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Chronic inflammatory demyelinating polyradiculoneuropathy—Diagnostic pitfalls and treatment approach

Amro M. Stino MD[1] | Elie Naddaf MD[2] | Peter J. Dyck MD[2] | P. James B. Dyck MD[2]

[1]Division of Neuromuscular Medicine, Department of Neurology, University of Michigan School of Medicine, Ann Arbor, Michigan

[2]Department of Neurology, Mayo Clinic, Rochester, Minnesota

Correspondence
Amro M. Stino MD, Division of Neuromuscular Medicine, Department of Neurology, University of Michigan School of Medicine, Ann Arbor, Michigan 48109.
Email: amstino@med.umich.edu

Abstract

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is characterized by progressive weakness and sensory loss, often affecting patients' ability to walk and perform activities of daily living independently. With the lack of a diagnostic biomarker, the diagnosis relies on clinical suspicion, clinical findings, and the demonstration of demyelinating changes on electrodiagnostic (EDx) testing and nerve pathology. As a result, patients can often be misdiagnosed with CIDP and unnecessarily treated with immunotherapy. Interpreting the EDx testing and cerebrospinal fluid findings in light of the clinical phenotype, recognizing atypical forms of CIDP, and screening for CIDP mimickers are the mainstays of the approach to patients suspected of having CIDP, and are detailed in this review. We also review the currently available treatment options, including intravenous immunoglobulin (IVIg), corticosteroids (CCS), and plasma exchange (PE), and discuss how to approach treatment-refractory cases. Finally, we emphasize the need to adopt objective outcome measures to monitor treatment response.

KEYWORDS

CIDP, diagnosis, IVIg, plasma exchange, steroids, treatment

1 | INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired autoimmune disorder of peripheral nerve and nerve root function, typically presenting with proximal and distal symmetrical weakness, areflexia, and disease progression that continues beyond 8 weeks.[1] The condition was first described and named by Peter J. Dyck in 1975.[2] The clinical features are predominantly those of large myelinated fiber involvement producing muscle weakness and sensory ataxia. The annual incidence is estimated to be around 1 per 100 000 persons; prevalence figures vary greatly, from 3 to 9 cases per 100 000 population, depending on diagnostic criteria and patient ascertainment techniques used.[3-5]

CIDP is caused by macrophage-mediated inflammatory demyelination involving proximal greater than distal nerve segments.

Abbreviations: AL, acquired light chain; A-CIDP, acute onset CIDP; CCS, corticosteroids; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMT, Charcot-Marie-Tooth; CSF, cerebrospinal fluid; DADS, distal acquired demyelinating sensorimotor neuropathy; EDx, electrodiagnostic; EFNS/PNS, European Federation of Neurological Society/Peripheral Nerve Society; EMG, electromyography; IVIg, intravenous immunoglobulin; GBS, Guillain-Barré syndrome; I-RODS, Inflammatory Rasch-built Overall Disability Scale; Ig, immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; IVMP, intravenous methylprednisolone; MAG, myelin-associated glycoprotein; MCID, minimal clinically improvement difference; MGUS, monoclonal gammopathy of unknown significance; MRI, magnetic resonance imaging; PE, plasma exchange; NIS, neuropathy impairment score; POEMS, polyneuropathy organomegaly endocrinopathy M-protein, and skin changes; SCIg, subcutaneous immunoglobulin; SIDP, subacute inflammatory demyelinating polyneuropathy; TTR, transthyretin.

The objectives of this activity are to understand the clinical, electrodiagnostic, and pathological features in order to be able to diagnose CIDP and differentiate it from other disorders; to be able to recognize CIDP variants; and to develop and implement treatment plans for patients with CIDP.

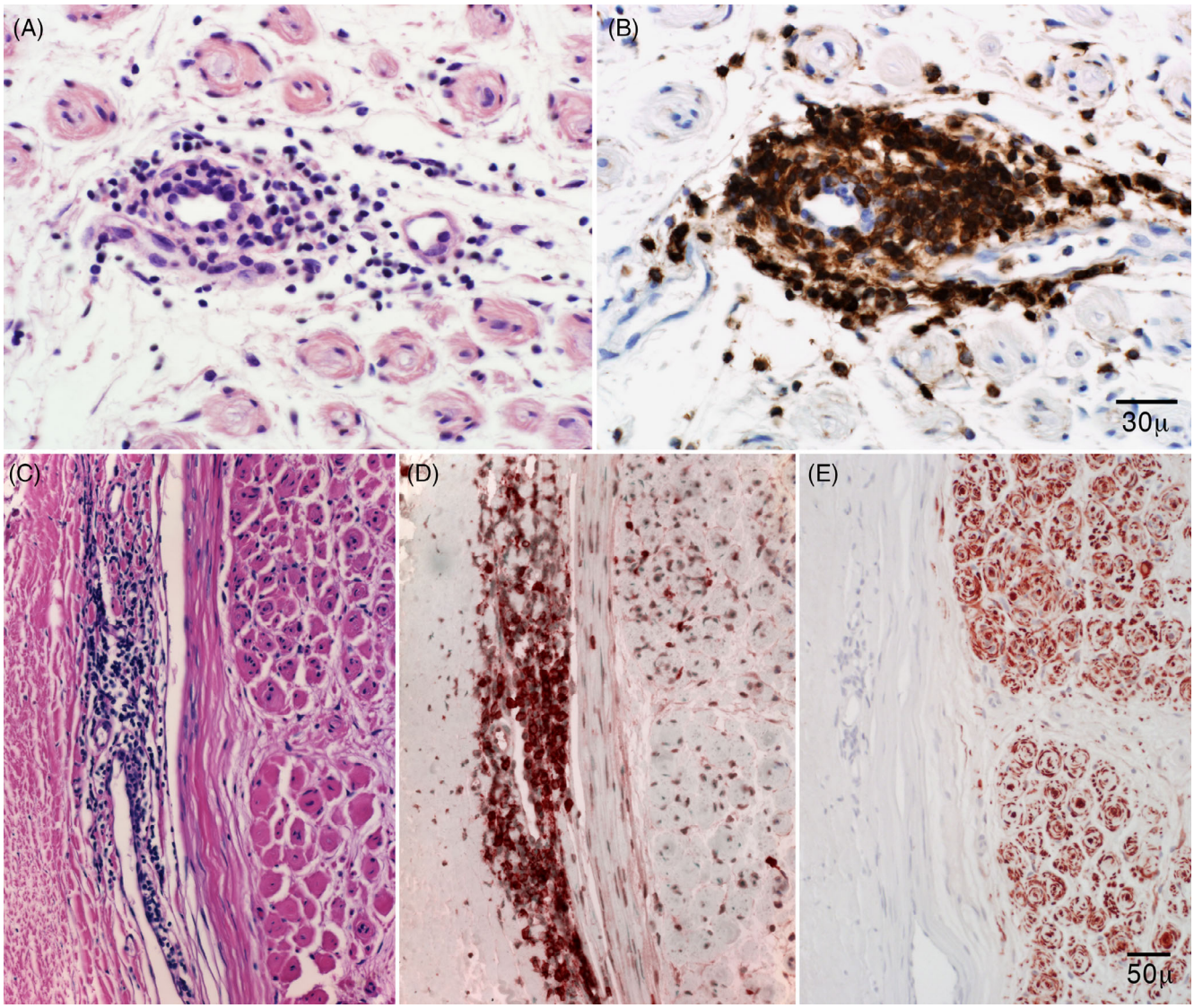

FIGURE 1 Inflammation and onion bulbs (OB) seen in transverse paraffin sections from two patients with CIDP. Serial sections stained with hematoxylin-eosin (A) and CD45 (B) show a perivascular endoneurial collection of inflammatory cells and background OB in a patient with CIDP. Three consecutive paraffin cross-sections show hematoxylin-eosin stain of a large inflammatory collection in epineurium adjacent to the perineurium (C) that carries antibody to T cells (CD3) (D). OB are confirmed by their reactivity to a Schwann-cell preparation (S-100) (E). Inflammatory infiltrates are more common in acquired neuropathies.[6]

Inflammatory infiltrates are adjacent to myelinated fibers or perivascularly in the epineurium (Figure 1). Early in the disease course, segmental demyelination predominates (best seen on teased nerve fiber preparations), but with time and ongoing demyelination there is development of onion bulbs (stacks of Schwann-cell processes) that accrue in abortive remyelination attempts, producing hypertrophic nerves.[2] The onion bulbs in CIDP often occur in a "mixed pattern" (Figure 2), because patchy inflammatory demyelination produces myelinated nerves surrounded by large onion bulbs adjacent to normal myelinated fibers.[6] This unequal demyelination explains the electrodiagnostic (EDx) findings of temporal dispersion typically found in CIDP. Immune mechanisms, involving such pathways as macrophage-mediated expression of costimulatory molecules B7-1 and B7-2, are directed toward Schwann cells and myelin epitopes, although the exact immune targets are unknown.[7] The emergence of specific antibodies, namely neurofascin-155 and contactin-1, points to nodal or paranodal specific pathology in a subset of patients.[8] However, these cases respond differently to treatment. Treatment-wise, intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg), corticosteroids (CCS), and plasma exchange (PE) all show benefit in classical CIDP, albeit each with limitations.

The diagnosis of CIDP remains clinical, supported by EDx studies. In this review, we address the diagnostic pitfalls of CIDP and provide a practical approach to its evaluation. We then discuss currently available treatments and our own treatment approach.

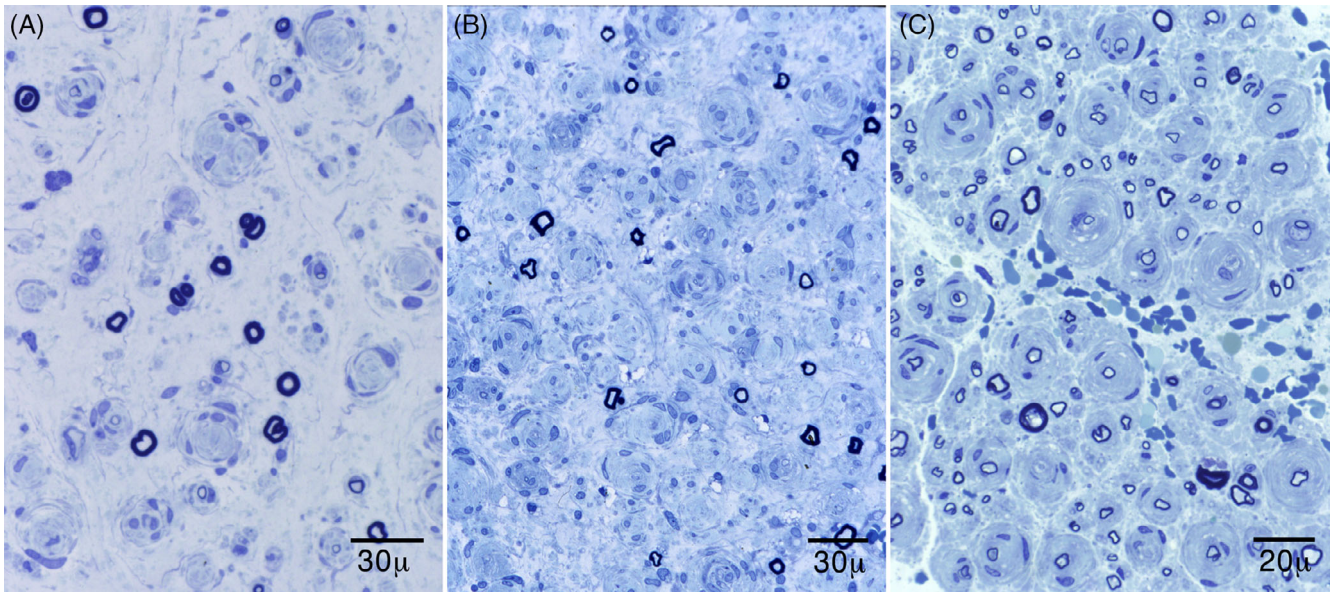

FIGURE 2 Mixed onion bulbs (OBs) seen in nerve biopsy epoxy sections stained with methylene blue, showing OBs surrounding some fibers, whereas other myelinated fibers do not have OBs, as seen in CIDP (acquired) with biopsy from nerve root (A), CIDP (acquired) (B), and focal hypertrophic neuropathy of the median nerve (focal CIDP, acquired) (C). The mixed pattern is found much more commonly in acquired neuropathies.[6]

2 | PHENOMENON OF CIDP MISDIAGNOSIS AND OVERTREATMENT

Despite established diagnostic criteria, best set out in the European Federation of Neurologic Societies/Peripheral Nerve Society (EFNS/PNS) criteria,[9] and well-recognized clinical characteristics of typical CIDP, misdiagnosis is not uncommon and immunotherapy unnecessarily administered. This misdiagnosis of other neuropathies as CIDP is best described in a study by Allen et al in which 28 of 59 (47%) patients referred for a putative diagnosis of CIDP did not eventually meet the clinical and EDx criteria for CIDP.[10] The authors found that the diagnostic error was mostly due to the overreliance on mild nerve conduction abnormalities falsely interpreted as demyelination, insignificant elevation of cerebrospinal fluid (CSF) protein, or self-reported rather than objective improvement with therapy.

With regard to EDx testing, findings that are commonly misinterpreted as suggesting CIDP include amplitude-dependent slowing in length-dependent neuropathies, amplitude-independent slowing in diabetic polyneuropathies, isolated distal latency changes in the fibular nerve (when recording over the extensor digitorum brevis), and focal slowing across common entrapment sites.[11] Thus, it is important to interpret the EDx findings in light of the clinical phenotype of a particular patient, and to consider alternative etiologies when patients display atypical clinical features, unusual laboratory findings, and no objective evidence of response to treatment.

Another issue of importance is that of overtreatment of CIDP even when the diagnosis is correct. This may occur in situations where physicians do not vigorously wean treatment, when patients become psychologically reliant on treatment (even if not indicated), and in chronic cases of CIDP with secondary axonal loss, wherein immunotherapy may not be effective.[12,13]

3 | CLINICAL FEATURES OF TYPICAL CIDP

The classical CIDP phenotype is a symmetrical, sensory and motor polyradiculoneuropathy, with combined proximal and distal weakness, with areflexia, but without much associated pain. Chronic refers to progression beyond 8 weeks. Distal motor deficits are usually more pronounced and the sensory deficits are large-fiber-predominant. The reason for this is that the fibers with the most myelin are most severely involved pathologically. Any clinical presentation that deviates from this picture should be promptly considered for alternative etiologies or an atypical form of CIDP (Table 1). A pure large-fiber sensory neuropathy with ataxia should lead to consideration for disease mimickers, separate entities altogether, or the CIDP variant termed chronic immune sensory polyneuropathy (CISP).[14] In addition, multifocal, asymmetric, and upper-limb–predominant disease should be promptly considered for multifocal CIDP.[15] Furthermore, typical CIDP patients do not usually have associated systemic symptoms such as fever, malaise, severe pain, or dysautonomia.[16]

4 | EDX FEATURES AND ANCILLARY TESTING

As alluded to earlier, clinical features should be considered first and foremost as part of good clinical practice before interpreting EDx findings. Validated demyelinating criteria, such as the EFNS/PNS criteria, should be used to determine whether the EDx findings are truly demyelinating. However, detecting demyelination may be limited by "the ceiling effect" of EDx testing, where sensory and motor responses may be low or absent in electrophysiologically advanced cases. This can be due to secondary axonal loss, temporal dispersion, or conduction block. Furthermore, when demyelination is confined to

TABLE 1 Potentially useful laboratory tests in the evaluation of CIDP variants and mimickers

Clinical presentations of CIDP variants or disease mimickers	Potentially helpful laboratory tests
Length-dependent sensory greater than motor, axonal predominant peripheral neuropathy	HbA1C, vitamin B_{12}, methylmalonic acid, copper, zinc, ceruloplasmin, TSH
Non–length-dependent sensory ganglionopathy/ neuronopathy	SSA and SSB antibodies, minor salivary gland biopsy, anti-Hu, anti-CRMP antibodies, MR imaging of nerve roots, somatosensory evoked potentials, CSF evaluation
Upper limb predominant	GM1 and disulfated heparin disaccharide (NS6S) antibodies (MMN), complete blood count, sedimentation rate, C-reactive protein, ANCA profile, ANA, extractable nuclear antigen profile, chronic hepatitis screen, nerve biopsy, genetic testing (PMP22 if HNPP suspected)
Sensory and motor demyelinating neuropathy	Genetic testing (PMP22), complete blood count, monoclonal protein screen, myelin-associated glycoprotein antibodies, VEGF level, skeletal survey
Sensory and motor axonal polyradiculoneuropathy	Monoclonal protein screen, serum-free light chains, NT-proBNP, and fat aspirate; genetic testing (TTR) and ^{99m}Tc-PYP scan (TTR)

Abbreviations: AL, acquired light-chain; ANA, antinuclear antigen; ANCA, anti-neutrophil cytoplasmic antibodies; CRMP, collapsin response mediator protein; CSF, cerebrospinal fluid; HbA1C, hemoglobin A1C; HNPP, hereditary neuropathy with liability to pressure palsy; MMN, multifocal motor neuropathy; MR, magnetic resonance; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; PMP22, peripheral myelin protein 22; ^{99m}Tc-PYP; 99m-technetium-pyrophosphate; TSH, thyroid-stimulating hormone; TTR, transthyretin; VEGF, vascular endothelial growth factor.

the nerve roots, patients may have no clear demyelinating features on EDx testing, especially when F waves are absent. In these cases, needle electrmyography (EMG) is essential. A predominantly demyelinating process (conduction block or temporal dispersion) should be suspected when the changes on needle EMG are unexpectedly mild (reduced recruitment with only mildly enlarged motor unit potentials and only scarce abnormal spontaneous activity), even in the presence of low-amplitude motor responses. Last, it is worth noting that other demyelinating neuropathies may fulfill EDx criteria for CIDP, but have distinctive clinical and laboratory features.

CSF protein elevation is not mandatory for many CIDP experts, but is a supportive laboratory finding present in more than 90% of CIDP patients.[17] However, it is nonspecific, as it is influenced by age and other comorbid conditions such as diabetes mellitus and degenerative spinal stenosis.[18] Raising the upper reference limit for CSF protein to greater than 45 mg/dL increases its specificity in diagnosing CIDP without compromising its sensitivity (specifically using cutoffs of 50 mg/dL for patients <50 years and 60 mg/dL for patients ≥50 years).[19] Magnetic resonance imaging (MRI) and ultrasound findings are not a major focus of this review, although nerve root thickening and plexus enlargement on MRI[20] as well as proximal median nerve and brachial plexus enlargement on ultrasound,[21,22] respectively, may be helpful in the diagnostic workup.

Nerve biopsy is not needed when the presentation is one of typical CIDP. However, nerve biopsy should be considered in rapidly progressive or treatment-refractory neuropathy, in multifocal cases, or when vasculitis, amyloidosis, or a neoplastic process are suspected.

5 | PATTERNS SUGGESTIVE OF ATYPICAL CIDP OR DISEASE MIMICKERS

In the following subection, we discuss clinical patterns and findings that should alert the health-care provider to atypical CIDP subtypes or disease mimickers (Table 1).

5.1 | Rapid clinical progression by definition

CIDP is a chronic disease that progresses beyond 8 weeks. A slowly progressive course is more common in adults, whereas a relapsing-and-remitting course is more common in children.[23] If symptoms reach a nadir within 4 weeks from onset, then Guillain-Barré syndrome (GBS) should be considered. Patients with treated GBS may also experience treatment-related fluctuation, which needs to be distinguished from CIDP.[24] Adding to the diagnostic challenge is the entity of acute-onset CIDP (A-CIDP), in which patients present acutely but continue to progress beyond 4 to 8 weeks, and which is further defined as at least three relapses after 9 weeks.[24] A-CIDP is not phenotypically an "atypical" form of CIDP (as far at the clinical and EDx features), but is atypical in its clinical course, with an unusually rapid onset. The challenge is to recognize it early and differentiate it from GBS, as A-CIDP will need ongoing immunotherapy. Certain features suggest A-CIDP as opposed to GBS. A-CIDP patients are less severely affected, do not need mechanical ventilation, rarely have cranial nerve involvement, and have more typical CIDP demyelinating findings on EDx when compared to those seen with GBS. Less commonly, patients may follow a monophasic course and reach a nadir in 4 to 8 weeks, a separate entity called subacute inflammatory demyelinating polyneuropathy (SIDP).[25,26] In patients presenting with subacute-onset neuropathy with coarse tremor, ataxia, and distal weakness, testing for the CIDP nodopathy subtypes should be pursued, particularly neurofascin-155 and/or contactin-1 antibodies.[27] Nodopathies represent variants of typical CIDP in which proteins near or at the node of Ranvier are targeted by immunoglobulin G4 (IgG4) antibodies, and constitute a sizeable minority of CIDP patients.[28] Finally, apparent worsening in CIDP may occur because the effect of treatment wears off; this wearing-off effect may be mislabeled as treatment-refractory CIDP.[29]

5.2 | Length-dependent sensory-greater-than-motor, axonal-predominant peripheral neuropathy

Length-dependent sensory predominant peripheral neuropathy can be due to many causes, and is often misdiagnosed as CIDP because of nonspecific EDx abnormalities interpreted as demyelinating. This phenotype is similar to the mild slowing of conduction velocities seen in length-dependent diabetic polyneuropathy.

5.3 | Non–length-dependent sensory ganglionopathy/neuronopathy

When there is a marked ataxic component with prominent large-fiber involvement at onset, a sensory ganglionopathy may be considered. Two causes of sensory ganglionopathy are paraneoplastic ganglionopathy and Sjögren syndrome. In addition, the sensory variant of CIDP— CISP—should be considered.[14,30] Although EDx studies are normal in CISP, somatosensory latencies are prolonged, CSF protein is elevated, and lumbar rootlet biopsies show loss of large myelinated nerve fibers, onion-bulb formation (evidence of ongoing demyelination and remyelination), and endoneurial macrophages.[14]

5.4 | Upper-limb-predominant neuropathy

Multifocal CIDP (multifocal asymmetric demyelinating sensory and motor neuropathy [MADSAM] or Lewis-Sumner syndrome) and multifocal motor neuropathy (MMN) should be considered in the setting of asymmetric-onset upper limb neuropathy. Herein, the weakness is asymmetric, patchy, and disproportionately distal, in contrast to typical CIDP, which is symmetrical. In axonal, upper-limb-predominant neuropathy, a motor neuron disease should be considered, especially when there is marked atrophy and asymmetry. When associated with troublesome pain, an inflammatory brachial plexus neuropathy (neuralgic amyotrophy or Parsonage-Turner syndrome) or vasculitis should be considered.

The EDx demyelinating features found in multifocal CIDP include slowing of conduction velocities, prolongation of F waves and distal latencies, temporal dispersion, and conduction block; this stands in contrast to MMN, where the main "demyelinating" feature is motor conduction block. The pathology of multifocal CIDP is inflammatory demyelination, similar to classical CIDP, and stands in contrast to the pathology of MMN, which involves axonal degeneration and unequal loss of myelinated nerve fibers.[31] In motor neuron disease, EDx findings may show slightly slowed motor velocities, but markedly reduced compound muscle action potential amplitudes, as well as dense fibrillation potentials on needle EMG.

5.5 | Sensory and motor demyelinating neuropathy

The main two entities under this category are hereditary motor and sensory demyelinating neuropathy or Charcot-Marie-Tooth disease type 1 (CMT1) and paraproteinemic neuropathy. CMT1 usually presents with a much slower progression. On clinical examination, the sensory and motor deficits are predominantly distal and associated with pes cavus and hammer toes, often with positive family history. On EDx testing, the demyelination most often consists of uniform slowing with no conduction block or temporal dispersion, and the F-wave latencies are not prolonged in comparison to the F-wave estimates.[32] Furthermore, on nerve biopsy evaluation, the onion-bulb pattern in CMT1 is generalized, and not mixed or multifocal as in CIDP.[6]

Paraproteinemic neuropathies are heterogeneous and encompass varied mimickers of typical CIDP (Table 2). IgM paraproteinemic neuropathy with distal acquired demyelinating symmetrical (DADS) phenotype[33] is a sensory-predominant neuropathy characterized by marked ataxia and gait unsteadiness.[34] Myelin-associated glycoprotein (MAG) antibodies are present in about half of IgM neuropathy patients. IgM-positive DADS neuropathy patients are generally treatment-refractory to standard CIDP immunotherapies.[33,35] Although the monoclonal gammopathy in IgM neuropathy is considered of unclear significance (MGUS), the presence of an IgG or IgA monoclonal gammopathy (especially if it is lambda) and of vascular endothelial growth factor (VEGF) may be associated with an underlying osteosclerotic myeloma, as seen in POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome.[36]

Clinically, POEMS syndrome presents with a severe sensory and motor demyelinating polyradiculoneuropathy, mimicking CIDP. POEMS patients often display systemic symptoms, namely malaise, marked edema, and skin changes. The presence of monoclonal protein, particularly in the setting of thrombocytosis, in a patient with suspected CIDP should prompt screening for POEMS syndrome.[37] Some important additional clinical clues in identifying POEMS syndrome are that it does not respond to typical CIDP immunotherapy and that patients typically have severe disabling pain, which is rarely found in CIDP. Many POEMS patients are initially diagnosed with CIDP. The EDx findings from POEMS syndrome show more uniform demyelination and axonal degeneration than that seen in CIDP.[38] Nerve biopsies from POEMS patients show more axonal degeneration and neovascularization with fewer onion bulbs and a similar degree of demyelination than do nerve biopsies from CIDP patients.[39]

5.6 | Sensory and motor axonal polyradiculoneuropathy

In addition to POEMS syndrome, light-chain (AL) and transthyretin (TTR) familial amyloid polyneuropathy (FAP) can also present with a sensory and motor axonal–predominant polyradiculoneuropathy.[40,41] Amyloidosis is usually associated with marked dysautonomia (orthostatic hypotension, gastrointestinal dysmotility, and erectile dysfunction), which is rare in CIDP,[16] and produces a rapidly progressive painful neuropathy that is refractory to standard CIDP therapies. Neurolymphomatosis is another condition that may mimic CIDP and

TABLE 2 Paraproteinemic neuropathy disease mimickers of CIDP

Monoclonal gammopathy subtype	Plasma cell disorder	Peripheral neuropathy phenotype	Autonomic involvement	Systemic symptoms	Helpful laboratory markers
IgM-kappa or -lambda	MGUS	Length-dependent, sensory predominant, demyelinating	–	–	MAG antibodies
	Waldenström macroglobulinemia	Similar to IgM-MGUS neuropathy with more common axonal involvement	–	Yes	Hemoglobin, platelet count, IgM levels, β_2-microglobulin
IgA- or IgG- lambda	POEMS syndrome	Sensory and motor, demyelinating more than axonal, polyradiculoneuropathy	+	Yes	Platelet count (thrombocytosis, VEGF, endocrine studies
Any type including light-chain only	AL amyloidosis	Length-dependent (or polyradiculoneuropathy) sensory and motor, axonal	+++	Yes (patients look the sickest)	24-hour urine total protein, complete blood count, creatinine, alkaline phosphatase, troponin, brain natriuretic peptide, or N-terminal pro-BNP levels

Abbreviations: AL, amyloidosis, acquired light-chain amyloidosis; BNP, brain natriuretic protein; DADS, distal acquired demyelinating sensorimotor neuropathy; EDx, electrodiagnostic; Ig, immunoglobulin; MAG, myelin-associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance; NCS, nerve conduction studies; N-terminal proBNP, N-terminal prohormone brain natriuretic peptide; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; VEGF, vascular endothelial growth factor.

should be considered when there is a history of lymphoma (especially non-Hodgkin), weight loss, and asymmetric course.[42] Finally, diabetic or nondiabetic lumbosacral radiculoplexus neuropathy often presents as a progressive polyradiculoneuropathy, which may mimic CIDP.[43] Patients usually report severe pain at onset, which is atypical for CIDP. However, a painless diabetic lumbosacral radiculoplexus neuropathy does exist, which often involves all four limbs, manifests as a symmetrical axonal polyradiculoneuropathy, and has ischemic features and microvasculitis on nerve biopsy, with the latter finding also seen in painful diabetic and nondiabetic radiculoplexus neuropathy.[44] One may ask how to treat patients with a motor-predominant axonal polyradiculoneuropathy that clinically presents like CIDP but does not meet EDx criteria. We believe that such patients should be given immunotherapeutic trials and have a rigorous evaluation after several months. If improvement is seen with quantitative endpoints, treatment should be continued and, if there is no improvement, then treatment should be discontinued.

6 | EXISTING THERAPIES: STANDARD OF PRACTICE AND COMPARATIVE EFFICACY

Treatment strategies in CIDP aim to achieve remission or to produce meaningful improvement in strength and function. Many patients with CIDP need treatment over very long periods of time, whereas, in others, the disease may go into remission. Irrespective of the therapy used, the dose and frequency of treatment should be appropriate for the severity of neuropathy. For all treatments, the goal should be to produce the most benefit at the smallest dose possible.

6.1 | IVIg

Current practice recommendations from the EFNS/PNS joint task force advocate the use of the lowest dose of IVIg necessary, with periodic dose reduction.[9] The efficacy of IVIg in CIDP was demonstrated in 1994 in a crossover study comparing IVIg at 0.4 g/kg per week vs PE, with both treatments being beneficial as judged by improvement in the neurological examination (change in neuropathy impairment score [NIS]).[45] Over time, IVIg efficacy has been established conclusively. A large, randomized, multicenter, placebo-controlled, crossover trial (ICE) established the efficacy of IVIg in both the short and long term, using a dosing regimen of 1 g/kg every 3 weeks, which helped secure US Food and Drug Administration approval.[46] The subsequent randomized, multicenter, parallel-group IVIg vs intravenous methylprednisolone (IVMP) for CIDP (IMC) trial compared IVIg with IVMP, and demonstrated comparable efficacy of IVIg to methylprednisolone, using an IVIg dosing regimen of 0.5 g/kg per day over 4 days, given monthly for 6 months.[47] A 2013 Cochrane Review concluded that IVIg improved CIDP disability for at least 2 to 6 weeks, with a number needed to treat of three (for every 3 CIDP patients treated, 1 CIDP patient will obtain a positive outcome [or avoid a negative disability outcome]).[48] However, IVIg does not

work for all patients with or all subtypes of CIDP. Identification of the IVIg-refractory IgG4 subtype nodopathies, namely neurofascin-155 and contactin-1, exposed the limitations of IVIg in treating certain forms of CIDP. IgG4 does not activate complement well and has low affinity for Fc receptors on effector cells.[49,50]

The topic of optimal IVIg dosing is the focus of ongoing investigation. Of all dosing schedules, the every 3- or 4-week regimens are the most widely used (based on the ICE and IMC trials) and likely represent the average needs of most CIDP patients. Nevertheless, the most important principle when treating CIDP is that there is no one standard dose that works for all CIDP patients and that dosing should be titrated to individual patients' need and response. Some have advocated an expedited IVIg wean. In such a model, a standard 2-g/kg loading dose is given followed by a repeat dose 6 weeks later if the patient does not fully stabilize. Afterward, the clinician observes for clinical deterioration, and uses this resultant *"time-to-deterioration"* period to guide future infusion frequency.[51] Others have focused on IgG level as a biomarker (the ΔIgG between pre- and posttreatment) to individually optimize IVIg dosing regimen, and this may help individualize treatment, although it did not correlate with best clinical response for the group.[52-54] Rajabally and Afzal explored the clinical and economic impacts of varied dosing regimens, and found an individualized dosing regimen to be clinically noninferior and more cost-effective than a standard dosing regimen.[55] Ongoing studies are exploring three different dosing levels (while maintaining frequency at every 3 weeks),[56] as well as reduced-dose, higher frequency (<14 days) administration.[54,57]

Central to the long-term use of IVIg in CIDP is a review of IVIg pharmacokinetics.[29,58] After intravenous infusion, IgG levels peak immediately and then drop within 2 to 4 days as IgG enters the extracellular volume space. The half-life of IgG varies from 21 to 30 days. Once IgG enters the intravascular space, its degradation proceeds as a first-order process. Key to its breakdown is the saturable endothelial cell receptor FcRn, which protects IgG from endocytosis and lysosomal degradation.[29] Furthermore, a large difference exists in the trough-to-peak difference in IgG level when comparing infrequent, high-dose IVIg infusions (2 g/kg per month) with more frequent, low-dose subcutaneous IgG infusions (0.5 g/kg per week).[59]

With regard to adverse events, patients may develop headaches, dermatological eruptions,[60] and more serious thromboembolic events. Caution should be used in patients with coronary artery disease, recent myocardial infarction, stroke, or thrombotic event; hypercoagulability (acquired or familial); oral contraceptive use; and planned travel. In addition, patients with advanced age, pre-existing renal compromise, and diabetes are more prone to renal injury. Preventive measures include pretreatment with antihistamines, CCS, or nonsteroidal anti-inflammatory drugs to mitigate allergic reactions and headaches. One study showed no difference in the likelihood of thromboembolic events as per the average monthly or daily dose of IVIg, but that vascular risk factors should be screened for before IVIg commencement.[61] Periodic monitoring of renal function is reasonable. Low-osmolality formulations should be pursued when possible, as sucrose is a major aggravator of renal injury and glucose of hyperglycemia.

6.2 | SCIg

In light of the established efficacy of IVIg,[46,48] the question arose as to whether immunoglobulin could be delivered in a more convenient fashion with fewer adverse events. SCIg emerged as a potential alternative to IVIg. A large, international, randomized, placebo-controlled trial confirmed both the efficacy and tolerability of SCIg.[62] Patients in the once-weekly high-dose (0.4 g/kg) and low-dose (0.2 g/kg) SCIg groups performed better than those in the placebo group, although there was no significant difference between the high- and low-dose groups. As compared with IVIg, the overall adverse-event profile of SCIg was favorable.

The major challenge with SCIg is skin irritation, which is dose-dependent, but also seems to lessen with time.[63] It is safe and reasonable to consider switching from IVIg to SCIg for convenience, poor intravenous access, end-of-dose wear-off effect, or adverse events with intravenous infusions.[64] However, before switching, patients must be stable on IVIg, as there is currently insufficient evidence for SCIg as inductive therapy in treatment-naive CIDP patients.

6.3 | CCS

Although CCSs represent another class of effective therapy, the primary concern is adverse events, especially with prolonged therapy. One of the first trials to demonstrate the efficacy of prednisone was conducted in 1982 by Dyck and colleagues, using a high-dose (120 mg) alternate-day regimen for 3 months.[65] Although patients may experience improvement soon after starting treatment, attaining maximal response can take an average of 3 to 6 months.[66,67] A well-planned tapering regimen is particularly important. Similar to IVIg, tapering is usually started after the patient stops improving and reaches a plateau. CCS can be tapered by decreasing the daily dose by 5 to 10 mg every 1 to 4 weeks, or by transitioning to an alternate-day regimen.

Other CCS formulations beyond oral prednisone have also been explored. Investigators studied the efficacy and tolerability of pulsed monthly dexamethasone, administered orally 4 days per month at 40 mg/day, as compared with daily standard prednisolone dosing. The dexamethasone arm showed a median time to remission of 20 weeks (as compared with 39 weeks), less deterioration after discontinuation, and less insomnia and cushingoid features.[67] A single-center, retrospective study explored the utility of pulsed CCSs in the form of IVMP as compared with daily oral prednisone and IVIg.[68] The most common dosing regimen for the IVMP arm was an induction dose of 1 g/day for 3 to 5 days followed by 1 g once per week, tapered in frequency and dose. IVMP patients had less weight gain and cushingoid features as compared with those on oral daily prednisone, with a higher response rate also seen in the intravenous arm at 6 months.

Comparison of IVIg and CCS is another area of focus. The IMC trial discussed earlier was a prospective 6-month European trial that further explored the efficacy and tolerability of IVMP, administered monthly in the form of 0.5 g/day for 4 days, as compared with IVIg administered monthly in the form of 0.5 g/kg per day for 4 days. Patients randomized to the IVIg arm showed faster remission and better compliance, with fewer adverse events. However, the IVMP arm had longer median disease remission (14 months) after drug discontinuation as compared with IVIg (4.5 months). In addition, a greater percentage of patients in the IVMP arm remained in remission at 6 months. Whether this holds true for longer follow-up remains to be seen. Finally, a retrospective study comparing characteristics between patients who could be withdrawn from treatment (treatment-withdrawal group) and those who could not (treatment-dependent) showed that the treatment-dependent group responded more frequently to IVIg, showed CCS treatment resistance, and presented more commonly with a multifocal deficit. However, successful treatment withdrawal occurred more often with CCS use.[69]

Given the improved long-term remission profile with IVMP, some have explored whether there is a role for combined IVMP and IVIg therapy from disease onset. To answer this question, a prospective trial (OPTIC) is underway, randomizing patients to either 1 g/kg IVIg every 3 weeks + 1 g IVMP every 3 weeks *or* 1 g/kg IVIg every 3 weeks + placebo, over a course of 18 weeks.[70]

In addition to the aforementioned adverse events, CCS carry numerous other risks, such as hyperglycemia, CCS-induced diabetes, osteopenia, infection, and gastritis, among many others, and which need to be discussed and addressed fully with patients from the start. These risks are beyond the focus of this review but are summarized in guidelines.[71]

6.4 | PE

PE is an effective therapy for treatment-refractory cases of CIDP, namely those that have not responded to IVIg or CCS. Furthermore, PE remains a useful alternative for patients unable to receive IVIg or CCSs due to adverse-event risk or contraindications. PE is postulated to remove circulating immunoglobulins, complement, cytokines, and antibodies. Data from a prospective, double-blind, sham-controlled trial in 1986 showed improvement in combined measures of nerve conduction as well as the NIS by week 3 in the PE group when compared with a sham group.[72] A crossover, sham-controlled, prospective trial conducted 10 years later redemonstrated the benefit of PE after 10 exchanges, with improvements noted in mean NISs, grip strength, clinical disability grade, and summated mean motor potential amplitudes and conduction velocities.[73] A 1994 crossover, prospective, observer-controlled study comparing PE with IVIg showed that both immunotherapies produced major neurological improvement as graded by the NIS and the summated compound muscle action potentials.[45] The authors concluded that, although both treatments were equally effective, IVIg may be preferable due to its ease of use.

PE is most often used initially in severely disabled patients, in patients refractory to CCS or IVIg, or as rescue therapy during CIDP exacerbations. Data regarding the efficacy of PE as a long-term treatment option for CIDP are limited. Of note, within weeks to months after completion of treatment, up to 50% to 67% of patients deteriorate. However, all three primary treatments of CIDP (CCS, IVIg, and PE) require ongoing use and cannot be given for a short time and then abruptly stopped without worsening of disease. PE can, however, sometimes be used intermittently either alone or as adjunctive therapy with CCS in the outpatient setting.

Adverse-event considerations include fluid overload, especially in those with congestive heart failure, liver disease, and renal disease, as well as infection risk. Angiotensin-converting enzyme inhibitors should be held 24 hours before exchange.[74]

7 | TREATMENT FAILURE AND ONGOING TRIALS

Despite the efficacy of IVIg, SCIg, CCS, and PE in the treatment of CIDP, some patients do not respond to any of these modalities. When lack of treatment response occurs, the first step is to confirm that the patient actually has CIDP. In our experience, if a patient has a rapidly progressing, ongoing demyelinating polyradiculoneuropathy that has not responded to conventional immunotherapy, the most likely explanation is a disease mimicker, most commonly POEMS syndrome, for which repeat immunofixation electrophoresis and VEGF levels should be obtained. Other possible reasons for poor treatment response include an IgM DADS subtype of CIDP or the nodopathy subtypes (neurofascin-155 and contactin-1). If the case is indeed treatment-refractory typical CIDP, combined PE and CCS or IVIg and CCS can be tried. In addition, patients with antibodies to neurofascin-155 are refractory to IVIg but are quite sensitive to rituximab and probably PE,[75] whereas those with antibodies to contactin-1 respond better to CCS than IVIg.[76] Irrespective of antibody status, rituximab appears to be a promising therapy even for antibody-negative, treatment-refractory CIDP, although not all patients respond.[75] Roux et al evaluated 28 antibody-negative CIDP patients and demonstrated that 75% of patients improved, although patients had concomitant hematological disorders or autoimmune disease.[77] Median time to improvement was 6 months and only two patients required retreatment by 2-year follow-up. Querol examined contactin-1– and neurofascin-155–positive, treatment-refractory CIDP patients receiving rituximab, and demonstrated clinical improvement and a decline in antibody titers. An ongoing Japanese randomized, controlled trial is evaluating the efficacy and safety of rituximab in CIDP patients with and without anti-paranodal antibodies (NCT03864185). High-dose pulsed cyclophosphamide also showed improvement in muscle strength, functional status, and EDx parameters in treatment-refractory CIDP, but potential side effects need to be carefully discussed with patients.[78-80]

Data regarding the role of other immunosuppressants is limited to case series, anecdotal experience, or mixed evidence at best.[81] For example, azathioprine combined with prednisone was not found to be

superior to prednisone alone in one trial, although the study was limited by short duration.[82] Two placebo-controlled, randomized trials found fingolimod[83] and low-dose methotrexate[84] not to be efficacious in CIDP. Ongoing clinical trials are evaluating the role of therapies targeting the neonatal Fc receptor (FcRn) (NCT04051944 and NCT04281472).

8 | OUTCOME MEASURES

CIDP is a heterogeneous disorder with marked variability in treatment response.[29] With effective treatment, long-term disability is generally limited, whereas poor outcome is tied to delay of therapy.[85] An ongoing multicenter, prospective study aims to better define the natural history of CIDP.[86] As CIDP currently has no established biomarkers, measurements of neuropathy severity are needed, not only for diagnosis, but also to monitor treatment response.

The NIS (previously called the Neurologic Disability Score) was among the first outcome measures used to establish IVIg and PE efficacy in CIDP.[45,72,87] The NIS is a summed score of a standard representative list of motor, sensory, and muscle stretch reflex impairments, which provides a robust quantification of the standard neuropathy exam to allow for objective visit-to-visit surveillance of treatment response. In a prospective, semiblinded, and standardized assessment of CIDP patients, investigators found the NIS as well as the NIS weakness subscore to scale with neuropathy abnormality.[88] In addition, the summated CMAP score (a sum of the CMAP of the ulnar, fibular, and tibial motor nerves) scaled with neuropathy abnormality and also correlated with the NIS. The NIS has evolved over time to apply to different types of neuropathy, including diabetic polyneuropathy, CIDP, and recently TTR amyloidosis neuropathy.[89]

Over the last decade, renewed interest has focused on capturing clinical outcome using multiple modalities for research trials in CIDP. A combined set of outcome measures for CIDP trials and clinical evaluation emerged, incorporating assessment of: (a) *disability* (Inflammatory Rasch-built Overall Disability Scale [I-RODS] and Inflammatory Neuropathy Cause and Treatment [INCAT]); (b) *strength* (grip strength testing, manual muscle testing, Medical Research Council summated score); (c) *gait assessment* (timed up-and-go test); and (d) *quality-of-life measures* (EuroQoL 5-Dimension Questionnaire, Patient Global Impression of Change).[90,91] Although this approach applies to research trials, it is equally important in the clinical setting.

Of such measures, three warrant particular attention, namely grip strength, the I-RODS, and the INCAT. Grip strength, performed using either a Jamar or Vigorometer device, is a well-validated and quick measure of impairment.[90] It provides objective evidence of global neurological status and correlates well with the I-RODS score.[92] In a Dutch study of 14 patients with CIDP, grip strength correlated with IgG levels 1 week after IVIg infusion, thus allowing individualization of IVIg dosing, given the notable interpatient variability in IVIg pharmacokinetics.[93] The I-RODS is a validated and disease-specific outcome measure for CIDP patients that is widely used.[94] The INCAT is another widely used primary outcome measure for CIDP trials,[66] although it is not without its limitations, such as disproportionate item weighting, insensitivity to minor changes, and inability to capture activity limitation from proximal arm weakness.[95] Important in the discussion of CIDP outcome measures is the concept of minimal clinically improvement difference (MCID), which was used to validate the efficacy of the ICE trial.[96] The MCID is "the smallest difference in score in the domain of interest which patients perceive as beneficial."[97]

9 | HOW WE TREAT CIDP

Although there is no uniformly agreed-upon approach to long-term treatment of CIDP, we conclude with a review of how we approach CIDP. Our approach is not definitive and other approaches should be given equal, if not more, consideration. We only share an approach that we have found over the years to be effective and practical.

Unless there is a contraindication, our first-line treatment is IVIg. As discussed earlier, there is no set IVIg dose or frequency for all CIDP patients. Dosing always depends on the individual patient. Severely affected, rapidly progressive patients require higher IVIg doses than milder, slowly progressive cases. As discussed earlier, many experts advocate a dosing schedule of every 3 or 4 weeks. However, some patients require more frequent dosing, whereas others require less. The concept of response-based immunotherapy should guide the long-term treatment of CIDP.[88] Thus, dosing should be titrated to individual patient need. Periodic and frequent assessment by a trained neuromuscular physician using validated outcome measures allows for individualization of dosing and proper and timely weaning of immunotherapy in CIDP patients over long-term follow-up.

On the basis of data from the early IVIg CIDP studies as well as more recent data on immunotherapy and SCIg dosing,[45,59,62,88] we usually start, in more severe cases, by loading with 2 g/kg over 5 days and then initiate 0.4 g/kg per week. In milder cases, a loading dose may not be necessary, and we may begin with IVIg 0.4 g/kg per week for 4 weeks and then every 2 weeks thereafter. In more severe cases, 0.4 g/kg twice per week is sometimes given. We maintain the patient on the same dose until improvement stops or reaches a plateau. The goal is not to get the patient's neurological examination back to normal but to substantially improve the patient's clinical examination as well as strength and function. We see the patient back in 3-month intervals unless there is rapid worsening, in which case we see them more frequently. Once plateau is achieved, we start a slow taper by increasing the interval between IVIg doses, typically every 3 months. There is no clear guidance on how fast the taper should be, but in most patients we attempt to completely taper off treatment at some stage. Patients may successfully discontinue treatment and remain in remission, or continue to require a variable dose of IVIg, ranging from once per week to once every 6 weeks. Therefore, the treatment is tailored on a case-by-case basis.

To reiterate, in this section we have only discussed the approach that we have found helpful in our centers' clinical experience. We encourage readers to refer to other IVIg dosing algorithms as described earlier in this review.

Depending on disease severity at presentation, we may add IVMP to IVIg, fully cognizant that formal data are still lacking in this regard, although the OPTIC data do show some early promise.[70] We use a maintenance dose of 1 g per week IVMP, typically coinciding with the weekly 0.4-g/kg IVIg infusions. However, we wean IVMP faster, due to its adverse-event profile. Although daily or alternate-day oral prednisone is efficacious, we prefer to avoid it whenever possible given its heightened adverse-event profile. However, it is an excellent option in patients with no venous access or poor tolerance to IVIg.

In cases of suboptimal response to IVIg and/or CCS, changing the treatment to PE can be considered. PE remains the first-line treatment in patients who are rapidly worsening. PE may be a temporary treatment until another effective treatment can be found. However, the authors have treated CIDP patients in whom CCS and IVIg do not work yet PE does work. If needed, we also combine PE with CCS in such treatment-refractory patients. In these patients, long-term PE is very effective, although it does present long-term challenges with venous access and infection.

In cases refractory to standard treatment, the first step is to revisit the diagnosis of CIDP. Depending on the clinical phenotype, we repeat a thorough evaluation, as delineated in Table 1. A nerve biopsy may be needed. Rituximab should be considered in patients with antibodies to neurofascin-155 and contactin-1. Rituximab or cyclophosphamide can also be considered in seronegative patients if no alternative etiology is identified, or in patients who respond to PE, although therapeutic efficacy data are still quite limited.

10 | CONCLUSIONS

The diagnosis of CIDP remains primarily clinical, supported by demonstrating demyelination on EDx testing after standardized criteria such as those of the EFNS/PNS. In some cases, CSF studies, MR or ultrasound imaging, and nerve pathology are helpful. Response to immunotherapy should be determined based on objective measures. There is an ongoing need for diagnostic and therapeutic biomarkers as well as alternative treatment options for patients who do not respond or cannot tolerate currently available agents.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

P. James B. Dyck https://orcid.org/0000-0003-0212-8254

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