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VALIDITY OF BRIGHTON CRITERIA IN THE DIAGNOSIS OF GUILLAIN–BARRÉ SYNDROME (GBS) IN PAKISTAN

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ABSTRACT

Objective: Guillain–Barré syndrome (GBS) case definitions have been developed in recent past for its quick diagnosis. However, they have not been adopted worldwide especially in developing countries like Pakistan. In this study, we validated the sensitivity of Brighton working group case definitions for GBS at Services Hospital Lahore. **Methods:** A total of 30 cases of GBS with available clinical history, neurological examination,cerebrospinal fluid(CSF) and nerve conduction studies (NCS) results, and exclusion of related diagnoses were selected (2014–2015). Sensitivity of the Brighton criteria for GBS for level 3 of diagnostic certainty which requires no clinical laboratory testing, level 2 which employs CSF or NCS, and level 1 which employs both, were calculated. **Results:** All the 30 cases of GBS (mean age 37±16 years, range 16-62; 31% females) met the GBS case definitions. These cases were characterized as AIDP (30%), AMSAN (56.7%), AMAN (5%) involving lower extremity hypotonia and weakness (100%), upper extremity hypotonia and weakness (100%), areflexia (82.8) and hyporeflexia (17.2%). Four limbs were involved in almost all the cases (100%). CSF (mean time to lumbar puncture 29 days) was not found normal in any case with cytoalbuminologic dissociation in 100% (mean protein 105 mg/dL, range 10–1000; mean cell count 11/μL, range 0–50s, with <50 cells/μL). The majority of cases (88%) fulfilled Brighton level 1 (88%), level 2 (10%), and level 3 (2%) of diagnostic certainty. **Conclusion:** In conclusion, GBS diagnosis using Brighton Working Group criteria can be made successfully in developing countries like Pakistan with moderate to higher sensitivity.

Key Words: Guillain–Barré syndrome; Brighton criteria; Validation; Pakistan

INTRODUCTION

Guillain–Barré syndrome (GBS) is a common cause of acute flaccid paralysis, characterized by symmetrical weakness of the limbs, and hyporeflexia or areflexia, which reaches a maximum severity within 4 weeks. Sensory symptoms, such as paraesthesia or numbness, usually start distally and have a symmetrical pattern. It is an immune mediated disorder of peripheral nerves with incidence of 1-2 cases per 100,000 populations.[1,2] and is more common in men than in women (ratio 3:2).[3] Worldwide, its incidence and prevalence vary; for example, a low rate of 0.40 per 100,000 person–years was reported in Brazil, in contrast to a high rate of 2.5 per 100,000 person–years in Curaçao and Bangladesh.[3] GBS seems to occur less frequently in children (0.34–1.34 per 100,000 person– years) than in adults, and its incidence increases with age. Based on electrophysiological findings, the most common subtypes of GBS are acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN). A less common subtype is Miller Fisher syndrome (MFS), which is characterized by ophthalmoplegia, ataxia and areflexia.[4] Overall, the clinical course, severity and outcomes of GBS are highly variable. GBS typically occurs after an infectious disease in which the immune response generates antibodies that crossreact with gangliosides at nerve membranes. This autoimmune response results in nerve damage or functional blockade of nerve conduction. True and early diagnosis of GBS could impact on its prognosis, as the benefit of immunotherapy is greatest when introduced early, in the first few weeks of disease.[2] In November, 2005, a Brighton Collaboration GBS Working Group was established with a total of 34 members from different backgrounds including public health, regulatory, clinical and academic, and industry. The Working Group identified the key clinical and epidemiologic features required for diagnosis of GBS.[4] Some previous studies (e.g. Sejvar et al.4 and Mateen et al.7) have reported these guidelines as useful tool for the correct diagnosis of GBS and its major subtypes. In the present study, we have aimed to test the validity of guidelines of Brighton working group criteria in the diagnosis of GBS in local settings of Pakistan.

MATERIALS AND METHODS

The present study was conducted in Department of Neurology at Services Institute of Medical Sciences and Services Hospital, Lahore, Pakistan. This prospective 1-year study (from July 2014 to July 2015) identified 30 patients who were admitted with the primary diagnosis of Guillain Barré Syndrome (GBS). The study included the patients of all ages with no diabetes diagnosis and excluded the patients with concurrent factors (drug addiction, alcohol intake) and having weaknesses due to diseases other than GBS. The patients were also excluded with Fisher syndrome.

Table 1. List of Brighton Working group clinical case definitions: Guillain–Barré syndrome. (Adapted from Sejvar et al.4)

Level 1 of diagnostic certainity	The presence of Acute onset of bilateral and relatively symmetric flaccid weakness/paralysis of the limbs Decreased or absent deep tendon reflexes at least in affected limbs Monophasic illness pattern, with weakness nadir reached between 12h and 28 days, followed by clinical plateau and subsequent improvement, or death Electrophysiologic findings consistent with GBS Presence of cytoalbuminologic dissociation (elevation of cerebrospinal fluid (CSF) protein level above laboratory normal value, and CSF total white cell count <50 cells/µl) Absence of an alternative diagnosis for weakness
Level 2 of diagnostic certainity	The presence of Acute onset of bilateral and relatively symmetric flaccid weakness/paralysis of the limbs Decreased or absent deep tendon reflexes at least in affected limbs Monophasic illness pattern, with weakness nadir reached between 12h and 28 days, followed by clinical plateau and subsequent improvement, or death Cerebrospinal fluid (CSF) with a total white cell count <50 cells/mm3(with or without CSF protein elevation above laboratory normal value) IF CSF not collected or results not available, electrodiagnostic studies consistent with GBS Absence of an alternative diagnosis for weakness
Level 3 of diagnostic certainity	The presence of Acute onset of bilateral and relatively symmetric flaccid weakness/paralysis of the limbs Decreased or absent deep tendon reflexes at least in affected limbs Monophasic illness pattern, with weakness nadir reached between 12h and 28 days, followed by clinical plateau and subsequent improvement, or death Absence of an alternative diagnosis for weakness

We fulfilled the diagnostic criteria from the National Institute of Neurological Disorders and Stroke (NINDS) from 1990.5 The diagnosis of GBS in these patients was made on the basis of clinical presentation, CSF findings, electromyography and nerve conduction studies. A structured questionnaire was used to record the following demographic and clinical variables as part of this study: sex, date of birth, place of residence, date and site of AFP onset, number of limbs affected at nadir, presence of fever, clinical descriptive history, and complete neurological examination. Each patient's nerve conduction study report including data and wave forms was reviewed by at least one qualified neurologist and assigned a classification based on the criteria published by the Plasma Exchange/ Sandoglobulin Guillain–Barré Syndrome Trial Group (1998).6 In addition, blood studies, cerebrospinal fluid examination, and radiographs for each case were also conducted as per discretion of the treating physicians. The Brighton Collaboration GBS Working Group 2010 guidelines reported in Sejvar et al.4 were applied to each case (see Table 1). All cases in which GBS was considered to be the final diagnosis and met our inclusion criteria of having both CSF and NCS were analyzed for sensitivity.

Statistical Analyses

The descriptive statistical analysis included examinations of means, standard deviations, frequencies, ranges, and percentages. Sensitivity was defined as the proportion of all cases of GBS meeting the given criteria of interest out of the total number of cases with CSF and NCS diagnosed with GBS. The statistical packages SPSS (Version 20) and MS Excel (MS Office 2010) were used.

RESULTS

Demographics and severity of weakness:

Over one year of period (2014-2015), a total of 30 patients admitted in department of neurology who were categorized with GBS. These cases were reviewed in detail during this period. In all of the 30 patients, cerebrospinal fluid analysis (CSF) and nerve conduction studies (NCS) were performed. All the patients studied were predominately came from Punjab region of Pakistan and disease incidence was reported during almost all the seasons of the year. Mean age of the admitted cases of GBS was 37±16 years with a range of 16-62. Males were greater in number (70%) and male to female ratio was 2:2.1 in present study. The details of studied cases including their demographic characteristics and clinical features are listed in Table 2. All the GBS cases reported in present study were classified into four major sub-groups on the basis of electrophysiological pattern of nerve conduction studies (Figure 1), as AIDP (30%), AMSAN (56.7%), AMAN (5%) and Equivocal (8.3%). Acute inflammatory demyelinating polyneuropathy and acute motor sensory axonal neuropathy were the predominant subtypes. Out of all, more than 86% of the patients switched between these two conditions. Cerebrospinal fluid (CSF) was categorized as normal (protein between 15 and 45mg/dL, cell count ≤5/mL, glucose ≥2/3 of serum glucose or within normal laboratory range) or abnormal at the time of first lumbar puncture.6 Increased levels of protein in cerebrospinal fluids without increase in cell count was found in almost all cases and albuminocytological dissociation was in 100% of the cases. Brighton criteria for level 1 was met by 88% of the patients, for level 2 by 10% and only 2% for level 3 (Figure 2).

Table 2. Demographic and clinical characteristics of all GBS patients studied.

Characteristics	Value
Female (% cases)	31
Male to Female ratio	2:2.1
Mean age ± SD (range)	37±16 (16-62)
All limbs affected (%)	100
Mean time to maximal weakness	15 days
Hypotonia (%)	>80
Areflexia (%)	82.8
Hyporeflexia (%)	17.2
Symmetrical weakness (%)	100
Ascending weakness (%)	100
Cerebrospinal fluid examination	
Protein concentration > normal value	100%

Figure 1. Electrophysiological pattern of GBS on nerve conduction studies.

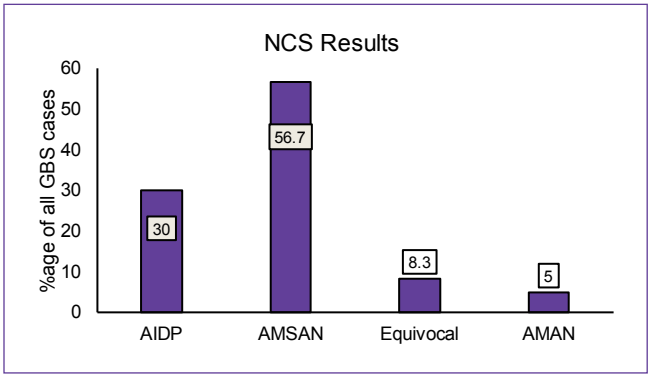
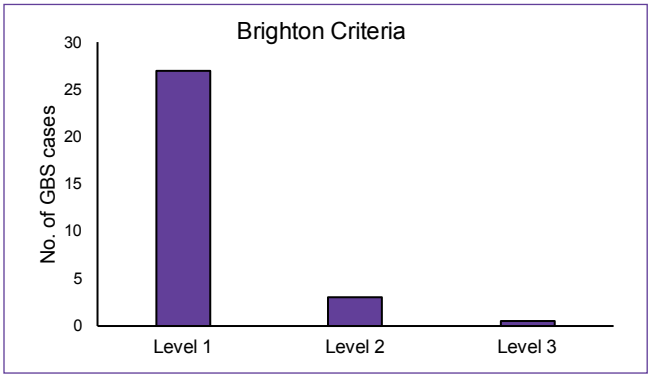


Figure 2. Graph showing the sensitivity of Brighton Diagnostic Levels of Certainity.



DISCUSSION

The present study evaluated the clinical, electro physiological and laboratory features in 30 adult patients diagnosed with Guillain-Barre syndrome. The diagnostic criteria for Guillain-Barre syndrome developed by the NINDS in 1990 were met by the patients with certain caveats.5 In our study, almost 98.9% of the patients reached the nadir of their disease within a month. At admission, 83% of the patients had a symmetrical limb weakness and 17% had reduced reflexes in all limbs. During disease progression, all patients developed reduced reflexes in the legs, although a few patients retained upper limb reflexes throughout their illness despite arm weakness. All patients with an examination of the CSF showed a cell count < 50 cells/ml and almost all nerve conduction studies showed evidence for a neuropathy. Until 1990, the high variability of Guillain-Barre Syndrome had been reported by many authors, including variants, and overlap syndromes, with an equally large variation in type of preceding infections and specificity of antibodies to nerve glycolipids.9,10 It was in 2009, when Brighton working group criteria presented more valid criteria with GBS case definitions to better identify the patients.4 Better and fast identification of GBS patients by this criteria led to timely and proper management and for vaccine safety studies. The major advantages of the Brighton criteria are the clear and detailed case definitions and the classification in four levels of diagnostic certainty depending on the patient characteristics and the availability of the data.[8] The GBS can be diagnosed in developing countries like Pakistan by using Brighton Working Group criteria. A good number of clinically diagnosed GBS cases in present study met the basic clinical definition of GBS. Out of 30, 27 (88%) of the patients could be classified as level 1. High percentage of reaching to this level was a protein concentration in CSF which was higher than normal in 100% of the patients. Fokke et al.4 reported only 61% diagnostic values for level 1. They attributed this low percentage to a normal protein concentration in CSF (33%). Other causes were a prolonged phase of 428 days (2%), and the absence of a monophasic disease course (clinical deterioration beyond 8 weeks of onset of weakness) (4%). However, level 3 of the Brighton criteria is dependent only on clinical criteria and does not rely on additional investigations. This category was designed particularly with resource-poor settings in mind, in situations where electrophysiological and CSF examination may be difficult, and/or unavailable. Our study emphasized that accurate and thorough documentation of clinical signs should allow for better classification of Guillain-Barre syndrome in developing countries. In some countries such as in Netherlands, additional investigations such as CSF examination or serial nerve physiology may not be conducted routinely in clinical practice if alternative diagnoses could be trusted.[4] Although incidence of all forms of AFP is significant in developing countries including Pakistan and India, the incidence of GBS in Pakistan has not been reported widely. In 1968 from a tertiary care center in India, Chhuttani et al.11 reported the clinical features of 63 patients with GBS out of a total of 710 peripheral neuropathy patients observed from 1953 to 1965. Case

fatality was 28.5%. More recent clinical studies have found a high incidence of cranial nerve palsies (76%) in children, respiratory paralysis (40%), and lower case fatalities (11-16%).12 The relative predominance of electrophysiological subtypes of GBS is known to differ geographically. Asian populations, including cohorts in Japan and China, demonstrate axonal predominance compared to the demyelinating subtype which is most common in Western populations.13 In our study, the demyelinating subtype (30%) and axonal subtype (56%) were seen. This finding is also in contrast to a recent study conducted in India that reported AIDP (25%) subtype to be more common compared to ASMAN (18%).7 Further studies in Pakistan would be of interest to delineate which electrophysiological patterns predominate at different ages, regions, and socio-economic levels. Patients in whom the diagnosis of GBS is uncertain may require both NCS and CSF analyses in order to rule out alternative etiologic diagnoses for clinical purposes. Brighton criteria are designed for monitoring, evaluation, and surveillance rather than guiding the care of an individual hospitalized patient. It is possible that milder cases of GBS are not reported since they get managed before reaching medical attention. Diagnosis of GBS Brighton Working Group criteria will become increasingly important in Pakistan and other developing countries as we mentioned in our study. As poliomyelitis eradication is achieved and widespread vaccination continues, the relative burden and need to monitor and report GBS will also rise. A field-tested, pragmatic, validated, and sensitive case definition of GBS will help achieve monitoring in times of both active and AFP surveillance.

CONCLUSION

This study aimed to validate Brighton working group criteria for GBS diagnosis in local settings of Pakistan. We conclude that Brighton criteria for GBS diagnosis can be used with acceptable sensitivity for level 3 of diagnostic certainty which requires no clinical laboratory testing, level 2 which employs CSF or NCS, and level 1 which employs both. In our study, 30 cases of GBS (mean age 37±16 years, range 16-62; 31% females) met the GBS case definitions. GBS patients reported in Services hospital Lahore can be classified according to following subtypes of GBS: AIDP (30%), AMSAN (56.7%), AMAN (5%). These patients have >80% areflexia and weakness of all four limbs was shown in almost all the cases (100%) in our study. CSF (mean time to lumbar puncture 29 days) was not found normal in any case with cytoalbuminologic dissociation in 100% (mean protein 105 mg/dL, range 10–1000; mean cell count 11/μL, range 0–50, with <50 cells/μL). The majority of cases (88%) fulfilled Brighton level 1, level 2 (10%), and level 3 (2%) of diagnostic certainty. In conclusion, GBS diagnosis using Brighton Working Group criteria can be made successfully in local settings of Pakistan.

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Author's Contribution:
Dr. Safia Bano: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review
Dr. Ahsan Numan: Study concept and design, protocol writing, Data analysis, manuscript writing, manuscript review
Dr. Abubakar Siddique: Data collection, data analysis, manuscript writing, manuscript review
Dr. Inamul Haq: Data collection, data analysis, manuscript writing, manuscript review