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Περίληψη

Η Χρόνια Φλεγμονώδης Απομυελινωτική Πολυνευροπάθεια αποτελεί μια χρόνια, ανοσοδιαμεσολαβούμενη διαταραχή του περιφερικού νευρικού συστήματος. Παρά την πρόοδο στα διαγνωστικά κριτήρια, η CIDP παρουσιάζει σημαντικές προκλήσεις λόγω της κλινικής της ετερογένειας και της επικάλυψης με πολλές μιμητικές καταστάσεις, όπως οι αυτοάνοσες κομβοπάθειες, οι παραπρωτεϊναιμικές νευροπάθειες και οι κληρονομικές διαταραχές. Αυτή η συστηματική ανασκόπηση περιγράφει την κλινική προσέγγιση στη νόσο, με έμφαση στους διαφορετικούς της φαινοτύπους, τα διαγνωστικά κριτήρια, τις υποστηρικτικές εξετάσεις και τη διαφορική διάγνωση. Οι ηλεκτροφυσιολογικές μελέτες, η ανάλυση του εγκεφαλονωτιαίου υγρού, η απεικόνιση και οι αιματολικές εξετάσεις προσεγγίζονται στο πλαίσιο της διαγνωστικής τους αξίας και των περιορισμών τους. Δίνεται έμφαση στην αναγνώριση παγίδων, όπως η υπερβολική εξάρτηση από μη ειδικά ευρήματα και η λανθασμένη ερμηνεία αποτελεσμάτων. Μέσω της ολοκληρωμένης ανάλυσης κλινικών, ηλεκτροφυσιολογικών και υποστηρικτικών δεδομένων, οι κλινικοί γιατροί μπορούν να διακρίνουν με ακρίβεια τη νόσο από τους πιθανούς μιμητές και να διασφαλίσουν την έγκαιρη διάγνωση της . Αυτή η ανασκόπηση στοχεύει στην παροχή ενός δομημένου πλαισίου για τη βελτιστοποίηση της διάγνωσης και της προσέγγισης αυτής της περίπλοκης διαταραχής.

Λέξεις-κλειδιά: χρόνια φλεγμονώδης απομυελινωτική πολυνευροπάθεια, κλινικά κριτήρια, διαφορική διάγνωση, ηλεκτροφυσιολογικός έλεγχος, περιφερική νευροπάθεια

CONTEMPORARY CLINICAL APPROACH AND DIAGNOSTIC PITFALLS IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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ABSTRACT

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a chronic, immune-mediated disorder of the peripheral nervous system. Despite advancements in diagnostic criteria, CIDP presents significant challenges due to its clinical heterogeneity and overlap with numerous mimicking conditions, including autoimmune nodopathies, paraproteinemic neuropathies, and hereditary disorders. This review outlines the clinical approach to CIDP, focusing on its diverse phenotypes, diagnostic criteria, supportive investigations, and differential diagnosis. Electrodiagnostic studies, cerebrospinal fluid analysis, imaging, and serologic testing are discussed in the context of their diagnostic value and limitations. Emphasis is placed on identifying

pitfalls, such as overreliance on nonspecific findings and misinterpretation of test results. By integrating clinical, electrophysiological, and ancillary data, clinicians can accurately distinguish CIDP from mimics and ensure timely intervention. This review aims to provide a structured framework to optimise diagnosis and management in this complex condition.

Keywords: chronic inflammatory demyelinating polyneuropathy (CIDP), Clinical criteria, differential diagnosis, electrodiagnostic studies, peripheral neuropathy

INTRODUCTION

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is characterised as a rare, autoimmune-based peripheral nerve disorder that is amenable to treatment.[1] The reported incidence of CIDP is about 1 per 100,000 in general population and can ascend to 20% in patients older than 60 years of age.[2,3] Characterised by progressive or relapsing-remitting motor and sensory dysfunction, CIDP encompasses a broad spectrum of clinical manifestations and phenotypic variants, necessitating a nuanced diagnostic approach.[4] The underlying pathophysiology involves immune-mediated attacks on the myelin sheath, resulting in demyelination, axonal damage, and subsequent disability if left untreated.[5] Early diagnosis and intervention are critical to preventing irreversible nerve damage and functional decline.[6]

Since the original description of CIDP in the 1970s, over 15 sets of diagnostic criteria have been proposed.[7] The criteria published in 2021 by the European Academy of Neurology / Peripheral Nerve Society (EAN/PNS) were developed for use during routine clinical care and are available in the public domain.[6] These criteria provide clinicians with an invaluable resource by which the data collected during the evaluation of the patient with possible CIDP can be interpreted.[6] However, numerous mimics—ranging from autoimmune nodopathies and paraproteinemic neuropathies to genetic and systemic disorders—complicate the differentiation of CIDP from alternative diagnoses.[8] In addition, CIDP variants and atypical presentations further obscure the diagnostic landscape, underscoring the importance of an individualised and systematic approach.[9] This review provides a comprehensive exploration of the diagnostic framework for CIDP, including its clinical characteristics, electrodiagnostic features, and supportive investigations. Emphasis is placed on diagnostic pitfalls and the importance of distinguishing CIDP from its numerous mimics through a structured differential diagnosis. By synthesising current evidence, this review aims to offer clinicians practical insights into optimising diagnostic accuracy and ensuring appropriate management for patients with suspected CIDP.

CLINICAL PHENOTYPES

CIDP is a heterogeneous disorder with a wide spectrum of clinical presentations.[10] The most recent classification divides CIDP into three categories: typical CIDP, CIDP variants, and autoimmune nodopathies.[11]

Typical CIDP

Typical CIDP is characterised by a symmetrical, sensory, and motor polyradiculoneuropathy with combined proximal and distal weakness, areflexia, and minimal associated pain.[11,12] It accounts for 50% to 60% of all cases.[11,12] Distal motor deficits tend to be more pronounced, while sensory deficits predominantly involve large fibers due to their extensive myelination.[13,14] Cranial nerve and bulbar involvement are observed in approximately 10% to 20% of patients with CIDP.[15] These manifestations can contribute to significant functional impairment and complicate the clinical presentation.[15] Additionally, tremor has been identified as a prevalent symptom in multiple studies, further highlighting the variability in CIDP presentations and the importance of comprehensive neurological assessment.[16] Autonomic involvement in these patients is generally mild and localised, with symptoms such as constipation and urinary retention typically emerging only in more advanced stages of the disease.[17] The majority of patients with typical CIDP experience a **slowly progressive course**, although a **relapsing-remitting pattern** is observed in at least one-third of cases.[18] This relapsing-remitting presentation appears to be more common in younger individuals, underscoring the variability in disease progression across different age groups.[18] Symptoms that persist for more than eight weeks define the chronic nature of the condition.[19] Any presentation deviating from this pattern warrants consideration of alternative aetiologies or atypical forms of CIDP.[19] For instance, pure large-fibre sensory neuropathy with ataxia may indicate disease mimickers, distinct entities, or chronic immune sensory polyneuropathy (CISP).[19] Multifocal, asymmetric, or upper-limb-predominant involvement raises the suspicion of multifocal CIDP.[20] Typical CIDP rarely involves systemic symptoms such as fever, malaise, severe pain, or dysautonomia.[17] Patients with typical CIDP generally exhibit a favourable response to immunomodulatory therapies, including intravenous immunoglobulin (IVIG), subcutaneous immunoglobulin (SCIg), corticosteroids, and plasmapheresis.[21] However, individual responses

may vary, emphasising the importance of monitoring treatment outcomes and tailoring therapy to each patient's clinical course.

CIDP Variants

Pure Motor CIDP

Pure motor CIDP, which constitutes 4%-10% of cases mimics typical CIDP but with preserved sensation even on sensory conduction studies.[11] This preservation of sensation is a common clinical and electrophysiological feature in multifocal motor neuropathy (MMN). In MMN, however, conduction velocity away from the site of the block may remain normal, at least at the early stages.[21] Moreover, in the latter condition, weakness is typically focal in the distribution of individual nerves rather in the distribution of limbs.[22] The term motor-predominant CIDP is utilised, if sensory conduction studies show abnormalities.[23] While earlier reports suggested that some patients with CIDP might experience worsening symptoms with corticosteroid treatment, more recent studies have not substantiated these findings.[23] Current evidence indicates that most patients respond favourably to both intravenous immunoglobulin (**IVIG)** and **steroid therapy**, highlighting their effectiveness as key treatment modalities in CIDP management.[23]

Pure Sensory CIDP

Pure sensory CIDP accounts for about 35% of CIDP cases,[11,24] and is characterised by impaired vibration and joint position sense, along with gait ataxia, while muscle strength remains intact.[11,24] If motor conduction abnormalities are noted, the term sensory-predominant CIDP is applied.[6] Research suggests that sensory CIDP often represents a transient stage that precedes weakness in 70% of cases.[6] The condition primarily affects large myelinated fibers, which are responsible for proprioception and fine touch, while sparing the small unmyelinated fibers associated with pain and temperature sensation. As a result, patients with sensory CIDP typically do not experience pain or disturbances in thermal perception.[6] In sensory CIDP, the response to standard immunomodulatory treatments, such as IVIG and corticosteroids, is also favourable in most cases.[5,10] However, treatment efficacy may vary depending on the stage of the disease, particularly in cases where sensory dysfunction precedes motor involvement.[5,10]

Distal Acquired Demyelinating Symmetric (DADS) Neuropathy

DADS neuropathy involves distal sensory loss in all four limbs, often accompanied by gait disturbances.[4,11] Distal weakness may also occur, primarily in the lower limbs, but without proximal involvement.[25] It constitutes 2%–17% of all CIDP cases and typically progresses slowly, with high-amplitude, low-frequency tremors being a common feature.[26] Two-thirds of DADS cases are associated with immunoglobulin M (IgM) paraproteinemia, and within this subgroup, most individuals have anti-myelin-associated glycoprotein (MAG) antibodies.[27] This differentiation is particularly relevant when anti-MAG antibodies are present, as this subtype of DADS is generally recognised as a separate entity from CIDP.[13] Moreover, it demonstrates limited responsiveness to the standard immunomodulatory treatments commonly employed for CIDP and may exhibit favourable response to rituximab.[6]

Asymmetric sensorimotor (multifocal) CIDP

Asymmetric sensorimotor (multifocal) CIDP, which accounts for 6%–15% of cases, is also referred to as multifocal demyelinating neuropathy with persistent conduction block (Lewis-Sumner syndrome) or multifocal acquired demyelinating sensory and motor neuropathy (MADSAM).[19,24] Patients with multifocal CIDP typically present with a distinctly asymmetric and multifocal clinical picture that is often indistinguishable from other forms of mononeuropathy multiplex.[19,24] This pattern results in a combination of sensory and motor signs confined to the distributions of individual nerves.[6,28,29] Symptoms can originate in any nerve distribution, varying significantly among patients.[6,28,29] In addition to motor and sensory deficits, some individuals may experience autonomic symptoms, neuropathic pain, or cranial nerve involvement.[6,28,29] Rarely, multifocal CIDP presents as a **focal form**, where symptoms are restricted to a single limb or nerve.[6,28,29] These focal presentations pose a diagnostic challenge due to their limited distribution and overlap with other focal neuropathies.[6,28,29] Asymmetric sensorimotor CIDP typically responds well to IVIG, with some patients requiring adjunctive therapies like corticosteroids or plasmapheresis for adequate symptom control.

Focal CIDP

Focal CIDP, a rare form representing 1% of cases, affects the brachial or lumbosacral plexus or individual nerves.[11] It is often considered a localised form of MADSAM.[6] The majority of patients with **focal forms of CIDP** demonstrate a favourable response to **IVIG** therapy.[30]

Disorders not Classified as CIDP by European Academy of Neurology/Peripheral Nerve Society Task Force

Chronic Inflammatory Sensory Polyradiculopathy (CISP) and CISP plus

CISP constitutes 5%–12% of CIDP cases and is

regarded as a pure sensory form of CIDP, with preganglionic nerve root involvement.[6] This feature results in normal sensory conduction studies due to the integrity of postganglionic fibres.[6] Somatosensory evoked potentials (SSEPs) often reveal slowing of responses, particularly at N13 latencies or N9–N13 interpeak latencies.[6] If motor fibers are also affected at proximal sites, neurophysiology is expected to reveal conduction block at plexus and root level, absence of F-waves with normal motor conduction at distal and intermediate segments.[31] Elevated cerebrospinal fluid (CSF) protein is observed in 92% of cases, and MRI frequently shows spinal root enhancement.[30,32]

Autoimmune Nodopathies

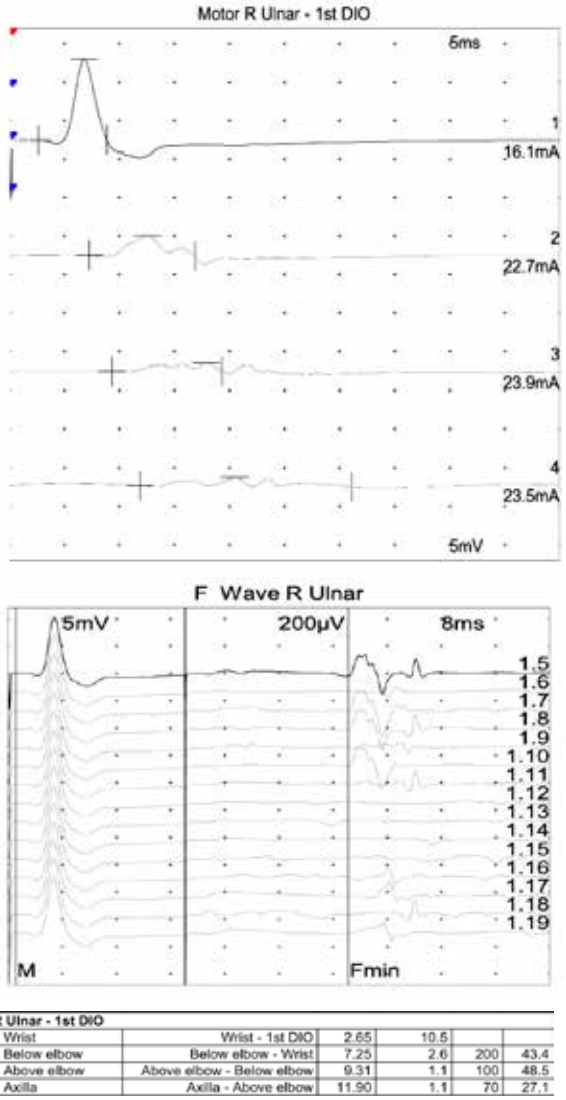
Autoimmune nodopathies are the most recently described CIDP mimics, involving autoantibodies targeting specific molecules within the nodes of Ranvier.[6] Identified antibodies include those against neurofascin 155 (NF155), neurofascin 186 (NF186), contactin 1 (CNTN1), and contactin-associated protein 1 (CASPR1).[6,33,34] These autoantibodies, predominantly immunoglobulin G4, do not activate complement or bind to immunoglobulin receptors, which may explain the poor response to IVIg emphasising the need for alternative therapeutic approaches (**Figure 2**).[5] Clinical features vary depending on the antibody subtype.[5] Anti-NF155 antibodies are associated with distal weakness and low-frequency, high-amplitude tremors, whereas anti-CNTN1 antibodies can present with acute to subacute severe weakness, tremors, and glomerulonephritis.[33,35–37] In contrast, anti-CASPR1 or anti-CNTN1/CASPR1 complex antibodies often resemble Guillain-Barré syndrome, with acute presentation and cranial nerve involvement.[38–40] Neuropathic pain is common across these conditions.[38–40] Physiologically, nodal and paranodal disorders may exhibit conduction changes similar to those observed in CIDP.[6] However, from a pathological perspective, **autoimmune nodopathies** are not definitively classified as demyelinating conditions.[6]

Diagnostic Criteria

The diagnosis of CIDP is established through a combination of clinical and electrodiagnostic criteria, as outlined in the 2021 European Academy of Neurology (EAN) and Peripheral Nerve Society (PNS) guidelines.[6]

Electrodiagnostic Criteria

Electrodiagnostic testing is a cornerstone in confirming the clinical diagnosis of CIDP, with the 2021 EAN/PNS guidelines emphasising motor nerve conduction findings as critical diagnostic markers.[6] Nerve conduction studies (NCS) are pivotal for identifying electrophysiological signs of peripheral nerve demyelination, including prolonged motor distal latencies, reduced motor conduction velocities, motor conduction block, temporal dispersion, and prolonged or absent F-waves (**Figure 1**).[6,41,42] Sensory responses are frequently diminished or entirely absent in both the upper and lower limbs, further aiding diagnosis.[6,41,42] However, accurately interpreting "demyelinating" findings on NCS can be challenging.[6,41,42] Electrodiagnostic guidelines are indispensable for addressing ambiguities encountered during routine



R Ulnar - 1st DIO					
Wrist	Wrist - 1st DIO	2.65	10.5		
Below elbow	Below elbow - Wrist	7.25	2.6	200	43.4
Above elbow	Above elbow - Below elbow	9.31	1.1	100	48.5
Axilla	Axilla - Above elbow	11.90	1.1	70	27.1

Figure 1. Motor conduction study of the right ulnar nerve in a 19-year-old female patient newly diagnosed with CIDP. The study revealed normal distal latency (2.65 ms) but showed evidence of conduction block in the Below Elbow–Wrist segment, indicated by a 75% drop in the amplitude of the CMAP and mild slowing of the motor conduction velocity (44m/sec). Additionally, significant slowing of motor conduction velocity was observed in the Axilla–Above Elbow segment (27m/sec). A prolonged minimal F-wave latency of 50.3 ms, consistent with demyelination, was also noted.
CIDP: chronic inflammatory demyelinating polyneuropathy; CMAP: compound muscle action potential.

evaluations.[6,41,42] If electrophysiological evidence of demyelination is absent, clinicians must explore alternative diagnoses.[6]

Several factors can complicate the interpretation of NCS in CIDP. Reduced compound muscle action potential amplitudes may lead to a loss of faster-conducting fibers, necessitating a significantly slower conduction velocity to confirm true demyelination.[43] Additionally, low limb temperatures (<30°C for lower limbs, <32°C for upper limbs) can artificially prolong distal latencies and slow conduction velocities, potentially mimicking demyelination.[6,41] However, distinguishing CIDP from conditions like POEMS syndrome can be particularly difficult, as their electrodiagnostic features often overlap.[44] This underscores the importance of integrating clinical, electrophysiological, and laboratory findings to ensure accurate diagnosis.

Supportive Criteria

Cerebrospinal Fluid

A hallmark finding in CIDP is **albuminocytologic dissociation**, characterised by elevated CSF protein levels alongside normal leukocyte counts (<10 cells/μL).[7] This finding has a sensitivity of 50%-77%.[7] Mild protein elevations may also occur in individuals with diabetes, and protein levels tend to increase with age, with a cutoff of 0.6 g/L applied for individuals over 50 years.[45] Leukocyte counts exceeding 50 cells/μL should prompt evaluation for alternative diagnoses, such as malignancy or infection.[46]

Serologic Testing

Comprehensive screening for serum monoclonal proteins using **serum protein electrophoresis** and **immunofixation** is recommended for all patients suspected of having CIDP.[6] Specific tests for **anti-MAG antibodies** and **nodal/paranodal antibodies** (e.g., anti-NF155, anti-CNTN1) provide both diagnostic clarity and prognostic insights.[47,48] Additionally, elevated levels of **vascular endothelial growth factor (VEGF)** can be indicative of Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes Syndrome. Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes **(POEMS) syndrome**, particularly in cases involving painful distal neuropathy, helping to differentiate it from CIDP.[49]

Nerve Biopsy

Nerve biopsy is reserved for instances where diagnostic uncertainty persists despite other evaluations.[6] To reduce the risk of complications, biopsies should be performed on severely affected nerves.[50] Histopathological hallmark findings include **thinly myelinated axons, small onion bulbs, demyelinated internodes,** and **perivascular macrophage clusters**, which are characteristic of CIDP.[50]

Imaging

Imaging studies can provide valuable insights into CIDP. Magnetic resonance imaging (MRI) often reveals nerve hypertrophy and gadolinium enhancement in the brachial or lumbosacral plexuses, aiding in the assessment of proximal nerve involvement.[6,51] MRI is typically reserved for **atypical cases**, particularly when clinical and electrophysiological findings suggest a focal pattern, such as in **multifocal CIDP**, or when alternative causes of neuropathy and infiltrative pathologies need to be excluded.[52] Studies employing various MRI techniques, most notably brachial plexus MRI, have reported nerve **enlargement or enhancement** in approximately 40% to 80% of patients with CIDP.[6,51,52] Ultrasound is a useful adjunct for evaluating diagnostic uncertainties.[6] However, findings such as nerve hypertrophy are not specific to CIDP and may also appear in conditions like hereditary neuropathies, lymphoma, sarcoidosis, or infections.[6,53]

Response to Treatment

Diagnostic confirmation can be supported by a significant therapeutic response to treatments like IVIg, plasmapheresis, or corticosteroids.[6,25] Improvements measured on scales such as the **Inflammatory Neuropathy Cause and Treatment (INCAT)** disability scale or the **Medical Research Council (MRC)** sum score lend additional evidence.[54] Patient-reported outcomes assessed through the **Inflammatory Rasch-Built Overall Disability Scale (I-RODS)** may further substantiate the diagnosis.[54] As showed in ICE study, assessing hand grip strength by dynamometer is a quick and sensitive estimate for monitoring CIDP patients.[55]

Additional Testing

Somatosensory evoked potentials (SSEPs) are particularly useful in diagnosing pure sensory CIDP, especially when standard electrodiagnostic criteria are not met.[6,56] Studies suggest that SSEPs can detect nerve root involvement in up to 100% of individuals with **chronic immune sensory polyradiculopathy (CISP)** who fail to meet conventional CIDP criteria.[6,56] These findings expand the diagnostic toolkit for evaluating atypical CIDP presentations.[6,56]

Diagnostic Pitfalls in CIDP

Despite the availability of established diagnostic criteria, the process for CIDP diagnosis is fraught with challenges that can lead to misdiagnosis.[6] Awareness of these obstacles is essential to avoid errors and ensure accurate identification of the condition.[6] A study by Allen et al highlighted this issue, reporting that nearly half (47%) of 59 patients referred with a presumptive diagnosis of CIDP ultimately failed to meet the clinical and electrodiagnostic (EDx) criteria.[57] The primary sources of diagnostic errors included

overinterpretation of minor nerve conduction abnormalities as demyelination, trivial elevations in CSF protein, and reliance on subjective reports of improvement following treatment rather than objective measures.[57]

CIDP is recognised as a syndrome encompassing a **"typical" phenotype** and multiple variants.[6] While motor and sensory deficits are the hallmark features across all forms of CIDP, other symptoms such as fatigue and distal extremity pain are frequently reported.[58,59] Fatigue often persists throughout all stages of the disease, even when it is no longer immunologically active.[58] Pain, commonly affecting one-third or more of patients, tends to be localised to the distal limbs.[59] Less commonly, tremor (affecting up to 50% of patients), mild autonomic dysfunction (25%), and cranial nerve involvement (5% to 20%, primarily involving the facial nerve) are observed.[15,17,60] While these symptoms are crucial for management, reliance on nonspecific features like pain or fatigue in the absence of characteristic patterns of numbness or weakness conforming to known CIDP variants may lead to misdiagnosis.[6]

The diagnostic complexity increases with **CIDP variants**. Typical CIDP, characterised by symmetric proximal and distal neuropathy progressing over at least two months, is generally easier to diagnose when supported by electrophysiological evidence of demyelination and the exclusion of other conditions such as paraproteinemia or genetic abnormalities.[56,61] In contrast, CIDP variants often mimic other disorders: **distal CIDP** may resemble length-dependent axonal neuropathies or genetic conditions, **multifocal CIDP** can be confused with mononeuropathy multiplex caused by inflammatory, traumatic, or genetic factors, **motor CIDP** may be mistaken for multifocal motor neuropathy or motor neuron diseases, and **sensory CIDP** may be misdiagnosed as various neuropathic or non-neuropathic disorders that affect skin sensation.[56,61]

Electrodiagnostic testing, a cornerstone of CIDP diagnosis, may also pose interpretive challenges.[22,41] Demyelinating features identified in **NCS** can be misinterpreted in several scenarios.[22,41] For example, amplitude-dependent slowing caused by the loss of fast-conducting fibers in axonal neuropathies, focal slowing at compressible sites, or amplitude-independent slowing in diabetic patients can mimic demyelination.[22,41] Clinicians should interpret prolonged distal latencies, reduced conduction velocities, or proximal amplitude reductions cautiously, particularly in cases with very low motor response amplitudes (<1 mV).[22,41] Fibular nerve recordings targeting the extensor digitorum brevis (EDB) muscle are especially prone to errors.[22,41] Additionally, failure to account for limb temperature—where lower limits are 30°C for lower limbs and 33°C for upper limbs—can artificially prolong distal latencies or slow conduction velocities, mimicking demyelination.[22,41] Overlooked anatomical variations, such as Martin-Gruber anastomoses, or improper stimulation techniques may further contribute to misinterpretations.[22,41]. To minimise these pitfalls, clinicians must thoroughly examine waveform quality and adhere to standardised procedural protocols, ensuring accurate and reliable diagnostic findings.[22,41] Therefore, the **EAN/PNS CIDP diagnostic guidelines** provide a comprehensive framework for differential diagnosis, which is essential for accurately distinguishing between CIDP and its variants (**Figure 2**).[6]

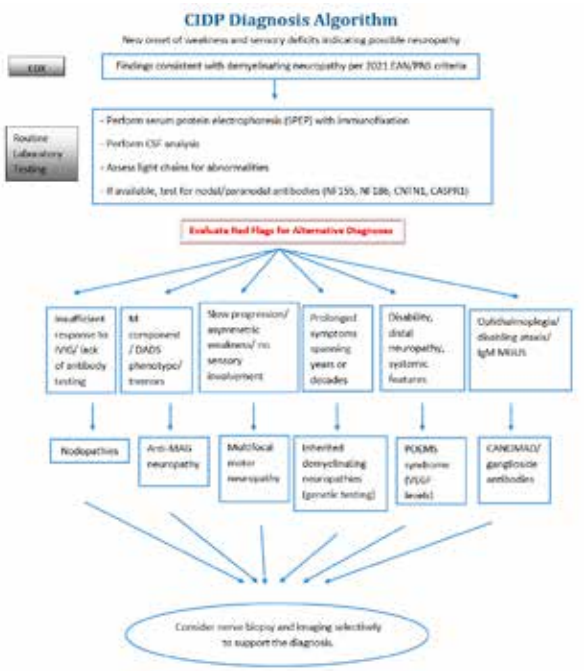


Figure 2. Diagnostic flowchart for chronic inflammatory demyelinating polyneuropathy (CIDP) diagnoses. **ab: antibody;** CANOMAD: chronic ataxic neuropathy with ophthalmoplegia: IgM paraprotein: cold agglutinins: and disialosyl antibodies; CASPR1: contactin-associated protein 1; CNTN1: contactin 1; DADS: distal acquired demyelinating symmetric neuropathy; EAN/PNS: European Academy of Neurology/Peripheral Nerve Society; EDX: electrodiagnostic studies; IgM: immunoglobulin M; IVIg: IV immunoglobulin; MAG: myelin-associated glycoprotein; MMN: multifocal motor neuropathy; MGUS: monoclonal gammopathy of undetermined significance; NF155: neurofascin 155; NF186: neurofascin 186; POEMS: polyneuropathy: organomegaly: endocrinopathy: monoclonal gammopathy: and skin changes; SPEP: serum protein electrophoresis; VEGF: vascular endothelial growth factor.

DIFFERENTIAL DIAGNOSIS IN CIDP

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) and Related Conditions

CIDP is a chronic disorder characterised by progression beyond eight weeks.[11,62] When symptoms reach

their nadir within four weeks of onset, Guillain-Barré syndrome (GBS) should be considered.[63] However, distinguishing between CIDP and GBS can be complicated by treatment-related fluctuations in GBS, which may resemble CIDP.[63]

A specific diagnostic challenge arises with **acute-onset CIDP (A-CIDP)**, a form that begins acutely but continues to progress beyond four to eight weeks and is characterised by at least three relapses within nine weeks.[63] While A-CIDP is not considered phenotypically atypical in terms of clinical and EDx features, its rapid onset sets it apart.[63] Early recognition is critical, as A-CIDP requires ongoing immunotherapy. Key features distinguishing A-CIDP from GBS include its milder severity, rare cranial nerve involvement, and the absence of a need for mechanical ventilation.[63] Moreover, A-CIDP typically exhibits classic CIDP demyelinating features on EDx, which are not seen early in GBS.[63]

Less frequently, CIDP may present as **subacute inflammatory demyelinating polyneuropathy (SIDP)**, characterised by a monophasic course with symptoms peaking within four to eight weeks.[64] Patients presenting with subacute-onset neuropathy accompanied by tremor, ataxia, and distal weakness should be evaluated for CIDP variants, particularly **nodopathies.**[65] Lastly, it is important to differentiate **treatment-related worsening** in CIDP from treatment-refractory disease.[66] Worsening may result from the waning effects of therapy rather than true resistance to treatment, which could lead to misclassification as refractory CIDP.[66] Careful monitoring and re-evaluation of therapeutic response are essential to avoid such diagnostic errors.[66]

Demyelinating Neuropathies

Paraproteinemic Neuropathies

Paraproteinemic neuropathies represent a diverse group of disorders associated with the presence of monoclonal paraproteins in the serum.[67,68] These paraproteins, abnormal immunoglobulins produced by clonal plasma cells, can include heavy chains (e.g., IgA, IgM, IgG) or light chains (kappa or lambda).[67,68] They are often linked to hematologic conditions such as lymphoma, multiple myeloma, or primary amyloidosis but most commonly occur as **monoclonal gammopathy of undetermined significance (MGUS).**[27,67] MGUS, which becomes more prevalent with age, involves a single abnormal plasma cell clone in the bone marrow without malignant proliferation.[27,67] One subtype, **IgM paraproteinemic neuropathy** with a DADS phenotype, is a sensory-predominant condition marked by ataxia and gait instability (**Figure 2**).[26] Myelin-associated glycoprotein (MAG) antibodies are detectable in approximately 50% of individuals with IgM paraproteinemic neuropathy.[67,68]

Anti-MAG Neuropathy

Anti-MAG neuropathy is a slowly progressive condition that shares clinical similarities with DADS.[26,67,69] The disorder predominantly presents with distal sensory symptoms, while motor weakness is minimal or absent.[67,69] A distinguishing feature is the presence of tremors characterised by high amplitude and low frequency.[67,69]

Diagnosis is supported by the detection of **anti-MAG antibodies** alongside an **IgM paraprotein** in the serum (**Figure 2**).[67,69] In anti-MAG neuropathy, motor distal latencies are disproportionately prolonged relative to conduction velocity, creating distinct electrodiagnostic patterns.[67,69] Specifically, a reduced TLI (Terminal Latency Index) is particularly useful in distinguishing anti-MAG neuropathy from CIDP, as CIDP generally exhibits uniform demyelination throughout the nerve, resulting in less significant distal latency abnormalities compared to changes in conduction velocity. While the condition primarily affects distal nerves, cases involving proximal disease often respond favourably to **rituximab**, underscoring its role as a therapeutic option in selected patients.[67,69]

POEMS syndrome

POEMS syndrome is a multisystemic disorder associated with plasma cell proliferation, most commonly restricted to lambda light chains.[44,49] It is characterised by a severe, rapidly progressive subacute demyelinating neuropathy, often distal in nature, that can result in significant pain.[44,49] The monoclonal protein involved is predominantly a lambda light chain paired with either IgG or IgA heavy chains, distinguishing it from IgM-associated conditions such as MGUS and anti-MAG neuropathy.[67]

Diagnostic criteria for POEMS syndrome include the co-occurrence of demyelinating neuropathy and monoclonal gammopathy.[44,49] Elevated vascular endothelial growth factor (VEGF) levels, indicative of increased microvascular permeability, are a key feature and contribute to symptoms like papilledema and dependent lower-extremity oedema (**Figure 2**).[44,49] Osteosclerotic myeloma is frequently associated with POEMS syndrome and can be identified through imaging techniques such as X-ray skeletal surveys, low-dose total-body CT scans, or MRI.[44,49]

Additional minor criteria include endocrinopathies, though common conditions like diabetes and thyroid disorders are insufficient to qualify.[44,49] Distinctive skin changes, including hyperpigmentation, hypertrichosis, or haemangiomas, are often observed, along with hematologic abnormalities such as thrombocytosis or leucocytosis.[44,49] Organomegaly, particularly involving the liver or spleen, is another characteristic feature.[44,49]

EDx studies in POEMS syndrome typically show

uniform demyelination and axonal degeneration, more pronounced than in CIDP.[70] Nerve biopsies reveal axonal degeneration, neovascularisation, and fewer onion bulbs, alongside a degree of demyelination comparable to CIDP.[71]

Chronic Ataxic Neuropathy with Ophthalmoplegia, IgM Paraprotein, Cold Agglutinins, and Disialosyl Antibodies. Chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies (CANOMAD)

CANOMAD is a rare neuropathy that closely resembles chronic Miller Fisher syndrome, with hallmark features of ataxia, areflexia, and ophthalmoplegia. The condition is often severely disabling due to profound ataxia. It is associated with specific antibodies, including anti-ganglioside, anti-GD1b, and anti-GQ1b.[5] The presence of IgM paraprotein and cold agglutinins further aids in diagnosis (**Figure 2**).[5]

Multifocal Motor Neuropathy

MMN is characterised by asymmetric weakness predominantly affecting the upper limbs and is classified as a pure motor mononeuropathy.[21,72] Unlike CIDP, MMN lacks sensory involvement, which helps differentiate the two conditions.[7,21,72] Muscle atrophy is often evident, even in the early stages, with approximately one-third of patients initially presenting with foot drop preceding upper limb involvement.[21,72] Men are more commonly affected, and the median age of onset is approximately 40 years, younger than the typical onset age for CIDP.[7,21,72] Other clinical features of MMN include cramps and fasciculations, which occur in about 40% of cases, with symptoms often exacerbated by cold exposure.[21,72] Electrodiagnostic studies reveal conduction block, a hallmark neurophysiological finding for MMN. Additional findings may include slightly slowed motor velocities, significantly reduced compound muscle action potential amplitudes, and fasciculations on needle electromyography (EMG).[7,21,72-73] Anti-GM1 antibodies are present in roughly 40% of cases (**Figure 2**).[21,72] The treatment of choice for MMN is IVIg, which is typically required on a long-term basis to manage the condition effectively.[21,72]

Axonal Polyneuropathies

Diabetes: Distinguishing between diabetes-related neuropathy and CIDP is a frequent clinical challenge, as both conditions can present with progressive peripheral neuropathy.[74,75] Diabetic neuropathy, most commonly diabetic sensorimotor polyneuropathy (DSPN), typically presents as a slowly progressive, length-dependent neuropathy. Symptoms often begin in the distal lower extremities, characterised by numbness, burning pain, and tingling. In advanced stages, the upper extremities may also be involved.[74,75] Autonomic symptoms, such as orthostatic hypotension, gastrointestinal dysmotility, or erectile dysfunction, are common in diabetes and can help differentiate it from CIDP.[76] In diabetic neuropathy, findings typically include axonal features such as reduced amplitudes of sensory and motor nerve action potentials and mild slowing of conduction velocities.[75] Diabetic neuropathy can occasionally show non-amplitude-dependent slowing of conduction velocities, which can make differentiation from CIDP challenging.[75] Multifocal or proximal findings strongly suggest CIDP.[75] It is important to note that diabetes and CIDP can coexist.[74-75] In such cases, the presence of clear demyelinating features on electrodiagnostic studies, proximal weakness, and response to immunotherapy support a diagnosis of CIDP.[74-75]

Sjögren's syndrome: It is an important differential diagnosis to consider in patients presenting with features suggestive of CIDP, particularly when there is prominent sensory involvement.[74-75] Peripheral neuropathies associated with Sjögren's syndrome can mimic CIDP in their presentation.[79] The most common phenotype is a sensory ganglionopathy (dorsal root ganglionopathy), which typically presents with marked sensory ataxia and asymmetrical sensory loss, predominantly involving large fibers.[77,78] This can create a clinical picture that overlaps with sensory-predominant CIDP and CISP. Unlike CIDP, however, motor involvement is often absent or minimal in Sjögren's-associated neuropathy.[77,78] Electrodiagnostic studies in Sjögren's syndrome-related neuropathy may show absent or severely reduced sensory nerve action potentials (SNAPs), reflecting the ganglionopathy, whereas motor nerve conduction studies are typically normal or only mildly affected.[77–79] In contrast, CIDP demonstrates widespread demyelinating features, including prolonged distal latencies, conduction block, and temporal dispersion.[77–79]

Amyloidosis: Among the paraproteinemic neuropathies, primary amyloidosis, particularly AL amyloidosis, is a significant differential diagnosis.[80,81] AL amyloidosis is caused by the deposition of misfolded immunoglobulin light chains (kappa or lambda) produced by a clonal plasma cell disorder.[80] The neuropathy in AL amyloidosis typically presents as a painful, length-dependent axonal polyneuropathy with prominent autonomic involvement, such as orthostatic hypotension, gastrointestinal dysmotility, and erectile dysfunction.[17,80] These features are less common in CIDP and can help differentiate AL amyloidosis.[80,81] Additionally, nerve biopsies in AL amyloidosis reveal amyloid deposition, which can be confirmed using Congo red staining.[80,81] Patients with AL amyloidosis may initially be misdiagnosed with CIDP, especially if

they present with weakness and sensory ataxia.[80,81] However, the presence of systemic symptoms (e.g., weight loss, nephrotic syndrome, or hepatomegaly) and resistance to standard CIDP therapies should prompt further evaluation for amyloidosis, including serum and urine electrophoresis with immunofixation, and biopsy of affected tissues.[80,81]

Genetic mimics

Charcot-Marie-Tooth (CMT) disease: This is the most common hereditary neuropathy and a significant mimic of CIDP.[82] Particularly, CMT1A, adult-onset CMT1B, CMT1X, and recessive forms such as CMT4 (e.g., CMT4C due to SH3TC2 genetic variants) can present with features suggestive of CIDP.[82,83] Electrodiagnostically, the majority of CMT subtypes are characterised by uniform demyelination and a lack of conduction block, which is consistent with their hereditary origin and linkage to specific genetic mutations.[83] The absence of conduction block serves as a crucial distinguishing factor between CMT and CID.[83] A careful family history and genetic testing, such as sequencing for peripheral myelin protein 22 (PMP22) gene duplications or deletions, can help confirm the diagnosis (**Figure 2**).[82,83]

Hereditary neuropathy with liability to pressure palsies (HNPP): This is another important genetic mimic of CIDP.[84,85] HNPP is characterised by susceptibility to focal neuropathies at compression sites, such as the ulnar or peroneal nerves.[84,85] Electrodiagnostic findings in HNPP reveal conduction slowing at entrapment sites, which may resemble electrophysiological findings seen in CIDP.[84,85] However, the clinical presentation of recurrent, transient focal neuropathies and the identification of PMP22 deletions help differentiate HNPP from CIDP (**Figure 2**).[84,85]

Transthyretin (TTR) familial amyloid polyneuropathy (FAP): It is a genetic condition caused by pathogenic variants in the TTR gene.[86,87] Although typically presenting as an axonal polyneuropathy, TTR-FAP can occasionally manifest with features of a demyelinating neuropathy that overlap with CIDP. Late-onset (>50 years) sporadic forms of TTR-FAP are particularly challenging to distinguish from CIDP.[86,87] Clinical clues include prominent pain, dysautonomia (e.g., orthostatic hypotension and gastrointestinal dysmotility), distal upper limb motor deficits, and an extension of small fibre sensory loss above the wrists.[86,87] The absence of ataxia and resistance to standard CIDP therapies may further suggest TTR-FAP.[86,87] Genetic testing for TTR mutations is essential for diagnosis, and the availability of targeted therapies, such as TTR stabilisers or gene-silencing agents, underscores the importance of accurate identification of this condition (**Figure 2**).[86,87]

CONCLUSIONS

CIDP is a complex condition with a wide range of clinical presentations, making the diagnostic process challenging.[9,23] Accurate diagnosis requires careful interpretation of clinical and diagnostic data to avoid misdiagnosis.[6,9,25] The extent of diagnostic evaluation should be tailored to each case. For typical CIDP, where no concerning features are present, minimal additional testing—such as screening for monoclonal proteins—may be sufficient.[6,9,25]

Several red flags can complicate the diagnosis and suggest alternative explanations for the symptoms.[6] These include dominant pain and fatigue rather than the characteristic numbness and weakness of CIDP; relentlessly progressive weakness with preserved or heightened reflexes, which is atypical.[6,58,59] Additional factors such as a family history of neuropathy, or clinical findings such as prominent distal atrophy or pes cavus may raise suspicion of a genetically determined neuropathy rather than CIDP.[6,83,88]

In cases with atypical features or diagnostic uncertainty, supportive testing may be useful but requires careful interpretation.[25] CSF analysis often reveals elevated protein levels with normal cell counts (albuminocytologic dissociation) in CIDP; however, mild elevations (<100 mg/dL) can also occur in diabetes, hereditary neuropathies, or with aging.[56] Overreliance on this finding should be avoided.[56] Imaging, particularly MRI, can show nerve hypertrophy or enhancement, but these findings are not specific to CIDP and may be seen in hereditary or infiltrative neuropathies.[6,51,52] Imaging is most appropriate in atypical cases to rule out other causes of neuropathy.[6,51,52] Nerve biopsy, while reserved for cases of diagnostic uncertainty, may show characteristic findings such as thinly myelinated axons, onion bulb formations, or perivascular inflammation.[50] However, these findings are not definitive for CIDP and must be interpreted within the broader clinical and electrophysiological context.[9] Improvements following immunomodulatory treatments like IVIg or corticosteroids should be measured objectively, as subjective responses can be misleading.[30,89]

The diagnostic process for CIDP requires a systematic approach that integrates clinical presentation, electrophysiological findings, and selectively applied diagnostic tools.[25] Overemphasis on nonspecific findings, such as modestly elevated CSF protein, ambiguous imaging results, or subjective treatment responses, can lead to diagnostic errors.[7] By carefully considering clinical features and utilising appropriate diagnostic tests, CIDP can be accurately distinguished from other neuropathies, ensuring proper management.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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