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Albuminocytological dissociation in different electrophysiological gbs variants

Ali Zohair Nomani
Pakistan Institute of Medical Sciences,Islamabad,Pakistan, alin9432@gmail.com

Mansoor Iqbal
Pakistan Institute of Medical Sciences,Islamabad,Pakistan

Haris Majeed
Pakistan Institute of Medical Sciences, Islamabad,

Mazhar Badshah
Pakistan Institute of Medical Sciences, Islamabad, Pakistan

Sumaira Nabi
Pakistan Institute of Medical Sciences,Islamabad, Pakistan

See next page for additional authors

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Authors
Ali Zohair Nomani, Mansoor Iqbal, Haris Majeed, Mazhar Badshah, Sumaira Nabi, Zakir Jan, and Uzma Jamil

ALBUMINOCYTOLOGICAL DISSOCIATION IN DIFFERENT ELECTROPHYSIOLOGICAL GBS VARIANTS

Ali ZohairNomani, Mansoor Iqbal, Haris Majid Rajput, Mazhar Badshah, Sumaira Nabi, Zakir Jan, Uzma Jamil, Hanin Bashar Mustafa Tanich, Rao Suhail Yasin Khan,Muhammad Irshad
Department of Neurology, Pakistan Institute of Medical Sciences, 44000, Islamabad, Pakistan.

Correspondence to: *Ali Zohair Nomani, Department of Neurology, Pakistan Institute of Medical Sciences, 44000, Islamabad, Pakistan. Email: alin9432@gmail.com*
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ABSTRACT

Objectives: The objective of our study was to determine the distribution of different electrophysiological variants of GBS and its relationship with albuminocytological dissociation (ACD). The rationale of the study was to determine whether presence or absence of albuminocytological dissociation has any association with NCS findings and whether can be relied upon as an indirect predictor of axonal variant which warrants poor patient out comes versus demyelinating. **Materials and Methods:** A consecutive series of 76 patients who presented at PIMS over a 12 month period with GBS were included. Nerve Conduction studies (NCS) and Electromyographic (EMG) findings with CSF characterization for albuminocytological dissociation were recorded. P value < 0.05 was taken significant. **Results:** NCS revealed AIDP as the most common variant (44; 57.8%) followed by AMAN (19; 25%) and AMSAN (7; 9.2%).For 5(6.5%) patients with normal NCS, EMG revealed early neuropathic changes in 4 (80% of normal NCS; 5.2% of total) (suggesting axonal degeneration). Total axonal degenerative type accounted for (AMAN + AMSAN + axonal neuropathy on EMG=30) 39.4% while demyelinating (AIDP + prolonged/absent F-wave=45) 59.2%. ACD was found in 60 (78.9%) patients.There was no signification association between ACD and NCS variants (p>0.05). **Conclusion:** AIDP is the most prevalent (58%) GBS variant in our population, at least in the vicinity of Islamabad. There is high prevalence of axonal variants (≈40% of total) as compared to Western countries. There is no correlation between ACD and NCS variants. ACD cannot be used as an independent predictor of NCS variant. Presence or absence of ACD has no definite predilection for axonal variant which itself warrants poor patient outcomes versus demyelinating type.

Key Words: GullainBarré Syndrome; variants; nerve conduction studies; electromyography; albuminocytological dissociation; cerebrospinal fluid, association.

INTRODUCTION

Acute flaccid paralysis (AFP) has a wide spectrum of etiologies.[1,2] One such common preventable cause is poliomyelitis which is still being reported in Pakistan. With marked decline in the incidence of polio, Guillain-Barré syndrome is now a common cause of acute flaccid paralysis. Two-thirds of GBS patients develop the neurologic symptoms 2-4 weeks after respiratory or gastrointestinal infection.[3] The initial symptoms are subtleparesthesias in the toes and fingertips, followed by lower extremity weakness that may ascend over hours to days to involve the arms, cranial nerves, and in severe cases the muscles of respiration. Respiratory muscle weakness is a poor prognostic sign.[3, 4, 5] At some point during their illness, up to 10 percent of patients require mechanical ventilation.[6] GBS has several electro physiological manifestations and variants namely AIDP (Acute Inflammatory Demyelinating Polyneuropathy), AMAN (Acute Motor Axonal Neuropathy), AMSAN (Acute Motor Sensory Axonal Neuropathy) or normal. Each has its own diagnostic and prognostic significance and guides management at least to some extent on individual basis.[3, 4, 5, 6] CSF is characteristically acellular. Protein levels may be normal during the first week of the illness, but the majority will have an increase in protein if measured 2 or 3 weeks later, called albuminocytological dissociation (raised protein concentration without pleocytosis).[6] Since the knowledge about novel presentations of GBS is currently evolving, one must remain abreast not only with the worldwide spectrum of GBS but of its local variants, both clinical and electro physiological. Meanwhile, the importance of albumino cytological dissociationcannot be denied both diagnostically and prognostically.[7, 8, 9] The rationale of the study was to determine whether presence or absence of albumino cytological dissociation has any association with NCS findings and whether can be relied upon as an indirect predictor of axonal variant which warrants poor patient outcomes versus demyelinating.

MATERIALS AND METHODS

This study was a single-center, observational, descriptive

study carried out at Department of Neurology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan; from 1st July 2013 to 30th June 2014 i-e-, 12 months period. Seventy six patients of GBS aged more than ≥ 12 years (only adult population is received at our centre) were included and analyzed in the final data set. This study was an independent project of the department and was not funded by any pharmaceutical organization. The study was reviewed by ethics committee and performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008. Patients fulfilling the inclusion criteria were enrolled after taking informed written consent from the patients and/ or relatives. All the patients were admitted when they first presented to the facility without delay. Criterion for GBS was ascertained according to Brighton Collaboration criterion for GBS (clinical, laboratory and NCS) and the following information was collected:[10] age, gender, duration of illness, clinical presentation and routine laboratory tests (complete blood counts, liver function tests, renal function tests, blood sugar random, serum electrolytes, urine routine examination, urine culture, blood cultures, arterial blood gases (ABGs), electrocardiogram, chest x-rays, toxicology screen, ESR, CPK, LDH, hepatitis screening). Electrodiagnostic tests i-e-, nerve conduction studies (NCS) and electromyography (EMG) were carried out using Cadwell Sierra II Wedge NCS EMG machine by a neurologist. Electrodiagnostic tests were performed in all patients and data was recorded. Lumbar puncture was done for CSF R/E (cerebrospinal fluid routine examination) in all patients consenting. CSF protein estimation with albuminocytological dissociation was calculated. Albuminocytological dissociation was defined as CSF with raised protein (>45mg/dl; lab reference at our centre) and total cell count of ≤ 10/mm^3.[6] Patients with alcoholism, any trauma affecting muscles or nerves, renal or metabolic dysfunctions, peripheral vascular diseases, myopathy, motor neuron disorders, any genetic or other disorders affecting nerve and muscles, CIDP (Chronic Inflammatory Demyelinating Polyneuropathy), diabetic peripheral neuropathy were excluded. Electrophysiologically, based on NCS, the following variants were defined: AIDP (Acute Inflammatory Demyelinating Polyneuropathy), AMAN (Acute Motor Axonal Neuropathy), AMSAN (Acute Motor Sensory Axonal Neuropathy) or normal. The nerve conduction studies were performed within 24-72 h of hospitalization in all cases. Needle EMG was also performed. At least one motor and one sensory nerve were tested on the upper and lower limbs. F-wave responseswere recorded in all the extremities. Additionally, routine motor conduction studies were performed on the median, ulnar, peroneal and tibial nerves using conventional procedures. Sensory nerve studies were performed on the median, ulnar and sural nerves. The amplitude of the negative phase was measured for compound muscle action potentials and sensory nerve action potentials. Patients were classified into AIDP or AMAN based on the existing electrodiagnostic criteria.[11] 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.Millar-Fischer Syndrome (MFS) was defined as triad of ataxia, opthamoplegia and areflexia without other possible causes.[6] Polyneuritis cranialis was defined as that only involving multiple cranial nerves while paraparetic as that only involving legs.[6] People were offered plasma exchange (PE), Intravenous Immunoglobulin (IVIG), PE followed by IVIG or none accordingly. The data was analyzed using SPSS version 17.0. Mean and standard deviation were calculated for numerical variables. Descriptive statistics were used to determine frequency and percentages for categorical variables and results were expressed either graphically or tabulated. Chi-square *(x^2)* test was used and p values were calculated. P value < 0.05 was taken significant.

RESULTS

Mean age was 34.7 ± 18.0 years ranging from 12-75 years. Gender distribution revealed male preponderance; 59 (77.6%) males and 17 (22.4%) females; 3.5:1. Mean duration of illness before presentation to hospital was 9.7 ± 7.6ranging from 4 to 21 days. Most common clinical presentation was quadriparetic variety (73 out of 76; 96.1%). Other variants included one (1.3%) Miller-Fischer, one (1.3%) polyneuritis cranialis and one (1.3%) paraparetic variant.NCS revealed AIDP as the most common variant (44; 57.8%) followed by AMAN (19; 25%) and AMSAN (7; 9.2%); axonal (AMAN + AMSAN=26, 34.2%)(Figure 1).

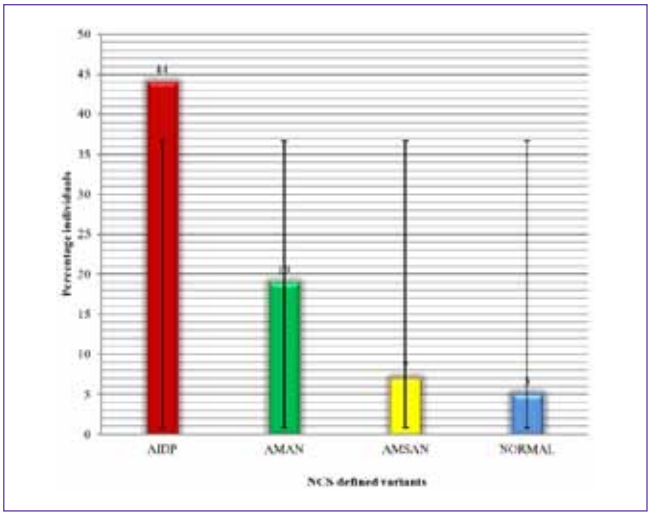

Figure 1: NCS based defined variants of GullainBarré Syndrome.AIDP (Acute Inflammatory Demyelinating

Polyneuropathy), AMAN (Acute Motor Axonal Neuropathy), AMSAN (Acute Motor Sensory Axonal Neuropathy).

For 5 (6.5%) patients with normal NCS, EMG revealed early neuropathic changes in 4 (80% of normal NCS; 5.2% of total) (suggesting axonal degeneration) while one (20% of normal NCS; 1.3% of total) proved to be Millar-Fischer Syndrome. The remaining one (1.3% of total) only had the finding of prolonged/ absent F-wave markers as the sole sign of proximal demyelination. Total axonal degenerative type accounted for (AMAN + AMSAN + axonal neuropathy on EMG=30) 39.4% while demyelinating (AIDP + prolonged/absent F-wave=45) 59.2% (Figure 2).

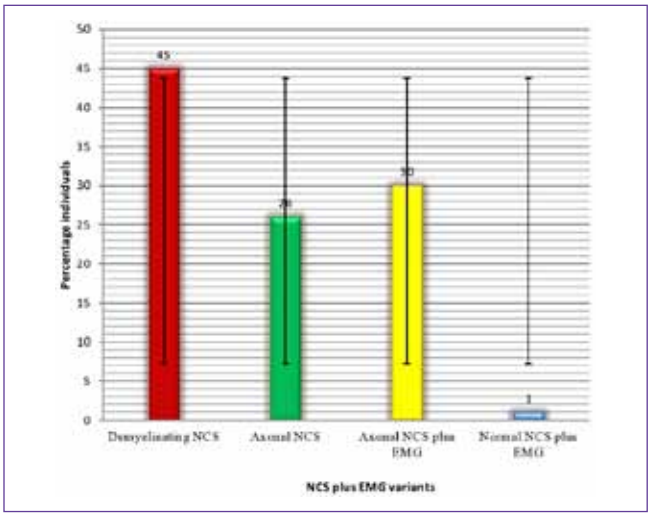

Figure 2: NCS and EMG based differentiation of variants of GullainBarré Syndrome.

ACD was found in 60 (78.9%) patients.Mean CSF protein was 131.1 ± 110 mg/dl ranging from 19 to 467 mg/dl (for all patients with CSF reports whether ACD or not). However, there was no correlation between ACD and NCS/EMG variants (p>0.05) (Table 1).

Table 1: Relationship of Nerve Conduction Study variants with Cerebro Spinal Fluid protein

Electrophysiological variant	Albuminocytological dissociation in CSF		Statistical significance
	Yes n (%)	No n (%)	*p value*
NCS defined variant			
AIDP	37 (61.7)	7 (43.7)	0.32
AMAN	15 (25)	4 (25)	
AMSAN	4 (6.7)	3 (18.7)	
Normal	3 (5.0)	2 (12.5)	
Only P/A F-wave	1 (1.7)	0 (0)	
Total	60 (100)	16 (100)	
NCS plus EMG differentiation			
Demyelinating	38 (63.3)	7 (43.7)	0.10
Axonal	22 (36.7)	8 (50)	
Normal	0 (0)	1 (6.2)	
Total	60 (100)	16 (100)	

Table 1: Relationship of Nerve Conduction Study variants with Cerebro Spinal Fluid protein. AIDP (Acute Inflammatory Demyelinating Polyneuropathy), AMAN (Acute Motor Axonal Neuropathy), AMSAN (Acute Motor Sensory Axonal Neuropathy), P=prolonged, A=absent.

DISCUSSION

GBS is a common cause of acute flaccid paralysis. Distinguishing patients with different variants of GBS from one another can be of great prognostic value. Prognosis depends on the time of presentation and delay in treatment. Despite all improvements in treatment and supportive care, the death rate is still around5%, even in the best intensive care units.[6] Worldwide, the death rate runs slightly higher, mostly from a lack of availability of life-support equipment during the lengthy plateau lasting four to six weeks and in some cases up to one year, when a ventilator is needed in the worst cases.[6] Poor prognostic factors include age over 40 years, duration of active disease, high CSF protein content, rapid progression of motor weakness, preceding diarrheal illness, marked disability at presentation, electrophysiological signs of axonal neuropathy, requirement ofventilatory support, high anti-GM1 titer and poor upper-limb muscle strength.[1, 2, 6, 7] Incidence of GBS, according to a rough estimate is much higher in South-Asia as compared to Europe and America and axonal variants account for a much larger proportion.[12] An epidemiologic study reported an 8-13% mortality rate despite ICU management in GBS, although the rate may be less than 5% in tertiary care centers with a team of medical professionals who are familiar with GBS management.[6] The most prevalent clinical variant, to our observation, wasthe quadripareticvariety in which all four limbs were involved usually in ascending manner.NCS revealed AIDP as the most common variant (44; 57.8%) followed by AMAN (19; 25%) and AMSAN (7; 9.2%); axonal (AMAN + AMSAN=26, 34.2%) (Figure 1).Upon review of data from local literature, Zaheer et al. in 2005 commented on a set of 25 patients from Lahore region that the break down of different patterns of neuropathy was 36% demyelinating, 12% axonal and 52% of mixed variety having both demyelinating and axonal components.[11] They concluded that the pattern of neuropathy in GBS is nearly the same as reported in most European and local studies except Chinese endemic cases where axonal form is more frequent. However, other authors like Khan et al. did not concur with their findings.[12] They suggested that axonal variants constitute 40% of GBS. The variants, according to them were distributed as AIDP-60%, AMAN-30% and AMSAN-10% i-e-, axonal-40%. Their data set consisted of 40 patients from vicinity of Rawalpindi region and their results were much similar to ours when reported in 2010.They concluded that a high frequency of the axonal variants persists in Pakistan.[12] Siddiqui and colleaguesin 2013 studied a group of 29 GBS patients

having AIDP-62%, AMAN-27.5% and AMSAN-10.3%(≈ axonal-38%) and concluded likewise.[13] A study by Yadegariet al.from Tehran, Iran done over a period of 11 years on 121 GBS patients concluded in 2007a distribution pattern of 63%, 23% and 14% of AIDP, AMAN and AMSAN respectively (axonal-37%).[14] Meta-analysis reports from Europe and the United States state that 60–80% of people with GBS have demyelinating subtype (AIDP) and AMAN affects only a small number (6–7%).These reports suggest thatin Asia and Central and South America, the proportion of axonal GBS is significantly higher (30–65%).[8] Our findings of demyelinating variant (AIDP + prolonged/absent F-wave=45) being ≈ 59% and axonal (AMAN + AMSAN + axonal neuropathy on EMG=30) ≈ 40% is in agreement with these international reports suggesting a relatively poor overall prognosis of GBS in our population (Figure 2). Our findings support the dictum that there is high prevalence of axonal variants (≈40% of total) in our population (Asians) as compared to Western countries.[6]
We found that 6.5% NCS were normal and EMG had to be done in order to revealearly neuropathic changes of axonal degeneration in 4 (66.7% of normal NCS; 5.2% of total). This highlights the fact that when NCS does not reveal overt demyelination or axonopathy, EMG is mandatory and most of the time reveals neuropathic changes even earlier in the course of disease suggesting axonal degeneration. A paper by Shabbir et al.published in 2012 identified that out of a set of 18 patients with axonal GBS, 12 showed fibrillation potentials, positive sharp waves and increased insertional activity within 4-12 days of symptoms onset and 6 beyond that period.[15] Active denervation in the form of fibrillation potentials and positive sharp waves were noted frequently and decreased interference pattern in almost all patients. On the basis of their observations of finding fibrillation potentials, positive sharp waves and decreased interference pattern early in the course of disease i-e-, before two weeks of symptom onset, they raised the query for a possible new hyperacute or fulminant variant of GBS.[15] The 4 of our patients with normal NCS revealed similar earlier changes of axonal neuropathy (all NCS/EMG done within 24-72 hours and symptom onset in all of these 4 patients being 3-4 days only) supporting their idea but needs further confirmation. It also suggests that when clinically indicated, NCS should be combined by detailed EMG study especially if NCS turns out to be normal. In a study by Akbayramet al.done in 36 children in 2010-11, 51.4% showed albuminocytological dissociation on cerebrospinal fluid examination.[6] According to Yadegari and colleagues, higher levels of CSF protein are more frequent in AIDP subtype. They commented that although the rise in CSF protein is more frequent in demyelinating variant, it may not have enough sensitivity to discriminate AIDP from axonal subtypes. Hence, the diagnosis of GBS and defining its subtypes should not be made based on a single finding.[14] We found ACD in 60 (78.9%) patients with mean CSF protein of 131.1 ± 110 mg/dl ranging from 19 to 467 mg/dl. However, there was no correlation between ACD and NCS/EMG variants ($p>0.05$) (Table 1). Our findings therefore concur with that of Yadegariet al.[14] and further augments their findings signifying that NCS/EMG are not only essential diagnostic tools but prognostic as well by helping differentiate between axonal and demyelinating typesirrespective of whether ACD is present or not (Table 1). Classifying patients on the basis of nerve conduction studies and electromyography can be helpful in guiding the prognosis of GBS in addition to being diagnostically pertinent. It helps stratify patients at beginning and thus help modify management plans accordingly with the hope of better patient outcomes. However, this classification should be based on a comprehensive and compact agreement between clinical presentation, CSF findings and detailed electrophysiological studies and not on a single factor. While high CSF is suggested by some to be a marker of poor patient outcomes, ADC per se does not differ among different NSC variants and mere presence or absence of ACD cannot predict axonal or demyelinating neuropathy which themselves are independent predictors of outcome.

CONCLUSION

AIDP is the most prevalent (58%) GBS variant in our population, at least in the vicinity of Islamabad. There is high prevalence of axonal variants (≈40% of total) as compared to Western countries. There is no correlation between ACD and NCS variants. ACD cannot be used as an independent predictor of NCS variant.Presence or absence of ACD has no definite predilection for axonal variant which itself warrants poor patient outcomes versus demyelinating type.

CONFLICT OF INTEREST

The authors declare that they do not have any competing interests.

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All authors contributed equally to this work. They performed the literature search, did data collection, analyzed the data and wrote the paper. All the authors meet the criteria for authorship as established by ICMJE.

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