A THESIS REPORT ON

UTILITY OF MULTIPLE SEGMENT STIMULATION AND SERIAL NERVE CONDUCTION STUDIES IN GUILLAIN BARRE SYNDROME

Submitted in partial fulfilment of the requirements for the degree of DM Neurology

Of

The Tamil nadu Dr M G R Medical University

DEPARTMENT OF NEUROLOGICAL SCIENCES

CHRISTIAN MEDICAL COLLEGE VELLORE

CERTIFICATE

This is to certify that the Dissertation titled "Utility of multiple segment stimulation and serial nerve conduction studies in Guillain Barre Syndrome" is the bonafide work of Dr. Ajith. M submitted in fulfilment of the DM – Neurology examination conducted by The Tamil Nadu Dr. M.G.R Medical University, Chennai, in August 2011.

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LIST OF ABBREVIATIONS

GBS - Guillain-Barre Syndrome

AIDP - Acute Inflammatory Demyelinating Polyradiculoneuropathy

AMAN - Acute Motor Axonal Neuropathy

AMSAN - Acute Motor Sensory Axonal Neuropathy

CB - Conduction Block

CMAP - Compound Muscle Action Potential Amplitude

EDX - Electrodiagnostic studies

SNAP - Sensory Nerve Action Potential

CV - Conduction velocity

DML - Distal motor latency

ABSTRACT

INTRODUCTION: -

Guillain-Barre syndrome is a common cause of acute and severe generalised neuropathic weakness. Nerve conduction studies are the most important diagnostic tests. It is classified into various subtypes based on the electrophysiological characteristics. Prolonged distal motor latency and conduction block are features of AIDP. The characteristic electrophysiological features of AMAN are reduced amplitude or absence of distal compound muscle action potentials indicating axonal degeneration. Recently there is growing recognition of reversible conduction blocks in AMAN.

OBJECTIVES: -

To evaluate the utility of multiple segment stimulation of motor nerves, proximal conductions and serial nerve conduction studies in patients with Guillain Barre syndrome.

METHODS: -

Ten patients admitted within the first week of onset of weakness diagnosed with GBS were included in the study and underwent multiple segment stimulation of upper limb motor nerves as well as proximal conductions as part of the electrophysiological study and were followed up with serial nerve conduction study every week till they improved by one

Hughes grade or till 4 weeks. The data was analysed using the SPSS software and the chi – square test was used for analysis of significance.

RESULTS: -

H-reflex abnormalities and prolonged / absent F-wave latencies were the most common electrophysiological abnormalities in the nerve conduction study done in the first week of illness. Multiple segment stimulation of motor nerves showed a higher yield of detecting conduction blocks in the first week especially across the entrapment sites. Two patients who had conduction blocks in the multiple segment stimulation in the first study and fulfilling the criteria for AIDP, had completely in-excitable motor nerves in the second conduction done one week later with evidence of active denervation on needle EMG suggestive of an axonal pathology.

CONCLUSION: -

Multiple segment stimulation helps in the detection of a higher percentage of conduction blocks in patient with GBS. Serial nerve conductions are important as there can be change in the electrophysiological classification with time. Some of the motor nerves showing conduction blocks may be on follow up show evidence of axonal degeneration and may indicate an electrophysiological feature of acute motor axonal neuropathy.

TABLE OF CONTENTS

INTRODUCTION

Guillain-Barre Syndrome (GBS) is a clinical condition that is characterized by rapidly evolving symmetrical limb weakness, loss of tendon reflexes, absent or mild sensory signs and variable autonomic dysfunction. After the eradication of poliomyelitis, GBS is the most common cause of acute flaccid paralysis.[1] Initially the term GBS was used synonymously with the term Acute inflammatory demyelinating polyradiculoneuropathy (AIDP). However over the years with the discovery of newer antibodies and distinct pathophysiological mechanisms being elucidated, the clinical spectrum has widened. There has been a change in the taxonomy to include three major subgroups also like - Acute motor axonal neuropathy (AMAN), Acute motor sensory axonal neuropathy (AMSAN) and Miller–Fisher syndrome.[1] A few other variants have also been described. There are geographical differences in the incidence of the various subtypes and an inter-play of microbial and host factors determine the susceptibility to develop the clinical disease. All these make GBS a phenotypic syndrome. The role of antecedent infections resulting in immuno- targeting of the specific components of the peripheral nerve have been better studied and there has been a paradigm shift in the knowledge of the target of the autoimmune process from the myelin related epitopes to the axolemma in the various subtypes.[2]

Nerve conduction studies are the most important ancillary diagnostic test and have helped in characterizing the various subtypes as AIDP, AMAN, AMSAN are difficult to distinguish on clinical grounds. The electrodiagnostic yield depends on the duration of the disease and the timing of the study. During the first day or two it may be difficult to identify the neurophysiological abnormalities. The electrophysiological abnormalities may not be sufficiently widespread for definite diagnosis in the first week,[3] however early diagnosis is important, because treatment arrests the progression of the disease, reduces the time/obviates the need for receiving mechanical respiratory assistance and lessens the

overall morbidity. Electrodiagnostic (EDX) studies in AIDP often show evidence of patchy demyelination, manifested as delayed distal motor latencies, conduction block, slowed motor conduction velocities (CVs) and dispersed responses. The diagnosis of AMAN is currently based on the absence of demyelinating features and reduction in the distal compound muscle action potential amplitude.[4] However, studies with serial nerve conduction recordings have shown that GBS patients with anti- ganglioside antibodies show in addition to axonal features, conduction block and conduction slowing without development of temporal dispersion and prolonged F- wave latencies which are restored in the subsequent conduction study. It was thought that these findings are incompatible with demyelination and remyelination and thereby indicated that AMAN is characterized not only by axonal degeneration but also by "reversible conduction failure" possibly induced by antiganglioside antibodies at the axolemma of the node of Ranvier.[5] Most of the published studies till date are cross sectional studies and there is paucity of studies from India which have looked at serial conductions in Guillain – Barre syndrome.

The goal of this study was to determine if there are characteristic electrodiagnostic findings within the first week using multiple segment stimulation of motor nerves including proximal segment stimulation to understand if there are early patterns that are suggestive of GBS and also to follow up these patients with repeat conductions to investigate how serial recordings changed the initial classification.

REVIEW OF LITERATURE

Guillain-Barre Syndrome is an acute onset immune mediated disorder of the peripheral nervous system. It is the most frequent cause of post infectious neuromuscular weakness worldwide. [6]

HISTORICAL PERSPECTIVE

The first description of the clinical features of Guillain Barre Syndrome was by Landry in 1859. Eichorst, in 1877 and Leyden in 1880, described the pathological findings of lymphocytic inflammation of the nerve in some cases of peripheral neuropathy. The description of the CSF findings characteristic of the disease was in 1916 by three French neurologists - Georges Guillain, Jean- Alexandre Barre and Andre Strohl in two soldiers who developed acute areflexic paralysis followed by gradual recovery. The CSF in these patients showed a raised protein and a normal cell count.[4] Over time it has become clear that this clinical picture now called Guillain-Barre Syndrome can have different pathological subtypes and is related to other less common disorders.

The three common subtypes are acute inflammatory demyelinating polyradiculoneuropathy (AIDP)[7,8], acute motor axonal neuropathy (AMAN) where the neurological deficit is purely motor [9,10,11,12] and acute motor and sensory axonal neuropathy (AMSAN), where sensory fibers are also affected. [13]A review of literature has shown that in North America and Europe typical patients usually have AIDP as the underlying subtype and only 5 % have axonal subtypes of the disease. In contrast, axonal forms of the syndrome constitute 30 - 47% of cases as per studies from northern China, Japan and central and south America.[10, 11, 12] The neuromuscular weakness in AIDP and the axonal subtypes may affect all four limbs and the cranial nerves and respiration.[14,15] AIDP patients, especially severe cases with respiratory failure tend to have more autonomic involvement than AMAN. Another subtype described are cases of acute dysautonomia

without involvement of the somatic nerves presumed to have an inflammatory or possibly autoimmune etiology. [16]

Guillain-Barre Syndrome and related disorders and typical antiganglioside antibodies: - [2]

	Antibodies
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Unknown
Acute motor axonal neuropathy (AMAN)	GM1, GM1b, GD1a
Acute motor and sensory axonal neuropathy (AMSAN)	GM1,GM1b,GM1a, GalNac-GD1a
Acute sensory neuropathy	GD1b
Acute pan dysautonomia	
Regional variants Fisher's syndrome Oropharyngeal	 GQ1b, GT 1a GT1a
Overlap Fisher's syndrome / Guillain –Barre syndrome overlap	GQ1b, GM1,GM1b, GD1a, GalNac-GD1a

In 1956, C Miller Fisher described a clinical triad of acute opthalmoplegia, areflexia and ataxia and postulated that this set of features were a form of Guillain Barre Syndrome. Now known as Fisher's syndrome, this subset of patients may have facial and lower cranial nerve involvement. Over lap forms with limb weakness and respiratory involvement are not rare. Also encountered are Formes- fruste with various combinations of opthalmoplegia, facial palsy, bulbar palsy and sensory neuropathy.[17]

Epidemiology

World wide incidence

The reported incidence of typical Guillain-Barre syndrome is relatively uniform throughout the world and ranges between 0.6 and 4 cases per 100000 per year, but the most recent best estimate of the overall incidence of GBS was between 1.1/100,000/year and 1.8/100,000/year.[18] All reports agree that men are 1.5 times more likely to be affected than women. Fisher's syndrome is much less common and an incidence of 0.1 per 100000 has been reported by Italian researchers. European and North American data show that the incidence of GBS increases with age after 50 years from 1.7/100,000/year to 3.3 /100,000 / year**.** [19,20, 21, 22]

In China, the reported incidence in children is about the same and much less in adults as elsewhere, giving an overall annual incidence of 0.66 per 100000 for all ages.[23] Similar studies from other regions report that the incidence of Guillain-Barre syndrome has been relatively stable over successive years. Most cases are sporadic, but there are reports of small clusters occurring in association with outbreaks of bacterial enteritis caused by contaminated water and campylobacter jejuni has been implicated in cases of summer epidemics in northern China.[23]

Preceding infection detected serologically in two large series of patients with GBS:-

	Netherlands [22] [1987-1996] (n=476)	North America and Europe [24] [1993-95] (n=383)
Campylobacter jejuni	32	23
Cytomegalovirus	18	8
Epstein – Barr Virus	7	2
Mycoplasma pneumoniae	9	Not tested

All series report that two thirds of patients have had an infection within the previous 6 weeks, most commonly a flu-like illness or gastroenteritis. [24] The responsible organism is often not identified, but a range of bacteria and viruses have been implicated in various observational and case control studies. The infection may elicit an immune response that cross reacts with axolemmal or Schwann cell antigens, thus damaging the peripheral nerve.[24]

The possibility of Guillain-Barre syndrome being triggered by certain immunisations in susceptible individuals was raised following reports of a slightly increased incidence after swine-flu vaccines were given in USA in 1976. [25,26,27] Other influenza vaccines have not been associated with the same risk and reports show that between 1990 and 2003 there has been a steady decline in the number of cases of Guillain-Barre syndrome associated with influenza vaccine.[28] Other conventional vaccines have not been associated with a significant risk despite many individual case reports.[29] However, rabies vaccine that contain sheep brain material is associated with Guillain- Barre syndrome in about one in 1000 cases.[30]

CLINICAL FEATURES AND DIAGNOSIS -

The onset of Guillain-Barre syndrome is usually abrupt with distal and relatively symmetrical onset of paraesthesias. Progressive limb weakness usually accompanies or quickly follows the sensory disturbances. A definite date of onset of symptoms is identified by the patients. Usually there is a rapid progression of weakness with approximately 50% of patients reaching the clinical nadir by 2 weeks and more than 90% reach by 4 weeks. By current diagnostic criteria the duration of progression to clinical nadir is defined as less than 4 weeks.[31] It is possible to differentiate between subacute and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), in which the onset

phase lasts 4 to 8 weeks [32, 33] or more than 8 weeks [34] respectively, only retrospectively. When patients have recurrent attacks of Guillain-Barre syndrome such cases can overlap with CIDP resulting in difficulties in classification.[35, 36] There are reports of one or more episodes of worsening after initial improvement in approximately 8% and 16% of patients presenting with a Guillain-Barre like illness. Data from one study showed that patients who deteriorated more than 9 weeks after the onset of their neuropathy or who had more than two treatment-related fluctuations were more likely to develop CIDP.[37]

Approximately 80 to 90% of patients with GBS become non-ambulatory during the course of their illness.[38,39] Pain is prominent complaint in approximately 50% of patients.[40] Neurological examination will demonstrate relatively symmetrical weakness distally and often proximal as well. In the early phase of disease, sensory examination is often normal.[41] Wide spread areflexia or hyporeflexia is the rule especially in AIDP. Cranial nerve involvement, usually in the form of facial or pharyngeal weakness as well as diaphragmatic weakness due to phrenic nerve involvement is seen.[42] Mechanical ventilation is required in approximately one third of hospitalized GBS patients because of respiratory muscle or oropharyngeal weakness.[43,44,45]Autonomic disturbance is documented in more than 50%, more common in patients with AIDP than in AMAN.[46,47] The usual manifestation is tachycardia but more serious dysfunction, including life-threatening arrhythmias, hypotension, hypertension and gastrointestinal motility dysfunction may occur.[48,49]

The ancillary tests supportive for diagnosis of GBS includes CSF analysis and electrodiagnostic testing, both of which may be normal in the early phase of GBS.[38] The limitations of the above tests in the early phase combined with the importance of prompt treatment of GBS underlines the importance of clinical diagnosis based solely on history

and examination. Reports show that an elevated CSF protein concentration (with normal cell count) is only found on initial CSF analysis in ~50% of patients; while elevated CSF protein concentration occurs in more than 90% of patients at clinical nadir.[41] There is routinely no reason to repeat the CSF analysis if the initial CSF is normal and clinically, if there is a reasonable degree of certainty about the diagnosis. CSF pleocytosis (> 10 cells) is not seen in GBS and possibilities to be considered in this scenario are those of – infectious causes like (HIV, CMV, Lyme) and other etiologies like sarcoid, carcinomatous, or lymphomatous polyradiculoneuropathy. [41]

The range of differential diagnosis is wide and it is imperative on the clinician seeing the patient, to recognise that the problem is an acute peripheral radiculoneuropathy.

Differential diagnosis of acute flaccid paralysis:- [4]

Brainstem stroke

Brainstem encephalitis

Acute anterior poliomyelitis

- Caused by poliovirus
- Caused by other neurotropic viruses

Acute myelopathy

- Space-occupying lesions
- Acute transverse myelitis

Peripheral neuropathy

- Guillain-Barre syndrome

- Post-rabies vaccine neuropathy
- Diphtheritic neuropathy
- Heavy metals, biological toxins or drug intoxication
- Acute intermittent porphyria
- Vasculitic neuropathy
- Critical illness neuropathy
- Lymphomatous neuropathy

Disorders of neuromuscular transmission

- Myasthenia gravis
- Biological or industrial toxins

Disorders of muscle

- Hypokalemia
- Hypophosphatemia
- Inflammatory myopathy
- Acute rhabdomyolysis
- Trichinosis

Channelopathies- Periodic paralysis

Immunopathologic and Electrophysiological correlates in Guillain-Barre syndrome subtypes:-

AIDP and the demyelinative conduction block-

The pathologic picture classically described in AIDP is segmental demyelination with multifocal mononuclear cell infiltration throughout the peripheral nerves. The macrophages have been shown to invade and strip the myelin sheath denuding the axon. Macrophages are targeted to antigens on the surface of Schwann cells or myelin by activated T cells. They are the major acting components in the model of experimental autoimmune neuritis predominantly caused by T-cell mediated immunity against peptides from the myelin proteins.[50] The role of humoral factors, like antibody and complement is also considered important in view of the therapeutic efficacy of plasma exchange which is presumably related to the removal of humoral factors, but not T cells.

During plasma exchange, the cytokines produced by T cells are also removed, but their circulating half lives are only a few hours and the efficacy, if limited to this, would be short term. Recently, pathologic studies done at early stages of AIDP have identified vesicular myelin degeneration as a prominent process and demonstrated complement activated products on the outer surface of Schwann cells of myelinated fibers.[51] Because of the background endoneurial staining, specific binding of immunoglobulin on the Schwann cell surface was not identified. It also showed extensive lymphocytic infiltrates and large numbers of foamy macrophages in the endoneurial space. The above findings suggest that the primary change in AIDP is binding of auto antibodies to unidentified targets at the ab-axonal Schwann cell plasmalemma, with consequent activation of complement, although one cannot entirely abandon the T-cell-mediated hypothesis. The demyelination, especially at the early phase, may be limited to nerve roots and distal intramuscular nerves where the blood-nerve barrier is weak and later it may be widespread and extensive throughout the nerve length.[51]

Schwann cells proliferate and migrate into the lesion sites to remyelinate the denuded axons producing generally good recovery in AIDP. The axons may be affected in AIDP secondary to the pathological events of demyelination (so-called bystander injury), and in some instances significant axonal damage may develop influencing the residual disability and long-term outcome.[51] Extensive electrodiagnostic examination is recommended in the diagnosis of GBS subtypes, which should include at least three motor nerves with multiple site stimulation and F-wave recordings, three sensory nerves and bilateral tibial H-reflex.

The characteristic features of demyelination – remyelination are demonstrated in the electrophysiology study in AIDP:- [52]

• Reduced nerve conduction velocity

• Prolonged distal motor latency (DML)

• Prolonged or absent F-wave

• Conduction block (CB), defined as an abnormal amplitude / area reduction of compound muscle action potential (CMAP) from proximal stimulation compared with the CMAP after distal stimulation

• Excessive temporal dispersion which is characterized by an abnormal duration of CMAP.

The duration of the disease determines the electro-diagnostic yield. In AIDP, the characteristic electrophysiological picture is usually demonstrable at 2- 3 weeks after onset. Because of the patchy nature of demyelination, in early AIDP, the nerve conduction studies may be normal (up to 13%) or non diagnostic.[14] During the first day or two, it may be difficult to identify the neurophysiological abnormalities. Gordon et al,[53] in a retrospective analysis of 31 patients with GBS evaluated within seven days of onset of weakness, detected the following findings :- H-reflex was absent in 30 (97%), upper

extremity SNAP was of low amplitude or unrecordable in 19 (61%), F waves were abnormal in 25(84%), reduced CMAP in 22 (71%), prolonged distal latency in 20(65%), temporal dispersion in 18 (58%), slowed motor conduction velocity in 16 (52%) and conduction blocks in 4 (13%) patients. Definite diagnosis was possible in 17(58%) patients but not commonly until the fifth day. The above study highlighted that absent H-reflex was most sensitive for diagnosis of early GBS but it is not specific. Also abnormal upper extremity SNAPs' with normal sural SNAPs' and absent F-wave responses were characteristic of early GBS.[53] Studies also showed that in the upper extremities conduction block is more frequent in nerve terminals, across the elbow and in the axillary to spinal root segments. This supports the hypothesis that certain regions, perhaps because of a relative deficiency of the blood–nerve barrier, may be more vulnerable.[52]

Patients', early in the disease course or those with a mild form of the disease may not always meet the criteria for an abnormal study. Moreover, definitive assignment to a GBS subtype may be difficult when motor nerves are in-excitable. In such patients it is difficult to determine whether a non-recordable CMAP is due to distal conduction block or axonal degeneration. Reduced motor unit action potential recruitment with fast firing of motor unit potentials in seen in needle electromyography. Secondary axonal degeneration is responsible for the presence of spontaneous activity in a few muscles', if seen. Markedly reduced amplitude of summated CMAPs' of median, ulnar, peroneal and tibial nerves from distal stimulation has been associated with poor long-term prognostic outcome in several studies.[52]

Thus in AIDP, conduction block due to acute demyelination and axonal degeneration secondary to demyelination are the electrophysiological correlates of muscle weakness. Prolonged distal motor latency, excessive temporal dispersion and reduced nerve conduction velocity are the characteristic correlates of the remyelinating phase. These

abnormalities may be associated with a reduced safety margin for impulse conduction. Physiologically they correlate with activity- dependent hyper polarization and conduction block occurring during sustained voluntary contraction.[54] However, they are not the major determinants of muscle weakness.

Conduction block is defined as the failure of action potential propagation at a given site along a structurally intact axon.[55] The leakage of current through the axon between the nodes of Ranvier is prevented by the myelin sheath which provides high impedance and low capacitance and also enables saltatory conduction of the nerve. Action current, through sodium channels at the activated nodes of Ranvier, produces inward ionic (sodium) current, which subsequently causes outward capacitive current at the next node to be excited (driving current). This depolarizes the nodal membrane to the threshold, opening the sodium channels and initiating another cycle of inward ionic current. Safety factor of transmission is defined as the ratio of driving current to threshold current. The safety factor is five or more in normal myelinated fibers. To assure conduction through an inter node it has to be more than one. The transmission of impulses is impaired by demyelination by changing the properties of para-nodal and inter-nodal membranes - increasing capacitance, decreasing resistance, thus dissipating the current over a larger area. Therefore, it takes more current and a longer time to depolarize the enlarged node to threshold with the result of an increased inter-nodal conduction time. The current becomes insufficient to depolarize the node to threshold as demyelination progresses and the safety factors falls below unity resulting in conduction block.[55]

The activation of potassium channels that are normally localized in the para- nodal axolemma and exposed by para-nodal demyelination is another factor aggravating the block. The potassium channels are activated for repolarization, when the paranodal axon exposed by demyelination undergoes depolarization. This shortens the duration of the

active current through the node, thereby reducing the safety factor for transmission even more. Reduction of the CMAP amplitude on proximal stimulation versus distal stimulation occurs when conduction block affects an adequate number of axons in a nerve segment. Excessive temporal dispersion due to increased difference among the conduction times along axons, may result in abnormal reduction of proximal CMAP.[55]

Due to temporal dispersion, there are de- synchronization and phase cancellations between the positive and negative phases of the motor unit action potentials which compound the CMAP. Hence, strict electrophysiological criteria should be applied to distinguish 'pure' conduction block from an abnormal CMAP amplitude / area reduction due to excessive temporal dispersion. The above mentioned findings indicate that, in AIDP, acute segmental demyelination and CB due to an immune attack of myelin and Schwann cells are the pathologic and electrophysiological correlates of muscle weakness.[55]

Acute motor axonal neuropathy and axonal degeneration -

The reported frequency of acute motor axonal neuropathy (AMAN) varies around the world. It totals 4% of all GBS in a multi-center study including 11 Western countries, 7% in England[56], 8% in India[57], 22% in Israel[58], 38% in Japan[59], 38% in Mexico [60] and 65% in northern China.[61] The onset of weakness in AMAN is abrupt, with rapid progressive ascending weakness clinically indistinguishable from AIDP.[62] There is less frequent facial and extraocular muscles involvement. [63,64] The 'Finger drop' sign has been described in AMAN patients. In AMAN there are no sensory symptoms or signs and deep tendon reflexes may be preserved throughout the disease course. They may even be hyper-excitable in the acute or recovery phase.[65,66] AMAN has been epidemiologically associated with antecedent *Campylobacter jejuni* infection. In AMAN, autoantibodies to gangliosides GM1 and GD1a have been found in 40 % and 30% of patients, respectively.[59] Studies have

demonstrated that the lipo-oligosaccharide of *C. jejuni* carry GM1- and GD1a-like structures and an animal model of AMAN has been produced by sensitization with such lipo-oligosaccharide.[67,68] The above observations demonstrate that AMAN subsequent to *C. jejuni* infection is a true case of molecular mimicry.

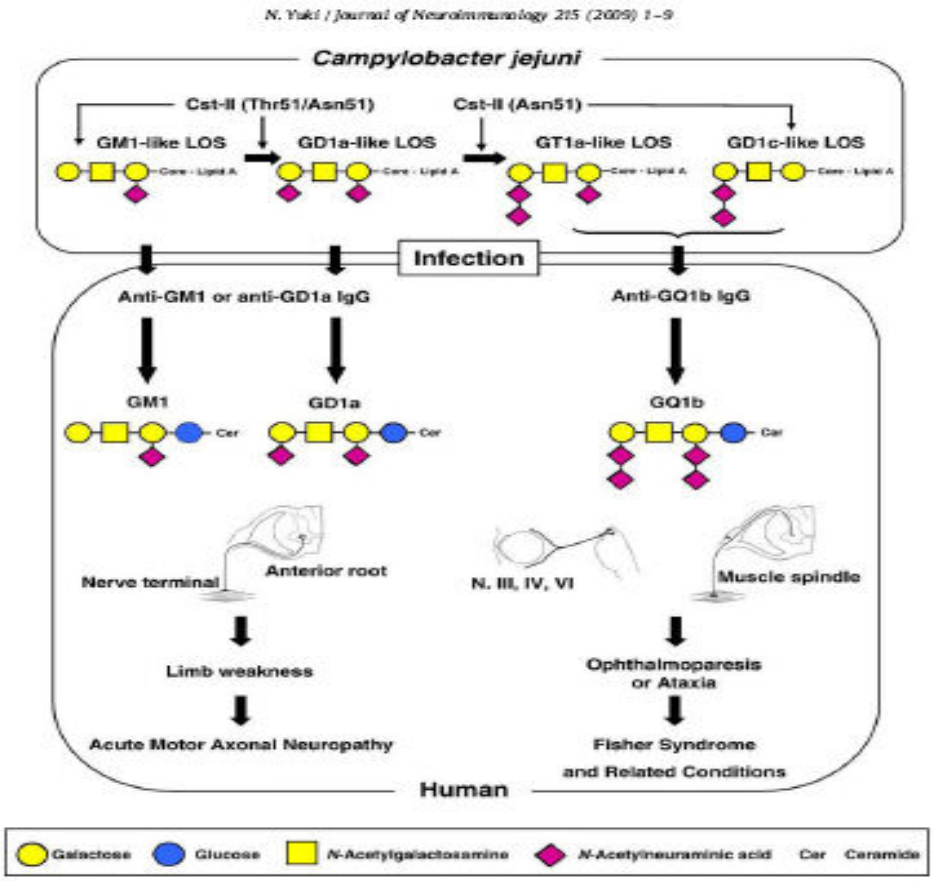


Figure 1- shows the role of C.jejuni with respect to the immunopathogenesis of AMAN and Miller Fisher syndrome - (reproduced with permission- Yuki; Journal of Neuro immunology 2009)

The primary target for immune attack in AMAN is the axolemma in contrast to AIDP. Pathological changes ranging from minimal to severe wallerian-like degeneration with deposits of IgG and complement at the nodes of Ranvier have been seen in autopsy studies of AMAN patients.[12] The presence of macrophages in the peri axonal space surrounding or displacing the axon, and even localized intra-axonally is a prominent feature. There is little or no evidence of demyelination or lymphocytic inflammation in AMAN.

Reduced amplitude or absent distal CMAPs were the electrophysiological features firstly described in AMAN patients.[62] From 1995 onwards, the proposed criteria for diagnosis of AMAN were the absence of demyelinating features, as derived from Albers and colleagues,[69] and the decrease in distal CMAP amplitude to less than 80% of the lower limit of normal.[61] The sensory nerve conductions including sensory action potential amplitude (SNAPs') and somato-sensory evoked potentials (SSEP) are normal in AMAN.[70,71]

On the contrary, electrophysiological evidence of involvement of sensory nerves has been reported in up to 80% of patients by the third week of illness in AIDP.[69] Motor-point biopsy from an AMAN patient revealed denervated neuromuscular junctions but relatively preserved intramuscular motor axons. This indicates the possibility of very distal motor terminal damage.[72]

An abnormal amplitude reduction of proximal CMAP mimicking a demyelinative conduction block may be found in the early stage of AMAN. Serial conduction studies on the following days, may demonstrate that the amplitude of proximal CMAP equalizes to the distal CMAP without development of excessive temporal dispersion.[72]

The progressive loss of excitability in nerve fibers undergoing axonal degeneration results in a length-dependent reduction of CMAP amplitude and can be interpreted as pseudo conduction block.[73, 74] In acute axonal injury, the distal CMAP is greater than the proximal CMAP because, the axons distal to the lesion remain excitable and viable for days, whereas stimulation above the injury site cannot generate a potential capable of travelling through the lesion. The axonal in-excitability in the axon distal to the lesions progresses over days depending on the length of the nerve.[74]

AMAN and reversible conduction failure –

The neurophysiology of AMAN is complex. In the early phase of the disease, the electrophysiology of patients with IgG antibodies to GM1, GM1b, GD1a and GalNAc - GD1a showed nerves with reduced distal CMAP amplitude, CB at common entrapment sites or with isolated absence of F-waves.[75,76,77] Some of these patients on follow up showed progression to axonal degeneration typical of the AMAN pattern. Others had a rapid normalization of distal or proximal CMAP amplitudes without prolonged duration and/or restoration of F-waves without increased latency. In patients categorized as AMAN some nerves showed prolonged DMLs'. However, the DML increase was milder than in AIDP nerves in these patients and it rapidly resolved or persisted unchanged in sequential recordings. On the contrary, in AIDP in serial studies there is a progressive increase in DML usually.[62, 73]

All the previously mentioned findings indicated that, the distinction between AMAN and AIDP is difficult or even impossible in the early phase of the disease, and that sequential electrophysiologic recordings are necessary for identification of GBS subtypes. Thus these studies suggested that the AMAN subtype was characterized not only by axonal degeneration but also by a reversible conduction failure; which is possibly mediated by antiganglioside antibodies.[64, 75]

Acute motor conduction block neuropathy -

Capasso *et al* in 2003, reported about two interesting patients who developed acute onset of symmetric weakness without any associated sensory symptoms.[78] There was history of antecedent diarrhoea in both patients (*C. jejuni was isolated from one of them)* and they carried high titres of IgG antibodies to GM1 and GD1a. Electrophysiological studies had shown distal CMAP amplitudes to be reduced, and also early partial motor CB in intermediate nerve segments (in ulnar nerves in the above - below elbow segment) with

normal sensory conductions even across the sites of motor CB and normal somato-sensory evoked potentials'. The muscle weakness improved and the distal CMAP amplitudes normalized and CB resolved in 2–5 weeks, without development of excessive temporal dispersion of either distal or proximal CMAPs'. There was a slowing of the motor nerve CV in the across elbow segment of the ulnar nerves', in the range usually considered to be in the demyelinating range. This slowing was present from the very first recording, when CB was at maximum. Sequentially, the CV increased with the decrease of CB and returned to normal range when CB had disappeared without the development of excessive temporal dispersion of proximal CMAP. The above findings indicate that conduction slowing at CB sites, like the increased DML described in some AMAN nerves, are due to neither demyelination nor remyelination.

It may be explained by preferential block of large diameter fastest conducting fibers, or altered resting membrane potential and sodium channel inactivation with delay of the action potential rising time. There are similar reports of five other patients. There was serological evidence of *C. jejuni* infection in four out of the five patients and another had diarrhoea.[79, 80,81,82,83] Three patients had anti-GM1 and one anti-GM1b IgG antibodies, four patients recovered after IV Immunoglobulin or plasmapheresis in a few weeks. However, one patient worsened and progressed on to axonal degeneration.

The above subgroup of patients were considered to represent a rare GBS subtype named 'acute motor CB neuropathy' (AMCBN).[78] Both AMCBN and AMAN have in common *C. jejuni* enteritis and antiganglioside IgG antibodies are associated with both groups. Also these AMCBN patients had the 'reversible conduction failure pattern' described in some AMAN patients in most of the tested nerves.[75] Hence, it was hypothesized that AMCBN represents an 'arrested AMAN'. Pathologically in these patients the anti-ganglioside

antibodies are thought to bind to the nodal axolemma and induce physiologic CB not progressing to axonal degeneration in any nerves.[77]

It has been noted that even in AMAN patients with axonal degeneration, the recovery is more rapid and greater in grade than expected or when compared with other axonal neuropathies.[84] Studies indicates that, in AMAN patients, axonal damage develops predominantly in the motor nerve terminal and only occasionally more proximal, providing the possibility for a good recovery as also shown by the time course of electrophysiological regeneration.

Thus the term AMAN should no longer convey the meaning of "axonal degeneration" exclusively considering the dynamic process in AMAN pathogenesis. It is also debatable whether AMCBN or AMAN with reversible conduction failure should be recompiled in AMAN subtype or kept distinct.[85] Therefore, the individuation of this form by proper interpretation of sequential electrophysiological findings is crucial to characterize GBS subtypes and establish prognosis.

Acute motor and sensory axonal neuropathy -

A total of eight patients with an acute motor and sensory neuropathy (AMSAN) were described by Feasby and colleagues, [86] who met the clinical criteria for GBS, but in whom almost all motor and sensory nerves become in-excitable 4 to 10 days after onset of symptoms. Electromyography in these patients revealed extensive denervation.[87] Most of the patients required mechanical ventilation and the outcome was poor. Autopsies and nerve biopsies in these patients showed axonal degeneration without evidence of demyelination or inflammation. AMSAN has been seldom reported, representing 1% of GBS in Japan[88], 6% in India [57] and 15% in Israel [58]. Anti-GM1, -GM1b and - GD1a IgG antibodies were present in two patients and one of the patients had serologic evidence of

C. jejuni infection.[89] Similar to AMAN, the pathology in AMSAN is consistent with an antibody-mediated pathogenesis with the difference being that here the dorsal as well as the ventral roots are affected. [87] AMSAN can be considered to be the severe end of axonal GBS since AMAN and AMSAN share a common immunological profile and immunopathology.

Electrophysiological criteria for GBS subtypes -

Electrophysiology plays a critical role in the diagnosis of GBS and categorization into the various subtypes. However, even for the AIDP subtype, there is no consensus as yet over which of the published criteria offers the greatest diagnostic yield. Comparing the sensitivity of six criteria, two studies done showed that the number of patients that could be categorized as AIDP varied from 21 to 72%. [90, 91] The criteria proposed by Albers and colleagues [69] reached the highest sensitivity (64-72%). [90, 91] Ho and colleagues in 1995, modified the Albers criteria to differentiate AIDP from AMAN in the Chinese GBS population.[61] ' Unequivocal temporal dispersion' but not CB was enclosed among the parameters to assess demyelination in Ho's criteria. However, how much temporal dispersion should be considered 'unequivocal' was not defined. AMAN was diagnosed by the absence of demyelinating features and the decrease of distal CMAP amplitude to less than 80% of lower limit of normal.[61]

According to these criteria, 65% of GBS patients examined within the first 2 weeks of diseases had AMAN, 24% had AIDP and 11% were unclassified. Hadden and colleagues[14] substituted unequivocal temporal dispersion with CB in a revised version of Ho's criteria. As it is known that motor nerves with very low CMAP amplitude due to axonal degeneration may have prolonged DML and F-wave latency or reduced CV, the presence of any single nerve with distal CMAP amplitudes less than 10% of the lower limit of

normal and 'demyelinating features' was not allowed to change the electrophysiological classification from primary axonal to demyelinating. The results of two electrophysiological tests performed approximately 4 weeks apart in 369 GBS patients from 11 Western countries, were examined. At the first test, 69% of patients met the criteria for AIDP and 3% the criteria for AMAN. At the second test, although the final proportion of AIDP (66%) and AMAN (4%) were similar, many individuals changed classification.[14]

Hadden's criteria enclosed CB in the definition of primary demyelination. However, CB, promptly recovering without temporal dispersion and other characteristics of remyelination, has been described in AMCBN and AMAN patients with 'reversible conduction failure'.[75,76,78]

In a GBS series from Japan analysed utilizing Ho's criteria, some of the patients carrying anti ganglioside antibodies recorded sequential change in electrophysiology from AIDP to AMAN or recovered from the AMAN pattern or from the 'isolated F-wave absence' pattern to normal. [59, 64]

Difficulty in distinguishing AMAN and AMCBN from AIDP arises from the fact that some of the electrophysiological features attributed to segmental demyelination can occur with variable degrees of nodal injury in axonal GBS. Also, some patients with AIDP may develop such profound secondary axonal involvement that demyelinating features may no longer be evident.

In an Indian study, by Kalita et al [57](cross sectional study) with 51 GBS patients, of whom 25 patients had presented in the first week of the onset of symptoms, 16 in the second week and 10 patients who presented in the third week of illness were analysed, the sensitivity of the various criteria were analysed and the results were as follows:-

Criteria	1st week (25 patients)	2nd week (16 patients)	3rd week (10 patients)
Alber's	88 %	87.5 %	90 %
Alber's & Kelly	48 %	43.8 %	60 %
Cornblath	32 %	37.5 %	60 %
Ho's	88 %	81.3 %	90 %

In a recent study by Uncini et al [4], it was found that out of 55 patients who underwent at least two serial electrophysiological studies with a mean duration of 28 days between the tests , in the first test electrodiagnosis using the Ho and Hadden criteria were identical : 65-67 % were classifiable as AIDP,18 % were classifiable as Axonal GBS and 14- 16 % were equivocal .At follow up it was found that there was a change in classification in 24 % of patients : AIDP decreased to 58%, axonal GBS increased to 38 % and equivocal patients decreased to 4%. It was noticed that the majority of shifts were from AIDP and equivocal groups to axonal GBS. Again the main reason was that serial recordings were able to recognise the reversible conduction failure and length dependent CMAP amplitude reduction as expression of axonal pathology.

Thus, it is important to note that serial electrophysiological studies are helpful and should be mandatory for the identification of GBS subtypes and to elucidate the pathophysiologic mechanisms of muscle weakness among demyelination, axonal degeneration and physiologic CB. In order to determine if physiologic conduction failure or demyelination underlie CB, electrophysiological recordings should be repeated through some weeks in order to document increased CMAP duration due to excessive temporal dispersion, which is the electrophysiological correlate of remyelination.

AIMS AND OBJECTIVES

The primary aims and objectives of the study were:-

- To evaluate the utility of multiple segment stimulation- including proximal Conduction - in nerve conduction studies of patients with Guillain-Barre Syndrome.
- To determine whether multiple segment stimulation of nerves helps in the early detection of conduction blocks in patients who present in the first week of illness.
- To do serial nerve conductions studies and investigate what changes are seen and its influence on the initial classification as per established published criteria.

MATERIALS AND METHODS

DATA COLLECTION

Setting:

Patients admitted under the Department of Neurology at Christian Medical College, Vellore and diagnosed to have Guillain- Barre Syndrome were included in the study. The study protocol was approved by the Institutional Review Board (IRB) of the institution.

Period of recruitment:

14 months (January 2010 to February 2011)

Participants:

Inclusion Criteria

All newly diagnosed, treatment naïve patients above 18 years of age who presented within first week of illness and satisfying the clinical diagnostic criteria for typical Guillain-Barre syndrome who consented for the study were included for clinical evaluation and serial nerve conduction recordings.

Clinical diagnostic criteria for typical Guillain- Barre Syndrome: -

Features required for diagnosis:-

Progressive weakness in both arms and both legs

Areflexia

Features strongly supporting diagnosis:-

Progression of symptoms over days to four weeks

Relative symmetry of symptoms

Mild sensory symptoms or signs

Cranial nerve involvement especially bilateral weakness of facial muscles

Recovery beginning 2- 4 weeks after progression ceases

Autonomic dysfunction

Absence of fever at onset

High concentration of protein in cerebrospinal fluid with fewer than 10 cells

Exclusion criteria

1. Diagnosis of botulism, myasthenia, poliomyelitis or toxic neuropathy
2. Abnormal porphyrin metabolism
3. Recent diphtheria
4. Purely sensory syndrome without weakness

Electrophysiological criteria for GB syndrome- AIDP variant

	Albers et al (1 in 2 nerves)	Albers& Kelly (3 or more)	Ho et al (1 in 2 nerves)	Dutch GBS study group (1 in 2 nerves)	Cornblath et al (3 or more)	Italian GBS study group (1 in 1 nerve)
Conduction velocity reduction **A > 50%** **A < 50%**	<95% <85%	<90% <80% **(2 nerves)**	<90% <85%	<70%	<80% **(A>80%)** <70% **(A<80%)** **(2 nerves)**	<80% <70% **(2 nerves)**
Distal latency prolongation **A : Normal** **A < Normal**	>110% >120 %	>115% >125 % **(2 nerves)**	>110% >120 %	>150%	>125% >150 % **(2 nerves)**	>125% >150 % **(2 nerves)**
Temporal dispersion (Prox-distal duration increase)	>30%	> 30% **(1nerve)**	> 30%	Distal-prox duration >150%, distal duration>300%	>15%, with >20% amplitude decrease **(1nerve)**	> 30% **(1nerve)**
Conduction block (Prox:Dist amplitude ratio)	<0.7	<0.7 **(1nerve)**		Amplitude decrease>ULN	<15%, with >20% amplitude decrease	<0.7 **(1nerv**
F-wave latency prolongation	>120%	>125% **(1nerve)**	>120%	>150%	>120% >150 % **(2 nerves)**	>120% >150 % **(2nerves)**

Abbreviations:-

Amp - CMAP amplitude (lower limits of normal); dist – distal

dur - CMAP duration; NP – negative peak; prox – proximal.

AIDP – Hadden et al -

At least one of the following in each of at least two nerves or at least two of the following in one nerve if all others in excitable and d CMAP ≥ 10 % LLN

- Motor conduction velocity < 90 % LLN (< 85 % if d CMAP < 50 % LLN)
- Distal motor latency > 110 % ULN (> 120 % if dCMAP < 100 % LLN)
- pCMAP/ d CMAP ratio < 0.5 and d CMAP ≥ 20 % LLN
- F response latency > 120 %

Of the above seven criteria, we used the following five criteria for the analysis of the electrophysiology data in our study:- Set 1 (Alber's), Set 2 (Alber's and Kelly), Set 3 (Cornblath) , Set 4 (Ho's criteria), Set 5 (Hadden's criteria).

AMAN CRITERIA :-

Ho *et al* . (1995)

- No evidence of demyelination as described in AIDP
- dCMAP <80 % LLN in atleast two nerves

Hadden *et al* .(1998)

- None of the features of demyelination in any nerve as defined in AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10 % LLN
- dCMAP < 80 % LLN in at least two nerves

  Sensory action potential amplitudes normal

AMSAN CRITERIA:-

Feasby et al (1993); Rees et al (1995)

No evidence of demyelination

- d- CMAP < 80 % LLN in at least two nerves or in excitable nerves
- Sensory nerve action potential amplitude <50 % LLN

Methods:

All patients with Guillain- Barre syndrome, who fulfil the inclusion criteria, were recruited in the study after informed consent. Demographic information, etiological factors and laboratory data were collected as per study protocol (Appendix 1). The study subjects then underwent a nerve conduction study at temperature greater than 32 degree Celsius using a standard ENMG machine (Nicolet Viking Quest).Stimulus duration was 0.2 ms in all examinations, with the intensity ranging from 20 to 100 mA for obtaining supramaximal stimulation.

a) Motor nerve conduction parameters :- compound muscle action potential- amplitude (peak to peak), latency, duration, velocity- of two motor nerves each in bilateral upper (median and ulnar nerves) and lower limbs (peroneal and tibial nerves).

- Multiple segment stimulation of – bilateral median and ulnar in the upper limb including Erb's point stimulation were done as part of nerve conduction study for patients admitted with suspected Guillain Barre syndrome at the time of admission and once weekly thereafter till the power improved by one Hughes grade or till discharge.

Median nerve stimulation at the following sites and CMAP recording done at the abductor pollicis brevis muscle:-

1) Wrist 2) Elbow

3) Axilla 4) Erb's point

Ulnar nerve stimulation at the following sites and CMAP recording was done at the abductor digiti minimi muscle:-

1) Wrist 2) Below elbow

3) Above elbow 4) Erb's point

Peroneal nerve stimulation at the ankle and fibular head and CMAP recording was done at the extensor digitorum brevis muscle.

Tibial nerve stimulation at the ankle and popliteal fossa and CMAP recording was done at the abductor hallucis muscle.

The CMAP parameters determined to evaluate conduction abnormalities in the forearm segment and across the elbow segment were:-

Amplitude decrement (%) - calculated as (distal CMAP amplitude – proximal CMAP amplitude) × 100 / (distal CMAP amplitude);

Temporal dispersion (%) - calculated as (proximal CMAP duration / distal CMAP duration) × 100.

Based on the consensus criteria of the American Association of Electrodiagnostic Medicine, definite partial conduction block was defined as an amplitude decrement of more than 50% with <30% temporal dispersion. Probable partial conduction block was defined as an amplitude decrement of 40–49% with <30% temporal dispersion. The above criteria were applied only to a nerve in which the distal CMAP amplitude was 20% or more of the lower limit of normal.

ROOT STIMULATION – TECHNIQUE - Patients who gave consent underwent a monopolar electrical stimulation across the C8 root to abductor digiti minimi, to assess for any conduction block - Electrical stimulation was done using a 75 mm mono polar needle with a 3mm bare tip placed onto the C7 lamina with a surface anodal plate lateral to it. Supramaximal stimuli were given and evoked response was measured for latency, area and amplitude.

The following parameters were also studied:-

a) Sensory nerve conduction – amplitude and conduction velocity

(Bilateral median and ulnar in the upper limbs and bilateral superficial peroneal and sural nerves in the lower limbs).

b) F- wave latencies in the upper and lower limbs nerves

- Upper limbs - bilateral median and ulnar nerves.
- Lower limbs - bilateral peroneal and tibial nerves.

c) H reflex - bilateral - amplitude and latency - evaluates the S1 root

d) Phrenic nerve stimulation – bilateral - latency and amplitude -

Technique - Electrical stimuli at 100 - 200 msec are applied at the posterior border of the sternomastoid, cathode being inferior to anode about 3 cm above the clavicle. The active recording electrode is placed at the xiphisternum and reference at the costal margin 16 cm away from the active electrode. Neck should be neutral or slightly extended.

e) Femoral nerve stimulation – was stimulated above and below the inguinal ligament just lateral to the femoral artery. Surface recording electrodes are placed over the belly of the vastus medialis and the reference electrode just proximal to the patella.

f) Blink reflex

g) Facial nerve conduction – Bilateral

h) Sympathetic Skin Response - in the upper and lower limbs

- which assesses the function of the small diameter fibres.

i) Needle EMG study: findings - insertional activity, motor unit potential - amplitude, duration, interference

Lower limbs - Tibialis Anterior, Vastus lateralis

Upper limbs - Abductor pollicis Brevis, Biceps

For DML, CV, F - wave latency, CMAP and SNAP amplitude we defined the upper and lower limits of normal as the mean plus / minus 2 SD of the control values of our laboratory which gives a 95% CI.

Control values at our electrophysiological laboratory:-

Nerve	Dist latency (msec)	Amp(mV, microV)	Conduction velocity(m/s)	F wave (msec)
Median motor	3.12 ± 0.62	12.0 ± 5.0	54.9 ±10.9	26.6 ±3.5
Median sensory	2.27 ± 0.44	25.6 ±10.0	57.4 ± 11.9	
Ulnar motor	2.17 ± 0.55	9.0 ± 3.0	59.4 ±10.9	26.6 ± 3.5
Ulnar sensory	1.8 ± 0.62	20.4 ± 9.6	56.4 ± 10.7	
Peroneal	3.56 ± 1.22	8.0 ± 2.62	46.5 ± 7.78	47.8 ± 5.9
Sural sensory	2.36 ±0.62	8.0 ±2.62	48.2 ± 9.8	

Since we did not have a control value for the tibial nerve conduction parameters and proximal stimulation was technically difficult it was not included in the final analysis. In serial recordings of the same patients, distal CMAP amplitude was considered significantly

increased when higher than 50 % of the values found at the first study. Electrophysiology was performed in all patients at least twice and five patients had at least three conductions done.

CLINICAL GRADING: - HUGHES FUNCTIONAL GRADING-

Hughe's grade was assessed for all patients at admission and at discharge. Any change during the course of hospital stay was also noted.

HUGHES GRADE	Clinical status
GRADE 0	Normal
GRADE 1	Minimal signs and symptoms, able to run
GRADE 2	Ambulates independently
GRADE 3	Able to walk 5 metres with aid
GRADE 4	Bed bound
GRADE 5	Requires mechanical ventilation
GRADE 6	Dead

Other variables:- CSF – TC, DC, Sugar, Protein

Blood – HIV, serum Potassium

Urine - porphobilinogen

STATISTICAL ANALYSIS:-

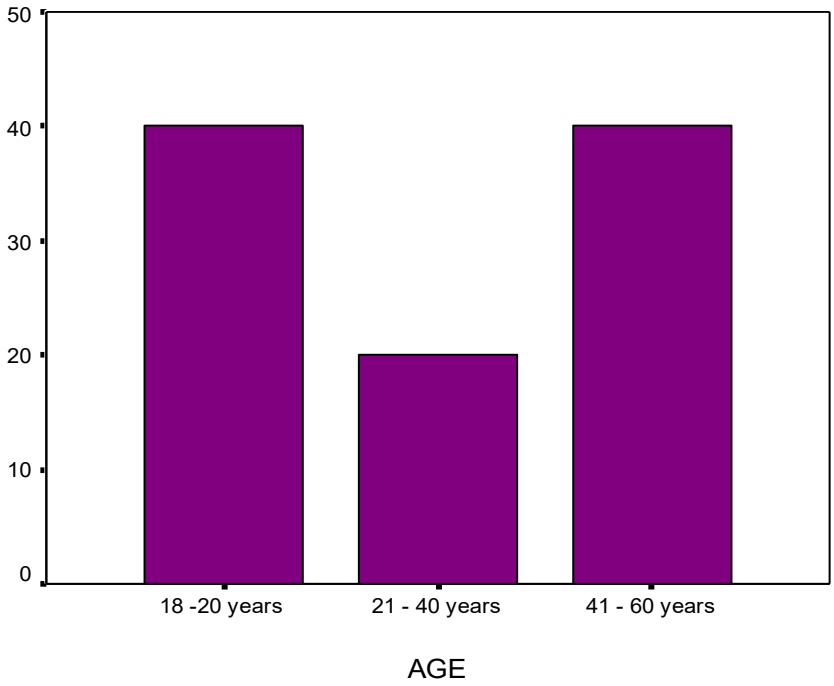
All the data was entered into SPSS (version 15 for windows) .The mean distal motor latency, CMAP amplitudes and F- wave latencies (with standard deviation) were calculated for the first and second nerve conduction study. Chi- square test was done for testing the significance of the involvement of the upper limb median SNAP's compared to that of the sural SNAP's. Probability value (p value) less than 0.05 was considered statistically significant.

RESULTS

Data was collected from a total of ten patients who presented within the first week of onset of symptoms and admitted with a clinical diagnosis of Guillain -Barre syndrome (fulfilling the inclusion and exclusion criteria) during the study period. All the ten patients had at least two electrophysiology tests with a minimum gap of seven days while five patients had atleast three conductions (one patient in this group had six conductions). The third conduction was done approximately twenty days after the onset of the illness. The mean time from the onset of neurological symptoms to the first electrophysiological study was 4.1 days.

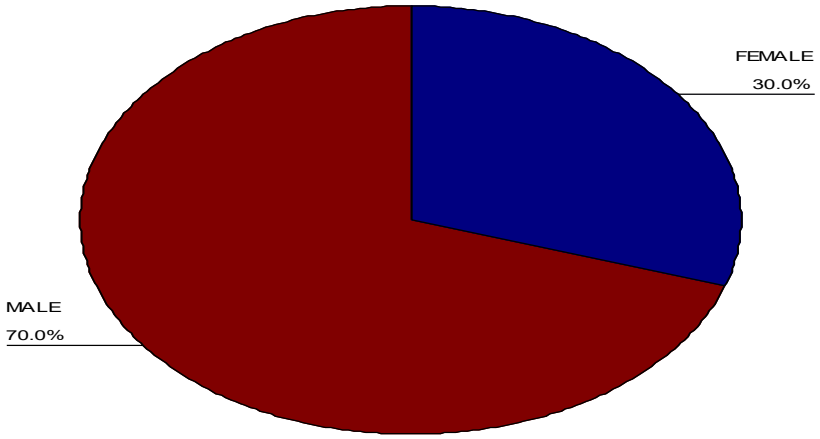
The baseline characteristics of the study population are as follows:-

1) Age distribution:-



Of the ten patients in the study group, four patients were in the age group of 18 to 20 years and another four were in the age group of 41 to 60 years. There was no patient with age less than 18 years or more than 60 years in the study group.

2) Sex distribution:-



3) Antecedent events:-

Events	No of patients
Diarrhoea	2
Upper Respiratory Infection	1
Fever with arthralgia	2
Vaccination	0
No events	5

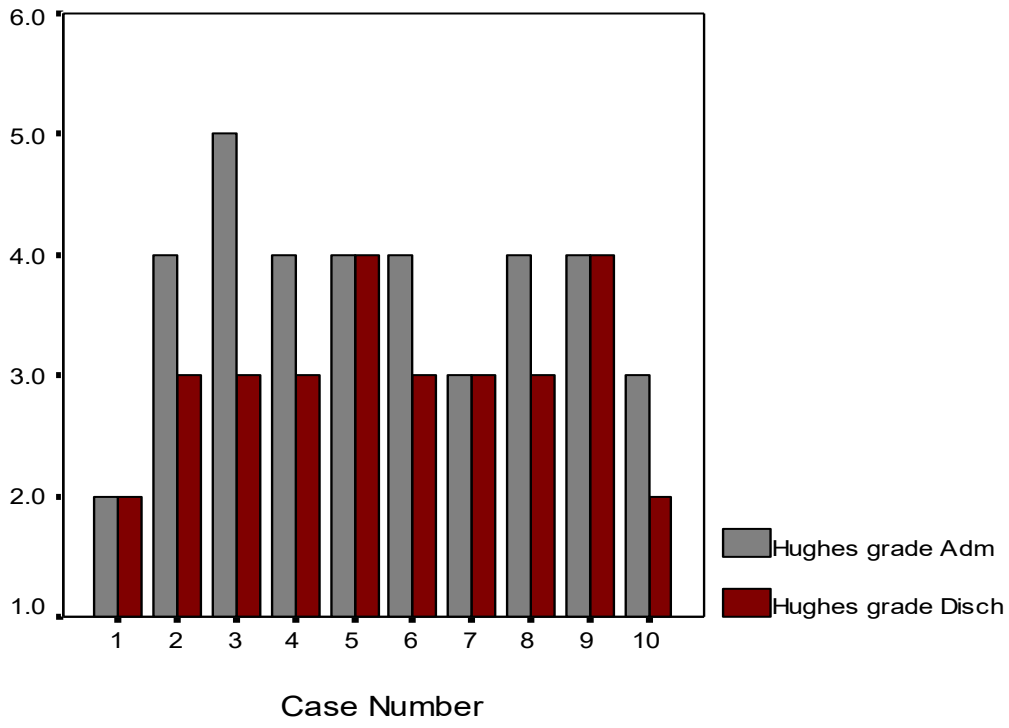
4) Duration from onset to nadir:-

	No of patients
24 - 36 hours	1
36 - 72 hours	1
72 hrs – 7 days	6
8days – 14 days	1

5) Cranial nerve Involvement:-

Cranial Nerve Involvement	No of patients
Extra-ocular Involvement	0
Bifacial weakness	7
Bulbar weakness	4

6) Hughes Grade at admission and discharge: - The following bar diagram depicts the Hughes grade at admission and discharge in the ten patients who were treated with plasmapheresis.



Patient number 5 - at admission had a Hughes grade 4; however on the fourth day he worsened and was mechanically ventilated (grade 5). He was gradually weaned off after 110 days of ventilation and discharged for rehabilitation (grade 4).

7) Deep tendon reflexes: - Nine out of ten patients had absent deep tendon reflexes. The remaining one had her reflexes just elicitable during the course of her illness though her conductions were classified as acute demyelinating polyradiculoneuropathy.

8) Sensory Symptoms: -

Sensory Complaints	Yes	No
Painful Paraesthesias	6	4
Sensory loss	1	9

Of the ten patients, one patient complained of whole body paraesthesias with involvement of the trunk and face.

9) Hughes grade improvement after treatment at follow up (1 month):-

	Number of patients	Percentage (%)
Improvement by at least one grade	9	90
No improvement	1	10
Total	10	100

10) Urinary Bladder Involvement:-

Of the ten patients in the study only one patient had bladder complaints in the form of urinary retention on the fourth day of illness (first day of admission) necessitating catheterisation and it persisted till ten days .(Trial of catheter removal was done but had to be reinserted due to retention). A MRI screening of the whole spine was done for this patient to rule out any spinal cord pathology which was normal. She also had other

features of significant autonomic involvement- like abnormal blood pressure responses during plasmapheresis.

LAB INVESTIGATIONS:-

All the ten patients were evaluated to rule out underlying HIV infection - (HIV Elisa negative in all patients) and the serum potassium and CPK assay were within normal limits. The urine porphobilinogen assay was also negative in all the patients.

11) CSF abnormality:-

	Normal	Elevated	Total patients
Total cell count	10	-	10
CSF Protein	6	4	10

The CSF protein was elevated (> 45 mg /dl) in only four patients out of ten which is expected as the CSF study was done in the first week of illness. Of these, only two patients had CSF protein > 60 mg /dl.

12) Treatment: -

All the ten patients were treated with plasmapheresis (mean volume removed – 5 litres). Of this, one patient could not tolerate plasmapheresis after 3.3 litres - as she developed severe hypotension and bradycardia (associated with severe autonomic dysfunction). Hence she was started on treatment with IV Immunoglobulin (2gms/ Kg).

13) Average duration of Hospital stay: -

The average duration of hospital stay was around twenty days for nine patients while one patient had a prolonged stay of around five months requiring long term mechanical ventilation for 110 days.

ELECTROPHYSIOLOGICAL PARAMETERS

We analysed the results of the multiple segment stimulation of the median and ulnar nerves in the upper limbs to assess for the presence of conduction blocks across the different segments and also the results of the proximal conductions (blink reflex, facial nerve, phrenic nerve, H -reflex and femoral and saphenous conductions) in the first week to assess for any abnormality indicative of proximal involvement in the early stages of Guillain Barre syndrome.

14) Motor nerve conduction studies: -

Total number of nerves studied:-

Nerves studied	First study (n = 10)	Second study (n = 10)	Third study (n = 5)
Median	20	20	10
Ulnar	20	20	10
Peroneal	20	20	10
Total	60	60	30

n = number of patients studied

The various published criteria (Alber's, Alber's and Kelly, Cornblath, Ho et al and Hadden criteria - for AIDP and the Ho et al Criteria - for AMAN) were used to analyse the sequential nerve conduction studies. Then we analysed the number of patients who satisfied the criteria in the first week and in the subsequent study and assessed whether there was a change in the classification in the subsequent study.

15) Results of the **first nerve conduction study (motor nerves)** in patients with Guillain Barre Syndrome: -

Nerve	Distal Latency (msec)	CMAP amplitude (mV)	CV (m/s)	F wave latency (ms)
Median (n=20)				
In excitable	0 (0 %)	0 (0 %)	0	3 (15 %)
Abnormal	8 (40 %)	7 (35 %)	1 (5 %)	8 (40 %)
Normal	12 (60 %)	13 (65 %)	19 (95 %)	9 (45 %)
Mean (SD)	3.87 (1.23)	8.94 (5.29)	56.2 (6.60)	33.02 (11.22)
Ulnar (n =20)				
In excitable	0 (0 %)	0 (0 %)	0	7 (35 %)
Abnormal	12 (60 %)	9 (45 %)	3 (15 %)	7 (35 %)
Normal	8 (40 %)	11 (55 %)	17 (85 %)	6 (30 %)
Mean (SD)	3.03 (0.53)	6.34 (4.76)	63.20(6.69)	32.03
Peroneal (n=20)				
In excitable	0 (0 %)	1 (5 %)	0	3 (15 %)
Abnormal	9 (45 %)	10 (50 %)	2 (10%)	8 (40 %)
Normal	11 (55 %)	9 (45 %)	18 (90%)	9 (45 %)
Mean (SD)	5.11 (1.91)	4.63 (3.08)	47.00 (7.13)	56.83 (22.05)

n= number of nerves studied.

The most common abnormalities detected in the first nerve conduction study were the prolonged F- wave latency (35- 40 %) **/** in-excitable F- waves (15 -35 %) and prolonged distal motor latency (range from 40 - 60 %) in both the upper and lower limb nerves. Around 40 to 50 % of nerves showed a decrease in the CMAP amplitude. The conduction velocities showed abnormalities only in 10- 15 % of the nerves. Majority of the abnormalities were picked up in the ulnar nerves.

16) Results of the **second nerve conduction study (motor nerves)** in patients with Guillain - Barre Syndrome –

Nerve	Distal Latency (msec)	CMAP amplitude (mV)	CV (m/s)	F wave latency (ms)
Median (n=20)				
In excitable	4 (20 %)	4 (20 %)	4 (20%)	4 (20 %)
Abnormal	9 (45 %)	8 (40%)	4 (20 %)	9 (45 %)
Normal	9 (45 %)	8 (40 %)	12 (60 %)	7 (35 %)
Mean (SD)	5.18 (2.14)	6.78 (4.75)	40.85 (22.43)	34.87 (13.15)
Ulnar (n =20)				
In excitable	4 (20 %)	4 (20 %)	4 (20 %)	8 (40 %)
Abnormal	10 (50 %)	9 (45 %)	6 (30 %)	7 (35 %)
Normal	6 (30 %)	7 (35 %)	10 (50 %)	5 (25 %)
Mean (SD)	4. 17 (1.94)	4.90 (3.41)	42.75 (23.60)	34.71(16.84)
Peroneal (n=20)				
In excitable	4 (20 %)	4 (20%)	4 (20 %)	6 (30 %)
Abnormal	9 (45 %)	10 (50 %)	6 (30 %)	7 (35 %)
Normal	7 (35 %)	6 (30%)	10 (50 %)	7 (35 %)
Mean (SD)	6.72 (2.41)	2.78 (2.30)	32.10 (17.98)	59.86 (26.08)

n = number of nerves studied.

At the time of the second conduction study, in two patients all the motor nerves became in excitable. There was an increase in the mean distal motor latency in the rest of the nerves and more number of nerves showed a prolongation of the distal motor latency and F wave latencies compared to the first conduction. (This is as expected during the course of AIDP).There was a corresponding decrease in the mean compound muscle action potential amplitude in all the three motor nerves studied compared to that in the first conduction.

17) Results **of sensory nerve conduction abnormalities** (amplitude) in the first and second conductions: -

Nerve (SNAP)	Ist conduction (n = 20)	2 nd conduction(n= 20)
Median sensory		
In excitable	0	0
Normal	16 (80 %)	14 (70 %)
Abnormal	4 (20 %)	6 (30 %)
Mean (SD)	28.80 (12.23)	29.55 (21.93)
Ulnar sensory		
In excitable	0	0
Normal	17 (85 %)	15 (75 %)
Abnormal	3 (15 %)	5 (25 %)
Mean (SD)	20.85 (7.20)	22.15 (11.26)
Sural sensory		
In excitable	0	0
Normal	20 (100%)	19 (95 %)
Abnormal	0 (0 %)	1 (05 %)
Mean (SD)	25.05 (12.84)	20.90 (8.91)

n= number of nerves studied

There was greater involvement of the upper limb sensory conductions (more number of Median and Ulnar sensory action potential amplitudes were in the below normal range) compared to the lower limb sensory conductions (sural sensory action potential amplitude) in both the first and second study with a significant p- value (median to sural 1st conduction p = 0.037, 2 nd conduction p = 0.021) .

18) Results of **third nerve conduction study** in patients with Guillain Barre Syndrome. (number of patients studied is five)

Nerve	Distal Latency (msec)	CMAP amplitude (mV)	CV (m/s)	F wave latency (ms)
Median (n=10)				
In excitable	2	2	2	4
Normal	2	2	3	1
Abnormal	6	4	3	5
Mean (SD)	5.78 (1.87)	4.38 (3.65)	32.85	34.27 (14.25)
Ulnar (n =10)				
In excitable	2	2	2	5
Normal	0	3	2	1
Abnormal	6	5	4	4
Mean (SD)	4.62 (1.10)	2.56 (2.41)	40.64 (22.16)	35.73(16.84)
Peroneal (n=10)				
In excitable	2	2	2	5
Normal	0	2	3	1
Abnormal	6	4	5	4
Mean (SD)	6.82 (1.32)	2.46 (1.26)	26.10 (15.73)	59.74 (24.08)

Only five patients were followed up with a third nerve conduction study. Of these, two patients had completely in excitable motor nerves with sensory nerves being elicitable. There was a prolongation of the mean distal motor latency and reduced CMAP amplitude in the rest of the patients compared to the second study.

19) Analysis of conduction block across multiple segments of **Median nerve** in the first and second serial nerve conduction tests: -

Conduction block	1st study (n=20)		2nd study (n=20)	
Segments studied	Definite	Probable	Definite	Probable
Wrist / Elbow	2 (10%)	4 (20 %)	3 (15 %)	3 (15 %)
Elbow / Axilla	0	1 (5 %)	0	0

Though multiple segment stimulation was done including the axilla to Erb's point stimulation the proximal stimulation values were not used in the final analysis of conduction block due to the possibility of technical fallacies with Erb's point stimulation – especially in an intensive care setting. At the time of second study in two patients all the motor nerves became in-excitable while the sensory nerves were excitable. Hence there is an apparent decrease in the number of motor nerves showing conduction block in the second study.

20) Analysis of conduction block across multiple segments of the **Ulnar nerve** in the first and second serial nerve conduction tests.

Conduction block	1st study (n=20)		2nd study (n=20)	
Segments studied–	Definite	Probable	Definite	Probable
Wrist / Below elbow	4 (20 %)	1 (5%)	3 (15 %)	0
Below / Above elbow	8 (40 %)	0	2 (10 %)	3 (15 %)

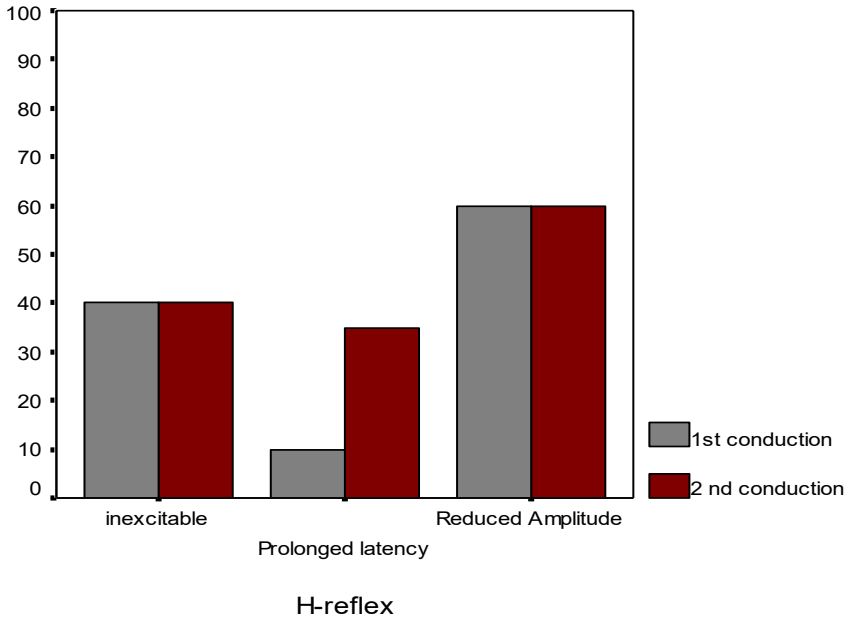
21) Analysis of conduction block in the **peroneal nerve** in the first and second conduction:-

	1st study (n=20)		2nd study (n =20)	
	Definite	Probable	Definite	Probable
Conduction block	6(30%)	3 (15%)	10 (50 %)	1 (5 %)

22) Patterns of H - reflex abnormality in the study group:-

	1st study (n =20)	2nd study (n=20)
In- excitable	8 (40 %)	8 (40 %)
Reduced amplitude	12 (60 %)	12 (60 %)
Prolonged latency and Reduced amplitude	2 (10 %)	7 (35 %)

(Reference value - prolonged latency - > 35 ms. Reduced amplitude reference value < 3.7 mv).



The amplitude of the H - reflex response was grossly reduced in all the ten patients bilaterally in both studies and there was no response to stimulation in eight of the studied responses.

23) Analysis of Phrenic nerve conductions in the first and second study:-

The phrenic nerve latencies and amplitude were studied in the ten patients. The upper limit of normal latency was taken as 8.4 ms and the lower limit of normal amplitude was taken

as 300 microvolt. Though a total of five patients showed conduction abnormalities in the unilateral or bilateral latency or amplitude variables, of these only two patients required ventilatory support.

Phrenic nerve conduction abnormalities	1st study (10 pts)	2nd study(10pts)
Prolonged latency - U/L	2	1
Prolonged latency - B/ L	2	2
Reduced amplitude - U/L	1	0
Reduced amplitude - B/L	0	2
Prolonged latency & reduced amplitude –B/L	0	0
No response - B/L	1	1

The first patient was intubated and ventilated within one hour of admission. He had no response to phrenic stimulation bilaterally in the first study. He was weaned off the ventilator after nine days and in him the phrenics became excitable with reduced amplitude and prolonged latency at the time of the second conduction(9^{th} day).In the second patient the phrenic nerve stimulation showed only prolonged latency bilaterally in the first study. He was intubated on the fourth day after admission following breathing difficulty and arterial blood gas analysis showed carbon dioxide retention. Phrenic nerves became totally in excitable in the second conduction and he was on ventilatory support for 110 days. The motor nerves as well as the phrenic nerves were totally in-excitable during this period. The phrenic nerves became excitable (on one side on 100^{th} day) and he was gradually weaned off the ventilator.

24) **Blink reflex abnormality**: -

Of the ten patients in the first study only one (patient no- 3) had evidence of blink reflex abnormality in the form of prolonged ipsilateral and contralateral R 2 latency with bilateral

involvement. In the second conduction, two patients (patient 3 and 7) had evidence of bilateral blink reflex abnormality. (None had unilateral abnormality in either of the two studies).

25) **Femoral nerve conductions**: -

The femoral nerves were excitable in all the patients studied (only eight patients studied). The latencies were within normal limits but there was gross asymmetry between the amplitudes between the right and the left sides in four of these patients in the first conduction. Two patients had femoral nerve stimulation done only on one side due to the placement of the femoral catheter line for plasmapheresis.

In one of these patients the femoral nerve response showed significant increase in amplitude in the second study as the patient started improving in motor power while there was no improvement in the other parameters. In patient no: - 5 the femoral nerves which were excitable in the first conduction however became in- excitable in the second conduction (along with the other motor nerves).

26) **Root stimulation**: -

Cervical root stimulation (C8) and recording was done on the abductor digiti minimi muscle in one of these patients and it showed the presence of definite conduction block – decrease in the CMAP across the axilla to root segment. (print out added in the annexure)

27) **Sympathetic skin response**: -

Of the ten patients in the study group, eight patients underwent sympathetic skin response testing as a part of autonomic function test evaluation. The Sympathetic skin response was absent in both the upper and lower limbs in five of the eight patients.

28) **Summary of the proximal conduction abnormalities in the study group in the first and second conduction** –

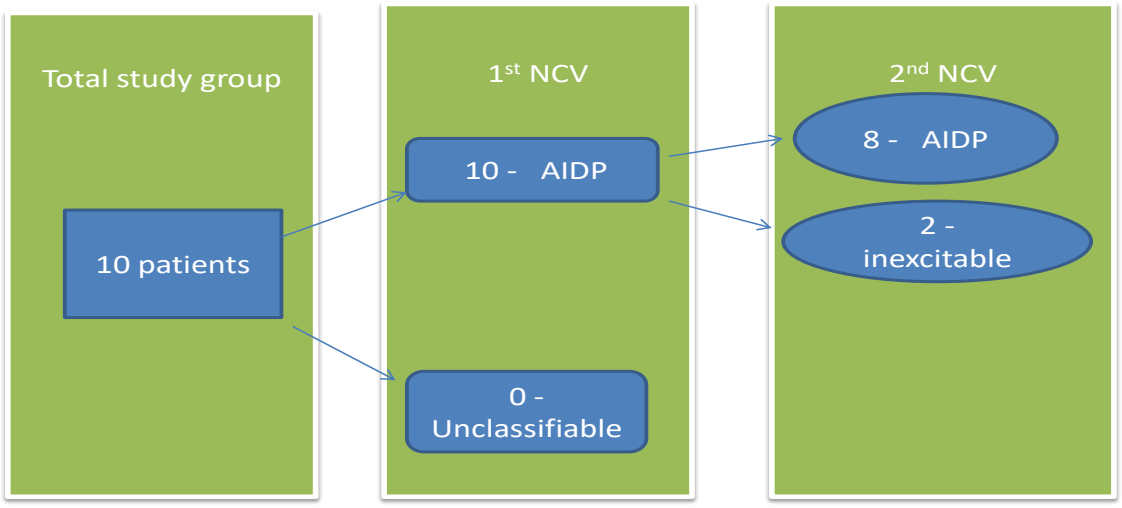
Parameters			1st study	2nd study
H – reflex abnormalities			100 %	60 %
F – waves - upper limbs		Median	55 %	45 %
		Ulnar	70 %	55 %
F –waves - lower limbs - Peroneal			55 %	45 %
Blink reflex			10 %	20 %
Conduction blocks	Median	Wrist / elbow	30 %	30 %
		Elbow / axilla	5 %	0 %
	Ulnar	Wrist / below elb	25 %	15 %
		Across elbow	40 %	25 %
	Peroneal		45 %	50 %
Femoral response(8 pts studied)			50%	
Phrenic Nerve stimulation			50 %	50 %

The most common abnormalities in the first conduction were H- reflex and F- wave parameters. (In the second conduction as two patients showed complete in-excitability of the motor nerves these abnormalities could not be commented upon in these patients.) The femoral nerve stimulation also showed significant abnormality (with asymmetrical amplitude) suggestive of proximal involvement.

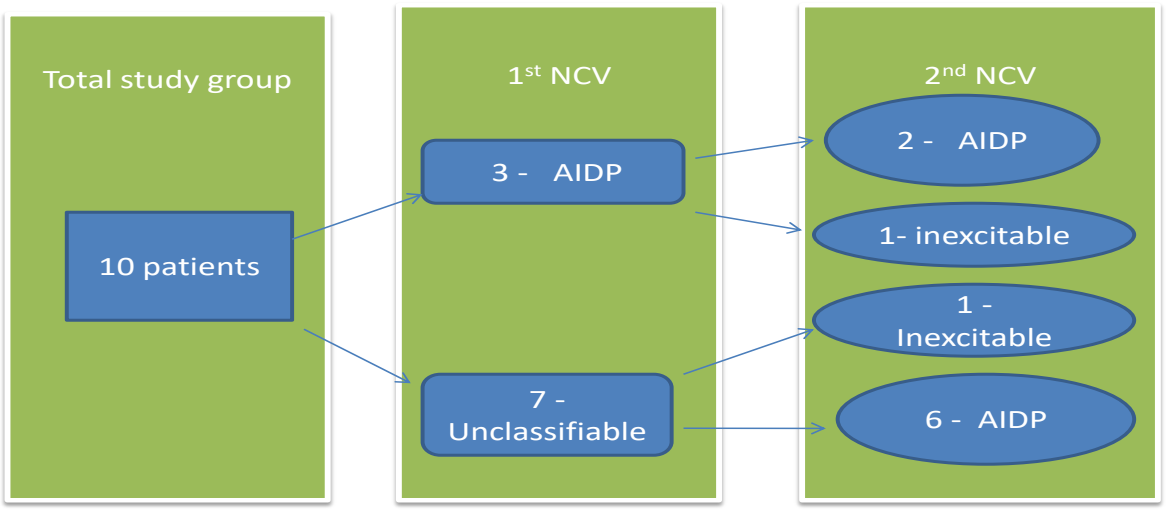
29) **Needle EMG**: - Needle EMG of the APB and the Tibialis anterior was done in (patient No - 5 - who went on to require prolonged conduction) about two weeks into the illness (at the time of second conduction). The needle EMG showed moderate evidence of active denervation in the form of fibrillations and positive sharp waves. The corresponding nerve conduction test had showed that all the motor nerves were totally in-excitable.

30) Classification of the serial electrophysiological studies by the application of the five electrophysiological criteria:-

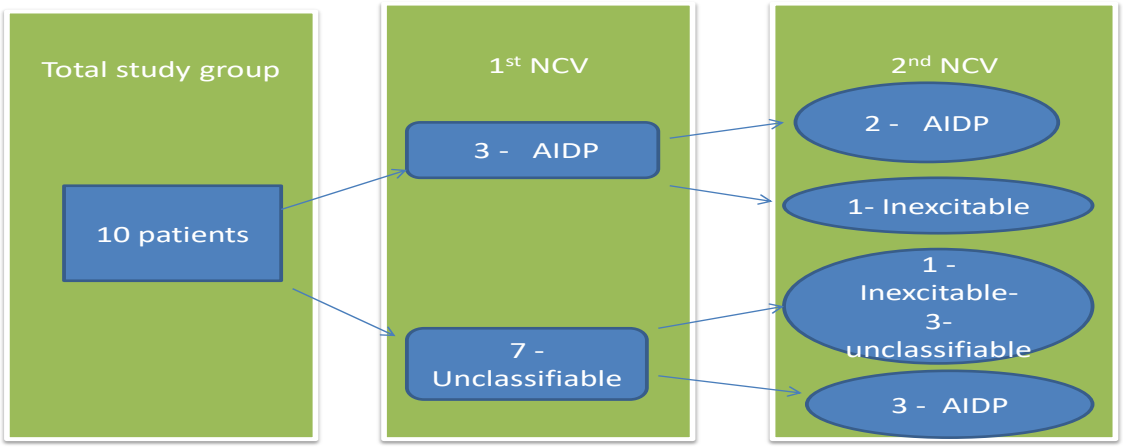
SET (I) Flow chart showing the **Alber's Criteria** applied to the first and second conduction:



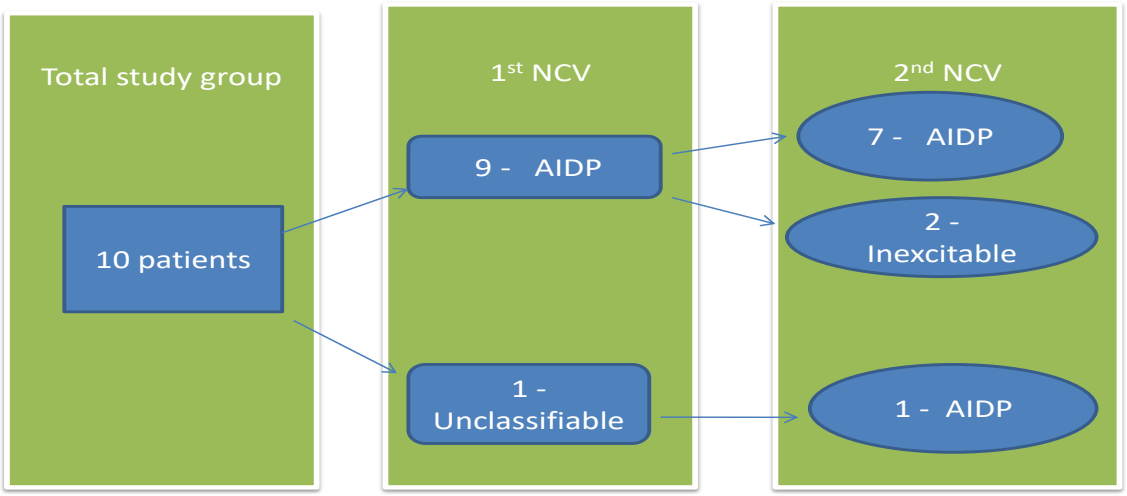
SET (II) Flow chart showing the **Alber's and Kelly Criteria** applied to first and second conduction :-



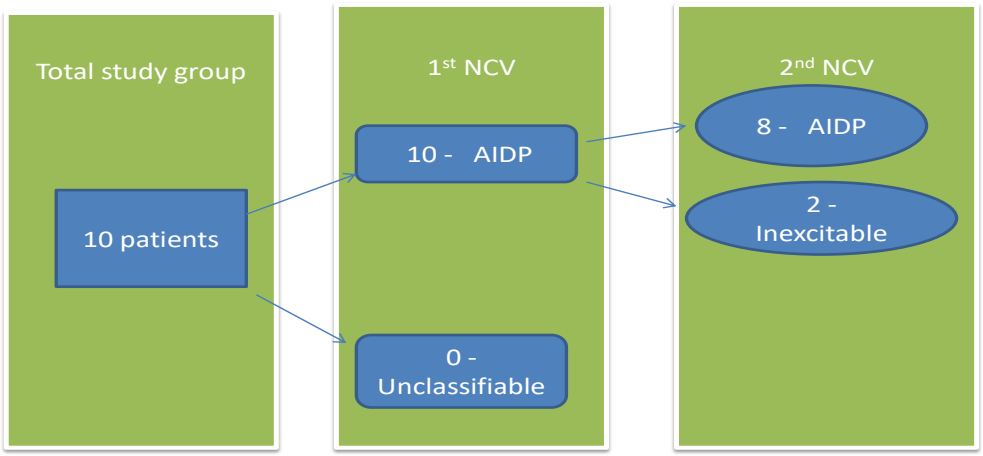
SET (III) Flow chart showing the **Cornblath criteria** applied to the first and second conduction :-



SET (IV) Flow chart showing the **Ho et al** criteria applied to the first and second conduction :-



SET (V) **Hadden's criteria** applied to the first and second conduction :-



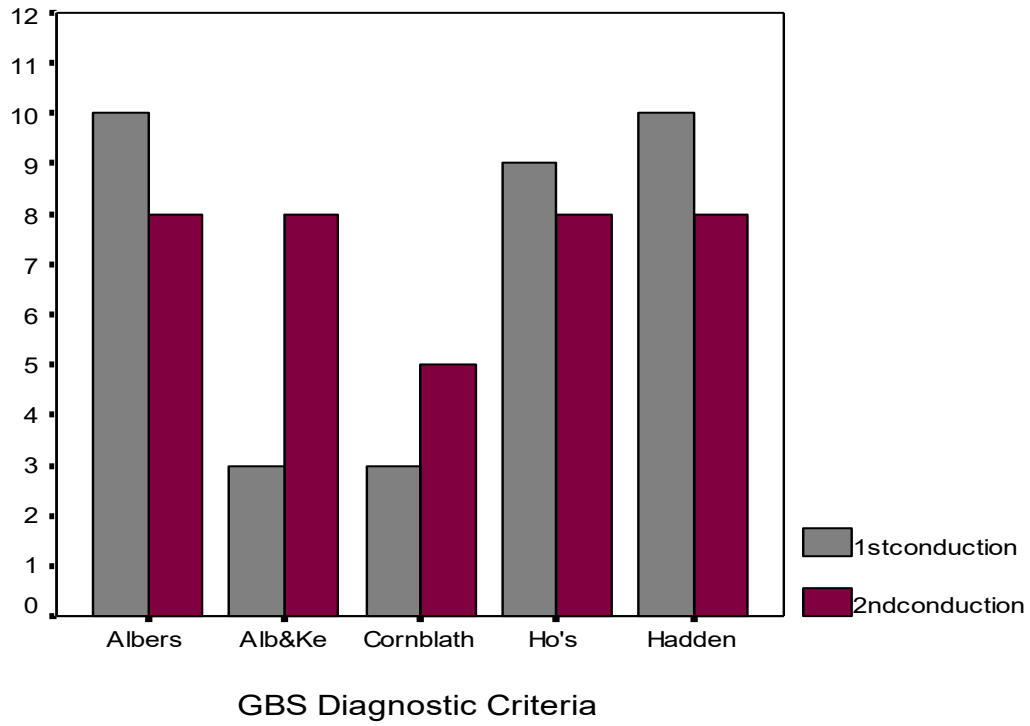
(VI) Sensitivity of the various criteria (in percentage) in the diagnosis of AIDP in the first, second and third conductions: -

Criteria	1st conduction (n = 10)	2nd conduction (n = 10)	3 rd conduction (n = 5)
Alber's criteria	100 %	80 %	80 %
Albers and Kelly	30 %	80 %	80 %
Cornblath criteria	30 %	50 %	60 %
Ho's criteria	90 %	80 %	80 %
Hadden's criteria	100 %	80 %	80 %

Two patients who initially satisfied the Alber's and Hadden's criteria at the first conduction progressed to completely in-excitable motor nerves at the time of the second conduction. Otherwise the rest of the eight patients satisfied the various criteria for AIDP except Cornblath's criteria in the second conduction. Only five patients were followed up in the third week conduction (of these one patient had in-excitable motor nerves. The

second patient with in excitable nerves was discharged at request).Analysis again showed high sensitivity with all the criteria except Cornblath's criteria.

Figure: - Comparison of the various criteria applied to the first and second conduction. (Third conduction not shown as only five patients were studied)



One of the two patients with completely in-excitable motor nerves in the second conduction (with rapid progression to nadir with no significant response to treatment with plasmapheresis); also had evidence of active denervation in EMG in the second study and it was taken as being suggestive of an axonal pathology. (Acute motor axonal neuropathy-AMAN).In the other patient needle EMG was not done at the time of the second conduction and hence cannot be classified as AMAN with accuracy. In these patients the first conduction had shown evidence of conduction block and fulfilled the criteria for AIDP. However both patients had antecedent history of diarrhoea and both did not have significant facial nerve involvement. Both these patients had poor response to treatment.

DISCUSSION

Various studies have shown that the diagnostic yield of the different electrophysiological criteria may vary in the different subtypes of Guillain- Barre syndrome, whose prevalence varies in the different geographical areas of the world. The percentages of patients diagnosed with demyelinating and axonal Guillain- Barre syndrome has been found to vary substantially in different published series. This may be attributed to the following factors - genetic susceptibility, different triggering factors, electrophysiological criteria used and whether the electrodiagnosis was based on a single study or serial studies. Majority of the published studies are cross sectional studies.

In this study, we have done serial conductions in ten patients who presented within the first week of onset of symptoms – either till they improved by one grade or till four weeks. Thus, in the group studied all ten patients had at least two conductions with a minimal interval between the studies of seven days and five patients had at least three conductions with the mean interval being twenty days after the onset of symptoms. We had done nerve conduction studies in all four limbs as it has been shown to increase the diagnostic yield and helps in classifying the GBS patients.

In this study, the bilateral median and ulnar nerves were stimulated at multiple points to assess for the presence of conduction block across the various segments and attempted to stimulate as proximally as possible – Erb's point stimulation. We also analysed the utility of other proximal segment stimulation – like H reflex, F waves, blink, facial and femoral and saphenous conductions.

Motor nerve conduction studies

Distal motor latency: - In our study, in the initial nerve conduction study done into the first week of illness, 40 - 60 % of nerves showed a prolonged distal motor latency [median (40 %), ulnar (60 %) and peroneal (45%)]. This is in comparison to the study by Gordon et

al,[52] where in a retrospective analysis of 31 patients who presented in the first week of GBS, evaluation showed that the distal latency was prolonged in at least one nerve in 65 % of patients.(in multiple nerves in 45 % patients and in just one nerve in 19 %).

In the second conduction study, while in two patients all motor nerves became in-excitable, the percentage of nerves showing prolonged distal motor latency were median (45 %), ulnar (50 %), peroneal (45 %). Cornblath et al,[90] in a study of 34 adult patients evaluated within four weeks of onset of illness detected that 57 % of nerves had a prolonged distal latency.

Conduction Block: -

In the case of median nerve stimulation, it was detected that almost 30 % of nerves had evidence of conduction block (10 % definite and 20 % probable) in the first study when the results of stimulation at the wrist and elbow points were compared and another 5 % of nerves had definite block in the elbow to axilla segment. While in the second study, 30 % (15 % definite and 15 % probable) showed block only in the wrist to elbow segment.

It has to be taken into account that in two patients (i.e. four median nerves) became in-excitable at the time of the second conductions. Gordon et al[52] in a study of 31 patients reported an incidence of 13 % conduction block in the first week of GBS, however multiple segment stimulation was not done in this study .

In the case of ulnar nerve stimulation, in the first study 40 % of nerves showed evidence of definite conduction block across the elbow segment in the first week. However, in the second study, the prevalence of the across elbow segment conduction block reduced to 25 % (10 % definite and 15 % probable). In comparison, the analysis of the wrist to below elbow segment, showed that 25 % had evidence of conduction block (definite (20 %) +

probable (5 %)) in the first week while 15 % showed definite block in the second study. Since the majority of our patients with conduction block could move their arms freely at the time of the first electrophysiology study, it is unlikely that all the conduction blocks were due to nerve compression.

It has been reported by several investigators that the conduction abnormalities in GBS tend to be present at the distal nerve terminals, nerve roots and common entrapment sites of the peripheral nerves, where the blood-nerve barrier is thought to be relatively deficient or weak.[55] Conduction blocks across the elbow segment were present in the majority of the patients with GBS when the examinations including the elbow segment were done. These findings were also detected in this study and showed that the conduction abnormalities at the common entrapment sites are a characteristic neurophysiologic feature observed in Guillain-Barre syndrome. One of our patients underwent a C8 root stimulation which again showed evidence of definite conduction block.

In our study, the highest frequency of conduction block was detected in the ulnar nerves followed by the peroneal and median nerves.

Ropper et al,[92] in a study of 113 patients evaluated in the first three weeks of illness detected isolated proximal conduction block alone in 27 % of patients and proximal associated with a distal lesion in another 27 %.(However in this study by Ropper et al, the involvement of the F- waves was taken as suggestive of a proximal conduction block.)

Cornblath et al,[90] in a study of 112 adult nerves evaluated within the first four weeks of illness detected that 26 % had evidence of partial conduction block.(Here, partial conduction block was defined as >20 % reduction in the peak to peak amplitude or the negative peak area).

In a study of conduction block in Acute motor axonal neuropathy, Uncini et al [4] (done in two weeks of onset of illness) detected that twelve of the 18 patients (67%) had probable or definite conduction block. With respect to the forearm segments, conduction block was definite for one patient (6%) in the median nerve, probable for two patients (11%) in the median nerve and for three patients (16%) in the ulnar nerve. A common entrapment site (across the elbow segment of the ulnar nerve) showed definite conduction block in seven patients (39%) and probable conduction block in two patients (11%). In four of these seven patients, bilateral definite conduction blocks were observed. The time from disease onset in the first study of the 12 patients with AMAN who had conduction block (median 3 days, range 2–8 days) was similar to that in the six who did not (median 5 days, range 3–11 days,). On sequential evaluation, rapid resolution was found in seven (58%) of the 12 patients who had probable or definite conduction block.

CMAP amplitude –

In our study, there was a decrease in the CMAP amplitude in 35- 50 % of nerves in the first week. [median (35 %), ulnar (45 %) and peroneal (50 %)]. Gordon et al, [52] reported reduced CMAP amplitude in 71 % of patients in the first week. In the second conduction study, after excluding the four motor nerves which became in- excitable, the decrease in the CMAP amplitude was seen in median (40 %), ulnar (45 %) and peroneal (50 %).

Proximal Conductions:-

The analysis of the proximal conductions showed the findings of absent H- reflex response in 40 %, reduced amplitude in 60 % in the first conduction – i.e. 100 % of patients showed abnormality. This is similar to other studies reflecting these findings as one of the early abnormalities in GBS. Gordon et al,[52] reported that the H-reflex was absent in 30 patients (97%).

F- wave abnormalities, were picked up in the first conduction in around 55- 70 % of the nerves studied. (Ulnar -70 %, Median –55 % and peroneal 55 %). Gordon et al, [52] reported that F- waves were abnormal in 84% in the first week of illness.

In the second conduction study while four motor nerves became in-excitable, isolated F-wave in-excitability was seen in 20 % of median and 10 % of nerves. Cornblath et al,[90] in a study within four weeks of illness reported that 64 % of adult nerves (n= 86) had abnormal F -wave latencies.

Blink Response:-

The blink reflex study showed that only one patient (10 %) had abnormality in the first study while two patients (20 %) had abnormality in the second study. Kimura et al,[93] had reported almost 50 % of patients with AIDP having blink reflex abnormality. Ropper et al [92] in 1990, in a study of 113 patients reported an abnormal blink reflex in 46 % of patients and all except one patient had facial weakness either symmetric or asymmetric.

Sensory conductions :-

The presence of sensory conduction abnormalities in the median nerves with relatively preserved sural SNAP s' as described by several authors was also detected in this study. In the first conductions 20 % of patients had an abnormal median SNAP s' with absolutely preserved sural SNAP s', while this increased to 30 % in the second conduction.

Gordon et al,[52] reported that SNAP in the upper extremity was of low amplitude or un-recordable in 19 of 31 patients (61%) in the first week. Kuwabara et al [72], analysed the sensory conductions in 59 patients with GBS and detected abnormality in 86 % of AIDP (26 patients) and only in 6 % of AMAN (33 patients).

Phrenic nerve conduction: -

Abnormalities of the phrenic nerve conductions (mostly unilateral) were seen in 50 % of the ten patients. However only two patients (20 %) had bilateral abnormalities and required mechanical ventilation. Bilateral abnormalities of the phrenic neve conductions can be early predictors of necessity for mechanical ventilation.[94]

Sympathetic skin response: -

The SSR response was absent in both the upper and lower limbs in five of the eight patients studied (60 %). Of these four were classifiable as AIDP and one as Axonal. Ropper et al [92] analysed the SSR in 23 patients had detected it to be absent in 4 (17 %) patients.

COMPARISON OF ELECTROPHYSIOLOGICAL CRITERIA: -

In our study, for the first electrophysiological test done in the first week of onset of symptoms the sensitivity of the various criteria (Set I to Set V) in diagnosis of Guillain Barre syndrome - AIDP - ranged between 30 and 100 % , with higher sensitivity of set I (Albers - 100 %) , set IV (Ho's criteria- 90 %) and set V (Haddens- 100 %). It was noted that the sensitivity of the various sets of electrophysiological criteria was irrespective of the clinical presentation of GBS (i.e. pure motor, sensorimotor). The difference in the sensitivity of different electrophysiological criteria in the same patient population may be attributed to the difference in the requirements of number of demyelinating features, the number of nerves with demyelinating features and definition of conduction block. In set I, IV and V for fulfilling the criteria, requires the presence of only one demyelinating feature (prolonged distal latency, conduction block, dispersion, slowed conduction velocity, prolonged F-wave latency) in two nerves. However set II (Albers and Kelly) and set III (Cornblath) requires three of these demyelinating features in at least one to two nerves.

In an Indian study, by Kalita et al [57] (cross sectional study) of 51 GBS patients, of whom 25 patients had presented in the first week of the onset of symptoms, the sensitivity was 88 % with Albers criteria (Set I), 48 % with Albers and Kelly's criteria (Set II), 32 % with Cornblath criteria (Set III) and 88 % with Ho's criteria (Set IV). In the second electrophysiological test done in our study group it was found that the motor nerves were totally in-excitable in two patients and the sensitivity of the various criteria in the diagnosis of AIDP ranged from 50 % to 80 %. The sensitivities were as follows 80 % (set I), 80 % (set II), 50 % (set III) ,80 % (set IV), 80 % (set V) .

In the study by Uncini et al,[4] a comparison was made between two serial electrodiagnostic tests done at least four weeks apart in the same group of 55 patients. At the first test the electrodiagnosis was identical with both criteria (Ho and Hadden) - 65 – 67 % of patients were classifiable as AIDP, 18 % were classifiable as Axonal GBS and 14 – 16 % was equivocal. However at follow up, there was a change in the classification in 24 % of patients. AIDP decreased to 58 %, axonal GBS increased to 38 % and equivocal patients decreased to 4 %. It was noted that the majority of shifts were from AIDP and equivocal groups to axonal GBS. The main reason was that by serial recordings it was recognised that reversible conduction failure and length dependent compound muscle action potential amplitude reduction patterns were an expression of axonal pathology.

LIMITATIONS OF THE STUDY:-

The sample size is small, which is one of the main constraints of the study.

In view of the above findings, this study with its limitations stresses the need for looking at longitudinal nerve conduction studies in a larger group of patients to further characterise better the incidence and pattern of electrophysiological subtypes and the change in the yield of the various published criteria.

CONCLUSIONS

1) The most common abnormality in the first electrophysiological study conducted in the first week of illness was the H- reflex abnormality (100 %).

2) The yield of the other conduction parameters in the first conduction study were as follows:-

a) F- waves - in- excitability and prolonged latency. (55 – 70 % of nerves)

b) Phrenic nerve conductions – 50 %

c) Conduction blocks - 35 to 65 % of nerves.

d) Femoral nerve conductions' - abnormal in 50 % of nerves studied.

e) Sensory conductions – abnormal in 15 to 20 % of upper limb nerves.

3) Multiple segment stimulation helps in the detection of a higher percentage of conduction blocks in patient with GBS. The order of nerves with decreasing frequency of conduction blocks is as follows: - Ulnar (65%) > Peroneal (45%) > Median (35%).

4) Sequential conduction in Guillain- Barre syndrome results in a change in the electrophysiological classification varying from 20 % to 50 % depending on the criteria used.

5) Some of the motor nerves showing early conduction blocks (20%) showed evidence of axonal degeneration on serial conduction studies and this may indicate an electrophysiological feature of acute motor axonal neuropathy.

6) Sensory conduction abnormalities are more common in the upper limb nerves than in the lower limbs (abnormal median / normal sural) and is statistically significant.

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PATIENT INFORMATION AND INFORMED CONSENT

I understand that the department of Neurological sciences is conducting a study to –

(1) To evaluate the utility of multiple segment stimulation in nerve conduction studies and proximal conductions in patients with Guillain – Barre syndrome.
(2) To determine whether multiple segment stimulation of nerves helps in the early detection of conduction block in patients in the first week of illness compared to routine conductions.

Nerve conduction study is the standard diagnostic electrophysiological test for the diagnosis of the disease condition – Guillain- Barre syndrome with which I / (my patient) have been admitted in the hospital. I understand that in this study, the nerves will be stimulated at multiple points and studied for any abnormality.

The study also involves collection of patient information – clinical data, findings of clinical examination and test reports done as part of regular clinical care. I understand that some of the tests done in connection with the study may directly benefit me / my patient whereas the other tests are likely to benefit other patients with the disease.

I understand that my withdrawal from the study, at any time will not affect the treatment being given.

Study Title: **Utility of multiple segment stimulation in nerve conduction studies in Guillain-Barre syndrome**

Serial Number: _____ Subject's Name: _____
Date of Birth / Age:_____

Please initial box

(Subject)

(i) I confirm that I have read/ have been explained to in my own language and have fully understood the information sheet for the above study and have had the opportunity to ask any questions that I had. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator'sName: Dr Ajith.M / Dr.MathewAlexander _____

Signature of the Witness:

_____

GLOSSARY

– coding for the data in the data sheet

Sex – Female (1) ; Male (2)

Presence of Risk Factors – Diarrhoea – Yes (1), No (0)

- Upper respiratory infection – Yes (2) , No (0)
- Vaccination - Yes (3) , No (0)
- Viral Fever - Yes (4) , No (0)

Facial and Bulbar weakness – 0 – absent,

1 - mild involvement

2 – moderate involvement.

3 – severe weakness

Tone - 1 – hypotonia , 2 – normal tone.

Power (coding – modified MRC grading)

- 0 – 0 , 1 - 1, 2 – 2, 3 – 3 , 4 – 4, 5 – 4-, 5 – 4 , 6 – 4+, 7 - grade 5

ANNEXURES
DATA COLLECTION PROFORMA

GUILLAIN BARRE SYND

Name:	**Address:**
Hospital Number:	**Telephone/E-mail:**
Dob: **Age:**	**Seen by:**
M/F	**Date:** **Time:**
	Serial number

History Date of diagnosis::

History Days since onset of symptoms:: 1 week ( ) 2 weeks ( )
3 weeks( ) 4 weeks ( )

Preceding history :- Diarrhoea ( ) URI ( ) Vaccination ( )

– code - diarrhoea –yes – 1 , URI – yes - 2 , Vaccinat – yes - 3
No - 0 No - 0 No - 0

Co-morbidities :

Hypertension	Y□ / N□	Diabetes	Y□ / N□
Smoking	Y□ / N□	Hypercholesterolaemia	Y□ / N□
IHD	Y□ / N□	Alcohol	Y□ / N□
PVD	Y□ / N□	Obesity	Y□ / N□
Chronic diarhea	Y□ / N □	Organo phos exp	Y□ / N□
Renal failure	Y□ / N□	Vegetarian	Y□/ N□
Native medication	Y□ / N□	Other toxins	Y□ / N□

General Examination:

Temp: Pulse:- reg/irreg
Blood pressure: lying:- sitting :- /

Height: weight: BMI :

CVS Abdo: Chest:

Coding of Symptoms:

Sensory Parasthesia	1 .Symptoms limited to fingers or toes 5- trunk involvement	2 .Symptoms extend to above knee with involvement of hands 6 – Face involvement	3. Symptoms extend to above knee or elbow	4. Symptoms above knees or elbows/ trunk
Sensory loss	1 Symptoms limited to fingers or toes 5- Trunkal involvement	2 Symptoms extend to ankle or wrist 6- face involvement	3 Symptoms extend to knee or elbow	4 Symptoms above knees or elbows
pain	1 .Symptoms limited to fingers or toes	2 .Symptoms extend to ankle or wrist	3. Symptoms extend to knee or elbow	4. Symptoms above knees or elbows, or functionally disabling
Type of pain	1 Burning type	2 Pricking type		
Motor	1 Difficulty in hand grip	2 Difficulty in combing, reaching up to shelf	3 Difficulty in turning in bed	4 Bulbar symptoms
	5 Difficulty in gripping foot wear, footwear slipping of with knowledge	6 Twisting of ankle, buckling of knee	7 Difficulty in getting up from squat	8 Complete paralysis
Bladder	0 absent	1- Hesitancy	2- urgency , urge incontinence	3 – transientetention

Symptoms **Duration of symptoms:**

	Week 1	week 2	week 3	week 4
Paresthesias				
Pain				
Pain type				
Sensory loss				
Motor				
Bladder				

HUGHES GRADING :- -- ------

GRADE 0 :- Normal
GRADE 1 :- minimal signs and symptoms , able to run
GRADE 2 :- ambulates independently
GRADE 3 :- able to walk 5 metres with aid
GRADE 4 :- bed bound
GRADE 5 :- requires mechanical ventilation
GRADE 6 :- dead

Neurological examination:

Cranial Nerves

0 = normal , 1 = abnormal

Cranial nerves	week 1	week 2	week 3	week 4
Fundus				
EOM				
Trigeminal				
Facial				
9, 10				
Sternomastoid				
Tongue				

Motor Examination

Bulk and Tone

WASTING	week 1	week 2	week 3	week 4
EDB				
Tib Ant				
Gastronemius				
Quadriceps				
Hand muscles				
Tone				

WASTING :- yes – 1 , no – 2

TONE :- 0 = normal, 1 = decreased , 2 - increased

Motor Examination

Power

	week 1		week 2		weeek 3		week4	
Power	R	L	R	L	R	L	R	L
Neck flx								
Neck ext								
Trunk								
Should Ab								
Should Add								
Elbow Flx								
Elbow Ext								
Wrist Flx								
Wrist Ext								
Hip Flx								
Hip Ext								
Knee Flex								
Knee Ext								
Dorsiflx								
Plantarflx								

MRC Grading
0 No movement
1 Flicker
2 Movement not against gravity
3 Movement against gravity
4 Against resistance
5 Normal

Reflexes

	week 1		week 2		week 3		week 4	
Reflexes	R	L	R	L	R	L	R	L
Biceps								
Brachiorad								
Triceps								
Knee								
Ankle								
Sup abd								
plantar								

Reflex Grading
0 Absent
+/- Present with reinforcement
+ Decreased
++ Normal
+++ Increased
C With clonus

Investigations

Hb		**Urine porphobilinogen**	
TC		**Ca**	
DC		**Phosp**	
Platelets		**Na**	
ESR		**K**	
AC		**Total protein**	
PC			
Creat			

Electrophysiology

	week1	week2	week3	week4
NCV				
EMG				
phrenic				
Con.bloc				

0 = normal, 1 = abnormal

Type of Neuropathy : AIDP /AMSAN/ AMAN

CSF – TC
DC
SUGAR
PROTEIN

BBVS :-