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REVIEW

Challenges in the Early Diagnosis and Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy in Adults: Current Perspectives

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Abstract: Diagnosing Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) poses numerous challenges. The heterogeneous presentations of CIDP variants, its mimics, and the complexity of interpreting electrodiagnostic criteria are just a few of the many reasons for misdiagnoses. Early recognition and treatment are important to reduce the risk of irreversible axonal damage, which may lead to permanent disability. The diagnosis of CIDP is based on a combination of clinical symptoms, nerve conduction study findings that indicate demyelination, and other supportive criteria. In 2021, the European Academy of Neurology (EAN) and the Peripheral Nerve Society (PNS) published a revision on the most widely adopted guideline on the diagnosis and treatment of CIDP. This updated guideline now includes clinical and electrodiagnostic criteria for CIDP variants (previously termed atypical CIDP), updated supportive criteria, and sensory criteria as an integral part of the electrodiagnostic criteria. Due to its many rules and exceptions, this guideline is complex and misinterpretation of nerve conduction study findings remain common. CIDP is treatable with intravenous immunoglobulins, corticosteroids, and plasma exchange. The choice of therapy should be tailored to the individual patient's situation, taking into account the severity of symptoms, potential side effects, patient autonomy, and past treatments. Treatment responses should be evaluated as objectively as possible using disability and impairment scales. Applying these outcome measures consistently in clinical practice aids in recognizing the effectiveness (or lack thereof) of a treatment and facilitates timely consideration of alternative diagnoses or treatments. This review provides an overview of the current perspectives on the diagnostic process and first-line treatments for managing the disease.

Keywords: CIDP, treatment, diagnosis, NCS, imaging

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. CIDP incidence ranges from 0.5 to 3.3 cases per 100,000 people, which increases with age and is more common in males.[1–3] 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. In daily practice, when NCS reveals abnormalities, it can be challenging to determine if a potentially "demyelinating" result indicates true peripheral nerve demyelination or if it stems from another cause, such as a reduced motor nerve conduction velocity (MNCV) in nerves with low compound muscle action potential (CMAP) due to the loss of large axonal fibers.[3,4] The rarity, heterogeneous presentation, lack of highly

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specific diagnostic tests and absence of blood-based biomarkers make diagnosing CIDP challenging.[5] Because CIDP is treatable[6] and because under- and misdiagnosis are common, delay in treatment or overtreatment is frequently seen.[7] Timely diagnosis and initiating treatment early may decrease the risk of permanent disability resulting from axonal damage.[8–11] The European Academy of Neurology (EAN) and the Peripheral Nerve Society (PNS) published the revised 2021 guideline on the diagnosis and treatment of CIDP.[12] Despite advances in diagnostic criteria and tests, several challenges still persist. Distinguishing CIDP from other (demyelinating) neuropathies, especially in the case of a suspected CIDP variant, requires in-depth knowledge of the differential diagnosis, available diagnostic tests, and interpretation of diagnostic findings. There is ample evidence for the treatment of CIDP with immunomodulatory drugs, but tailoring the best treatment regimen to the individual patient continues to be a common challenge. Treatment response may differ between patients and timing of evaluation, as objectively as possible, is of utmost importance. Evaluating a treatment too early or underdosing can lead to dismissing a potentially effective treatment. On the other hand, evaluating a treatment too late or not using objective outcome measures can lead to overtreatment with an ineffective drug. This review aims to explore these challenges in diagnosing and treating CIDP, their implications for patient care, and potential strategies to overcome them.

Clinical Signs and Symptoms

Typical CIDP manifests as symmetrical sensorimotor neuropathy with proximal and distal limb involvement with absent or reduced tendon reflexes. Weakness must be more or less symmetric in all four limbs and the severity of proximal and distal weakness should be similar. Sensory disturbances are to be found in at least two limbs. The CIDP variants, which were formerly referred to as atypical CIDP variants,[13] are specific clinical syndromes that share the same signs that are supportive of demyelination and respond to the same therapies and are therefore considered to be on the same disease spectrum as sensorimotor CIDP. The CIDP variants are divided into several groups based on the distribution of muscle weakness and sensory disturbances. Asymmetric CIDP, also known as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis-Sumner syndrome, is characterized by proximal and distal weakness in at least 2 limbs and sensory disturbances in the same multifocal distribution.[14,15] It predominantly affects the upper limbs, although lower limbs can be affected as well, while cranial nerve deficits are more common in this phenotype.[16–20] Focal CIDP is rare and similar to multifocal CIDP, but sensory and motor symptoms are limited to only one limb. In distal CIDP, also referred to as distal acquired demyelinating symmetric neuropathy (DADS), weakness and sensory disturbances are found predominantly in the lower limbs.[16] Sensory CIDP presents with sensory disturbances in four limbs without weakness. If any of the motor conduction criteria are fulfilled, it would be classified as sensory-predominant CIDP.[12] A long-term follow-up study revealed that 70% of patients who initially presented with a sensory CIDP phenotype, developed weakness over time and eventually evolved into a typical phenotype.[21] Motor CIDP is characterized by symmetric, proximal and distal weakness in four limbs without any sensory symptoms. It is classified as motor-predominant CIDP if any sensory abnormalities are found through NCS.

Misdiagnosis is more likely to happen when a patient presents with signs that are consistent with any of the CIDP variants as opposed to typical CIDP, which is why it's important to recognize the phenotypes and how to differentiate them from other diseases.[7] Notably, length-dependent axonal neuropathies, length-dependent demyelinating anti-MAG neuropathy or genetic neuropathies can easily be misdiagnosed as distal CIDP, particularly when there is extensive axonal damage that could even result in (amplitude-dependent) conduction slowing. A more extensive overview of clinical characteristics of typical CIDP and the CIDP variants, red flags and important considerations for the differential diagnosis is presented in Table 1.

Diagnostic Criteria

The diagnosis of CIDP involves a combination of clinical evaluation, diagnostic tests consisting of nerve conduction studies (NCS), laboratory tests and potentially imaging, CSF examination, nerve biopsy, and treatment response. There have been many diagnostic criteria sets throughout the years, but generally the first revision of the European Federation

Table 1 Clinical Characteristics of CIDP Variants, Red Flags and Considerations

Phenotype	Weakness	Sensory Disturbances	Red Flags	Differential Diagnosis
Typical CIDP	Symmetric in 4 limbs	In ≥2 limbs	Onset < 4 weeks	Guillain-Barré syndrome
			Motor > sensory and/or weakness distal > proximal	Auto-immune nodopathies (anti-NF155, anti-CNTN1, anti-CASPR1)
			Ataxia	CANOMAD (in combination with ophthalmoplegia), anti-NF155, anti-CNTN1
			Cranial nerve or bulbar involvement	Anti-NF140/NF186, anti-CASPR1
			M-protein presence	Monoclonal gammopathy (POEMS, AL amyloidosis, multiple myeloma)
			Poor response to IVIg	Reassess CIDP diagnosis; prompt further testing and evaluate differential diagnoses based on other red flags
Multifocal/ focal variant	In ≥2 limbs in multifocal distribution	In ≥2 limbs in multifocal distribution	Diabetes mellitus	Diabetic radiculopathy or plexopathy
			Pain	Vasculitic neuropathy (mononeuritis multiplex), diabetic polyradiculopathy or plexopathy, amyotrophic neuralgia, cryoglobulinemia
			No sensory disturbances	MMN, motor neuron disease
			Close to entrapment sites	Entrapment neuropathies, HNPP (in case of multiple entrapments and/ or family history of HNPP)
	Only 1 limb	In distribution of affected nerve(s)	Single nerve	Peripheral nerve tumors (schwannoma, perineurioma, lymphoma, neurofibroma), nerve entrapment
Distal variant	Distal, predominantly in lower limbs	In ≥2 limbs	M-protein and/or anti-MAG presence	Anti-MAG IgM neuropathy, POEMS, multiple myeloma, cryoglobulinemia
			Diabetes mellitus	Diabetic neuropathy
			Family history of neuropathy	Hereditary neuropathies with demyelinating features (CMT1, CMTX1, CMT4, metachromatic leukodytrophy, Refsum disease, adenomyeloneuropathy, ATTR-v polyneuropathy),
			Pain and/or asymmetry	Vasculitic neuropathy, cryoglobulinemia
Motor variant	Symmetric in 4 limbs	None	Asymmetry	Motor neuron disease
			Bulbar weakness	Motor neuron disease, myasthenia gravis
			Family history of neuropathy	Hereditary motor neuropathies (spinal muscular atrophy, porphyria)
			Elevated CK, normal tendon reflexes	Inflammatory myopathies
			Fluctuation of symptoms	Neuromuscular junction disorders (myasthenia gravis, Lambert-Eaton)
Sensory variant	None	Symmetric in 4 limbs	Pain	Small-fiber neuropathy
			Family history of neuropathy	Hereditary sensory neuropathies
			Ataxia	CANVAS, dorsal column lesions (vitamin B12 deficiency, paraneoplastic, syphilis, copper deficiency)
			Normal motor and sensory conduction	CISP
			Diabetes mellitus	Diabetic polyneuropathy
			Chemotherapy or other neurotoxic treatments/ supplements	Toxic neuropathies (eg chemotherapy, vitamin B6 toxicity)
			Slow progression	Idiopathic sensory neuropathies

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-1; CISP, chronic immune sensory polyradiculopathy; CMT, Charcot-Marie-Tooth; CNTN-1, contactin-1; 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.

of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria is regarded as the most widely used and accurate set.[12,13,22,23] 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 when comparing the two guidelines in their own group of patients as compared to historical literature data.[24] Another study found that the revised guideline had a lower sensitivity, but a higher specificity in their cohort of patients as compared to their control group consisting of patients with axonal peripheral neuropathy, most with diabetic polyneuropathy.[25] NCS are crucial for demonstrating electrophysiological abnormalities that are supportive of peripheral nerve demyelination (Table 2). Some notable changes from the previous guideline include the removal of distinctions

Table 2 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 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 limit of normal.

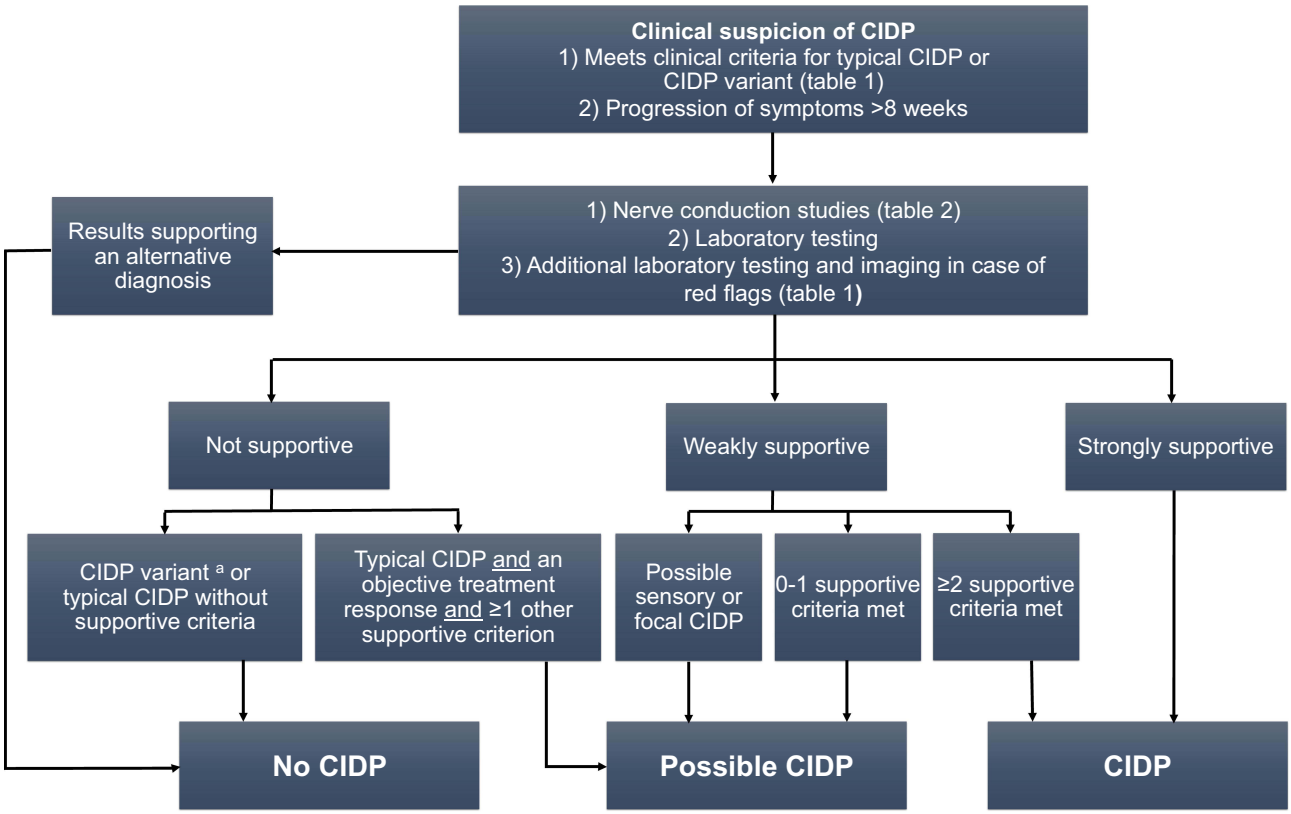

Figure 1 Visualization of the diagnostic process when following the EAN/PNS 2021 guideline.
Notes: [a]Regardless of supportive criteria.

between "definite" and "probable" conduction blocks, consolidating them into a singular category of conduction blocks. Furthermore, tibial nerve conduction blocks are no longer included and the threshold for temporal dispersion in the tibial nerve has been adjusted to necessitate at least a 100% increase in CMAP duration. Sensory criteria have transitioned from being merely supportive to being integral to the electrodiagnostic criteria. The sensory demyelinating conduction criteria are now mandatory for possible sensory CIDP, while sensory conduction abnormalities are required for typical CIDP and other CIDP variants except for motor CIDP phenotype, where sensory conduction should be normal in at least four nerves.

Additionally, the revision now introduces variant-specific electrodiagnostic criteria (Table 2), meaning that patients with a sensory or motor phenotype can meet the criteria for (possible) CIDP, despite the absence of motor or sensory conduction criteria respectively. When it comes to the supportive criteria, nerve ultrasound, which can be used to show an increase of cross-sectional area of the peripheral nerve and nerve roots,[26–28] has now been included in the supportive criteria. Evidence supporting the use of somatosensory evoked potentials (SSEP) is still very limited and SSEP's are no longer part of the supportive criteria.[12] The guideline emphasizes that the diagnostic process is complex (Figure 1) and that a combination of clinical, electrophysiological, and sometimes laboratory or imaging findings are necessary for a CIDP diagnosis (Table 3).

Diagnostic Tests

Nerve Conduction Studies

NCS remains to be the most important diagnostic tool when diagnosing CIDP. There is a strong support for demyelination if the motor conduction criteria (Table 2) are present in at least 2 nerves with distal negative peak CMAP amplitudes of 1.0 mV or higher.[29] The reason for this amplitude cut-off is that axonal loss may decrease nerve

Table 3 Laboratory and Imaging Studies

Diagnostic Test	Typical Findings in CIDP	Which Patients to Test?	Pitfalls & Cautions
Lumbar puncture	Elevated CSF protein and normal white blood cell count	• When infectious or malignant causes are suspected • Helpful when NCS findings are weakly supportive and clinical criteria are met	• Mildly elevated protein also found in patients with diabetes mellitus and can increase with age • Unnecessary when diagnostic criteria already met • No additional diagnostic value when NCS and clinical criteria are not met
Nerve ultrasound	Enlargements of cross-sectional area of peripheral nerves or cervical nerve roots/ brachial plexus	• Suspicion of focal nerve compression • Helpful when NCS findings are weakly supportive and clinical criteria are met, or to exclude CIDP	• Does not differentiate between CIDP and other inflammatory neuropathies or hereditary neuropathies (MMN, CMT, vasculitis) • Availability of institutional nerve imaging expertise • No additional diagnostic benefit when NCS **and** clinical criteria are not met
MRI	Enlargement or abnormal contrast enhancement of cervical/lumbar nerve roots or brachial/lumbar plexus	• Helps differentiate when spinal cord pathology is suspected	• Nerve imaging expertise necessary, high inter-rater variability • No additional diagnostic benefit when NCS **and** clinical criteria are not met
Nerve biopsy	Onion bulbs, macrophage-associated demyelination, signs of demyelinated and remyelinated nerve fibers	• High (clinical) suspicion of CIDP, but unable to prove through electrodiagnostic, laboratory or nerve imaging tests • When vasculitis, amyloidosis, sarcoidosis, nerve (sheath) tumors is suspected	• High risk of permanent damage of biopsied nerve • Signs of demyelination often not seen in a biopsy leading to a low diagnostic yield
M-protein screening	None (no monoclonal antibodies, including immunofixation)	• All patients suspected of CIDP • Repeat in case of no treatment response, especially in case of a distal phenotype or ataxia	• Monoclonal proteins are common and not always relevant (MGUS)
Auto antibodies	None [a]	• In case of clinical "red flags" (tremor, ataxia) • No or insufficient treatment response • In case of IgM(+), consider anti-MAG testing	• Not helpful for patients who have a good treatment response • Antibody analysis needs to be done in a laboratory with paranodal antibody testing experience
SSEP	None, limited evidence for the usage of SSEP in CIDP	• Clinical sensory CIDP, especially with predominant sensory ataxia, with normal motor and sensory NSC who may have CISP	• Sensitivity for CIDP unknown, not recommended unless CISP is considered

Notes: [a](Para)nodal antibodies are specific for autoimmune (para)nodopathies, which are not classified as CIDP but as a different disease entity.[12]
Abbreviations: CISP, chronic immune sensory polyradiculopathy; CMT, Charcot-Marie-Tooth; MAG, myelin-associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; SSEP, somatosensory evoked potentials.

conduction velocity if the fastest conducting axons are damaged. In general, any signs that are supportive of demyelination should be interpreted with caution if the distal CMAP amplitude is <1.0 mV and will therefore officially not meet the criteria of demyelination.

Nerve compression at entrapment sites can produce focal abnormalities similar to those seen in demyelinating neuropathies. Therefore, EMG abnormalities at common nerve entrapment sites should be disregarded.[30,31] In some patients, this compression may even affect a larger portion of the nerve around the entrapment site. Technical

difficulties, such as submaximal stimulation, costimulation with coregistration, and anastomosis (such as Martin-Gruber) can produce apparent CMAP amplitude/area reductions. These reductions can be mistakenly identified as a conduction block or they might obscure a genuine CMAP amplitude/area reduction, causing a missed conduction block. Absence of F waves can be caused by other conditions, such as radiculopathies or plexopathies,[32] and is not specific for CIDP, which is why this criterion has to be present in combination with one other nerve conduction criterion in one other nerve. The many caveats in interpreting NCS findings emphasize the need for neurophysiological expertise, especially when signs that are supportive of demyelination are detected in only one or two nerves.[33] The extent to which NCS are conducted can vary considerably. When too few nerves or nerve segments are tested, it may lead to missed diagnoses.[33] The 2021 EAN/PNS guideline recommends testing at least the median, ulnar (with stimulation below the elbow), peroneal, and tibial nerves on one side. If the conduction criteria are not met, the suggested next step is to test the same nerves on the opposite side and to expand the ulnar and median nerve measurements by stimulating both nerves at the axilla and Erb's point. However, it can be justified to include the median and ulnar nerve measurements up to Erb's point from the start, inclusive of F-waves. Demyelinating features are more prevalent in the arms, especially in the proximal segments between the elbow and Erb's point, compared to the legs.[34–36] An important challenge is to interpret the NCS results in the clinical context, because the nerve conduction findings that are defined in the guidelines as strongly supportive of demyelination are not equivalent to classical demyelination as found in nerve biopsy. In essence these findings are markers for functional disruption or slowing of the salutatory conduction of the myelinated axons, which may be primarily demyelinating, but may also be primarily axonal through eg disorganization at the nodes of Ranvier.[37] As such, other diseases that can meet the electrodiagnostic criteria for CIDP are autoimmune nodopathies, multifocal motor neuropathy (MMN), hereditary neuropathies with demyelinating features (demyelinating and intermediate types, hereditary neuropathy with liablity to pressure palsy), Guillain-Barré Syndrome (GBS), polyneuropathies associated with monoclonal gammopathies (anti-MAG neuropathy), amyloidosis, medication-induced neuropathies, vasculitic neuropathies, and lumbosacral radiculoplexus neuropathies.

Imaging

Nerve ultrasound and contrast-enhanced Magnetic Resonance Imaging (MRI) can be useful for assessing more proximal segments of the nerves and nerve roots, which is a region that is hard to study with NCS. Segmental or diffuse nerve hypertrophy may be visible, which is thought to be indicative of demyelination and remyelination processes and is mostly found in the brachial plexus and/or proximal median nerve segments.[27] However, nerve enlargement and/or contrast enhancement are not specific for CIDP, as they can be found in other diseases, such as diabetes mellitus, amyotrophic neuralgia, vasculitis, demyelinating or intermediate Charcot-Marie-Tooth (CMT) disease.[38,39]

Nerve ultrasound has emerged as a valuable diagnostic tool in the evaluation of chronic inflammatory demyelinating polyneuropathy in the last decade. This non-invasive imaging can be used to measure nerve cross-sectional area (CSA) to detect nerve (root) enlargement, which has found to be the case in 69–100% of CIDP patients.[40–43] Furthermore, nerve ultrasound may also be useful in guiding nerve biopsy and assisting in the monitoring of disease progression or treatment response. In a multicenter study, the inter-observer variability was good as the differences in CSA measurements between investigators were small.[44] One study was able to use nerve ultrasound to identify patients who responded to treatment but did not meet the CIDP criteria.[26] Nerve ultrasound can be helpful to identify CIDP patients who did not (fully) meet the electrodiagnostic criteria and can increase the diagnostic certainty.

In some cases, MRI of the brachial and lumbosacral plexus can be helpful by revealing nerve root hypertrophy, increased signal intensity, or gadolinium enhancement.[27,45] MRI may be considered when patients suspected of CIDP fulfill the criteria for "possible" CIDP and ultrasounds results are non-contributory or nerve ultrasound is unavailable. Most hospitals have access to MRI, but there is a high intra-observer variability, even amongst experienced raters.[46–48] The lack of objective cut-off values is also a major limitation for MRI; only a handful of studies used an objective cut-off value for abnormal nerve root diameter for the assessment of plexus MRI.[49,50]

CSF Examination

Cerebrospinal fluid (CSF) examination can be a very useful diagnostic tool when the diagnostic criteria are not fully met or to exclude other diagnoses. Up to 90% of patients with typical CIDP present with elevated protein levels in combination with a normal white blood cell count in their CSF.[51–53] However, in patients with a CIDP variant such as multifocal CIDP, CSF protein elevation is less frequent or only slightly increased.[20] On the other hand, elevated CSF protein is not specific for CIDP, as patients with diabetes mellitus or hereditary demyelinating neuropathies may also exhibit mildly elevated protein levels.[54,55] CSF protein levels tend to get higher with age, so to reduce the risk of misdiagnosis, recent recommendations advice raising the CSF protein cut-off value to 0.6 g/l for patients over 50 years of age.[56] One study found that with these cut-offs, the sensitivity of CSF protein elevation was 68%.[57] It is yet unknown what the specificity is of higher values of CSF protein (>1.0 g/l) for the diagnosis of CIDP. If elevated leukocyte counts (>10/mm^3) are detected, an infectious or malignant cause should be considered. However, slightly elevated leukocyte counts (10–50/mm^3) have been reported in up to 11% of CIDP patients, indicating that this finding does not necessarily exclude the diagnosis.[58–60] A leukocyte count exceeding 50/mm^3 is very rare in CIDP patients, and compels further investigation for alternative causes, but it does not unequivocally rule out CIDP. One study found that 57% of patients with slightly elevated leukocytes experienced a (sub)acute disease onset, with leukocyte counts decreasing spontaneously over time.[60] CSF examination in CIDP patients already meeting the clinical and electrodiagnostic criteria provides limited added value, unless there are signs of an underlying infectious or malignant disease, including a rapid onset and disease course.[12]

Autoantibodies

During recent years, the role of autoantibodies in inflammatory demyelinating neuropathies as diagnostic and prognostic biomarkers has been one of the most compelling laboratory research topics and the knowledge is quickly expanding. IgG antibodies against neurofascin 155 (NF155), 140 (NF140) and 186 (NF186), contactin-1 (CNTN1) and contactin-associated protein 1 (CASPR1) have been identified.[61,62] It is estimated that 25–40% of CIDP patients carry antibodies that target certain structures of the peripheral nerve, but the target antigens for most CIDP patients remain unknown.[1,61,62] Patients with (para)nodal antibodies tend to have a more aggressive and more (sub)acute course, and often respond poorly to IVIg, which is why guideline recommends testing for antibodies in patients who do not respond to first line treatments, especially if they have atypical symptoms such as pain, tremors, and severe ataxia. Routinely testing for antibodies is not yet recommended, but is becoming increasingly more common in Europe and Japan. However, it should be noted that there are different techniques used for testing auto-antibodies with different diagnostic performances and not every testing technique is widely available or meets the quality standards.[63] The EAN/PNS 2021 guideline recommends a cell-based assay with mammalian expression vectors and an enzyme-linked immunosorbent assay (ELISA) or teased-nerve immunohistochemistry as a confirmatory test. An interlaboratory study is being conducted to validate these testing recommendations.[63] A change in the EAN/PNS guidelines is the Task Force's advice to classify "autoimmune nodopathies" as a separate disease from CIDP. This distinction is based on their unique clinical features, pathophysiological differences, and poor response to IVIg.

Screening for monoclonal proteins (M-protein) including immunofixation is recommended for all patients with a clinical suspicion of CIDP.[12] In case of no treatment response and a distal phenotype, repeating the M-protein analysis and testing for anti-myelin-associated glycoprotein (MAG) antibodies should be considered in order to reduce the risk of a misdiagnosis. Two earlier studies, encompassing a combined total of 113 patients, identified six patients who met the diagnostic criteria for CIDP and tested positive for anti-MAG antibodies without IgM paraproteinemia.[64,65] The clinical presentation and progression in these patients were similar to that of anti-MAG positive patients who had an IgM paraproteinemia. Three out of these six patients tested positive for an M-protein later during follow-up. One should note that in these studies a cut-off value of 1000 Bühlmann Titre Units (BTU) was used, which is considerably lower than the recommended threshold of 7000 BTU.[66] The available evidence does not support testing for anti-MAG in patients without M-protein, pending further large-scale studies using accurate cut-off values.

Nerve Biopsy

Nerve biopsy can be helpful when CIDP is highly suspected but cannot be proven with nerve conduction studies or made more likely with the help of imaging and/or CSF examination. Generally, sensory nerves are selected such as the sural of the peroneal superficial nerve. It can also help to differentiate between CIDP and vasculitic neuropathy, amyloidosis, sarcoidosis, neurolymphatosis, or nerve sheath tumors, especially if an alternative diagnosis is being considered after limited or no treatment response. Findings that support CIDP are onion bulbs (caused by demyelination and remyelination), thinly myelinated axons and perivascular macrophage collections.[67–71] However, nerve biopsy findings are often not specific or even absent in clinically moderate or mild cases, leading to a relatively low diagnostic yield.[72] Another downside is that a nerve biopsy will cause damage to the nerve and this may result in sensory disturbances, which means that the severity of symptoms must be high enough to justify the potential morbidity resulting from a peripheral nerve biopsy and relatively low accuracy. In summary, a nerve biopsy should only be considered when there is a strong suspicion of CIDP despite negative NCS, CSF, and imaging results, or when other potential underlying causes necessitate a nerve biopsy.

Treatment Strategies

First Line Treatments

CIDP can be managed with immunomodulatory drugs and up to 81% of patients show improvement from first-line treatments.[6] These first-line treatments include intravenous immunoglobulin (IVIg), corticosteroids, and plasma exchange (Table 4). [12,73] IVIg is generally well-tolerated and effective in improving disability after one month,[74] but the costs are high, averaging between approximately €45,000 per year in Europe and $137,000 per year in the United States.[75] Potential side effects must also be considered, such as headache, skin rash and venous thromboembolic events.[76,77] Despite its efficacy, patients are often treated for years due to the low remission rate and relapsing

Table 4 First Line Treatment Options

Treatment	When to Start	How to Dose	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

(*Continued*)

Table 4 (Continued).

Treatment	When to Start	How to Dose	When to Evaluate	Notable Side Effects & Cautions
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 (1 g 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.

nature of the disease, with the risk of overtreatment.[78–80] Therefore, periodic weaning trials are necessary to justify long-term use. Subcutaneous immunoglobulin (SCIg) is an equally effective alternative maintenance treatment that is generally well-tolerated.[81] The biggest upside is that patients or caretakers can (self-)administer SCIg outside the hospital or without a home-care nurse, relieving some of the patients burden. A recent study compared IVIg and SCIg treatments and found that they similarly impacted specific immune cells, but IVIg had a broader influence on serum cytokines than SCIg.[82] It is suggested that IVIg and SCIg have distinct pharmacokinetics, leading to different post-infusion cytokine patterns in CIDP patients. However, there were no therapeutically meaningful differences. When it comes to SCIg as an induction treatment, one randomized controlled trial study has shown that SCIg and IVIg have a similar positive effect on muscle weakness when administered to treatment naïve CIDP patients.[83]

Corticosteroids, while effective as an induction therapy, will on average take at least two to three months before improvement of symptoms takes place and may cause more severe and sometimes long-term side effects if administered for prolonged periods, such as diabetes mellitus, hypertension, osteoporosis, opportunistic infections and weight gain.[79,84] For this reason, most recent studies restricted its use to relatively short period.[84–87] Corticosteroids can be administered orally on a daily basis, or given in pulses, either in oral or intravenous form. There is no difference between these treatment modalities in terms of safety and efficacy.[79,86] Compared to IVIg, corticosteroids show no significant difference in long-term improvement of disability, and possibly have a higher remission rate and longer duration of remission.[73] Furthermore, oral administration obviates the need for intravenous treatments, negating the requirement for home care or hospital admissions. They present a much lower cost alternative compared to IVIg. Interestingly, patients with a (pure) motor CIDP variant are more likely to deteriorate when treated with corticosteroids.[84,88,89]

Plasma exchange is an effective treatment, particularly in severe cases.[90,91] It is considered a first-line treatment, but in daily practice it is typically reserved for patients who do not respond well to one of the other first-line treatments. Improvement of symptoms can be seen within days. However, the requirement of specialized equipment and personnel, necessary expertise and invasiveness of the treatments are some of the several logistical drawbacks that limit its use. An analysis of data from a combined registry indicated that adverse events were rare and usually mild.[92] Adverse events that

Table 5 Tools for Objectifying Treatment Response

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.

were reported most often included access problems, hypotension, tingling, and urticaria. Plasma exchange with albumin or saline can cause a drop in blood-clotting factors, leading to a slightly prolonged clotting time, but clinically relevant hemorrhages are very rare. There is no data on the safety and effectiveness of plasma exchange as maintenance treatment.[9]

Evaluating Treatment Response

Timely and consistent treatment response evaluation is essential because a poor treatment response is an important reason to reconsider the CIDP diagnosis and treatment plan. It should be emphasized that stabilization of symptoms after induction treatment should generally not be regarded as proof of efficacy as one would expect symptoms to remain unchanged for longer periods of time with most other causes of (axonal) neuropathies. In a cohort of patients who were misdiagnosed with CIDP and were given immunomodulatory treatment, 85% reported that they "felt better".[7] This was without any objective measurements, merely patient-reported perception of improvement, and this shows how important it is to include objective measurements to (dis)prove a treatment response. It is recommended that treatment response is evaluated using standardized disability and impairment scales (Table 5). [12] The use of minimal clinically important differences (MCIDs) to define meaningful improvement or deterioration can be useful, but do not rule out normal daily or irrelevant fluctations.[93] Optimal timing for evaluating treatment and dosing can be found in Table 4. Based on the selected treatment modality, a therapeutic response often manifests after several weeks or months. However, insufficient dosage or treatment duration can lead to therapeutic inefficacy, highlighting the importance of allowing sufficient time for treatment to take effect.[94]

Discussion

There are several challenges to arrive at an early CIDP diagnosis. The diagnostic process for typical CIDP can be very straightforward, including only NCS and laboratory screening.[95] However, the disease may manifest with various different phenotypes and it gets especially challenging when the electrodiagnostic criteria are not (fully) met. NCS is very helpful when it is strongly supportive of demyelination and the CIDP guidelines as reported in the EFNS/PNS 2010 first revision and the EAN/PNS 2021 second revision have a good sensitivity when used correctly, but even then, demyelination is not exclusive for CIDP. When the NCS results are weakly or not supportive, laboratory and imaging studies can be helpful to rule out other conditions or make the CIDP diagnosis more likely to allow a treatment trial, but caution should remain as most findings are not very specific for CIDP. A treatment response using objective outcome measures may upgrade the diagnostic certainty from "possible CIDP" to "CIDP", or even from "no CIDP" to "possible

CIDP" when the clinical criteria for typical sensorimotor CIDP and one other supportive criterion is met. Combining probable and definite conduction blocks leads to some simplification of the criteria but may also lead to a lower specificity for possible CIDP. Previously, one definite conduction block was required for possible CIDP. Now, a conduction block previously deemed probable is considered sufficient and increases the risk of over diagnosis and should be interpreted with caution. The inclusion of sensory criteria is another notable adjustment. Previously part of the supportive criteria, sensory conduction criteria (sural sparing, sensory nerve conduction velocities in the demyelinating range) have now been transitioned to an electrodiagnostic criterion for possible sensory CIDP. Sensory nerve conduction abnormalities, including slowing of sensory nerve conduction velocities not in demyelinating range, prolonged distal sensory latencies, and low sensory nerve action potential (SNAP) amplitudes, are now required to meet the electrodiagnostic criteria, even though they are not specific for demyelination. Furthermore, since sensory nerve conduction abnormalities were not mandatory for diagnosis with the former criteria, NCS were often limited to one or two sensory nerves. This means that some patients with prevalent CIDP would not fulfill the current criteria based on the NCS conducted at the time of diagnosis, whereas nowadays sensory measurements would be continued until also the sensory nerve conduction criteria are met in two nerves or sensory conduction must be normal in all of at least four nerves to confirm the clinical diagnosis of motor CIDP.

An important shift from the previous guideline is that auto-immune nodopathies are no longer classified as a CIDP subtype, but rather a different disease entity requiring a different disease management strategy from CIDP.[96] Additionally, chronic immune sensory polyradiculopathy (CISP) is also not considered as a CIDP subtype anymore. The evolving terminology over the years reflects our deepening understanding that CIDP belongs to a spectrum of autoimmune disorders affecting the peripheral nerves, characterized by heterogeneous presentations. The term CIDP, coined in 1982, initially described the disease's most common characteristics: timing of onset, pathophysiology, affected tissue components, and its anatomical distribution. Over time, however, it became clear that several patients who were diagnosed as CIDP did not exhibit the characteristics originally associated with CIDP. Furthermore, CIDP was initially seen as a clearly distinct disease from other chronic neuropathies such as MMN, and monoclonal gammopathies. However, some of these neuropathies would meet the supportive criteria, including treatment response, and are hard to differentiate with NCS. A more modern view is to see CIDP as part of a spectrum, which is shared with autoimmune nodopathies, CISP, MMN and even monoclonal gammopathies.[96] The umbrella term "chronic autoimmune neuropathies" would adequately describe this spectrum, considering that an autoimmune etiology is a shared (suspected underlying) feature of these neuropathies, which also have similar diagnostic approaches (NCS, laboratory testing, and imaging), and may benefit from immunomodulatory treatment.[5] Currently, given the absence of specific biomarkers, CIDP continues to be a clinical diagnosis, with the goal to demonstrate autoimmunity in most CIDP patients yet to be achieved. Future research should aim to develop specific immunological tests that can be added to the diagnostic work-up.

When it comes to induction treatments, corticosteroids, IVIg and plasma-exchange are proven to be effective and well-tolerated. Most patients with CIDP respond well to at least one of the first line treatments, meaning that lack of improvement by itself can be considered a "red flag" and a reason to reconsider the diagnosis. Therefore, initial assessment and monitoring of a treatment response is important and should be done with disability and impairment outcome measurements. Treatment response can easily be under- or overestimated and standardized objective outcome measurements can be very helpful in clinical practice to help monitor as objectively as possible. However, not every assessment is suitable for every patient.[97] MRC sum scores are less suitable for patients with a CIDP variant with asymmetric, distal or no weakness. These patients will have fairly high MRC sum scores and due to a ceiling effect clinical improvement or deterioration will be harder to confirm. The I-RODS is not specific for CIDP and may be influenced by comorbidities, cultural differences, and lifestyle. Grip strength of the affected arm may be more helpful for these patients, but these might also fluctuate more over time.[98] Therefore, changes are sometimes difficult to interpret. Utilizing MCIDs can aid in recognizing meaningful changes in impairment and disability scales. However, using the current MCIDs, it can be challenging to differentiate genuine clinical deterioration from variability over time at an individual level.[93] The revised EAN/PNS 2021 guideline strongly recommends the use of at least one impairment and one disability scale to determine deterioration. While combining multiple MCIDs might enhance the accuracy, it has yet to be validated.

In conclusion, despite these many challenges, CIDP is a diagnosis based on a set of clinical criteria, electrodiagnostic features and, when in doubt, additional laboratory, and imaging studies. NCS remains to be the most useful tool for detecting features that are supportive of demyelination, as long as the tests are being conducted and interpreted correctly. IVIg, corticosteroids, and plasma exchange have proven safe and effective for treating CIDP. However, it is crucial to use objective outcome measurements for evaluating treatment efficacy. Poor treatment response gives a good reason to reconsider the CIDP diagnosis and initiating additional diagnostic testing.

Disclosure

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