CLINICAL, ELECTROPHYSIOLOGICAL AND SEROLOGICAL MARKERS IN PATIENTS WITH GUILLAIN-BARRÉ SYNDROME

THESIS

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DECLARATION

I hereby declare that the thesis titled **"Clinical, Electrophysiological and Serological markers in patients with Guillain-Barré Syndrome"** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled **"Clinical, Electrophysiological and Serological markers in patients with Guillain-Barré Syndrome"** has been conducted by **Dr. Apoorv Patel** under our supervision and guidance in the Department of Neurology, All India Institute of Medical Sciences, Jodhpur, Rajasthan. The results and observations of this study have been checked and verified by us from time to time. The thesis contains the candidate's own genuine and independent work.

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ABBREVIATIONS

Abbreviation	Full form
A-CIDP	Acute onset Chronic Inflammatory Demyelinating Polyradiculoneuropathy
AIDP	Acute Inflammatory Demyelinating Polyneuropathy
AMAN	Acute Motor Axonal Neuropathy
AMSAN	Acute Motor Sensory Axonal Neuropathy
APC	Antigen Presenting Cell
APTT	Activated Partial Thromboplastin Time
BBE	Bickerstaff Brainstem Encephalitis
CB	Conduction Block
CBC	Complete Blood Count
CI	Confidence Interval
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
C. Jejuni	Campylobacter Jejuni
CMAP	Compound Muscle Action Potential
CMV	Cytomegalovirus
CNS	Central Nervous System
COVID-19	Corona Virus Disease 2019
CPK	Creatine Phosphokinase
CSF	Cerebro-Spinal Fluid
CTS	Carpel Tunnel Syndrome
CV	Conduction Velocity
CVS	Cardio Vascular System
dCMAP	Distal Compound Muscle Action Potential
DML	Distal Motor Latency
EBV	Epstein-Barr Virus
ECG	Electrocardiography
EDX	Electrodiagnostic
EGOS	Erasmus GBS Outcome Scale
EGRIS	Erasmus GBS Respiratory Insufficiency Score
EMG	Electromyography

ESR	Erythrocyte Sedimentation Rate
FVC	Forced Vital Capacity
GalNac	N-Acetylgalactosamine
GBS	Guillain-Barré syndrome
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGOS	International Guillain-Barre syndrome Outcome Study
IVIg	Intravenous Immunoglobulin
LFT	Liver Function Test
LLN	Lower Limit of Normal
MAC	Membrane Attack Complex
mEGOS	Modified Erasmus GBS Outcome Scale
MFS	Miller Fisher Syndrome
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NCS	Nerve Conduction Study
NINDS	National Institute of Neurological Disorders and Stroke
NSAID	Non-Steroidal Anti-inflammatory Drug
PCB	Pharyngeal-Cervical-Brachial
pCMAP	Proximal Compound Muscle Action Potential
PE	Plasma Exchange
PO_2	Partial Pressure of Oxygen
PT	Prothrombin Time
QSART	Quantitative Sudomotor Axon Reflex Test
RCF	Reversible Conduction Failure
RCT	Randomised Controlled Trial
RFT	Renal Function Test

RNA	Ribonucleic Acid
RR	Relative Risk
RS	Respiratory System
RT PCR	Reverse Transcription Polymerase Chain Reaction
SARS-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SID	Second Intravenous Immunoglobulin Dose
SNAP	Sensory Nerve Action Potential
SSR	Sympathetic Skin Response
TD	Temporal Dispersion
TRF	Treatment Related Fluctuations
TSH	Thyroid Stimulating Hormone
URTI	Upper Respiratory Tract Infection

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SUMMARY

Background: Guillain-Barré syndrome (GBS) is an acute immune mediated disorder of peripheral nervous system – most commonly triggered by infections or other antecedent events. Majority of patients improve with early diagnosis and treatment and leading to a better outcome. Various factors affect the outcome of the patients. Serial nerve conduction studies (NCS) at different intervals from onset help to classify electrophysiology pattern accurately.

Objective: The study aimed to assess the clinical, serological and electrophysiological profile of patients with Guillain-Barré syndrome as well to compare the patterns of recovery amongst various electrophysiological subtypes of GBS using serial NCS.

Methods: Total 30 patients with GBS were enrolled. Basic demographic details and clinical profile was collected on admission. Complete neurological examination and evaluation with disability scales was done in all the patients. Both NINDS and Brighton's criteria were used for clinical diagnosis. Routine blood investigation, CSF evaluation and serum ganglioside panel was done in majority patients. NCS was done at admission and follow up on day 15, day 30 and day 90. Electrophysiological classification was done using Hadden's and Rajabally's criteria. Changes in electrophysiological patterns on serial NCS were evaluated using both these criteria.

Results: Majority patients (86.66%) belonged to <60 years age group with male: female ratio of 5:1. Antecedent event was present in 56.67% patients. Most common antecedent event was URTI. 88.46% patients achieved nadir within 14 days. MRC sum score was evaluated at admission and at every follow up. On admission 43.33% patients had <36 and 56.66% patients had ≥36 MRC sum score. At admission, 76.67% patients had Hughes disability score ≥4 and 23.33% patients had <4 score. The disability scores improved gradually along with clinical improvement. On day 90, 16.67% patients had Hughes disability score ≥4 and 83.33% patients had <4. Mean CSF protein was 105.35±103.52 (Mean± SD) mg/dl. Albuminocytological dissociation was found in 69.23% patients. Ganglioside panel came positive for 35% patients. Most common antibodies were anti GM-1 and anti GD-1b. Electrophysiological classification was done using Hadden's and Rajabally's criteria. According to Hadden's criteria at

admission, on day 15, on day 30 and on day 90, 58.62%, 52% 63.64% and 38.1% patients were classified as primary demyelinating category, while 20.69%, 36%, 22.73% and 28.57% patients were classified as primary axonal category respectively. At the same tine according to Rajabally's criteria, 48.28%, 48%, 40.9% and 33.33% patients were classified as primary demyelinating category, while 48.28%, 44%, 45.45% and 42.86% patients were classified as primary axonal category. 46.67% patients received plasma exchange, 16.67% patients received IVIg and 16.67% patients received both plasma exchange and IVIg. Two patients showed TRF. Greater number of patients with high EGRIS score had required mechanical ventilator. Greater number of patients with high EGOS and mEGOS score were unable to walk independently.

Conclusion: Majority of patients were of younger age group with significant male preponderance. More than half of the patients had history of antecedent event. Patients with low MRC sum score, high Hughes disability score at admission and higher EGOS and mEGOS score had poor outcome. As compared to Hadden's criteria, Rajabally's criteria is more sensitive for diagnosing primary axonal category and less sensitive but more specific for primary demyelinating category. Serial NCS helped to classify electrophysiology pattern accurately as well as to identify reversible conduction failure.

INTRODUCTION

Guillain-Barré Syndrome (GBS) or Landry-Guillain-Barré-Strohl syndrome, also known as post-infectious polyneuropathy or acute idiopathic polyneuritis 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.[1] It affects 0.9 to 2/100,000 persons in a year, with a worldwide distribution.[2,3] The subtypes of Guillain-Barré Syndrome have different incidence rates in different parts of the world. In Europe and North America AIDP is dominant contributing to 90% of the cases. In contrast in China and Japan AMAN being the most common subtype.[4,5] The picture is intermediate when we look at other population.

In the Indian context, the incidence of AIDP and AMAN is variable although AMAN is more common in younger patients.[6] There seems to be a slight preponderance of AIDP in studies by Gupta et al[7] and by Meena et al.[8,9] Similarly Bhargava et al[10] and Taly et al[11] showed higher incidence of AIDP in India. Different Indian studies have shown different seasonal variation in incidence of Guillain-Barré Syndrome. A study by Geetanjali et al[12] has shown highest incidence in summer, whereas Sudulugunta et al[13] has shown maximum incidence in winter season. In western countries, Guillain-Barré Syndrome is common in the 5th decade, but in India it occurs more commonly at a younger age.[14,15] Guillain-Barré Syndrome is equally common in men and women and can occur at any age. There is a male preponderance among the hospitalized population.[14,16]

Guillain-Barré Syndrome manifests itself with the clinical picture characterised by gait disturbance, pain and weakness, rapidly ascending symmetric flaccid muscle paralysis, areflexia with distal predominance (involving lower motor neuron), sensory disturbance, variable autonomic involvement, and increased cerebrospinal fluid (CSF) protein without pleocytosis. Despite the availability of partially effective forms of treatment, outcome in patients with Guillain-Barré Syndrome has not significantly changed in the last two decades.[17–20] Natural history studies show that about 10 to 20% of patients remain severely disabled and about 5% die.[17–20] About two- thirds of patients

who develop GBS report symptoms of an infection in the 6 weeks preceding the onset of the condition.[21,22]

The most common subtypes of the GBS include acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN). Other rare variants like Miller Fisher Syndrome, Cervico-brachial-pharyngeal, acute pan-dysautonomia, Bi-brachial, Paraparetic, Bickerstaff brainstem encephalitis and etc. have also been described.[8] The diagnosis of GBS is based on clinical history and examination, and is supported by ancillary investigations such as Cerebrospinal fluid examination and electrodiagnostic studies.[22]

However, because of the evolving nature of nerve damage and possible secondary pathological changes e.g., secondary axonal damage in AIDP[23,24] or because of critical illness[25,26], subtype classification can change during the disease course. Furthermore, ganglioside antibodies directed against (para)nodal structures in AMAN can cause conduction failure, which either resolves rapidly or leads to secondary Wallerian-like axonal degeneration.[26] The electrophysiological correlate of the former is denoted as reversible conduction failure (RCF), which can only be detected by serial NCS.[26]

This study is to be undertaken to study the clinical and serological profile of patients with Guillain-Barré Syndrome, changes in electrophysiological patterns in serial NCS 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

Guillain-Barré 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 Barré and Andre Strohl reported two cases with similar clinical features, loss of tendon reflexes and albuminocytological dissociation. The term Guillain-Barré syndrome 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.[27]

In 1956, C. Miller Fisher, a US doctor, described three patients with acute external ophthalmoplegia (eye paralysis), sluggish pupil reflexes, ataxia (lack of balance) and areflexia (absent tendon reflexes).[27] The presence of several subtypes of GBS has been known.

The combination of rapidly progressive symmetrical weakness in the arms and legs with or without sensory disturbances, hyporeflexia 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.[28] The disease is thought to be autoimmune and triggered by a preceding infection in two thirds of cases, most frequently respiratory or gastrointestinal infections.[29,30] This induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots.[17,31] 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.

EPIDEMIOLOGY

Most of the incidence rates of GBS reported were between 0.9-2.0/100,000/year with lower rates reported in children (<16 years) of 0.4-1.4/100,000/year. Most of the studies are from Europe and North America where the rates found were similar. Indian studies

also showing similar rates. 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. 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. For instance, an incidence of ~ 0.40 cases per 100,000 persons/year was reported in Brazil, 0.84 – 1.91 cases per 100,000 persons/year in Europe and North America and 2.1–3.0 cases per 100,000 persons/year in Iran, Curaçao and Bangladesh.[32] Indian study showed high incidence in young adults between 18 to 29 years of age. Seasonal preponderance in winter and summer was found.[33]

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. A number of studies have commented on a bimodal pattern of incidence by age, with peaks occurring in young adults and the elderly. 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.[34–36]

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.[37] 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.[38–41] 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 Hubei 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.[42] 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).[41]

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.[35,37,39] Cytomegalovirus is particularly common in young female GBS patients, and the clinical picture is notable for prominent involvement of the sensory and cranial nerves.[35] Many such patients have high serum titres of antibodies reacting with GM gangliosides and with sulphated glycolipids. 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-l is well recognized and occurs usually around the time of seroconversion.[43] 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. Recent evidence from Colombia, French Polynesia, and Puerto Rico have shown that infection with Zika virus, a mosquito borne RNA Flavivirus, plays an important role in the development of GBS.[44]

Coronavirus disease 2019 (COVID-19) has been shown to be associated with a lot of neurological complications, of whom Guillain-Barré syndrome is an important post-infectious consequentiality. More than 220 patients with GBS have been reported thus far. Commonly GBS occurs as a result of a post-infectious process but in a few cases where the symptoms of COVID-19 and GBS occur concurrently, corresponding to the

viremic phase, separate pathogenesis needs to be thought of probably neuro invasive potential of SARS-Cov-2.[45]

TABLE 1: Antecedent events for Guillain-Barré Syndrome

INFECTIONS		
Viral	**Bacterial**	**Parasites**
EBV CMV HIV Influenza virus Coxsackie virus Herpes simplex Hepatitis A and C viruses Zika virus	Campylobacter jejuni Mycoplasma pneumonia Escherichia coli	Malaria Toxoplasmosis
SYSTEMIC ILLNESSES	**OTHER MEDICAL CONDITIONS**	
Hodgkin's lymphoma Chronic Lymphocytic Leukemia Hyperthyroidism Collagen vascular disorders Sarcoidosis Renal disease	Pregnancy Surgical procedures Bone marrow transplants Immunizations Envenomation	

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.[46] 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.[47] 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.[48]

The possibility that GBS might be triggered by live attenuated oral poliovirus vaccine was suggested in a report from Finland.[49] 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 wildtype 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.[50]

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.[51] 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.

Few cases of GBS after COVID-19 vaccinations have been reported. Most commonly it caused AIDP variant. One study from Taiwan reported the bilateral facial palsy with paresthesia variant and initial onset symptoms of facial diplegia more frequently in GBS case-patients after COVID-19 vaccination.[52] Despite the benefits (e.g., increase in the number of persons not susceptible to infection and decrease in severe outcomes after infection) of COVID-19 vaccination far outweighing the potentially severe adverse events after infection, there is the need for vigilance in patients with neurologic symptoms after COVID-19 vaccination and for postvaccination surveillance programs to assess causality of GBS.[52]

CLINICAL PRESENTATION

In typical Guillain-Barré syndrome, rapidly progressive bilateral weakness is the key presenting symptom in most patients.[3,53,54] Weakness is classically described as ascending, and usually starts in the distal lower extremities, but can start more proximally in the legs or arms. The latter pattern can give the false clinical impression of a pyramidal lesion (i.e., at the level of the spinal cord or above), but can be easily explained by focal conduction block at the level of the lumbar and cervical nerve roots, rather than along the length of the nerve fibre. A small number of patients present with paraparesis, which can remain during the course of the disease.[55] Others might present with cranial nerve involvement resulting in facial, oculomotor, or bulbar weakness, as in Miller Fisher syndrome, which might then extend to involve the limbs. In addition to weakness, patients might initially have sensory signs, ataxia, and features of autonomic dysfunction.

Muscle pain or radicular pain, often but not always in the spinal region, is another frequent initial sign, which can complicate the diagnosis because pain can precede weakness in about a third of patients.[56] Symptoms of preceding infection might be too vague to add to the clinical presentation, but could be more informative, especially in the case of florid gastroenteritis. Most patients have, or develop, reduced tendon reflexes in the affected limbs. Reflexes can initially be normal especially in pure motor and axonal forms of the disorder or in a few cases, even be hyper-reflexic.[57]

According to various diagnostic criteria for Guillain-Barré syndrome, patients can have progression of weakness within 4 weeks. Most patients, however, reach the nadir within 2 weeks.[58] Progression can last up to 6 weeks after onset (subacute Guillain-Barré syndrome) in some rare cases.[59] During the progressive phase, 20–30% of patients develop respiratory failure and need ventilation at an intensive care unit (ICU).[58] The clinical condition of at least 25% of patients deteriorates during or shortly after treatment with IVIg or plasma exchange the inference of which is that they would be worse without therapy, rather than an indication of complete treatment resistance.[60]

Several clinical variants of GBS have been recognized as described in table.[8]

TABLE 2: Clinical variants of GBS

Clinical Variant	Presentation
Acute inflammatory demyelinating polyradiculoneuropathy	Predominantly motor, bilateral facial and pharyngeal, occasional sensory, and autonomic disturbances
Acute motor axonal neuropathy	Only motor neuropathy
Acute motor sensory axonal neuropathy	Motor and sensory neuropathy
Miller Fisher syndrome	Ophthalmoplegia, ataxia, areflexia
Acute pan dysautonomia	Pure autonomic neuropathy - both sympathetic and parasympathetic
Pure sensory GBS	Pure sensory neuropathy
Cervico-brachial-pharyngeal	Motor weakness predominantly affecting cervico-brachial and pharyngeal muscles
Bi-brachial	Motor weakness confining to both the upper limbs with areflexia
Distal limb variant	Motor weakness confined to distal muscles of upper and lower limbs with no sensory and cranial nerve involvement
Oculopharyngeal	Motor weakness predominantly affecting ocular and pharyngeal muscles
Paraparetic variant	Motor weakness predominantly confined to lower limbs
Pure ophthalmoplegia	Weakness of bilateral ocular muscles
Bilateral facial palsy with paraesthesia	Weakness of bilateral facial muscles with paraesthesia
Ropper's variant	Bilateral sixth and seventh cranial nerve palsy
Pure generalized ataxia	Symmetrical limb and axial ataxia
Polyneuritis cranialis	Symmetrical or asymmetrical multiple cranial neuropathy
Bickerstaff brainstem encephalitis	Ophthalmoplegia, ataxia, areflexia, pyramidal tract signs and impaired consciousness, often overlapping with sensorimotor GBS

The severity and duration of disease is highly diverse in patients and can range from mild weakness, from which patients recover spontaneously, to patients becoming quadriplegic and ventilator-dependent without signs of recovery for several months or longer. Eventually, however, all patients start improving, although recovery could follow a protracted course and result in severe, permanent disability. During the acute

phase, the stable phase, or even during recovery, patients might have signs or symptoms of autonomic dysfunction like cardiac arrhythmia that occasionally necessitates a pacemaker, excessive sweating, blood pressure instability, or ileus.[31]

PATHOGENESIS AND CLINICAL SPECTRUM

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULO-NEUROPATHY (AIDP)

Until very recently, the eponym Guillain-Barré 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.[61] AIDP is the most prevalent form of sporadic GBS in western countries and accounts for 85-90% of cases.[38] 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.[62,63]

The classic pathological picture of Guillain-Barré syndrome is of multifocal mononuclear cell infiltration throughout the peripheral nervous system in which the distribution of inflammation corresponds to the clinical deficit.[17,64] Macrophages invade the myelin sheaths and denude the axons. For the most part, macrophages seem to invade intact myelin sheaths, as occurs in experimental autoimmune neuritis.[17,65] According to one hypothesis, the activated macrophages are targeted to antigens on the surface of Schwann cells or the myelin sheath by activated T lymphocytes, which are major actors in experimental autoimmune neuritis. The initial invasion of the Schwann cell basement membrane is a consequence of matrix metalloproteinases, toxic nitric oxide radicals, and other mediators released by activated macrophages.[17,66] According to an alternative, but not mutually exclusive hypothesis, the initial event is the binding of antibodies to the surface of the Schwann cell, fixation of complement, probable damage to the Schwann cell, and vesicular dissolution of myelin in advance of cell

invasion. Evidence for this theory comes from autopsy material early in the course of the disease.[67] Various antibodies to nerve-cell components, notably anti glycolipids such as anti-GM1, have been detected in serum from GBS patients, but a direct causal link to the neuropathy has not yet been shown.[68] In severe lesions, the axons are also damaged probably as a secondary or "bystander" consequence of the toxic enzymes and radicals released by the immune mediated inflammatory response directed against the myelin. The degree of complicating axonal loss in AIDP is an important determinant of the speed of recovery, the lasting deficits, and the ultimate prognosis.

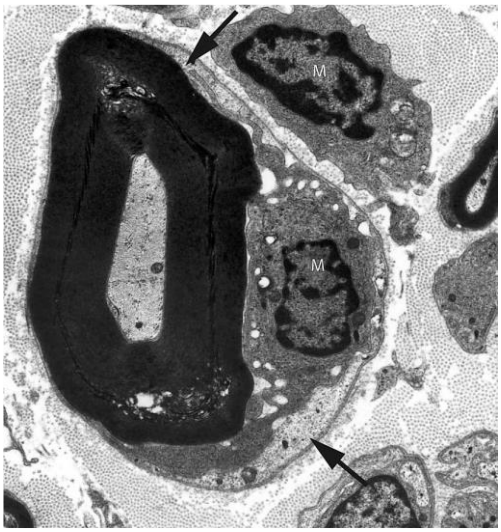


FIGURE 1: Electron micrograph of nerve fibre from patient with AIDP[17]

Electron micrograph shows a macrophage (M) has invaded Schwann cell basement membrane and stripped the abaxonal Schwann cell cytoplasm (arrows).

Electrodiagnostic (EDX) testing is performed to support the clinical impression. EDX testing of GBS patients often demonstrates features of demyelination, such as temporal dispersion, significantly slow conduction velocities, and prolonged distal and F-wave latencies.[8] Often, the first-detected NCS abnormalities are prolonged or absent F-waves, although other conduction abnormalities become evident as the disease progresses.[31] Electrodiagnostic testing features of acquired demyelination (e.g. conduction block, temporal dispersion, nonuniform slowing of conduction velocities) are particularly helpful because these findings are characteristic of immune-mediated demyelinating neuropathies. In early GBS, prolonged distal compound muscle action potential (CMAP) latencies and temporal dispersion are more commonly demonstrated than are slow motor conduction velocities and conduction block.[8]

- Electrodiagnostic features suggestive of acquired demyelinating neuropathy[8]:
  - Conduction velocity reduced in two or more nerves
  - CMAP conduction block or abnormal temporal dispersion in 1 or more nerves
  - Prolonged distal motor latencies in 2 or more nerves
  - Prolonged minimum F-wave latency or absent F-wave

ACUTE MOTOR-AXONAL NEUROPATHY (AMAN)

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, GD1a, and GD1b) and these paralleled the clinical course.[69] Sporadic AMAN cases have been observed worldwide; they represent 10-20% of GBS patients in contemporary prospective series.[37]

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.[70] Electro-physiological examination and necropsy in some cases confirmed a pure motor and axonal neuropathy pattern.[71]

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.[72] 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.[63]

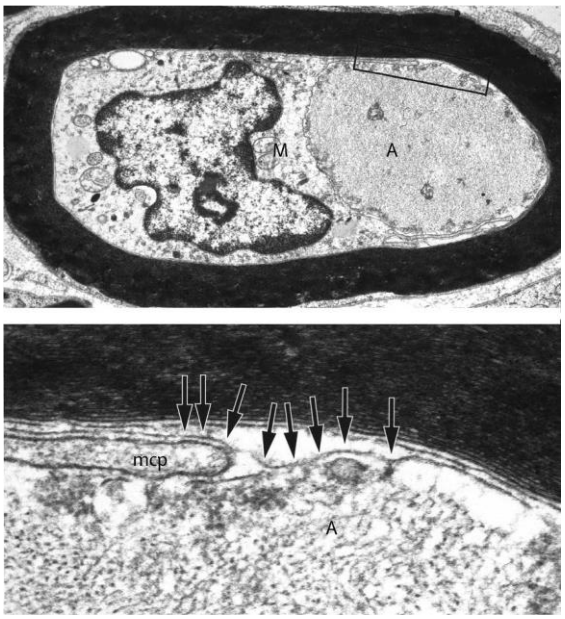


FIGURE 2: Electron micrograph of nerve fibre from patient with AMAN[17]

Electron micrograph shows macrophage (M) that has invaded the periaxonal space and axolemma (arrows) surrounding the axon (A).

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.[73] 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.[71] 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.[74] 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.[75] The anti-GM1 and anti-GD1a antibodies bind to the nodal axolemma,

leading to complement activation followed by MAC formation and disappearance of voltage-gated sodium channels.[31] 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.[76] 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 vigorousness of the immune response; it could range from limited degeneration of motor terminals to generalised and more widespread Wallerian-like degeneration of motor fibres.[73] 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.[77]

- Electrodiagnostic features suggestive of axonal neuropathy[8]
  - No evidence of significant reduction in conduction velocity.
  - No evidence of abnormal temporal dispersion.
  - Prolonged distal latency NOT considered demyelination if amplitude < 10% LLN.
  - Decrease in CMAP (AMAN) and SNAP (AMSAN) to <80% of LLN or inexcitable (absent evoked response) in 2 or more nerves.

ACUTE MOTOR-SENSORY AXONAL NEUROPATHY (AMSAN)

Feasby and colleagues[78] 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.[79]

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.[80] 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.[78] The observations were subsequently confirmed and extended by Griffin and colleagues in detailed analysis and morphological study of similar case presentations from northern China.[71,73] 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).

MILLER FISHER SYNDROME (MFS)

Another variant form of GBS-the Miller Fisher syndrome 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.[81,82] 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.[83,84] 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.[85] 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. The ataxia is attributed to a peripheral mismatch between proprioceptive input from the muscle spindles and the kinaesthetic information from joint receptors. Motor strength

is characteristically preserved, although overlap with typical GBS seems to occur when some patients progress to develop quadriparesis. There are other GBS variants which are relatively rare.

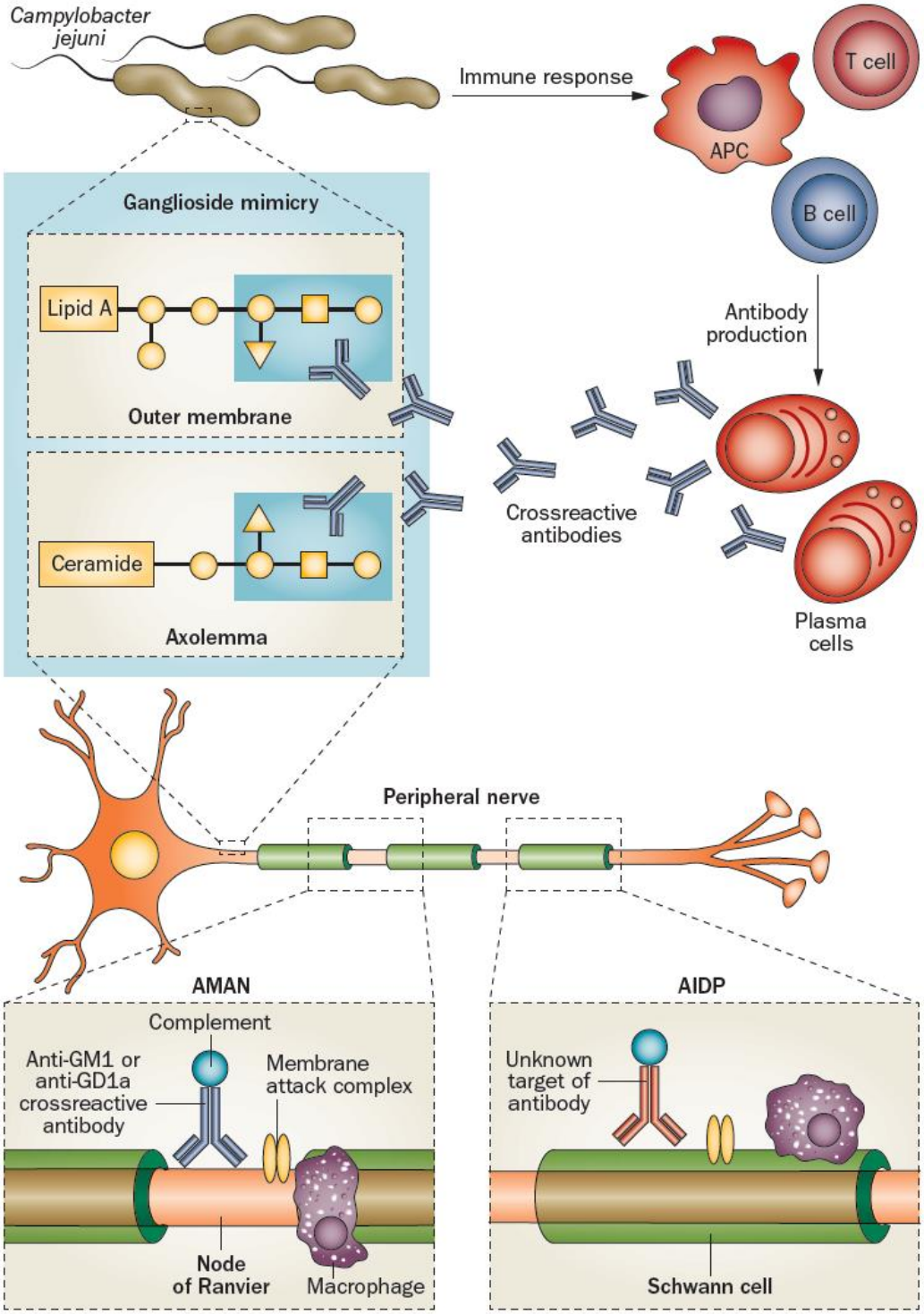


FIGURE 3: Immunopathogenesis of GBS[31]

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.[86] The important differential diagnosis to be considered is Sjögren syndrome and paraneoplastic sensory ganglionopathy.

PURE DYSAUTONOMIA

It is a rare variant of GBS, characterized by the rapid onset of combined sympathetic and parasympathetic failure without somatic sensory and motor involvement. Initial symptoms are pertaining to gastrointestinal tract such as abdominal pain, vomiting and diarrhoea or constipation. There may be possible history of viral infection. These patients develop severe orthostatic hypotension, heat intolerance, anhidrosis, dry eyes and mouth, fixed pupils, fixed heart rate, and disturbances of bowel and bladder function.[87] Orthostatic hypotension and syncope may the disabling features. Although areflexia and mild sensory symptoms may be evident, there is no motor weakness. About half of patients have autoantibodies to ganglionic acetylcholine receptors, which may play a pathogenetic role by blocking cholinergic transmission in autonomic ganglia. 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[88]

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.

DIFFERENTIAL DIAGNOSIS OF GBS[22]

The differential diagnosis of Guillain-Barré syndrome is broad and highly dependent on the clinical features of the individual patient.

CNS

- Inflammation or infection of the brainstem (for example, sarcoidosis, Sjögren syndrome, neuromyelitis optica or myelin oligodendrocyte glycoprotein antibody- associated disorder)
- Inflammation or infection of the spinal cord (for example, sarcoidosis, Sjögren syndrome or acute transverse myelitis)
- Malignancy (for example, leptomeningeal metastases or neurolymphomatosis)
- Compression of brainstem or spinal cord
- Brainstem stroke
- Vitamin deficiency (for example, Wernicke encephalopathy, caused by deficiency of vitamin B1, or subacute combined degeneration of the spinal cord, caused by deficiency of vitamin B12)

Anterior horn cells

- Acute flaccid myelitis (for example, as a result of polio, enterovirus D68 or A71, West Nile virus, Japanese encephalitis virus or rabies virus)

Nerve roots

- Infection (for example, Lyme disease, CMV, HIV, EBV or varicella zoster virus)
- Compression
- Leptomeningeal malignancy

Peripheral nerves

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Metabolic or electrolyte disorders (for example, hypoglycaemia, hypothyroidism, porphyria or copper deficiency)
- Vitamin deficiency (for example, deficiency of vitamins B1-beriberi, B12 or E)
- Toxins (for example, drugs, alcohol, vitamin B6, lead, thallium, arsenic, organophosphate, ethylene glycol, diethylene glycol, methanol or N- hexane)
- Critical illness polyneuropathy
- Neuralgic amyotrophy
- Vasculitis
- Infection (for example, diphtheria or HIV)

Neuromuscular junction

- Myasthenia gravis
- Lambert–Eaton myasthenic syndrome
- Neurotoxins (e.g., botulism, tetanus, tick paralysis or snakebite envenomation)
- Organophosphate intoxication

Muscles

- Metabolic or electrolyte disorders (for example, hypokalaemia, thyrotoxic/ hypokalemic periodic paralysis, hypomagnesaemia or hypophosphatemia)
- Inflammatory myositis
- Acute rhabdomyolysis
- Drug induced toxic myopathy (for example, induced by colchicine, chloroquine, emetine or statins)
- Mitochondrial disease

Other

- Conversion or functional disorder

DIAGNOSTIC CRITERIA[3,22]

The two most commonly used sets of diagnostic criteria for GBS were developed by the National Institute of Neurological Disorders and Stroke (NINDS) in 1978 (revised in 1990) (by Asbury and Cornblath)[53] and the Brighton Collaboration in 2011[22]. Both sets of criteria were designed to investigate the epidemiological association between GBS and vaccinations but have since been used in other clinical studies and trials. NINDS criteria is considered to be more suited to the clinician as they present the clinical features of typical and atypical forms of GBS, although the criteria from the Brighton Collaboration are also important, widely used, and can help the clinician to classify cases with (typical) GBS or MFS according to diagnostic certainty.

REVISED NINDS CRITERIA[22]

- **Features required for diagnosis**
  - Progressive bilateral weakness of arms and legs (initially only legs may be involved)
  - Absent or decreased tendon reflexes in affected limbs (at some point in clinical course)

- **Features that strongly support diagnosis**
  - Progressive phase lasts from days to 4 weeks (usually <2 weeks)
  - Relative symmetry of symptoms and signs
  - Relatively mild sensory symptoms and signs (absent in pure motor variant)
  - Cranial nerve involvement, especially bilateral facial palsy
  - Autonomic dysfunction
  - Muscular or radicular back or limb pain
  - Increased protein level in cerebrospinal fluid (CSF); normal protein levels do not rule out the diagnosis
  - Electrodiagnostic features of motor or sensorimotor neuropathy (normal electrophysiology in the early stages does not rule out the diagnosis)

- **Features that cast doubt on diagnosis**
  - Increased numbers of mononuclear or polymorphonuclear cells in CSF (>50 × 10^6/l)
  - Marked, persistent asymmetry of weakness
  - Bladder or bowel dysfunction at onset or persistent during disease course
  - Severe respiratory dysfunction with limited limb weakness at onset
  - Sensory signs with limited weakness at onset
  - Fever at onset
  - Nadir <24 h
  - Sharp sensory level indicating spinal cord injury
  - Hyperreflexia or clonus
  - Extensor plantar responses
  - Abdominal pain
  - Slow progression with limited weakness without respiratory involvement
  - Continued progression for >4 weeks after start of symptoms
  - Alteration of consciousness (except in Bickerstaff brainstem encephalitis)

BRIGHTON COLLABORATION DIAGNOSTIC CRITERIA[22]

TABLE 3: Brighton collaboration diagnostic criteria for GBS[22]

Level 1	Level 2	Level 3
Bilateral AND flaccid paralysis of the limbs AND	Bilateral AND flaccid paralysis of the limbs AND	Bilateral AND flaccid paralysis of the limbs AND
Decreased or absent tendon reflexes in weak limbs AND	Decreased or absent tendon reflexes in weak limbs AND	Decreased or absent tendon reflexes in weak limbs AND
Monophasic illness pattern and interval between onset AND nadir of weakness between 12 h and 28 days with subsequent clinical plateau AND	Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days with subsequent clinical plateau AND	Monophasic illness pattern, interval between onset and nadir of weakness between 12 h and 28 days, with subsequent clinical plateau AND
Electrophysiological findings consistent with Guillain-Barré syndrome AND	CSF total white cell count <50 cells/µl (with or without CSF protein elevation above laboratory normal value) OR	Absence of an identified alternative diagnosis for weakness
Cerebrospinal fluid (CSF) protein level above laboratory normal value AND CSF total white cell count <50 cells/µl) AND	If CSF not collected or results not available, electrophysiologic studies consistent with GBS AND	
Absence of an identified alternative diagnosis for weakness	Absence of an identified alternative diagnosis for weakness	

These diagnostic criteria are not applicable to all variants of GBS.

LABORATORY STUDIES

1. 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 1.0 gm/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.[89] A spinal fluid cell count of more than 50 cells/mm suggests infection with human immunodeficiency virus or Lyme infections.

2. ELECTRO DIAGNOSTIC STUDIES

Since the 1990s the electrodiagnosis of GBS have become more complicated because besides AIDP, two primary axonal subtypes: AMAN and AMSAN, associated with antecedent Campylobacter jejuni infection and autoantibodies against gangliosides were recognized.

About half of the patients have normal NCSs during the first 4 days of illness (except for absent H reflexes), while only about 10% of them have normal studies by the first week of illness.[90] Electrodiagnostic criteria have been advocated over the years, with sensitivities ranging from 20% to 70%.[91] In general, about two-thirds of patients fulfil the criteria for highly suggestive or definite AIDP in the first 2 weeks of illness, with high specificity (95%–100%). In general, the electrodiagnostic studies become more specific for multifocal demyelination during the third and fourth weeks of illness.[92] Electrodiagnostic parameters are the most reliable indicators of prognosis. Mean distal CMAP amplitude of less than 20% of the lower limit of normal (LLN) was associated with poor outcome in the North American GBS study.[93]

To differentiate AIDP and AMAN, Ho's (1995) and Hadden's (1998)[94] criteria sets have been used in the last two decades; Hadden's criteria (Annexure 15.2), differentiated GBS into Primary Demyelinating, Primary Axonal, Inexcitable and Equivocal variants according to parameters.[94] The major difference from Ho's criteria is that CB, instead of ''unequivocal" TD, is considered for AIDP diagnosis.[95] To achieve the highest diagnostic accuracy of GBS subtype, Rajabally and colleagues proposed a criteria set in 2015 (Annexure 15.3) with more conservative cut-offs for demyelinating parameters and introduced the absence of F wave and proximal/distal CMAP amplitude <0.7, without other features of demyelination, as indicative of axonal GBS.[96] Rajabally's criteria, compared to Hadden's criteria, showed a remarkable increase of sensitivity in the diagnosis of axonal GBS but a lower sensitivity in the diagnosis of AIDP. In 2017, Uncini et al. proposed criteria with the cut-off for distal motor latency, which is intermediate between Hadden's and Rajabally's values; the duration of distal CMAP and the results of sensory conduction studies were also taken into consideration, and proximal/distal CMAP amplitude <0.7 was considered only for axonal GBS.[95]

However, in AMAN and AMSAN patients it has been shown that abnormal CMAP amplitude reduction and conduction slowing can promptly recover at serial studies without the development of TD suggestive of remyelination.[97] This electrophysiologic feature, named reversible conduction failure (RCF), was not contemplated in the old electrodiagnostic criteria.

Because of the evolving nature of nerve damage and possible secondary pathological changes e.g., secondary axonal damage in AIDP or because of critical illness, subtype classification can change during the disease course. Furthermore, ganglioside antibodies directed against (para)nodal structures in AMAN can cause conduction failure, which either resolves rapidly or leads to secondary Wallerian like axonal degeneration. The electrophysiological correlate of the former is denoted as reversible conduction failure (RCF), which can only be detected by serial NCS and, in contrast to classical conduction blocks in AIDP, is not caused by segmental demyelination.[26]

RCF is thought to be caused by an anti-ganglioside antibodies and complement-mediated attack at the node of Ranvier inducing a transient dysfunction of excitability not progressing to axonal degeneration.[95,98–100] RCF can be demonstrated in all motor nerve segments. In RCF distal CMAP amplitude rapidly increases and CB in the intermediate nerve segments promptly resolves, without the development of excessive TD and polyphasia of CMAPs. Moreover, the resolution of RCF in the distal segment can reveal an additional abnormal amplitude reduction in the intermediate segment. Some nerves show normal conduction with no recordable F waves that recovers without increased latency indicating an isolated RCF in the proximal nerve segments. RCF has been shown also in sensory fibres in AMSAN and GBS variants such as Miller Fisher syndrome and acute sensory ataxic neuropathy.[95,101–103] The cut-offs for RCF were recently established. Regarding the motor fibres, there is a general agreement on the cut-off that proposed in distal nerve segments: at least 50% increase of distal CMAP amplitude without increased CMAP duration at second study.[104,105] For the other nerve segments, proposed as RCF a <0.7 proximal/distal (p/d) CMAP amplitude at first study which improves, at follow-up, more than 0.2 without abnormal TD.[95] Van den Bergh and colleagues defined RCF as the resolution of CB by at least 30% increase of p/d CMAP amplitude.[105] Chan and colleagues defined RCF as the resolution of CB due to

increase of proximal CMAP amplitude with accompanying increase (≥10%) in CV or decrease (≥10%) in proximal CMAP duration.[104]

Apart from the possible detection of RCF, the value of repeated NCS is currently debated[26,106] with some studies showing no or only minor benefit[96,105,107] and other studies reporting a more accurate subtype classification.[97,103]

Acute Inflammatory Demyelinating Polyradiculoneuropathy (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.[92,94,96,97]

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.[108] 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. 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.

Reduced amplitude or absent SNAPs in the upper extremity combined with normal sural SNAPs (sural sparing pattern) are changes highly specific for the diagnosis of AIDP and occur in about 50% of patients during the first 2 weeks of the illness.[90,92] Sural sparing combined with abnormal F waves is highly specific (96% specific) for

the diagnosis of AIDP, is present in about half of the patients with AIDP and in about two-thirds of patients younger than 60 years during the first 2 weeks of illness.[92] A sensory ratio (sural + radial SNAPs/median + ulnar SNAPs) is a good substitute for sural sparing pattern, particularly in elderly patients who have absent sural SNAP or those with pre-existing CTS. A high ratio (>1) is fairly specific and distinguishes GBS from other axonal polyneuropathies such as diabetic neuropathies.[109] Conduction block of motor axons, the electrophysiological correlate of clinical weakness, is recognized by a decrease of greater than 50% in CMAP amplitude from distal to proximal stimulation in the absence of temporal dispersion. Conduction block at non-entrapment sites is highly specific for demyelination, but it occurs only in 15%–30% of early GBS, depending on the number of nerves and nerve segments studied. Patients with weakness that is related primarily to conduction block tend to have a faster and more complete recovery than those with diffusely low motor amplitudes. Prolonged distal motor latencies, reduction in distal CMAP amplitudes, significant CMAP dispersion, and slowing of motor conduction velocities are less common and tend to occur later in the course of the disease.[92,110]

Acute Motor Axonal Neuropathy (AMAN)

In patients with AMAN, the main abnormality in motor conduction studies is reduced compound muscle action potential amplitudes and absent F-wave responses.[111] 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.

Acute Motor Sensory Axonal Neuropathy (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 inexcitability of motor nerves, which can be found as early as 3-5 days of onset.[80] Sensory nerve action potentials are also lost. Abundant fibrillation potentials and positive sharp waves can appear quite early.

Miller Fisher syndrome (MFS)

Electrodiagnostic studies demonstrate an axonal process affecting predominantly sensory nerve fibres, with no or only mild motor nerve conduction abnormalities. SNAP amplitudes are normal in half of the patients and reduced or absent with a sural sparing pattern in one-third of patients.[112] Motor conduction studies, F-wave latencies, and needle EMG are usually normal.

3. SEROLOGICAL TESTS

The value of specific serological tests in the diagnosis of GBS is limited except in MFS and AMAN.[113] There is no specific ganglioside antibody that appears to be associated with AIDP. Elevated anti-GQ1b ganglioside antibodies are consistently found in about 95%-98% of patients with MFS. Preceding C. jejuni infection has been linked to AMAN variant and high titres of anti-GM1, anti-GD1b, anti-GD1a, and anti-GalNAc-GD1a ganglioside antibodies of the IgG class.[39] Various GBS subtypes and associated distinct anti-ganglioside antibodies are as below.[9,17]

TABLE 4: Association of anti-ganglioside antibodies with GBS subtypes[9]

Subtypes/Variants	IgG antibodies against
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	None
Acute motor axonal neuropathy (AMAN)	GM1, GM1b, GD1a and GalNAc-GD1a
Acute motor and sensory axonal neuropathy (AMSAN)	GM1, GM1b and GD1a
Acute motor conduction block neuropathy	GM1 and GD1a
Pharyngeal-cervical-brachial (PCB) variant	GT1a (less frequently with GQ1b and GD1a)
Miller Fisher syndrome (MFS)	GQ1b and GT1a
Acute ataxic neuropathy (without ophthalmoplegia)	GQ1b and GT1a
Pure sensory ataxic variant	GD1b (less frequently with GQ1b and GT1a)
Bickerstaff brainstem encephalitis (BBE)	GQ1b and GT1a

Serological tests for C. jejuni infection are difficult both to perform and interpret. Other studies confirmed the presence of IgG antiglycolipid antibodies in 10%-40% of patients with GBS but failed to show a correlation with C. jejuni infection.[42] Elevated serum

antibodies to Mycoplasma, CMV, or C. jejuni can pinpoint the preceding infection. Anti-galactocerebroside antibodies have been detected in patients with precedent Mycoplasma infection. Complement-fixing antibodies to peripheral nerve myelin are present in most patients during the acute phase of GBS.

4. IMAGING STUDIES

MRI of the brain and spine, are most useful to exclude brainstem or spinal cord disease as a cause of the weakness. MRI of the lumbar spine with gadolinium may be abnormal in GBS and may show nerve root enhancement of the cauda equina, particularly in children with GBS.[114]

A new potential diagnostic tool in GBS is ultrasound imaging of the peripheral nerves, which has revealed enlarged cervical nerve roots early in the disease course, indicating the importance of spinal root inflammation as an early pathological mechanism.[22,115] This technique might, therefore, help establish a diagnosis of GBS early in the disease course, although further validation is required.

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.

Approximately 15% of GBS patients have a mild condition, remain ambulatory, and recover after a few weeks. Conversely, 5%–20% of patients have a fulminant course and develop flaccid quadriplegia, ventilator dependence, and axonal degeneration, often within 2 days from the onset of symptoms. The recovery is delayed and virtually always incomplete and most have substantial residual motor deficits at 1-year follow up.

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.[116] 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.[117] Similar figures were reported in other series. Several clinical factors have been identified that assist in the early prediction of outcome.

Up to 30% of patients with GBS develop respiratory insufficiency requiring assisted ventilation, and between 2% and 5% die of complications.[118] After progression stops, patients enter a plateau phase lasting 2–4 weeks or longer before recovery begins. Although most patients recover functionally, 20% still have residual motor weakness 1 year later. Up to 5% of patients may have a recurrence following recovery.

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.[119] 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.[77] 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 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[120] (Annexure 15.4) is the most popularly used. MRC disability scale[121], Modified Rankin's disability scale[122] (Annexure 15.4) and functional evaluation by Barthel Index are also used for disability assessment.

TREATMENT

Treatment of GBS usually combines multidisciplinary supportive medical care and immunotherapy.

SUPPORTIVE CARE

General supportive management is the mainstay of treatment. The reduction in mortality to less than 5% reflects improvements in modern critical care. The prevention of complications, of which respiratory failure and autonomic dysfunction are the most important, provides the best chance for a favourable outcome.[123] Respiratory and bulbar function, ability to handle secretions, heart rate, and blood pressure should be closely monitored during the progressive phase. Reasons to admit patients to the intensive care unit (ICU) include the following: evolving respiratory distress with imminent respiratory insufficiency, severe autonomic cardiovascular dysfunction (for example, arrhythmias or marked variation in blood pressure), severe swallowing dysfunction or diminished cough reflex, and rapid progression of weakness.[22] Respiratory failure requiring mechanical ventilation develops in up to 30% of patients with GBS. A state of imminent respiratory insufficiency is defined as clinical signs of respiratory distress, including breathlessness at rest or during talking, inability to count to 15 in a single breath, use of accessory respiratory muscles, increased respiratory or heart rate, vital capacity <15–20 ml/kg or <1 litre, or abnormal arterial blood gas or pulse oximetry measurements. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) prognostic tool was developed for this purpose and calculates the probability (1–90%) that a patient will require ventilation within 1 week of assessment.[124] It includes rapid disease progression (onset to admission in <7 days), severity of limb weakness (MRC Sum score), presence of facial weakness, and bulbar weakness.[124]

Signs of impending respiratory failure include deterioration in forced vital capacity (FVC), declining maximal respiratory pressures, and hypoxemia caused by atelectasis. Initially it may be necessary to monitor FVC and negative inspiratory pressure every 4–6 hours while the patient is awake. Patients should be monitored by pulse oximetry, especially at night, for the early detection of oxygen desaturation. Serial measures of decline in respiratory function that could predict future respiratory failure include vital capacity of less than 20 mL/kg or a decline by 30% from baseline, maximal inspiratory pressure less than 30 cm H_2O, and maximal expiratory respiratory pressure of less than 40 cm H_2O.[125] This so-called 20-30-40 rule allows patients at risk to be identified and transferred to an ICU for even closer monitoring. In a series of 200 patients, short disease duration, inability to lift the head from the bed, and a vital capacity of less than 60% predicted the need for mechanical ventilation in 85% of patients with all three risk factors.[126] Elective intubation for ventilatory assistance should be performed when FVC falls below 12–15 mL/kg or below 18 mL/kg in patients with severe oropharyngeal weakness, or when arterial PO_2 values fall below 70 mm Hg with inspired room air. When respiratory assistance is needed for longer than 2 weeks, a tracheostomy should be performed.

In the event of cardiac arrhythmias or marked fluctuations of blood pressure, continuous ECG and blood pressure monitoring allow early detection of life-threatening situations that require prompt treatment. Antihypertensive and vasoactive drugs must be used with extreme caution in the presence of autonomic instability. Tracheal suctioning may trigger sudden episodes of hypotension or bradyarrhythmia. Back and radicular pain often respond to NSAIDs. At times, oral or parenteral opioids are required for adequate pain control. Increased metabolic requirements together with negative caloric intake caused by impaired swallowing may lead to a state of relative starvation in severely affected patients. Nutritional requirements should be met by providing a high-caloric protein diet or by beginning enteral feedings as early as possible.

Subcutaneous heparin or low-molecular-weight heparin together with calf compression devices should be ordered routinely in immobilized patients to lower the risks of venous thrombosis and pulmonary embolism. Infections of the lung and urinary tract develop in almost half of patients with GBS in the ICU. Prevention and prompt treatment of nosocomial infections are important aspects of care. Chest physical therapy and

frequent oral suctioning aid in preventing atelectasis in patients with impaired cough and sigh. Skilled nursing care with regular turning and attention to skin, eyes, mouth, bowel, and bladder are essential. Exposure keratitis is avoided in cases of facial diplegia by using artificial tears and by taping the eyelids closed at night. Pressure-induced ulnar or fibular nerve palsies are prevented by proper positioning and padding. Physical therapy is started early because it helps prevent contractures, joint immobilization, and venous stasis. Psychological support and constant reassurance about the potential for recovery are important for the morale of patients and family members. In the recovery phase, skilled physical therapy and rehabilitation hasten recovery.

IMMUNOTHERAPY

Several randomised controlled trials (RCTs) studying the effect of immunotherapy in Guillain-Barré syndrome have been done in the past few decades. IVIg and plasma exchange have proved effective.[3,18,127] Immunotherapy is usually started if patients are not able to walk 10 m unaided (GBS Disability Scale score ≥3).[18,20,31] Plasma exchange and IVIg have pleiotropic immunomodulatory effects, but we have yet to establish which effects explain their therapeutic efficacy in GBS, and whether the same effects are involved in all patients and all subtypes of GBS. If IVIg or plasma exchange will be started, they should, in principle, be started as soon as possible, before irreversible nerve damage has taken place.[3]

Plasma exchange

Plasma exchange became accepted as the gold standard treatment for Guillain-Barré syndrome almost 20 years ago. Evidence to support this practice has accumulated from six trials, but not all studies provided all the outcome measures of interest. Most used a 7-point Guillain-Barré syndrome disability grade scale. In four trials, including 585 participants with available data, plasma exchange increased the improvement after 4 weeks by an average of 0·89 grades (95% CI 0·63 1·14). In five trials with 623 participants, plasma exchange almost halved the proportion of patients requiring ventilation after 4 weeks from 27% to 14% (relative risk [RR] 0·53 [95% CI 0·39–0·74]; p=0·0001). In four trials with 204 participants, plasma exchange increased the proportion of patients who recovered full strength within a year from 55% to 68% (RR 1·24 [1·07–1·45]).[17,127]

Plasma exchange is thought to remove neurotoxic antibodies, complement factors and other humoral mediators of inflammation.[18,31,127] Plasma exchange is beneficial when performed within the first 4 weeks after onset of weakness in patients who are unable to walk unaided (GBS Disability Scale score ≥3), but the largest effect is seen when treatment is started within the first 2 weeks.[18,31,127,128] The usual plasma exchange regimen consists of five treatments administered over 2 weeks, involving a total of about five plasma volumes. The effect of plasma exchange in mildly affected patients and the optimal number of exchanges were investigated by the French Cooperative Group on Plasma Exchange (1997).[129] In mildly affected patients (still able to walk), however, two plasma exchange sessions induced more-rapid onset of motor recovery than did no plasma exchange.[129]

The recommended plasmapheresis schedule entails a series of four to five exchanges (40–50 mL/kg) with a continuous flow machine on alternate days, using saline and albumin as replacement fluid. A Cochrane review confirmed the value of plasma exchange over supportive therapy in hastening the recovery from GBS when started within 30 days after disease onset.[127] Most serious complications are linked to venous access problems, including hematoma formation at puncture sites, pneumothorax after insertion of central lines, and catheter-related septicaemia. Septicaemia, active bleeding, and severe cardiovascular instability are contraindications for plasmapheresis. Filtration-based plasma exchange techniques, which use porous membranes for filtration, has similar safety and efficiency when compared to centrifugal plasma exchange. A single study comparing these two modalities in patients with GBS demonstrated a shorter time to onset of effect and greater change in disability with centrifugal plasma exchange. However, mortality and outcome after 6 months were not different between the two therapeutic modalities.[130]

Intravenous immunoglobulin (IVIg)

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. The two treatments were compared for their effectiveness in a multicentre study of 150 GBS patients in the Netherlands.[131] 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.

In the Cochrane review of IVIg with an additional four trials that included a total of 536 participants, there was no difference between the two treatments in the improvement in disability after 4 weeks. There was also no significant difference between the two treatments with respect to duration of mechanical ventilation, death, or residual disability.[60]

Two treatments were assessed again in a large, multicentre, randomised trial coordinated by Hughes.[132] 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.

The regimen almost always used has been 0.4 g/kg per day for 5 days.[17] Whether rapid IVIg treatment over 2 days is superior to treatment with the same total dose (2 g/kg) administered over 5 days has not been fully evaluated. However, one trial demonstrated that children receiving treatment over 2 days more frequently had treatment-related fluctuations than did children receiving treatment over 5 days.[133] The mechanism of action of IVIg is probably multifactorial, possibly involving blockade of Fc receptors, provision of anti-idiotypic antibodies, interference with complement activation, and T-cell regulation.[134]

Minor side effects such as headaches, myalgias and arthralgias, flulike symptoms, fever, and vasomotor reactions are observed when infusion flow rates are excessive.

More serious complications such as anaphylaxis in IgA-deficient individuals (1 per 1000 population, who develop anti-IgA antibodies after the first course of IgA-containing IVIg infusions), aseptic meningitis, congestive heart failure, thrombotic complications (venous thrombosis and cerebral and myocardial infarctions), and transient renal failure, have been reported.[135] The rate of vascular complications, particularly cerebral and myocardial infarctions, is higher in patients with vascular risk factors treated with a more rapid infusion rate. To prevent headache and possibly aseptic meningitis, patients should be pretreated with oral acetaminophen, 500–1000 mg, or ibuprofen, 800 mg, a few hours before each infusion; the dose can be repeated 6 hours later if headache develops. For patients with hyperviscosity, congestive heart failure, chronic renal failure (especially that due to diabetes), or congenital IgA deficiency, IVIg is contraindicated and plasma exchange is preferred.

GBS patients receiving the standard dose of IVIg (0.4 g/kg/day × 5 days) have a large variation of IgG levels measured 2 weeks after infusion, and those with a smaller increase in IgG level do worse, independent of other prognostic factors.[136] It is not yet known whether the infusion of additional IVIg to patients who show a small increase in IgG levels is beneficial.

Combination of plasma exchange followed by IVIg is not significantly better than plasma exchange or IVIg alone.[132] No evidence exists that shows a second course of IVIg is effective in patients with Guillain-Barré syndrome who continue to deteriorate. Researchers in the Netherlands are investigating whether patients with Guillain-Barré syndrome with a poor prognosis, defined using the modified Erasmus GBS outcome scale (mEGOS), might benefit from a second IVIg course when given shortly after the first IVIg course (SID-GBS RCT trial).[3,137,138] Investigators of an international variant of the SID-GBS trial (I-SID-GBS) are studying this effect using an observational, prospective open study design. The I-SID-GBS study is being done as part of the International Guillain-Barré syndrome Outcome Study (IGOS), supported by the Inflammatory Neuropathy Consortium, which aims to contribute to a broader understanding of the major causal factors in the disease.

Corticosteroids

Contrary to expectation, corticosteroids proved to be of no benefit in GBS. The balance of evidence from six trials with 587 participants is that corticosteroids are ineffective.[17,139] Improvement has most commonly been measured by assessing change on the 7-point Guillain-Barré syndrome disability scale. In four trials of oral corticosteroids with a total of 120 participants, there was significantly less improvement after 4 weeks with corticosteroids than without (weighted mean difference 0·82 of a disability grade less improvement [95% CI 0·17–1·47]).[139] In two trials with a combined total of 467 participants, there was a non-significant trend towards more benefit from intravenous corticosteroids (weighted mean difference 0·17 of a disability grade more improvement after 4 weeks than with placebo [95% CI –0·06 to 0·39]).[139] Likewise, there was also no significant improvement in patients treated with corticosteroids for other important outcomes including time to recovery of unaided walking, time to discontinue ventilation in the subgroup who need ventilation, death, and disability after 1 year. In one trial, however, there was a non-significant trend toward more rapid improvement when intravenous methylprednisolone 500 mg daily for 5 days was added to IVIg.[140] This effect became significant in a post-hoc analysis after correction for prognostic factors including age and initial disability. The combination of IVIg with methylprednisolone failed to find significant long-term advantage over IVIg alone in one trial. A recent Cochrane review confirms that corticosteroids do not produce significant benefit or harm.[141] The lack of a more obvious effect of corticosteroids is difficult to explain in an inflammatory disease, especially since such treatment is beneficial in the related condition of chronic inflammatory demyelinating polyradiculoneuropathy. Possible explanations for the lack of effect could be that corticosteroids adversely affect the recovery process by inhibiting macrophage clearance of myelin debris and so hamper remyelination or aggravate the damage of denervated muscle fibres.[17,142,143]

OTHER MEDICATIONS

A completely new approach is being investigated in an RCT of the drug, eculizumab - a humanised monoclonal antibody that binds with high affinity to the complement factor C5 and prevents its cleavage to C5a and the proinflammatory, cytolytic C5b-9 complex.[3,144,145]

A small trial showed that interferon beta-1a would be safe in patients with Guillain-Barré syndrome, but the sample size was too small to detect anything other than a very large effect.[17,146] If T cells were shown to be of prime importance in AIDP then drugs which interdict T-cell cytokines or prevent the passage of T cells into the endoneurium should be considered, dependent on their safety record. Protection of the axons by sodium channel blockade was a successful strategy in experimental autoimmune neuritis and should be considered for Guillain-Barré syndrome.[147] one trial studying a 6 week course of mycophenolate mofetil combined with standard IVIg versus IVIg alone, did not indicate beneficial effects of these treatments.[31,148] A pilot trial of brain-derived neurotrophic factor in Guillain-Barré syndrome was discontinued when the company undertaking the research withdrew the drug from development,[149] but other trophic factors or combinations of trophic factors may be worth pursuing.

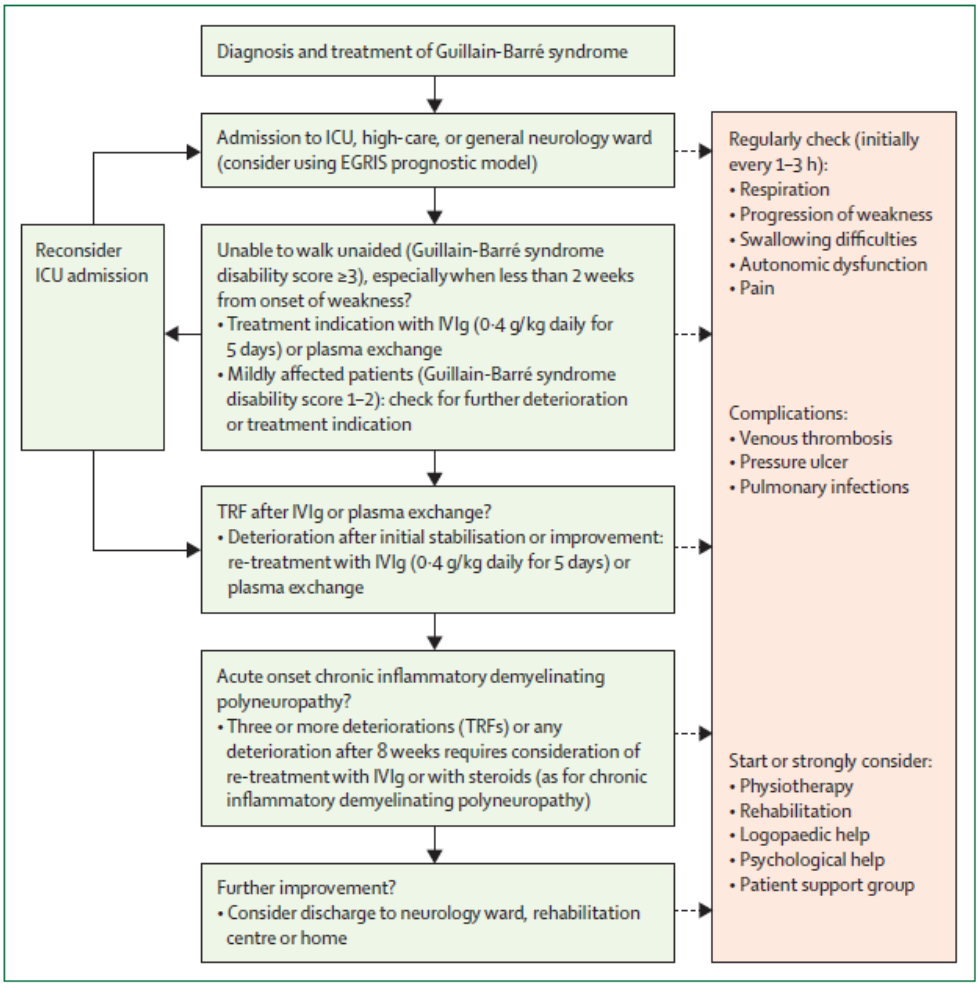


FIGURE 4: Treatment approach for GBS

TREATMENT RELATED FLUCTUATIONS (TRF)

About 10% of patients treated with IVIg or plasma exchange will deteriorate after initial improvement or stabilisation i.e., they will have a TRF.[3,150] These TRFs usually occur within the first 8 weeks after start of treatment. Repeated treatment (2 g IVIg/kg in 2–5 days) has been observed to be beneficial in these patients. Although no RCTs have shown that re-treatment is beneficial in case of a TRF, it is common practice in many centres to do so.[54] Patients with Guillain-Barré syndrome with a TRF are likely to have a prolonged immune response that causes sustained nerve damage or functional blockade, which needs more prolonged treatment than standard care.

ACUTE ONSET CHRONIC INFLAMMATORY DEMYELINATING NEUROPATHY

Some patients initially diagnosed with Guillain-Barré syndrome can have several episodes of deterioration. Others initially have a rapidly progressive course like Guillain-Barré syndrome, but subsequently have further progression exceeding 4 weeks. In these patients, the question often arises as to whether the diagnosis is still consistent with Guillain-Barré syndrome, or the patient has chronic inflammatory demyelinating polyneuropathy with acute onset. In a prospective study series, about 5% of patients initially diagnosed with Guillain-Barré syndrome were eventually found to have acute onset chronic inflammatory demyelinating neuropathy.[3,138,151] The diagnosis of acute onset chronic inflammatory demyelinating neuropathy should especially be considered in patients initially diagnosed with Guillain-Barré syndrome who have one or more of these findings: (1) deteriorate after 8 weeks; (2) have more than two treatment-related fluctuations, particularly when they occur beyond 1 month of the illness; (3) have prominent sensory symptoms or signs; (4) have multifocal enlargement of peripheral nerves on ultrasound; or (5) develop new prominent demyelinating features on follow-up EDX studies many months after the initial presentation.[138] These secondary deteriorations should be recognised because patients with Guillain-Barré syndrome with a TRF might improve after re-treatment, and patients with acute onset chronic inflammatory demyelinating neuropathy usually need chronic maintenance treatment with IVIg or a switch to corticosteroid treatment.

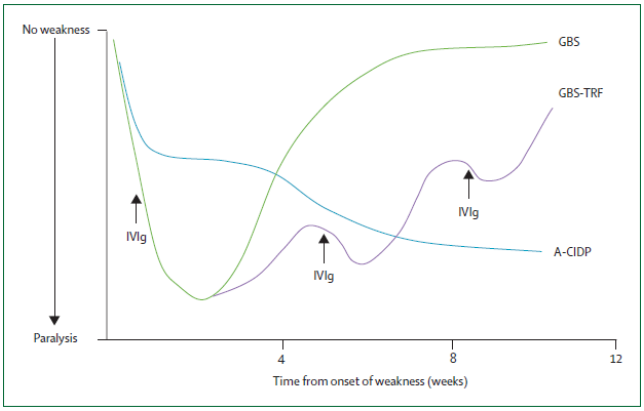


FIGURE 5: Clinical course with GBS, TRF and A-CIDP[20]

GBS OUTCOME

As the clinical course and outcomes of GBS are highly variable, their accurate prediction is important to enable clinicians to tailor supportive care and treatment to the individual patient's needs and to inform patients and relatives about the expected clinical course.[31]

PREDICTORS OF NEED FOR VENTILATION

Three large studies have been performed to predict the probability of respiratory insufficiency in patients with GBS. A French study including 722 patients found that time from onset to admission of <7 days, inability to cough, inability to stand, inability to lift the elbows or head from the bed, and increased liver enzyme levels were predictors of an increased probability of need for artificial ventilation.[126] A second French study found that peroneal nerve conduction block and low vital capacity correlated with a high risk of respiratory failure.[152] The third study was conducted in the Netherlands, and used data from a derivation cohort of 397 patients with GBS to identify clinical predictors of mechanical ventilation, which were validated in an independent cohort of 191 patients with GBS.[124]

The results of the Dutch study led to development of the Erasmus GBS Respiratory Insufficiency Score (EGRIS) (Annexure 15.5).[124] EGRIS is an accurate prediction model that can be used in the emergency room to predict the probability of respiratory insufficiency in the first week after admission for GBS.[124,153] The model incorporates the following parameters: severity of weakness (expressed as the MRC sum score), the

number of days between onset of weakness and admission, and facial and/or bulbar weakness. If a patient's predicted chance of developing respiratory insufficiency is high, it can be advisable to admit the patient to the ICU rather than to a general neurology ward.

Factors that are predictive of successful weaning from the ventilator are age <60 years,[154] lack of autonomic dysfunction, and vital capacity >20 ml/kg or an improvement in vital capacity of 4 ml/kg.[155] Autonomic dysfunction, advanced age and pulmonary comorbidity are associated with a long duration of mechanical ventilation and the need for tracheostomy.[155,156]

PREDICTORS OF POOR LONG-TERM OUTCOMES

Several clinical factors have been identified that assist in the early prediction of outcome.

Predictors for poor recovery (<20% probability of walking independently at 6 months):[157]

1. Older age (>60 years),
2. History of preceding diarrheal illness,
3. Recent CMV infection,
4. Ventilatory support,
5. Rapid progression reaching maximum deficit in less than 7 days,
6. Hyponatremia, and
7. Low distal CMAP amplitudes (20% of LLN or less) or inexcitable nerves.

The overall prognosis of GBS is also influenced by the patient's age, the severity of illness at its peak, and whether immunomodulating therapies are initiated early. Complications such as acute hypoxic-ischemic encephalopathy and infectious episodes also probably worsen the prognosis.

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.[158] 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 <40 pre-

treatment were predictors of a poor outcome.[159] 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.[160] The findings were then validated in 374 other patients who had participated in another international randomised trial.[132] 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) (Annexure 15.6) was derived, where score ranged from 1 to 7, with three categories for age (>60 (1 point), 41-60 (0.5point), <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.[137] 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' (Annexure 15.7), 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.

ONGOING RESEARCH

Nearly a century after it was first described, GBS is still a life-threatening disorder that results in a poor outcome in at least 20% of patients and has persistent residual effects in the majority. Further research is urgently required to improve this situation. From a clinical perspective, the following are the most challenging needs: to develop improved diagnostic criteria for use in daily clinical practice, trials and vaccine safety studies; to determine the burden of disease caused by GBS worldwide; to develop new and better GBS outcome measures; to establish the precipitating events and patient-related factors

that lead to GBS; to define biological and clinical predictors of the clinical course and outcome in individual patients; and, most importantly, to develop more-effective and specific treatments, as well as protocols for supportive care.[31]

These aims can probably only be achieved by large-scale international and multidisciplinary collaborations, such as the International GBS Outcome Study (IGOS), which was launched in 2012. Tissue samples and detailed, standardized clinical data are being collected during a follow-up period of 1–3 years with the intention of including at least 1,000 patients with GBS from all over the world. By January 2017, more than 1400 patients with GBS had been included in IGOS by 143 active sites from 19 countries across five continents.[161] On 5th May 2021 IGOS completed 2000 patient inclusion. After that they had stopped recruiting further new patients. They will collect follow up data for next 3 years till May 2024.[162]

AIM AND OBJECTIVES

AIM

1. To assess the clinical, serological and electrophysiological profile of patients with Guillain-Barré syndrome
2. To identify determinants that can be used for early identification of patients with poor prognosis.

OBJECTIVES

PRIMARY OBJECTIVE

1. To study the clinical, demographic and electrophysiological profile of Guillain-Barré syndrome patients in a tertiary care center and to identify determinants of outcome in Guillain-Barré syndrome.

SECONDARY OBJECTIVES

1. To classify various subtypes of Guillain-Barré syndrome by serological markers and Electrophysiological studies using Hadden's and Rajabally's criteria.
2. To compare the patterns of recovery amongst various electrophysiological subtypes of Guillain-Barré Syndrome using serial nerve conduction studies.

MATERIALS AND METHODS

1. STUDY DESIGN

Prospective Cohort study.

2. CASE SELECTION

All patients attended our institute (AIIMS Jodhpur) during study period with clinical diagnosis of Guillain-Barré syndrome were included in the present study.

INCLUSION CRITERIA

1. Fulfil the diagnostic criteria for Guillain-Barré syndrome of the National institute of Neurological Disorders and Stroke (NINDS) revised by Asbury and Cornblath (1990).
2. Fulfil the electro diagnostic criteria for diagnosis of various subtypes of Guillain-Barré syndrome by Hadden et al.
3. Presentation within 4 weeks of symptom onset.
4. Inclusion of all males and females of all age groups, independent of disease severity.
5. Patients with Miller Fisher syndrome and all other variants of Guillain-Barré syndrome, including overlap syndromes, can be included.
6. Patients willing to participate in the study and provide written informed consent.

EXCLUSION CRITERIA

1. Pregnancy.
2. Known severe allergic reaction to properly matched blood products.
3. Known selective IgA deficiency.
4. Previous steroid therapy for current illness.
5. Other causes of acute flaccid quadriparesis.
6. Patients not willing to participate in the study.

3. SAMPLE SIZE

Total 30 patients admitted in Departments of Neurology and General Medicine at AIIMS Jodhpur with diagnosis of GBS during study period were included in this study.

4. STUDY DURATION

The study was conducted from January 2020 to June 2021.

5. METHODOLOGY

This prospective cohort study was conducted after obtaining the ethical clearance certificate number: AIIMS/IEC/2019-20/972 from the institute's ethical committee. It was done in patients diagnosed with Guillain-Barré syndrome to study the clinical profile and identify the clinical and electrophysiological determinants of outcome at 15, 30 and 90 days. All patients with diagnosis of GBS or GBS variants presented within four weeks of onset of weakness were included in this study. The NINDS GBS criteria revised by Asbury and Cornblath (1990) and the Brighton Collaboration criteria (2011) were used for the diagnosis of cases.

All consecutive patients admitted with a diagnosis of GBS in our institute (AIIMS Jodhpur), who fulfilled inclusion criteria were included in the study. A total of 30 patients were included in this study over the study period of January 2020 to June 2021.

Detailed history was taken with regards to onset of symptoms, duration and progression. All patients were evaluated for history of fever, diarrhea and upper respiratory tract infection. All patients were evaluated for other factors like vaccination, past history of diabetes or other illnesses.

Detailed general examination was done including vital examination. Oxygen saturation, single breath count and tidal percussion were done in all patients. Systemic examination including RS, CVS and neurological examination was done in detail.

All patients had a complete neurological examination (cranial nerve examination, muscle power charting, reflexes, and sensory examination, GBS disability scale) at admission, day 15, day 30 and day 90. Guillain-Barré syndrome was diagnosed clinically as areflexic quadriparesis without early bowel and bladder involvement.

Patients with suspected myelitis, were confirmed by imaging and CSF analysis and were excluded from the study.

Twenty one patients out of 30 underwent nerve conduction study of upper limb and lower limb at entry time, 15 days, 30 days and 90 days. One patient underwent for nerve conduction study at entry time, day 15 and day 30. Three patients underwent nerve conduction study at entry time and day 15. Four patients underwent nerve conduction study on entry time only. Nerve conduction study could not be performed for one patient due to technical reasons related to admission in suspected COVID-19 ward. Data from subsequent conduction studies were collected. NCS was performed on at least 4 motor (median, ulnar, common peroneal, and posterior tibial) and 3 sensory (median, ulnar, and sural) nerves using the conventional and standard techniques. The following parameters were noted: distal motor and sensory latencies, motor and sensory conduction velocities, compound muscle action potential (CMAP) amplitude, F latencies, conduction blocks, and sensory nerve action potential (SNAP) amplitude. The value of each variable was then compared with the upper or lower normal limits, as set by our laboratory. According to that they were classified in primary demyelinating, primary axonal, inexcitable and equivocal group as per Hadden's criteria (Annexure 15.2) and Rajabally's criteria (Annexure 15.3).

Patients were classified into different grades according to Hughes classification and MRC disability scale at entry time, day 15, day 30 and day 90.

Complete blood workup including CBC, ESR, Serum Electrolytes, Cerebrospinal fluid analysis, RFT, LFT, CPK total, viral markers, PT with INR, APTT, serum TSH were done in all patients. Antiganglioside antibody panel was done for selected patients.

Treatment modalities used and complications were recorded for analysis. A record of follow up at day 15, day 30 and day 90 was obtained for all patients based on assessment of disability with Hughes and MRC disability scale on follow up at our neuromuscular clinic. The primary outcome measure was the GBS disability score at 15 days, 30 days and 90 days.

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), serological markers and electro-physiological parameters.

6. STATISTICAL ANALYSIS

Descriptive analysis was used mainly. Whenever needed the data was analyzed using SPSS version 21 software (SPSS Inc., Illinois, and Chicago). Continuous variables are described with means ± SD.

7. ETHICAL CONSIDERATIONS

Informed written consent was taken from all the study subjects. No pressure or coercion was exerted on subjects for participation in study. Enrolment in the study did not pose any additional risk to the patient and did not increase the cost of the treatment. The ethical clearance certificate number: AIIMS/IEC/2019-20/972 was obtained from the institute's ethical committee.

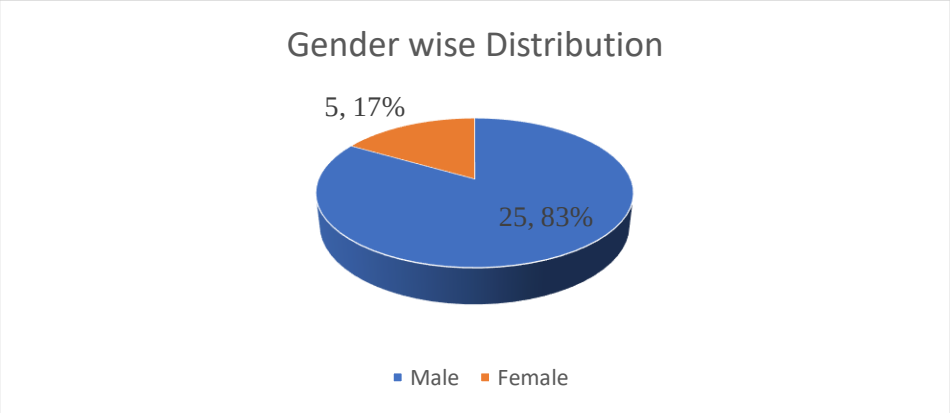
RESULTS

Total 30 patients with a diagnosis of GBS were evaluated.

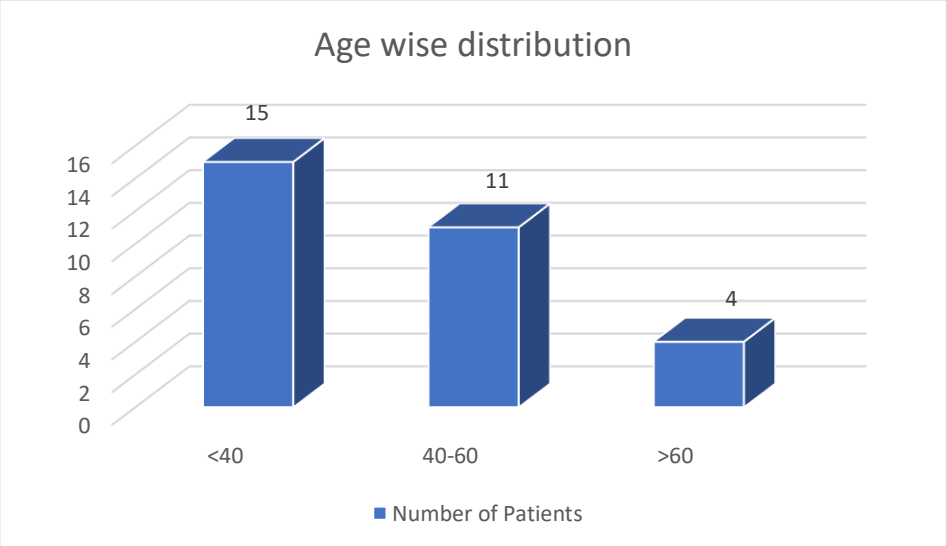
AGE AND GENDER

Among these 30 patients, 25 were male and 5 were female. Male: Female ratio was 5:1 showing male preponderance. Mean age of patients in the study was 42.97±17.22 years (Mean± SD). Patients were divided in 3 age groups. (<40 years, 40-60 years and >60 years). Fifteen patients (50%) were in <40 years group, 11 patients (36.66%) were in 40-60 years group and 4 patients (13.33%) were in >60 years age group.

GRAPH 1: Distribution of subjects on the basis of Gender



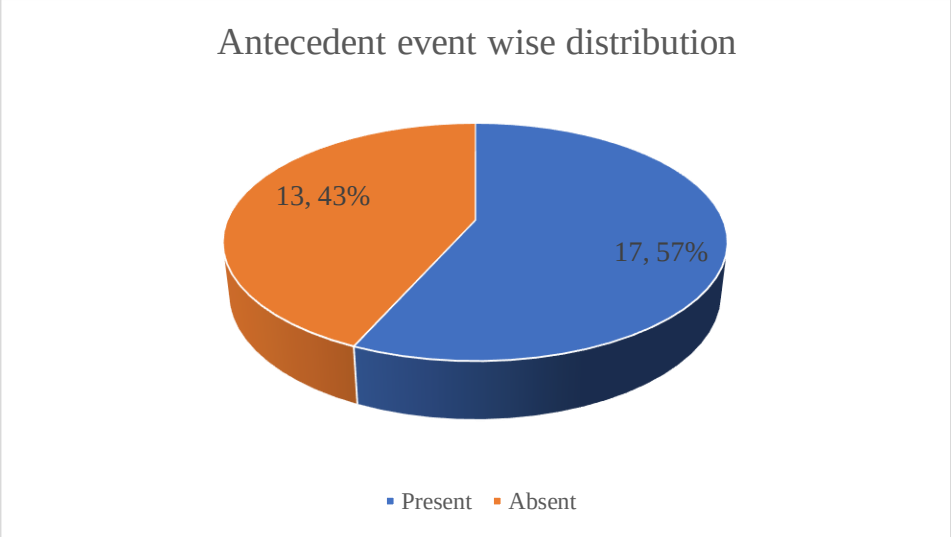
GRAPH 2: Distribution of subjects on the basis of Age



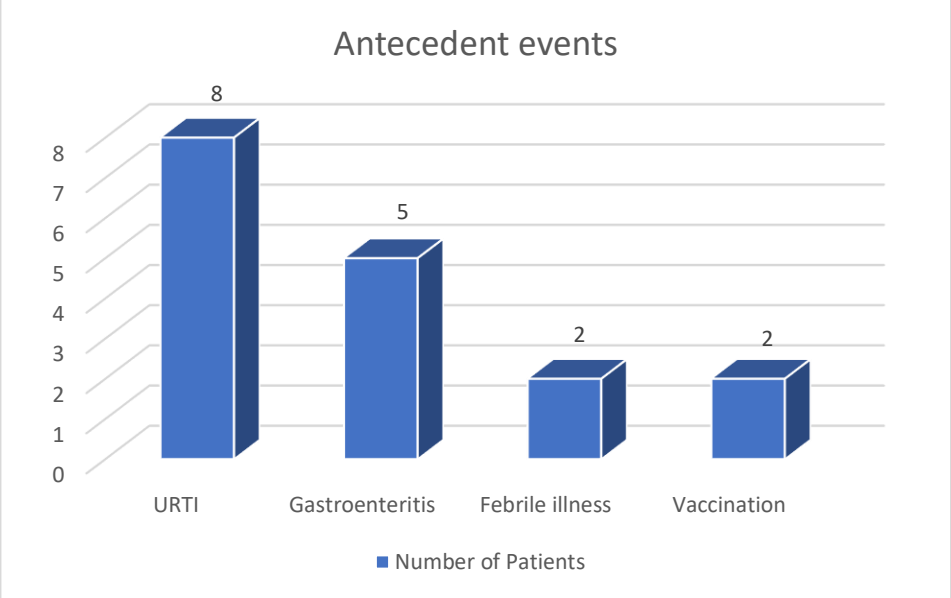
ANTECEDENT EVENTS

Out of 30 patients in this study, 17 (56.67%) patients had an antecedent illness within 4 weeks of onset of illness. Five (16.67%) patients had gastroenteritis and Eight (26.67%) patients had upper respiratory tract infection. Two (6.67%) patients had febrile illness. Two (6.67%) patients had history of vaccination (COVID 19 vaccine) within 4 weeks before onset of symptoms. Out of those two patients one patient had COVID 19 vaccination and after 7 days of that had COVID 19 infection with positive RT PCR.

GRAPH 3: Distribution of subjects on the basis of Antecedent event



GRAPH 4: Frequency of various antecedent events

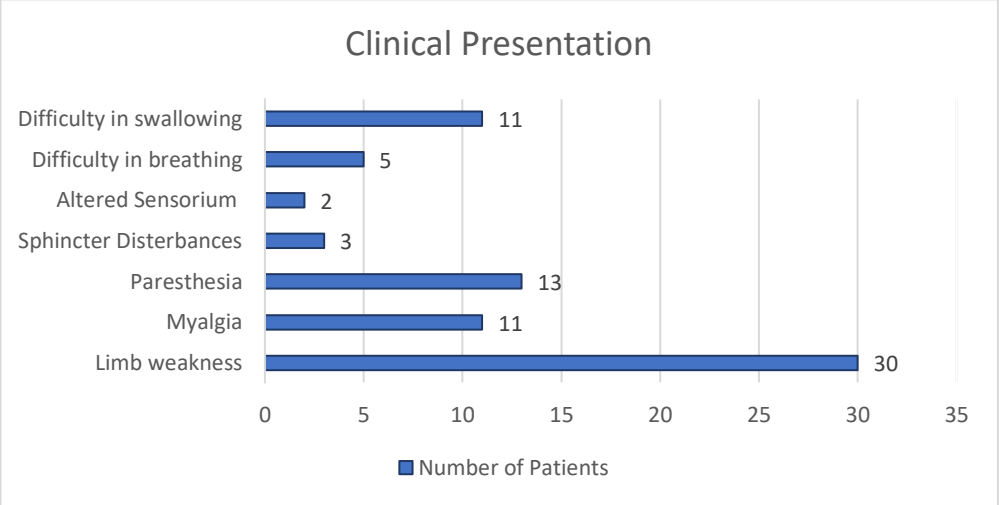


CLINICAL PRESENTATION

All the 30 patients presented with limb weakness. Eleven (36.67%) patients had myalgia during presentation. Thirteen (43.33%) patients had paresthesia in either upper or lower limb during presentation. Only three (10%) patients had sphincter disturbance during presentation. Only two (6.67%) patients had altered sensorium during presentation. Five (16.67%) patients had difficulty in breathing during presentation. Eleven (36.67%) patients presented with difficulty in swallowing with bulbar involvement.

Out of the 30 patients 5 (16.67%) patients were either static or was in the improving phase at the time of admission.

GRAPH 5: Clinical presentation of subjects



FEATURES ON CLINICAL EXAMINATION

Cranial nerve involvement was noted in 12 (40%) patients at the time of admission. Most common cranial nerve involved was facial nerve (7) followed by lower cranial nerves (bulbar) (9,10). Ophthalmoparesis was noted in 2 patients, one with MFS overlap and another was Bickerstaff brainstem encephalitis. At 90 days follow up only 2 patients had cranial nerve involvement and was improved as compared to previous. Neck flexion weakness was present in 22 (73.33%) patients at the time of admission. Nineteen (63.33%) patients presented with generalized areflexia. Two (6.67%) patients presented with normal tendon reflexes, while 9 (30%) patients had hyporeflexia at presentation. Five (16.67%) patients had objective sensory loss at the time of presentation. Autonomic dysfunction was present in 3 (10%) patients at admission.

Heart rate variability and blood pressure fluctuations was most common and present in all 3 patients.

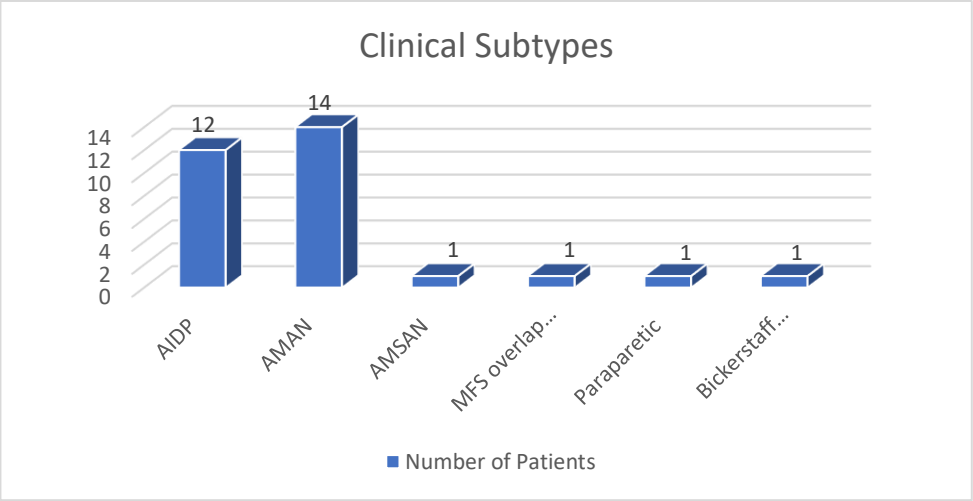
TABLE 5: Clinical findings on examination

Clinical Examination at Admission	Number of Patients
Cranial Nerve involvement	12 (40%)
Neck Flexor weakness	22 (73.33%)
Generalized Areflexia	19 (63.33%)
Objective sensory loss	5 (16.67%)
Autonomic Dysfunction	3 (10%)

CLINICAL SUBTYPES

After clinical examination of all 30 patients, they were categorized into different categories as described earlier. Out of 30 patients, 12 (40%) patients were categorised as AIDP, 14 (46.67%) patients as AMAN, 1 (3.33%) patient as AMSAN, 1 (3.33%) patient as MFS overlap syndrome, 1 (3.33%) patient as paraparetic variant and 1 (3.33%) patient as Bickerstaff brainstem encephalitis.

GRAPH 6: Distribution of subjects according to clinical subtypes of GBS

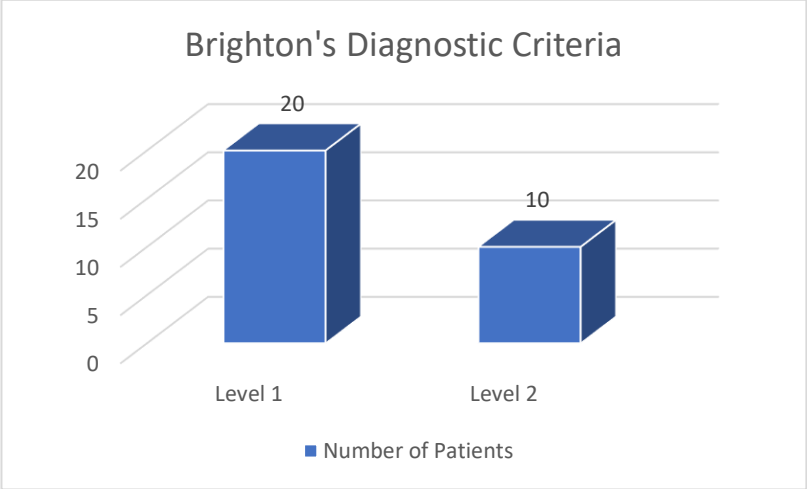


FULFILMENT OF NINDS AND BRIGHTON'S CRITERIA

All the 30 patients in this study were assessed using both the NINDS and Brighton's diagnostic criteria for GBS. All the 30 patients fulfilled NINDS criteria. According to Brighton Collaboration criteria patients were divided in Level 1, Level 2 or Level 3 of

diagnostic certainty. Out of the 30 patients, 20 (66.67%) patients fulfilled Level 1 of diagnostic certainty and 10 (33.33%) patients fulfilled Level 2 of diagnostic certainty.

GRAPH 7: Distribution of subjects according to Brighton's diagnostic criteria



RECURRENT GBS

In our study only one patient (3.33%) had previous history of GBS before 10 years. He was treated with IVIg at that time. Residual deficit was present after that in the form of bilateral foot drop. During this admission he was treated with plasma exchange. His antiganglioside antibody panel showed presence of IgG antibodies against GD1b and GQ1b.

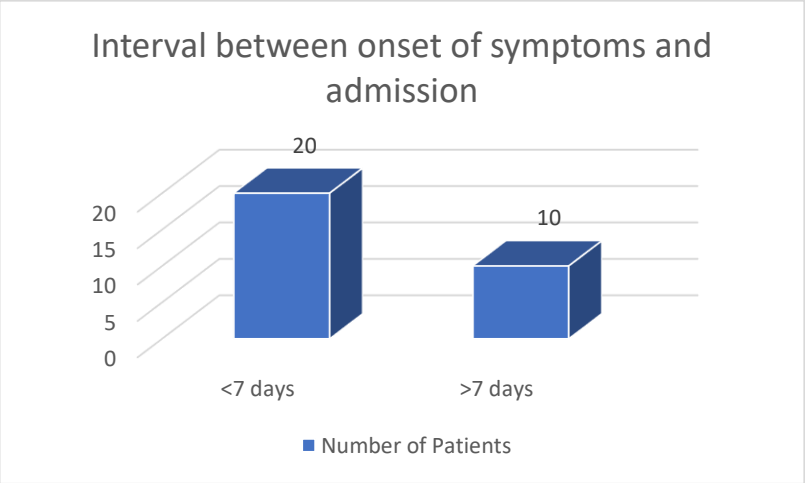
INTERVAL BETWEEN ANTECEDENT EVENT AND ONSET OF GBS

In 17 patients who had antecedent events, the mean interval between onset of antecedent event and symptoms of GBS were 10.875 (±6.07) days. In eight patients with upper respiratory tract infection as antecedent event, interval between antecedent event and onset of GBS ranged from 6 to 27 days with mean (±SD) of 12.25 (±6.54) days. In six patients with gastroenteritis as antecedent event, interval between antecedent event and onset of GBS ranged from 1 to 19 days with mean (±SD) of 8.6 (±6.88) days. The two patients with history of vaccination had interval of 27 days and 12 days respectively between antecedent event and onset of GBS. The two patients with history of febrile illness had interval of 7 days and 14 days respectively between antecedent event and onset of GBS.

INTERVAL BETWEEN ONSET OF SYMPTOMS AND ADMISSION

The mean days between the onset of symptoms and admission was 6.13 (±5.78) days. Out of the 30 patients, 20 (66.67%) patients were admitted within 7 days of onset of symptoms while rest of the 10 (33.33%) patients were admitted after 7 days of symptom onset.

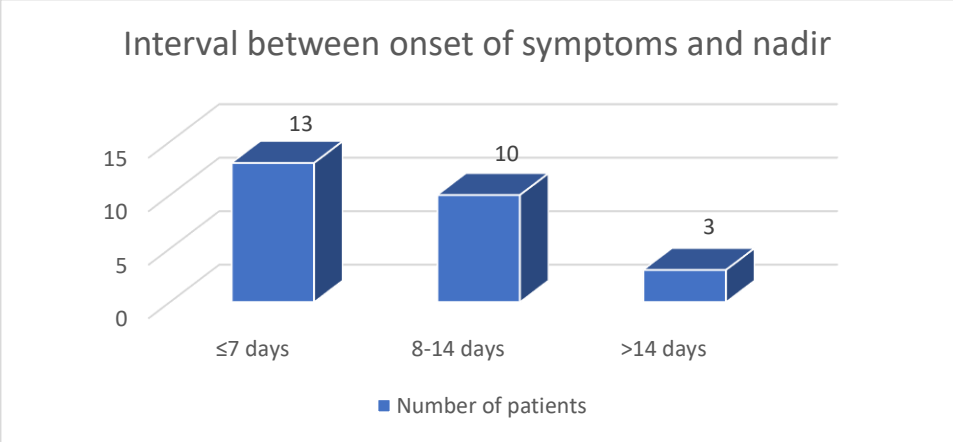
GRAPH 8: Distribution of subjects according to interval between onset of symptoms and admission



INTERVAL BETWEEN ONSET OF SYMPTOMS AND NADIR

Nadir was defined as achievement of maximum weakness during the course of illness. As 3 patients died during the course of illness and one patient took discharge against advice, the achievement of nadir was not established in these 4 patients and they were excluded from evaluation. Mean interval between onset of symptoms and nadir was 9.31(±6.23) days. Out of 26 patients, 13 (50%) patients achieved nadir ≤ 7 days from the onset of symptoms, 10 (38.46%) patients achieved nadir between 8-14 days and 3 (11.54%) patients achieved nadir after 14 days of onset of symptoms. All 26 patients achieved nadir within 28 days from onset of symptoms.

GRAPH 9: Distribution of subjects according to interval between onset of symptoms and nadir

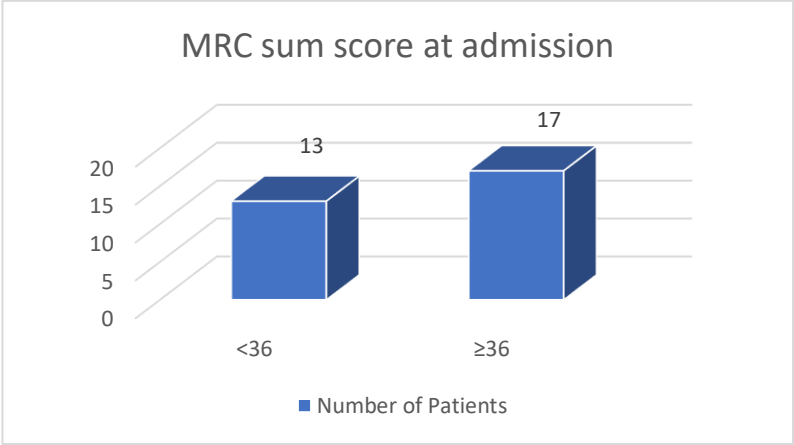


MRC SUM SCORE

The Medical Research Council (MRC) sum score evaluates strength in three muscle groups of all four limbs. A score between 0 and 5 is assigned to each of them, which renders a maximum total score of 60. This score was developed for and validated in patients with Guillain-Barré syndrome. Patients with an MRC sum-score below 36 were labeled as having ‘‘severe weakness,’’ as this corresponds to inability of muscle groups to act against resistance.[163] MRC sum score was calculated for all patients at the time of admission and follow ups at day 15, day 30 and day 90. It also used in calculation of mEGOS.

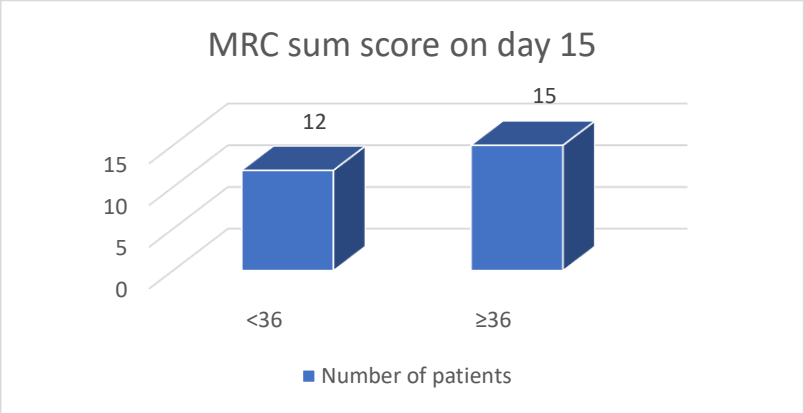
Mean MRC sum score at admission was 32.93±16.43. Out of 30 patients, 13 (43.33%) patients had MRC sum score <36, while rest of the 17 (56.66%) patients had MRC sum score ≥36.

GRAPH 10: Distribution of subjects according to MRC sum score at admission



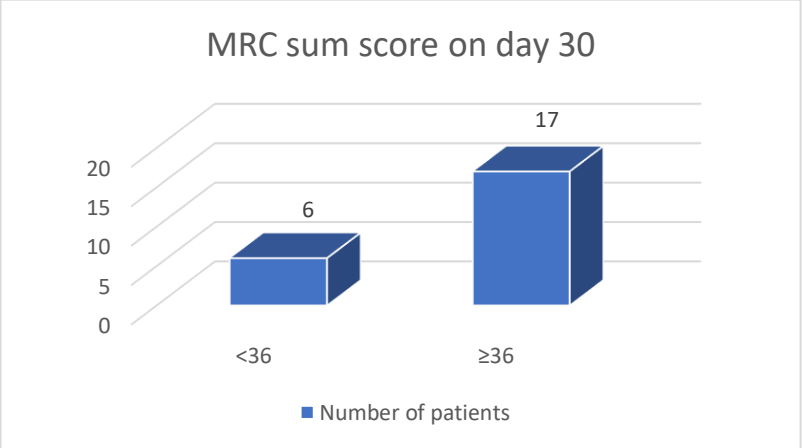
On day 15, mean MRC sum score was 36.3±18.94. Out of 27 patients, 12 (44.44%) patients had MRC sum score <36, rest of the 15 (55.56%) patients had MRC sum score ≥36.

GRAPH 11: Distribution of subjects according to MRC sum score on day 15



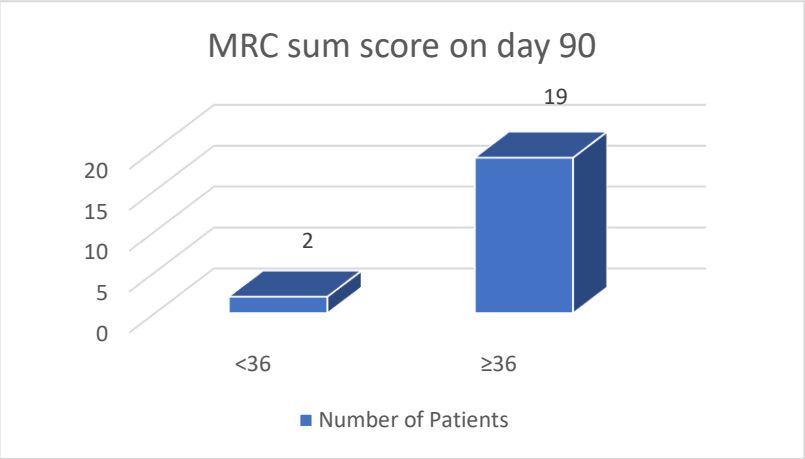
On day 30, mean MRC sum score was 42.57±14. Out of 23 patients, 6 (26.09%) patients had MRC sum score <36, while rest of the 17 (73.91%) patients had MRC sum score ≥36.

GRAPH 12: Distribution of subjects according to MRC sum score on day 30

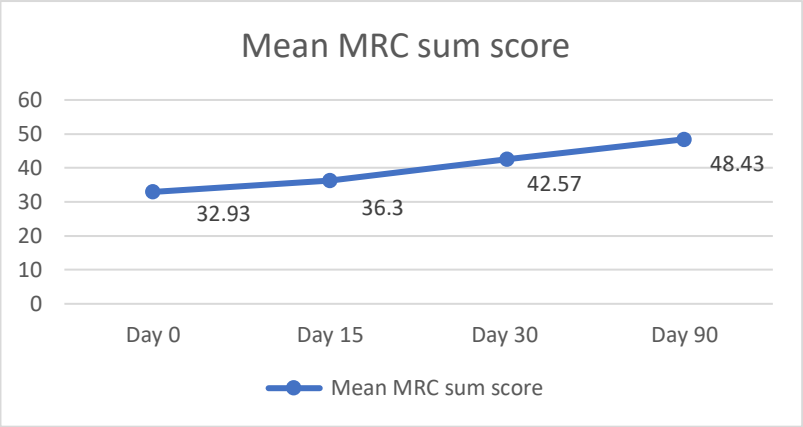


On day 90, mean MRC sum score was 48.43±11.44. Out of 21 patients, 2 (9.52%) patients had MRC sum score <36, while rest of the 19 (90.48%) patients had MRC sum score ≥36.

GRAPH 13: Distribution of subjects according to MRC sum score on day 90



GRAPH 14: Mean MRC sum score at different intervals



Mean MRC sum score showed gradual increment during follow up showing overall improvement in motor weakness.

SERIAL ASSESSMENT ACCORDING TO HUGHES DISABILITY SCALE

The GBS disability score (Hughes score) is a widely accepted scale for assessing the functional status of patients with GBS, ranging from 0 (normal) to 6 (death).

AT ADMISSION (DAY 0)

A GBS disability score (Hughes score) of 4 was the most common score at admission and was seen in 18 (60%) patients, followed by 6 (20%) patients with score of 3 and 5 (16.67%) patients with score of 5. Only one (3.33%) patient had Hughes score of 2 at the time of admission. So, at the time of admission 23 (76.67%) patients had Hughes score ≥4, indicating they were not able to walk even with support and were bed ridden. Rest of the 7 (23.33%) patients had Hughes score <4.

TABLE 6: Distribution of subjects according to Hughes score at admission

Hughes score	Number of patients	Percentage
0	0	0
1	0	0
2	1	3.33%
3	6	20%
4	18	60%
5	5	16.67%
6	0	0
Total	**30**	**100%**

ON DAY 15

Out of the 30 patients, 2 (6.67%) patients achieved Hughes score of 1, 3 (10%) patients achieved Hughes score of 2, 7 (23.33%) patients achieved Hughes score of 3, 13 (43.33%) patients had Hughes score of 4 and 4 (13.33%) patients had Hughes score of 5, one (3.33%) patient died before follow up on day 15 so included as Hughes score 6. On day 15, out of the 30 patients, 18 (60%) patients had Hughes score ≥4 while 12 (40%) patients had Hughes score <4.

TABLE 7: Distribution of subjects according to Hughes score on day 15

Hughes score	Number of patients	Percentage
0	0	0
1	2	6.67%
2	3	10%
3	7	23.33%
4	13	43.33%
5	4	13.33%
6	1	3.33%
Total	**30**	**100%**

ON DAY 30

Out of the 30 patients, 4 (13.33%) patients had Hughes score of 1, 8 (26.67%) patients had Hughes score of 2, 8 (26.67%) patients had Hughes score of 3, 6 (20%) patients had Hughes score of 4 and only 1 (3.33%) patient had Hughes score of 5. Three (10%)

patients died before follow up on day 30, so they were included as Hughes score 6. Out of the 30 patients, 10 (33.33%) patients had Hughes score ≥4 while 20 (66.67%) patients had Hughes score<4.

TABLE 8: Distribution of subjects according to Hughes score on day 30

Hughes score	Number of patients	Percentage
0	0	0
1	4	13.33%
2	8	26.67%
3	8	26.67%
4	6	20%
5	1	3.33%
6	3	10%
Total	**30**	**100%**

ON DAY 90

Out of the 30 patients, 8 (26.67%) patients had Hughes score of 1, 11 (36.67%) patients had Hughes score of 2, 4 (13.33%) patients had Hughes score of 3, 2 (6.67%) patients had Hughes score of 4 and 2 (6.67%) patient had Hughes score of 0. Three (10%) patients died before follow up on day 30, so they were included as Hughes score 6. Out of the 30 patients, 5 (16.67%) patients had Hughes score ≥4 while 25 (83.33%) patients had Hughes score <4.

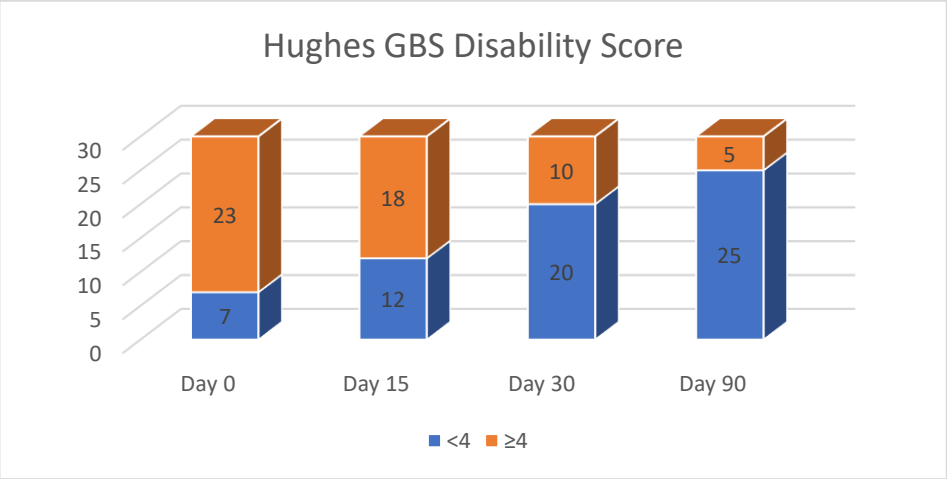
TABLE 9: Distribution of subjects according to Hughes score on day 90

Hughes score	Number of patients	Percentage
0	2	6.67%
1	8	26.67%
2	11	36.67%
3	4	13.33%
4	2	6.67%
5	0	0
6	3	10%
Total	**30**	**100%**

TABLE 10: Serial assessment according to Hughes disability score

Hughes Score	At Admission	On Day 15	On Day 30	On Day 90
<4	7 (23.33%)	12 (40%)	20 (66.67%)	25 (83.33%)
≥4	23 (76.67%)	18 (60%)	10 (33.33%)	5 (16.67%)

GRAPH 15: Serial assessment according to Hughes disability score



A good outcome is defined as the ability to ambulate without assistance (Hughes score ≤2); a poor outcome, as the inability to ambulate independently (Hughes score ≥3).[164] At the time of admission 29 (96.67%) patients had Hughes score of ≥3. So, they were not able to walk with support at the time of admission. On follow up at Day 90, 21 (70%) patients out of 30 had Hughes score of ≤2. Accordingly, majority of patients were able to walk without support at 90 days follow up. 9 (30%) patients out of 30 were having Hughes score ≥3 at 90 days. Accordingly, these patients had poor outcome at day 90 even after treatment.

SERIAL ASSESSMENT ACCORDING TO MRC DISABILITY SCALE

All the patients were also assessed using MRC disability scale ranging from 0 (Normal) to 10 (Death), at admission and follow ups on Day15, Day 30 and Day 90. MRC disability scale of 7 corresponded to Hughes score of 4, defining as inability to walk with support and patient is bed ridden. So, we divided patients in groups as MRC score <7 and MRC score ≥ 7 accordingly.

AT ADMISSION

Out of the 30 patients, 17 (56.67%) patients had MRC disability score of 7, 3 (10%) patients had MRC disability score of 8, 2 (6.67%) patients had MRC disability score of 9, 2 (6.67%) patients had MRC disability score of 6, 5 (16.67%) patients had MRC disability score of 5 and only one (3.33%) patient had MRC disability score of 2 at the time of admission. Out of the 30 patients, 22 (73.33%) patients had MRC disability score of ≥ 7 while 8 (26.67%) patients had MRC disability score of <7.

TABLE 11: Distribution of subjects according to MRC disability score at admission

MRC disability score	Number of patients	Percentage
0	0	0
1	0	0
2	1	3.33%
3	0	0
4	0	0
5	5	16.67%
6	2	6.67%
7	17	56.67%
8	3	10%
9	2	6.67%
10	0	0
Total	**30**	**100%**

ON DAY 15

Out of the 30 patients, 9 (30%) patients had MRC disability score of 7, 3 (10%) patients had MRC disability score of 8, 2 (6.67%) patients had MRC disability score of 9, 4 (13.33%) patients had MRC disability score of 6, 4 (13.33%) patients had MRC disability score of 5, 2 (6.67%) patients had MRC disability score of 4, one (3.33%) patient had MRC disability score of 3, 2 (6.67%) patients had MRC disability score of 2 and 2 (6.67%) patients had MRC disability score of 1. One (3.33%) patient died before follow up on day 15, so included as MRC disability score 10. Out of the 30 patients, 15

(50%) patients had MRC disability score ≥ 7 while 15 (50%) patients had MRC disability score <7.

TABLE 12: Distribution of subjects according to MRC disability score on day 15

MRC disability score	Number of patients	Percentage
0	0	0
1	2	6.67%
2	2	6.67%
3	1	3.33%
4	2	6.67%
5	4	13.33%
6	4	13.33%
7	9	30%
8	3	10%
9	2	6.67%
10	1	3.33%
Total	**30**	**100%**

ON DAY 30

Out of the 30 patients, 4 (13.33%) patients had MRC disability score of 1, 3 (10%) patients had MRC disability score of 2, 3 (10%) patients had MRC disability score of 3, 2 (6.67%) patients had MRC disability score of 4, 7 (23.33%) patients had MRC disability score of 5, 3 (10%) patients had MRC disability score of 6, 4 (13.33%) patients had MRC disability score of 7 and only 1 (3.33%) patient had MRC disability score of 8. Three (10%) patients died before follow up on Day 30, so they were included as MRC disability score 10. Out of the 30 patients, 8 (26.67%) patients had MRC disability score ≥ 7 while 22 (73.33%) patients had MRC disability score <7.

TABLE 13: Distribution of subjects according to MRC disability score on day 30

MRC disability score	Number of patients	Percentage
0	0	0
1	4	13.33%
2	3	10%

3	3	10%
4	2	6.67%
5	7	23.33%
6	3	10%
7	4	13.33%
8	1	3.33%
9	0	0
10	3	10%
Total	**30**	**100%**

ON DAY 90

Out of the 30 patients, 8 (26.67%) patients had MRC disability score of 1, 9 (30%) patients had MRC disability score of 2, one patient had MRC score of 3 (3.33%), 2 (6.67%) patients had MRC score of 4, 3 (10%) patients had MRC score of 5, 2 (6.67%) patients had MRC score of 7 and 2 (6.67%) patient had MRC score of 0. Out of the 30 patients, only 5 (16.67%) patients had MRC disability score ≥ 7 while 25 (83.33%) patients had MRC disability score <7.

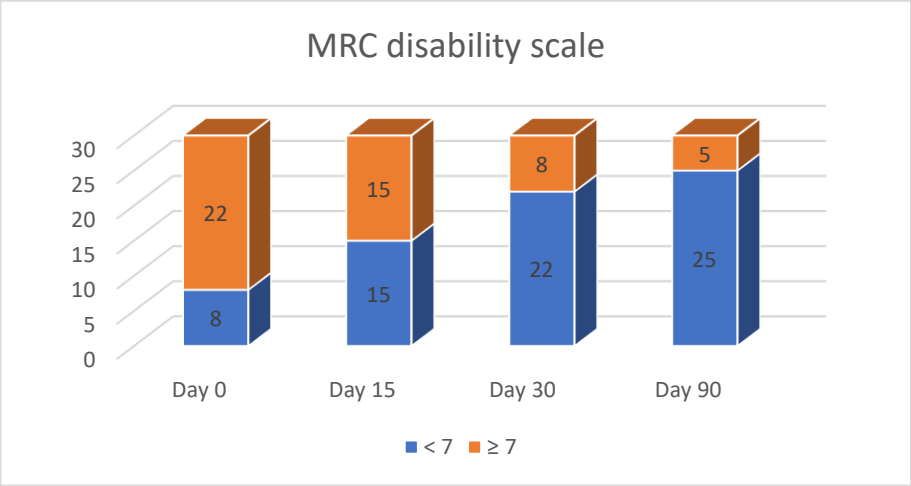
TABLE 14: Distribution of subjects according to MRC disability score on day 90

MRC disability score	Number of patients	Percentage
0	2	6.67%
1	8	26.67%
2	9	30%
3	1	3.33%
4	2	6.67%
5	3	10%
6	0	0
7	2	6.67%
8	0	0
9	0	0
10	3	10%
Total	**30**	**100%**

TABLE 15: Serial assessment according to MRC disability score

MRC Disability scale	Day 0	Day 15	Day 30	Day 90
<7	8 (26.67%)	15 (50%)	22 (73.33%)	25 (83.33%)
≥7	22 (73.33%)	15 (50%)	8 (26.67%)	5 (16.67%)

GRAPH 16: Serial assessment according to MRC disability score



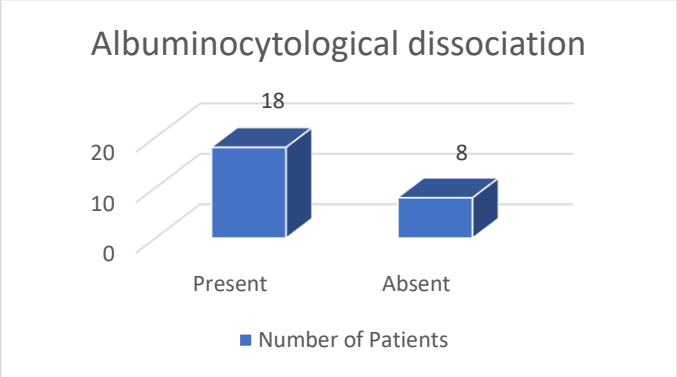
CSF EVALUATION

CSF evaluation was done in 26 (86.67%) patients out of 30 patients. Out of 26 patients, albuminocytological dissociation was seen in 18 (69.23%) patients. Mean CSF cell count was 8.23. Three patients out of 26 patients had CSF cell counts ≥ 20. Infective causes were ruled out in those patients and, all cultures were sterile in them. Nine (34.62%) patients out of 26 had CSF protein values >100 mg/dl. Five patients had normal CSF protein values. Mean CSF protein was 105.35±103.52 (Mean± SD) mg/dl. None of the patients had abnormal CSF sugar values.

TABLE 16: Distribution of subjects according to CSF protein levels

CSF Protein	Number of Patients
≥100 mg/dl	9 (34.62%)
<100 mg/dl	12 (46.15%)
<45 mg/dl (Normal)	5 (19.23%)

GRAPH 17: Distribution of subjects according to Albuminocytological dissociation



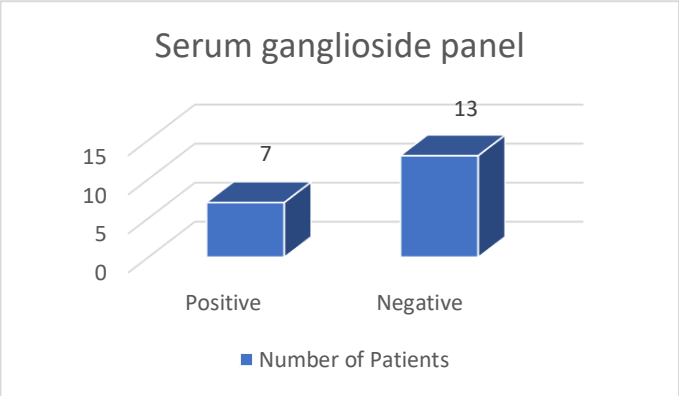
SERUM GANGLIOSIDE PANEL EVALUATION

Out of the 30 patients, serum ganglioside panel was sent for 20 (66.67%) patients. Out of those 20 patients, 7 (35%) patients had positive results on serum ganglioside panel. Out of those 7 patients with positive results, 3 (42.86%) patients had equivocal results and 4 (57.14%) patients had strongly positive results. Out of the 3 patients with equivocal results, 2 (66.67%) patients had equivocal results for both IgG and IgM for GM-1 and GD-1b, remaining one (33.33%) patient had equivocal result for IgG for GM-1 and GD-1b. Out of the 4 patients with strongly positive results, 2 (50%) patients had positive result for IgG for GD-1b and GM-1, one (25%) patient had positive result for IgG for GD-1b and GQ-1b while remaining one (25%) patient had positive result for both IgG and IgM for GM-1, GD-1b and GQ-1b.

TABLE 17: Correlation of serum ganglioside panel with electrophysiological classification in subjects

Sr. No.	Ganglioside Antibody Panel		Electrophysiology Criteria	
	Result	Specific Antibody	Hadden's	Rajabally's
1	Equivocal	GM-1 IgG and IgM	AIDP	AIDP
2	Equivocal	GM-1 IgM and GD-1b IgG	AIDP	AIDP
3	Equivocal	GM-1 IgG and GD-1b IgG	AIDP	AMSAN
4	Positive	GM-1 IgG and GD-1b IgG	AMAN	AMAN
5	Positive	GM-1, GD-1b, GQ-1b IgG and IgM	AIDP	AIDP
6	Positive	GD-1b IgG and GQ-1b IgG	AIDP	AIDP
7	Positive	GM-1 IgG and GD-1b IgG	AIDP	AIDP

GRAPH 18: Distribution of subjects according to serum ganglioside panel



IMAGING STUDIES

Out of the 30 patients, 7 (23.33%) patients underwent for MRI Brain and Whole spine screening. Out of the 7 patients, 3 (42.86%) patients showed cauda equina nerve root enhancement on spine screening. Two (28.57%) patients showed multiple cranial nerve enhancement. Three (42.86%) patients had normal MRI Brain and Spine screening. None of the patients showed changes of myelitis.

ELECTROPHYSIOLOGY STUDY ON ADMISSION

Out of the 30 patients, 29 patients underwent nerve conduction study on admission. Nerve conduction study was performed on all 4 limbs. Motor conduction study was done on bilateral Median, Ulnar, Peroneal and Tibial nerves. Sensory conduction study was done on bilateral Median, Ulnar and Sural nerves. Parameters evaluated during nerve conduction studied include, Distal Motor latency (DML), Compound Muscle Action Potential (CMAP), Motor conduction velocity, F wave latency, Sensory Nerve Action potential (SNAP), Sensory conduction velocity and Proximal/Distal CMAP ratio. All the patients were evaluated with both the Hadden's and Rajabally's criteria for electrophysiological classification and they were categorized in different groups accordingly.

At the time of admission (Day 0) total 29 patients underwent nerve conduction studies. According to Hadden's criteria 17 (58.62%) patients were categorized as primary demyelinating (AIDP) pattern, while 6 (20.69%) patients were categorized as primary axonal pattern, 4 (13.79%) patients as inexcitable and 2 (6.9%) patients as equivocal.

TABLE 18: Electrophysiological classification according to Hadden's and Rajabally's criteria and sensory conduction pattern at admission

Day 0 (At admission)			
Serial No	**Hadden's Criteria**	**Rajabally's Criteria**	**Sensory Conduction Pattern**
1	Demyelinating	Demyelinating	Equivocal
2	Demyelinating	Demyelinating	Inexcitable (Sural sparing)
3	Axonal	Axonal	Equivocal
4	Axonal	Axonal	Normal
5	Demyelinating	Demyelinating	Normal
6	Inexcitable	Axonal	Equivocal
7	Demyelinating	Demyelinating	Normal
8	Demyelinating	Demyelinating	Inexcitable (Sural sparing)
9	Inexcitable	Axonal	Inexcitable
10	Axonal	Axonal	Inexcitable (Sural sparing)
11	Demyelinating	Equivocal	Equivocal
12	Axonal	Axonal	Axonal
13	Demyelinating	Demyelinating	Inexcitable
14	Demyelinating	Axonal	Axonal
15	NA	NA	NA
16	Demyelinating	Axonal	Equivocal
17	Demyelinating	Demyelinating	Normal
18	Inexcitable	Axonal	Inexcitable
19	Demyelinating	Demyelinating	Inexcitable
20	Demyelinating	Demyelinating	Axonal (Sural absent)
21	Axonal	Axonal	Inexcitable
22	Inexcitable	Axonal	Inexcitable
23	Demyelinating	Demyelinating	Equivocal
24	Equivocal	Axonal	Equivocal
25	Axonal	Axonal	Equivocal
26	Demyelinating	Demyelinating	Inexcitable
27	Demyelinating	Demyelinating	Equivocal
28	Demyelinating	Demyelinating	Normal
29	Demyelinating	Demyelinating	Normal
30	Equivocal	Axonal	Normal

According to Rajabally's criteria 14 (48.28%) patients were categorized as primary demyelinating (AIDP), 14 (48.28%) patients as primary axonal pattern and one (3.44%) patient as equivocal.

Out of the 29 patients, sensory conduction study was abnormal in 22 (75.86%) patients. Out of these 22 patients, 3 (13.64%) patients showed sural sparing pattern, 7 (31.82%) patients showed all sensory nerves inexcitable, 9 (40.91%) patients showed equivocal pattern and 3 (13.64%) patients showed axonal pattern on sensory conduction study. Remaining 7 (24.14%) patients showed normal sensory conduction study.

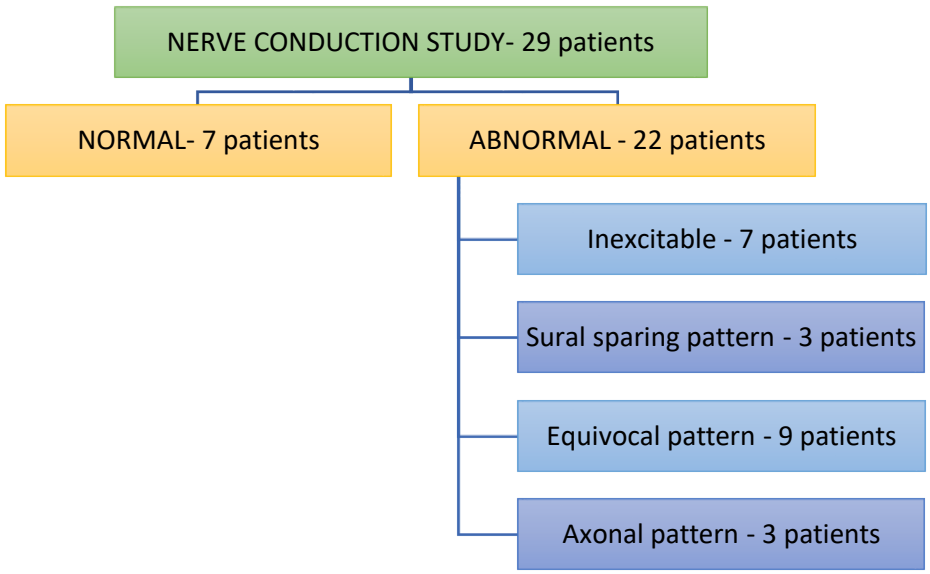


FIGURE 6: Distribution of subjects according to sensory nerve conduction study

Out of the 29 patients, during clinical examination 5 (17.24%) patients showed objective sensory loss, whereas 24 (82.76%) patients showed normal sensory examination. Out of those 5 patients with objective sensory loss, 2 (40%) patients showed absent Median and Ulnar sensory nerve conduction with preserved sural conduction study (sural sparing pattern), one (20%) patient showed equivocal pattern, one (20%) patient showed inexcitable sensory nerves and one (20%) patient did not undergo for nerve conduction study.

Out of those 24 patients who were normal on sensory examination, 17 (70.83%) patients showed abnormality on sensory conduction. Out of those 17 patients, 8 (41.18%)

patients showed equivocal pattern on sensory conduction study, 5 (29.41%) patients showed inexcitable all sensory nerves, one (5.88%) patient showed sural sparing pattern, 3 (17.65%) patients showed axonal pattern. Remaining 7 (29.17%) patients showed normal sensory nerve conduction study.

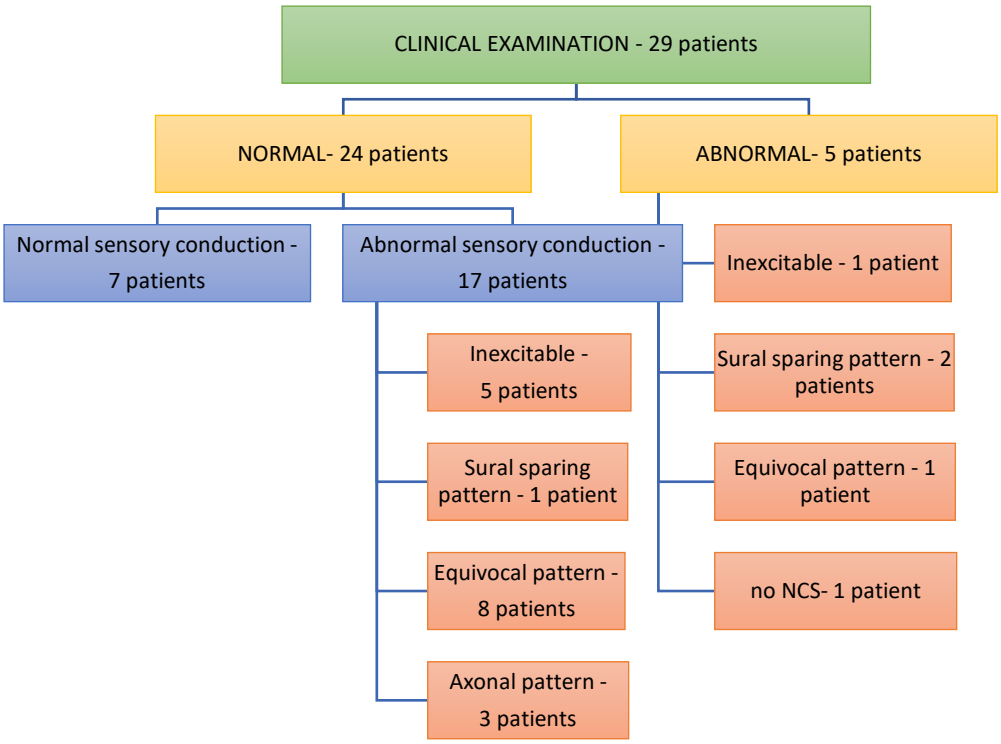


FIGURE 7: Distribution of subjects according to clinical sensory examination

TREATMENT

Out of the 30 patients, 14 (46.67%) patients underwent plasma exchange, 5 (16.67%) patients underwent both IVIg + Plasma exchange, 5 (16.67%) patients received IVIg and 6 (20%) patients received only steroid therapy. Almost all patients (28 out of 30) received steroid treatment during course of therapy along with other type of treatment. All patients received dedicated physiotherapy from Physical and Medical Rehabilitation department. Out of 14 patients who received plasma exchange, 3 patients were not able to complete the 5 cycles of plasma exchange. Out of these 3 patients, 2 patients developed severe hypotension and sepsis, thereby preventing plasma exchange and they eventually died. Remaining one patient had allergic reaction to blood components used during plasma exchange, so only 2 cycles of plasma exchange could be completed. This patient started improving after 2 cycles of plasma exchange, so no further immunomodulatory therapy was given.

TABLE 19: Distribution of subjects according to treatment type

Treatment Type	Number of patients
Plasma exchange	14 (46.67%)
IVIg	5 (16.67%)
Plasma exchange + IVIg	5 (16.67%)
Steroid alone	6 (20%)
Total	**30 (100%)**

Only 2 (6.67%) patients out of 30 showed treatment related fluctuations. Both the patients were initially treated with plasma exchange and showed worsening of symptoms at 30 days follow up. Both patients were treated with IVIg infusion and showed improvement in symptoms.

Interval between onset of recovery and treatment institution

Out of 30 patients, 3 patients expired during disease course, 3 patients were in recovery phase, one patient was in static phase and one patient took discharge against advice. So total 22 patients were taken in analysis for duration to onset of recovery. Mean days of onset of recovery after starting treatment was 4.55±3.74 days.

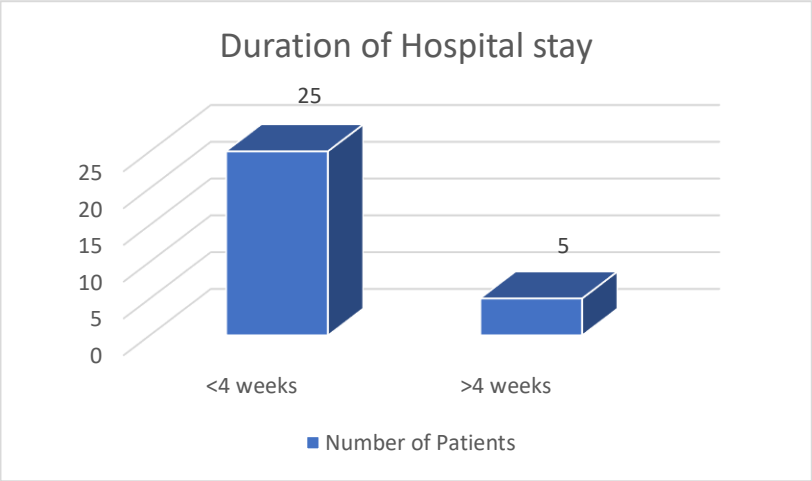
Requirement of Assisted Ventilation and Other Complications

Out of 30 patients, 8 (26.67%) patients required assisted ventilation during the course of hospital stay. Out of 30 patients, 9 (30%) patients developed complications during course of hospital stay and treatment. Most common complications were pneumonia (5 patients), sepsis (4 patients) and urinary tract infection (3 patients).

DURATION OF HOSPITAL STAY

Patients were admitted either in ward or ICU as per requirement of monitoring and ventilatory support. Depending on progression of disease, they were shifted to ICU from ward. In our study, the mean duration of hospital stay was 18.27±13.58 days (Mean± SD). Out of 30 patients, 5 (16.67%) patients had duration of hospital stay more than 4 weeks.

GRAPH 19: Distribution of subjects according to duration of hospital stay



MORTALITY

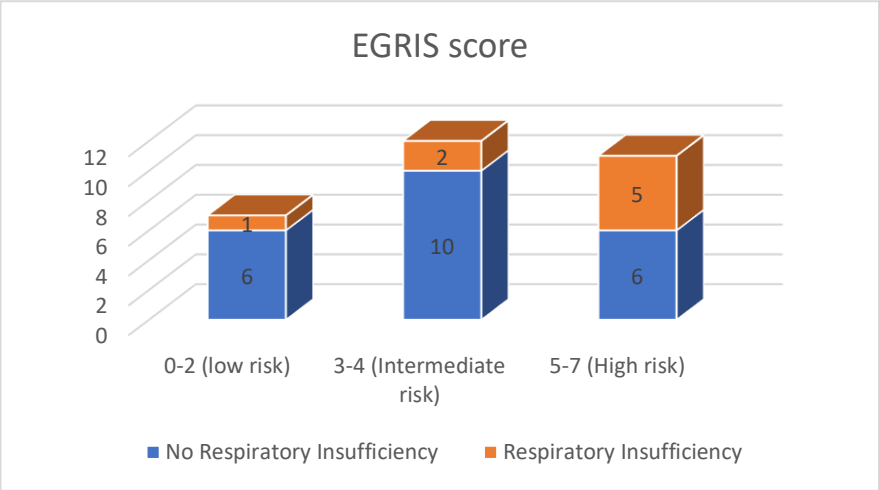
Out of 30 patients, 3 (10%) patients did not survive even after best possible treatment. All 3 patients had severe sepsis and pneumonia along with hypotension. Even after aggressive treatment with higher antibiotics, ventilator support and inotropic support, they did not improve.

PROGNOSTIC SCORES

EGRIS

EGRIS (Erasmus GBS Respiratory Insufficiency Score) predicts the probability of respiratory insufficiency in the first week after admission for GBS. EGRIS score ranges from 0-7.[124] Values of 0-2 indicate low risk of respiratory insufficiency, 3-4 indicate intermediate risk and 5-7 indicate high risk of respiratory insufficiency.[124] Out of 30 patients, 7 (23.33%) patients had EGRIS score of 0-2 indicating low risk of respiratory insufficiency and out of them, only one (14.29%) patient required assisted ventilation during the hospitalization. Out of 30 patients, 12 (40%) patients had score of 3-4 indicating intermediate risk and out of them, only 2 (16.67%) patients required assisted ventilation during the hospitalization. Out of 30 patients, 11 (36.67%) patients had score of 5-7 indicating high risk for respiratory insufficiency and out of them, 5 (45.45%) patients required assisted ventilation during the hospitalization. Out of 30 patients, total 8 (26.67%) patients required assisted ventilation during course of hospital admission.

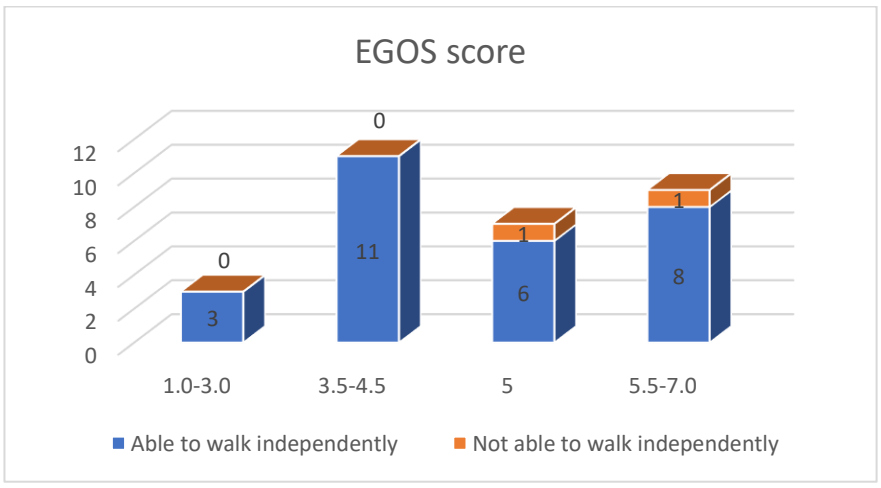
GRAPH 20: Distribution of subjects according to EGRIS score



EGOS

EGOS is a predictor score for poor outcome (inability to walk independently) at 6 months after disease onset. The score ranges from 1 to 7. An EGOS of 1-3 implies a mean risk of inability to walk independently at 6 months of 0.5%, an EGOS of 3.5-4.5 implies a mean risk of 7%, an EGOS of 5 implies a mean risk of 27% and an EGOS of 5.5-7 implies a mean risk of 52%.[160] EGOS was calculated for all the patients at the time of 15 days from starting of illness. Out of 30 patients, 3 (10%) patients had EGOS score between 1-3, 11 (36.67%) patients had score of 3.5-4.5, 7 (23.33%) patients had score of 5 and 9 (30%) patients had score between 5.5-7. At 90 days follow up, out of 21 patients, 6 (28.57%) patients were unable to walk independently. At 6 months follow up, out of 21 patients, 2 patients were unable to walk independently. Out of these 2 patients, one patient had EGOS score 5 and another patient had EGOS score 6.5.

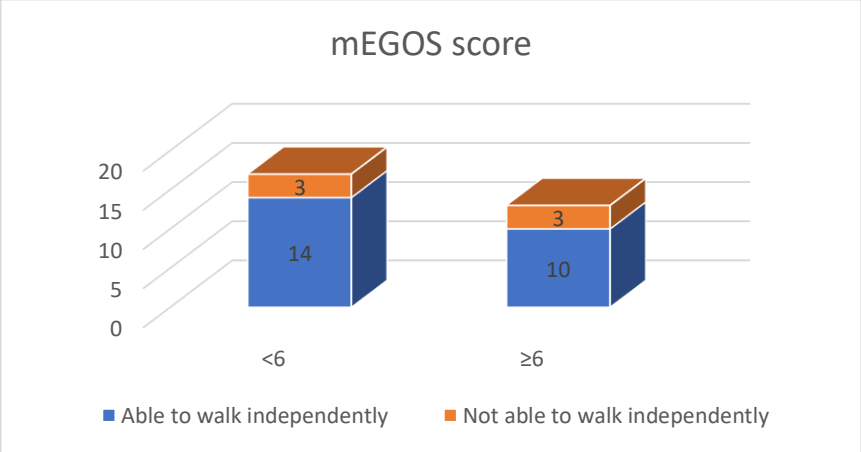
GRAPH 21: Distribution of subjects according to EGOS score



MODIFIED EGOS

mEGOS was calculated for all patients at the time of admission. According to the study scores of ≥6 points were associated with a higher proportion of patients with poor outcomes ($p < 0.01$).[137] Patients with mEGOS score ≥6 at the time of admission implied that 15% patients would not be able to walk independently at 3 months.[137] We also took cut off score of ≥6. Out of 30 patients 13 (43.33%) patients had mEGOS score ≥6. At 90 days follow up, out of 21 patients, 6 (28.57%) patients were unable to walk independently. Out of these 6 patients, 3 patients had mEGOS score of <6 and remaining 3 patients had mEGOS score of ≥ 6.

GRAPH 22: Distribution of subjects according to mEGOS score



COMPARISON OF DIFFERENT CRITERIA FOR ELECTRODIAGNOSTIC CLASSIFICATION

Nerve conduction studies were done at the time of admission and serially at follow up on Day 15, Day 30 and Day 90. These were evaluated with both the criteria (Hadden's and Rajabally's) and divided into various categories as per it.

Electrophysiological classification by both the criteria at specified intervals is as per tables given below.

TABLE 20: Comparison of Hadden's and Rajabally's criteria on day 0 and 15

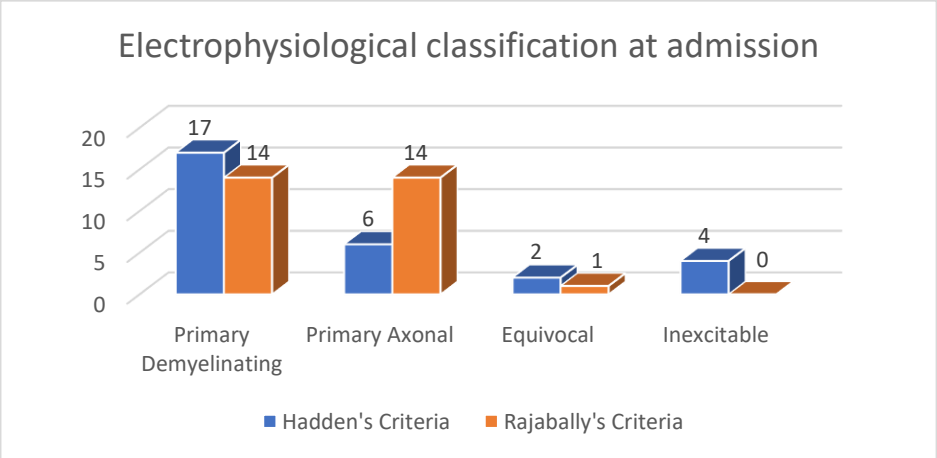
Serial No	Day 0 (At admission)		Day 15	
	Hadden's Criteria	Rajabally's Criteria	Hadden's Criteria	Rajabally's Criteria
1	Demyelinating	Demyelinating	Demyelinating	Demyelinating
2	Demyelinating	Demyelinating	Inexcitable	Axonal
3	Axonal	Axonal	Axonal	Axonal
4	Axonal	Axonal	Demyelinating	Demyelinating
5	Demyelinating	Demyelinating	NA	NA
6	Inexcitable	Axonal	Axonal	Axonal
7	Demyelinating	Demyelinating	Axonal	Axonal
8	Demyelinating	Demyelinating	Demyelinating	Demyelinating
9	Inexcitable	Axonal	NA	NA
10	Axonal	Axonal	Axonal	Axonal
11	Demyelinating	Equivocal	Demyelinating	Equivocal
12	Axonal	Axonal	Axonal	Axonal
13	Demyelinating	Demyelinating	Demyelinating	Demyelinating
14	Demyelinating	Axonal	NA	NA
15	NA	NA	NA	NA
16	Demyelinating	Axonal	Equivocal	Equivocal
17	Demyelinating	Demyelinating	Demyelinating	Demyelinating
18	Inexcitable	Axonal	Axonal	Axonal
19	Demyelinating	Demyelinating	Demyelinating	Demyelinating
20	Demyelinating	Demyelinating	Demyelinating	Demyelinating
21	Axonal	Axonal	NA	NA
22	Inexcitable	Axonal	Inexcitable	Axonal
23	Demyelinating	Demyelinating	Axonal	Axonal
24	Equivocal	Axonal	Demyelinating	Demyelinating
25	Axonal	Axonal	Axonal	Axonal
26	Demyelinating	Demyelinating	Demyelinating	Demyelinating
27	Demyelinating	Demyelinating	Demyelinating	Demyelinating
28	Demyelinating	Demyelinating	Demyelinating	Demyelinating
29	Demyelinating	Demyelinating	Demyelinating	Demyelinating
30	Equivocal	Axonal	Axonal	Axonal

TABLE 21: Comparison of Hadden's and Rajabally's criteria on day 30 and 90

Serial No	Day 30		Day 90	
	Hadden's Criteria	Rajabally's Criteria	Hadden's Criteria	Rajabally's Criteria
1	NA	NA	NA	NA
2	Inexcitable	Axonal	Demyelinating	Demyelinating
3	Axonal	Axonal	Axonal	Axonal
4	Demyelinating	Demyelinating	Demyelinating	Demyelinating
5	NA	NA	NA	NA
6	Axonal	Axonal	Axonal	Axonal
7	Axonal	Axonal	Axonal	Axonal
8	NA	NA	NA	NA
9	NA	NA	NA	NA
10	Demyelinating	Demyelinating	Demyelinating	Demyelinating
11	Demyelinating	Equivocal	Equivocal	Normal
12	NA	NA	NA	NA
13	Demyelinating	Demyelinating	Equivocal	Equivocal
14	NA	NA	NA	NA
15	NA	NA	NA	NA
16	Equivocal	Equivocal	Equivocal	Equivocal
17	Demyelinating	Demyelinating	Demyelinating	Demyelinating
18	Axonal	Axonal	NA	NA
19	Demyelinating	Demyelinating	Inexcitable	Axonal
20	Demyelinating	Demyelinating	Demyelinating	Demyelinating
21	NA	NA	NA	NA
22	Inexcitable	Axonal	Inexcitable	Axonal
23	Demyelinating	Axonal	Axonal	Axonal
24	Demyelinating	Equivocal	Equivocal	Equivocal
25	Demyelinating	Axonal	Axonal	Axonal
26	Demyelinating	Demyelinating	Demyelinating	Demyelinating
27	Demyelinating	Demyelinating	Demyelinating	Demyelinating
28	Demyelinating	Axonal	Axonal	Axonal
29	Demyelinating	Demyelinating	Demyelinating	Axonal
30	Axonal	Axonal	Equivocal	Equivocal

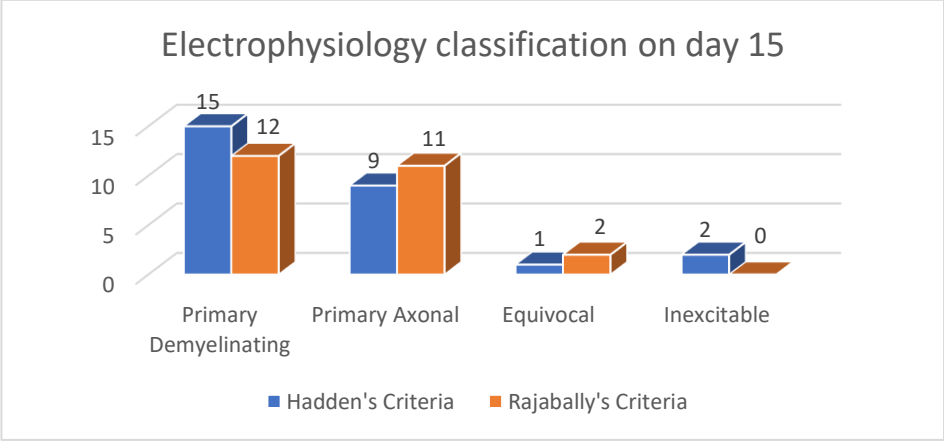
At the time of admission out of 29 patients, as previously seen according to Hadden's criteria more number (58.62%) of patients categorized as primary demyelinating (AIDP) pattern, as compared to (20.69%) as primary axonal pattern, (13.79%) as inexcitable and (6.9%) as equivocal. According to Rajabally's criteria patients were equally categorized as primary demyelinating (AIDP) and as primary axonal pattern.

GRAPH 23: Distribution of subjects according to Hadden's and Rajabally's criteria at admission



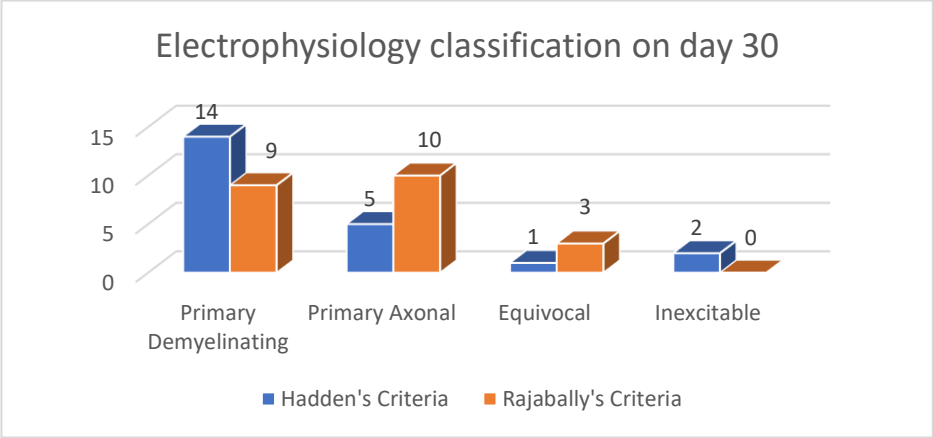
At day 15, 25 patients underwent nerve conduction studies. According to Hadden's criteria, 13 (52%) patients were categorized as primary demyelinating (AIDP) pattern, 9 (36%) patients as primary axonal pattern, 2 (8%) patients as inexcitable and one (4%) patient as equivocal. According to Rajabally's criteria, 12 (48%) patients were categorized as primary demyelinating (AIDP) pattern, 11 (44%) patients as primary axonal pattern and 2 (8%) patient as equivocal pattern.

GRAPH 24: Distribution of subjects according to Hadden's and Rajabally's criteria on day 15



At day 30, 22 patients underwent nerve conduction studies. According to Hadden's criteria, 14 (63.64%) patients were categorized as primary demyelinating (AIDP) pattern, 5 (22.73%) patients as primary axonal pattern, 2 (9.09%) patients as inexcitable and one (4.55%) patient as equivocal. According to Rajabally's criteria, 9 (40.91%) patients were categorized as primary demyelinating pattern, 10 (45.45%) patients as primary axonal and 3 (13.64%) patients as equivocal pattern.

GRAPH 25: Distribution of subjects according to Hadden's and Rajabally's criteria on day 30



At day 90, 21 patients underwent for nerve conduction studies. According to Hadden's criteria, 8 (38.1%) patients were categorized as primary demyelinating (AIDP) pattern, 6 (28.57%) patients as primary axonal pattern, 2 (9.52%) patients as inexcitable and 5 (23.81%) patients as equivocal pattern. According to Rajabally's criteria, 7 (33.33%) patients were categorized as primary demyelinating (AIDP) pattern, 9 (42.86%) patients as primary axonal pattern, 4 (19.05%) patients as equivocal pattern and one (4.76%) patient had normal NCS.

GRAPH 26: Distribution of subjects according to Hadden's and Rajabally's criteria on day 90

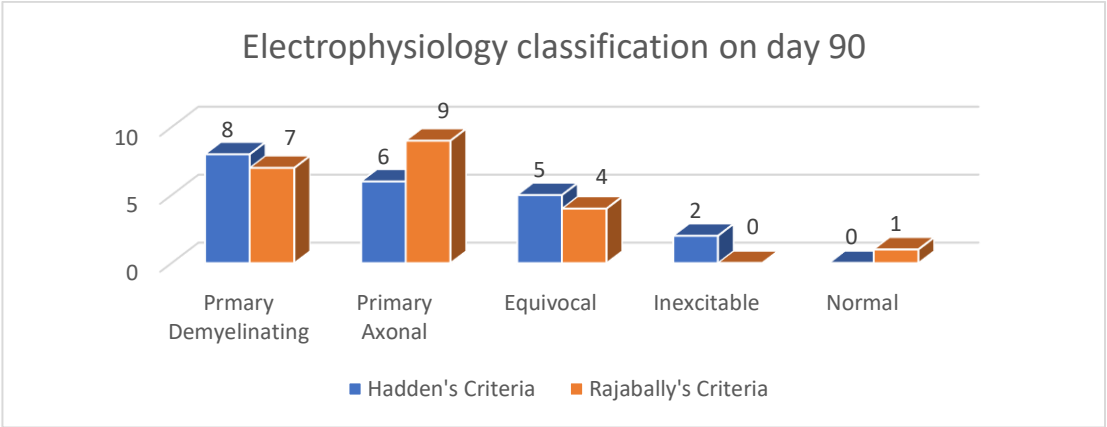


TABLE 22: Comparison of Hadden's and Rajabally's criteria at different intervals

EDX Class	Day 0		Day 15		Day 30		Day 90	
	HC	RC	HC	RC	HC	RC	HC	RC
PD	17 (58.62%)	14 (48.28%)	13 (52%)	12 (48%)	14 (63.64%)	9 (40.91%)	8 (38.1%)	7 (33.33%)
PA	6 (20.69%)	14 (48.28%)	9 (36%)	11 (44%)	5 (22.73%)	10 (45.45%)	6 (28.57%)	9 (42.86%)
IE	4 (13.79%)	NA	2 (8%)	NA	2 (9.09%)	NA	2 (9.52%)	NA
EQ	2 (6.9%)	1 (3.44%)	1 (4%)	2 (8%)	1 (4.55%)	3 (13.64%)	5 (23.81%)	4 (19.05%)
Normal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.76%)
Total	29 (100%)	29 (100%)	25 (100%)	25 (100%)	22 (100%)	22 (100%)	21 (100%)	21 (100%)

(EDX – Electrodiagnostic, PD – Primary Demyelinating, PA- Primary Axonal, IE – Inexcitable, EQ –Equivocal, HC – Hadden's Criteria, RC – Rajabally's Criteria)

From table we can see that initially at the time of admission, Hadden's criteria favors more primary demyelinating category while Rajabally's criteria favors more primary axonal category. At the time of admission according to Hadden's criteria around 20% patients were classified as inexcitable/equivocal category. We were able to classify these patients as either primary demyelinating or primary axonal category by using Rajabally's criteria.

By applying Hadden's and Rajabally's criteria at admission and follow ups on Day 15, Day 30 and Day 90, we can see that every time a greater number of patients were categorized as Primary Demyelinating as per Hadden's criteria, whereas a greater number of patients were categorized as Primary Axonal as per Rajabally's criteria.

ASSESSMENT OF SERIAL CHANGES IN NCS

SERIAL CHANGES IN NCS USING HADDEN'S CRITERIA

Nerve conduction studies were done on admission and follow ups on Day 15, Day 30 and Day 90. Patients were classified in different categories as per Hadden's criteria. Serial changes in NCS using Hadden's criteria were evaluated and given in table 23.

TABLE 23: Electrophysiological classification according to Hadden's criteria at different intervals

Serial No	Day 0	Day 15	Day 30	Day 90
	Hadden's Criteria	Hadden's Criteria	Hadden's Criteria	Hadden's Criteria
1	Demyelinating	Demyelinating	NA	NA
2	Demyelinating	Inexcitable	Inexcitable	Demyelinating
3	Axonal	Axonal	Axonal	Axonal
4	Axonal	Demyelinating	Demyelinating	Demyelinating
5	Demyelinating	NA	NA	NA
6	Inexcitable	Axonal	Axonal	Axonal
7	Demyelinating	Axonal	Axonal	Axonal
8	Demyelinating	Demyelinating	NA	NA
9	Inexcitable	NA	NA	NA
10	Axonal	Axonal	Demyelinating	Demyelinating
11	Demyelinating	Demyelinating	Demyelinating	Equivocal
12	Axonal	Axonal	NA	NA
13	Demyelinating	Demyelinating	Demyelinating	Equivocal
14	Demyelinating	NA	NA	NA
15	NA	NA	NA	NA
16	Demyelinating	Equivocal	Equivocal	Equivocal
17	Demyelinating	Demyelinating	Demyelinating	Demyelinating
18	Inexcitable	Axonal	Axonal	NA
19	Demyelinating	Demyelinating	Demyelinating	Inexcitable
20	Demyelinating	Demyelinating	Demyelinating	Demyelinating
21	Axonal	NA	NA	NA
22	Inexcitable	Inexcitable	Inexcitable	Inexcitable
23	Demyelinating	Axonal	Demyelinating	Axonal
24	Equivocal	Demyelinating	Demyelinating	Equivocal
25	Axonal	Axonal	Demyelinating	Axonal
26	Demyelinating	Demyelinating	Demyelinating	Demyelinating
27	Demyelinating	Demyelinating	Demyelinating	Demyelinating
28	Demyelinating	Demyelinating	Demyelinating	Axonal
29	Demyelinating	Demyelinating	Demyelinating	Demyelinating
30	Equivocal	Axonal	Axonal	Equivocal

According to Hadden's criteria, on comparing NCS between Day 0 (at admission) and Day 15, out of 25 patients, 9 (36%) patients showed changes in electrophysiological classification. Out of 9 patients, 2 (22.22%) patients showed change from Primary Demyelinating to Primary Axonal category, one (11.11%) patients showed change from Primary Axonal to Primary Demyelinating category, one (11.11%) patient showed change from Primary Demyelinating to Inexcitable category, one (11.11%) patient showed change from Equivocal to Primary Demyelinating category, one (11.11%) patient showed change from Equivocal to Primary Axonal category, 2 (22.22%) patients showed change from Inexcitable to Primary Axonal category and one (11.11%) patient showed change from Primary Demyelinating to Equivocal category.

TABLE 24: Change in electrophysiological category from day 0 to day 15 according to Hadden's criteria

Electrophysiological Category Change from Day 0 to Day 15		**No of Patients (Percentage)**
Day 0 (At Admission)	**Day 15**	
Primary Demyelinating	Primary Axonal	2 (22.22%)
Primary Axonal	Primary Demyelinating	1 (11.11%)
Primary Demyelinating	Inexcitable	1 (11.11%)
Equivocal	Primary Demyelinating	1 (11.11%)
Equivocal	Primary Axonal	1 (11.11%)
Primary Demyelinating	Equivocal	1 (11.11%)
Inexcitable	Primary Axonal	2 (22.22%)
Total		**9 (100%)**

On comparison between Day 0 (at admission) and Day 30, out of 22 patients, 10 (45.45%) patients showed changes in electrophysiological classification. Out of 10 patients, one (10%) patient showed change from Primary Demyelinating to Primary Axonal category, 3 (30%) patients showed change from Primary Axonal to Primary Demyelinating category, one (10%) patient showed change from Primary Demyelinating to Inexcitable category , 2 (20%) patients showed change from Inexcitable to Primary Axonal category, one (10%) patient showed change from Primary Demyelinating to Equivocal category, one (10%) patient showed change from Equivocal to Primary Demyelinating and one (10%) patient showed change from Equivocal to Primary Axonal category.

TABLE 25: Change in electrophysiological category from day 0 to day 30 according to Hadden's criteria

Electrophysiological Category Change from Day 0 to Day 30		No of Patients (Percentage)
Day 0 (At Admission)	**Day 30**	
Primary Demyelinating	Primary Axonal	1 (10%)
Primary Axonal	Primary Demyelinating	3 (30%)
Primary Demyelinating	Inexcitable	1 (10%)
Equivocal	Primary Demyelinating	1 (10%)
Equivocal	Primary Axonal	1 (10%)
Primary Demyelinating	Equivocal	1 (10%)
Inexcitable	Primary Axonal	2 (20%)
Total		**10 (100%)**

On comparison between Day 0 (at admission) and Day 90, out of 21 patients, 10 (47.62%) patients showed changes in electrophysiological classification. Out of 10 patients, 2 (20%) patients showed change from Primary axonal to Primary Demyelinating category, 3 (30%) patients showed change from Primary Demyelinating to Primary Axonal category, 3 (30%) patients showed change from Primary Demyelinating to Equivocal category, one (10%) patient showed change from Inexcitable to Primary Axonal category and one (10%) patient showed change from Primary Demyelinating to Inexcitable category (TRF).

TABLE 26: Change in electrophysiological category from day 0 to day 90 according to Hadden's criteria

Electrophysiological Category Change from Day 0 to Day 90		No of Patients (Percentage)
Day 0 (At Admission)	**Day 90**	
Primary Axonal	Primary Demyelinating	2 (20%)
Primary Demyelinating	Primary Axonal	3 (30%)
Primary Demyelinating	Equivocal	3 (30%)
Primary Demyelinating	Inexcitable	1 (10%)
Inexcitable	Primary Axonal	1 (10%)
Total		**10 (100%)**

On comparison between Day 15 and Day 30, out of 22 patients, 3 (13.64%) patients showed changes in electrophysiological classification. All the 3 patients showed change from Primary Axonal to Primary Demyelinating category.

TABLE 27: Change in electrophysiological category from day 15 to day 30 according to Hadden's criteria

Electrophysiological Category Change from Day 15 to Day 30		**No of Patients (Percentage)**
Day 15	**Day 30**	
Primary Axonal	Primary Demyelinating	3 (100%)
Total		**3 (100%)**

On comparison between Day 15 and Day 90, out of 21 patients, 8 (38.1%) patients showed changes in electrophysiological classification. Out of 8 patients, one (12.5) patient showed change from Primary Demyelinating to Primary Axonal category, one (12.5%) patient showed change from Primary Axonal to Primary Demyelinating category, 3 (37.5%) patients showed change from Primary demyelinating to Equivocal category, one (12.5%) patients showed change from Primary Axonal to Equivocal category, one (12.5%) patient showed change from Primary Demyelinating to Inexcitable category (TRF) and one (12.5%) patient showed change from Inexcitable to Primary Demyelinating category.

TABLE 28: Change in electrophysiological category from day 15 to day 90 according to Hadden's criteria

Electrophysiological Category Change from Day 15 to Day 90		**No of Patients (Percentage)**
Day 15	**Day 90**	
Primary Demyelinating	Primary Axonal	1 (12.5%)
Primary Axonal	Primary Demyelinating	1 (12.5%)
Primary Demyelinating	Equivocal	3 (37.5%)
Primary Axonal	Equivocal	1 (12.5%)
Primary Demyelinating	Inexcitable	1 (12.5%)
Inexcitable	Primary Demyelinating	1 (12.5%)
Total		**8 (100%)**

On comparison between Day 30 and Day 90, out of 21 patients, 9 (42.86%) patients showed changes in electrophysiological classification. Out of 10 patients, 3 (33.33%) patients showed change from Primary Demyelinating to Primary Axonal category, 3 (33.33%) patients showed change from Primary Demyelinating to Equivocal category, one (11.11%) patient showed change from Primary Axonal to Equivocal category, one (11.11%) patient showed change from Primary Demyelinating to Inexcitable category (TRF) and one (11.11%) patient showed change from Inexcitable to Primary Demyelinating category.

TABLE 29: Change in electrophysiological category from day 30 to day 90 according to Hadden's criteria

Electrophysiological Category Change from Day 30 to Day 90		**No of Patients (Percentage)**
Day 30	**Day 90**	
Primary Demyelinating	Primary Axonal	3 (33.33%)
Primary Demyelinating	Equivocal	3 (33.33%)
Primary Axonal	Equivocal	1 (11.11%)
Primary Demyelinating	Inexcitable	1 (11.11%)
Inexcitable	Primary Demyelinating	1 (11.11%)
Total		**9 (100%)**

SERIAL CHANGES IN NCS USING RAJABALLY'S CRITERIA

Nerve conduction studies were done on admission and follow ups on Day 15, Day 30 and Day 90. Patients were classified in different categories as per Rajabally's criteria. Serial changes in NCS using Rajabally's criteria were evaluated and given in table 30.

According to Rajabally's criteria, on comparing NCS done at Day 0 (at admission) and Day 15, out of 25 patients, 6 (24%) patients showed changes in electrophysiological classification. Out of 6 patients, 3 (50%) patients showed change from Primary Demyelinating to Primary Axonal category, 2 (33.33%) patients showed change from Primary axonal to Primary Demyelinating category and one (16.67%) patient showed change from Primary Axonal to equivocal.

TABLE 30: Electrophysiological classification according to Rajabally's criteria at different intervals

Serial No	Day 0	Day 15	Day 30	Day 90
	Rajabally's Criteria	Rajabally's Criteria	Rajabally's Criteria	Rajabally's Criteria
1	Demyelinating	Demyelinating	NA	NA
2	Demyelinating	Axonal	Axonal	Demyelinating
3	Axonal	Axonal	Axonal	Axonal
4	Axonal	Demyelinating	Demyelinating	Demyelinating
5	Demyelinating	NA	NA	NA
6	Axonal	Axonal	Axonal	Axonal
7	Demyelinating	Axonal	Axonal	Axonal
8	Demyelinating	Demyelinating	NA	NA
9	Axonal	NA	NA	NA
10	Axonal	Axonal	Demyelinating	Demyelinating
11	Equivocal	Equivocal	Equivocal	Normal
12	Axonal	Axonal	NA	NA
13	Demyelinating	Demyelinating	Demyelinating	Equivocal
14	Axonal	NA	NA	NA
15	NA	NA	NA	NA
16	Axonal	Equivocal	Equivocal	Equivocal
17	Demyelinating	Demyelinating	Demyelinating	Demyelinating
18	Axonal	Axonal	Axonal	NA
19	Demyelinating	Demyelinating	Demyelinating	Axonal
20	Demyelinating	Demyelinating	Demyelinating	Demyelinating
21	Axonal	NA	NA	NA
22	Axonal	Axonal	Axonal	Axonal
23	Demyelinating	Axonal	Axonal	Axonal
24	Axonal	Demyelinating	Equivocal	Equivocal
25	Axonal	Axonal	Axonal	Axonal
26	Demyelinating	Demyelinating	Demyelinating	Demyelinating
27	Demyelinating	Demyelinating	Demyelinating	Demyelinating
28	Demyelinating	Demyelinating	Axonal	Axonal
29	Demyelinating	Demyelinating	Demyelinating	Axonal
30	Axonal	Axonal	Axonal	Equivocal

TABLE 31: Change in electrophysiological category from day 0 to day 15 according to Rajabally's criteria

Electrophysiological Category Change from Day 0 to Day 15		No of Patients (Percentage)
Day 0 (At Admission)	**Day 15**	
Primary Demyelinating	Primary Axonal	3 (50%)
Primary Axonal	Primary Demyelinating	2 (33.33%)
Primary Axonal	Equivocal	1 (16.67%)
Total		**6 (100%)**

On comparison between Day 0 (at admission) and Day 30, out of 22 patients, 8 (36.36%) patients showed changes in electrophysiological classification. Out of 8 patients, 4 (50%) patients showed change from Primary Demyelinating to Primary Axonal category, 2 (25%) patients showed change from Primary Axonal to Primary Demyelinating category and 2 (25%) patients showed change from Primary Axonal to Equivocal category.

TABLE 32: Change in electrophysiological category from day 0 to day 30 according to Rajabally's criteria

Electrophysiological Category Change from Day 0 to Day 30		No of Patients (Percentage)
Day 0 (At Admission)	**Day 30**	
Primary Demyelinating	Primary Axonal	4 (50%)
Primary Axonal	Primary Demyelinating	2 (25%)
Primary Axonal	Equivocal	2 (25%)
Total		**8 (100%)**

On comparison between Day 0 (at admission) and Day 90, out of 21 patients, 12 (57.14%) patients showed changes in electrophysiological classification. Out of 12 patients, 5 (41.67%) patients showed change from Primary Demyelinating to Primary Axonal category, 2 (16.67%) patients showed change from Primary Axonal to Primary Demyelinating category, one (8.33%) patient showed change from Primary demyelinating to Equivocal category, 3 (25%) patients showed change from Primary

Axonal to Equivocal category and one (8.33%) patient showed change from Equivocal to Normal category.

TABLE 33: Change in electrophysiological category from day 0 to day 90 according to Rajabally's criteria

Electrophysiological Category Change from Day 0 to Day 90		No of Patients (Percentage)
Day 0 (At Admission)	**Day 90**	
Primary Demyelinating	Primary Axonal	5 (41.67%)
Primary Axonal	Primary Demyelinating	2 (16.67%)
Primary Axonal	Equivocal	3 (25%)
Primary Demyelinating	Equivocal	1 (8.33%)
Equivocal	Normal	1 (8.33%)
Total		**12 (100%)**

On comparison between Day 15 and Day 30, out of 22 patients, 3 (13.64%) patients showed changes in electrophysiological classification. Out of 3 patients, one (33.33%) patient showed change from Primary Axonal to Primary Demyelinating category, one (33.33%) patient showed change from Primary Demyelinating to Primary Axonal category and one (33.33%) patient showed change from Primary Demyelinating to Equivocal category.

TABLE 34: Change in electrophysiological category from day 15 to day 30 according to Rajabally's criteria

Electrophysiological Category Change from Day 15 to Day 30		No of Patients (Percentage)
Day 15	**Day 30**	
Primary Axonal	Primary Demyelinating	1 (33.33%)
Primary Demyelinating	Primary Axonal	1 (33.33%)
Primary Demyelinating	Equivocal	1 (33.33%)
Total		**3 (100%)**

On comparison between Day 15 and Day 90 out of 21 patients, 9 (42.86%) patients showed change in electrophysiological classification. Out of 9 patients, 3 (33.33%)

patients showed change from Primary Demyelinating to Primary Axonal category, 2 (22.22%) patients showed change from Primary Axonal to Primary Demyelinating category, 2 (22.22%) patients showed change from Primary Demyelinating to Equivocal category, one (11.11%) patient showed change from Primary Axonal to Equivocal category and one (11.11%) patient showed change from Equivocal to Normal category.

TABLE 35: Change in electrophysiological category from day 15 to day 90 according to Rajabally's criteria

Electrophysiological Category Change from Day 15 to Day 90		**No of Patients (Percentage)**
Day 15	**Day 90**	
Primary Demyelinating	Primary Axonal	3 (33.33%)
Primary Axonal	Primary Demyelinating	2 (22.22%)
Primary Axonal	Equivocal	1 (11.11%)
Primary Demyelinating	Equivocal	2 (22.22%)
Equivocal	Normal	1 (11.11%)
Total		**9 (100%)**

On comparison between Day 30 and Day 90 out of 21 patients, 6 (28.57%) patients showed changes in electrophysiological classification. Out of 6 patients, 2 (33.33%) patients showed change from Primary Demyelinating to Primary Axonal category, one (16.67%) patient showed change from Primary Axonal to Primary Demyelinating category, one (16.67%) patient showed change from Primary Demyelinating to Equivocal category, one (16.67%) patient showed change from Primary Axonal to Equivocal category and one (16.67%) patient showed change from Equivocal to Normal category.

TABLE 36: Change in electrophysiological category from day 30 to day 90 according to Rajabally's criteria

Electrophysiological Category Change from Day 30 to Day 90		No of Patients (Percentage)
Day 30	**Day 90**	
Primary Demyelinating	Primary Axonal	2 (33.33%)
Primary Axonal	Primary Demyelinating	1 (16.67%)
Primary Axonal	Equivocal	1 (16.67%)
Primary Demyelinating	Equivocal	1 (16.67%)
Equivocal	Normal	1 (16.67%)
Total		**6 (100%)**

TABLE 37: Serial changes in electrophysiological classification according to Hadden's and Rajabally's criteria

Serial Changes in Electrophysiological Classification						
Electrophysiology Criteria	Day 0 to 15	Day 0 to 30	Day 0 to 90	Day 15 to 30	Day 15 to 90	Day 30 to 90
Hadden's Criteria	9/25 (36%)	10/22 (45.45%)	10/21 (47.62%)	3/22 (13.64%)	8/21 (38.1%)	9/21 (42.86%)
Rajabally's Criteria	6/25 (24%)	8/22 (36.36%)	12/21 (57.14%)	3/22 (13.64%)	9/21 (42.86%)	6/21 (28.57%)

In both the criteria used for electrophysiological classification of GBS, serial NCS at frequent intervals showed changes in electrophysiological category for same patient at different interval. Rapid Change from Primary Demyelinating to Primary Axonal category occur mainly due to reversible conduction failure more as compared to axonal degeneration of nerves.

By using both the criteria, in our study only 3 (13.64%) patients showed changes in electrophysiological classification between Day 15 and Day 30. There were minimal changes in electrophysiological classification between Day 15 and Day 30, hence maximum accurate electrophysiological classification can be done by doing NCS on Day 15.

Comparing Hadden's criteria with Rajabally's criteria, by using Rajabally's criteria a smaller number of patients showed changes in electrophysiological classification. As per Rajabally's classification from Day 0 to Day 15 only 24% patients, from Day 0 to Day 30 36.36% patients and from Day 30 to Day 90 28.57% patients showed changes. Therefore, it has emerged that by using Rajabally's criteria we were able to classify patients more accurately in any category of GBS as compared to Hadden's criteria.

By using Rajabally's criteria more patients showed change from Primary Demyelinating to Primary Axonal category which is marker for reversible conduction failure as compared to Hadden's criteria. From day 0 to day 15, as per Hadden's criteria only 2 patients showed changes from primary demyelinating to primary axonal category, whereas as per Rajabally's criteria 3 patients showed change from primary demyelinating to primary axonal category. From day 0 to day 30, as per Hadden's criteria, one patient showed changes from primary demyelinating to primary axonal category, whereas as per Rajabally's criteria 4 patients showed change from primary demyelinating to primary axonal category. Also, with use of Rajabally's criteria we could identify reversible conduction failure more often as compared to Hadden's criteria.

DISCUSSION

GBS is an acute immune mediated disorder affecting the peripheral nerves with clinical variants that differ in their phenotype, electrophysiology, prognosis and outcome.[3] It is known to commonly occur as a postinfectious or para-infectious event with regional and geographical variations.[11,12] 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.[17,18] Accurate electrodiagnosis of GBS is important as it offers insight into the underlying pathophysiology. 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.[137,157–159] A few prognostic models also have been developed to predict the outcome.[160] The pathophysiology of GBS is dynamic and NCS is supposed to reflect the electrophysiological changes commensurate with the pathophysiological changes in the nerves. Serial nerve conduction studies may allow a more accurate diagnosis of subtypes.[165]

This prospective cohort study was conducted at a tertiary care centre in western India in 30 patients over an 18-month period from January 2020 to June 2021 to assess their clinical, serological and electrophysiological profile of GBS. We attempted to classify various subtypes of GBS by serological markers and electrophysiological studies using Hadden's and Rajabally's criteria. Serial nerve conduction studies were done to look for patterns of recovery and changes in electrophysiological classification over time.

Gender distribution in our study showed male preponderance with Male: female ratio of 5:1 (Graph 1). Diseases with an autoimmune aetiology usually show a clear gender difference in prevalence, whereby females are more commonly affected. Contrary to this, GBS studies show a clear male preponderance.[2,30,118,166,167] A hospital based observational study between 2000 and 2004 by Alsheklee et al[118] reported 2739 (55.3%) patients were male and 2217 (44.7%) patients were female, indicating increased prevalence in male. A recent study from India by Dhadke et al[166] also showed higher prevalence in males with male: female ratio of 1.5: 1. A study from Central India by Shrivastava et al showed clear male preponderance with male: female ratio of 2.4:1.[167]

Mean **age** of patients in our study was 42.97±17.22 years (Mean± SD). Majority of patients (50%) were of younger age group (<40 years) (Graph 2). This was similar to a retrospective analysis of 66 patients with GBS done by Shrivastava et al[167] from Central India, which reported mean age of 40.69 years. Several studies have shown a bimodal age peak in GBS.[168] Dowling et al had reported a bimodal peak in young and elderly.[169] Our study showed no evidence of bimodal distribution of age-specific incidence in adult life.

A history of **antecedent illness** within 4 weeks is usually reported in GBS. In our study 56.6% patients had history of an antecedent event within 4 weeks of onset of illness (Graph 3). The most common antecedent event was URTI which was reported in 26.67% patients, followed by gastroenteritis which was reported in 16.67% patients (Graph 4). A systematic literature review of 36 studies by Mcgrogen et al[168] has shown that 40-70% of cases of GBS are associated with an antecedent infection. In these studies, too 22–53% patients had reported upper respiratory tract infection and 6–26% patients had reported gastrointestinal infection.[168] A study done by Thota et al[170] between 2017 and 2018 from tertiary care center in southern India showed antecedent illness in one third with viral respiratory tract infection as most common event. Another study from central India by Shrivastava et al[167] reported that 24.2% patients had respiratory tract infection and 13.6% patients had gastroenteritis as antecedent event. The incidence and pattern of antecedent infections in our study were comparable to those described in other studies. In our study the mean interval between antecedent event and onset of GBS was 10.875 (±6.07) days. Patient with upper respiratory tract infection as antecedent event had mean interval of 12.25 (±6.54) days while patients with gastroenteritis as antecedent event had mean interval of 8.6 (±6.88) days. From above findings we can infer that, patients with gastroenteritis as antecedent event had shorter interval as compared to upper respiratory tract infection. Out of 5 patients with gastroenteritis as antecedent event 4 patients had axonal variant of GBS. Out of 8 patients with URTI as antecedent event 5 patients had primary demyelinating variant of GBS. This observation is consistent with Hiraga et al[171] who had found that enteritis was more commonly associated with AMAN variety of GBS and URTI was associated with AIDP variety of GBS.

In our study all the patients had limb weakness as **clinical presentation**. Along with limb weakness some patients had other symptoms also at the time of presentation. 36.67% patients had myalgia, 43.33% patients had paraesthesia in either upper or lower limbs and 10% patients had sphincter disturbance at the time of presentation. 16.67% patients had respiratory insufficiency and 36.67% patients had difficulty in swallowing at the time of presentation (Graph 5). A study from central India by Dhadke et al[166] showed that all patients presented with limb weakness and 32.5% patients had sensory complaints at presentation. A study done by Shrivastava et al[167] from Central India showed 21.2% patients had respiratory insufficiency at the time of presentation.

On **clinical examination**, additional feature that emerged included cranial nerve involvement noted in 12 (40%) patients in our study (Table 5). Most common cranial nerve involved was facial followed by lower cranial nerves (9 and 10 cranial nerves). In a study by Bhargava et al[10] analysing cranial nerve palsies in GBS, 62.3% patients had cranial nerve palsies. In another recent study by Khan et al[172] 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 2 patients, one with MFS-GBS overlap syndrome and another with Bickerstaff brainstem encephalitis. Neck flexor weakness was seen in 22 (73.33%) patients. Generalized areflexia was seen in 19 (63.33%) patients. While 2 patients had normal deep tendon reflexes at presentation. Five (16.67%) patients had objective sensory loss at presentation. Autonomic dysfunction was seen in 3(10%) patients at presentation. Heart rate variability and blood pressure fluctuations were present in all these 3 patients. A study by Meena et al[173] reported 13.9% patients of GBS had autonomic disturbance at presentation. On the other hand, Singh et al[174] reported 41.53% patients with autonomic dysfunction in which 13.6% patients had heart rate variability and blood pressure fluctuations.

In our study, according to **clinical subtype** classification, 12 (40%) patients were categorized as AIDP, 14 (46.67%) patients were categorized as AMAN, one (3.33%) patient as AMSAN, one (3.33%) patient as MFS GBS overlap, one (3.33%) patient as paraparetic variant and one (3.33%) patient as Bickerstaff brainstem encephalitis (Graph 6). A slight preponderance of AMAN variant as compared to AIDP was noted. A retrospective study from northwest India done by Jain et al[33] reported equal

distribution of patients as AIDP and Axonal category. However, studies by Bhargava et al[10] and Taly et al[11] showed higher incidence of AIDP in India. Analysis of 1000 patients recruited in IGOS showed AIDP as predominant category in Europe and western countries, while almost equal distribution of patients between AIDP and AMAN were seen from Bangladesh.[21]

In our study both **NINDS** and **Brighton's diagnostic criteria** for GBS were applied to all the patients. All the patients fulfilled NINDS criteria. Out of 30 patients, 20 (66.67%) patients fulfilled level 1 of diagnostic certainty, while 10 (33.33%) fulfilled level 2 of diagnostic certainty as per Brighton's criteria (Graph 7). None of the patients had level 3 of diagnostic certainty. A study conducted by Fokke C et al[58] for diagnosis of GBS and validation of Brighton criteria showed similar results with 61% patients classified as level 1 and 33% patients classified as level 2 of diagnostic certainty. Another study by J Rath et al[26] reported 71% patients classified as level 1 and 26% patients classified as level 2 of diagnostic certainty.

Only, one patient (3.33%) had history of **recurrent GBS**. He had first episode of GBS 10 years prior to present event with respiratory insufficiency and required tracheostomy and assisted ventilation at that time. He was treated with IVIg to which he responded. Residual deficit in the form of bilateral foot drop was present in between two episodes. Second episode was less severe as compared to first, he presented with quadriparesis and bulbar involvement without respiratory insufficiency with Hughes score 4 at admission. This was different from the previous studies which had shown the second event to be more severe than the first. During this admission he was treated with plasma exchange to which he responded and improved up to previous baseline over next 3 months. His antiganglioside antibody panel done during this admission, showed presence of IgG antibodies against GD1b and GQ1b. Das et al[175] and Grandmaison et al[176] had found a similar prevalence (2-5%) of recurrent GBS in their studies.

In our study, mean **interval between onset of symptoms and admission** was 6.13 (±5.78) days. Majority of patients (66.67%) were admitted within 7 days of onset of symptoms while remaining 33.33% patients were admitted after 7 days of onset of symptoms (Graph 8). The mean **interval between onset of symptoms and nadir** was 9.31(±6.23) days within present study. Majority of patients (88.46%) achieved nadir

within 14 days of onset of weakness, remaining 11.54% patients achieved nadir after 14 days of onset of weakness (Graph 9). All the patients achieved nadir within 28 days of onset of weakness. This was earlier than the previous study by Dimachkie et al[177], where in most reached nadir by 2 weeks, 80% by 3 weeks and 90% by 4 weeks.

MRC sum score was calculated at admission and follow up on day 15, day 30 and day 90. Mean MRC sum score at admission was 32.93±16.43. Thirteen (43.33%) patients had MRC sum score <36 at admission, indicating severe weakness (Graph 10). Out of these 13 patients, 5 (38.46%) patients had poor outcome at 90 day follow up and had Hughes disability score ≥3. The remaining 17 (56.66%) patients had MRC sum score ≥36 at admission. Out of these 17 patients, 4 (23.53%) patients had poor out come at 90 day follow up with Hughes disability score ≥3. From above findings we could conclude that low MRC sum score at onset of disease was associated with poor outcome in follow up. Mean MRC sum score improved gradually over subsequent follow up. As shown in graph 14, mean MRC sum score was 36.3±18.94 on day 15, 42.57±14 on day 30 and 48.43±11.44 on day 90. A clinical prognostic model proposed by Walgaard et al[137] 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. This correlation of MRC sum score was clearly reflected in our study.

Hughes GBS disability score and **MRC disability score** was applied to all the patients at admission and on follow up on day 15, day 30 and day 90 in our study. At admission, 23 (76.67%) patients had **Hughes score** ≥4, indicating majority of patients were having significant disability on admission (Table 6). Only 7 patients (23.33%) had Hughes score <4. As the patients improved gradually, we could see on subsequent follow up that the number of patients with Hughes score ≥4 decreased as they gradually shifted to category with Hughes score <4. On day 15, 12 (40%) patients had Hughes score <4 (Table 7). On day 30, 20 (66.67%) patients had Hughes score <4 (Table 8). On day 90, 25 (83.33%) patients had Hughes score <4 (Table 9). These findings indicate gradual improvement of patients on follow up (Table 10, Graph 15). A good outcome is defined as the ability to ambulate without assistance (Hughes score ≤2); a poor outcome, as the inability to ambulate independently (Hughes score ≥3).[164] On follow up at Day 90, 21 (70%) patients out of 30 had a good outcome with Hughes score of ≤2. Accordingly,

majority of patients were able to walk without support at 90 days follow up. Nine (30%) patients out of 30 were having Hughes score ≥3 at 90 days. Out of these 9 patients, 7 (77.78%) patients had Hughes disability score ≥4 at admission. Accordingly, these patients had poor outcome at day 90 even after treatment. We can conclude that high GBS disability score at admission is associated with poor outcome. These findings are consistent with a study by Koningsveld et al.[160] Another study by Shangab et al[178] showed that out of 64.6% patients with high Hughes score (Hughes score ≥4) at admission, 30.5% patients had poor outcome.

MRC disability scale of 7 corresponded to Hughes score of 4, defined as inability to walk with support and patient being bed ridden. Accordingly at admission, 22 (73.33%) patients had MRC disability score of ≥7 (Table 11). Eight (26.67%) patients had MRC disability score <7. Subsequently on follow up day 15, day 30 and day 90, as patients gradually improved, the number of patients with MRC disability score ≥7, gradually decreased and shifted to MRC disability score <7 category, indicated improvement (Table 15, Graph 16). On follow up at day 90, 25 (83.33%) patients had MRC disability score <7 (Table 14). These findings showed that majority of patients had improved. Therefore, the findings with Hughes disability score and MRC disability score were similar.

In our study **CSF evaluation** was done in 86.67% patients. Albuminocytological dissociation was found in 18 (69.23%) patients (Graph 17). Dhadke et al[166] showed albuminocytological dissociation in 65.3% of patients. Our findings are comparable to this study. In our study mean CSF protein value was 105.35± 103.52 mg/dl. Findings in current study is almost similar to study by Verma et al[179] which showed mean CSF protein value of 108.60±53.24.

Serum ganglioside evaluation panel was sent in 20 (66.67%) patients. Out of these 20 patients, 7 (35%) patients had positive results (Graph 18). Out of these 7 patients with positive result on ganglioside panel, 5 (71.43%) patients were classified as AIDP variant and 2 (28.57%) patients were classified as axonal variant by Rajabally's criteria for electrophysiological classification (Table 17). Previous studies showed association of ganglioside antibodies with AMAN.[98,113] A prospective study by Sekiguchi et al[180] reported 36% patients in both Japanese and Italian cohort had positive ganglioside

antibodies. Out of these patients with positive ganglioside antibodies, in Japanese cohort, 41% patients were classified as AMAN and 30% patients as AIDP category. In Italian cohort, 37% patients were classified as AMAN and 26% patients as AIDP category. There has been variable association with ganglioside antibodies as per Indian studies. A study by Naik GS et al[9] from southern India showed 56.2% patients with positive results on ganglioside panel. Electrophysiological classification of patients with positive results in that study showed 51.2% patients were categorized as AIDP variant and 36.6% as axonal variant. Another study from a tertiary care centre in southern India by Mani et al[165] reported ganglioside antibodies were present in 46.1% patients, with slight predominance in axonal category as compared to AIDP.

Radiological assessment of brain and spine was done in 7 (23.33%) patients in our study. Out of 7 patients, 3 (42.86%) patients showed cauda equina nerve root enhancement. Two (28.57%) patients showed multiple cranial nerve enhancement. Three (42.86%) patients had normal MRI Brain and Spine screening. In a prospective study conducted by Gorson et al[181] MRI lumbosacral spine with contrast was obtained in 24 patients. Out of these 24 patients, 20 (83.33%) patients had nerve root enhancement.

Electrophysiological classification in present study was done by using both Hadden's and Rajabally's criteria at admission and follow up on day 15, day 30 and day 90 to see if there were significant variations in the classification across criteria. This was based on recent studies that showed that the Hadden criteria may underdiagnose axonal subtype of GBS leading to recent attempts to modify the electrodiagnostic criteria.[95,96] Using Hadden's criteria at admission, 58.62% patients were categorized as primary demyelinating and 20.69% patients as primary axonal. So, the most prevailing electrophysiological class at admission in our study was primary demyelinating according to Hadden's criteria. However, on using Rajabally's criteria, 48.28% patients were categorized as primary demyelinating and 48.28% patients as primary axonal category (Graph 20). Thus, using this criteria, we could say that patients were equally distributed between both the categories. Mani et al[165] conducted a retrospective study among patients at tertiary care centre in southern India to understand utility of serial nerve conduction study in GBS. The authors also utilised both the Hadden's and Rajabally's criteria for electrophysiological classification and to look for category

change in serial NCS. In that study, after the first NCS, according to Hadden's criteria, 71% patients were categorized as primary demyelinating category and 29% patients as primary axonal, while according to Rajabally's criteria, 45.2% patients were categorized as primary demyelinating and 54.8% patients as primary axonal category. Another study done by Rath et al[26] to look for influence of timing of NCS and value of repeated NCS in GBS reported during first NCS according to Hadden's criteria 70% patients were classified as primary demyelinating and 6% patients as primary axonal category, while according to Rajabally's criteria 38% patients were classified as primary demyelinating and 30% patients as primary axonal category. In another study, using Hadden's criteria, Uncini et al[97] found 67% of patients to have AIDP, 18% to have axonal GBS, and 15% to have equivocal electrodiagnosis on the first NCS. Therefore, the results of our study were comparable to these studies by Mani et al, Uncini et al and Rath et al. This conformed that Hadden's criteria over diagnosed AIDP which were better classified as axonal as per Rajabally's criteria.

Abnormal **sensory conductions** were seen in 22 (75.86%) patients in our study at admission (Table 18). Sural sparing pattern was seen in 3 (13.64%) patients, while 7 (31.82%) patients showed all sensory nerves inexcitable, 9 (40.91%) patients showed equivocal pattern and 3 (13.64%) patients showed axonal pattern (Figure 6). A study by Gordon et al[90] reported 61% patients had abnormal sensory conduction study in GBS. Sural sparing pattern was found in 48% of patients. During clinical examination 24 (82.76%) patients had normal sensory examination. Out of these 24 patients, 17 (70.83%) patients had abnormal sensory nerve conduction study (Figure 7). Thus, we were able to pick up a greater number of patients with sub-clinical sensory abnormalities with help of sensory nerve conduction studies. Out of 3 patients with sural sparing pattern of sensory conduction study, 2 patients were classified as primary demyelinating category according to both Hadden's and Rajabally's criteria, while one patient was classified as primary axonal category by both these criteria. These findings are consistent with study by Meena et al[8] that sural sparing pattern is more commonly seen with primary demyelinating GBS. Further detailed discussion about comparison of both the electrophysiological criteria and serial NCS had been done in later part of discussion.

Considering **treatment** options, 14 (46.67%) patients received plasma exchange, 5 (16.67%) patients received IVIg and 5 patients received both plasma exchange and IVIg (Table 19). All the 5 patients treated with both plasma exchange and IVIg had bad outcome at day 90. All these patients had severe weakness at onset itself. Probably this could explain bad out come in these 5 patients. Out of these 5 patients, 2 patients had TRF. Both of them were previously treated with plasma exchange and after that received IVIg. Most observational studies show higher number of patients undergoing treatment with IVIg but in our study a greater number of patients received plasma exchange. This may be because our centre is one of the few regional centres offering plasma exchange as a treatment modality for GBS and patients with severe grade of weakness are specifically referred for the same. Majority of patients (76.67%) in our study were having severe weakness (Hughes score ≥4) at the time of admission. The higher expense for treatment with IVIg as compared to plasma exchange also contributed to a few of the patients opting for plasma exchange. On day 90 follow up, 3 (21.43%) out of 14 patients treated with plasma exchange and 1 (20%) out of 5 patients treated with IVIg had bad outcome. Otherwise, there is no significant difference between two treatment options. In our study, a greater number of patients had severe weakness at onset and greater number of patients underwent plasma exchange as compared to IVIg. Mean duration of **onset of recovery after starting treatment** was 4.55±3.74 days in our study. The Plasma Exchange Sandoglobulin GBS Trial[132] showed similar outcome between plasma exchange, IVIG and plasma exchange followed by IVIg groups. A meta-analysis by Ortiz-Salas P et al[182] reported no evidence for superiority in the efficacy or safety of immunoglobulin or plasma exchange in the management of GBS. Hughes et al[60] had observed that patients treated within two weeks from onset with IVIg had recovery as much as plasma exchange. On the other hand, El-Bayoumi et al[183], in pediatric population, found that the plasma exchange group had a significant shorter duration of mechanical ventilation compared to IVIg group.

In our study, 8 (26.67%) patients required **mechanical ventilation** during the course of illness. Out of these 8 patients, 4 (50%) patients had bad outcome at day 90 follow up. They had Hughes score ≥ 3 at 90 days follow up, they were not able to walk without support. These patients also had severe weakness at onset and this could possibly explain their bad outcome. A study by Dhadke et al[166] reported 30% patients from study

population required mechanical ventilation during course of illness. Our results are comparable to this study but lower than other studies. Sudulagunta et al[13] in a study from southern India reported 38.5% patients required mechanical ventilation. A prospective observational study from tertiary care centre from south India by Thota et al[170] also reported 37.5% patients required mechanical ventilation during course of illness.

The **EGRIS** can predict probability of respiratory insufficiency in GBS patients in the first week of admission. In this study we had calculated EGRIS scores of all the patients and divided them into different groups according to risk of respiratory insufficiency. Out of 30 patients, 7 (23.33%) patients had score 0-2, 12 (40%) patients had score 3-4 and 11 (36.67%) patients had score 5-7 (Graph 20). One (14.29%) patient with score 0-2, 2 (16.67%) patients with score 3-4 and 5 (45.45%) patients with score 5-6 developed respiratory insufficiency. From these findings, we could conclude that a greater number of patients with higher EGRIS developed respiratory insufficiency as compared to lower EGRIS score. These findings correspond to a study by Walgaard et al[124] that predicted that patients with higher EGRIS score have higher probability of respiratory insufficiency in the disease course.

In our study 30% patients developed **complications** during course of hospital stay. Most common complication was pneumonia followed by septicaemia. This was similar to Thota et al[170] who reported pneumonia as most common complication followed by thrombophlebitis and bedsores.

Majority of patients in our study were admitted in Neurology ward. As per requirement of ventilator support and monitoring they were shifted to ICU from ward. Mean **duration of hospital stay** was 18.27±13.58 days in our study. Five (16.67%) patients had duration of hospital stay > 4 weeks (Graph 19). This was at par with a recent study by Leuween et al[184] where the mean duration of hospital stay was 17 days with most patients being admitted in neurology wards (82%).

Mortality rate in GBS patients is variable across the studies. In our study, **mortality** rate was 10% (3 patients) even after best possible treatment. A prospective study by Kalita et al[185] from a tertiary care center in Northern India reported 6.8% mortality rate

among GBS patients. A hospital based observational study between 2000 and 2004 by Alsheklee et al[118] in a large US cohort reported 2.58% mortality rate among GBS patients.

The **EGOS** is a predictor of poor outcome at 6 months. It predicts probability of inability to walk independently at 6 months. In our study 2 patients had poor outcome at 6 months. Both of these patients had higher EGOS score. One patient had score of 5 and another patient had score of 6.5. These findings are comparable with findings reported by Koningsveld et al[160], that found that patients with higher EGOS score was predictive of poor outcome.

The **mEGOS** score was also calculated for all the patients at admission. It is also a predictor of poor outcome.[137] In our study 13 (43.33%) patients had mEGOS score ≥ 6 (Graph 22). Out of these 13 patients, 3 (23.08%) patients had poor outcome at 3 months. According to a study by Walgaard et al[137], around 15% patients with mEGOS score ≥ 6 can have poor outcome at 3 months. This was similar to our observations.

Comparison of Hadden's and Rajabally's criteria for electrodiagnostic classification

There are various electrodiagnostic criteria for classification of GBS. Hadden's criteria was described in 1998, and it is most commonly utilized for last 2 decades. In 2015, Rajabally and colleagues proposed a criteria with more conservative cut offs for demyelinating parameters. Electrophysiological classification was done using both these criteria in our study to look for significant variation in the classification across criteria at admission and on follow up on day 15, day 30 and day 90. Details of different classification of individual patient by both the criteria at defined intervals are as per Table 20 and Table 21. This was based on recent studies that showed that the Hadden criteria may underdiagnose axonal subtype of GBS leading to recent attempts to modify the electrodiagnostic criteria.[96] Utilizing the concept of reversible conduction failure as possible evidence of axonal pathology, the Rajabally criteria may help in earlier classification of GBS subtype and may help eliminate need for serial NCS to rule out reversible conduction failure.[96]

At admission according to Hadden's criteria majority patients (58.62%) were classified as primary demyelinating as compared to 20.69% patients as primary axonal pattern. At the same time utilizing Rajabally's criteria, showed equal distribution between (48.28%) primary axonal category and (48.28%) primary demyelinating category (Graph 23). According to table 22, we could say that at admission according to Hadden's criteria 4 out of 29 patients were classified as inexcitable and 2 out of 29 patients were classified as equivocal category. At the same time using Rajabally's criteria we could classify these subgroups into either primary demyelinating or primary axonal category. On day 15, 30 and 90 according to Hadden's criteria 52%, 63.64% and 38.1% patients were classified as primary demyelinating category respectively, while 36%, 22.73% and 28.57% patients were classified as primary axonal category respectively. At the same time according to Rajabally's criteria, 48%, 40.91% and 33.33% patients were classified as primary demyelinating category respectively, while 44%, 45.45% and 42.86% patients were classified as primary axonal category respectively (Graph 24,25,26). Accordingly, we could say that a greater number of patients were classified as primary axonal as compared to primary demyelinating with the use of Rajabally's criteria including those with inexcitable nerves. On the other hand, at the same time, a greater number of patients were categorized as primary demyelinating according to Hadden's criteria. On follow up, the number of patients classified as equivocal by both criteria were noted to increase (Table 22), suggesting improvement in nerve conductions over time. These findings are consistent with a study by Uncini et al[95,106] showing Rajabally's criteria being more sensitive for diagnosing primary axonal category and less sensitive but more specific for primary demyelinating category. In that study according to Hadden's criteria, 67% patients were classified as primary demyelinating category and 18% patients as primary axonal category, while according to Rajabally's criteria 45% patients were classified as primary demyelinating category and 35% patients as primary axonal category.

Hadden's criteria is more simplified for categorization. For classification as primary demyelinating GBS, the cut offs are very narrow. So many patients are easily classified as Primary demyelinating. On the contrary in Rajabally's criteria, cut offs for primary demyelinating classification are more conservative, and also along with conduction block (proximal/distal CMAP ratio < 0.7 instead of <0.5), one demyelinating feature is require in any other nerve to classify as primary demyelinating category. Thus, for

classification in primary axonal category instead of relying only on CMAP values alone, presence of only conduction block without any demyelinating feature in any other nerve has also been taken into consideration. This helps in identification of reversible conduction failure correctly. Hadden's criteria rely only on CMAP values for classification as primary axonal category. This can easily misclassify many patients as primary demyelinating instead of primary axonal pattern, which are having reversible conduction failure. So, with the help of Rajabally's criteria we can identify reversible conduction failure more accurately.

Assessment of serial changes in NCS

Electrophysiology of GBS subtype is dynamic. GBS subtypes evolve pathophysiologically and electrophysiologically during the disease course. In AIDP, demyelinating features cannot be evident at early studies but progressive prolongation in distal motor latency and slowing of nerve conduction develop in 5– 8 weeks likely reflecting demyelination.[95] RCF is a typical example of a dynamic change. RCF may be accompanied by prolongation of distal motor latency and reduction of motor conduction velocity that normalize in parallel with CMAP amplitude. These findings may be confusing as, in the common belief, slow conduction velocity is assumed to be a characteristic of a demyelinating process. Therefore, only serial studies may provide a full understanding of the GBS pathophysiology.[95]

In our study we had done serial NCS at admission and follow up on day 15, day 30 and day 90. We had evaluated category shift between different intervals for all the cases with both Hadden's and Rajabally's criteria and serial changes in each case according to both the criteria are depicted in table 23 and table 30, respectively.

By comparing serial changes in electrophysiological category between **day 0 and day 15**, as per table 24 using Hadden's criteria, 9 (36%) patients showed changes in electrophysiological category. Out of these 9 patients, 2 (22.22%) patients (case number 7 and 23) showed change from primary demyelinating to primary axonal category, probably indicating RCF. From rest of all patients no specific pattern could be identified, and we could see changes in almost all categories. During the same interval, by using Rajabally's criteria, as per table 31, 6 (24%) patients showed changes in electrophysiological category. Out of these 6 patients, 3 patients (case number 2, 7 and

23) showed change from primary demyelinating to primary axonal category, probably indicating RCF. Two patients showed change from primary axonal to primary demyelinating, which could be due to initial misclassification. One patient showed change from primary axonal to equivocal category, probably indicating improvement.

On comparing changes between **day 0 and day 30**, as per table 25 using Hadden's criteria, 10 (45.45%) patients showed changes in electrophysiological category. Out of these 10 patients, one (10%) patient (case number 7) showed change from primary demyelinating to primary axonal category, probably indicating RCF. From rest of all patients no specific pattern could be identified, as changes were seen between all the categories. During the same interval, by using Rajabally's criteria, as per table 32, 8 (36.36%) patients showed changes in electrophysiological category. Out of these 8 patients, 4 patients (case number 2, 7, 23 and 28) showed change from primary demyelinating to primary axonal category, probably indicating RCF. Two patients showed change form primary axonal to primary demyelinating category and could be due to initial misclassification while remaining 2 patients showed change from primary axonal to equivocal category, probably indicating improvement.

Comparison between **day 0 and day 90**, as per table 26, according to Hadden's criteria, 10 (47.62%) patients showed change in electrophysiological category. Out of 10 patients, 3 patients (case number 7, 23 and 28) showed change form primary demyelinating to primary axonal category. Probably initially they were classified as primary demyelinating but with gradual improvement of RCF they could be classified as primary axonal. One patient (case number 19) who showed change from primary demyelinating to inexcitable category, had TRF and worsening of symptoms at that time. Accordingly, this was reflected by the worsening in electrophysiological pattern also. Two patients showing change from primary axonal to primary demyelinating category could be due to initial misclassification, which could be reclassified correctly on serial NCS. Remaining patients showing changes in electrophysiological class indicated improvement upon serial NCS. During the same interval, by using Rajabally's criteria, as per table 33, 12 (57.14%) patients showed changes in electrophysiological category. Out of these 12 patients, 5 patients showed change from primary demyelinating to primary axonal category probably indicating RCF in 4 patients (case number 7, 23, 28 and 29) and TRF in one patient (case number 19). Two patients

showed primary axonal to primary demyelinating category, probably indicating initial misclassification which could be corrected on serial NCS. Remaining patients showed category changes due to improvement in conduction studies over time.

On comparing changes between **day 15 and day 30**, as per table 27, according to Hadden's criteria, 3 (13.64%) patients showed change from primary axonal to primary demyelinating category, which could be due to initial misclassification. During same interval, by using Rajabally's criteria, as per table 34, 3 (13.64%) patients showed changes in electrophysiological category. Out of these 3 patients, one patient (case number 28) showed change from primary demyelinating to primary axonal category, probably indicating RCF. One patient showed change from primary axonal to primary demyelinating category, probably indicating initial misclassification. Remaining one patient showed change from primary demyelinating to equivocal category, indicating improvement.

Comparison between **day 15 and day 90**, as per table 28, according to Hadden's criteria, 8 (38.1%) patients showed changes in electrophysiological category. Out of these 8 patients, one patient (case number 28) showed change from primary demyelinating to primary axonal category, probably indicating RCF. One patient showed change from primary axonal to primary demyelinating category, probably due to initial misclassification. One patient with TRF showed change from primary demyelinating to inexcitable category. Remaining patients showed category changes probably due to improvement. During same interval, as per table 35, according to Rajabally's criteria, 9 (42.86%) patients showed changes in electrophysiological category. Out of these 9 patients, 3 patients showed change from primary demyelinating to primary axonal category, probably indicating RCF in 2 patients (case number 28 and 29) while TRF in one patient (case number 19). Two patients showed change from primary axonal to primary demyelinating category, probably indicating initial misclassification. Remaining patients showed category changes due to improvement in nerve conductions over time.

On comparing changes between **day 30 and day 90**, as per table 29, according to Hadden's criteria, 9 (42.86%) patients showed change in electrophysiological category. Out of these 9 patients, 3 patients (case number 23, 25 and 28) showed change from

primary demyelinating to primary axonal category, probably indicating RCF. One patient with TRF showed change from primary demyelinating to inexcitable category. Remaining patients showed category changes due to improvement in nerve conductions over time. During same interval, as per table 36, according to Rajabally's criteria, 6 (28.57%) patients showed changes in electrophysiological category. Out of these 6 patients, 2 patients showed change from primary demyelinating to primary axonal category, probably indicating one patient (case number 29) with RCF and one patient (case number 19) with TRF. One patient showed change from primary axonal to primary demyelinating category, probably indicating initial misclassification. Remaining patients showed category changes due to improvement in nerve conductions over time.

From above findings we can conclude that, according to both the criteria minimal changes in electrophysiological patterns are seen between day 15 and day 30 (Table 37). The majority of the electrophysiological category changes between day 15 – day 90 and day 30 – day 90 are due to improvement in nerve conductions. So, for majority of patients accurate electrophysiological classification by both the criteria can be done by doing NCS on day 15. By using Hadden's criteria in serial NCS, we could identify total 3 patients (case number 7, 23 and 28) with RCF. Out of these 3 patients we could pick up RCF reversal in 2 patients (case number 7 and 23) on day 15 and for remaining one patient (case number 28) on day 90. However, utilizing Rajabally's criteria in serial NCS, we could identify 4 patients (case number 7, 23, 28 and 29) with RCF. Out of these 4 patients, we could identify RCF reversal in 2 patients (case number 7 and 23) on day 15, for one patient (case number 28) on day 30 and remaining one patient (case number 29) on day 90. From above findings we could infer that by Rajabally's criteria can identify a greater number of patients with RCF and relatively early as compared to Hadden's criteria.

There is a lack of studies internationally as well as from India looking at the utility of serial NCS in the management of patients with GBS. One retrospective study from a tertiary care center from southern India by Mani et al[165] tried to investigate the utility of serial NCS studies in GBS patients. They retrospectively evaluated the data of GBS patients, who underwent at least 2 NCS during the course. They applied Cornblath's, Hadden's and Rajabally's criteria for electrophysiological classification to all the

patients and evaluated shifts in different categories. The interval between two studies was at an average 2 weeks in that study. No longer follow up was done. In that study, 9.6% patients as per Hadden's criteria and 16.1% patients as per Rajabally's criteria showed shifting in electrophysiology category. In our prospective study with NCS done at admission and day 15, 36% patients as per Hadden's criteria and 24% patients as per Rajabally's criteria showed shift in category. Uncini et al[95] found that 23.6% of patients changed subtype, using Hadden's criteria and the majority of the shifts were from AIDP and equivocal groups to axonal GBS. In our study also majority shifts were between primary demyelinating to primary axonal category. This was mainly due to the recognition of RCF by serial NCS. A single NCS can't distinguish between demyelinating conduction block and RCF and can misclassify patients with axonal GBS as having AIDP. RCF is an a posteriori diagnosis and can be identified only on serial NCS.

On the other hand, the major reason for shifts from axonal GBS to AIDP was the misclassification of subtypes due to inherent flaws in the criteria. With the Hadden's criteria, there is a tendency for underdiagnoses of axonal GBS, primarily due to misclassification as AIDP.[95] Uncini and Kuwabara et al[186] have suggested at least two NCS in the first 4–6 weeks of the disease. Shahrizaila et al[187] have suggested that performing NCS at two-time intervals, 1st NCS at admission and 2nd NCS at an interval of 3–8 weeks after disease onset can make an accurate electrodiagnosis of GBS.

A further illustration of some of the **cases** showing significant serial changes in electrophysiological categories as per table 23 and 30, are discussed below.

Case number 2 had been classified as primary demyelinating category by both criteria at admission. She had progression of disease after admission and developed respiratory insufficiency. On day 15 and day 30 she had all peripheral nerves inexcitable, which indicated progression of disease. According to Hadden's criteria she was classified as inexcitable category. As inexcitable category has been classified as primary axonal category as per Rajabally's criteria, she was classified as primary axonal category on day 15 and day 30 as per it. Gradually she had significant improvement till day 90. NCS done on day 90 showed primary demyelinating category according to both the criteria. Accordingly, we could say that she was having primary demyelinating pattern from

beginning only, but due to progression of disease she was classified as primary axonal category in view of inexcitable peripheral nerves. But again, as she improved, she was again classified as primary demyelinating category. In conclusion, this case exemplifies an inherent fallacy of Rajabally's criteria. So, we could say that severe disease process can also misclassify electrophysiology pattern.

Case number 4 was classified as primary axonal category by both the criteria at admission. Subsequently he was classified as primary demyelinating category by serial NCS on day 15, day 30 and day 90 by both the criteria. In this case he was having primary demyelinating pattern from onset only, but on initial NCS done at admission CMAP amplitudes were very low. From this case we could conclude that, with very low CMAPs demyelinating features on NCS are difficult to capture. So, he was misclassified as primary axonal pattern at admission by both criteria. But subsequently as he improved and demyelinating pattern on NCS became more evident then, we could pick up an accurate electrophysiological category on subsequent NCS.

Case number 7 was classified as primary demyelinating category by both criteria at admission. He had prolonged DML in lower limb nerves and one upper limb nerve, along with proximal/distal CMAP ratio < 0.7 in more than 2 nerves. According to these features he was classified in primary demyelinating category. On subsequent NCS on day 15, some nerves became inexcitable, CMAP amplitude decreased in remaining nerves but DML improved to normal range in remaining all nerves and also only one nerve had conduction block. Accordingly, he was classified as primary axonal category by both the criteria. Further NCS on day 30 and day 90 also showed primary axonal category by both criteria. This was case of RCF and we could identify that on serial NCS and classify the accurate electrophysiological category subsequently.

Case number 10 was classified as primary axonal category at admission using both the criteria. NCS at admission was showing only 2 nerves as excitable while, rest all nerves were inexcitable. Conduction block was present in one of these nerves, but CMAPs were reduced significantly in both these nerves. With Hadden's criteria according to CMAP, he was classified as primary axonal category. There was no supporting demyelinating feature in any other nerve, so according to Rajabally's criteria also he was classified as primary axonal category. Similarly, NCS on day 15 also showed

majority nerves as inexcitable and according to both criteria, he was classified as primary axonal category. As he improved, serial NCS on day 30 showed improvement in CMAPs. Conduction block was present in 2 nerves, along with prolonged DML in upper limb nerves. Lower limb nerves were still inexcitable. According to Hadden's criteria he was classified as primary demyelinating category on the basis of DML cut offs. According to Rajabally's criteria, along with conduction block in 2 nerves, supporting demyelinating feature in one nerve in the form of prolonged DML more than cut off was present in one nerve. With these findings he was classified as primary demyelinating category. Subsequent NCS on day 90 showed further improvement in CMAP amplitudes, conduction block was present in 2 nerves, DML improved in upper limbs, but lower limb DML were prolonged. According to both the criteria he was classified as primary demyelinating category. This bring forth a possible lacuna when both criteria may be restrictive for diagnosing demyelination with low/ absent CMAPs and only one feature being satisfied.

Case number 16 was classified as primary demyelinating category as per Hadden's criteria and primary axonal as per Rajabally's criteria at admission. NCS at admission was showing prolonged DML in lower limb nerves. It was greater than cut off of DML by Hadden's criteria. So, according to Hadden's criteria she was classified as primary demyelinating category. But it was below the cut off of DML described by Rajabally's criteria. She also had proximal/distal CMAP ratio <0.7 in bilateral median and tibial nerves. But no other supportive feature of demyelinating criteria was there. So, according to Rajabally's criteria she was classified as primary axonal category. Gradually on subsequent NCS conduction blocks improved and she was classified as equivocal category by both the criteria on day 15, day 30 and day 90. This shows the inherent bias of Hadden's criteria for primary demyelinating category and Rajabally's criteria for primary axonal category.

Case number 19 was classified as primary demyelinating category according to both the criteria at admission, day 15 and day 30. He had worsening of symptoms on subsequent follow up and NCS done on day 90 showed inexcitable motor nerves. Accordingly, he was classified as inexcitable category as per Hadden's criteria and primary axonal category as per Rajabally's criteria. With the above history he was identified as case of TRF. Serial NCS can be helpful for identification of TRF, which

shows worsening of NCS parameters after initial improvement. In case of TRF, preliminary classification should probably prevail in deciding type of GBS.

Case number 23 was classified as primary demyelinating category at admission according to both the criteria. NCS at admission was showing proximal/distal CMAP ratio <0.5 in bilateral median, peroneal and right tibial nerves along with prolonged DML in lower limb nerves. With these features he was classified as primary demyelinating category by both Hadden's and Rajabally's criteria. Subsequent NCS on day 15 showed improvement in conduction block but CMAPs were reduced. So, he was classified as primary axonal category by both the criteria. NCS on day 30 showed resolution of conduction block, but DML in lower limb nerves were prolonged than cut off by Hadden's criteria for primary demyelinating category but not fulfilling Rajabally's criteria. So, he was classified as primary demyelinating category as per Hadden's criteria and as primary axonal category as per Rajabally's criteria. NCS on day 90 showed improvement in DML in all nerves, but CMAPs were still reduced. So, he was classified as primary axonal category by both the criteria. This was a case of RCF. Initial NCS showed conduction block with prolonged DML which classified him as primary demyelinating, while subsequent NCS showed resolution of conduction block and improvement in DML which rapidly converting him to primary axonal category. From this case we could say that lower limb DML should be checked carefully, as it can solely fallaciously classify patient as primary demyelinating category. Another point is that cut off for primary demyelinating category by Rajabally's criteria are more stringent than Hadden's criteria. So, patients are not loosely classified as primary demyelinating category even though other features are favouring primary axonal category.

Case number 25 was classified as primary axonal category according to both the criteria at admission and on day 15. NCS on day 30 showed reduced conduction velocity in bilateral median and ulnar nerves below the cut off for primary demyelinating category according to Hadden's criteria. Accordingly, he was classified as primary demyelinating category, while it was above the cut off by Rajabally's criteria. Rest of the features favoured primary axonal category. Accordingly, he was classified as primary axonal category by Rajabally's criteria. Subsequent NCS on day 90 showed improvement in conduction velocity and accordingly he was classified as

primary axonal category by both the criteria. From this case we could say that, relying only single parameter like DML or conduction velocity can falsely classify as demyelinating category while rest of the features favours axonal category. As Rajabally's criteria has very strict cut off for Demyelinating category, it classifies patients more accurately than Hadden's criteria.

Case number 28 was classified as primary demyelinating category at admission and on day 15 as per both the criteria. Both the NCS showed conduction block with prolonged DML in majority of nerves. NCS done on day 30 showed improvement in conduction block and DML in all the nerves. DML was prolonged as per Hadden's cut off but was not fulfilling Rajabally's cut off. So, he was classified as primary demyelinating category according to Hadden, while primary axonal category as per Rajabally's criteria. Subsequent NCS on day 90 showed improvement in conduction block and DML, but CMAPs were reduced. So, he was classified as primary axonal category according to both the criteria. This was also a case of RCF, which showed rapid improvement in conduction block and DML, where the reversal could be picked up earlier using Rajabally's criteria.

Case number 29 was classified as primary demyelinating category by both the criteria at admission, day 15 and day 30. NCS at admission was showing conduction blocks with prolonged DML and reduced conduction velocity. Accordingly, he was classified as primary demyelinating category by both the criteria. Subsequent NCS on day 15 and day 30 showed improvement in conduction block, DML and conduction velocity. Though, still within range of primary demyelinating category by both the criteria. Subsequent NCS on day 90 showed improvement in all parameters. Conduction blocks resolved and conduction velocity came to normal limits. But DML in lower limb nerves was still slight prolonged. So, according to Hadden's criteria he was classified as primary demyelinating category, while as per Rajabally's criteria classified as primary axonal category. This could also be the case of RCF, which showed rapid improvement in conduction block and other parameters except only prolonged lower limb DMLs that categorised him as primary demyelinating on day 90 as per Hadden's criteria, while Rajabally's criteria could pick up primary axonal category early. Again, from this case we could say that lower limb DMLs should be checked and taken into account carefully, to prevent misclassification.

From above cases we can conclude that Rajabally's criteria is having more stricter criteria for primary demyelinating type as compared to Hadden's criteria, thereby more accurately classifying patients. Also, RCF can be identified with Rajabally's criteria more frequently. However, there is still a requirement for further revision of electrophysiological criteria for accurate classification of patients on single NCS. Serial NCS helps make a more accurate diagnosis by demonstrating RCF, TRF, improvements and misclassification, which is helpful for further management. Serial NCS at least minimum baseline and 2-4 weeks later should be considered for all the patients of GBS.

CONCLUSION

In this prospective cohort study on 30 GBS patients, certain salient features emerged. GBS was found to have significant male preponderance. Majority of patients were of younger age group (<40 years). History of antecedent events was present in slightly more than half of the patients. Upper respiratory tract infection was major antecedent event, followed by gastroenteritis. Upper respiratory tract infection was most commonly associated with primary demyelinating pattern, while majority of patients with gastroenteritis had primary axonal pattern. Patients with gastroenteritis had shorter interval between antecedent event and onset of GBS. Few patients had history of febrile illness and COVID 19 vaccination as antecedent event.

All the patients presented with limb weakness with majority having quadriparesis followed by paraesthesia and then myalgia. Almost 1/3rd of patients had difficulty in swallowing and cranial nerve involvement was present in 40% of patients at admission. A greater number of patients had neck flexor weakness and generalized areflexia. Only few patients had objective sensory loss and autonomic dysfunction at admission. Major clinical subtype was AMAN (pure motor) followed by AIDP variant. Only one patient each had MFS-GBS overlap syndrome, paraparetic variant and Bickerstaff brainstem encephalitis. Only one patient had recurrent GBS with IgG antibodies against GD1b and GQ1b. Mean interval between onset of symptoms and admission was 6.13 (±5.78) days with majority getting admitted within 7 days of onset of symptoms.

Majority of patients achieved nadir within 14 days of onset with almost half achieving nadir within 7 days of onset. Almost half of the patients had MRC sum score <36 at admission, indicating severe weakness. Patients with low MRC sum score at admission had poor outcome at follow up. Similarly, Hughes and MRC disability score at admission helped in predicting outcome. Majority of patients with higher Hughes and MRC disability score at admission had poor outcome at 90 days follow up.

A greater number of patients showed albuminocytological dissociation on CSF examination, ganglioside antibodies were present in 35% of patients tested. Majority of patients with positive ganglioside antibodies were classified as primary demyelinating

category as compared to primary axonal category on electrophysiology studies. MRI brain and spine was done in 23.33% patients, showed spinal nerve root or cranial nerve enhancement in about half of the patients.

Serial NCS was done in the study at admission and at 15, 30 and 90 day follow up. At admission Hadden's criteria classified a greater number of patients as primary demyelinating category compared to primary axonal category, while according to Rajabally's criteria patients were equally divided between primary demyelinating and primary axonal category. Almost 75% patients had abnormal sensory nerve conduction at admission. Subclinical electrophysiological abnormal sensory conductions were seen in 70% patients with normal sensory clinical examination. This highlights the importance of sensory NCS in GBS patients.

Comparison between Hadden's and Rajabally's criteria for electrophysiological classification at admission and specified intervals showed that Hadden's criteria is more simplified and is very sensitive for primary demyelinating category. On the other hand, Rajabally's criteria is more sensitive for diagnosing primary axonal category and less sensitive but more specific for primary demyelinating category. Therefore, it does not loosely classify patients into primary demyelinating category. Hence, for accurate electrophysiological classification with single electrophysiological study, we suggest using Rajabally's criteria, as it can classify patients more accurately. Evaluation of serial NCS using Hadden's and Rajabally's criteria showed that there was less category shift on serial NCS with Rajabally's criteria as compared to Hadden's criteria. Serial NCS helps identify RCF and classify their evolution. RCF could be identified earlier with Rajabally's criteria. We conclude that serial NCS should be done in all patients with GBS as it can help us to understand pathophysiology and guiding further management. If multiple serial NCS is not possible, a minimum of two NCS should be done in every patient, first at admission and the next between 15 – 30 days. Second NCS after 15 days helped in the most accurate electrophysiologic classification.

Regarding treatment outcomes, almost half of the patients were treated with plasma exchange and 16.67% patients with IVIg. Around 17% patients with severe weakness and TRF received both plasma exchange and IVIg. No significant outcome difference was noticed between treatment options. Around 27% patients required mechanical

ventilation during course of illness of which, around 50% had bad outcome at 90 days. Thus, we could identify that, patients with requirement of mechanical ventilator during the course have greater risk of bad outcome compared to those without. Around 30% patients developed complications during course of the illness, commonest being pneumonia followed by septicaemia. Mean duration of hospital stay was 18.27±13.58 days.

Various prognostic scores such as EGRIS, EGOS and mEGOS have been proposed to predict course and outcome in patients with GBS. These scores should be used routinely in clinical practice, that can help us to plan and execute treatment strategies and prevent complications that subsequently leads to better outcome.

LIMITATIONS

- In view of COVID-19 pandemic a lesser number of patients could be recruited. Certain restrictions during pandemic also affected their follow up and some of the patients could not be followed up.
- Various electrophysiology criteria for GBS are described. In this study, 2 most commonly used criteria were utilised and compared. For future studies we can use other different criteria for classification and comparison as well.
- NCS of every patient should be done by same person at admission and at all the follow ups to prevent any interobserver variability.

Future Directions

- Further revisions of electrophysiology criteria are required for accurate classification of patients with single NCS only. Even though Rajabally's criteria has more stringent cut offs, still we require stricter criteria to prevent misclassification.
- Majority of criteria for electrophysiology classification are based on only motor conduction studies only. Sensory conduction abnormalities should also be included for classification.
- We should not rely only on DML for classification as primary demyelinating category. This can lead to misclassification as primary demyelinating category. Considering abnormality in both DML and CV will improve specificity for primary demyelinating category and prevent misclassification.

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ANNEXURES

ANNEXURE 15.1: Ethical Clearance Certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/2048 **Date: 01/01/2020**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/972**

Project title: **"Clinical, electrophysiological and serological markers in patients with Guillain-Barre Syndrome"**

Nature of Project:	**Research Project**
Submitted as:	**D.M. Dissertation**
Student Name:	**Dr.Patel Apoorv Dahyabhai**
Guide:	**Dr. Samhita Panda**
Co-Guide:	**Dr. Mahendra Kumar Garg**

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

Page 1 of 2

ANNEXURE 15.2: Electrodiagnostic criteria by Hadden et al

Electrodiagnostic criteria by Hadden et al (1998)[95]

1. **Primary demyelinating**

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

- MCV <90% LLN (85% if dCMAP <50% LLN)
- DML >110% ULN (120% if dCMAP <100% LLN)
- pCMAP/dCMAP amplitude ratio <0.5 and distal CMAP ≥20% LLN
- F-response latency >120% ULN

2. **Primary axonal**
    - None of the above features of demyelination in any nerve (except one demyelinating feature allowed in one nerve if distal CMAP <10% LLN) AND
    - dCMAP <80% LLN in at least two nerves
3. **Inexcitable**
    - dCMAP absent in all nerves (or present in only one nerve with distal CMAP <10% LLN)
4. **Equivocal**
    - Does not exactly fit criteria for any other group.

ANNEXURE 15.3: Electrodiagnostic criteria by Rajabally et al

Electrodiagnostic criteria by Rajabally et al (2015)[95]

1. Acute inflammatory demyelinating polyneuropathy (AIDP)

At least one of the following in at least two nerves:

- MCV <70% LLN
- DML >150% ULN
- F-response latency >120% ULN, or >150% ULN (if distal CMAP <50% of LLN)

  OR
- F-wave absence in two nerves with dCMAP ≥20% LLN, with an additional parameter, in one other nerve

  OR
- pCMAP/dCMAP amplitude ratio <0.7 (excluding the tibial nerve), in two nerves with an additional parameter, in one other nerve

2. Axonal GBS (including inexcitable forms)

Axonal GBS

None of the above features of demyelination in any nerve (except one demyelinating feature allowed in one nerve if dCMAP <10% LLN), and at least one of the following:

- dCMAP <80% LLN in two nerves
- F-wave absence in two nerves with distal CMAP ≥20% LLN, in absence of any demyelinating feature in any nerve
- pCMAP/dCMAP amplitude ratio <0.7, in two nerves (excluding the tibial nerve)
- F-wave absence in one nerve with distal CMAP ≥20% LLN

  OR
- pCMAP/d CMAP amplitude ratio <0.7 (excluding the tibial nerve), in one nerve; with **IN ADDITION**, dCMAP <80% LLN in one other nerve

Inexcitable

- If dCMAP absent in all nerves (or present in only one nerve with dCMAP <10% LLN)

Equivocal

- Abnormal range findings however not fitting criteria for any other group

ANNEXURE 15.4: GBS disability scales

Hughes GBS disability Scale[120]

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[121]

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 grade3.
8. Respirator and/or severe quadriparesis; maximum strength MRC grade 2.
9. Respirator and quadriplegia.
10. Death.

Rankin's disability scale[122]

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.

ANNEXURE 15.5: Erasmus GBS Respiratory Insufficiency Score (EGRIS)[124]

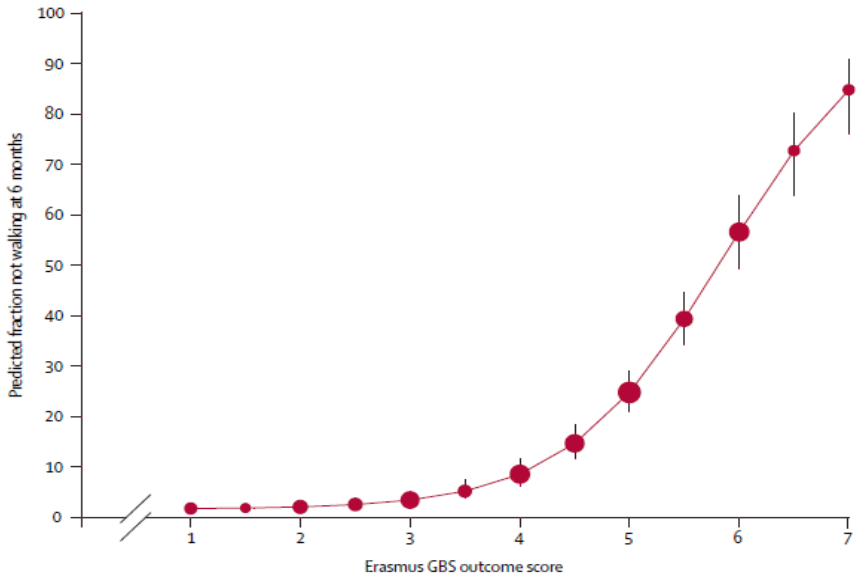
Measure	Categories	Score
Days between onset of weakness and hospital admission	>7 days	0
	4–7 days	1
	≤3 days	2
Facial and/or bulbar weakness at hospital admission	Absence	0
	Presence	1
MRC sum score at hospital admission	60–51	0
	50–41	1
	40–31	2
	30–21	3
	≤20	4
EGRIS		0–7

Low risk	EGRIS 0-2
Intermediate risk	EGRIS 3–4
High risk	EGRIS 5–7

ANNEXURE 15.6: Erasmus GBS Outcome Score (EGOS)[160]

Prognostic factor	Patient characteristic	Score points	The patient's points
Age(years)	<40 41-60 >60	0 0.5 1	
Diarrhea within 4 weeks before GBS symptoms	No diarrhea prior to GBS Diarrhea preceded GBS	0 1	
Degree of disability at 2 weeks into illness	1. minor symptoms; able to run 2. can walk unassisted but cannot run 3. needs cane or walker to walk 4. bed or chair bound 5. on ventilator	1 2 3 4 5	
Meaning of Total Score	**1-3: very good chance of walking at 6 months** **7: poorer recovery**	**Total Score (1-7) =**	

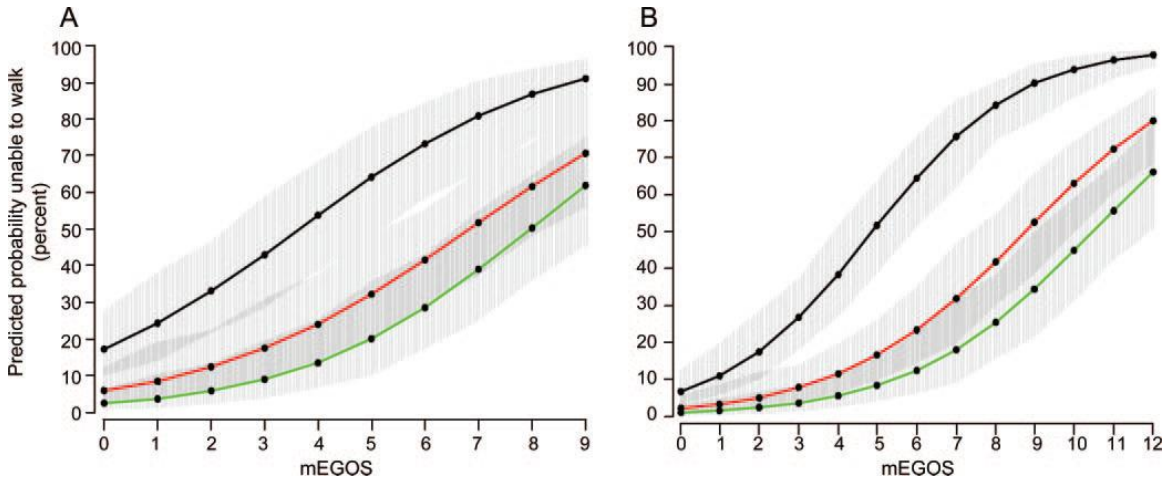
Predicted fraction of patients unable to walk independently at 6 months.



ANNEXURE 15.7: Modified Erasmus GBS Outcome Score (mEGOS)[137]

Prognostic factors	Score	Prognostic factors	Score
Age at onset		Age at onset	
≤40	0	≤40	0
41-60	1	41-60	1
>60	2	>60	2
Preceding diarrhea		Preceding diarrhea	
Absent	0	Absent	0
Present	1	Present	1
MRC sum score at hospital admission		MRC sum score at 7 days of admission	
51-60	0	51-60	0
41-50	2	41-50	3
31-40	4	31-40	6
0-30	6	0-30	9
mEGOS	0-9	mEGOS	0-12

Predicted fraction of patients unable to walk independently according to modified Erasmus GBS Outcome Score (mEGOS)



ANNEXURE 15.8: Normal values of NCS

Median Nerve

Motor

Stimulation	Latency (ms)	Amplitude (mV)	NCV (m/s)
Wrist	3.77±0.40	8.10±2.62	
Elbow	7.62±0.65	7.84±2.25	58.52±3.76
Axilla	10.12±1.17	8.80±2.30	61.75±8.27
Erb's	13.89±1.21	6.90±2.70	

Sensory

Latency (ms) (mean± SD)	Amplitude (µV) (mean± SD)	NCV (m/s) (mean± SD)
3.06±0.41	8.91±4.48	45.45±9.40

Ulnar Nerve

Motor

Site	Latency (ms) (mean± SD)	Amplitude (mV) (mean± SD)	NCV (m/s) (mean± SD)
Wrist	2.59±0.40	8.51±2.03	
Below elbow	6.13±0.65	8.07±1.97	61.45±5.73
Above elbow	8.67±0.83	7.74±1.85	59.34±5.52
Axilla	10.51±0.98	7.56±1.81	61.55±6.43
Erb's point	13.28±2.00	6.42±2.07	

Sensory

Parameters	Misra and Kalita (mean± SD)
Latency (ms)	2.83±0.40
Amplitude(µV)	5.54±2.37
NCV (m/s)	54.17±6.10

Peroneal Nerve

Stimulation	Latency (ms)	Amplitude (mV)	NCV (m/s)
Below knee	4.55±0.59	4.23±1.61	
Above knee			46.54±4.4

Sural Nerve

NCV (m/s)	50.9±5.4
SNAP (µV)	18.0±10.5

Tibial Nerve

Conduction Velocity (m/s) – 48.3±4.5

Superficial Peroneal Nerve

NCV (m/s)	49.0±3.4
SNAP (µV)	3.5±1.5

ANNEXURE 15.9: Proforma

BASIC PATIENT DETAILS	
Date:	Patient ID: AIIMS/JDH/ / /
Name:	Age:
Gender:	Occupation:
Address:	Phone no.:
Weight:	Date of hospital admission:
Date of discharge:	

	YES	NO
Previous episode of GBS-	Date of admission:	
Co-morbidity affecting mobility		
Co-morbidity affecting respiration		
Transfer from other hospital	(Name and date)	

CLINICAL PROFILE

PART 1-HISTORY

	YES	NO
Weakness		
Myalgia		
Paresthesia		
Sphincter disturbance		
Alteration of Consciousness		
Difficulty in breathing		
Difficulty in swallowing		

ANTECEDENT EVENTS (< 4 WEEKS OF ADMISSION DATE)

	YES	NO
Upper respiratory tract infection		
Febrile Illness		
Common cold		
Gastroenteritis, diarrhea		
Urinary tract infection		
Vaccination		
Surgery		
Drug History		
None		
Other		

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? Hughes scale MRC Disability scale	

PART 2-GENERAL EXAMINATION

Temperature	
Pulse	
Blood Pressure	
Respiratory Rate	
SPO_2	
Single Breath Count	
Tidal Percussion	

GBS disability score	0 day	15 days	30 days	90 days
Hughes Disability Scale				
MRC Disability Scale				

PART 3-CNS EXAMINATION

	0 day	15 days	30 days	90 days
Higher Mental Function- GCS				
CRANIAL NERVE INVOLVEMENT				
MUSCLE TONE				
Right upper limb				
Left upper limb				
Right lower limb				
Left lower limb				
WEAKNESS OF NECK MUSCLES (MRC SCORE)				
Flexion				
Extension				
WEAKNESS UPPER LIMBS (MRC SCORE)				

	0 day		15 days		30 days		90 days	
SHOULDER	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Abduction (Deltoid)								
Adduction								
Flexion								
Extension								
ELBOW								
Flexion (Biceps)								
Extension								

WRIST								
Flexion								
Extension								
Ulnar Deviation								
Radial Deviation (ECRL)								
HAND GRIP								
WEAKNESS LOWER LIMBS (MRC SCORE)								
HIP								
Flexion (Ilio psoas)								
Extension								
Abduction								
Adduction								
KNEE								
Flexion								
Extension (Quadriceps)								
ANKLE								
Dorsiflexion (Anterior Tibial)								
Plantarflexion								
TOES								
Flexion								
Extension								
REFLEXES (0: absent, 1: low, 2: normal, 3: high)								
Biceps reflex								
Triceps reflex								
Supinator reflex								
Knee reflex								
Ankle reflex								
Plantar								
Superficial reflexes								
SENSORY DEFICITS: (light touch, pain, temperature, vibration, joint position)								

If yes	0 day	15 days	30 days	90 days
Face				
Upper limb				
Lower limb				

No				
Unable to examine				
Ataxia (Yes/ No)				

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

PART- 4 AUTONOMIC DYSFUNCTION

Autonomic dysfunction	Yes/ No	
If Yes:	TYPE OF DYSFUNCTION	
	Cardiac (arrhythmia, tachycardia, bradycardia)	
	Blood pressure (fluctuations, hypertension, hypotension)	
	Gastro-enteric	
	Bladder dysfunction	
	Pupil dysfunction	
	Other:	

PART-5 CSF EXAMINATION

CSF EXAMINATION	Yes/ No	
CSF Biochemistry	Protein	
	Sugar	
	Chloride	
CSF Cytology	RBC	
	WBC	

PART-6 SEROLOGICAL MARKERS

Serum Ganglioside Panel	

PART-7 ELECTROPHYSIOLOGY (NERVE CONDUCTION STUDY)

ELECTROPHYSIOLOGY CLASSIFICATION	Tick Appropriate
Acute Motor Axonal Neuropathy (AMAN)	
Acute Motor and Sensory Axonal Neuropathy (AMSAN)	
Acute Inflammatory Demyelinating Neuropathy (AIDP)	
Unresponsive Nerves	
Responsive Nerves but Not Classifiable (Equivocal)	

NERVE CONDUCTION STUDY

PARAMETER	0 Day	15 days	30 days	90 days
DML				
F Wave Latency				
MCV				
Distal CMAP				
Temporal Dispersion				
Proximal CMAP/Distal CMAP Ratio				

TREATMENT

GBS specific treatments	IVIg	Plasmapheresis/exchange	Other treatment
Type of treatment			
First day			
Last day			
Dosage		-No. Of Cycles: -Volume exchange/cycle:	
Completed			
Adverse events			

Required assisted ventilation: Yes/No
Days of onset of recovery from start of treatment:
Days of Hospitalization:

COMPLICATIONS

Pneumonia	
Sepsis	
Deep venous thrombosis	
Lung embolism	
Pressure ulcer	
Hyponatraemia	
Other	
None	

ANNEXURE 15.10: Informed Consent Form (English)

All India Institute of Medical Sciences
Jodhpur, Rajasthan

Informed Consent Form

Title of Thesis/Dissertation: Clinical, Electrophysiological and Serological markers in patients with Guillain-Barré Syndrome

Name of investigating Student: Dr. Patel Apoorv Dahyabhai Tel. No. 9825025658

Patient/ Volunteer Identification No.: _____

I, _____ S/o or D/o _____

R/o_____

give my full, free, voluntary consent to be a part of the study: "**Clinical, Electrophysiological and Serological markers in patients with Guillain-Barré Syndrome**", the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions. I understand that my participation is voluntary and I am aware of my right to opt out of the study at any time without giving any reason. I understand that the information collected about me and any of my medical records may be looked at by responsible individual from _____ (Company Name) or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of PG Student

Witness 1

_____
Signature
Name: _____
Address: _____

Witness 2

_____
Signature
Name: _____
Address: _____

ANNEXURE 15.11: Informed Consent Form (Hindi)

अखिल भारतीय चिकित्सा विज्ञान संस्थान

जोधपुर, राजस्थान

Informed Consent Form

परियोजना का शीर्षक : गिलियन-बैर सिंड्रोम के रोगियों में नैदानिक, इलेक्ट्रो-फिजियोलॉजिकल और सीरोलॉजिकल मार्कर

प्रधान अन्वेषक का नाम : डॉ . पटेल अपूर्व दूरभाष नंबर:9825025658

Patient/ Volunteer Identification No. :_____

मैं_____ ओ / ओ या डी / एस _____ ,

आर _____ ओ /

अध्ययन का एक हिस्सा बनने के लिए मेरी पूर्ण, स्वतंत्र, स्वैच्छिक सहमति दें "**गिलियन-बैरिएक सिंड्रोम के रोगियों में नैदानिक, इलेक्ट्रो-फिजियोलॉजिकल और सीरोलॉजिकल मार्कर**", जिस प्रक्रिया और प्रकृति को मुझे अपनी पूरी संतुष्टि के लिए अपनी भाषा में समझाया गया है। मैं पुष्टि करता हूं कि मुझे प्रश्न पूछने का अवसर मिला है।मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मुझे किसी भी कारण दिए बिना किसी भी समय अध्ययन से बाहर निकलने का मेरा अधिकार है। मैं समझता हूं कि मेरे और मेरे मेडिकल रिकॉर्ड के बारे में एकत्रित की गई जानकारी को _____ (कंपनी नाम) या विनियामक प्राधिकरणों से जिम्मेदार व्यक्ति द्वारा देखा जा सकता है। मैं इन लोगों के लिए मेरे रिकॉर्डों तक पहुंच की अनुमति देता हूं।

तारीख : _____

_____

जगह: _____ हस्ताक्षर / बाएं अंगूठे का छाप

यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त की गई है

तारीख : _____

_____

जगह: _____ पीजी छात्र के हस्ताक्षर

गवाह 1

_____

हस्ताक्षर

नाम: _____

पता: _____

गवाह 2

_____

हस्ताक्षर

नाम : _____

पता : _____

ANNEXURE 15.12: Patient Information Sheet (English)

PARTICIPANT INFORMATION SHEET (PIS)

Title of Thesis/Dissertation: **Clinical, Electrophysiological and Serological markers in patients with Guillain-Barré Syndrome**

Name of PG Student: **Dr. Patel Apoorv Dahyabhai** Tel. No. 9825025658

I have been explained in my own understanding language by the principal investigator that they are doing this study to assess the Clinical, Electrophysiological and Serological markers in patients with Guillain-Barré Syndrome.

Guillain Barre Syndrome (GBS), also known as post-infectious polyneuropathy or acute idiopathic polyneuritis 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.

The subtypes of GBS have different incidence rates in different parts of the world. GBS consist of distinct pathogenic subgroups in which disease onset and progression is influenced by different types of preceding infections, antineural antibodies and genetic polymorphisms.

This study will be undertaken to study the clinical, electrophysiological and serological markers of patients with GBS and to identify determinants that can be used for early identification of patients with poor prognosis

I have been informed that I can refuse to answer any question and can withdraw myself from study at any time .

The data obtained from me will be used for the purpose of the study only .All my records will be kept confidential.

ANNEXURE 15.13: Patient Information Sheet (Hindi)

अखिल भारतीय चिकित्सा विज्ञान संस्थान जोधपुर, राजस्थान

भाग लेने वालों के लिए सूचना पत्र (पीआईएस)

परियोजना का शीर्षक : **गिलियन-बैर सिंड्रोम के रोगियों में नैदानिक, इलेक्ट्रो-फिजियोलॉजिकल और सीरोलॉजिकल मार्कर**

प्रधान अन्वेषक का नाम : **डॉ . पटेल अपूर्व** दूरभाष नंबर: 9825025658

मुझे मुख्य जांचकर्ता द्वारा अपनी समझ की भाषा में समझाया गया है कि वे इस अध्ययन को गिलियन-बैर सिंड्रोम के रोगियों में नैदानिक, इलेक्ट्रो-फिजियोलॉजिकल और सीरोलॉजिकल मार्कर के लिए कर रहे हैं।

गिलियन-बैर सिंड्रोम (GBS), जिसे पोस्ट-संक्रामक पोलीन्युरोपैथी या एक्यूट इडियोपैथिक पोलिनेरिटिस के रूप में भी जाना जाता है, परिधीय तंत्रिका तंत्र का एक तीव्र, स्व-सीमित, भड़काऊ, ऑटोइम्यून विकार है जो आमतौर पर एक जीवाणु या वायरल संक्रमण या अन्य एंटीकेडेंट घटनाओं से शुरू होता है।

जीबीएस के उपप्रकारों में दुनिया के विभिन्न हिस्सों में अलग-अलग घटनाएं होती हैं। जीबीएस में अलग अलग रोगजनक उपसमूह शामिल हैं जिसमें रोग की शुरुआत और प्रगति विभिन्न प्रकार के पूर्ववर्ती संक्रमणों, एंटीनेरल एंटीबॉडी और आनुवंशिक बहुरूपताओं से प्रभावित होती है।

यह अध्ययन जीबीएस के साथ रोगियों के नैदानिक, इलेक्ट्रोफिजियोलॉजिकल और सीरोलॉजिकल मार्करों का अध्ययन करने और निर्धारकों की पहचान करने के लिए किया जाएगा जो खराब रोग के रोगियों के शुरुआती पहचान के लिए उपयोग किए जा सकते हैं।

मुझे यह सूचित कर दिया गया है कि मैं किसी भी प्रश्न का जवाब देने से मना कर सकने के लिए स्वतंत्र हूं एवम् कभी भी बिना कोई कारण बताए स्वयं शोध को छोड़ सकता हूं। एकत्रित जानकारी केवल इस अध्ययन में ही उपयोग की जाएगी तथा मेरे सभी रिकॉर्ड पूरी तरह से गोपनीय रखें जायेंगें।