been specified[33]. Link et al found that leukocyte counts may increase between 10 days to 4 months and gradually normalizes later[34]. But all of our patients had cell counts in normal range. CSF findings may change over time in GBS patients which might confuse the treating physician suggesting judicious management is warranted correlating with clinical findings[35].

Western studies have higher AIDP incidence, whereas axonal variants in most Asian studies[2, 4]. In this current study, we also found predominant axonal variants, AMAN being the commonest variant. Nerve conduction studies were done between 1 and 3 weeks of symptoms onset and all of the patients showed patterns correlating with one of the GBS variants. Kokubun et al found that conduction studies done in early period might show majority with equivocal reports, but few weeks later axonal variants will be
predominant[13]. Axonal variants present as reversible conduction block during early period which shows the importance of follow-up neurophysiological evaluation. Hadden et al also studied about repeat conduction studies at 5 weeks and found Wallerian like degeneration might be the reason for transformation of demyelinating to axonal variant later[21]. However, there were also cases of axonal pattern which transformed in to demyelinating pattern and the above hypothesis couldn’t explain it clearly. An Iranian study reported that sensory amplitude is usually affected later than motor amplitude resulting in sensory involvement is lately found[32].

Feasby et al found that axonal variants were found to be clinically severe than demyelinating variants[36]. Our study also showed axonal variants were found to be clinically more severe than demyelinating group with high ODSS and GBS disability score both at nadir and discharge. Among GBS variants, AMAN was found to have higher GBS disability score than AIDP. During discharge, both ODSS and GBS disability score of AMAN were significantly higher than AIDP. Delayed recovery in AMAN could be due to severe axonal loss[29, 36]. An early recovery in AIDP patients was found which could be due to demyelination without severe secondary axonal injury[5]. However, Mitsui et al and Ho et al didn’t find any difference in clinical outcome between axonal and demyelinating variants[37, 38].

Previous studies had shown that poor prognosis was associated with older age, antecedent diarrhea, need for mechanical ventilation, rapid onset of weakness and severe muscle weakness during admission[39, 40]. In age group comparison (<40 and ≥ 40 years), no significant difference in clinical outcome reported till discharge and hospital stay duration was found. No significant difference was found among antecedent infections (acute
gastrointestinal infection, upper respiratory tract infection and non-infective events) which was measured by ODSS and GBS disability score at discharge. In this current study, axonal variants were more prone to need for mechanical ventilation than demyelinating variant, which was similar to an Indian study[6]. In contrast to our findings, a French study reported demyelinating variant as a predictor of need for mechanical ventilation [41].

It is a single center study and less number of patients were recruited, but none of them were lost to follow-up. Other GBS variants besides AMAN, AMSAN and AIDP couldn’t be recruited in our study. We didn’t repeat nerve conduction study in 4-6 weeks which could be an important predictor of long term outcome. Laboratories facilities to isolate organisms of antecedent infection and measurement of ganglioside antibodies are the other supportive means for the diagnosis of GBS which is not available at our center.

Conclusions

GBS is more common in male patients. In our study, axonal neuropathy variants are found to be predominant among Nepalese population. Motor axonal neuropathy are clinically severe than demyelinating variants. Further, prospective study of longer duration to include larger number of patients will be needed to shed more light on the above stated conclusions.

Abbreviations

AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor and sensory axonal neuropathy; ANOVA: One-way Analysis of Variance; CSF: Cerebrospinal Fluid; GBS: Guillain Barre Syndrome; MFS: Miller Fisher Syndrome; MRC: Medical Research Council; ODSS: Overall disability sum score.

Declarations
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Availability of data and materials

All data and materials are available from corresponding author.

Authors’ contributions

RO participated in the definition of intellectual content, study concepts, study design, statistical analysis, data acquisition, data analysis and manuscript preparation and editing. KKO participated in study concepts, study design, selection of studies and manuscript editing. BPG, RK, RR, GK participated in manuscript review, literature research and study concepts. HDY participated in manuscript review and editing. RS carried out the selection of studies, data analysis and statistical analysis. All authors participated in revising the manuscript and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted according to the criteria of the declaration of Helsinki. Study protocol was reviewed and approved by the Institutional Review Board of Tribhuvan University Teaching Hospital, Kathmandu, Nepal. We obtained the written consent from all participants after detailed explanation of research purpose, and assurance of maintaining
privacy and confidentiality.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1: Baseline demography of GBS patients
| Clinical Characteristics                  | Male (n=32) | Female (n=14) | Total  |
|------------------------------------------|-------------|---------------|--------|
| Age (mean ± SD) years                    | 35.9±17.7   | 37.7±12.4     | 36.5±  |
| Age group                                |             |               |        |
| Below 40 years                           | 23 (72%)    | 9 (64.3%)     | 32     |
| ≥40 years                                | 9 (28%)     | 5 (35.7%)     | 14     |
| Antecedent Events                        |             |               |        |
| URTI                                     | 9 (28.1%)   | 6 (42.9%)     | 15     |
| AGE                                     | 12 (37.6%)  | 6 (42.9%)     | 18     |
| AGE and URTI (both)                      | 1 (3.1%)    | 0             | 1      |
| Rashes                                   | 1 (3.1%)    | 0             | 1      |
| Surgery                                  | 1 (3.1%)    | 0             | 1      |
| None                                     | 8 (25%)     | 2 (14.3%)     | 10     |
| Nadir Duration (days)                    | 10.8±4.1    | 10.5±4.6      | 10.7±  |
| Hospital Admission (days)                | 14.0±7.5    | 19.6±14.2     | 15.7±  |
| ODSS at Nadir                            | 7.8±2.2     | 8.7±2.2       | 8.1±2. |
| ODSS at Discharge                        | 5.5±1.8     | 6.0±1.7       | 5.6±1. |
| GBS Disability score (Nadir)             | 3.6±0.9     | 3.8±0.9       | 3.6±0. |
| GBS Disability score (Discharge)         | 2.7±0.7     | 2.8±0.9       | 2.7±0. |
| Received IVIg                             | 14 (43.7%)  | 9 (64.3%)     | 23     |
| Mechanical Ventilation needed            | 8 (25.0%)   | 4 (28.6%)     | 12     |
| Variants                                 |             |               |        |
| AMAN                                     | 15 (46.9%)  | 3 (21.4%)     | 18     |
| AMSAN                                    | 9 (28.1%)   | 5 (35.7%)     | 14     |
| AIDP                                     | 8 (25.0%)   | 6 (42.9%)     | 14     |
| Brighton Criteria                        |             |               |        |
| Level 1                                  | 16 (50%)    | 4 (28.6%)     | 20     |
| Level 2                                  | 16 (50%)    | 10 (71.4%)    | 26     |

Data are expressed as n (%) or mean ± standard deviation (SD); Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor and sensory neuropathy; URTI: Upper respiratory tract infection, AGE: acute gastroenteritis; ODSS: Overall disability sum score; GBS: Guillain Barre Syndrome; IVIg: Intravenous Immunoglobulin; No patients fulfilled the Level 3 and Level 4 diagnostic certainty of Brighton Criteria.

Table 2: Evaluation of Disability Score of younger and older GBS patients
Data are expressed as mean±standard deviation; ODSS: Overall disability sum score

Table 3: Overall disability Sum Score (ODSS) of GBS Variants at Nadir

| Tests | (I) diagnosis | (J) diagnosis | Mean Difference (I-J) | Std. Error |
|-------|---------------|---------------|-----------------------|------------|
| AMAN  | AMSAN         | -0.26984      | 0.75162               |
| AMSAN | AMAN         | 0.26984       | 0.75162               |
| AIDP  | AMSAN         | 1.71429       | 0.79722               |
| AIDP  | AMAN         | -1.44444      | 0.75162               |

AMAN: Acute motor axonal Neuropathy; AMSAN: Acute motor sensory axonal neuropathy; AIDP: Acute inflammatory demyelinating polyneuropathy.

* The mean difference is significant at the 0.05 level. Both Tukey HSD and Bonferroni Tests of ANOVA showed no significant difference in GBS disability score among GBS Variants.
Table 4: GBS Disability score of GBS subtypes at Nadir

| Tests   | (I) diagnosis | (J) diagnosis | Mean Difference (I-J) | Std. Error |
|---------|---------------|---------------|-----------------------|------------|
| Bonferroni | AMAN          | AMSAN         | 0.15873               | 0.31225    |
|         | AMSAN         | AIDP          | 0.80159*              | 0.31225    |
| AMSAN   | AMAN          | -0.15873      | 0.31225               |            |
|         | AMSAN         | AIDP          | 0.64286               | 0.33119    |
| AIDP    | AMAN          | -0.80159*     | 0.31225               |            |
|         | AMSAN         | -0.64286      | 0.33119               |            |

AMAN: Acute motor axonal Neuropathy; AMSAN: Acute motor sensory axonal neuropathy; Acute inflammatory demyelinating polyneuropathy.

* The mean difference is significant at the 0.05 level. Both Tukey HSD and Bonferroni Tests of ANOVA showed GBS disability score of AMAN is higher than AIDP (P<0.05) at nadir.

Table 5: Overall disability sum score (ODSS) of GBS variants at discharge

| Tests   | (I) diagnosis | (J) diagnosis | Mean Difference (I-J) | Std. Error |
|---------|---------------|---------------|-----------------------|------------|
| Bonferroni | AMAN          | AMSAN         | 0.43651               | 0.60103    |
|         | AMSAN         | AIDP          | 1.50794*              | 0.60103    |
| AMSAN   | AMAN          | -0.43651      | 0.60103               |            |
|         | AMSAN         | AIDP          | 1.07143               | 0.63749    |
| AIDP    | AMAN          | -1.50794*     | 0.60103               |            |
|         | AMSAN         | -1.07143      | 0.63749               |            |

AMAN: Acute motor axonal Neuropathy; AMSAN: Acute motor sensory axonal neuropathy; Acute inflammatory demyelinating polyneuropathy; Overall disability Sum Score (ODSS)

*Both Tukey HSD and Bonferroni Tests of ANOVA showed ODSS of AMAN is higher than AIDP at discharge (P<0.05)
Table 6: GBS Disability Score of GBS subtypes at Discharge

| Tests   | (I) diagnosis | (J) diagnosis | Mean Difference (I-J) | Std. Error |
|---------|---------------|---------------|-----------------------|------------|
| Bonferroni | AMAN          | AMSAN         | 0.26984                | 0.26907    |
|         |               | AIDP          | 0.69841*              | 0.26907    |
| AMSAN   | AMAN          | -0.26984      | 0.26907               |            |
|         |               | AIDP          | 0.42857               | 0.28539    |
| AIDP    | AMAN          | -0.69841*     | 0.26907               |            |
|         | AMSAN         | -0.42857      | 0.28539               |            |

AMAN: Acute motor axonal Neuropathy; AMSAN: Acute motor sensory axonal neuropathy; Acute inflammatory demyelinating polyneuropathy.

* The mean difference is significant at the 0.05 level. Both Tukey HSD and Bonferroni Tests of ANOVA showed GBS disability score of AMAN is higher than AIDP (P<0.05)

Figures
ODSS score of axonal and demyelinating variants at Nadir. Axonal variants have higher ODSS than demyelinating variant at nadir (8.5±2.2 vs 7.0±1.8; p=0.024).

ODSS: Overall disability sum score.
Figure 2

ODSS score of axonal and demyelinating variants at Discharge. Axonal variants have higher ODSS than demyelinating variant at discharge (6.0±1.8 vs 4.7±1.1; p=0.004). ODSS: Overall disability sum score.