GUILLAIN-BARRÉ SYNDROME-PREDICTORS OF OUTCOME

Thesis
Submitted in partial fulfilment of the rules and regulations for the requirement of the degree of

DM in Neurology

Dr. PAUL J ALAPATT
DM Neurology Resident
2015-2017

DEPARTMENT OF NEUROLOGY
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM – 695011, India
DECLARATION

I Dr. Paul J Alapatt, hereby declare that the project in this book was undertaken by me under the supervision of Dr. Muralidharan Nair, Professor Senior Grade and Head of Department of Neurology and Dr. Abraham Kuruvilla Professor, Department of Neurology, Sree Chithra Tirunal Institute for Medical Sciences and Technology, Thiruvanthapuram

Date:

Paul J Alapatt
Senior Resident
Neurology

Forwarded

The candidate, Dr. Paul J Alapatt, has completed the project under my guidance

Dr. Muralidharan Nair
Professor Senior Grade &
Head of the Department
Department of Neurology
SCTIMST, Thiruvananthapuram

Dr. Abraham Kuruvilla
Professor
Department of Neurology
SCTIMST, Thiruvananthapuram
Forwarded

The candidate, Dr. Paul J Alapatt, has carried out the minimum required project.

Thiruvananthapuram

Dr. Muralidharan Nair

Date:  

Professor and Head  
Department of Neurology
ACKNOWLEDGEMENT

I take this opportunity to express my sincere gratitude to Dr. Muralidharan Nair, Professor Senior grade and Head of Department of Neurology, SCTIMST and Dr. Abraham Kuruvilla, Professor of Neurology, my guides for the study, for their expert guidance, constant review, kind help and keen interest at each and every step of the study.

I express my sincere gratitude to Dr. Sruthi S Nair, Assistant Professor of Neurology, SCTIMST for her valuable input and assistance to the study.

I express my sincere thanks to Dr. Sakara Sarma, P, Professor and Dr. Jissa V.T, Scientist, Achutha Menon Centre for Health Sciences for helping me with the statistical analysis of the study.

I am extremely thankful to the staff of Neurology department, Nursing staff in Neuro-medical ICU and Neurology wards, medical records department and my colleagues for helping me during the study.

Last but not the least, I thank all the patients, relatives and primary caregivers who willingly participated in this study.
## INDEX

<table>
<thead>
<tr>
<th>SL NO.</th>
<th>CONTENTS</th>
<th>PAGE NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>REVIEW OF LITERATURE</td>
<td>4</td>
</tr>
<tr>
<td>3.</td>
<td>AIMS AND OBJECTIVES OF THE STUDY</td>
<td>35</td>
</tr>
<tr>
<td>4.</td>
<td>MATERIALS AND METHODS</td>
<td>37</td>
</tr>
<tr>
<td>5.</td>
<td>RESULTS</td>
<td>40</td>
</tr>
<tr>
<td>6.</td>
<td>DISCUSSION</td>
<td>70</td>
</tr>
<tr>
<td>7.</td>
<td>CONCLUSIONS</td>
<td>80</td>
</tr>
<tr>
<td>8.</td>
<td>BIBLIOGRAPHY</td>
<td>82</td>
</tr>
<tr>
<td>9.</td>
<td>ANNEXURE</td>
<td>97</td>
</tr>
</tbody>
</table>

A. ABBREVIATIONS  
B. ETHICS COMMITTEE LETTER  
C. STUDY PROFORMA  
D. PLAGIARISM CHECK REPORT
INTRODUCTION
Introduction

Guillain Barre Syndrome (GBS) is an acute, self-limited, inflammatory, autoimmune disorder of the peripheral nervous system triggered usually by a bacterial or viral infection or other antecedent events. It affects 0.9 to 2/100,000 persons in a year, with a worldwide distribution. Despite the availability of partially effective forms of treatment, outcome in patients with GBS has not significantly changed in the last two decades.\textsuperscript{1-4} Natural history studies show that about 10 to 20\% of patients remain severely disabled and about 5\% die.\textsuperscript{1-4}

One explanation for this apparent lack of improvement is the highly variable clinical course of GBS.\textsuperscript{4,5} Determinants of disease progression and recovery in GBS are still poorly understood. GBS consist of distinct pathogenic subgroups in which disease onset and progression is influenced by different types of preceding infections, anti-neural antibodies and genetic polymorphisms.\textsuperscript{4-6} Optimal treatment of individual patients may depend on the pathogenesis and clinical severity.\textsuperscript{1-6} Patients with severe forms of GBS may need more intensive treatment to recover. Other patients show a complete recovery after standard therapy and in these patients more aggressive forms of treatment may only induce more side effects. Selective additional treatment of patients with poor prognosis would require data that accurately predict the outcome in individual patients.\textsuperscript{4,5} Such data ideally should be based on clinical and electrophysiological predictors acquired in the acute phase of disease, when immunomodulatory treatment is considered to be most effective. Prognostic models could help to guide selective trials with more effective, but potentially hazardous drugs.
Previous studies indicate that outcome in GBS depends on a defined set of clinical, laboratory and electrophysiological features. Recently, in one of these studies a prognostic model was developed, the Erasmus GBS outcome score (EGOS), which was based on three clinical characteristics: age, presence of preceding diarrhoea, and GBS disability score at two weeks after admission. The EGOS relatively accurately predicts the chance of walking after six months. The EGOS provides a proof of principle that the variable outcome in GBS can be predicted in the acute phase of disease. Additional prognostic models have been developed to predict respiratory insufficiency and clinical course.

This study was undertaken to study the clinical and demographic profile of patients with GBS in our region and to identify determinants that can be used for early identification of patients with poor prognosis, which may ultimately translate into better management strategies for our patients.
REVIEW OF LITERATURE
**Review of Literature**

Guillain Barre syndrome is an acute immune-mediated paralytic polyneuropathy. It was first described in 1859, Jean-Baptiste Octave Landry when he described a case of ascending weakness preceded by fever, malaise and pain leading to death from respiratory failure. Subsequently Georges Guillain, Jean-Alexandre Barre´ and Andre Strohl reported two cases with similar clinical features, loss of tendon reflexes and albumonocytologic dissociation. The term Guillain Barre syndrome (GBS) defines a recognizable clinical entity that is characterised by rapidly evolving symmetrical limb weakness, loss of tendon reflexes, absent or mild sensory signs, and variable autonomic dysfunction. GBS has remained a descriptive diagnosis of a disorder for which there are no specific diagnostic tests. The combination of rapidly progressive symmetrical weakness in the arms and legs with or without sensory disturbances, hypoflexia or areflexia, in the absence of a CSF cellular reaction, remains the hallmark for the clinical diagnosis of GBS. Since the virtual elimination of poliomyelitis, GBS has become the leading cause of acute flaccid paralysis in western countries.\(^1\)\(^0\) The disease is thought to be autoimmune and triggered by a preceding infection in two thirds of cases, most frequently respiratory or gastrointestinal infections.\(^1\)!\(^1\)-\(^1\)\(^2\) This induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots.\(^1\)!\(^3\)-\(^1\)!\(^4\) There is molecular mimicry between microbial and nerve antigens which leads to the development of the disorder especially in cases of *Campylobacter jejuni* infection. However, the interplay between microbial and host factors that dictates if and how the immune response is shifted towards unwanted auto reactivity is still not well understood. Furthermore, genetic and environmental factors that affect an
individual’s susceptibility to develop the disease are unknown. Unwanted autoimmunity does not arise in most individuals (>99%) exposed to an immune stimulus as a result of Guillain-Barré syndrome associated infections such as C. jejuni. Many antecedent infections have been identified—including Campylobacter jejuni, cytomegalovirus (CMV), Mycoplasma pneumonia, Epstein-Barr virus, and influenza virus. Immunization and parturition have also been associated with GBS. GBS was thought to be a single clinical entity. However now GBS can be classified into four main clinical and electrophysiological subtypes such as acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motorsensory axonal neuropathy (AMSAN) and miller fisher syndrome (MSF). AIDP is characterized by demyelination, AMAN is limited to pure motor involvement and AMSAN is a more severe disease with motor-sensory involvement. Weakness can develop acutely or subacutely and reaches a plateau, with subsequent spontaneous resolution of paralysis.

The diagnosis of GBS remains descriptive. To facilitate epidemiological research and outcome assessments of therapeutic trials, a set of generally accepted clinical, laboratory, and electrodiagnostic criteria has been set forth, delineating the prevailing clinical presentation.

Epidemiology

Most of the incidence rates of GBS reported were between 1.1/100,000/year and 1.8/100,000/year with lower rates reported in children (<16 years) of 0.4/100,000/year to 1.4/100,000/year. Most of the studies are from Europe and North America where the rates found were similar. A number of studies have
commented on a bimodal pattern of incidence by age, with peaks occurring in young adults and the elderly. The majority of studies used the recognised NINCDS criteria or a comparable set of diagnostic criteria, and this allowed comparisons to be made between studies. GBS has been the subject of 35 population-based surveys from defined geographical areas of Europe, Australia, and North and Latin America during the past 40 years. In the past 20 years, accuracy of case ascertainment and collection have improved. All epidemiological studies, however, continue to be hampered by the absence of a reference diagnostic test that would allow a positive confirmation of the diagnosis. Nevertheless, most reports document similar figures for annual incidence. Such observations indicate that GBS occurs evenly throughout the western hemisphere, without geographical clustering and with only minor seasonal variations. GBS is known to occur at all ages, though it is rare in infancy. The incidence remains almost uniform below the age of 40, ranging from 1-3 to 1-9 per 100 000 annually. Most surveys show a slight peak in late adolescence and young adulthood, coinciding with an increased risk of infections with cytomegalovirus and Campylobacter jejuni, and a second peak in the elderly. A hospital record-based study from the USA, published in 1997, measured the annual incidence as 8-6 per 100 000 in people over the age of 70; GBS associated morbidity and mortality increased in parallel.

These observations require confirmation and remain unexplained. A failing of immune-suppressor mechanisms in elderly people has been postulated as an explanation for increased susceptibility to autoimmune disorders.
Preceding events

Antecedent infections

GBS is the prototype of a post infectious illness; two-thirds of patients report an antecedent, acute infectious illness, most commonly a respiratory-tract infection or gastroenteritis that has resolved by the time neuropathic symptoms begin. The interval between the prodromal infection and the onset of GBS symptoms varies between 1 week and 3 weeks, occasionally longer; it averaged 11 days in several large series. In many instances, the pathogen that caused the prodromal illness remains unidentified. Although various infections and events such as surgery have been put forward as possible triggers, the link with GBS is not firmly established and remains anecdotal.

C jejuni, a major cause of bacterial gastroenteritis worldwide, has become recognised as the most frequent antecedent pathogen for GBS. The association has been documented in many case reports and in 14 large series of GBS patients that were collected prospectively, together with appropriate case controls. Serological or culture evidence of a recent C jejuni infection ranged from 26% to 41% in series of sporadic GBS cases from the UK, the Netherlands, the USA, and Japan. This gastrointestinal pathogen was also strongly associated with an acute motor-axonal neuropathy variant of GBS observed in yearly summer epidemics among rural children in northern China. In a 2-year prospective study from Hebei Province, China, serological evidence of a recent C jejuni infection was found in 66% of GBS patients, as opposed to only 16% of village controls. Moreover, C jejuni infections
are also the most frequent trigger of the Miller Fisher syndrome, (MFS), a variant of GBS characterised by ophthalmoplegia, ataxia, and areflexia.\textsuperscript{26,27}

The organism may be cultured from stool for several weeks after the end of the diarrhoeal illness. In Japan, the majority of C jejuni isolates from GBS patients were of Penner serotype 19(HS-19). Those pathogens for which there is convincing and statistically valid evidence of an association with GBS are listed in the table. Cytomegalovirus infections, experienced clinically as upper respiratory-tract infection, pneumonia, or nonspecific flu-like illness, account for the most common viral triggers of GBS, ranging from 10\% to 22\% in several large series.\textsuperscript{17,20,22}

Cytomegalovirus is particularly common in young female GBS patients, and the clinical picture is notable for prominent involvement of the sensory and cranial nerves.\textsuperscript{17} Many such patients have high serum titres of antibodies reacting with GM gangliosides and with sulphated glycolipids.\textsuperscript{29-31} The specificity of such antibodies and their significance for the pathogenesis of GBS remains unknown. Associations of GBS with Epstein-Barr virus (10\%) or varicella zoster virus are more common than in matched populations. The association of GBS and HIV-1 is well recognized and occurs usually around the time of seroconversion.\textsuperscript{32} Clinical presentation does not differ from ordinary AIDP; lymphocytic pleocytosis in the cerebrospinal fluid should raise suspicion of HIV-1 infection, prompting the search for confirmation.
GBS and vaccine

Several anecdotal case reports or small case series have linked GBS to vaccinations on the grounds of a mere temporal association, but no causal relation has been established and potentially confounding coincidental infections were not ruled out. There is, however no doubt that rabies vaccine prepared from the infected brain tissues of adult animals carried an increased risk of inducing GBS, probably because of contamination with myelin antigens. Controversy surrounded the alleged association of GBS and receipt of swine-flu influenza vaccine, administered to 45 million Americans in 1976 and 1977. After re-examination of the data, a panel of experts concluded that a small excess risk of developing GBS existed for up to 6 weeks after the immunisation. The cause was never established. Carefully conducted surveillance studies of subsequent mass influenza-vaccination programmes of the US Army found no increased incidence of GBS. The possibility that GBS might be triggered by live attenuated oral poliovirus vaccine was suggested in a report from Finland. It described an unusually high incidence of GBS within weeks of a national campaign of vaccination with oral polio vaccine. The observation remains unique. Moreover, a careful epidemiological re-evaluation identified a coincidental influenza epidemic and widespread persistence of the wild-type poliovirus during the relevant period. Both could have contributed as potential triggers to the transient GBS peak occurrence. In addition, the number of GBS cases had started to rise before the vaccination campaign. Thus, the causal relation between GBS and administration of oral polio vaccine is questionable. In addition, a large survey of GBS among children in South America showed no temporal association or increased incidence of GBS during programmes of mass
immunisation with oral polio vaccine. Altogether, whether oral polio vaccine is associated with increased risk of GBS is still uncertain.\textsuperscript{37} Most other currently used vaccines do not seem to be associated with any increased risk. Surveillance during a mass measles-vaccination programme of more than 70 million children in South America found no increased risk of GBS. Two case-control surveys of approximately 200 GBS patients from southeast England, which included individuals immunised with influenza, typhoid, cholera, and diphtheria tetanus-pertussis vaccines, did not show any significant association between occurrence of GBS and a previous immunization.\textsuperscript{39} These observations do not exclude an association, but the investigators judged that any increase in absolute risk was unlikely to be greater than five-fold. Therefore, in any person who has recovered from GBS, the risk of any vaccination should be weighed against the risk of exposure.
Antecedent events for Guillain Barre Syndrome

Infections

Viral

EBV

CMV

HIV

Influenza virus

Coxsackie virus

Herpes simplex

Hepatitis A and C viruses

Bacterial

Campylobacter jejuni

Mycoplasma pneumonia

Escheria coli

Parasites:

Malaria

Toxoplasmosis
Systemic illnesses

Hodgkin’s lymphoma

Chronic Lymphocytic Leukemia

Hyperthyroidism

Collagen vascular disorders

Sarcoidosis

Renal disease

Other medical conditions

Pregnancy

Surgical procedures

Bone marrow transplants

Immunizations

Envenomation

Clinical spectrum

Acute inflammatory demyelinating polyradiculoneuropathy

Until very recently, the eponym Guillain Barre syndrome was used interchangeably with AIDP, which refers to the salient pathological findings: the early lymphocytic infiltrates in spinal roots and peripheral nerves, and the
subsequent macrophage-mediated segmental stripping of myelin. Such segmental loss of the insulating properties of myelin is known to cause profound defects in the propagation of electrical nerve impulses, resulting eventually in conduction block and in the functional correlate of flaccid paralysis. AIDP is the most prevalent form of sporadic GBS in western countries and accounts for 85-90% of cases. It is generally viewed as an autoimmune disorder, triggered in most cases by an antecedent bacterial or viral infection. The target of the aberrant immune response seems to be within the Schwann-cell surface membrane or the myelin, resulting in primary inflammatory demyelination as the major pathological finding.

Humoral immune responses seem to be of particular importance, but there is also clear evidence of T-cell activation. The precise target epitopes of the immune reaction are not known. Early in the course of AIDP there is infiltration of nerves by lymphocytes and, in particular, the deposition of activated complement components along the outer Schwann-cell surface membrane of myelinated nerve fibres. The myelin sheaths of such fibres undergo a process of vesicular disruption, progressing from outside inward. These fine structural changes occur before the recruitment of macrophages and their invasion of nerve fibres. These findings led to the idea that binding of complement-fixing antibodies to epitopes exposed on the outer Schwann-cell surface membrane might lead to complement activation, which in turn, would initiate the disruption of compact myelin; the recruitment of macrophages would then complete the process of segmental demyelination. These observations identify the Schwann cell or myelin as the target of the immune reaction, underscoring the importance of circulating antibodies in the pathogenesis of GBS. Various antibodies to nerve-cell components, notably antiglycolipids such as anti-GMI, have been
detected in serum from GBS patients, but a direct causal link to the neuropathy has not yet been shown.\textsuperscript{44}

AIDP is viewed as a reactive, self-limited, autoimmune disease. The primary consequence of the immune process is the multifocal disruption of myelin segments, which leads to characteristic electrophysiological findings: slowing of nerve conduction velocities, prolongation of distal and F-wave latencies, and conduction block. Once the immune reactions come to a halt, repair and remyelination set in promptly, which correlates with a quick and, in most cases, complete recovery from the flaccid paralysis. In many AIDP patients, however, particularly those with severe disease, inflammatory demyelination is accompanied by variable disruption and loss of nerve axons.\textsuperscript{45,46} Breakdown of axons in this setting is thought to be a secondary "bystander" event, caused possibly by intense inflammation, oedema, and swelling of nerves.\textsuperscript{45-48} The degree of complicating axonal loss in AIDP is an important determinant of the speed of recovery, the lasting deficits, and the ultimate prognosis.\textsuperscript{49}

**Acute motor-sensory axonal neuropathy**

Over the years, some case reports alluded to the possibility that the clinical spectrum of GBS is more heterogeneous. Based on clinical, electrophysiological, and pathological observations, the suggestion was made that a similar clinical presentation might result from a primary immune attack directed towards nerve axons.\textsuperscript{50-52} This idea, which became the subject of much controversy, is now supported by direct evidence.\textsuperscript{53,54}
Feasby and colleagues\textsuperscript{50} drew attention to the unusual findings in seven of their GBS patients who presented with fulminant onset of paralysis after a diarrhoeal or flu-like illness. All had severe generalised paralysis and six needed assisted ventilation within 2-4 days from onset of neurological symptoms. Serial electrophysiological examinations, within 2-7 days, showed very reduced or absent evoked responses on distal supramaximal stimulation of motor and sensory nerves, progressing rapidly to total loss of electrical excitability. This pattern was most consistent with findings observed in nerve fibres undergoing acute axonal degeneration.\textsuperscript{52}

Accordingly, patients showed severe, generalised muscle atrophy with delayed and very poor recovery. Examination of nerve tissue taken by biopsy early in the disease course and in two patients at necropsy after 1 month and 19 months from onset of the illness, disclosed severe axonal degeneration of motor and sensory nerve fibres with only scant lymphocytes and little demyelination. Changes extended to the most proximal portions of nerve roots, yet parent neurons were spared and retained the capacity for regeneration.\textsuperscript{47} The pathological findings indicated a severe and probably primary insult to motor and sensory nerve axons and led to the concept of an acute axonal form of GBS.\textsuperscript{50} The observations were subsequently confirmed and extended by Griffin and colleagues in detailed analysis and morphological study of similar case presentations from northern China.\textsuperscript{53,54} The disorder was notable for the fulminant onset of severe paralysis and sensory deficits. Detailed immunopathology and examination of fine structure in very early disease stages provided strong evidence for a primary immune attack on nerve axons.
Griffin and colleagues introduced the descriptive term now generally used: acute motor-sensory axonal neuropathy (AMSAN).

**Acute motor-axonal neuropathy**

The concept of axonal variant form of GBS was further supported by case reports of sporadic acute, purely motor-axonal neuropathies, now termed AMAN, which were triggered in many cases by an enteric infection with C jejuni. Serum samples from such patients contained high titres of antibody to gangliosides (GM1, GDla, and GDlb) and these paralleled the clinical course.\(^{55,56}\) Sporadic AMAN cases have been observed worldwide; they represent 10-20% of GBS patients in contemporary prospective series.\(^{22}\)

The term AMAN was introduced originally with the case descriptions of acute ascending paralysis that had been observed among rural children in northern China, occurring annually as a summer epidemic. 76% of Chinese AMAN cases were also seropositive for C jejuni and a substantial number had IgG antibodies to GM1.\(^{25}\) Electro-physiological examination and necropsy in some cases confirmed a pure motor and axonal neuropathy pattern.\(^{53,54}\)

Electrophysiological studies showed a reduction or absence of distally evoked compound motor-action potentials early signs of denervation on needle electromyography—but normal conduction velocities and normal action potentials in sensory nerves. These observations were also typical for sporadic AMAN cases. The findings suggest that the axonal degeneration primarily involves the motor-nerve terminals. These predicted changes were demonstrated in muscle and nerve tissue from a sporadic AMAN case. The biopsy samples showed severe and selective loss
of terminal motor axons, whereas the distal sensory fibres were completely intact. Yet, in severe and advanced AMAN cases studied by detailed necropsy, the axonal pathology was much more severe and widespread. Motor axons were shown to have degenerated along their entire length. The earliest demonstrable pathological change seemed to be the binding of IgG and activated complement components to the axolemma at nodes of Ranvier in large motor fibres. Macrophages became attracted to such nodes and tracked underneath the detached myelin lamellae along the periaxonal space, dissecting the axon from the overlying Schwann cell and compact myelin. Axolemma, in contact with invading macrophages, was focally destroyed; axons showed progressive degenerative changes to the point of total disintegration. In some patients, however, who had died early, the morphological changes were very scant despite severe clinical paralysis. On the basis of these observations, the sequence of events has been postulated to take place as follows. C jejuni strains associated with the AMAN pattern of GBS are known to have in their liposaccharide membrane GM1-like epitopes that contain the Gal(31-3) GalNac moiety. The host generates antibodies against GM1 or related gangliosides that bear Gal(31-3) GalNac, the terminal disaccharide that is a candidate epitope. Axolemma at nodes of Ranvier and at terminal motor axons are enriched with Gal(pa-3)GalNac. Binding of cross-reacting complement-fixing antibodies to these epitopes on axolemma might initially result in potentially reversible physiological failure of conduction without morphological change. Subsequent activation of complement could induce the observed early structural changes in nerve axons and initiate recruitment of macrophages, which then cause further axonal damage. Severity of axonal destruction might vary, depending on the
vigor of the immune response; it could range from limited degeneration of motor terminals to generalised and more widespread Wallerian-like degeneration of motor fibres. The time span of recovery would vary accordingly. Regeneration of motor-nerve terminals over the required short distance can happen quickly because the potential for nerve regeneration is probably greatest in childhood, which could explain the rapid recovery from paralysis in many children with AMAN and their overall good prognosis.

**Miller Fisher syndrome**

Another variant form of GBS—the Miller Fisher syndrome (MFS)—has distinct immunological and pathological features. The MFS pattern is triggered by certain *C. jejuni* strains that give rise to a characteristic pattern of antibodies to GQ1b-ganglioside. IgG antibodies to GQ1b are seen in 96% of MFS cases and parallel the disease course. The antibodies recognise epitopes that are expressed specifically in the nodal regions of oculomotor nerves, but also in dorsal-root ganglion cells and cerebellar neurons. This pattern corresponds with the clinical features of ophthalmoplegia, ataxia, and areflexia. Anti-GQ1b-containing serum from MFS patients interfered with neuromuscular transmission in a mouse phrenic nerve/diaphragm preparation, probably by blocking the release of acetylcholine from motor-nerve terminals. The effect seemed specific, and may offer an explanation for the motor weakness seen in patients with MFS. Antibodies to GQ1b cross-reacted with epitopes contained in the liposaccharide of MFS-associated *C. jejuni* strains, again suggesting the possibility of molecular mimicry. There are other GBS variants which are relatively rare.
Pure sensory variant

It is characterised by a rare occurrence of acute sensory polyneuropathy with elevated CSF proteins and demyelinating features on electrodiagnostic studies. There is a rapid onset of large fibre sensory loss with resultant sensory ataxia, positive Romberg sign, pseudoathetosis, tremor, lesser involvement of small fibre sensory function. The important differential diagnosis to be considered is Sjogren syndrome and paraneoplastic sensory ganglionopathy.

Pure Dysautonomia

It is a rare variant of GBS, with initial symptoms pertaining to gastrointestinal tract such as abdominal pain, vomiting and diarrhoea or constipation. There may be possible history of viral infection. Orthostatic hypotension and syncope may the disabling features. Although areflexia and mild sensory symptoms may be evident, there is no motor weakness. Routine electrodiagnostic studies are normal, hence autonomic testing such as heart rate variability, tilt-table testing, sympathetic skin response (SSR), and sweat testing (QSART) may be needed. Most people recover slowly after few months.

Pharyngo Cervico Brachial variant

It is a rare regional GBS variant, affecting predominantly, cervical, brachial or oropharyngeal muscles. Some studies have documented high titres of GT1a antibodies. Patients may initially suffer with neck and pharyngeal weakness which may involve later the upper but not the lower limbs. Electrodiagnostic studies may show demyelinating changes in the upper limbs.
Other less common entities are:

1. Paraparetic variant
2. Acral parasthesias with diminished reflexes in either arms or legs
3. Facial diplegia or abducens palsies with distal parasthesias
4. Isolated post infectious ophthalmoplegia
5. Bilateral foot drop with upper limb parasthesias.
6. Acute ataxia without ophthalmoplegia

Diagnostic criteria for Guillain-Barre syndrome (GBS)

Features required for diagnosis

Progressive weakness in both arms and legs (might start with weakness only in the legs)
Areflexia (or decreased tendon reflexes)

Features that strongly support diagnosis

Progression of symptoms over days to 4 weeks
Relative symmetry of symptoms
Mild sensory symptoms or signs
Cranial nerve involvement, especially bilateral weakness of facial muscles
Autonomic dysfunction Pain (often present)
High concentration of protein in CSF
Typical electrodiagnostic features
**Features that should raise doubt about the diagnosis**

Severe pulmonary dysfunction with limited limb weakness at onset

Severe sensory signs with limited weakness at onset

Bladder or bowel dysfunction at onset

Fever at onset

Sharp sensory level

Slow progression with limited weakness without respiratory involvement

Marked persistent asymmetry of weakness

Persistent bladder or bowel dysfunction

Increased number of mononuclear cells in CSF (>50x10^6/L)

Polymorphonuclear cells in CSF

**Laboratory Studies**

*Cerebrospinal fluid studies*

Approximately 90% of patients with GBS demonstrate spinal fluid protein elevation without leucocytosis at the time of maximal weakness. Though the range is broad, values greater than 1.0gm/dl are rare and suggest another diagnosis. Although there are usually less than 10 cells /mm3 spinal fluid, it is important to remember that a pleocytosis of 10-20cells/mm3 is seen in approximately 5% of patients and should not dissuade one from the diagnosis if the clinical and electrophysiological features are otherwise typical. A spinal fluid cell count of more than 50 cells/mm suggests infection with human immunodeficiency virus.
Electro diagnostic studies

AIDP

Several sets of electro-diagnostic guide lines for the identification of peripheral nerve demyelination in GBS have been published, and the number of patients diagnosed with AIDP can vary greatly depending on which criteria for demyelination are applied.\textsuperscript{70-72}

Majority of AIDP patients will fulfil the criteria by the end of fourth or fifth week, it is more important to have an appreciation for the earlier and sequential changes that are likely to be encountered in patients with AIDP. Conduction block is the hallmark of a demyelinating lesion accounting for the weakness and sensory loss in AIDP. Brown and Feasby found partial motor conduction block in one or more motor nerves in nearly three fourths of AIDP patients within 2 weeks of the onset of paralysis. To find this high frequency of partial motor conduction block, however, needle electrode stimulation at proximal sites is required. About 50% of AIDP patients demonstrate prolonged distal motor and F-wave latencies when first studied.\textsuperscript{72} Conduction velocities in the demyelinating range occur mostly in third or fourth weeks.

Electromyographic findings depend on the extent and severity of axonal involvement. Early in the course, abnormal spontaneous activity is absent and motor unit potentials are normal. But volitional contraction may reveal a pattern of fast firing motor units typical of neurogenic recruitment. Fibrillations and sharp waves develop after the second week depending on the degree of axonal disruption.
AMSAN

Electrophysiological studies in patients with AMSAN are indicative of axonal loss at both acute and chronic stages. The characteristic feature is marked reduction in the compound muscle action potential amplitude or electrical inexitability of motor nerves, which can be found as early as 3-5 days of onset. Sensory nerve action potential are also lost. Abundant fibrillation potentials and positive sharp waves can appear quite early.

AMAN

In patients with AMAN, the main abnormality in motor conduction studies is reduced compound muscle action potential amplitudes and absent F-wave responses. Nerve conduction velocity, distal latency and F-minimum latency are normal. Partial motor conduction block or abnormal temporal dispersion is absent. Sensory nerve conduction studies are normal. Needle EMG examination shows fibrillations and positive sharp waves in the affected muscles by 2-3 weeks after the onset of weakness.

Course of illness

Most patients with AIDP become maximally weak within 11-12 days of onset and essentially all reach a nadir by 4 weeks. Those with AMSAN and AMAN usually reach their nadir within 6 days. Occasional patients may have stepwise or stuttering course. Despite improvement in supportive and immunomodulating therapy, the mortality rate remains 3-5% for GBS with predominant weakness.
Prolonged disability occurs in a surprisingly high percentage of cases, especially in those with AMSAN. Many of these patients are still unable to walk, one year after the onset of their illness. Permanent disability, usually affecting the lower limbs and requiring arthrodesis of ankle and foot occur in about 10% of patients. A smaller percentage of patients may have residual disability, for years with wheelchair dependence and impaired quality of life.\textsuperscript{75} In a large series involving almost 300 patients, the mean time to onset of recovery was 28 days, while the mean time to complete recovery in those with a complete response was 200 days. Rates of clinical recovery at 12 and 24 weeks were 70% and 80% respectively. This indicates that about 20% of patients will have a recovery period extending beyond 6 months. The time and extend of recovery are similar for both AMAN and AIDP.\textsuperscript{63} Whereas patients with AMSAN usually have more prolonged periods of recovery and more severe neurological residual deficits.

Approximately 10% of GBS patients may have a malignant course characterized by prolonged stays in the intensive care units, ventilator dependence (extending 4-6 months) and longer periods of rehabilitation. These patients usually have AMSAN, with rapid onset of quadriplegia, severe axonal changes with reduced motor action potentials.
In general poor prognostic factors identified are:

1. Older age.
2. Rapid onset prior to presentation.
4. Inexcitable or reduced amplitude motor evoked responses.
6. Preceding diarrheal illness

In order to document the stage of illness and to assess a particular effect of treatment appropriate scales has to be applied. In GBS studies the 7 point Hughes GBS disability scale is the most popularly used. Modified Rankin’s disability scale, MRC disability scale and functional evaluation by Barthel Index are also used for disability assessment.
The following are some of the scales used

**GuillainBarre Syndrome disability Scale**

0. Healthy

1. Minor symptoms or signs of neuropathy but capable of manual work / capable of running.

2. Able to walk without support of a stick (5m across an open space), but incapable of manual work or running.

3. Able to walk with a stick, appliance or support (5m across an open space).

4. Confined to bed or chairbound

5. Requiring assisted ventilation (for any part of the day or night)

6. Death

**MRC Disability Scale**

0 Normal

1. No disability, minor sensory signs or areflexia.

2. Mild disability; ambulatory for 200m; mild weakness in one or more limbs and sensory impairment.

3. Moderate disability; ambulatory for 50m without stick; moderate weakness MRC grade 4 and sensory impairment.

4. Severe disability; able to walk 10m with support of stick; motor weakness MRC grade 4 and sensory impairment.
5. Requires support to walk 5m; marked motor and sensory signs.
6. Cannot walk 5m, able to stand unsupported and able to transfer to wheelchair, able to feed independently.
7. Bedridden, severe quadriparesis; maximum strength MRC grade 3.
8. Respirator and/or severe quadriparesis; maximum strength MRC grade 2.
9. Respirator and quadriplegia.
10. Death.

**Rankin’s disability scale**

1. No disability
2. Slight disability; unable to carry out some previous activities but looks after own affairs without assistance
3. Moderate disability; needs some help but walks without assistance.
4. Moderately severe disability; unable to walk and do bodily care without help.
5. Severe disability; bedridden, incontinent; constant nursing care needed.

**Treatment**

Patients with GBS need to be admitted to hospital for close observation. Care for these patients is best provided in tertiary centres, with intensive-care facilities and a team of medical professionals who are familiar with the special needs of GBS patients. The evolution and severity of the neuropathy is variable; it can happen with alarming speed so that intubation and mechanical ventilation may be necessary 24-48 h from onset of symptoms. Admission to an intensive-care unit and ventilatory support is needed in 33% of GBS patients, who will often also show haemodynamic instability and autonomic dysfunction. Utmost vigilance and anticipation of potential
complications are necessary to optimise the chances of a favourable outcome. Areas to be aware of include: prevention of thromboembolic complications; online cardiac monitoring; serial assessments of the ventilatory reserve, oropharyngeal weakness, and airway protection; appropriate bowel care and pain management; adequate nutrition and psychological guidance and support.

Progression of disease varies in duration: about 75% of patients reach their nadir within 2 weeks; 92% within 3 weeks and 94% within 4 weeks. After a brief plateau phase, improvement begins with gradual resolution of paralysis over weeks to months. Outcome is generally favourable. An epidemiological survey in 1993-94 of 140 GBS patients in southeast England showed that 70% had made a complete recovery 1 year later, 22% were unable to run, and 8% were unable to walk unaided. In this series, ten patients (7%) died and three patients remained bedridden or ventilator-dependent at 1 year; all 13 patients were over 60 years old. Similar figures were reported in other series. Several clinical factors have been identified that assist in the early prediction of outcome. The most reliable indicators for significant residual disability at 12 months from onset are: age over 60 years, rapid disease progression to quadriparesis in less than 7 days, need for ventilator support, and a mean distal motor amplitude of less than 20% of the lower limit of normal. A preceding diarrhoeal illness adds to a poor prognosis. The mortality rate remains at 5-8%, even with the most modern intensive-care medicine. Prognosis is better in children, who need less time on ventilation and show a more rapid recovery from paralysis.
Plasma exchange

Three large, multicentre, controlled trials have demonstrated unequivocal benefit from plasma exchange when it is used within the first 2 weeks of disease. In the North American trial of 245 patients with severe GBS, 122 patients were randomly assigned plasma exchange (five exchanges of 50 mL/kg body weight each, given over 7-14 days), and 123 were assigned conventional treatment. On average, patients treated by plasma exchange improved more rapidly, could be weaned from assisted ventilation earlier (24 vs 48 days), and reached ambulation 1 month earlier (53 vs 85 days). This meant a considerable saving, because patients spent less time in intensive-care units and hospital. Plasma exchange was ineffective when started later than 2 weeks from onset of symptoms. These results were corroborated by two French studies that also established that plasma exchange is beneficial in milder GBS and that it improves long-term outcome. At 1 year, 71% of patients treated by plasma exchange recovered full motor strength, as opposed to 52% of controls. Observations were consistent and reproducible, which addresses the criticism that has been voiced over the lack of a sham-pheresis control group and thereby the lack of allocation concealment.

Within 1-2 weeks of initial improvement after plasma exchange, secondary worsening may be seen in about 10% of patients. These limited relapses may be due to persistent active disease or to antibody rebound; additional treatments by plasma exchange lead to renewed improvement. The current recommendations are to use two plasma-exchange treatments for mild GBS and four or five for severe GBS, starting as soon as possible on a schedule of alternating days. Should the
patient show secondary worsening, it is usually best to resume additional plasma-exchange treatments, although intravenous infusion with Ig may be used as an alternative. Plasma exchange is reasonably safe, but not totally free of risk, particularly in haemodynamically unstable GBS patients. Such risks, the high cost, and the limited availability of plasma exchange facilities prompted the search for alternative treatments.

High-dose intravenous immunoglobulin

Intravenous Ig is a promising therapy in various disorders with a presumed autoimmune basis, and has the advantage of low risk and ease of application. This therapy was therefore introduced as an alternative to plasma exchange. The two treatments were compared for their effectiveness in a multicentre study of 150 GBS patients in the Netherlands. Intravenous Ig was given at a dose of 0-4 g/kg bodyweight for 5 days consecutively, and plasma-exchange treatments followed the conventional schedule. At 4 weeks significantly more patients showed functional improvement with intravenous IgG (p=0.024) and the investigators concluded that the two treatments were of equal efficacy. However, the two groups were not equally matched and the study lacked masking. Therefore, these two treatments were assessed again in a large, multicentre, randomised trial coordinated by Hughes. Plasma exchange was compared with intravenous IgG (Sandoglobulin, 0-4 g/kg bodyweight for 5 days) and with a combined treatment of plasma exchange (five times over 10-1 days), followed by intravenous IgG (0-4 g/kg bodyweight for 5 days) in 379 adult patients with severe GBS. At 4 weeks from randomisation, the functional disability--measured by a seven-point disability scale--was assessed by
an observer unaware of treatment allocation. On analysis, the three groups did not differ significantly in this outcome criterion, nor did they differ significantly in any of the secondary outcome measures (time to recover unaided walking; time to discontinue ventilation; recovery from disability during 48 weeks). The study concluded that plasma exchange and intravenous IgG had equivalent efficacy and that combination of the two treatments did not confer a significant advantage. Because of the ease of application, intravenous IgG is currently the preferred treatment of GBS. Limited relapses may also be observed in about 10% of patients treated with intravenous IgG; most respond equally well to a series of repeated infusions.

Corticosteroids

Contrary to expectation, corticosteroids proved to be of no benefit in GBS. In a large, double-blind, placebo-controlled, multicentre trial of methylprednisolone (500 mg intravenously for 5 days within 2 weeks of onset) versus placebo, the groups did not differ significantly in any of the outcome measures. The study is based on pilot observations that suggested a beneficial interaction between intravenous IgG and steroids. Without doubt; there will be advances in treatment as the pathogenesis of GBS is further elucidated. These advances should address the needs of the patients who are left with severe motor sequelae 1 year from onset—about 20% of the total. Recovery of these patients depends on axonal regeneration, which might be promoted by administration of nerve-growth factors. Immuno regulatory cytokines that are involved in terminating the disease process are being discovered and may become useful in treatment. More importantly, preventive
measures that control, or even eliminate certain C jejuni infections will be the best means to lower the incidence of GBS.

**GBS OUTCOME**

Analysis of data from the Plasma Exchange/Sandoglobulin trial participants demonstrated that death or inability to walk at 48 weeks was associated with preceding diarrhoea, severe arm weakness and age >50 years. Visser et al, using data of 147 patients who had participated in the Dutch GBS trial comparing IVIg and PE, found that a previous gastrointestinal illness, age >50 years and MRC Sum Score <40pretreatment were predictors of a poor outcome. Subsequently, using data from 388 patients previously included in trials van Koningsveld et al derived a clinical prognostic scoring system for GBS outcome at 6 months. The findings were then validated in 374 other patients who had participated in another international randomised trial. All data had been prospectively collected. In the multivariate analysis, age, preceding diarrhoea and GBS disability score at 2 weeks after study entry emerged as the three main predictors of poor outcome at 6 months. An ‘Erasmus GBS Outcome Score’(EGOS) was derived, where score ranged from 1 to 7, with three categories for age (>60 (1 point), 41-60 (0.5 point), <40 (0 point)), two categories for diarrhoea (presence(1 point) or absence (0 point)) and five categories for GBS disability score (grade 0 or 1 (1 point), 2 (2 points), 3 (3 points), 4 (4 points) or 5 (5 points)), at 2 weeks. An EGOS of 1-3 implied a mean risk of inability to walk independently at 6 months of 0.5%, an EGOS of 3.5-4.5 implied a mean risk of 7%, an EGOS of five implied a mean risk of 27% and an
EGOS of 5.5-7 implied a mean risk of 52%. More recently, Walgaard et al also published a clinical prediction model applicable early in the course of GBS predicting outcome at 6 months. In this study high age, preceding diarrhoea and low MRC Sum Score at admission and day 7 were independently associated with being unable to walk at 4 weeks, 3 months and 6 months. The authors as a result proposed a ‘modified EGOS’, which they claimed, in contrast to the EGOS, could be used at hospital admission and day 7, with a greater prognostic accuracy when used at day 7, when MRC Sum Score proves a more accurate predictor. The main difference with the EGOS was the use of the MRC Sum Score rather than the GBS disability score, as the model using the former performed better.
AIMS AND OBJECTIVES
**Aims of the study**

1. To identify the clinical and electrophysiological determinants of outcome in early Guillain-Barré syndrome.

2. To study the clinical and demographic profile of Guillain-Barré syndrome in a tertiary care centre.

**Inclusion criteria**

1. Fulfil the diagnostic criteria for GBS of the National institute of Neurological Disorders and Stroke(NINDS) developed by Asbury and Cornblath (1990)

2. Presentation within 2 weeks of symptom onset

**Exclusion criteria**

1. Age less than 18 years

2. Not consenting for study
MATERIALS AND METHODS
Materials and Methods

This study was an observational (retrospective - prospective) study in patients with early Guillain- Barré syndrome (GBS) to study the clinical profile and identify the clinical and electrophysiological determinants of outcome at 12 weeks. All patients aged 18 years or more with diagnosis of GBS or GBS variants presenting within two weeks of onset of weakness were included in this study. The NINDS GBS criteria developed by Asbury and Cornblath (1990) was used for the diagnosis of cases.

All consecutive patients admitted with a diagnosis of GBS in the neurology department who fulfilled inclusion criteria were included in the study. A total of 38 patients were included in this study over the study period of 40 months from January 2014 to April 2017.

All patients had a complete neurological examination (cranial nerve examination, muscle power charting, reflexes, and sensory examination, GBS disability scale at admission) at admission. Patients underwent nerve conduction study (CMAP, SNAP and F response) of at least one upper limb and lower limb at entry time. Data was collected from subsequent conduction studies and CSF study done as part of routine clinical care. For the retrospective group of patients data was obtained and analysed from our case records. Treatment modalities used and complications were recorded for analysis. A record of follow up at 12 weeks was obtained for all patients which was a scale based assessment of disability (using GBS disability scale, adapted from Hughes et al.,1978) based on follow up at our neuromuscular clinic. For patients who did not show up for review, the GBS disability score was assessed telephonically. An accurate assessment of the GBS
disability scale was possible with telephonic follow up even if patient had not reported for review. The primary outcome measure was the GBS disability score at 12 weeks. The outcome was dichotomized as good (score 0 - 2) and poor (≥ 3) for analysis. The determinants examined were demographic features (age, gender), clinical and treatment parameters (antecedents, onset to nadir duration, distribution of weakness, disability at treatment initiation and at nadir, need for ventilation, treatment given) and electro-physiological parameters.

**STATISTICAL ANALYSIS**

The data was analysed using SPSS version 21 software (SPSS Inc, Illinois, Chicago). Categorical variables were analysed in proportions and compared using Fisher’s exact test and means compared with Student’s t test. As sample size was small multivariate analysis was not performed.
RESULTS
Results

A Total of 49 patients with a diagnosis of GBS were evaluated for eligibility, 3 were excluded as age was less than 18 years and 8 excluded as they presented after 2 weeks. A total of 38 subjects were found eligible for inclusion over a period of 40 months from January 2014 to April 2017. Out of the 38 cases 16 were prospectively followed up.

Demographic details:

Age and Gender

Among the 38 patients 21 were males and 17 females. There was a slight male preponderance with M:F ratio of 1.2:1. Mean age of patients in the study was 50.75 ± 15.16 years. Out of 38 patients, 21 were aged 50 years and above. Among the 38 patients recruited in the study divided into three age groups, the maximum patients were in the age group 40-60 years -17 (44.7%), followed by 11 (28.9%) patients in the above 60 years age group and 10 patients in the age group 20-40 years.
Figure 1

Age Distribution

No. of patients

<table>
<thead>
<tr>
<th>Age in years</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>10</td>
</tr>
<tr>
<td>40-60</td>
<td>17</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>11</td>
</tr>
</tbody>
</table>

Figure 2

GENDER DISTRIBUTION

- Male: 21 (55%)
- Female: 17 (45%)
Duration of hospital stay

Our patients were admitted to neuro-medical intensive care unit and ward. Depending on progression and treatment offered they were shifted from ward to the neuro-medical ICU. In our study, the mean duration of hospital stay was 24.03± 31.52 days with a majority of patients admitted in neuro-medical ICU (65%). Out of the 38 patients, 9 patients (23%) had duration of hospital stay more than 4 weeks. All 9 patients had prolonged ICU stay, 8 out of the 9 patients were managed with plasmapheresis and 6 out of the 9 required mechanical ventilation. These factors contributed to the duration of hospital stay.

Figure 3
Past history of GBS

In our study two patients (5.2%) had previous history of GBS. Both these patients were evaluated and treated in our centre, during the first episode more than 10 years prior to present admission. Both patients had normal clinical and electrophysiological parameters in between episodes.

Figure 4
**Seasonal distribution of cases**

The cases of GBS were relatively equitably distributed over the different seasons except from October to December, when a markedly low number of patients were registered.

**Figure 5**

![Seasonal distribution of cases](chart)

- January: 5
- February: 4
- March: 4
- April: 3
- May: 4
- June: 4
- July: 5
- August: 1
- September: 4
- October: 0
- November: 0
- December: 3
**Antecedent illness**

Out of the 38 patients in this study, 18 patients (47.4%) had an antecedent illness within 4 weeks of onset of illness. Both diarrhoeal and upper respiratory tract infection had equal incidence with 8 cases (21.1%) each. There were 2 cases of chicken pox.

**Figure 6**

![Pie chart showing antecedent event with 20.53% present and 18.47% absent]

**Figure 7**

![Bar chart showing no. of patients with URI, Diarrhoea, and Chicken pox: URI 8(21%), Diarrhoea 8(21%), Chicken pox 2(5%)]

46
Days between onset of disease and admission

The mean days between onset of disease and admission was 6.86±3.35. Out of 38 patients 22 (57.8%) were admitted within 1 week of weakness and the rest 16 (42.2%) within 2 weeks.

Figure 8

Onset to Nadir

In this study Nadir is defined as the time point at which maximum GBS disability score is reached. Based on the duration from onset to nadir, the study group was divided into two groups of less than 7 days and greater than 7 days. Among the patients in this study, majority 28 (74%) patients had an onset to nadir less than 7 days and 10 (26%) patients had an onset to nadir more than 7 days. None of the patients had an onset to nadir greater than 2 weeks. Only 2 out of the 38 (5.2%) patients were in the recovery phase when admitted in our centre.
The GBS disability score is a widely accepted scale for assessing the functional status of patients with GBS, ranging from 0 (normal) to 6 (death). A GBS disability score of 4 was the most common score at admission and was seen in 14 (37%) patients followed by 8 (21%) patients with a score of 3. In our study majority of patients had a high GBS disability score at admission. 29 (73.6%) patients had a GBS disability score greater than 3 indicating the inability to walk without support before treatment initiation.
Clinical Examination

Cranial nerve involvement was noted in 19 (50%) patients and the most common cranial nerve involved was facial followed by lower cranial (9,10, 12) nerves. Ophthalmoparesis was noted in the 4 MFS-GBS overlap cases and a case of fulminant GBS. Neck flexor weakness was seen in 14 (37%) patients. Thirty four out of the 38 (90%) patients had absent reflexes. Objective sensory impairment was present in 14(37%) patients. Autonomic dysfunction was present in 12 (32%) patients. The most common autonomic dysfunction was heart rate variability followed by blood pressure fluctuations. Other abnormalities noted were bladder and gastrointestinal dysfunction.
MRC sum score

MRC sum score was calculated for all patients and was divided into two groups of <40 and ≥ 40 MRC sum score. 16 out of the 38 (42%) patients had an MRC score less than 40. MRC sum score were categorized to facilitate the applicability in clinical practice.

<table>
<thead>
<tr>
<th>Clinical examination</th>
<th>Patients(n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve palsy</td>
<td>19(50%)</td>
</tr>
<tr>
<td>Neck flexor weakness</td>
<td>14(37%)</td>
</tr>
<tr>
<td>Absent reflexes</td>
<td>34(90%)</td>
</tr>
<tr>
<td>Sensory impairment</td>
<td>14(37%)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>5(13%)</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>12(32%)</td>
</tr>
</tbody>
</table>
Figure 11

MRC sum score

<table>
<thead>
<tr>
<th>MRC sum score</th>
<th>&lt;40</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16(42%)</td>
<td>22(58%)</td>
</tr>
</tbody>
</table>

Figure 12

MRC sum score and GBS disability score

No. of patients

GBS disability score at admission

<table>
<thead>
<tr>
<th>GBS disability score at admission</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

MRC sum score<40 | MRC sum score>40
CSF evaluation

The CSF was examined in 32 of the 38 (84%) patients. Out of the 32 patients albumin-cytological dissociation was seen in 24 (75%) patients. A significant number of patients had CSF protein higher than 100 (41%) mg/dl. The mean CSF protein value was 105.97±78.46 mg/dl. None of the patients had elevated total counts or abnormal CSF sugar. All cultures were sterile. The mean CSF cell count was 3.96 ± 1.01

Figure 13

Table 3

<table>
<thead>
<tr>
<th>CSF protein</th>
<th>Patients(n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>19 (59%)</td>
</tr>
<tr>
<td>≥100</td>
<td>13 (41%)</td>
</tr>
</tbody>
</table>
Nerve conduction study at admission

All patients underwent electrophysiological study within 24 hours of admission and were classified into 5 groups (primary demyelinating, primary axonal, equivocal, normal and unresponsive) according to Hadden et al. A demyelinating pattern was more common (noted in 14 (37 %) patients than axonal, which was noted in 10(26%) patients. Out of the 38 patients, 3 (8%) had unresponsive nerves and 6 (16%) had normal initial nerve conduction studies. Conduction was repeated after 1 week in the 6 patients and subsequently found to be abnormal. Follow up nerve conduction studies were done as required for each case at specified time points. All the patients did not undergo repeat electrophysiological studies especially if they were improving or had a normal clinical examination on follow up.

Figure 14
Treatment

In this study, 9 out of the 38 patients (24%) were watchfully observed for any progression and managed conservatively. Both IVIG and plasmapheresis were used in almost equal number of patients with 12 (41.3%) managed with IVIG and 11 (37.9%) with plasmapheresis. In 6 patients both plasmapheresis and IVIG were used. The mean volume of plasma exchanged per person was 13.02± 4.42 litres. None of the patients underwent small volume plasmapheresis. Two patients could not tolerate plasmapheresis due to hypotension which was then stopped and shifted to IVIG.
**ICU admission, ventilation and complications**

Majority of patients were admitted in the neuro-medical ICU (68%) and 7 patients (18%) required mechanical ventilation. Complications due to disease process and secondary to treatment were seen. The most common complication encountered was sepsis which occurred in 9 out of 38 patients (23%). The most common cause of sepsis was related to PLEX line (6 patients) followed by ventilator associated pneumonia (4 patients) and UTI(3 patients). In one patient the focus of sepsis could not be identified. Some patients had multiple foci for sepsis over the duration of hospital stay. Other major complications seen were SIADH (3 patients), hypotension related to plasmapheresis (3 patients) and pulmonary edema (1 patient). One patient with fulminant GBS had cardiac arrest from which he was successfully revived.

**Table 5**

<table>
<thead>
<tr>
<th>Patients(n=38)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU ADMISSION</td>
<td>26(68%)</td>
</tr>
<tr>
<td>MECHANICAL VENTILATION</td>
<td>7(18%)</td>
</tr>
<tr>
<td>COMPLICATIONS</td>
<td>13(34%)</td>
</tr>
</tbody>
</table>

**Follow up at 12 weeks**

All patients were followed up at 12 weeks. The disability at 12 weeks was assessed and GBS disability score at 12 weeks were analysed. The majority of patients 18(47%) had achieved a Hughes score of 1 at 12 weeks and 7 (18%) patients had a Hughes score of 0. One patient each had Hughes score of 5 and 6 at 12 week follow up.
Outcome at 12 weeks

In our study the primary outcome measured was the GBS disability score at 12 weeks. The outcome was dichotomized as good (score 0-2) and bad (£3). Out of the 38 patients, 28(74%) had good outcome and 10(26%) patients had bad outcome at 12 weeks. In this study majority of patients had a good outcome at 12 weeks.
GBS Variants

Out of the 38 patients, 6 were GBS variants with the most common variant being MFS-GBS overlap. There was one case each of pharyngeal variant and pure sensory variant.

Figure 19

Hughes score at end of study period

All patients were followed up at end of study (April 2017) to assess Hughes score and outcome. 36 out of the 38 patients (94%) had a good outcome at end of study while only 2 had a bad outcome. The mean duration of follow up was 24.66 ±10.76 months. One patient who expired in the initial period was transferred at request to another centre. He expired within 24 hours of transfer from a complication of sepsis. The other patient with poor outcome had a Hughes score of 3 after 9
months of disease onset and continues to have improvement of deficits. None of the patients at study endpoint had a Hughes score of 4 or 5. In this study 37 out of the 38 patients (97.3%) had an improvement in GBS disability score at study endpoint when compared to the score at admission.

Figure 20

![GBS disability score at end of study period](image)
Figure 21

Outcome at study endpoint

<table>
<thead>
<tr>
<th>Outcome at study endpoint</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>36 (94%)</td>
</tr>
<tr>
<td>Bad</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

Figure 22

Mean GBS disability score

Mean GBS disability score

At admission 12 weeks Study endpoint
Patients excluded from study

Out of the 49 cases with GBS 11 were excluded. Three were excluded as they were less than 18 years. Eight were excluded as they had presented after two weeks of onset. Out of the three paediatric cases excluded, two had a GBS disability score of 5 and had a hospital stay of more than 4 weeks while one patient had a GBS disability score of 3 and had a hospital stay of 5 days. Out of the eight patients excluded as they had presented beyond the two week window, 3 were cases of severe GBS with a Hughes GBS disability score of 5 and had a prolonged duration of hospital stay and were treated with plasmapheresis, while the other 5 had a Hughes score ≤ 3 and were managed with IVIG or conservatively.

OUTCOME PREDICTORS

The various demographic and clinical factors were analysed to predict patients with bad outcome at 12 weeks follow up.

Antecedent illness

Among the patients with antecedent infection of upper respiratory tract infection and diarrhoea, none of the 8 patients with upper respiratory tract infection had a bad outcome while 4 out of the 8 patients with a diarrhoeal illness had a bad outcome at 12 weeks. This was found to be significant with a p value of 0.02.
Table 6

<table>
<thead>
<tr>
<th>Antecedent illness</th>
<th>Outcome</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Bad</td>
<td></td>
</tr>
</tbody>
</table>
| URI                | 8       | 0     | 8   | 0.021
|                    | 100%    | 0.0%  | 100%|
| Diarrhoea          | 4       | 4     | 8   | 100.0%
|                    | 50.0%   | 50.0% | 100.0%|
| Total              | 12      | 4     | 16  | 25.0% 75.0% 100.0%
MRC sum score at admission

The MRC sum score of patients were stratified into two groups (<40 and ≥ 40) for analysis. Eight out of sixteen patients with low MRC score had a poor outcome at 12 weeks compared to 2 out of 22 patients with a good MRC score. This association was found to be significant and MRC score at admission can be used to predict outcome at 12 weeks (p = 0.005). The mean MRC score at admission for those with poor outcome (21.4±9.78) and good outcome (44.92±12.45) was also compared and there was a statistically significant difference (p value-0.004).

Figure 24

Table 7

<table>
<thead>
<tr>
<th>MRC sum score</th>
<th>Outcome</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>Good</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Bad</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>≥40</td>
<td>Good</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Bad</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Total</td>
<td>Good</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Bad</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73.7%</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

Table 8

<table>
<thead>
<tr>
<th>MRC sum score</th>
<th>Outcome at 12 weeks</th>
<th>Number</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>Bad</td>
<td>10</td>
<td>10.70</td>
<td>3.09</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>28</td>
<td>22.46</td>
<td>1.37</td>
</tr>
</tbody>
</table>

p value = 0.004
GBS Disability score at admission

In our study 6 out of 7 patients with GBS disability score of 5 and 4 out of 14 patients with GBS disability score of 4 had a poor outcome. None of the patients with GBS disability score of 1, 2 and 3 had a poor outcome. A high GBS disability score at admission was associated with a poor outcome (p = 0.001).

**Figure 25**

![GBS disability score at admission and outcome](image)

**Table 9**

<table>
<thead>
<tr>
<th>GBS disability score at admission</th>
<th>Outcome</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Bad</td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>17</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>100.0%</td>
<td>0.0%</td>
<td>100%</td>
</tr>
<tr>
<td>≥4</td>
<td>11</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>52.4%</td>
<td>47.6%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>73.7%</td>
<td>26.3%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Neck flexor weakness

Presence of neck weakness during the course of illness was found to be a predictor of poor outcome at 12 weeks with 8 out of 14 with neck flexor weakness having a bad outcome as against 2 out of 24 without neck flexor weakness (p = 0.002).

**Figure 26**

![Bar chart showing neck flexor weakness and outcome](chart.png)

**Table 10**

<table>
<thead>
<tr>
<th>Neck flexor weakness</th>
<th>Outcome</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Good</td>
<td>Bad</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>91.7%</td>
<td>8.3%</td>
<td>100%</td>
</tr>
<tr>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>42.9%</td>
<td>57.1%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>73.7%</td>
<td>26.3%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Presence of autonomic dysfunction was found to be associated with a poor outcome at 12 weeks (p = 0.045).

**Electrophysiology**

All three of the patients with unresponsive nerves had a bad outcome at 12 weeks (p value = 0.003).

**Table 11**

<table>
<thead>
<tr>
<th>NCS</th>
<th>Outcome</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>Bad</td>
<td></td>
</tr>
<tr>
<td>Inelicitable</td>
<td>0</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Elicitable</td>
<td>28</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>10</td>
<td>38</td>
</tr>
</tbody>
</table>
Duration of hospital stay, ventilation and complications

For analysis duration of hospital stay was divided into two groups, 7 out of 9 patients (77.8%) who stayed in the hospital for more than 4 weeks, had a bad outcome while those with a shorter duration of hospital stay (<4 weeks), only 3 (10.3%) patients had bad outcome (p =<0.0001). The mean duration of hospital stay was 24.03±31.5 with a majority of patients admitted in neuro-medical ICU. There was significant difference in the means of good outcome (14.18±8.62) and bad outcome (51.60±52.06) for duration of hospital stay (p value 0.049). If the course of the disease was complicated by sepsis, SIADH or cardiac problems, it was found to be a predictor of poor outcome (p =<0.001). In this study 7 patients were mechanically ventilated (18.4%). Among these patients, 6 had a poor outcome at 12 weeks while only 4 out of the 31 patients who were not ventilated had a poor outcome at 12 weeks (p value <0.001).

Figure 28
Age and sex

Age was analysed as a predictor of poor outcome. There was no significant difference in the means of age for good outcome (50.79±16.83) and poor outcome (49.60±9.73) in patients at 12 weeks. While comparing sex as a predictor of outcome, it was found that only 2 out of 15 females had bad outcome as against 8 out of 13 males with bad outcome. Males were more likely to have a bad outcome than females. This observation did not reach statistical significance (p value- 0.06).

Time to Nadir

In patients with GBS a shorter time to nadir indicates a severe disease and poor outcome. In our study there was no significant difference between means of time to nadir between good outcome(6.36±2.75) and bad outcome (5.30±2.26) (p value-0.246)
Clinical examination

In this study, cranial nerve involvement, sensory impairment and ataxia were not found to be predictors of poor outcome.

Electrophysiological subtype of GBS

In this study the 38 patients were classified into 5 groups according to the electrophysiological classification proposed by Hadden et al. The electrophysiological type of GBS was not found to be a predictor of poor outcome at 12 weeks.

CSF albuminocytological dissociation

In this study 1 out of the 8 patients without albuminocytological dissociation had bad outcome at 12 weeks. Out of the 24 patients with albuminocytological dissociation 8 had a bad outcome. This observation was not found to be statistically significant (p value- 0.386). Comparing the mean protein values of those with elevated CSF with poor outcome (122.38±105) and good outcome(133.88 ±62.42) there was no significant difference in values(p value-0.78).

Treatment

All patients who were managed conservatively had a good outcome at 12 weeks, while 10 out of 29 patients who underwent treatment had a bad outcome. This did not have any statistical significance(p value-0.079). Among the patients who underwent definitive management only 1 out of the 12 patients treated with IVIG had a bad outcome while 4 out of 11 patients who underwent plasmapheresis and 5 out of the 6 patients with IVIG + plasmapheresis had a bad outcome (p value-0.007). The mean plasma exchange volume was 13.02±4.42 litres and mean plasma volume exchanged between those with bad outcome(14.7±4.7litres) versus those with good outcome(11.05±3.73 litres) was not found to be significantly different(p= 0.106).
Table 12

<table>
<thead>
<tr>
<th></th>
<th>Good outcome(n=28)</th>
<th>Bad outcome(n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>13(61.9%)</td>
<td>8(38.1%)</td>
<td>0.136</td>
</tr>
<tr>
<td>Age &gt;50</td>
<td>15(71.4%)</td>
<td>6(28.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hospital stay&gt; 4weeks</td>
<td>2(22.2%)</td>
<td>7(77.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antecedent Diarrhoeal illness</td>
<td>4(50.0%)</td>
<td>4(50.0%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Time to Nadir&lt; 1 week</td>
<td>20(71.4%)</td>
<td>8(28.6%)</td>
<td>0.699</td>
</tr>
<tr>
<td>GBS disability score≥3</td>
<td>11(52.4%)</td>
<td>10(47.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>12(63.2%)</td>
<td>7(36.8%)</td>
<td>0.269</td>
</tr>
<tr>
<td>Neck flexor weakness</td>
<td>6(42.9%)</td>
<td>8(57.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>MRC sum score&lt;40</td>
<td>8(50%)</td>
<td>8(50%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Absent reflexes</td>
<td>24(70.6%)</td>
<td>10(29.4%)</td>
<td>0.556</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td>12(85.7%)</td>
<td>2(14.3%)</td>
<td>0.268</td>
</tr>
<tr>
<td>Ataxia</td>
<td>5(100%)</td>
<td>0(0.0%)</td>
<td>0.298</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>6(50%)</td>
<td>6(50%)</td>
<td>0.045</td>
</tr>
<tr>
<td>NCS-unresponsive nerves</td>
<td>0(0.0%)</td>
<td>3(100%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Conservative management</td>
<td>9(100%)</td>
<td>0(0.0%)</td>
<td>0.079</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1(14.3%)</td>
<td>6(85.7%)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Complication</td>
<td>5(38.5%)</td>
<td>8(61.5%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In our study, antecedent diarrhoeal illness, low GBS disability score, neck flexor weakness, low MRC sum score, unresponsive nerves, mechanical ventilation and presence of complications were associated with a poor outcome at 12 weeks. Age, sex, time to nadir, cranial nerve involvement, sensory impairment, ataxia, autonomic dysfunction, CSF albuminocytological dissociation, electrophysiological subtype of GBS and treatment administered were not found to be a predictor of poor outcome at 12 weeks.
DISCUSSION
Discussion

Guillain Barre Syndrome is the most common acute immune mediated paralytic neuropathy with well-defined clinical, electrophysiological and pathological features. Despite the availability of treatment, a certain subset of GBS patients do not have a good outcome. Around 5% of patients die and 20% remain disabled. These rates have remained static over the course of the last few decades.\textsuperscript{1,2} There is significant variability in clinical course and final outcome. Various studies have been performed to predict the course and outcome of GBS in the acute phase of the illness. A few prognostic models also have been developed to predict the outcome.\textsuperscript{7} This study was done to examine the demographic and clinical profile of patients with acute GBS attending a tertiary care hospital in South India and determine the determinants of 12 week outcome in them.

Demography and clinical features

In our study, there was a slight male preponderance with a M:F ratio of 1.2:1. This was comparable with previous epidemiological studies which had demonstrated a slight male preponderance. Diseases with an autoimmune aetiology usually show a clear sex difference in prevalence, whereby females are more commonly affected. Contrary to this, GBS studies show a clear male preponderance. A hospital based study by Alsheklee et al reported increased prevalence in males.\textsuperscript{93} A recent study from India by Dhadke et al also showed higher prevalence in males.\textsuperscript{94}

In our study a majority of patients were aged above 50 years. In population based studies that comprised incidence categorised by age, increase in rates were
observed in people aged 50 years or more. Several studies have shown a bimodal age peak in GBS. Dowling et al had reported a bimodal peak in young and elderly. Our study showed no evidence of bimodal distribution of age-specific incidence in adult life. This observation in our study was similar to the study done by Winner et al.

The cases of GBS were relatively equitably distributed over the different seasons except from October to December. There was no seasonal clustering. Unlike studies from the Western countries, studies from tropical countries including India have shown seasonal clustering of cases in summer months. This observation of seasonal clustering is attributed to the fact that major antecedent infections like gastroenteritis and influenza tend to occur in a seasonal pattern and hence increasing the risk of acquiring GBS. The lack of a clear clustering of cases around the summer season in our study could be due to the distribution of rains throughout the year in our state. It may also reflect a bias related to the referral patterns to our Institute.

A history of antecedent illness within 4 weeks is usually reported in GBS. In our study almost half of the patients reported an antecedent illness within 4 weeks of onset of illness. The most common illness reported was diarrhoea and upper respiratory tract infection. Previous studies have shown that 40-70% of cases of GBS are associated with an antecedent infection. In a study by Sunder et al, the rate of antecedent infection was reported as 52%. The incidence and pattern of antecedent infections were comparable to those described in other studies.
Our patients were admitted to neuro-medical intensive care unit and ward. Depending on progression and treatment offered, they were shifted from ward to the neuro-medical ICU. There was a slightly longer mean duration of hospital stay and higher rate of ICU admission in this cohort compared to other studies. In a recent study by Leuween et al the mean duration of hospital stay was 17 days with most patients being admitted in neurology wards(82%). In our study the mean duration of hospital stay was 24.03± 31.52 with a majority of patients admitted in neuro-medical ICU(65%). Patient transfer from ward to ICU was low, while in the previous studies there were higher incidence of transfers (40%). This increased incidence of ICU admission and duration of hospital stay may be due to our centre being a tertiary referral centre and the resulting referral bias towards patients with severe illness and our policy of admitting patients in neuro-medical ICU if the patient was in the stage of progression. Six patients had comorbidities affecting respiration and mobility. The most common comorbidity was bronchial asthma and chronic obstructive pulmonary disease. One patient had spinal canal stenosis. In a study by Dharaiya et al chronic lung disease and congestive heart failure was the most common co-morbidity affecting respiration and mobility. Two patients (5.2%) had previous history of GBS. Both these patients were evaluated and treated in our centre during the prior episodes. They had a normal clinical examination between both episodes and hence were classified as recurrent GBS than chronic inflammatory demyelinating polyradiculoneuropathy. Das et al and Grandmaison et al had found a similar prevalence (2-5%) of recurrent GBS in their
In our study the second episode was less severe than the first episode and had a Hughes score ≤ 3. During the first event both were managed with plasmapheresis and during the second event one was managed with IVIG and the other managed conservatively. This was different from the previous studies which had shown the second event to be more severe than the first.

In this study we have recruited patients presenting within 14 days of weakness as we were attempting to analyse clinical and biological parameters in the acute phase of disease which could determine the outcome. This is the phase when immunomodulatory treatment is considered to be the most effective. Majority of patients were admitted in our hospital within 1 week of onset of weakness and treatment initiated within 24 hours. In our study all patients reached nadir within 2 weeks. Majority of patients reached the nadir within a week. In the previous studies, most reached nadir by 2 weeks, 80% by 3 weeks and 90% by 4 weeks. This shorter time to nadir in our study may be because we have excluded patients who presented to us after 2 weeks of onset of weakness.

Cranial nerve involvement was noted in 19 patients (50%) and the most common cranial nerve involved was facial nerve followed by the lower cranial nerves. In a study by Bhargava et al analysing cranial nerve palsies in GBS, 62.3% patients had cranial nerve palsies. In another recent study by Khan et al one third of the patients had cranial nerve involvement. Most studies report cranial nerve involvement ranging from 30-60% with facial and bulbar nerves being commonly involved. Ophthalmoparesis was noted in 4 cases of MFS-GBS overlap cases and a case of fulminant GBS which was consistent with previous studies. Neck flexor
weakness was seen in 14 patients (36.8%). Objective sensory findings and ataxia were seen only in a few patients while areflexia was almost universal. Autonomic dysfunction was seen in 32% of our patients. It ranged from isolated tachy- or bradycardia without hemodynamic fluctuations to cardiac arrest. Verma et had found similar incidence and pattern of neurological deficits in a study conducted in India. One patient with fulminant GBS had a cardiac arrest from which he was revived. The incidence of autonomic dysfunction has varied in previously reported studies from 17% by Ashok et al to 66% in Singh et al.

Compared to previous studies our patients had a higher GBS disability score at treatment initiation. Most of our patients had a GBS disability score greater than 3 indicating significant disability before treatment initiation. This distribution was of disability score was similar to the study by Koningsveld et al. This may reflect a referral bias with more severe cases being preferentially referred to out institute and can also be an indicator of the department protocol wherein only those patients with Hughes grade 3 or more or are rapidly progressing are considered for definitive therapy. In our study, most of the patients had albumino-cytological dissociation on CSF examination performed after 1 week of illness. In our study mean CSF protein value was 105.97± 78.46 mg/dl. In the study by Verma et al mean CSF protein value was 108.60±53.24. The proportion of patients with protein elevation was also similar. The most common NCS pattern was demyelinating followed by axonal. This was consistent with previous studies by Hughes et al and Mishra et al were demyelinating pattern was most commonly seen followed by axonal. Higher prevalence of AMAN has been reported from China and has been attributed to
Campylobacter jejuni. There was no association between type of infection and electrophysiological pattern in our study, however Hiraga et al had found that enteritis was more commonly associated with AMAN variety of GBS and URTI was associated with AIDP variety of GBS. A meaningful record of ganglioside antibodies was lacking for majority of the patients. In our study almost an equal number of patients underwent IVIG and plasmapheresis. Most observational studies show higher number of patients undergoing treatment with IVIG but in our study there was an almost similar rate of IVIG and plasmapheresis. This may be because our centre is one of the few regional centres offering plasmapheresis as a treatment modality for GBS and patients with severe grade of weakness are specifically referred for the same. The higher expense for treatment with IVIg also contributed to a few of the patients opting for plasmapheresis.

In our study all patients were followed up at 12 weeks and also at study endpoint. None of the patients were lost to follow up. In our study 26% of the patients had a bad outcome at 12 weeks. In a study by Walgraad et al 30% of the patients had a bad outcome at 12 weeks. In an observational study conducted by Saravanan et al the 39% patients had a bad outcome. In our study the number of patients with bad outcome was lower compared to other studies. This may be because of our policy of admission for observation in ICU for progression of illness, early ventilation and higher rates of plasmapheresis with intensive neuro-rehabilitation programs.
Predictors of outcome

We had studied the predictors of outcome of patients at 12 weeks. The outcome measured was the GBS disability score at 12 weeks. This outcome was dichotomized as good (score 0-2) and poor (≥3). Age was not found to be a predictor of poor outcome at 12 weeks. In a study by Koningsveld et al older age was found to be a predictor for poor outcome at 6 months. In another study by Walgraad et al older age was found to be a predictor of poor outcome at 12 weeks.

Most studies have found a higher age as a predictor of poor outcome. A recent comprehensive review by Rajabally et al on outcome of GBS had found similar results. This difference may be because in our study subgroup analysis of age revealed patients with older age had a higher proportion of low GBS disability score (≤3) at admission. This in turn would have resulted in better outcome for patients at 12 weeks compared to previous studies. In this study low GBS disability score was not an exclusion criteria. In addition our study had a low number of patients. In our study a higher proportion of males had a bad outcome than females though this was not statistically significant. In most large outcome studies in GBS sex is not reported as a predictor of poor outcome. In a study by Dhar et al male sex is strongly associated with morbidity in GBS patients. Even though male sex is not a predictor of outcome, there is more chance for males having a poor outcome than females.

In our study the presence of antecedent diarrhoeal illness was found to be a predictor of poor outcome. The study by Koningsveld et al also found a similar finding and included it in the EGOS(Erasmus GBS outcome score). Paul et al also had demonstrated a poorer outcome in those with antecedent illness.
The mean duration of hospital stay was associated with poor outcome in our study, though it cannot be used as a predictor. In patients with GBS a shorter time to nadir indicates a severe disease and poor outcome. In our study there was no significant difference between scores of time to nadir between good and bad outcome. This finding is also consistent with studies by Walgraad et al and Koningsveld et al. There are some studies showing poor outcome in patients with shorter time to nadir. Visser et al had found an initial rapid progression of weakness to be a predictor of poor outcome.91

Majority of patients had a high GBS disability score at admission. A high GBS disability score at admission was seen to have a poor outcome (p = 0.001). Low MRC sum score at admission was also found to be associated with poor outcome at 12 weeks in this study(p=0.0005). A clinical prognostic model proposed by Walgaard et al revealed that higher age, preceding diarrhoea, and low MRC sum score on admission and at 1 week were independently associated with inability to walk at 4 weeks, 3 months, and 6 months.9 In our study these factors were seen to be associated with a poor outcome. In addition neck flexor weakness and autonomic dysfunction was also associated with poor outcome, similar to the study by Verma et al.109 CSF albuminocytological dissociation and the degree of protein elevation was not to be a predictor of outcome at 12 weeks. Electrophysiological studies were done at admission for all patients and classified according to Hadden et al classification. The electrophysiological subtype of GBS was not found to be a predictor of poor outcome though unresponsive nerves at admission was found to be a predictor of poor outcome.
at 12 weeks (p= 0.003). Verma et al had shown poor outcome at 6 months in patients with axonal variety of GBS. A study by Durand et al had shown higher incidence of mechanical ventilation in demyelinating subtype and a good outcome in axonal subtypes.\textsuperscript{116}

Type of treatment given was not associated with outcome at 12 weeks. This was consistent with studies which demonstrated equal efficacy with IVIG and plasmapheresis.\textsuperscript{117} As this was a strictly observational study treatment decisions were not made as part of study. Patients who were having severe GBS more commonly underwent plasmapheresis than IVIG except in cases with severe autonomic dysfunction. The treatment protocol was consistent with the practice parameters by Latov et al.\textsuperscript{117} ICU admission, mechanical ventilation, complications during hospital stay were also found to be associated with poor outcome.

In conclusion, predictors of poor outcome at 12 weeks identified in this study were presence of an antecedent diarrhoeal illness, low MRC sum score at admission, high GBS disability score at admission, neck flexor weakness, unresponsive nerves on electrophysiological testing, ICU admission, presence of complications and mechanical ventilation. In this study advancing age and shorter time to nadir were not found to be associated with poor outcome unlike reports from previous studies. Our study had certain limitations in that our centre is a tertiary referral centre where patients are referred from other hospitals especially for plasmapheresis and hence a referral bias towards severe GBS may be present. In addition sample size in this study was too small to reliably perform multivariate analysis.
CONCLUSIONS
**Conclusion**

1. In this cohort, Guillain-Barre syndrome had a male preponderance with older age groups more commonly affected and no seasonal clustering of cases.

2. An antecedent infection was seen in up to half the cases and the presence of diarrhoeal illness was associated with poor outcome at 12 weeks.

3. All patients had duration of onset to nadir within 2 weeks.

4. The most common electrophysiological subtype was demyelinating followed by axonal.

5. High GBS disability score at admission and low MRC sum score were associated with poor outcome at 12 weeks.

6. Age, time from onset to nadir, cranial nerve palsy, degree of CSF protein elevation, electrophysiological subtype and treatment administered were not associated with poor outcome.

7. ICU admission, ventilation, presence of complications and neck flexor weakness were associated with poor outcome at 12 weeks.

8. Most patients had a good outcome at end of study period (94%).
BIBLOGRAPHY
Bibliography


45. Fuller GN, Jacobs IM, Lewis PD, Lane. RIM. Pseudoaxonal Guillain-Barre syndrome: severe demyelination mimicking


61. Takigawa T, Yasuda H, Kikkawa R, et al. Antibodies against GM1 ganglioside affect K+ and Na+ currents in isolated rat
myelinated nerve fibres. Ann Neuro11995; 37: 436-42. 111


76. Jerry R Mendell, John T Kissel, David R Cornbloth. Guillain Barre Syndrome, Chapter 9. Diagnosis and management of peripheral nerve disorders.

77. Hughes RA, Newsom Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in Acute polyneuropathy. Lancet. 1978; 2: 750-753


79. Walter G Bradley, Robert B Daroff, Gerald M Fenichal, Chapter 54: Principles and practices of neurological rehabilitation page 1039 t.


88. van der Meche FGA, Schmitz PIM, Dutch Guillain-Barre Study Group. A randomized trial comparing intravenous immune


113. Rajabally Y, Uncini A. Outcome and its predictors in Guillian-Barre


ANNEXURE
LIST OF ABBREVIATIONS

AIDP  Acute Inflammatory Demyelinating Polyneuropathy
AMAN  Acute Motor Axonal Neuropathy
AMSAN  Acute Motor Sensory Axonal Neuropathy
CIDP  Chronic Inflammatory Demyelinating Polyneuropathy
CSF  Cerebrospinal fluid
DNA  Deoxyribonucleic acid
EGOS  Erasmus GBS Outcome Score
GBS  Guillain-Barre Syndrome
ICU  Intensive Care Unit
IVIg  Intravenous Immunoglobulins
MRC  Medical Research Council
MFS  Miller Fisher Syndrome
NINDS  National Institute of Neurological Disorders and Stroke
TRF  Treatment-related Fluctuation
Dear Dr. Paul J Alapatt,

Thank you for submitting documents related to your proposal titled "GUILLAIN-BARRE SYNDROME-PREDICTORS OF OUTCOME "(IEC/887) to the IEC for review.

List of Documents

1. Covering letter addressed to the Chairperson, IEC, SCTIMST, dated 22.03.2016 with check list
2. TAC Approval Letter
3. IEC Application Form
4. Project Proposal
5. Proforma
6. HOD forwarded letter received dated 22.03.2016.
7. Patient Information Sheet and Consent Form in English and Malayalam
8. CV of Principal Investigator and Co-Investigators

IEC Recommendations

1. Rewrite the Informed consent form replacing the word – donation with 'collected'
2. The sample size included is not adequate for meeting the objectives mentioned.
3. The ICF needs to provide the Member Secretary’s name for the participants to contact should they choose to.

One set of all the documents including those revised may be submitted. The covering letter should indicate the revisions made.

Sincerely,

Mala Ramanathan
Member Secretary, IEC
## PROFORMA

<table>
<thead>
<tr>
<th>Patient code</th>
<th>Date of birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Date of birth</td>
</tr>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>Date of inclusion</td>
<td></td>
</tr>
<tr>
<td>Date of hospital admission</td>
<td></td>
</tr>
</tbody>
</table>

### Previous episode of GBS

- □ yes: date of admission
- □ no

### Co-morbidity affecting mobility

- □ yes
- □ no

### Co-morbidity affecting respiration

- □ yes
- □ no

### Family members with GBS

- □ yes
- □ no

### Transfer from other hospital

- □ yes (name and date)
- □ no

### Antecedent events (< 4 weeks of admission date)

- □ upper respiratory tract infection
- □ common cold
- □ gastroenteritis, diarrhoea
- □ urinary tract infection
- □ vaccination:
  - □ Surgery:
  - □ other: □ none

### Date of onset of antecedent event:

### Date of onset of weakness:

### Is the patient in the recovery phase:

### Date when nadir was reached:

### What was the GBS disability score at nadir? (0-5)

- 0: A healthy state
- 1: Minor symptoms and capable of running
- 2: Able to walk 10 m or more without assistance but unable to run
- 3: Able to walk 10 m across an open space with help
- 4: Bedridden or chairbound
- 5: Ventilated

### Cranial nerve involvement

- □ oculomotor nerves
- □ facial nerve
- □ bulbar nerves
- □ other:
- □ no
- □ unable to examine
Weakness neck flexion (MRC score)
Weakness limbs (MRC score)  

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. houlder abduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. elbow flexion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W. wrist extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. hip flexion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. knee extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. ankle dorsiflexion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reflexes  
(0: absent, 1: low, 2: normal, 3: high)  
biceps reflex  triceps reflex  patellar reflex  Achilles reflex

Sensory deficits  
☐ yes  ☐ no  ☐ unable to examine

If yes, location of sensory deficits  
☐ Face  ☐ Arms  ☐ Legs

If yes, type of sensory deficits  
☐ light touch  ☐ pinprick  ☐ vibration  ☐ joint position

Ataxia  
☐ yes  ☐ no

Autonomic dysfunction  
☐ yes  ☐ no

If yes specify type of dysfunction  
☐ cardiac (arrhythmia, tachycardia, bradycardia)
☐ blood pressure (fluctuations, hypertension, hypotension)
☐ gastro-enteric  ☐ bladder dysfunction  ☐ pupil dysfunction  ☐ other:

Current GBS disability score (0 - 6)

Was the CSF examined?  
☐ no  ☐ yes

Date of spinal tap

CSF protein level (g/l) (normally 0.15-0.45 g/l in adults)

CSF leukocytes (/ul) (normally <5 ul; GBS <50 ul)

CSF erythrocytes (/ul)

Electrophysiology classification

Date of electrophysiology  
☐ acute motor axonal neuropathy (AMAN)
☐ acute inflammatory demyelinating neuropathy (AIDP)
☐ unresponsive nerves
☐ responsive nerves but not classifiable (equivocal)  ☐ normal  ☐ not performed

Follow up at 12 weeks

Is the diagnosis still GBS?  
☐ yes  ☐ no: alternative diagnosis:

Is the patient still admitted  
☐ yes  ☐ no:
Complications

- pneumonia
- sepsis
- deep venous thrombosis
- lung embolism
- pressure ulcer
- hyponatraemia (Na <130 mEq/l)
- other:
- none

GBS specific treatments (IVIg, plasmapheresis/exchange, other medical treatment)

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>First day</th>
<th>Last day</th>
<th>Dosage</th>
<th>Completed</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First day</td>
<td>Last day</td>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First day</td>
<td>Last day</td>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial nerve involvement (&gt; 1 option possible)</td>
<td>oculomotor nerves</td>
<td>facial nerve</td>
<td>bulbar nerves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other:</td>
<td>no</td>
<td>Unable to examine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weakness neck flexion (MRC score)

Weakness limbs (MRC score)

Right

- shoulder abduction
- elbow flexion
- wrist extension
- hip flexion
- knee extension
- ankle dorsiflexion

Left

Sensory deficits

- yes
- no
- unable to examine

If yes, location of sensory deficits

- Face
- Arms
- Legs

If yes, type of sensory deficits

- light touch
- pinprick
- vibration
- joint position

Ataxia

- yes
- no

GBS Variant

- no
- Pure motor GBS
- Pharyngeal-cervical-brachial weakness
- Miller Fisher syndrome (no limb weakness)
- Miller Fisher- GBS overlap syndrome
- Pure sensory GBS
- Ataxic form
- other

GBS Disability score at 12 weeks:
Dr. Paul thesis.do
Similarity Found: 2%

Date: Wednesday, October 04, 2017
Statistics: 99 words Plagiarized / 5470 Total words
Remarks: Low Plagiarism Detected - Your Document needs Optional Improvement.

INTERNET SOURCES:

- 0% - Empty
- 1% - http://www.cnmd.ac.uk/research/clinical_
- 1% - http://www.cnmd.ac.uk/research/clinical_
- 0% - http://jsms.sch.ac.kr/journal/view.php
- 0% - http://jnnp.bmj.com/content/79/3/289
- 1% - http://www.sciencedirect.com/science/art
- 1% - http://www.sciencedirect.com/science/art