

# FREQUENCY OF AXONAL VARIANTS OF GUILLAIN-BARRÉ SYNDROME IN PAKISTAN

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## ABSTRACT

**Objective:** To determine the frequency of axonal variants in our patients of Guillain-Barre Syndrome.

**Study Design:** Descriptive study.

**Place and Duration:** Department of Neurology, Military Hospital, Rawalpindi and Armed Forces Institute of Rehabilitation Medicine (AFIRM) from 01 Jan 2009 to 30 Jul 2010.

**Patients and Methods:** Forty adult patients meeting the National Institute of Neurological Disorders and Stroke criteria for Guillain-Barre Syndrome (GBS) were consecutively enrolled in the study. Patient's data, detailed history, examination and electrophysiological studies were carried out and recorded on a predesigned proforma. All patients were examined and reviewed by Consultant Physicians and Neurologists. Electromyography and Nerve conduction study testing was done by experienced electro-physiologists.

**Results:** Axonal variants of Guillain-Barre Syndrome constituted 16(40%) in our study. The variants of Guillain-Barre Syndrome were acute inflammatory polyradiculoneuropathy (AIDP) in 24(60%) patients followed by acute motor axonal neuropathy (AMAN) in 12(30%) and acute motor sensory axonal neuropathy (AMSAN) in 4(10%) patients.

**Conclusion:** We report a high frequency of the axonal variants of Guillain-Barre Syndrome in Pakistan.

**Keywords:** Axonal variants, Guillain-Barre Syndrome

## INTRODUCTION

In 1916 three French neurologists Georges Guillain, Jean-Alexandre Barre and Andre Strohl described two soldiers with an acute areflexia paralysis followed by spontaneous recovery<sup>1</sup>. They noted albuminocytologic dissociation in cerebrospinal fluid (an increase in protein without increase in cells). Over the years it has become clear that this clinical picture, now called the Guillain-Barre syndrome, can be produced by many different clinical and pathological subtypes and is related to other less common disorders<sup>2</sup>.

The Guillain-Barre syndrome (GBS) is a disease of the peripheral nervous system that is characterized by segmental demyelination and infiltration of mononuclear cells in peripheral nerves, nerve roots and deposition of complement with axonal degeneration in severe lesions<sup>3</sup>. GBS is often preceded by an infectious

illness. *Campylobacter jejuni* is the most commonly identified infectious trigger for GBS<sup>4,5</sup>. The cardinal clinical features of GBS are a progressive muscle weakness accompanied by absent or depressed deep tendon reflexes. Patients usually present a few days to three weeks after onset of symptoms. The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles.

Historically, GBS was considered a single disorder. It is now recognized as a heterogeneous syndrome with several variant forms. Each form of GBS has distinguishing clinical, pathophysiologic, and pathologic features<sup>2</sup>.

The most common underlying subtype of the syndrome is acute inflammatory demyelinating polyradiculoneuropathy (AIDP)<sup>6</sup> which accounts for most of the patients in the United States and Europe, representing approximately 85-90% of cases. Another subtype in which the neurological deficit is

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purely motor, is known as acute motor axonal neuropathy (AMAN)<sup>7,8</sup>. When the sensory fibers are also involved, this axonal subtype is known as the acute sensorimotor axonal neuropathy (AMSAN)<sup>9</sup>. Other, less frequent, clinical variants are the Miller Fisher syndrome<sup>10</sup> of ophthalmoplegia, ataxia and areflexia, pharyngeal-cervical-brachial variant, paraparetic variant (mainly involving the lower limbs), pure Sensory GBS and acute pandysautonomia. Large studies in Northern China<sup>7,8</sup>, Iran<sup>11</sup>, Japan<sup>12</sup>, Bangladesh<sup>13</sup> show that the axonal forms of GBS constitute 30-47% of patients in Asian populations. Out of three studies in Pakistan one<sup>14</sup> showed a higher percentage of axonal variants while two<sup>15,16</sup> showed similar results to US and European studies. Our study was conducted to find the frequency of axonal variants of GBS, as patients with these variants have a more severe form of the disease with sometimes differing clinical features, less response to treatment and generally a worse outcome. Recognition of these factors can have clinical, therapeutic and financial implications.

## **PATIENTS AND METHODS**

A descriptive study was carried out in the Department of Neurology, Military Hospital Rawalpindi and Armed Forces Institute of Rehabilitation Medicine (AFIRM) Rawalpindi from Jan 2009 to Jul 2010.

Forty adult patients meeting the National Institute of Neurological Disorders and Stroke (NINDS) criteria (Table-1),<sup>17</sup> for the diagnosis of Guillain-Barre Syndrome were consecutively enrolled. Patients data, detailed history, examination and electrophysiological studies were carried out and recorded on a predesigned proforma. All patients were examined and reviewed by consultant physicians/neurologists. Patients were admitted to the hospital and observed in Intensive care unit if required. Nerve conduction studies were done using surface electrodes and electromyography was done using 26 G concentric needle electrodes by Myoline and Medtronic. The systems used were the Xltek 1002 EMG/NCS Machine and

Medtronic EMG/NCS Machine. The studies were done by experienced electro-physiologists. Laboratory investigations and neuroimaging was done where appropriate, to rule out other causes of a flaccid paralysis.

Electrodiagnosis<sup>18</sup> consisting of Nerve conduction studies and Electromyography was done according to laid down protocol (Tables-2 & 3). The patients were classified as having AIDP when electro diagnostic criteria were met (Table 4). When patients had no evidence of demyelination as defined for AIDP and had decrease in compound muscle action potential CMAP to <80% of lower limit of normal in two or more nerves, patients were classified as having AMAN. Acute motor sensory axonal neuropathy (AMSAN) was defined as the presence of AMAN pattern in motor nerve studies and an amplitude reduction <50% of the normal limits of the sensory nerve action potentials (SNAPs) in two or more nerves. Axonal involvement was also shown by denervation potentials i.e. positive sharp waves and fibrillations in sampled muscles.

Exclusion criteria: All patients who did not suffer from GBS or had other causes of an acute flaccid paralysis were not included in the study. Similarly patients below the age of 18 yrs or those who could not undergo EMG/NCS for any reason were also excluded.

All patients were given specific treatment with either Plasmapheresis or Intravenous Immunoglobulins (IVIg) in addition to supportive and symptomatic therapy.

## **Data Analysis**

Data was analyzed using the IBM SPSS version 17. Frequency along with percentages was used to describe the data.

## **RESULTS**

A total of 40 patients of GBS were included in the study. Out of these 8(20%) were females and 32(80%) were males. The mean age of the participants of the study was 37.9 yrs with a minimum age of 18 and maximum age of 83 yrs. On careful history taking 30(75%) patients gave a history of an infective illness prior to the development of symptoms while

10(25%) patients could not recall such an event related to the illness. The most common presentation as far as motor weakness was concerned remained an ascending quadriparesis which occurred in 34(85%) of patients followed by paraparesis in 2(5%) patients, predominant upper limb weakness 2(5%) and an oculo-facio-brachial weakness in 2(5%) of patients. Thirty seven (92.5%) patients had absent reflexes with 2 (5%) patients having elicitable though depressed reflexes and 1(2.5%) patient had hyper reflexia. Three variants of GBS were found on NCS and EMG. The commonest of those was AIDP in 24(60%) patients followed by AMAN in 12(30%) and AMSAN in 4(10%) patients Fig 1. Thus axonal variants of GBS constituted 40% of patients in our study.

## DISCUSSION

GBS is the most common cause of acute or subacute generalized paralysis in clinical practice. GBS occurs in all parts of the world and in all seasons, affecting children and adults of all ages and both sexes. The incidence of GBS has varied between 0.4 and 4.0 cases per 100,000 per year, though most recent and careful studies in Europe report the incidence of 1.2 to 1.9 cases per 100,000<sup>19</sup>.

Diagnosis of GBS is not difficult for the neurologist. There is weakness that evolves more or less symmetrically, which starts distally but is more proximally. Weakness progresses in approximately 5% of patients to a total motor paralysis with respiratory failure within a few days. Reduced and then absent tendon reflexes are consistent findings. Some recent studies show hyper reflexia in patients with the AMAN variant. Our study showed only 1 patient of AMAN with hyper reflexia.

In 1986 Feasby et al described an acute areflexic polyneuropathy clinically similar to typical GBS but characterized pathologically by widespread and severe axonal degeneration<sup>20</sup>. Unlike the common form of demyelinating GBS, muscle atrophy became apparent relatively early in the axonal form. The outbreaks of motor neuropathy that occur seasonally in rural China<sup>7,8</sup> have many of the

same characteristics. These cases appear to be triggered largely by *C. jejuni* infections<sup>21</sup>. A proportion of axonal cases are associated with circulating antibodies to the GM1 ganglioside of peripheral nerve<sup>22,23</sup>.

Electrodiagnostics: Abnormalities of nerve conduction are dependable diagnostic indicators of GBS<sup>24,25,26</sup>. Elegant work on the subject was done by Preston and Shapiro<sup>27</sup>. The early electro diagnostic findings are a reduction in or absence of the compound muscle action potential (CMAP) amplitude, slowed conduction velocity, and conduction block in motor nerves singly or in combination. Prolonged distal latencies (reflecting distal conduction block) and absent F responses (indicating involvement of proximal parts of nerves and roots) are other important diagnostic findings, all reflecting focal areas of demyelination<sup>27</sup>. Features that indicate widespread axonal damage portend a poor and protracted recovery in both young and old patients<sup>24</sup>.

The severity of the disease at the peak of the illness, rapid onset of the illness and features of axonal involvement at initial EMG/NCS are bad prognostic factors. Plasma exchange and IVIG remain the mainstay of treatment. In AMAN and AMSAN, the axonal variants of GBS, administration of intravenous immune globulin (IVIG) and plasma exchange have had slight beneficial effect but their use is not associated with the degree of improvement seen in demyelinating cases<sup>28</sup>. A multidisciplinary rehabilitation program is as important as immunotherapy.

Is Axonal GBS Rare? Our study was necessitated by the fact that reports of Axonal form of GBS were more frequent in Asian populations. Studies from China<sup>7,8</sup>, Japan<sup>12</sup> and Iran<sup>11</sup> suggested that AMAN is more common. This is in contrast to the western populations. There were three earlier studies from Pakistan (two in Lahore and one in Karachi). One by Khan and, Nasrullah<sup>15</sup>. done in 1998 where they studied the electrophysiology of 40 cases of GBS, showing pure axonal variety of GBS in 5/40(12.5%) of the cases. In the second study

done in 2006 by Zaheer et al<sup>16</sup>. The electrophysiological patterns of neuropathy in GBS was studied and concluded that pure Axonal variant of GBS was there only in 12 % of the cases, a finding similar to the American and European literature<sup>17,18</sup>. However increasing population and less access to safe drinking water may lead to an increase in *C. Jejuni* and other GI infections which are an important cause of Axonal variants of GBS<sup>11,12,13</sup>. A study done by Shafqat S et al<sup>14</sup> had concluded that the axonal variants of GBS accounted for 31% of cases. The frequency of the Axonal variants of GBS i.e 40% in our study is a finding consistent with Chinese<sup>7,8</sup>, Japanese<sup>12</sup> and Iranian<sup>11</sup> studies. A study by Islam et al<sup>13</sup> studying Bangladeshi population found that in GBS occurring after *C. Jejuni* enteritis, the axonal variant was found in 67% of the cases. This percentage is, unusually, higher than our study and may be due to more water borne diarrheal infections or that the population studied was paediatric. Our study and the studies by Islam et al<sup>13</sup> and Shafqat et al<sup>14</sup> show that in our region the axonal variants of GBS are common. Most experience with the generalized axonal forms of GBS, AMAN and AMSAN, indicates that recovery is prolonged, complete resolution of weakness is uncommon and response to conventional therapy is not very encouraging<sup>28</sup>.

## CONCLUSION

We report a high frequency of the axonal variants of Guillain-Barre Syndrome in Pakistan and recommend a larger multi-center study on the subject.

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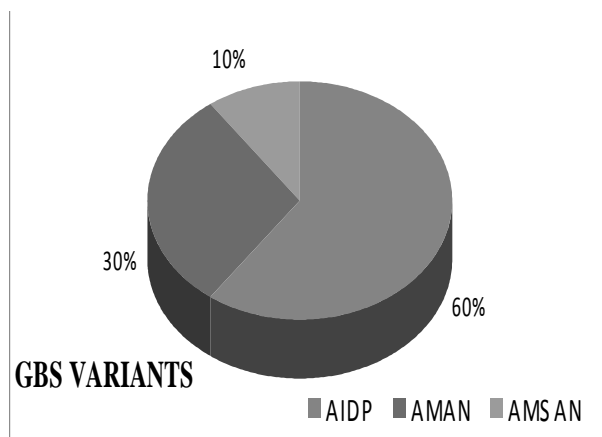


Fig:1 Frequency of the variants of Guillain-Barre Syndrome.

**Table 1. National Institute for Neurological Disorders and Stroke (NINDS) Diagnostic Criteria for Guillain Barre Syndrome**

These criteria are based on expert consensus.

**Required features include:**

Progressive weakness of more than one limb, ranging from minimal weakness of the legs to total paralysis of all four limbs, the trunk, bulbar and facial muscles, and external ophthalmoplegia  
 Areflexia: While universal areflexia is typical, distal areflexia with hyporeflexia at the knees and biceps will suffice if other features are consistent.

**Supportive features include:**

- Progression of symptoms over days to four weeks
- Relative symmetry
- Mild sensory symptoms or signs
- Cranial nerve involvement, especially bilateral facial nerve weakness
- Recovery starting two to four weeks after progression halts
- Autonomic dysfunction
- No fever at the onset

Elevated protein in CSF with a cell count  $<10 \text{ mm}^3$

Electrodiagnostic abnormalities consistent with GBS

*The following features make the diagnosis of GBS doubtful:*

Sensory level (decrement or loss of sensation below a spinal cord root level as determined by neurologic examination)

Marked, persistent asymmetry of weakness

Severe and persistent bowel and bladder dysfunction

More than 50 white cells in the CSF

#### **TABLE 2: Nerve Conduction Study Protocol**

Routine motor conduction studies:

1. Peroneal study, recording extensor digitorum brevis and stimulating ankle, below fibular neck, and lateral popliteal fossa
2. Tibial study, recording abductor hallucis brevis and stimulating ankle and popliteal fossa
3. Median study, recording abductor pollicis brevis and stimulating wrist and antecubital fossa
4. Ulnar study, recording abductor digiti minimi and stimulating wrist and below and above elbow

#### **Routine sensory studies:**

1. Sural SNAP, stimulating calf and recording posterior ankle
2. Median SNAP, stimulating wrist and recording digit 2
3. Ulnar SNAP, stimulating wrist and recording digit 5
4. Radial SNAP, stimulating forearm and recording snuffbox

#### **Late responses:**

1. F responses: Median, ulnar, peroneal and tibial
2. Soleus H reflexes (If required)

### TABLE: 3 Electromyography Protocol

*Lower extremity routine muscles:*

1. Extensor hallucis longus
2. Tibialis anterior
3. Soleus/ medial gastrocnemius
4. Quadriceps
5. Gluteus Medius and Gluteus Maximus

*Upper extremity routine muscles:*

1. First dorsal interosseous
2. Extensor indicis proprius
3. Pronator teres or flexor carpi radialis)
4. Biceps brachii

### TABLE.4: Electrophysiological Criteria for Acute Demyelinating Polyneuropathy

Show at least three of the following in motor nerves:

1. Prolonged DLs (two or more nerves, not at entrapment sites)  
DL >115% ULN (for normal CMAP amplitudes)  
DL >125% ULN (for CMAP amplitudes < LLN)
2. CV slowing (two or more nerves, not across entrapment sites)  
CV <90% LLN (for CMAP amplitudes >50% LLN)  
CV <80% LLN (for CMAP amplitudes <50% LLN)
3. Prolonged late responses:  
F response and H reflexes (one or more nerves)  
>125% ULN
4. Conduction block/temporal dispersion (one or more nerves)  
*Unequivocal conduction block:* Proximal/distal CMAP area ratio <0.50  
*Possible conduction block:* Proximal/distal CMAP amplitude ratio <0.70  
*Temporal dispersion:* Proximal/distal CMAP duration ratio >1.15

CMAP: Compound muscle action potential

CV: Conduction *velocity*

DL: Distal latency

LLN: Lower limit of normal

ULN: Upper limit of normal