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REVIEW ARTICLE

Immune-mediated Neuropathies in Clinical Practice: A Narrative Review

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Abstract:

The spectrum of immune-mediated polyneuropathies has expanded with the discovery of chronic, steroid-responsive polyneuropathy 50 years ago, and the identification of acute monophasic paralysis, later named Guillain-Barré syndrome, nearly a century ago. Numerous subtypes of these polyneuropathies are still being identified, such as multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and paraproteinemic neuropathies (PN). Most of these illnesses are thought to be brought on by autoimmunity against proteins found at the node of Ranvier or peripheral nerve myelin; however, not all disorders have been linked to disease-associated autoantibodies. The presence of certain anti-glycoconjugate antibodies suggests a molecular mimicking mechanism at work and can help classify these illnesses, albeit this approach often just confirms the clinical diagnosis. Presently, multifocal motor neuropathy with conduction block, another subgroup of treatable motor neuropathies, is characterized by the electrophysiological presence of conduction blocks. The many kinds of immune-mediated neuropathies make it difficult to make the correct diagnosis in day-to-day clinical practice. Immunotherapies, such as plasma exchange, intravenous immunoglobulin, and corticosteroids, are typically used in the therapy of these illnesses. The treatment choices for these debilitating diseases should be expanded by advancements in clinical criteria and the development of further immunotherapies targeted to individual diseases. The aim of this review is to get a glimpse at these different perspectives that may aid these diseases practical approach to diagnosis, management and prognosis.

Keywords: Immune-mediated Neuropathies, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy.

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Introduction:

Immune-mediated neuropathies are a diverse group of diseases affecting the peripheral nervous system (PNS) that result from immune-mediated response against antigens in the peripheral nerves[1]. The disease's course varies and might be acute, sub-acute, chronic, or relapsing-remitting. These can vary from a severe, life-threatening crisis to an asymptomatic, slowly progressing condition.[2] Immune-mediated neuropathies include Guillain-Barré syndrome (GBS) and its variants, chronic inflammatory demyelinating poly-radiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and paraproteinemic neuropathies (PN). [3] Overall, these diseases are treated with immunotherapies such as corticosteroids, intravenous immunoglobulin, or plasma exchange. Clinical criteria improvements and the development of additional disease-specific immunotherapies should expand the therapy choices for these debilitating illnesses[3].

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Guillain-Barré Syndrome:

Introduction:

Guillain-Barré syndrome (GBS) is an acute, autoimmune, polyradiculoneuropathy affecting the peripheral nervous system, usually triggered by an acute infectious process which leads to weakness, numbness, and tingling and can eventually cause paralysis[5]. The syndrome is named after the French neurologists Georges Guillain and Jean Alexandre Barré, who described it with André Strohl in 1916[6].

Epidemiology:

An annual global incidence of approximately 1–2 per 100,000 person years[7]. GBS occurs more frequently in males than in females and the incidence increases with age, although all age groups can be affected.[7] Race: No racial preponderance exists. It occurs at all ages. The mean age of onset is around 40 but many series have shown a bimodal distribution with a first peak in young adulthood (ages 15-35 y) and a second, higher one in middle-aged and elderly persons (ages 50-75 y). Rare cases have been noted in infants.[8]

Almost all reports record a greater frequency of GBS in men than women (~1.5:1.0), including those from Low

Table-I

Summary of the types of immune-mediated neuropathies and their key features[4].

Neuropathy	Variants	Ab or Immune-Complex Targets	Antibodies	Preceding Infections/ Associations	Treatment Options	Diagnostic Criteria
Guillain–Barre syndrome	(1) Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Schwann cell plasmalemma	none	*Campylobacter jejuni*, Mycoplasma, EBV, CMV, Varicella zoster, HIV, and Hodgkin's lymphoma	Intravenous immunoglobulin Plasma exchange	(1) Clinical presentation plateaus at 4 weeks (2) Increased CSF protein (3) Acellular CSF (4) Neurophysiological findings: • (i) demyelination ± axonal loss • (ii) prolonged distal motor latency • (iii) prolonged F wave latency • (iv) Temporal dispersion of compound muscle action potentials • (v) Conduction block
	(2) Acute motor axonal neuropathy (AMAN)	Axolemma	Anti-GM1, Anti-GM2, Anti-GQ1b, Anti-GT1a, Anti-GD1a, Anti-GD1b			
	(3) Acute motor and sensory axonal neuropathy (AMSAN)	Axolemma	As in (2)			
	(4) Sensory variant	Axolemma	As in (2)			
	(5) Miller–Fisher	Cranial motor nerves	Anti-GQ1b			
CIDP	Relapsing	As for GBS	Anti-gangliosides as for GBS (presumed to be involved in CIDP as well, but not yet documented). In a small proportion of patients, antibodies against proteins located at the node of Ranvier are detected (antibodies target neurofascin, contactin and contactin-associated protein 1)	Diabetes mellitus; Connective tissue diseases; infections; dysproteinaemias	Intravenous immunoglobulin ; Plasma exchange; corticosteroids; immunosuppression	Same as in GBS but clinical presentation is more progressive and prolonged
	Chronic monophasic					
	Slow progressive					
Neuropathy with conduction block	MMN	Probably the nodes of Ranvier are a major target but also the axolemma and Schwann cell plasmalemma	Anti-GM1	None	Intravenous immunoglobulin	Multifocal conduction abnormalities with conduction blocks and no sensory features electrophysiologically
	MADSAM		Negative for anti-GM1	None	Intravenous immunoglobulin and corticosteroids	Multifocal conduction abnormalities with conduction blocks and sensory abnormalities

Middle Income Countries (LMICs) including Bangladesh, India, Taiwan, Pakistan, Egypt, Morocco, Ethiopia, Tanzania, and Kenya.[9] In North America and Europe, where populations are aging.[9] GBS is therefore most prevalent in those aged 50 to 80 (2.0 to 4.0 cases per 100,000 persons/year). But according to data from

Asia (Bangladesh, China, India), South America (Brazil), and sub-Saharan Africa (Ethiopia, Tanzania) that is unaffected by population aging, GBS mainly affects people between the ages of 21 and 35.[10] In LMICs where Campylobacter infections are widespread, children are more frequently infected, and as people mature, infection ratios and rates of Campylobacter-related illness decrease.[11]

Antecedent infections:

About 90% of GBS patients have symptoms of viral respiratory or gastrointestinal infections during the 1–3 weeks prior to the onset of neurological symptoms (Table:2) .The serological studies have implicated a wide range of infective agents (Table:3). Cytomegalovirus (13%) and Campylobacter jejuni (in approximately 30%) are the most common. Epstein–Barr virus (10 per cent), Mycoplasma pneumoniae (5 per cent), human immunodeficiency virus (HIV) and childhood exanthems are also reported.Cytomegalovirus and campylobacter infections precipitate differing forms of GBS. Cytomegalovirus tends to occur in younger patients, with a high occurrence of respiratory muscle weakness, cranial nerve involvement, and significant sensory involvement. Campylobacter jejuni infection is associated with preceding diarrhoeal illness in 70%, a pure motor disorder (AMAN) is common[12].

Forms of Guillain–Barré syndrome precipitated by both campylobacter and cytomegalovirus show delayed recovery compared to cases unassociated with these two infections.[13]

Table-II

Antecedent Events of Guillain Barré Syndrome

Antecedent Event		Percentage
1.	Respiratory illness	58
2.	Gastrointestinal illness	22
3.	Respiratory and gastrointestinal illness	10
4.	Surgery	5
5.	Vaccination	3
6.	Other	2

Table-III

Serological Evidence of Specific Infectious Agents

Infectious Agents		Percentage
1.	Campylobacter Jejuni	26*
2.	Cytomegalovirus	15*
3.	Human Immunodeficiency Virus 1	?
4.	Epstein-Barr Virus	8
5.	Mycoplasma Pneumonia	10

*Percentages according to prospective case-controlled studies

Immunopathogenesis:

The causative agents contain lipopolysaccharide antigens similar to gangliosides and glycolipids, including GM1 and GD1b, which are present in peripheral nerve myelin tissues[14]. The immune response to bacterial capsular lipopolysaccharides also targets GM1 ganglioside, a complex glycosphingolipid found in great quantities on human nerve tissues, particularly in Ranvier nodes[14] (Figure:1). One example is the GM1 ganglioside, which can be impacted in 20-50% of cases, particularly those preceded by Campylobacter jejuni infections. Miller Fisher syndrome variant targets GQ1b ganglioside. Disease progression is influenced by both cellular and humoral immunological pathways[15].

Pathologic findings in GBS include lymphocytic infiltration of peripheral nerves, followed by macrophage-mediated, multifocal attack of myelin. Antigenic mimicry or molecular mimicry refers to immune responses that target foreign antigens (e.g., infectious agents or vaccines) but mistakenly target host nerve tissues. Autoimmune attacks on peripheral nerves can cause myelin inflammation, electrical nerve impulse defects, and conduction block, resulting in muscle paralysis and sensory or autonomic disturbances. In mild cases, axonal function can be preserved and recovery can be quick with remyelination. In extreme cases, such as AMAN or AMSAN types, axonal degradation occurs, and recovery depends on axon regeneration[16].

Recent studies show that 80% of patients have myelin loss, whereas the other 20% experience axon loss as the pathological characteristic of the disease. Recovery is longer and leaves greater residual damage[17].

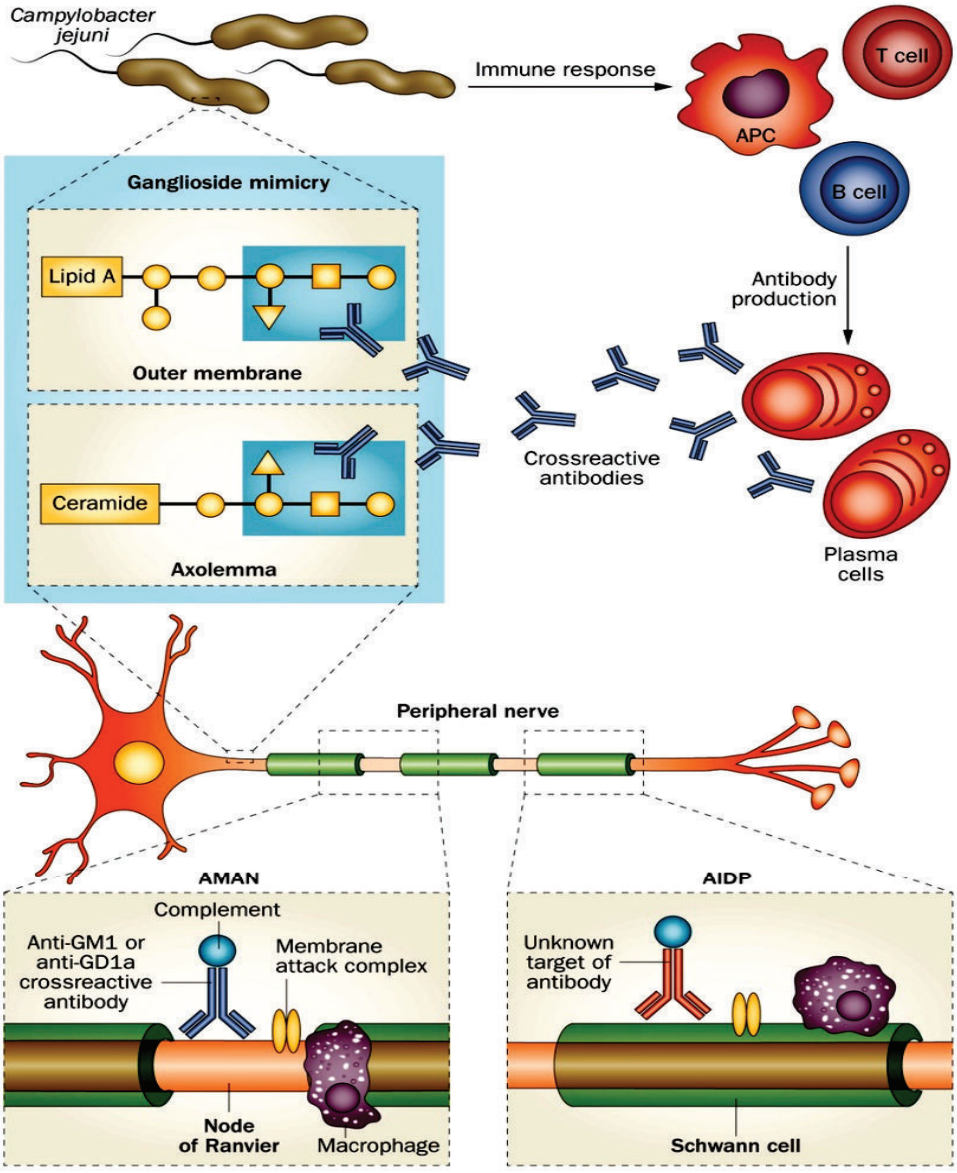


Figure 1: *Steps of Immunopathogenesis: Infections with pathogens, such as Campylobacter jejuni, can trigger humoral immune and autoimmune responses that result in nerve dysfunction and the symptoms of GBS.*

Abbreviations: APC, antigen-presenting cell; MAC, membrane attack complex.

Clinical features:

Most common presentations:

Rapidly evolving areflexic motor paralysis with or without sensory disturbance. The usual pattern is an ascending paralysis. Weakness typically evolves over hours to a few days. The legs > arms, and facial diparesis is present in 50% of cases.The lower cranial nerves are also frequently involved .Deep tendon reflexes usually disappear within the first few days of onset. Bladder dysfunction may occur in severe cases but is usually transient. If bladder dysfunction is a prominent feature and comes early in the course, possibilities other than GBS should be considered.[18]

Motor dysfunction:

Symmetric limb weakness often starts in the lower limbs and progresses to the upper extremities, truncal muscles,

and head. Difficulty standing or walking despite adequate strength, particularly if ophthalmoparesis or poor proprioception are present. Shortness of breath may indicate respiratory muscle weakness. Cranial nerve palsies (III-VII and IX-XII) may be present. Patients may experience facial paralysis, dysphagia, dysarthria, ophthalmoplegia, and pupillary problems, similar to Bell palsy. The Miller-Fisher variation is distinguished by the onset of cranial nerve impairments. The absence of deep tendon reflexes is a striking sign[18].Guillain-Barre´ syndrome disability scale (Scale of Hughes) (Table :4)

Table-IV

Guillain-Barre´ syndrome disability scale (Scale of Hughes)

Scale	Functional status
A. Grade 0	Normal functional state
B. Grade 1	Able to run with minor signs and symptoms
C. Grade 2	Able to walk 5m independently
D. Grade3	Able to walk 5 m with aid
E. Gade 4	Bed to chair bound
F. Grade 5	Requires assisted ventilation
G Grade 6	Death

Sensory dysfunction:

Paresthesia in GBS often starts in the toes and fingertips and extends to the wrists or ankles. Patients complaints of more pain in the shoulder girdle, back, buttocks, and thighs and can occur with little movements. Symptoms may also include loss of vibration, proprioception, touch, and distal pain[19].

Autonomic dysfunction in GBS:

Cardiovascular - tachycardia, bradycardia, dysrhythmias, wide fluctuations in BP and postural hypotension. Urinary retention due to sphincter disturbances and constipation due to bowel paresis and gastric dysmotility. Facial flushing and venous pooling secondary to abnormal vasomotor tone. Hyper salivation, anhydrosis., tonic pupils and papilledema secondary to elevated intracranial pressure is present in rare cases.Miller-Fisher variant presents with a predominance of cranial nerve findings, ataxia, and areflexia. Facial weakness, ophthalmoplegias, dysarthria and dysphagia may precede ataxia, areflexia and weakness.[20]

Diagnostic criteria for GBS:

Electrophysiological studies play a crucial role, offering evidence of peripheral nervous system dysfunction and aiding in the differentiation of GBS subtypes, namely acute inflammatory demyelinating neuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor sensory axonal neuropathy (AMSAN). Biochemical analysis, particularly through CSF studies, provides valuable insights into cellular and protein components, elucidating the intricate biochemical alterations associated with Guillain-Barre syndrome's progression and clinical diversity. [21,22], The Diagnostic Criteria for GBS in Table:5 [23]

Differential Diagnosis :(Table:6)

Table-V

Diagnostic Criteria for GBS

Required	**Laboratory Features**
1. Progressive weakness of 2 or more limbs due to neuropathy 2. Areflexia 3. Disease course <4 weeks	**Supportive of Diagnosis** 1. Typical CSF (Elevated CSF protein with<cells/ 10 µL- albuminocytologic dissociation) **2.** EMG/nerve conduction studies (characteristic signs of a demyelinating process in the peripheral nerves)
Clinical Features Supportive of Diagnosis	**Features that rule out the diagnosis**
1. Progression of symptoms over days to 4 weeks 2. Relative symmetry 3. Mild sensory signs or symptoms 4. Cranial nerve involvement, especially bilateral facial weakness 5. Recovery beginning 2 to 4 weeks after progression ceases 6. Autonomic dysfunction 7. Absence of fever at onset	1. Hexacarbon abuse 2. Vasculitis (polyarteritis nodosa, systemic lupus erythematosus, Churg-Strauss syndrome), 3. Abnormal porphyrin metabolism 4. Recent diphtheria infection 5. Toxins (organophosphates, lead), 6. Botulism, 7. Localized spinal cord or cauda equina syndrome 8. Excluding M. Fisher and other variant syndromes

Table-VI

Differential Diagnosis of GBS

1. Acute Polyneuropathies Hepatic porphyrias Critical illness polyneuropathy Diphtheria Vasculitis	1. Disorders of Neuromuscular Junction Botulism Myasthenia gravis (crisis) Tick paralysis
2. Toxins Lead , organophosphates, thallium, Arsenic, Neurotoxic fish, shellfsh poisoning (ciguatoxin, etrodotoxin, and saxitoxin)	2. Myopathies Hypokalemia Hypophosphatemia Rhabdomyolysis Polymyositis Critical care myopathy
3. Polyradiculopathies Inflammatory or neoplastic meningoradiculopathies Lyme radiculitis Cytomegalovirus lumbosacral radiculo-myelopathy	3. Anterior Horn Cell Disorders Poliomyelitis West Nile and enterovirus poliomyelitis
	4. Central Nervous System Disorders Transverse myelitis Basilar artery thrombosis Rabies

Investigations:

Diagnosis usually is made on clinical grounds. Laboratory studies are useful to rule out other diagnoses and to better assess functional status and prognosis.

A. Cerebrospinal fluid (CSF) analysis:

Elevated or rising protein levels in CSF on serial lumbar punctures and 10 or fewer mononuclear cells/mm strongly support the diagnosis. Most, but not all, patients have an elevated CSF protein level (>400 mg/L), with no elevation in CSF cell counts. Typical CSF finding is elevated CSF protein with<cells/ 10 µL-albuminocytologic dissociation. Normal CSF protein level does not rule out GBS because the CSF protein level remains normal in 10% of patients and because any rise in the CSF protein level may not be observed until 1-2 weeks after the onset of weakness. CSF pleocytosis is well recognized in HIV-associated GBS[23].

B. Nerve conduction studies (NCS):(Table :6)

Mild or absent in the early stages and lag the clinical evolution. In cases with demyelination prolonged distal latencies, conduction velocity slowing, evidence of conduction block, and temporal dispersion of compound action potential are the usual features. In cases with primary axonal pathology-reduced amplitude of compound action potentials without conduction slowing or prolongation of distal latencies.[24]

Table-VI

Electro-diagnostic findings in Guillain-Barre syndrome

Electrodiagnostic features suggestive of acquired demyelinating neuropathy
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
Electrodiagnostic features suggestive of axonal neuropathy
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.

CMAP, Compound muscle action potential; AMAN, Acute motor axonal neuropathy; AMSAN, Acute motor and sensory axonal neuropathy; SNAP, Sensory nerve action potential; LLN, Lower limits of normal

C. Biochemical screening:

Electrolyte levels; LFTs; CPK level; ESR; antiganglioside antibodies; and antibodies to C jejuni, cytomegalovirus, EB virus, HSV, HIV and M pneumoniae. SIADH occurs in some patients with GBS.Raised LFT in up to one third of patients.Raised CPK and ESR - myopathies or systemic inflammatory conditions.Miller-Fisher variant may have anti-GQ1b antibodies. Antibody subtype GM1 may have poorer prognoses.[25]

D. MRI of spine:

MRI is a sensitive yet non-specific examination. Gadolinium can generate nonspecific spinal nerve root augmentation in inflammatory situations due to blood-nerve barrier breakdown. Selective anterior nerve root enlargement clearly suggests GBS. 83% of patients have increased cauda equine nerve roots.[26]

E. Other Tests:

1. Stool culture for C jejuni

2. Forced vital capacity:

Forced vital capacity (FVC) is very helpful in guiding disposition and therapy. Patients with an FVC less than 20 mL/kg, maximum inspiratory pressure less than 30 cm H2O, or a maximum expiratory pressure less than 40 cm H2O generally progress to require prophylactic intubation and mechanical ventilation.[27]

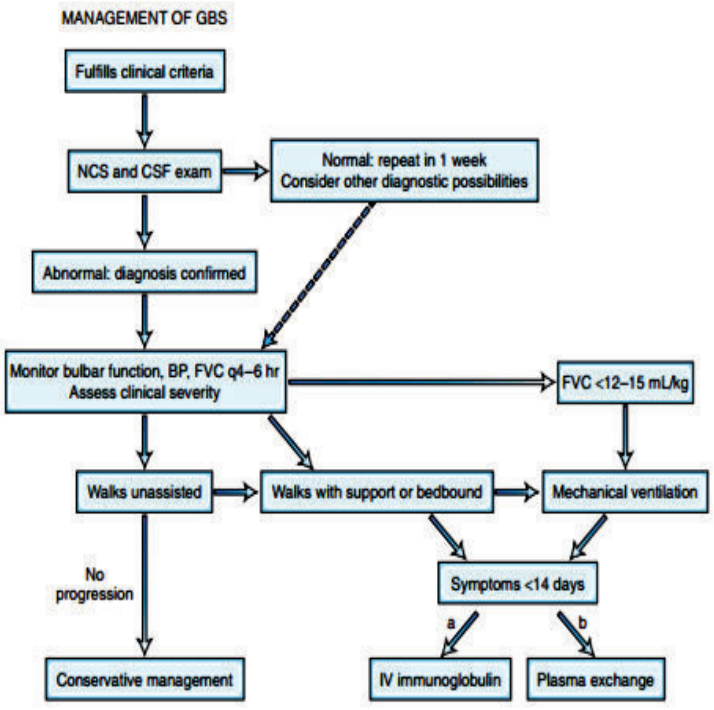
Management of GBS: (Flowsheet: 1)

Treatment of GBS patients requires a multidisciplinary approach. General supportive treatment includes monitoring and controlling pulse rate and blood pressure because 5% to 61% of GBS patients may suffer wide fluctuations in blood pressures and cardiac arrhythmias due to autonomic involvement.[42]

Vital capacity should be monitored because about 25% of GBS patients require artificial ventilation, which should be considered once the vital capacity falls below 15 mL/kg to 20 mL/kg[12].

Specific treatment: with Intravenous Immunoglobulin (IVIG) or Plasma Exchange (PE)

Immunomodulatory therapy should be started if patients are unable to walk independently for 10 m[28,29] , if these patients display rapidly progressive weakness or other severe symptoms such as autonomic dysfunction, bulbar failure or respiratory insufficiency[30,-32].



Flow sheet 1 : *Algorithms of Management of GBS*

Clinical trials have demonstrated a treatment effect for intravenous immunoglobulin (IVIg) when started within 2 weeks of the onset of weakness and for plasma exchange when started within 4 weeks[28,29].

Beyond these time periods, evidence on efficacy is lacking. IVIg (0.4 g/kg body weight daily for 5 days) and plasma exchange (200–250 ml plasma/kg body weight in five sessions) are equally effective treatments for GBS[28, 32].

Newly-Released Treatment for GBS:

A Phase II clinical trial for the first novel treatment for Guillain-Barre Syndrome in two decades is about to begin. The Food and Drug Administration initially authorized eculizumab, a humanized monoclonal antibody, in 2007 for the treatment of a rare blood condition.

Eculizumab is referred described as a "complement inhibitor" because it prevents antigen-associated antibodies from activating complements. It is thought that this "complement activation" contributes to the development of GBS.

Although complement and FcRn inhibitors are at the most advanced stages of development, a number of innovative immunomodulatory medicines that target IgG autoantibodies, the complement cascade, and FcãRs are now in the developmental phase.

Prognostic factors:

The following factors have been associated with adverse effect on outcomes in GBS such as preceding gastrointestinal infection or diarrheal illness, older age (57 years or older),poor upper extremity muscle strength,acute hospital stay of longer than 11 days, ICU requirement, need for mechanical ventilation, medical research council (mrc) score below 40 and discharge to rehabilitation

Course and Prognosis:

Patients should achieve their maximal deficit within 4 weeks of beginning. If the disease lasts longer, it is classed as subacute (less than 2 months) or CIDP (greater than 2 months). Approximately 2% of GBS patients have acute-onset CIDP, which is a long-lasting disease. Consider acute-onset CIDP for GBS patients who worsen after 8 weeks or experience more than two treatment-related fluctuations. Up to 30% of GBS patients experience respiratory insufficiency, necessitating assisted breathing, and 2% to 5% die from complications. Patients experience a plateau period that lasts 2 to 4 weeks or more before recovery starts. Although the majority of individuals recover functionally, 20% continue to have residual motor impairment a year later. Around 70% of patients recover in 12 months and 82% in 24 months. Up to 5% of patients may experience a recurrence after healing[22].

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Introduction:

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a heterogeneous group of immune-mediated neuropathies characterized by progressive, monophasic or relapsing-remitting sensorimotor neuropathy, affecting both the peripheral nerves and nerve roots[34]. In many ways, CIDP can be considered the chronic equivalent of AIDP.

Epidemiology:

CIDP incidence ranges from 0.5 to 3.3 cases per 100,000 people, which increases with age and is more common in males.[35]

Immunopathogenesis:

The suggested mechanism is an immunologic antibody-mediated response followed by T-cell and macrophage infiltration of the endoneurium, resulting in segmental demyelination and remyelination of peripheral nerves.[36]

Activated T-cells and macrophages serve as antigen-presenting cells, which promote demyelination.[37]T-helper (Th)17 cells are highly prevalent in peripheral blood and cerebrospinal fluid.

Nerve involvement is patchy, with demyelination occurring paranodal to the Ranvier nodes. CIDP pathology includes Schwann cell dysfunction in regenerating myelin sheaths. The disease may also include a reduction in regulatory and naïve T cells, which is linked to aging.[38]Increased natural killer cell activity has also been reported.

Clinical features:

The disease often begins slowly and progresses, either gradually (about 60%) or relapsingly (about one-third), with partial or total recovery between relapses. Periods of deterioration and recovery typically span many weeks

or months. Previous illnesses, including respiratory and gastrointestinal, were noted, but no causal organism was discovered. Initial symptoms include weakness in both limbs, with proximal muscles affected more severely than distal ones. Common sensory symptoms include tingling and numbness in the hands and feet, although motor symptoms are typically more prominent.

Approximately 16% of cases had an acute or subacute start, followed by a steady or variable course. Children typically have a more abrupt beginning. Symptoms must last at least 8 weeks to be diagnosed with CIDP. Autonomic system dysfunction may occur - orthostatic dizziness, problems with bowel and bladder function, and cardiac concerns.[36,39]

Physical examination:[39]

The physical examination should be comprehensive, with a focus on the following areas: in cranial nerves involvement Particularly CN VII- LMN type and diplopia -CN III, IV, or VI. , Rarely, bulbar muscles (e.g., palate, tongue) can be affected. High CSF protein levels (>1000 mg/mL) can cause papilledema and pseudotumor cerebri syndrome. Regarding Gait:The location of weakness and degree of proprioceptive loss determines gait type. Walk with steppage (high elevation of both feet to compensate for foot dorsiflexor insufficiency) or slapping gait (proprioception loss). Children have more significant gait impairments. In Motor system examination, the motor system often exhibits symmetric weakening of both proximal and distal muscles in the upper and lower limbs. Muscle tone may be normal or diminished and hypotonia, atrophy, and fasciculations may be seen. Deep tendon reflexes are typically decreased or absent, even in areas with modest weakening. Pathological reflexes (e.g. Babinski, Chaddock, Oppenheim) are typically not noticed. In Sensory system: Large-diameter, heavily myelinated fibers are affected most severely, leading to proprioceptive and vibratory deficits. Loss or decrease of pain (i.e., pinprick) and temperature sensations is less common. Stocking-glove distribution of sensory deficits and neuropathic pain in affected extremities. Patients with sensory ataxia and positive Romberg sign may have damage to nerve fibers that transmit proprioception, leading to coordination issues.

Diagnosis of CIDP:

The clinical presentations of CIDP can be highly variable, encompassing both typical and atypical clinical variants. Nerve conduction studies (NCS) are the most important tool in the diagnosis of CIDP by demonstrating electrophysiological findings that support peripheral nerve demyelination.

When NCS reveals abnormalities, it can be difficult to distinguish between true peripheral a potential "demyelinating" result, such as reduced motor nerve conduction velocity (MNCV) in nerves with low compound muscle action potential (CMAP) caused by the loss of large axonal fibers.[40,41]

EFNS/PNS diagnostic criteria for CIDP: [42]

Clinical Diagnostic Criteria:
Inclusion criteria:

Typical CIDP:

- Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and absent or reduced tendon reflexes in all extremities.

Exclusion criteria:

- *Borrelia burgdorferi* infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
- Hereditary demyelinating neuropathy
- Prominent sphincter disturbance
- Diagnosis of multifocal motor neuropathy
- IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
- Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy.
- PNS lymphoma and amyloidosis may occasionally have demyelinating features

Electrodiagnostic Criteria: (Flowsheet-2)

There have been many diagnostic criteria sets throughout the years, the first revision of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria and the second revision of this guideline by the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS), was published in 2021 and one study found a similar sensitivity and specificity for diagnosing CIDP (Table: 7).

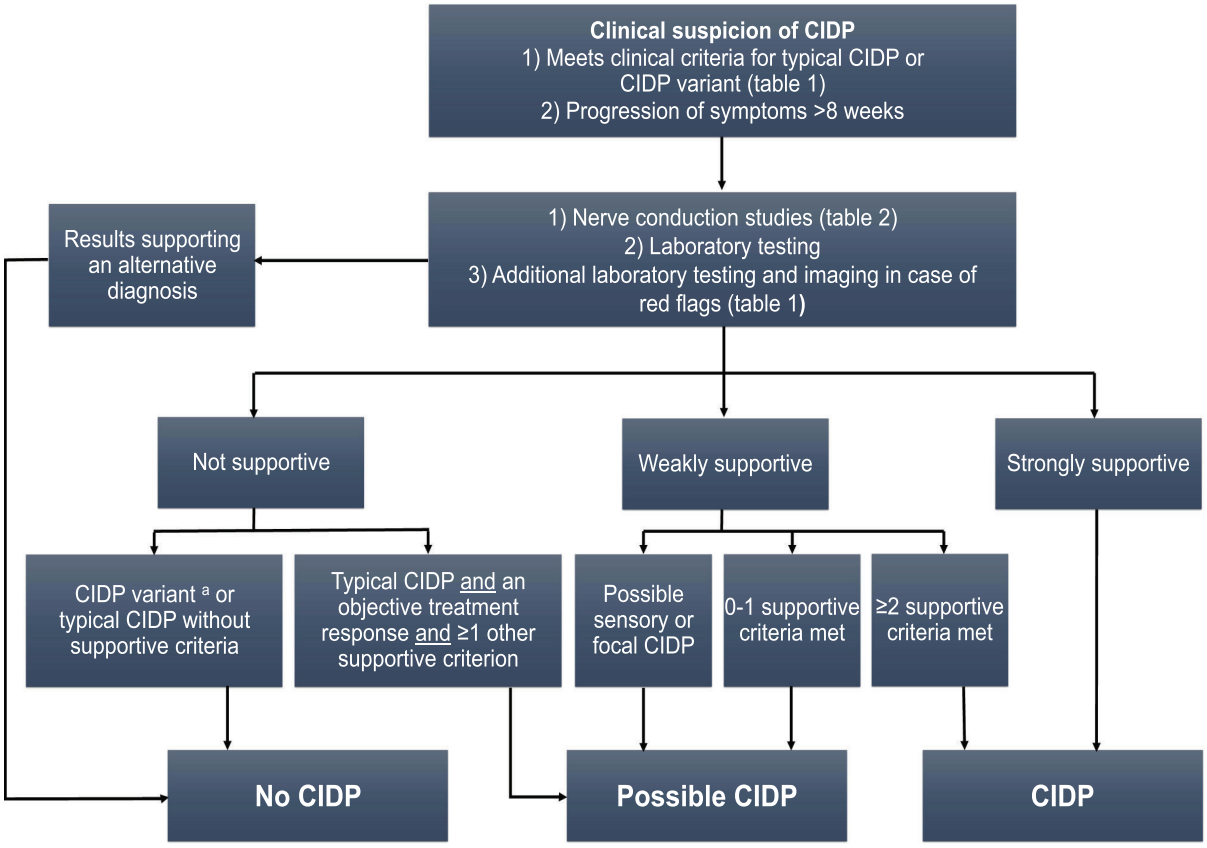
Table-VII

Motor and Sensory Nerve Conduction Criteria (EAN/PNS 2021 Guideline)

Motor nerve conduction criteria	
Strongly supportive of demyelination	At least one of the following:
	a. Motor distal latency prolongation of ≥50% above ULN in ≥2 nerves a
	b. Motor conduction velocity decrease ≥30% below LLN in ≥2 nerves
	c. F-wave latency prolongation: ≥20% above ULN (≥50% if amplitude is <80% LLN) in ≥2 nerves
	d. Absent F-waves: In two nerves if distal amplitude ≥20% LLN plus ≥1 other demyelinating parameter in ≥1 other nerve
	e. Motor conduction block: ≥30% reduction of the proximal-to-distal amplitude as long as distal amplitude is >20% LLN in ≥2 nerves (excluding tibial nerve) or in 1 nerve plus ≥1 other demyelinating parameter except absent F waves
	f. Abnormal temporal dispersion: >30% increase between the proximal and distal duration (≥100% in the tibial nerve) in ≥2 nerves
	g. Distal CMAP duration prolongation in ≥1 nerve plus ≥1 other demyelinating parameter in ≥1 other nerve
Weakly supportive of demyelination	As in "strongly supportive of demyelination" but only in one nerve, excluding criterion g
Sensory conduction criteria	
Sensory conduction abnormalities	At least one of the following in ≥2 nerves: ● Prolonged distal latency [a] ● Reduced SNAP amplitude ● Conduction velocity slowing outside of normal limits
Sensory conduction criteria [b]	● Sensory nerve conduction velocity <80% of LLN (for SNAP amplitude >80% of LLN) or <70% of LLN (for SNAP amplitude <80% of LLN) in ≥2 nerves ● Sural sparing pattern: abnormal median or radial SNAP with normal sural nerve SNAP, excluding carpal tunnel syndrome
Variant-specific criteria	
Typical CIDP	Motor conduction criteria, sensory conduction abnormalities
Multifocal/focal variant	Motor conduction criteria, sensory conduction abnormalities ● If in 1 nerve in 1 limb only: maximum diagnostic certainty is possible focal CIDP [c]
Distal variant	Motor conduction criteria (in upper limbs), sensory conduction abnormalities ● If motor conduction criteria only present in lower limbs, maximum diagnostic certainty is possible distal CIDP [c]
Sensory(-predominant) variant	Motor conduction criteria, sensory conduction abnormalities ● Pure sensory: sensory conduction criteria, motor conduction criteria normal in ≥4 nerves [c]
Motor(-predominant) variant	Motor conduction criteria, sensory conduction abnormalities ● Pure motor: motor conduction criteria, sensory conduction normal in ≥4 nerves

Notes: [a] Excluding median neuropathy at the wrist caused by carpal tunnel syndrome. [b] For possible sensory CIDP only. [c] Diagnostic certainty not upgradable with fulfillment of 2 supportive criteria.

Abbreviations: CMAP, compound muscle action potential; SNAP, sensory nerve action potential; LLN, lower limit of normal; ULN, upper



Flowsheet 2: *Algorithms to diagnosis of CIDP*

Management:

There are a number of treatments available to control CIDP. The best studied treatments that have been shown to be effective are glucocorticoids (steroids), intravenous immunoglobulin (IVIg) and plasma exchange (PLEx). [43] All the treatments suppress or modulate the immune system and there are increased risks of infection and cancer that must be considered when treatment decisions are being made. Decision-making pathway in the management of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in Flowsheet: 3.

Principles of treatment are as follows: [44]

CIDP requires treatment to prevent disability. Close follow-up care is necessary to adjust treatment. Surgical and orthopedic consultation may be required for sural nerve biopsy or severe disease with joint deformities. Consultation with a neurologist is recommended. Consultation with a physical medicine and rehabilitation specialist is appropriate for physical and occupational therapy and evaluation for orthotic devices. Physical treatment and maintaining an active lifestyle should be encouraged. The mainstays of treatment for CIDP are intravenous immune globulin (IVIG), glucocorticoids, and plasma exchange. These treatments appear to be equally effective.

The treatment choice is influenced by patient preference, side effects, treatment cost, duration, ease of administration, and availability. IVIG and plasma exchange may lead to a more rapid improvement in CIDP than glucocorticoid therapy, but are less likely than glucocorticoids to produce a remission. IVIG is expensive, and its supply is sometimes limited. Glucocorticoids are inexpensive, but chronic use is limited by common and clinically important side effects. Plasma exchange is expensive, invasive, and available only at specialized centers.

Treatment guide lines:[45]

For patients with CIDP who has clinically significant disability, immune modulating treatment using either intravenous immune globulin (IVIG), glucocorticoids, or plasma exchange is recommended. Most authorities initiate treatment for CIDP when progression is rapid or walking is compromised. For patients with severe and fulminant CIDP, suggest treatment with a rapid immune modulating therapy such as IVIG or plasma exchange rather than glucocorticoids. It is preferable to initiate treatment with IVIG if available because it is usually easier to administer than plasma exchange. For patients with more insidious CIDP, where the goal is to achieve remission, we suggest initial therapy with glucocorticoids with or without IVIG or plasma IVIG, administered as 2.0 g/kg body weight given in divided doses over 2–5 days; three monthly courses are generally recommended before concluding a patient is a treatment failure. If the patient responds, the infusion intervals can be gradually increased or the dosage decreased (e.g., 1 g/kg per month). PE, which appears to be as effective as IVIG, is initiated at two to three treatments per week for 6 weeks; periodic re-treatment may also be required. Treatment with glucocorticoids is another option (60–80 mg prednisone PO daily for 1–2 months, followed by a gradual dose reduction of 10 mg per month as tolerated).For patients who fail to respond to the initial mode of therapy, then think about substitute and alternative treatment. As an example, failure to respond to IVIG triggers intervention with plasma exchange or glucocorticoids.

Most patients with CIDP who respond to initial IVIG or plasmapheresis therapy will relapse when the therapy is discontinued and will require treatment for such patients, retreat and suggest repeating the initially successful treatment modality, patients on glucocorticoid therapy who relapse, stopping the taper and/or increasing the dose is reasonable. The timing and dose of ongoing intermittent treatments should be titrated to avoid relapses, patients with CIDP initially treated with IVIG who require high dose therapy for many months, we suggest adding glucocorticoid therapy. Likewise, recommend glucocorticoid therapy for patients who need multiple treatments over several months after receiving plasma exchange treatment.

For patients with severe CIDP who are refractory to treatment with IVIG, glucocorticoids, and plasma exchange, and are also refractory to glucocorticoids combined with IVIG or plasma exchange, or have unacceptable side effects with these regimens, suggest treatment with an alternative immunosuppressant and options include methotrexate, cyclosporine , azathioprine, mycophenolate, or cyclophosphamide. The choice among these agents must be individualized. Patients should be informed that the efficacy of these medications for CIDP is unknown, and that they are accompanied with a risk of major side effects. While the long-term prognosis for CIDP is generally good, data are limited, and up to 15% of patients remain severely handicapped despite treatment.

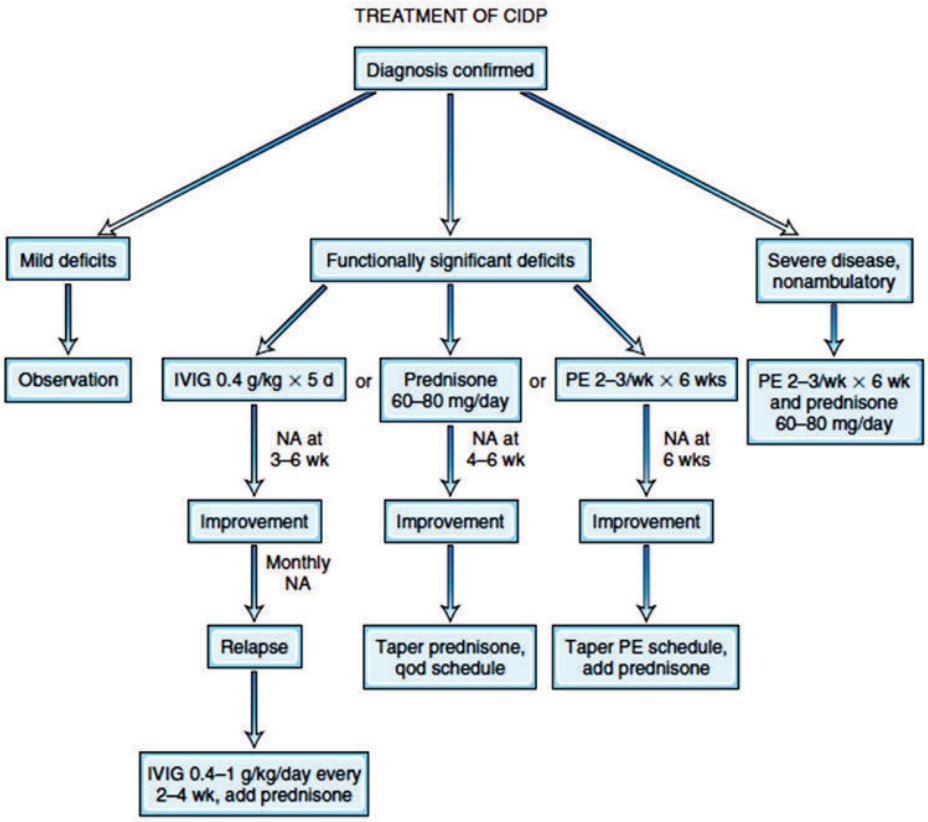
Other immune modulators: [46]

Several immunosuppressive agents have been reported to be beneficial for CIDP in observational studies, but none have been rigorously studied in randomized controlled trials with enough power to provide convincing evidence of effectiveness. The list of immune modulator drugs that have been used to treat CIDP includes the following: azathioprine, cyclophosphamide, cyclosporine, etanercept, interferon alpha, interferon beta, mycophenolate mofetil, tacrolimus . and methotrexate . Early experience with anti-CD20 (rituximab) has also shown promise.

Historically, azathioprine and cyclophosphamide have probably been the most commonly used drugs for CIDP from this list.

Newer treatment for CIDP:

The FDA has approved Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) in adults. Vyvgart Hytrulo combines efgartigimod alfa, a newborn Fc receptor blocker, with hyaluronidase, an endoglycosidase. Vyvgart Hytrulo is given as weekly subcutaneous (under the skin) injections to treat CIDP.[47]



Flow sheet 3: *Algorithms of Management chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). IVIG, Intravenous immunoglobulin; NA, neurological assessment; PE, plasma exchange.*

The ADHERE clinical trial (NCT04281472), which assessed the safety and effectiveness of Vyvgart Hytrulo as a treatment for CIDP, provided the basis for the approval. 322 adults with CIDP participated in this multicenter, phase 2 randomized, double-blind, placebo-controlled clinical study.[47]

Multifocal motor neuropathy (MMN) or Multifocal Motor Neuropathy with Conduction Block (MMNCB):

Introduction:

Multifocal motor neuropathy (MMN), also known as multifocal motor neuropathy with conduction block (MMNCB), is a rare, acquired motor neuropathy marked by gradual asymmetric weakening and no sensory abnormalities. The syndrome's nosographic location is very new, having been reported in 1986 .[48] It often affects the upper limbs more than the lower limbs.[49] Electrodiagnostic investigations frequently indicate an asymmetric motor neuropathy with a distinctive conduction block. Most patients have serum IgM anti-ganglioside antibodies (anti-GM1).[50]

Epidemiology:

Multifocal motor neuropathy is an uncommon illness with an estimated global frequency of fewer than one in every 100,000 persons. It is 2.7 times more frequent in men than in women.[50] Furthermore, the disease is diagnosed, especially in adults in their third to fifth decades, although it is also reported in children as young as 6 years of age and in the elderly.[50]

Immunopathogenesis:

Anti-GM1 antibodies, although common, are not present in all cases of MMNCB. In the absence of anti-GM1 antibodies, the pathophysiology of motor nerve dysfunction is controversial. These patients may either have low undetectable titers of anti-GM1 or probably different antibodies are present that are directed against different antigens. Even in peripheral motor nerves, the

greater concentration of GM1 is present around the nodes of Ranvier. However, the clinical characteristics are the same in MMNCB patients with or without anti-GM1 antibodies.[51]

Diagnostic Criteria:

In 2010, the European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society (PNS) Task Force revised the following diagnostic criteria to help in the diagnosis of MMN.[52]

Core Criteria (both must be present):

1. Slowly progressive, focal, asymmetric limb weakness, that is, motor involvement in the motor nerve distribution of at least two nerves, for at least 1 month (usually more than 6 months). If symptoms and signs are present only in the distribution of one nerve, only a possible diagnosis can be made.
2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs.

Supportive Clinical Criteria:

1. Predominant upper limb involvement
2. Decreased or absent tendon reflexes in the affected limb
3. Absence of cranial nerve involvement
4. Cramps and fasciculations in the affected limb
5. Response to immunomodulatory treatment

Exclusion Criteria:

1. Upper motor neuron signs
2. Marked bulbar involvement
3. Sensory impairment more marked than minor vibration loss in the lower limbs
4. Diffuse symmetric weakness during the initial weeks

Management:

IVIg is the major pharmacological therapy option for MMNCB. It is worth noting that more than 75% of patients react to IVIG. However, the response in muscular strength improvement is only temporary, with only 20% of patients achieving long-term remission. Most patients require periodic IVIg injections. Despite repeated IVIg infusions, motor impairments may gradually worsen due to subsequent axonal injury. A Cochrane study found that IVIG was more effective than placebo in the treatment of MMNCB (NNT 1.4, 95% CI 1.1-1.8).[53]

In non-responders, the treatment options are limited. Different immunomodulatory agents such as cyclophosphamide, mycophenolate mofetil, azathioprine, and rituximab, have been reported in the literature with variable results.[50] Oral cyclophosphamide has been reported effective in sustaining disease remission and reducing IGIg frequency but has significant adverse effects.[54] In 2007, an RCT comprising of 28 patients did not reveal a significant difference when mycophenolate mofetil was combined with IVIG as compared to IVIG alone in patients with MMN.[55] Multiple comparative randomized controlled trials (RCTs) are needed to establish the efficacy of immunomodulatory drugs in MMN.

Prognosis:

For multifocal motor neuropathy, the prognosis is often favorable. Eighty percent of patients show improvement with IVIG therapy. Of the patients, about 20% get long-term remission; the other patients need IVIG or SCIG treatments on a regular basis. Muscle weakening occurs slowly even in non-responders, and most patients are able to carry out their normal activities. In one research, almost 94% of participants kept their jobs[50] Researchers from the PeriNomS Study Group validated the Overall Disability Scale for MMN, which Rasch created, in 2015. This 25-item instrument was created to track the progression of the illness and the effectiveness of treatment.[56]

Paraproteinemia neuropathy:

Peripheral neuropathy is linked to certain disorders that produce monoclonal antibodies; in these cases, the group of neurological symptoms is commonly known as paraproteinemic neuropathy (PPN) [57,58].

PPN may be further described as a diverse set of neuropathies that have the common feature of a homogenous immunoglobulin in the serum, given that neuropathy is generally prevalent with M-protein and vice versa. PPN affects some or all sensory modalities, causing allodynia, hyperpathia, cramping, or moderate distal weakness (occasionally it can be coupled with more substantial motor symptoms). [59] It often manifests neurologically as a length-dependent axonal loss sensorimotor polyneuropathy. Occasionally, many organs are involved.

The symptoms of peripheral neuropathy may appear years before other clinical signs or the identification of

the antibody-producing illness, which might be monoclonal gammopathy of unknown significance or hematologic cancer [60]. Treatment options for PPN include IVIG, plasma exchange, corticosteroids, rituximab, and various chemotherapies, depending on the subtype and pathophysiology involved.[61]

Conclusion:

Immunologically mediated peripheral nervous system diseases are a class of illnesses in which immunological disorders play a significant role. It is critical to notice them since they are likely curable if detected early. In clinical practice, however, this can be challenging since these disorders frequently occur on a broad spectrum with ill-defined limits. This often influences how physicians communicate to their patients about their disease, as well as their treatment options in both the acute and maintenance phases.

Conflict-of-interest: There is no potential conflict of interest.

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