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Physician Booklet on CIDP

Rabani Remli
Tan Cheng Yin
Loo Lay Khoon
Hiew Fu Liong

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HEALTHCARE PROFESSIONALS ONLY

Authors:

Associate Prof. Dr. Rabani Remli
MBChB (Sheffield, UK), MMed (UKM)
Consultant Neurologist
Faculty of Medicine, UKM

Associate Prof. Dr. Tan Cheng Yin
MD (UKM), MMed (UM), FRCP (Edin)
Consultant Neurologist
Universiti Malaya Medical Centre

Dr. Loo Lay Khoon
MD (UPM), MRCP (UK)
Consultant Neurologist
Sunway Medical Centre Penang

Dr. Hiew Fu Liong
MBBS (IMU), MRCP (UK), MMed (Singapore)
Consultant Neurologist
Sunway Medical Centre

Author's Note:

This booklet serves as a quick reference to provide an easy explanation regarding CIDP to doctors and medical practitioners. We hope the important and updated information that has been included in this booklet will be beneficial to everyone treating patients with CIDP.

We would like to thank CSL Behring for the support in the production of this first edition of CIDP physician booklet.

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Chapter I: Introduction

a. Definition

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common type of autoimmune peripheral nerve disorder. CIDP is defined as an **immune-mediated, chronic progressive or relapsing polyradiculoneuropathy involving the myelin sheath of sensory and motor nerves.**[1]

CIDP typically affects both the proximal and distal parts of the limbs, impacting patients' ability to walk and perform daily tasks independently. It is caused by the immune system mistakenly attacking the nerves, resulting in various levels of symptoms from mild to severe disability. Treatment responses in CIDP vary due to the wide range of nerve involvement and symptom severity.[2]

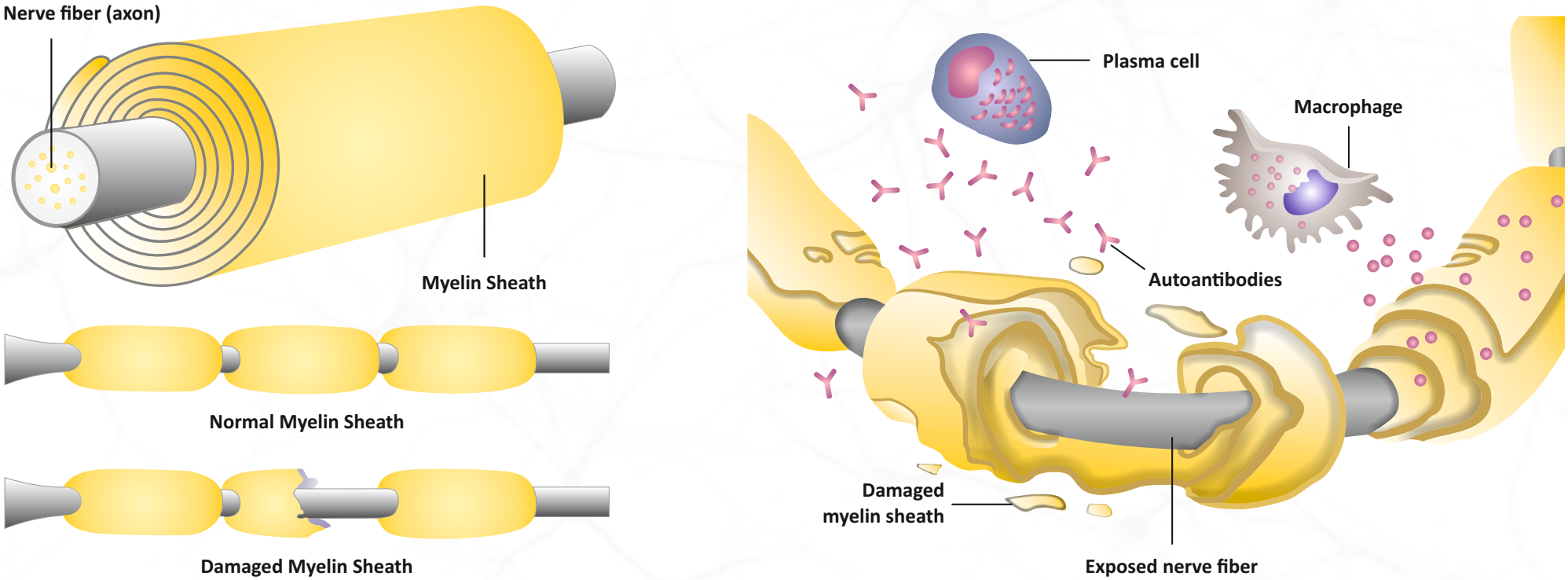


Figure 1. CIDP affects the myelin sheath of the peripheral nerves[3]

b. Epidemiology

CIDP is the **most prevalent chronic autoimmune neuropathy, with a global incidence of 0.33 per 100,000 person-years and a prevalence rate of 2.81 per 100,000 population.**[4] CIDP can manifest at any age. It typically occurs around **middle age,** with approximately 10% of cases affecting children, albeit rarely below age 1.[5] It shows a **male predominance** with the male-to-female ratio of 1.9.[6] Locally, in a retrospective study of 23 CIDP patients attending Neurology service at Kuala Lumpur Hospital, Malaysia, there were 15 (65%) males and 8 (35%) females with a mean age of 42.7 years (SD 14.4).[7] Nearly 16% of CIDP patients may present within 8 weeks, recognized as acute-onset CIDP.[8] Antecedent events such as exposure to foreign proteins through immunization or infectious diseases, are less frequent in CIDP compared to Guillain-Barré syndrome.[9]

Adapted from Inflammatory Neuropathy Consortium Base (INCbase) International Registry for CIDP (Updated 18/04/2023)

c. Impact on patients

CIDP places significant **physical and psychosocial challenges** on patients, affecting their physical abilities, causing pain, and impacting their overall health and mental well-being. Additionally, treatments for CIDP can be burdensome due to side effects and the need for assistance with administration, reducing patients' independence.[10] However, unlike many other neuropathies, **CIDP is treatable and potentially reversible.**[11] Although most patients with CIDP may require maintenance treatment for years or even decades, 30% of CIDP patients can achieve long-term stability without treatment or enter remission within 5 years.[12]

d. Purpose of this booklet

This **CIDP Physician Booklet** is developed to provide healthcare professionals and neurologists in Malaysia a quick reference with practical information on clinical presentation, differential diagnosis, variants and mimics, and therapeutic approaches, based on current practice, using a treatment algorithm that addresses patient management from the initiation of treatment to the follow-up period, including treatment monitoring and patient rehabilitation.

Chapter II: Understanding CIDP

a. Pathophysiology of CIDP

CIDP symptoms arise from **immune-mediated attacks on peripheral nerves,** involving both cellular and humoral pathways of the immune system.

Autoreactive T cells identify a specific autoantigen presented by major histocompatibility complex class II molecules on antigen-presenting cells or macrophages in the systemic immune system. Infections can trigger this response through molecular mimicry, where there's a cross-reaction between microbial and nerve antigens.

These activated T cells can breach the blood-nerve barrier using cellular adhesion molecules, matrix metalloproteinases, and chemokines. T-helper cells, macrophages, cytokines, and complement play roles in myelin degradation.

Autoantibodies crossing the blood-nerve barrier or locally produced by plasma cells also contribute to demyelination and axonal damage.

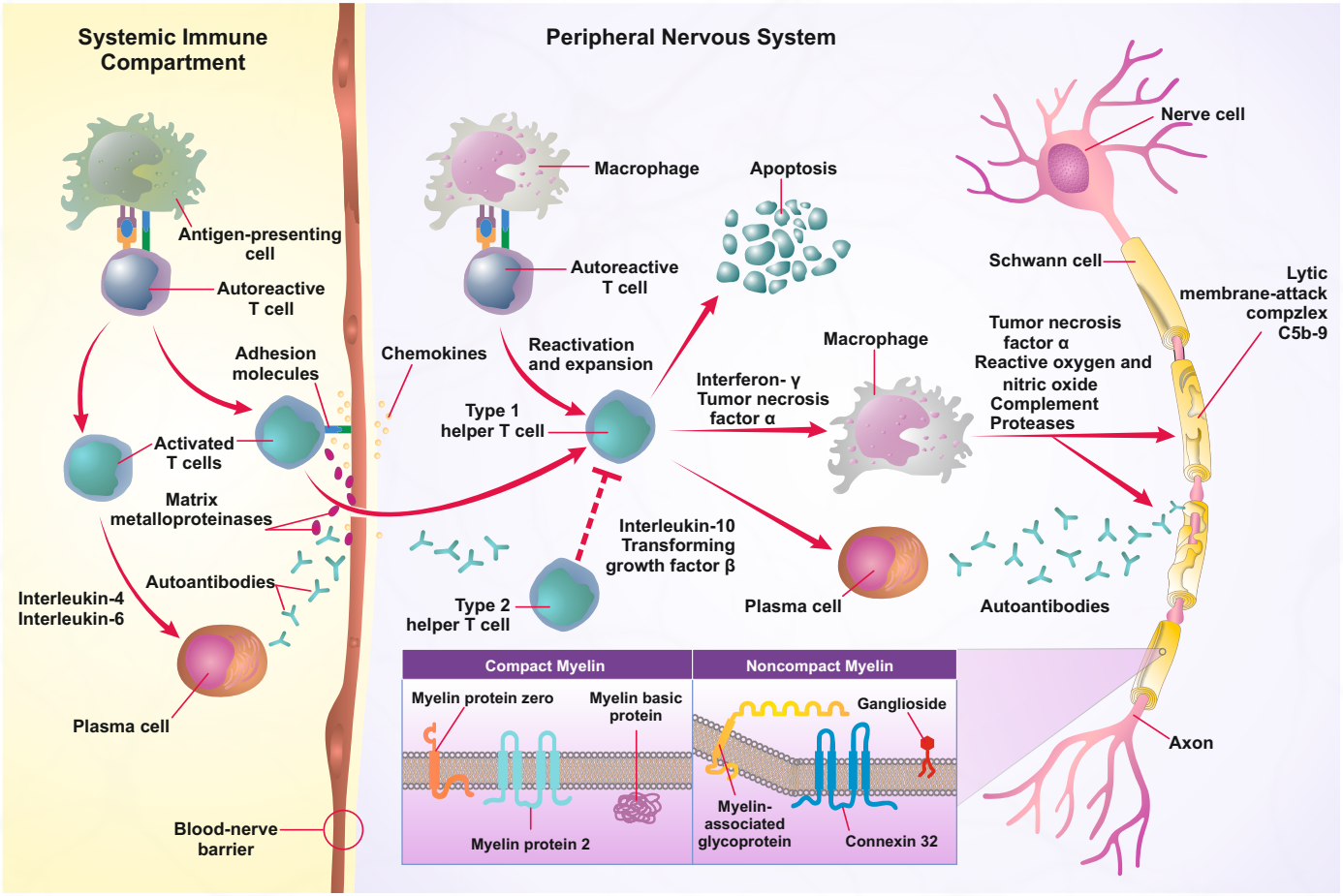


Figure 2. Pathophysiological mechanism of CIDP[13]

b. Risk Factors and antecedent events of CIDP

Risk factors for developing CIDP is unknown. Early research had indicated a potential link between diabetes and an increased risk of CIDP, but subsequent epidemiological studies have not confirmed this association.[14,15,16]

The relationship between antecedent infections and CIDP is unclear. Approximately 15.5% of CIDP patients report an antecedent event within 1-42 days before the onset of CIDP, including infections in 12% of cases and vaccinations in 1.5%.[17] These antecedent infections or vaccinations are more common in younger individuals and those with acute-onset CIDP.[18]

c. When do you suspect CIDP?

CIDP patients may present with diverse clinical manifestations and should be considered in cases of generalized or multifocal neuropathy. Clinical suspicion of CIDP is heightened by certain factors, including the **onset of symptoms during the 5th or 6th decades of life, progressive symmetrical weakness affecting both proximal and distal muscles of the lower and/or upper limbs, with partial or complete recovery between episodes, along with associated sensory impairment and reduced or absent tendon reflexes.** Upon suspicion of CIDP, the diagnostic approach revolves around clinical history and physical examination, identifying demyelinating changes through electrodiagnostic testing, cerebrospinal fluid analysis, +/- neuroimaging and exclusion of conditions that mimic CIDP.[19]

d. Clinical presentation of CIDP

CIDP may present as typical CIDP or as its rare variants. The clinical features of CIDP are **progressive symmetrical or asymmetrical polyradiculoneuropathy, relapsing or progressive course >8 weeks, proximal and distal weakness, large fiber sensory loss (vibration and joint position sense) and generalized hyporeflexia or areflexia.**[20]

The clinical and diagnostic criteria of CIDP are as follows:

For typical CIDP, individuals need to meet all 3 criteria:	For CIDP variant, individuals need to meet 1 of the following:
• Progressive or relapsing symmetric, proximal and distal weakness with sensory loss in at least 2 limbs • Symptoms developing over at least 8 weeks • Absent or diminished reflexes	• Distal CIDP: distal weakness and sensory loss, predominantly in lower limbs • Multifocal CIDP: weakness and sensory loss in a multifocal, asymmetric pattern; upper limb predominant and at least 1 limb • Focal CIDP: weakness and sensory loss in only 1 limb • Motor CIDP: only motor symptoms • Sensory CIDP: only sensory symptoms

Table 1. Clinical criteria for the diagnosis of CIDP as defined by the 2021 European Academy of Neurology (EAN)/Peripheral Nerve Society (PNS) Guideline[20]

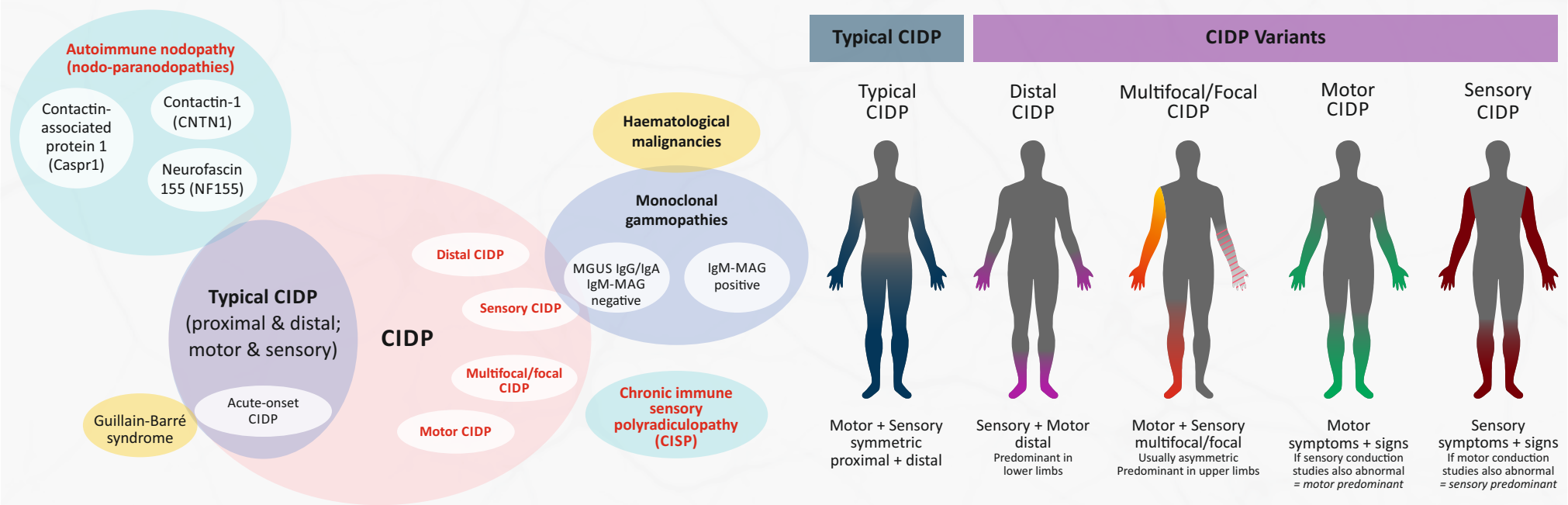


Figure 3. CIDP Variants

Phenotype	Weakness	Sensory Disturbances	Red Flags	Differential Diagnosis
Typical CIDP	Symmetric in 4 limbs	In ≥2 limbs	Onset < 4 weeks Motor > sensory and/or weakness distal > proximal Ataxia Cranial nerve or bulbar involvement M-protein presence Poor response to IVIg	Guillain-Barré syndrome Autoimmune nodopathies (anti-NF 155, anti-CNTN1, anti-CASPR1) CANOMAD (in combination with ophthalmoplegla), anti-NF I55, anti-CNTN1 Anti-NFI40/NF186, anti-CASPR1 Monoclonal gammopathy (POEMS, AL amyloidosis, multiple myeloma) Reassess CIDP diagnosis: prompt further testing and evaluate differential diagnoses based on other red flags
Multifocal/ focal variant	In ≥2 limbs in multifocal distribution Only I limb	In ≥2 limbs in mutifocal distribution In distribution of affected nerve(s)	Diabetes mellitus Pain No sensory disturbances Close to entrapment sites Single nerve	Diabetic radiculopathy or plexopathy Vasculitic neuropathy (mononeuritis multiplex), diabetic polyradiculopathy or plexopathy, amyotrophic neuralgia, cryoglobulinemia MMN, motor neuron disease Entrapment neuropathies, HNPP (in case of multiple entrapments and/ or family history of HNPP) Peripheral nerve tumors (schwannoma, perineurioma, lymphoma, neurafibroma), nerve entrapment
Distal variant	Distal, predominantly in lower limbs	In ≥2 limbs	M-protein and/or anti- MAG presence Diabetes mellitus Family history of neuropathy Pain and/or asymmetry	And-MAG IgM neuropathy, POEMS, multiple myeloma, cryoglobulinemia Diabetic neuropathy Hereditary neuropathies with demyelinating features (CMT I, CMTX I,CMT4, metachromatic leukodytrophy, Refsum disease, adenomyeloneuropathy, ATTR-v polyneuropathy), Vasculitic neuropathy, cryoglobulinemia
Motor variant	Symmetric In 4 limbs	None	Asymmetry Bulbar weakness Family history of neuropathy Elevated CK, normal tendon reflexes Fluctuation of symptoms	Motor neuron disease Motor neuron disease, myasthenia gravis Hereditary motor neuropathies (spinal muscular atrophy, porphyria) Inflammatory myopathies Neuromuscular junction disorders (myasthenia gravis, Lambert-Eaton)
Sensory variant	None	Symmetric in 4 limbs	Pain Family history of neuropathy Ataxia Normal motor and sensory conduction Diabetes mellitus Chemotherapy or other neurotoxic treatments/ supplements Slow progression	Small-fiber neuropathy Hereditary sensory neuropathies CANVAS, dorsal column lesions (vitamin BI2 deficiency, paraneoplastic, syphilis, copper deficiency) CISP Diabetic polyneuropathy Toxic neuropathies (eg chemotherapy, vitamin B6 toxicity) Idiopathic sensory neuropathles

Abbreviations: ATTR-v, amyloid transthyretin variant; **CANOMAD,** chronic ataxic neuropathy, ophthalmoplegia, immunoglobulin M [IgM] paraprotein, cold agglutinins, and disialosyl antibodies; **CANVAS,** cerebellar ataxia, neuropathy and vestibular areflexia; **CASPR1,** contactin-associated protein-I; **CISP,** chronic immune sensory polyradiculopathy; **CMT,** Charcot-Marie-Tooth; **CNTN-1,** contactin-I; **MAG,** myelin-associated glycoprotein; **MMN,** multifocal motor neuropathy; **NF-155/186/140,** neurofascin-155/186/140; **POEMS,** Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, Skin changes.

Table 2. CIDP variants, clinical presentations and differential diagnosis[21]

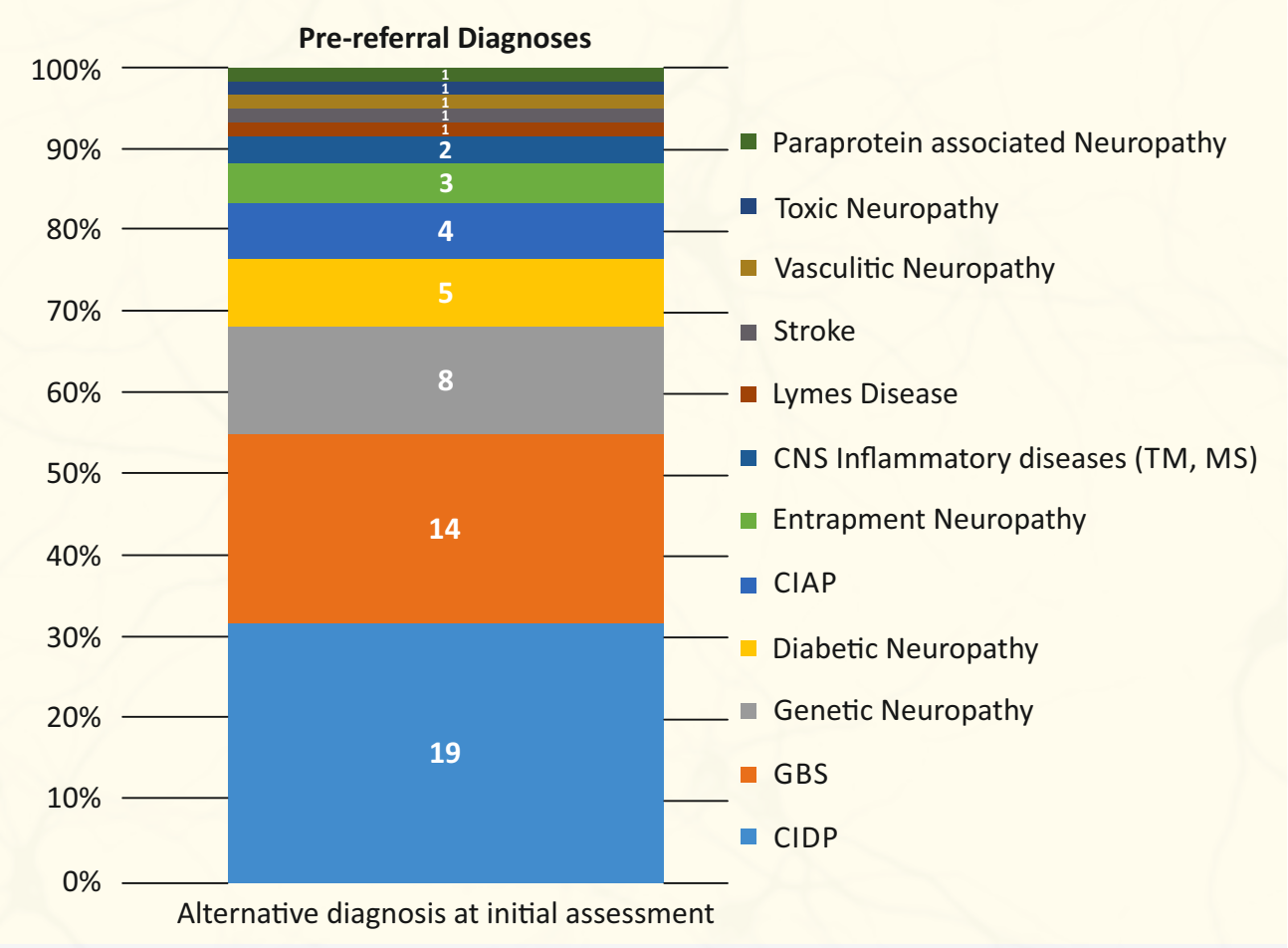
Chapter III: How do you diagnose CIDP?

a. Misdiagnosis and underdiagnosis of CIDP

Diagnosing CIDP can pose a significant challenge, particularly due to its heterogeneous clinical presentations. **Achieving an accurate diagnosis is crucial since CIDP is treatable.** CIDP is often underdiagnosed, reported in nearly 68.3% of CIDP patients, leading to significant delays in diagnosis and treatment.[22]

In contrast, overdiagnosis of CIDP is not uncommon. Nearly 47% of patients were misdiagnosed with CIDP in one study.[23] Among those misdiagnosed, 44% actually met European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS) 2010 clinical criteria for CIDP, and all of them exhibited features of atypical variants.

Common causes of misdiagnosis include relying too heavily on subjective patient-reported treatment benefits, overly liberal interpretation of electrophysiological evidence of demyelination, and placing excessive importance on mild or moderate cyto-albuminologic dissociation.



Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy, **GBS**, Guillain–Barré syndrome, **CIAP**, chronic idiopathic axonal polyneuropathy, **TM**, transverse myelitis, **MS**, multiple sclerosis.

Figure 4. Pre-referral diagnosis for CIDP patients

Misdiagnosis

There is a significant risk of misdiagnoses because there are a number of conditions that closely resemble CIDP

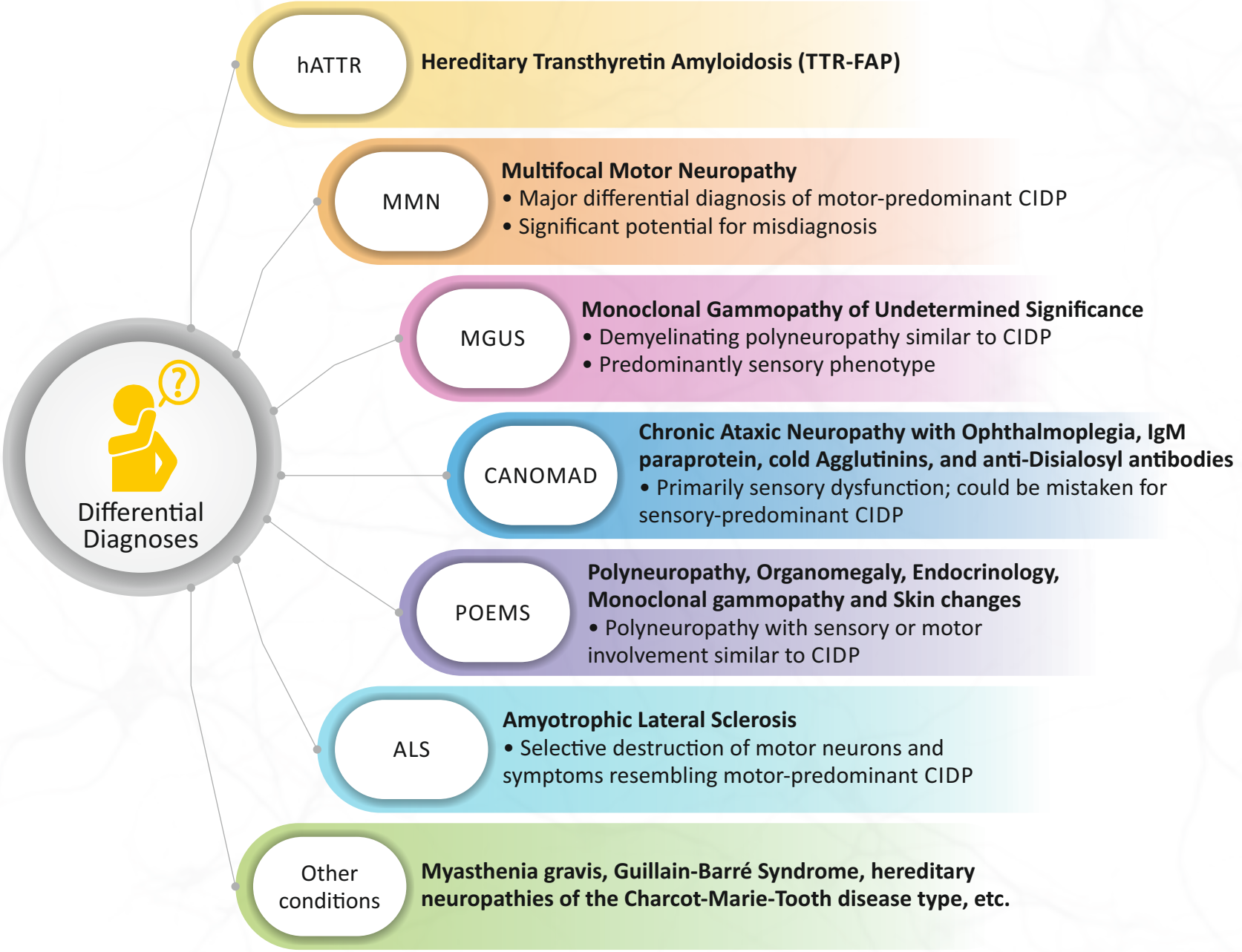


Figure 5. Common misdiagnosis of CIDP[23,24,25,26,27]

b. Diagnosis of CIDP

The most commonly utilized criteria in current clinical practice are those established by the EFNS/PNS 2010 and later revised version by European Academy of Neurology and the Peripheral Nerve Society (EAN/PNS) published in 2021.[28] According to EAN/PNS criteria, diagnosing CIDP relies on a **combination of clinical history, physical examination, electrophysiology, and supporting laboratory tests.**

c. Investigations in CIDP

CIDP diagnosis relies heavily on clinical evaluation and electrophysiological study, with supporting investigations such as cerebrospinal fluid (CSF) analysis, neuroimaging or nerve biopsy.

Strongly advised	Investigations to be performed if indicated	Additional investigations if indicated in CIDP variants
• Electrodiagnosis including motor and sensory nerve conduction studies • Serum and urine protein electrophoresis with immunofixation • Fasting blood glucose • Complete blood count • Renal function • Liver function	• Ultrasound of the bracial plexus and cervical nerve roots • MRI of cervical and lumbosacral nerve roots • CSF examination • Nerve biopsy • Glycosylated hemoglobin • Borrelia burgdorferri serology • C-reactive protein • Anti nuclear antibodies • HIV serology • Serum vascular endothelial growth factors • Anti-MAG antibodies • Nodal-paranodal protein antibodies • Skeletal survey • Chest X-ray • Genetic testing for hereditary neuropathy	**Distal CIDP** • Anti-MAG antibodies when IgM monoclonal gammopathy present **Multifocal and focal CIDP** • Erythrocyte sedimentation rate • Antinuclear antibodies and antineutrophil cytoplasmic antibodies • Anti-GM1 IgM antibodies **Motor CIDP** • Creatine kinase level • Muscle biopsy • Neuromuscular junction evaluation **Sensory CIDP** • IgM paraproteinaemic neuropathy with anti-MAG antibodies • Anti-ganglioside antibodies • Vitamin B1, B6 and B12 • Paraneoplastic antibody screen • Somatosensory evoked potentials when nerve conduction studies are normal

Table 3. Investigations for CIDP

Motor nerve conduction criteria	(1) Strongly supportive of demyelination: At least one of the following: (a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or (b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or (c) Prolongation of F-wave latency ≥20% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN), or (d) Absence of F-waves in two nerves (if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN) + ≥1 other demyelinating parameter in ≥1 other nerve, or (e) Motor conduction block: ≥30% reduction of the proximal relative to distal negative peak CMAP amplitude, excluding the tibial nerve, and distal negative peak CMAP amplitude ≥20% of LLN in two nerves; or in one nerve + ≥ 1 other demyelinating parameter except absence of F-waves in ≥1 other nerve, or (f) Abnormal temporal dispersion: >30% duration increase between the proximal and distal negative peak CMAP (at least 100% in the tibial nerve) in ≥2 nerves, or (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) prolongation in ≥1 nerve + ≥1 other demyelinating parameter in ≥1 other nerve • (LFF 2 Hz) median > 8.4 ms, ulnar > 9.6 ms, peroneal > 8.8 ms, tibial > 9.2 ms • (LFF 5 Hz) median > 8.0 ms, ulnar > 8.6 ms, peroneal > 8.5 ms, tibial > 8.3 ms • (LFF 10 Hz) median > 7.8 ms, ulnar > 8.5 ms, peroneal > 8.3 ms, tibial > 8.2 ms • (LFF 20 Hz) median > 7.4 ms, ulnar > 7.8 ms, peroneal > 8.1 ms, tibial > 8.0 ms (2) Weakly supportive of demyelination As in (1) but in only one nerve.
Sensory nerve conduction criteria	(1) CIDP Sensory conduction abnormalities (prolonged distal latency, or reduced SNAP amplitude, or slowed conduction velocity outside of normal limits) in two nerves. (2) Possible CIDP As in (1). Sensory CIDP with normal motor nerve conduction studies needs to fulfil a. or b. (a) sensory nerve conduction velocity <80% of LLN (for SNAP amplitude >80% of LLN) or <70% of LLN (for SNAP amplitude <80% of LLN) in at least two nerves (median, ulnar, radial, sural nerve), or (b) sural sparing pattern (abnormal median or radial sensory nerve action potential [SNAP amplitude] with normal sural nerve SNAP amplitude) (excluding carpal tunnel syndrome)

Table 4. Electrodiagnostic criteria for diagnosis of CIDP[20]

Patient presents with possible CIDP

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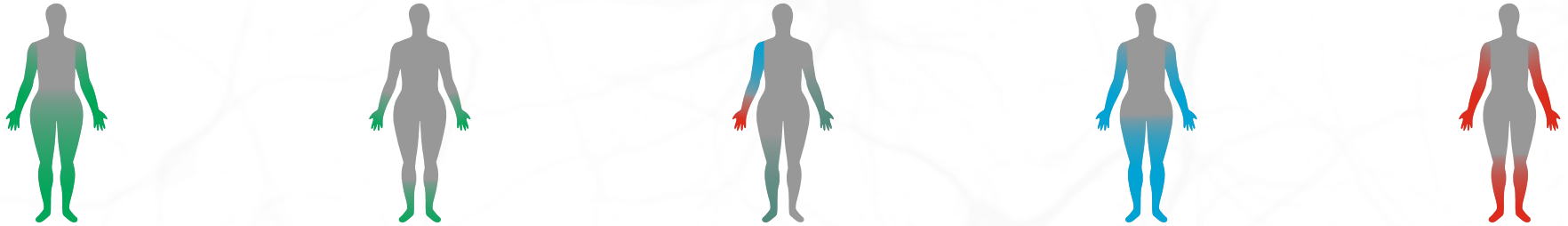
Assess limb weakness and sensory disturbance (clinical criteria)



Potential typical CIDP	Potential distal CIDP	Potential multifocal CIDP	Potential motor CIDP	Potential sensory CIDP
• Weakness symmetrical in 4 limbs, proximal & distal • Sensory disturbance in ≥2 limbs	• Weakness predominantly in upper limbs, distal • Sensory disturbance in ≥2 limbs	• Weakness in ≥2 limbs (multifocal) or 1 limb (focal) • Sensory disturbance in distribution affected nerves	• Weakness symmetrical in 4 limbs, proximal & distal • No sensory disturbance	• No limb weakness • Sensory disturbance symmetrical in 4 limbs

↓

Consider clinical and laboratory red flags and alternate diagnoses (see Table 2)

↓

No alternative diagnosis

↓

Assess motor and sensory conduction (electrodiagnostic criteria) and supporting evidence (see Table 4)

↓

Confirm level of certainty of diagnosis (CIDP, upgradeable possible CIDP or possible CIDP) based on clinical, electrodiagnostic & supportive criteria

Figure 6. Key approach in the diagnosis of typical CIDP and variants[29]

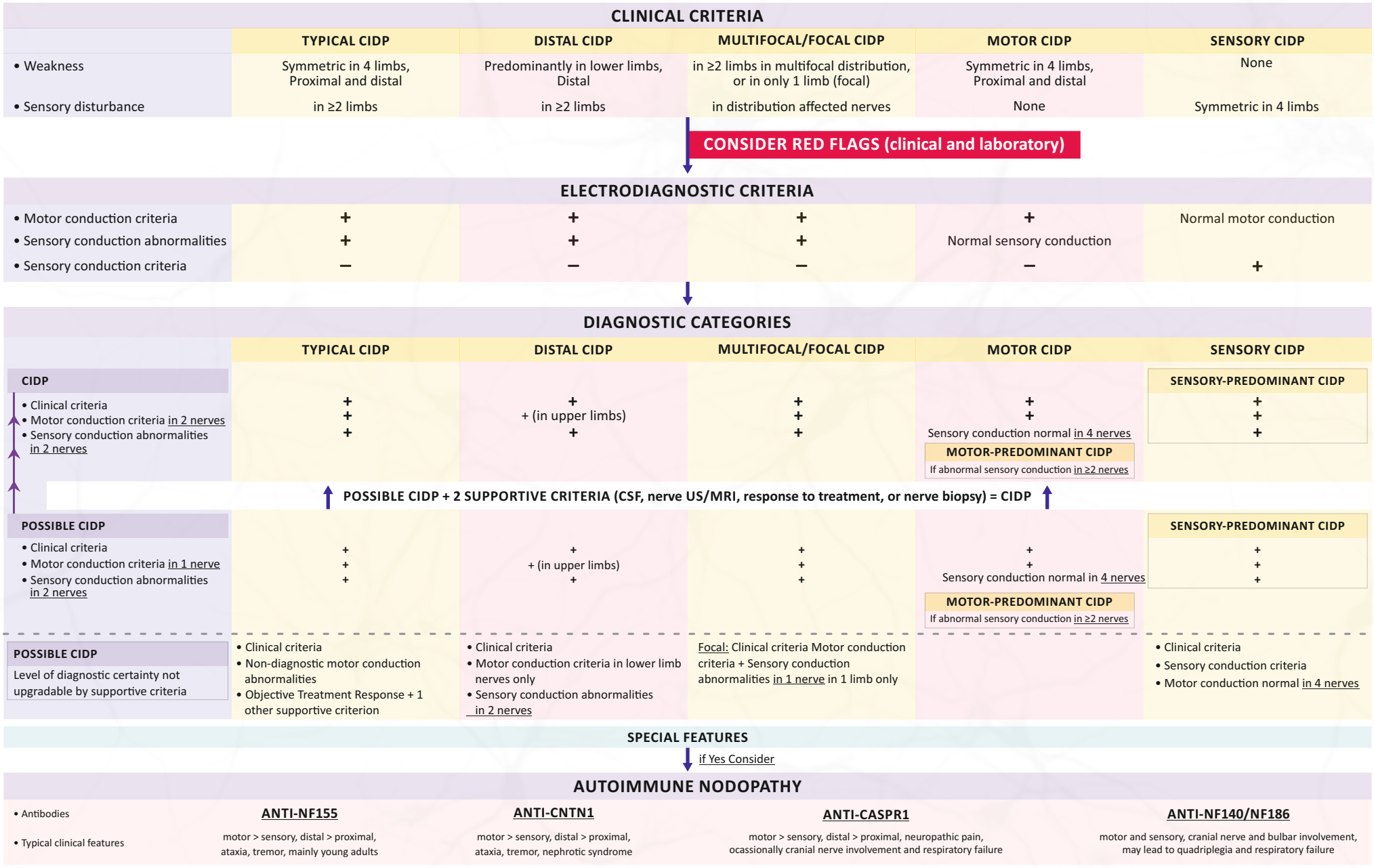


Figure 7. Diagnostic criteria and categories of CIDP and variants

As depicted in Figure 7, the initial step in diagnosis of CIDP involves assessing the pattern of weakness and sensory disturbance to classify the patient into either the typical CIDP or CIDP variants. Red flags indicating potential alternative diagnoses should be considered during this assessment. Subsequently, electrodiagnostic testing should be conducted. The third section integrates these findings to establish the diagnostic categories (Figure 7).

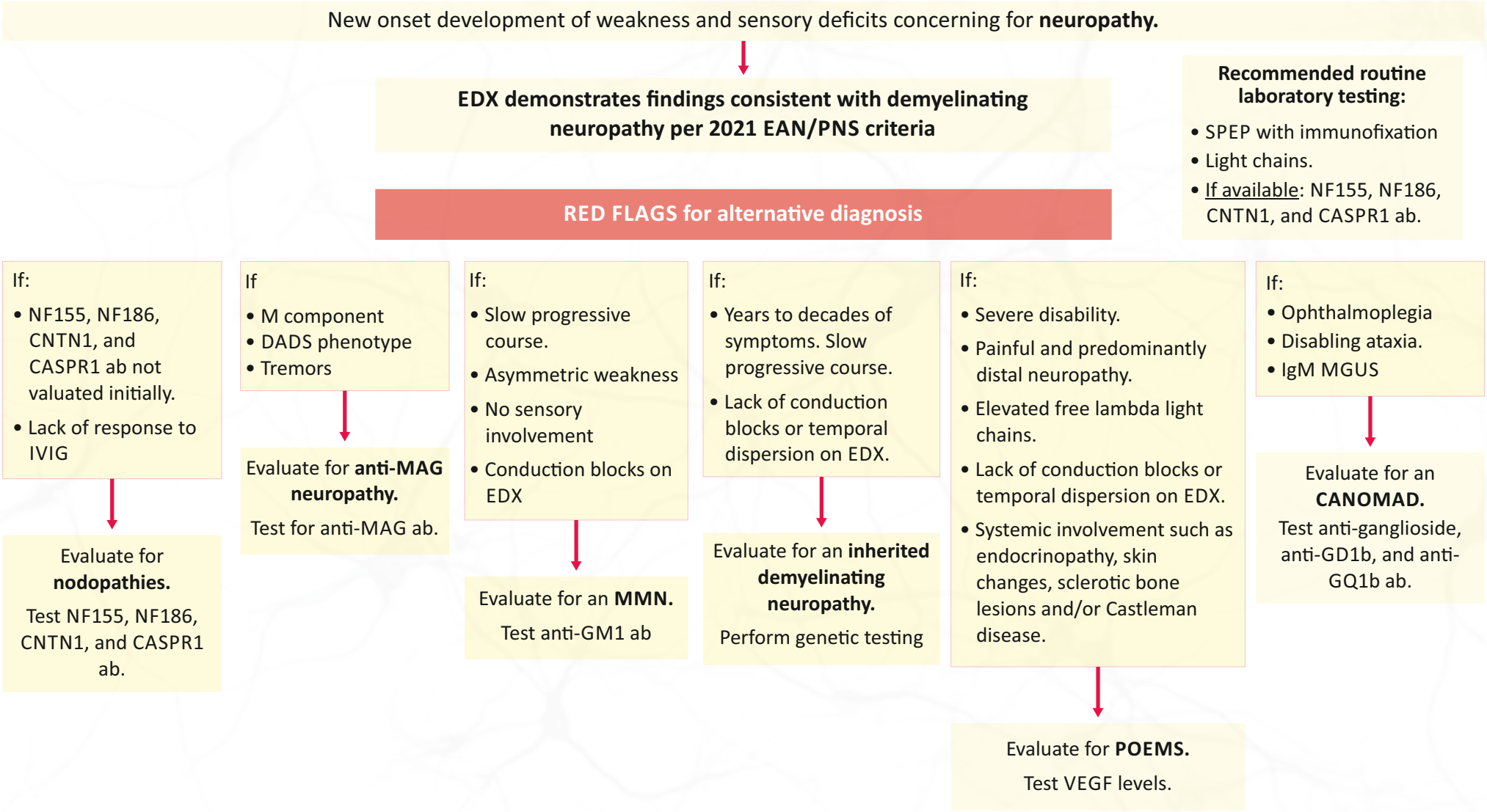


Figure 8. Red flags in the diagnosis of CIDP[30]

d. CIDP mimics

Several CIDP mimics may need to be considered when encounter cases of peripheral neuropathy with red flags (Figure 8).[31,32] The list below is not intended to be exhaustive.

- Guillain-Barré syndrome
- POEMS syndrome – polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes
- Hereditary transthyretin amyloidosis (hATTR amyloidosis); previously known as transthyretin familial amyloid polyneuropathy (TTR-FAP)
- Lumbosacral radiculoplexus neuropathy (LRPN); mostly diabetic-related but can be non-diabetic
- IgM anti-myelin associated glycoprotein (MAG) antibody mediated neuropathy (anti-MAG neuropathy)
- Light chain amyloidosis (AL Amyloidosis)
- Multifocal motor neuropathy (MMN)
- Charcot-Marie-Tooth disease (CMT)
- Osteosclerotic myeloma

e. Differential diagnosis of CIDP variants

The diagnosis of CIDP variants in patients who present with muscle weakness and sensory disturbances is often complex. Distinguishing it from other conditions is crucial.

• Distal CIDP

- Length-dependent axonal neuropathies e.g. diabetic polyneuropathy, TTR-FAP
- Anti-MAG neuropathy
- Inherited neuropathies e.g. CMT
- POEMS syndrome

• Multifocal CIDP

- Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) or diabetic amyotrophy
- MMN
- Hereditary neuropathy with liability to pressure palsy (HNPP)
- Vasculitic neuropathy (mononeuritis multiplex)

• Motor CIDP

- Hereditary motor neuropathy
- Motor neuron disease (MND)
- Inflammatory myopathies
- Neuromuscular junction disorders (e.g. myasthenia gravis)

• Sensory CIDP

- Sensory ganglionopathy (paraneoplastic, Sjögren syndrome, pyridoxine toxicity)
- Chronic immune sensory polyradiculopathy (CISP)
- Hereditary sensory neuropathy
- Any non-neuropathic disturbances of skin sensation

Chapter IV: How would you manage CIDP?

a. Aim of CIDP management

The aim of CIDP management is to provide symptom-relief and improve muscle and sensory function while balancing maintenance of long-term remission and avoiding over-treatment.[33,34]

b. Treatment options in CIDP Management

The evidence-based treatment options of CIDP include intravenous immunoglobulin (IVIg), corticosteroids, and plasma exchange, with subcutaneous immunoglobulin (SCIg) recently added as a maintenance option. The above treatment options are considered first-line therapy and have been shown to be effective in majority of the CIDP patients, either administered alone or in combination. Alternatively, there are many other treatments avenue such as immunosuppressants, monoclonal antibodies which have been and currently being explored especially among refractory cases. The Table 5 summarizes the treatment option for CIDP, detailing the indications, dosing, follow-up treatment assessment and common side effects.

Treatment	When to Start	How to Start	When to Evaluate	Notable Side Effects & Cautions
IVIg	• Loading dose followed by maintenance treatment, especially when there is significant disability due to symptoms and swift improvement is essential • Contra-indications for corticosteroids	• Loading dose 2.0 g/kg over 2-5 days • Maintenance 0.4-1.0 g/kg every 3 weeks	• Induction treatment after 3-6 weeks • Maintenance treatment after 2-5 treatments • Periodic weaning justification of long-term use (every 6-12 months first 2-3 years, then 1-2 years)	• Risk of VTE, especially in patients with previous VTEs without anti-coagulant therapy, skin reactions, headache
SCIg	Alternative to IVIg maintenance treatment, consider in case of: • Debilitating wearing-off symptoms • Infusion-related adverse events, such as skin reactions • If IVIg home treatments are not available or feasible • Patient preference, more autonomy	• 0.4 g/kg per week or 1:1 conversion from IVIg treatment dose divided by dose interval for weekly SCIg dose. • Administration frequency may vary from 1-3 times per week to once every 14 days	• Periodic weaning justification of long-term use (every 6-12 months first 2-3 years, then 1-2 years)	• Fewer systemic side effects compared to IVIg • Patients or a caretaker need to administer the treatment themselves • Not proven to be a suitable induction treatment option
Corticosteroids	• As induction and maintenance treatment • Contra-indications IVIg	• Pulsed dexamethasone (40 mg on 4 consecutive days every 4 weeks) for 6 months • Pulsed IV methylprednisolone (I g months every 3 weeks) for 6 months • Daily prednisone: starting with 60 mg daily and slowly taper over 6-8 months	• Two to three months	• Ample long-term side effects • Prophylactic treatment of osteoporosis necessary • Motor CIDP can deteriorate after corticosteroids, IVIg preferred
Plasma exchange	• No response to other first line treatments, fast progression • Auto-immune nodopathies	• No established protocol for CIDP	• After 2-4 weeks	• Relatively safe, but risk of central-line infections and thrombosis with prolonged use • Not suitable as long-term maintenance treatment, logistical and financial constraints

Abbreviations: IVIg, intravenous immunoglobulins; **SCIg,** subcutaneous immunoglobulins; **VTE,** venous thromboembolism.

Table 5. Treatment options for CIDP[21]

c. Induction treatment of CIDP

For induction treatment, IVIg or corticosteroids should be considered in typical CIDP and CIDP variants in the presence of disabling symptoms. Plasma exchange is similarly effective but may be less well tolerated and more difficult to administer. The presence of relative contraindications to any of these treatments may influence the choice.

The advantages and disadvantages should be explained to the patient who should be involved in the decision making. If the objective response is inadequate or the maintenance doses of the initial treatment (IVIg, corticosteroids, or plasma exchange) result in significant side-effects, **the other first-line treatment alternatives should be tried before considering combination treatments.** Adding an immunosuppressant or immunomodulatory drug may be considered. Treatment decisions should take into account whether there is active disease as evidenced by **progression, relapse or demonstration of persistent treatment dependence, and determination of deficits that cannot improve due to severe chronic axonal degeneration.** However, in motor CIDP, IVIg should be considered as the initial treatment of choice as corticosteroids may cause worsening of the muscle weakness.

d. Maintenance treatment of CIDP

For maintenance treatment, if the first-line treatment is effective, continuation should be considered until the maximum benefit has been achieved and then the dose can be reduced or the interval increased to find the lowest effective maintenance dose. SCIg and IVIg can both be considered as maintenance treatment in IVIg-responsive patients with active disease. Neuropathic pain should be treated with drugs according to published guidelines on treatment of neuropathic pain. Advice about foot care, exercise, diet, driving, and lifestyle management should be considered. Depending on the needs of the patient, orthoses, physiotherapy, occupational therapy, psychological support and referral to a rehabilitation specialist should be considered. Information about patient support groups should be offered.

e. Measurement and assessment of treatment response

It is important to quantify the treatment response using tools which are validated and reproducible. An objective treatment response not only guides physicians on future treatment regime but supports clinical diagnosis of CIDP, especially among patients with diagnosis of possible CIDP based on clinical, electrodiagnostic and other supportive criteria. However, physicians should aware that lacking of improvement following treatment does not exclude CIDP (in refractory cases) and a positive response is not specific for CIDP (other inflammatory neuropathies may response to immunomodulatory treatment).

Table 6 categorizes the validated assessment scales commonly used in CIDP both in clinical and research, detailing the modality and minimal clinically important difference.

Scale	Measurement	Modality (Range)	Minimal Clinically Important Difference[a]
Disability	I-RODS INCAT-DS	Questionnaire (0-48) Investigator reported arm (0-5) and leg (0-5) disability score (1-10)	↑ ≥4 centile points ↓ ≥1 point
Impairment	mISS scale Grip strength MRC Sum score	Investigator reported score (0-33) Handheld dynamometry Sum of MRC scores (0-60) [c]	↓ ≥2 points Martin Vigorimeter: ↑ ≥8-14 kPa b Jamar Hand grip dynamometer: ↑≥10% ↑ ≥2-4 points [b]

Notes: [a] Changes to objectify improvement have not been sufficiently validated yet, but these cut-offs for improvement are commonly used in CIDP trials. [b] Higher values improve specificity. [c] Including shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsiflexion.

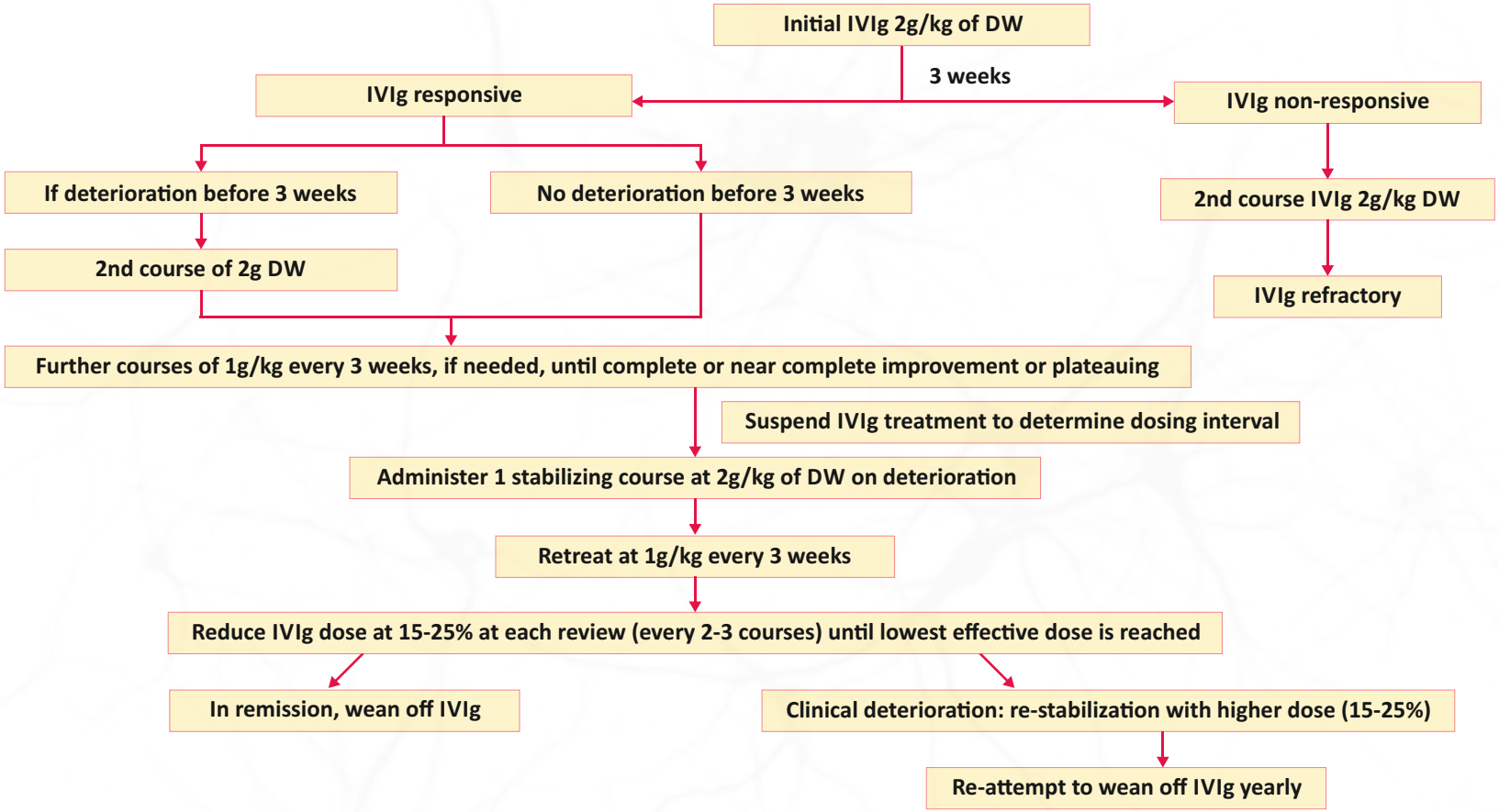
Abbreviations: I-RODS, Inflammatory Rasch-built Overall Disability Scale; **INCAT-DS,** Inflammatory Neuropathy Cause and Treatment disability scale; **mISS,** Modified INCAT Sensory Sum; **MRC,** Medical Research Council.

Table 6. Tools for measuring treatment response which are validated and can be performed during diagnosis, when initiating treatment and throughout follow-up[21]

f. Proven effective treatment

➤ Immunoglobulin therapy in the management of CIDP

Immunoglobulin (Ig) therapy is the first-line treatment for CIDP, which can be administered intravenously (IVIg) or subcutaneously (SCIg).[35] Both are blood products containing immunoglobulin G pooled from human donors. **IVIg therapy is superior to placebo in reducing the disability and impairment experienced by patients with CIDP. In addition, the relapse rate is significantly lower, and the time to deterioration significantly greater.** The effectiveness of IVIg is similar to that of the alternative treatment strategies of plasma exchange and oral corticosteroids. The standard initial dose of IVIg is 2 g/kg based on actual body weight, administered over 2-5 days, followed by a maintenance dose of 1 g/kg every 3 weeks. The long-term treatment dose of IVIG is titrated based on treatment response, duration of effectiveness and side effects. The aim is to achieve dose reductions until, if achievable, a complete remission with wean off treatment. IVIg may be suitable for patients who cannot tolerate or access alternative therapies. Figure 9 describes the IVIg treatment protocol for initiation and maintenance therapy, detailing the dose reduction steps for patients requiring long-term treatment.



Abbreviations: CIDP: chronic inflammatory demyelinating polyneuropathy; **DW:** Dosing weight; **IVIg:** intravenous immunoglobulins;

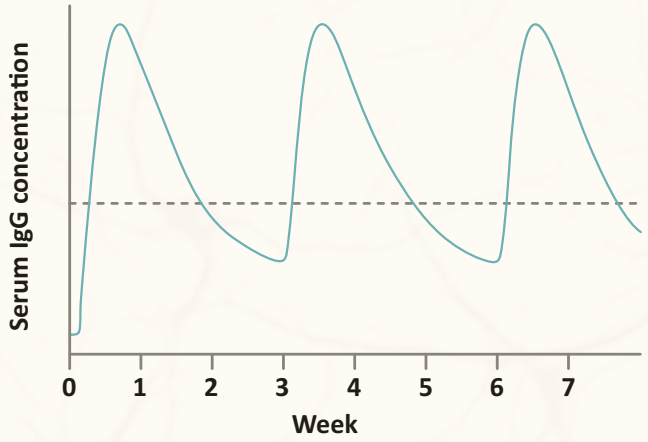
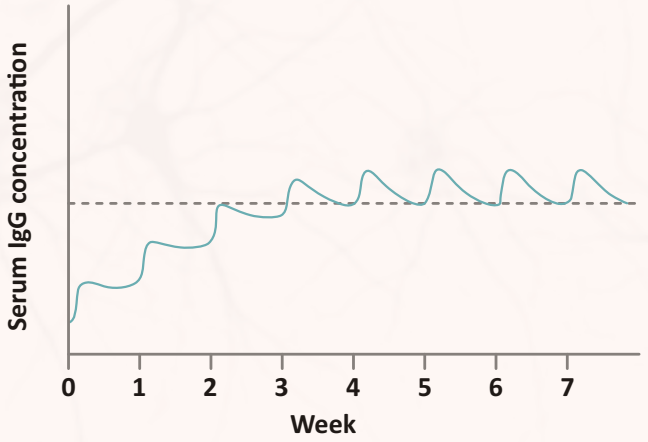
Figure 9. IVIg administration protocol in CIDP[36]

The efficacy of IVIg and SCIg is comparable in CIDP, but SCIg may offer some safety and quality of life advantages to some patients. The differences in pharmacokinetic profile and infusion regimens account for many of the differences between IVIg and SCIg.

Ig has a half-life between 21 and 30 days so typically IVIg infusions are initiated with 3–4-week intervals. However, Ig concentration declines rapidly over the next 48–72 h as it disperses into the extracellular volume. Therefore, IVIg is administered as a large bolus every 3–4 weeks intervals resulting in cyclic fluctuations in Ig concentration that have been linked to systemic adverse events (AEs) (potentially caused by high Ig levels) and end of dose "wear-off" effects (potentially caused by low Ig concentration).

SCIg is administered as a smaller weekly, or twice weekly doses, which better maintains Ig concentration between doses, resulting in narrower peak-to-trough serum levels and a near steady-state Ig levels that have been linked to continuously maintained function and reduced systemic AEs, but an increase in local reactions at the infusion site.

Table 7 details the difference between IVIg and SCIg in terms of infusion practicalities, safety profile and recommended criteria for selecting patients receiving IVIg or SCIg.

	IVIg	SCIg
Hypothetical serum Ig concentration following IVIg (every 3 weeks) and SCIg (weekly) infusions		
INFUSION PRACTICALITIES		
Induction/Loading dose	2 g/kg bw divided over 2–5 consecutive days	N/A—SCIg not approved for induction therapy
Maintenance dose	1 g/kg bw in 1–2 infusions over consecutive days	0.2–0.4 g/kg bw in 1–2 infusions
Infusion duration	3–5 h	1–1.5 h
Infusion frequency	Typically, 3–4 weeks	Typically, weekly
Infusion rate	0.3 mL/kg per hour for initial infusion, increasing up to ≤ 4.8 mL/kg per hour, as tolerated	≤ 20 mL/site per hour for initial infusion, increasing up to ≤ 50 mL/site per hour, as tolerated (≤ 8 sites simultaneously, typically 2–4 sites used)
Onset of action	1–2 weeks	4 weeks
Setting	Home, hospital, or infusion clinic	Home, school, work (or other convenient location)
HCP required	Yes	Typically, no

	IVIg	SCIg
TYPICAL SAFETY PROFILE		
Systemic Aes	Yes	Less frequent
Local Aes	Rarely	Yes
Premedication	Yes	Rarely
Venous access	Yes	No
Ig levels	Troughs and peaks	Stable—approaching steady-state
Wear-off effects	Can occur between doses	Rarely due to more frequent infusion
PATIENTS WHO MAY BE MORE SUITABLE TO RECEIVE IVIG OR SCIG		
Patients who may be more suitable to receive IVIg or SCIg	Patients lacking skill, confidence or drive to learn self-administration, including limitations in some elderly patients Patients whose compliance for self-administration is in question Patients with poor dexterity and lacking a reliable support network Patients preferring a clinic setting and/or treatment administered by an HCP Patients preferring more infrequent infusions Patients with excessive bruising and subcutaneous bleeding tendency	Patients with poor venous access or those where a port is being considered Patients experiencing intolerable side effects with IVIg infusions Patients experiencing treatment-related fluctuations between IVIg infusions Patients wanting more autonomy, freedom, or flexibility with their infusion location/schedule Patients preferring shorter, more frequent infusions Patients with comorbidities putting them at higher risk of severe Aes

Table 7. IVIg versus SCIg for management of CIDP

Corticosteroids in management of CIDP

Corticosteroids are efficacious in management of CIDP, and are easy to administer, cheap, and may lead to long-term remission in CIDP more often compared to IVIg. However, there are safety concerns associated with long-term treatment with corticosteroids.

Corticosteroids can be given as daily oral doses or in pulses during a relatively short period of time. A randomized controlled trial (RCT) of 41 patients (The PREDICT study) compared daily oral prednisolone with monthly pulse oral dexamethasone showed no difference in the primary outcome (remission without treatment at 12 months) or in any of multiple secondary outcomes, which included strength, sensory and quality of life measures.[44] The study showed pulsed monthly dexamethasone was significantly quicker in resulting in improvement (median time of 17 weeks vs 39 weeks) compared to daily oral prednisolone. Daily oral prednisolone also had more side-effect profile, including insomnia, cushingoid facies, as well as marked weight gain.[37]

Corticosteroids lead to improvement in 60% of patients and to remission in 61% of treatment responders.[38] CIDP patients treated with corticosteroids has been shown to achieve higher remission rate or longer treatment free remission period compared to those treated with IVIg. Therefore, this advantage justifies the use of corticosteroids in CIDP as first-line treatment over IVIg in selected subgroups of patients without contraindications.

Therapeutic plasma exchange in management of CIDP

Therapeutic plasma exchange (TPE), also called plasmapheresis separates and removes plasma from blood, eliminates pathological substances of high molecular weight such as antibodies and antigen–antibody complexes. It takes several hours and is usually repeated about five times over two weeks. Evidence shows that TPE improves outcome in CIDP rapidly, at least for short-term, however at the cost of subsequent re-deterioration in majority of the patients within the following 8 weeks. Therefore, following TPE, concurrent therapy is needed, frequently corticosteroids, to prevent relapse.

The important advantage of TPE over IVIg and corticosteroids is in some refractory cases of CIDP, especially those with unknown pathogenic antibodies and among those with autoimmune nodopathy.

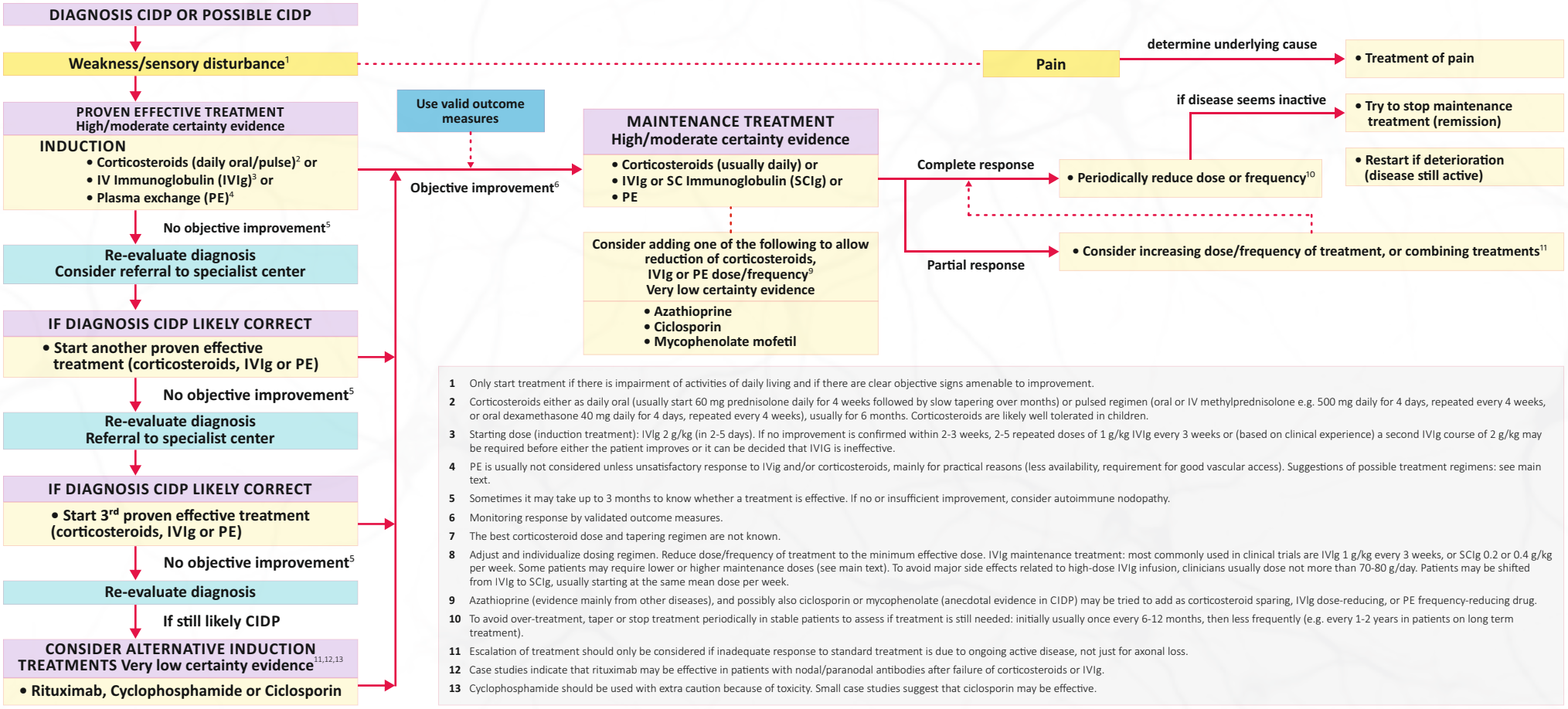
The usefulness of TPE is limited by its inconvenience, requirement for hospital attendance and specially trained staff, and the occurrence of AEs such as blood stream infection. These limitations may be improved using peripheral venous catheter which has been shown to be a safe and efficient alternative.

Immunosuppressant in management of CIDP

The evidence of immunosuppressant agents for CIDP is very limited. Available RCTs shows insufficient benefit to use azathioprine, interferon β-1a, methotrexate, cyclosporin, mycophenolate mofetil and fingolimod in the treatment of CIDP. Worth mentioning are cyclophosphamide and rituximab. Cyclophosphamide has been successful used to treat some of the refractory CIDP with high complete remission rate of up to 73.3% in case series-based evidence. Similarly, Rituximab, has also been found to be effective in refractory CIDP and in patients with autoimmune nodopathy.

Novel agents in CIDP

Neonatal Fc receptor (FcRn) blockers, complement pathway inhibitors and Bruton tyrosine kinase (BTK) have been under investigation for treatment in CIDP. A recent study on the use of Efgartigimod, a humanized IgG1 Fc fragment blocking the FcRn, has demonstrated significant reduction in risk of CIDP relapse compared to placebo. FcRn blockers work by reducing binding of pathogenic antibodies to the FcRn, subsequently reduces the protective effect of the FcRn on these antibodies from lysosomal degradation, and hence reducing auto-antibody serum life-span and it's pathogenic effects.[40] Other novel agents are currently still under investigations. Figure 10 shows the overview of comprehensive approach for management of CIDP.



1 Only start treatment if there is impairment of activities of daily living and if there are clear objective signs amenable to improvement.

2 Corticosteroids either as daily oral (usually start 60 mg prednisolone daily for 4 weeks followed by slow tapering over months) or pulsed regimen (oral or IV methylprednisolone e.g. 500 mg daily for 4 days, repeated every 4 weeks, or oral dexamethasone 40 mg daily for 4 days, repeated every 4 weeks), usually for 6 months. Corticosteroids are likely well tolerated in children.

3 Starting dose (induction treatment): IVIg 2 g/kg (in 2-5 days). If no improvement is confirmed within 2-3 weeks, 2-5 repeated doses of 1 g/kg IVIg every 3 weeks or (based on clinical experience) a second IVIg course of 2 g/kg may be required before either the patient improves or it can be decided that IVIG is ineffective.

4 PE is usually not considered unless unsatisfactory response to IVig and/or corticosteroids, mainly for practical reasons (less availability, requirement for good vascular access). Suggestions of possible treatment regimens: see main text.

5 Sometimes it may take up to 3 months to know whether a treatment is effective. If no or insufficient improvement, consider autoimmune nodopathy.

6 Monitoring response by validated outcome measures.

7 The best corticosteroid dose and tapering regimen are not known.

8 Adjust and individualize dosing regimen. Reduce dose/frequency of treatment to the minimum effective dose. IVIg maintenance treatment: most commonly used in clinical trials are IVIg 1 g/kg every 3 weeks, or SCIg 0.2 or 0.4 g/kg per week. Some patients may require lower or higher maintenance doses (see main text). To avoid major side effects related to high-dose IVIg infusion, clinicians usually dose not more than 70-80 g/day. Patients may be shifted from IVIg to SCIg, usually starting at the same mean dose per week.

9 Azathioprine (evidence mainly from other diseases), and possibly also ciclosporin or mycophenolate (anecdotal evidence in CIDP) may be tried to add as corticosteroid sparing, IVIg dose-reducing, or PE frequency-reducing drug.

10 To avoid over-treatment, taper or stop treatment periodically in stable patients to assess if treatment is still needed: initially usually once every 6-12 months, then less frequently (e.g. every 1-2 years in patients on long term treatment).

11 Escalation of treatment should only be considered if inadequate response to standard treatment is due to ongoing active disease, not just for axonal loss.

12 Case studies indicate that rituximab may be effective in patients with nodal/paranodal antibodies after failure of corticosteroids or IVIg.

13 Cyclophosphamide should be used with extra caution because of toxicity. Small case studies suggest that ciclosporin may be effective.

Figure 10. Overview of comprehensive approach for management of CIDP[20]

Chapter V: Prognosis and outcome of CIDP

CIDP can lead to significant disability and may impact work productivity, emotional well-being, social interactions, and family life. The pooled rate of CIDP remission is only 40.8%.[41] Almost 39% of patients require immune treatments in the long term and 13% develop severe disabilities.[18] A Japanese epidemiological survey showed that nearly 14% of CIDP patients were unresponsive to first-line treatments with 18% of patients were unable to walk independently at their last visit.[42]

Typical CIDP patients have the most severe disability prior to treatment, with 44% unable to walk independently.[42] **Duration of symptom onset, distribution of symptoms, and electrophysiological characteristics** are the prognostic factors for predicting a favorable outcome in CIDP.[43] The study found that younger age at onset, absence of muscle atrophy, and abnormal median-normal sural sensory nerve responses were associated with a higher likelihood of independent walking. Fewer distal CIDP and multifocal CIDP patients progress to typical CIDP than pure motor and sensory CIDP, although pure sensory CIDP patients progressed to typical CIDP faster than pure motor CIDP patients.[44]

Chapter VI: Conclusion

- Diagnosing and treating CIDP is complex with a great challenge.
- A comprehensive approach to diagnosis, including clinical presentation, electrophysiology, CSF studies, and imaging, is crucial.
- Adhering to CIDP guideline criteria minimizes the misdiagnosis probabilities.
- The first line therapeutic options for CIDP, including corticosteroids, IVIg/SCIg, and plasmapheresis are effective in 80% of the cases.
- Always re-evaluate the diagnosis if the cases are not responsive to the first-line treatment.
- Evidence-based therapeutic options are crucial, but personalized medicine approach is needed, considering varied treatment responses and individual risk-benefit assessment.
- A multidisciplinary approach involving neurologists, physiotherapists, occupational therapists, and other healthcare professionals is important in providing comprehensive care to CIDP patients.
- Regular monitoring with objective outcome measures, treatment optimization, patient education, and shared decision-making are essential elements in achieving optimal CIDP management and improving patient outcomes.

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