IS GUILLAIN-BARRÉ SYNDROME DIFFERENT IN PAKISTAN?

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ABSTRACT

Objective: To assess clinical presentations and subtypes of Guillain-Barré Syndrome (GBS) in Pakistan.
Study Design: Retrospective study.
Place and Duration of Study: CMH Lahore, Abbotabad, Quetta & Armed Forces Institute of Rehabilitation Medicine form Jan 2007 to Feb 2015.
Material and Methods: The relevant history, demographic features, clinical presentations and subtypes of GBS in 211 patients fulfilling the clinical and electrodiagnostic criteria were investigated.
Results: The average age of the patients was 37.36 years (62.7% M, 37.3% F). Clinically 66.8%, 17.8% and 15.4% presented as ascending paralysis, simultaneous quadriparesis and paraparesis respectively. About 38.1% of the patients presented with cranial nerves involvement, 87.4% presented with areflexia while 59.5% reported pain. The GBS subtypes identified were acute inflammatory demyelinating polyneuropathy (21.9%), acute motor axonal neuropathy (38.9%), acute motor sensory axonal neuropathy (35.6%) and fisher syndrome (3.6%).
Conclusion: The GBS presents in young, as an ascending paralysis, main subtypes of GBS in Pakistan are axonal and this highlights the importance of local management guidelines and preventive medicine.

Keywords: Acute inflammatory demyelinating polyneuropathy, Acute motor axonal neuropathy, Acute motor sensory axonal neuropathy, Fisher syndrome, Guillain-Barré syndrome.

INTRODUCTION

Guillain-Barré Syndrome (GBS) is an autoimmune inflammatory polyneuropathy presenting classically as a rapid, progressive ascending paralysis with global areflexia[1,2]. It involves the peripheral nervous system including motor, sensory and autonomic components. The typical history involves neurological symptoms a few weeks following an acute illness in most of the patients. The diagnosis of GBS is based upon history, relevant clinical examination, albumin-cytological dissociation in cerebrospinal fluid and characteristic electrophysiological studies[3]. The disease has clinically indistinguishable axonal, demyelinating or mixed types[4]. In a typical GBS history, there is a preceding history of infection[5-7], followed by weakness, which commonly involves the lower limbs initially. On the other hand, there is sometimes involvement of the upper limbs or facial muscles in the early course of the disease. Clinical examination typically reveals absent or impaired deep tendon reflexes with motor and sensory system involvement. The primary pathology may be demyelinating with secondary axonal or, demyelinating features may follow significant axonal loss on electrophysiological studies[8].

Acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN) and Fisher syndrome (FS) are three different variants of GBS described in the literature in addition to the classic acute inflammatory demyelinating polyneuropathy (AIDP). Initially, GBS was considered to be a demyelinating type of polyneuropathy[9-12] but later, with the introduction of electrophysiological studies in clinical practice, various subtypes were identified. The geographical distribution of various electrophysiological subtypes of GBS has been described in the literature[13-15], AIDP[5,6,16] being the most common as followed by AMAN[17,18] AMSAN[19] and Fisher

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Syndrome (FS)[20]. Fewer studies have been conducted on subtypes of GBS in Pakistan[21-24] and there is no study in literature as regards to the clinical presentation of GBS in Pakistan. As long-term, follow-up studies had shown different recovery patterns and pathophysiology in subtypes of GBS[25,26] it is important to identify the various subtypes, keeping in mind the diagnostic, therapeutic and financial implications.

With this background, this study was conducted in the Rehabilitation Medicine & Neurology Departments of the Combined Military Hospital (CMH) Lahore, the Combined Military Hospital Abbottabad, the Combined Military Hospital Quetta and the Armed Forces Institute of Rehabilitation Medicine, Rawalpindi between January 2007 to February 2015, in order to identify various clinical presentations and subtypes of GBS in Pakistan.

MATERIAL AND METHODS

We included all the patients presenting with acute progressive weakness, areflexia, and albuminocytological dissociation in the cerebrospinal fluid fulfilling the clinical criteria of Asbury et al[27] and electrodiagnostic criteria of Hadden et al[28] for GBS. The clinical and electrophysiological assessments were done by neurophysicians and physiatrists. Based upon available prevalence rate of GBS in international studies and confidence level 95%, 211 patients were inducted in the study.

The clinical features documented included the history of preceding infection, clinical examination including presentation and area of weakness, examination of deep tendon reflexes (DTR), sensory impairments, the autonomic nervous system, bladder involvement and pain. The motor weakness was documented

Table-I: Clinical diagnostic criteria for Guillain-Barré Syndrome[27].

Required Features
• Progressive weakness in both arms and legs
• Areflexia (or hyporeflexia)
Features Supportive of Diagnosis
• Progression of symptoms over days to 4 weeks
• Relative symmetry
• Mild sensory signs or symptoms
• Cranial nerve involvement, especially bilateral facial weakness
• Recovery beginning 2 to 4 weeks after progression ceases
• Autonomic dysfunction
• Absence of fever at onset
• Typical CSF and EMG/nerve conduction studies features.
Features Casting Doubt on the Diagnosis
• Asymmetrical weakness
• Persistent bladder and bowel dysfunction
• Bladder or bowel dysfunction at onset
• >50 mononuclear leukocytes/mm^3 or presence of polymorphonuclear leukocytes in CSF
• Distinct sensory level
Features That Rule Out the Diagnosis
• Hexacarbon abuse
• Abnormal porphyria metabolism, recent diphtheria infection
• Lead intoxication
• Other similar conditions: poliomyelitis, botulism, hysterical paralysis, toxic neuropathy

as ascending, paraplegia or simultaneous development of weakness in upper and lower limbs. DTR were recorded as absent, depressed, or exaggerated. Sensory impairment included hyperesthesia, dysesthesia or tingling sensation. Autonomic nervous system involvement was considered when the patient presented with bradycardia, tachycardia, flushes, orthostatic hypotension or altered sweating. Cranial nerve involvement was documented when the patient presented with facial weakness, double vision or difficulty in speech or swallowing. The pain was documented as neuropathic, nociceptive or visceral, keeping in view the type or character of the pain. Bladder involvement was considered when there was incontinence or urinary retention (table-I).

Electrophysiological studies were carried out within 4 weeks of the onset of weakness. The following parameters were measured in motor studies including nerve conduction velocities (NCV), distal motor latencies (DML), compound muscle action potential (CMAP), F-wave latencies and H-Reflex. In sensory nerves, sensory nerve action potential (SNAP) amplitudes, sensory latencies (SL) and sensory nerve conduction velocities (SNCV) were also measured (table-II). Skin temperature was maintained at >32°C. The values for each variable were compared with the upper and lower limits of normative values for our laboratory and age-adjusted for child cases. All measured segments of nerves (including entrapment sites) were included for the purpose of comparing the different classification criteria. The data were analysed using SPSS v20. Statistical analyses, where required, were performed using Fisher's exact test and chi-square tests. Demographic data, including age and gender, and other variables including subtypes of GBS are expressed in terms of percentages.

Table-II: Electrophysiological classification of Guillain- Barré Syndrome[28].

• At least 3 sensory nerves and 3 motor nerves with multi-site stimulation F-waves, and bilateral tibial H-reflexes, need to be evaluated. • At least one of the following in each of at least 2 nerves, or at least 2 of the following in one nerve if all others inexcitable and distal compound muscle action potential (dCMAP) >10% lower limit of normal (LLN)
• **AIDP :** Motor conduction velocity <90% LLN (85% if dCMAP <50% LLN) Distal motor latency >110% upper limit of normal (ULN) (>120% if dCMAP <100% LLN) P CMAP/dCMAP ratio <0.5 and dCMAP >20% LLN F-response latency >120% ULN
• **AMSAN:** None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP <10% LLN Sensory action potential amplitudes less than LLN
• **AMAN:** None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP <10% LLN Sensory action potential amplitudes normal
• **Inexcitable:**
• dCMAP absent in all nerves or present in only one nerve with dCMAP <10%

RESULTS

A total of 211 patients (62.7% M, 37.3% F) with GBS were studied with an average age of 35.96 years (range 8-67 years; SD 15.575). On history, 136 (64.45%) of the patients remembered

an infective ailment prior to the development of this condition.

The most common clinical presentation was ascending paralysis (66.35%), followed by tingling sensation with weakness in 65.4% of the patients, while 18.09% of the patients reported simultaneous upper and lower limb weakness and, 15.63% of the patients presented with paraparesis. About 38.1% presented with some kind of cranial nerves involvement, 87.4% of the patients presented with absent reflexes, 9.7% presented with depressed reflexes, while 2.8% had hyperreflexia. Autonomic nervous system involvement was observed in 68.4% of patients.

Table-III: Clinical presentations.

Clinical Presentations	Frequency	Percentage (%)
Ascending Weakness	140	66.35
Upper / Lower Limb Weakness	38	18.09
Paraparesis	33	15.63
Total	211	100.0

Table-IV: GBS Subtypes.

	Frequency	Percentage (%)
AIDP	46	21.8
AMAN	82	38.86
AMSAN	75	35.54
FS	8	3.79
Total	211	100.0

AIDP: Acute Inflammatory Demyelinating Polyneuropathy, AMAN: Acute Motor Axonal Neuropathy, AMSAN: Acute Motor Sensory Axonal Neuropathy, FS: Fisher Syndrome.

The pain of any type was reported by 59.5% of the patients, of these; 52% had pain related to movement, while 48% described it as dysesthesia. Bladder involvement was reported by 17.8% of patients. The clinical presentations and GBS subtypes identified are shown in table-III and IV respectively.

DISCUSSION

GBS is the commonest cause of acute flaccid paralysis (AFP) worldwide[5,6,16]. The disability caused by the condition is variable in severity and duration depending upon the type and severity[25,29]. The diagnosis of this condition is of utmost importance but in a country like Pakistan, where resources are scarce, it becomes even more important due to the likely heavy financial impact. As different treatment regimens are advocated for different subtypes of GBS, it is very important to distinguish between the subtypes in the early course of the disease. Moreover, identification of the subtype also helps in long-term rehabilitation planning due to expected variations in recovery pattern[30].

In the first place, the confirmation of the diagnosis of GBS is vital, as poliomyelitis is still prevalent in Pakistan and presentation of any flaccid paralysis in a paediatric population generates panic, because of the possibility that it could be poliomyelitis. Sometimes desperate measures taken to manage the condition lead to patients being managed by unqualified practitioners. As diagnostic facilities are not very easily accessible, especially in rural areas, the quackery and spiritual healing methods often lead to irreversible nervous system damage in the absence of appropriate timely management. Secondly, in the case of an axonal subtype of GBS, the patient will need a longer stay in the hospital. For poor people, because the health system in Pakistan involves considerable "out of pocket" expenditure, the financial burden of treatment is exceptionally high.

In this study, we observed that there is a clear difference in the types of GBS in Pakistan

in comparison to Western data. Our study is consistent with a few other studies carried out in Eastern populations, especially in China which revealed a higher frequency of axonal variants[17,18,21,28,31]. Our results show that it is likely that patients will have a longer inpatient stay, due to the high prevalence of axonal variants in the Pakistani population. There is dire need of early treatment with immunoglobulin therapy as advocated by other studies[32-34]. An investigation carried out by Yuqin et al in 2007 and a few other studies revealed a strong association of the axonal subtype of GBS with infectious aetiology secondary to the unboiled water[35,36]. Our study therefore also highlights the importance of personal hygiene, provision of clean water and patient education at the primary and rural health care level in Pakistan. During the process of this study, the need became apparent for a central disease registry for GBS in Pakistan for the purpose of better record management and policy-making. Moreover, there is an urgent need to develop local management guidelines due to peculiar circumstances in terms of health care facilities and finances. This study provides a platform for the development of guidelines for the provision of medical treatment in the acute phase and for long-term rehabilitation planning in patients suffering from this disabling condition in Pakistan. A long-term multi-center follow-up study is also suggested for development of better prevention and management plans.

CONCLUSION

The GBS presents in young, as an ascending paralysis, main subtypes of GBS in Pakistan are axonal and this highlights the importance of local management guidelines and preventive medicine.

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CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Lee JH, Sung IY, Rew IS. Clinical presentation and prognosis of childhood Guillain–Barre´ Syndrome. J Paediatr Child Health 2008; 44: 449-54.
2. Guillain G, Barre´ JA, Strohl A. Sur un syndrome de radiculone´vrite avec hyperalbuminose du liquid cephalo-rachidien sans reaction cellulaire. Remarques sur les caracteres cliniques et graphiques des reflexes tendineux. Bull Soc Med Hop Paris 1916; 40: 1462–70.
3. Asbury AK, Arnason BG, Karp HR, McFarlin DE. Criteria for the diagnosis of Guillain–Barre´ syndrome. Ann Neurol 1978; 3: 565–66.
4. Griffin JW, Li CY, Ho TW, Xue P, Macko C, Gao CY, et al. Guillain–Barre´ syndrome in northern China. Brain 1995; 118: 577-95.
5. Ropper AH, Wijdicks EFM, Truax BT. Guillain-Barré Syndrome. Philadelphia, FA Davis, 1991.
6. Ropper AH. The Guillain-Barré syndrome. N Engl J Med 1992; 326: 1130–36.
7. Kaldor J, Speed BR. Guillain–Barre´ syndrome and Campylo-bacter jejuni: A serological study. BMJ 1984; 288: 1867-70.
8. Brechenmacher C, Vital C, Deminiere C, Laurentjoye L, Castaing Y, Gbikpi-Benissan G, et al. Guillain–Barre´ syndrome: An ultrastructural study of peripheral nerve in 65 patients. Clin Neuropathol 1987; 6: 19–24.
9. Arnason BGW, Soliven B. Acute inflammatory demyelinating polyradiculoneuropathy. In Dyck PJ, Thomas PK, Griffin JW (eds): Peripheral Neuropathy, 3rd ed. Philadelphia,W.B. Saunders, 1993, pp 1437–97.
10. Brown WF, Feasby TE: Sensory evoked potentials in Guillain-Barré polyneuropathy. J Neurol Neurosurg Psychiatry 1984; 47: 288–91.
11. Kennedy RH, Danielson MA, Mulder DW, Kurland LT. Guillain-Barré syndrome: A 42-year epidemiologic and clinical study. Mayo Clin Proc 1978; 53: 93–99.
12. Loffel NB, Rossi LN, Mumenthaler M, lutschg J, Ludin HP: The Landry-Guillain-Barré Syndrome: Complications, prognosis and natural history in 123 cases. J Neurol Sci 1977; 33: 71–9.
13. Visser LH, Van-der MFG, Van-Doorn PA, Meulstee J, Jacobs BC, Oomes PG et al. Guillain Barre´ Syndrome without sensory loss (acute motor neuropathy). A subgroup with specific clinical, electrodiagnostic and laboratory features. Brain 1995; 118: 841-47.
14. Ogawara K, Kuwabara S, Mori M, Hattori T, Koga M, Yuki N. Axonal Guillain–Barre´ Syndrome: Relation to anti-ganglioside antibodies and Campylobacter jejuni infection in Japan. Ann Neurol 2000; 48: 624–31.
15. Dourado ME, Duarte RC, Ferreira LC, Queiroz JW, Illa I, Perez-Perez G, et al. Anti-ganglioside antibodies and clinical outcome of patients with Guillain–Barre´ Syndrome in northeast Brazil. Acta Neurol Scand 2003; 108: 102–8.
16. Alter M. The epidemiology of Guillain-Barré Syndrome. Ann Neurol 1990; 27(suppl): S7–12.
17. McKhann G, Cornblath D, Griffin J, Ho T, Li C, Jiang Z, et al. Acute motor axonal neuropathy: A frequent cause of acute flaccid paralysis in China. Ann Neurol 1993; 33(4): 333-42.
18. McKhann G, Cornblath D, Ho T, Griffin J, Li C, Bai A, et al. Clinical and electrophysiological aspects of acute paralytic

disease of children and young adults in northern China. Lancet 1991; 338(8767): 593-97.
19. Griffin J, Li C, Ho T, Tian M, Gao C, Xue P, et al. Pathology of the motor sensory axonal Guillain- Barré syndrome. Ann Neurol 1996; 39(1): 17-28.
20. Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). N Engl J Med 1956; 255(2): 57-65.
21. Islam Z, Jacobs B, Van Belkum A, Mohammad Q, Islam M, Herbrink P, et al. Axonal variant of Guillain-Barré syndrome associated with Campylobacter infection in Bangladesh. Neurol 2010; 74(7): 581.
22. Shafqat S, Khealani B, Awan F, Abedin S. Guillain–Barré syndrome in Pakistan: Similarity of demyelinating and axonal variants. Eur J Neurol 2006; 13(6): 662-5.
23. Khan N, Nasrullah M. Electrodiagnostic Study of 40 cases presenting as Guillain- Barré Syndrome. Pakistan J Neurol 1998; 4: 50-4.
24. Zaheer M, Naeem M, Nasrullah M. Electrophysiological pattern of neuropathy in Guillain- Barré syndrome. Ann King Edward Med Coll 2006; 12(4): 560-62.
25. Feasby TE, Gilbert JJ, Brown WF, Bolton CF, Hahn AF, Koopman WF, et al. An acute axonal form of Guillain– Barré polyneuropathy. Brain 1986; 109: 1115–26.
26. Wee AS, Abernathy SD. The sural sensory nerve is usually spared in Guillain– Barré syndrome. J Miss State Med Assoc 2003; 44: 251–55.
27. Asbury AK, Cornblath DR: Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990; 27(Suppl); S21–S24.
28. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, et al Electrophysiological classification of Guillain-Barré syndrome: Clinical associations and outcome. Plasma exchange/sandoglobulin guillain-barre syndrome trial group. Ann Neurol 1998; 44: 780-88.
29. Alter M: The epidemiology of Guillain-Barré syndrome. Ann Neurol 1990; 27(suppl): S7–12.
30. Yuki N, Yoshino H, Sato S, Miyatake T. Acute axonal polyneuropathy associated with anti-GM antibodies following campylobacter enteritis. Neurol 1990; 40: 1900–02.
31. Rees JH, Thompson RD, Smeeton NC, Hughes RA. Epidemiological study of Guillain–Barre´ syndrome in south east England. J Neurol Neurosurg Psychiatry 1998; 64: 74–77.
32. Toopchizadeh V, Barzegar M. Electrophysiologic features of childhood Guillain- Barré syndrome in Iran. J Pediatr Neuroradiol 2008; 6(1): 11-6.
33. Hiraga A, Mori M, Ogawara K, Hattori T, Kuwabara S. Differences in patterns of progression in demyelinating and axonal Guillain-Barre syndromes. Neurol 2003; 61: 4: 471.
34. Van der Meché FGA, Schmidtz PIM. The Dutch Guillain-Barré Study Group: A randomized trial comparing intravenous immunoglobulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992; 326: 1123-29.
35. Yuki N, Yoshino H, Sato S, Miyatake T. Acute axonal polyneuropathy associated with anti-GM antibodies following Campylobacter enteritis. Neurol 1990; 40(12): 1900.
36. Blaser MJ, Olivares A, Taylor DN, Cornblath DR, McKhann GM. Campylobacter serology in patients with Chinese paralytic syndrome. Lancet 1991; 338: 308.