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Review Article

What Is in the Literature

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Abstract

What is in the Literature focuses on chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a neuropathy with challenges in diagnosis and treatment. A recent revision of diagnostic criteria (EFN/PNS criteria) has helped define clinical features of typical and atypical variants and what is not considered CIDP. Initiating pathologic factors is not known for typical CIDP or variants. New treatment approaches are based on immunologic mechanisms. Rare patients with a CIDP-like clinical pattern are found to have antibodies to proteins at and around the node of Ranvier and are not considered to be CIDP but a nodal-paranodopathy. Although occurring mainly in adults, CIDP also occurs in children. CIDP may have clinical and electrodiagnostic features that overlap with hereditary neuropathies, and the latter might show some response to treatment. Articles published in the past year that address these issues are discussed in this review.

Key Words: chronic inflammatory demyelinating polyradicoloneuropathy, CIDP, diagnosis, treatment

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DIAGNOSIS OF CIDP

Diagnostic criteria for CIDP have been put forward based on consensus in 2010 as EFNS/PNS and a revision in 2021 as EFN/PNS with a few changes in nerve conduction criteria.[1,2] A review of patients (2010–2018) from a single center and followed over 1 year assessed how many fulfilled EFNS/PNS criteria and also looked at the clinical, electrodiagnostic, and nerve ultrasound findings in those who did not fill criteria.[3] Patients were referred for suspected diagnosis of an immune-mediated neuropathy. From 391patients, 203 were believed to have CIDP. At initial evaluation, 75% fulfilled electrodiagnostic criteria, and with follow-up studies within the 1 year, an additional 15% met criteria, for a total of 90%. Ten percent (21 patients) did not fulfill electrodiagnostic criteria, but with prolonged follow-up and testing (up to 6 years), 7 progressed to fill criteria. Thirty-six patients also had diabetes type 2, and 83% fulfilled electrodiagnostic criteria. Although response to treatment was not discussed in detail, patients with CIDP with diabetes responded similarly to those without diabetes. A conclusion is that repeat electrodiagnostic studies may be required.

Diagnostic designations differ between the EFNS/PNS and EFN/PNS electrodiagnostic criteria; with "definite," "probable," and "possible" for the former, and "CIDP" and "possible" for the latter.[1,2] It is likely that similar numbers of patients by the EFNS/PNS criteria in this study would also meet the EFN/PNS criteria.

PATHOLOGIC FEATURES OF TYPICAL CIDP

CIDP is a chronic neuropathy, and typical CIDP has clinical features of symmetric sensory and is used to support demyelination/conduction block, and there are EFN/PNS electrodiagnostic criteria to aid in separating CIDP from primary axonal neuropathies.[2] Nerve biopsies and rare postmortem examinations support inflammatory processes. The relative rarity of CIDP and lack of animal models that mimic human disease make study of underlying pathology difficult. CIDP variants (multifocal, focal, distal, motor, or sensory distributions) are clinically distinguishable from CIDP and suggest a variety of mechanisms are likely among the forms.

Initiating events that activate the immune system in typical CIDP are not

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known. Immunopathologic mechanisms can include cellular, humoral, and complement pathways that lead to a spectrum of structural changes including segmental demyelination, degrees of axonal damage, and nodal conduction block without structural changes.[4] Despite the lack of detectable antigens and antibodies in typical CIDP, humoral mechanisms are supported by the patient response to plasma exchange. Cellular mechanisms include breakdown of the blood–nerve barrier, interstitial edema with passage of activated T cells, and other lymphocytes and macrophages, which culminate with segmental demyelination and degrees of axonal damage. Compliment is activated through a number of pathways, and ultimately Cb cleaves C5 into C5a and C5b, and the latter goes on to form the membrane attack complex (MAC). Complement deposition has been found in some sural nerve biopsies in a limited sample.

NEWER CIDP TREATMENTS

New treatment modalities are being applied to CIDP. One is monoclonal antibodies that block the complement cascade, and SAR445088 (formally BIVV020) is an IgG 4 monoclonal antibody that blocks C1q in the complement cascade, and an open-label trial for CIDP is underway (NCT04658472). Drugs that bind to the fetal neonatal FC (FcRn) receptor accelerate the metabolism of IgG antibodies, both endogenous and pathogenic. Efgartigimod is effective in generalized myasthenia gravis and is being studied in CIDP (NCT04281472). Rozanolixizumab is another FcRn receptor antibody, and a small trial has been completed with results pending.

ANTIBODY-MEDIATED CIDP

Antibodies to nerve proteins are found in a small, variable percentage (5%–18%) of patients who have a CIDP-like clinical pattern and who respond poorly to therapy. The antibodies are to paranodal proteins and include neurofascin-155 (NF155), contactin-1 (CNTN1), and Caspr 1.[5] The variability in range likely reflects differences in patient selection (diagnostic criteria), but overall they represent a small percentage. Because the antibodies are directed to nodal and paranodal structures, the entity is considered a nodo-paranodopathy and is not included as CIDP in revised criteria EFN/PNS.[2]

Among antibodies to nodal-paranodal structures, anti-NF155 the most common, and includes IgG 4, IgG, and IgM classes. NF155 (with contactin-1) forms and stabilizes sodium channel clusters at the nodes of Ranvier. A study of such patients looked at nerve conduction and imaging findings, associated histolopathologic findings, and long-term outcomes.[6] From 214 patients with "CIDP," 6.5% (20) had Ig4 and 1% had IgG NF155 antibodies; while none of 23 patients with "AIDP" had these antibodies. Among patients with IgG4 NF155, there was greater distal than proximal weakness and weakness of cranial nerve innervated muscles (combinations of dysphagia/dysarthria, diplopia/ptosis, and unilateral facial weakness), sensory loss and tremor, and a high frequency of pain and sudomotor dysfunction, supporting additional small nerve fiber involvement. All met diagnostic criteria for demyelination, and most of them had prolonged R1 blink responses. Nerve root and lumbosacral enlargement and frequent contrast enhancement was observed in ~85%. The loss of nerve fibers (mild to marked) and teased fiber preparations showed segmental demyelination (highest in sciatic nerve fascicular biopsy), but onion bulb formations were not observed. Although most patients initially responded well to intravenous immune globulin (IVIG) or in combination with IV methylprednisolone or plasmapheresis, they became refractory over time, and some patient did not respond to IVIG. Most patients, therefore, needed secondary long-term immunosuppression with mycophenolate mofetil, rituximab, azathioprine, cyclosporine, and some needed addition of IVIG, prednisone, or plasmapheresis. Relapses occurred in half of the patients. IgG4 NF155 antibodies represent a unique subset of patients with "CIDP."

Another study looked at the frequency of antibodies in 276 patients fulfilling EFNS/PNS criteria for CIDP.[5] Antibodies to NF155 were found in 3.5%, to CNTN1 in 1.6%, Caspr 1 in 0.5%. Overall, it is not cost-effective to order these antibody tests in patients with CIDP unless there is prominent tremor and, importantly, poor response to prednisone or IVIG. Furthermore, with small numbers of such patients, clinical features are quite variable and not predictable.

ATYPICAL CIDP

The recent EAN/PNS CIDP criteria expand the description of atypical forms, which include distal acquired symmetric demyelinating neuropathy (DADS), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis–Sumner syndrome (LSS), focal CIDP, pure motor, and pure sensory forms.[2] Chronic immune sensory polyradiculoneuropathy (CISP) is not included. A review of the above neuropathies is informative for a discussion of their individual historical descriptions, beliefs on underlying pathology, and challenges in diagnosis.[7] Most of the patients with a distal phenotype (DADS) have either a monoclonal IgM protein (~60%) or anti–myelin-associated glycoprotein (anti-MAG) (~30%), and these are not included as CIDP. Multifocal CIDP (MADSAM or LSS) is asymmetric in distribution. Focal CIDP to one or 2 limbs may be considered as a separate entity or a version of multifocal CIDP. Pure motor CIDP excludes sensory symptoms and sensory nerve conduction abnormalities, but if sensory nerve studies are abnormal in motor CIDP, the term is motor-predominant CIDP. In a similar parcellation, pure sensory CIDP excludes subclinical motor nerve involvement, but if present, the term is sensory-predominant CIDP. The diagnosis of atypical CIDP can be difficult with the clinical variations (multifocal vs. focal) and the strictness of electrodiagnostic criteria (motor or sensory vs. motor-predominant or sensory-predominant) forms. There may be differences in underlying pathology and thus in treatment. A review of treatment response for each of the atypical CIDP forms is a useful resource.[8]

CHARCOT–MARIE–TOOTH NEUROPATHY MISDIAGNOSED AS CIDP

A review of 1104 patients from 16 hospitals in Europe originally diagnosed with CIDP, revealed that 35 (3.2%) were later found to have a form of Charcot–Marie–Tooth (CMT) neuropathy.[9] Nerve conduction criteria were available for 32 patients, and according to EFNS/PNS criteria 20433600, 69% fulfilled criteria for definite CIDP, one for possible CIDP, and 7 did not fulfill criteria.[1] The most common genetic finding was for *PMP22* gene mutations in 12, *MPZ* mutations in 11, and other CMT mutations in 12 (*GJB1, AARS, BSCL2, LRSAM1, NFN2, NEFH, PLEKHG5,* and *SH3TC2*). All 35 patients were treated (33 with IVIG; 5 with other immunosuppressive medications), and 7 were believed to respond (although quantitative measures were not available). Laboratory features were not distinct among the 35 patients with CMT. Clinical features favoring CMT were earlier age of symptom onset (39 years vs. 56 years), muscle atrophy at diagnosis, and pes cavus (in 20). The authors raise the question of whether gene panel testing, with its low cost compared with treating with IVIG, should be conducted in patients with symptom onset younger than 40 years, initial motor symptoms, and any family history of a neuropathy. This report emphasizes the importance of taking a full family history and close inspection for distal muscle atrophy and changes in foot structure.

PEDIATRIC CIDP

Neuropathy in the pediatric age range is not common, and most are hereditary (Charcot–Marie–Tooth—CMT), but CIDP occurs in children. A review of 37 children from one institution believed to have CIDP

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indicates that ~50% had an atypical presentation, which included the distal variant, pure motor variant, and rarely the sensory variant.[10] Sixty-eight percent tested negative for common genes (above). Nerve conduction studies can be difficult to perform in children, but 35 patients fulfilled EFNS/PNS criteria.[1] Spinal fluid was analyzed in 28, and cytoalbuminologic dissociation was found in 23. All patients were treated, ~50% with IVIG and ~50% with prednisone; ~15% needed IVIG plus steroids or addition of azathioprine, and rarely treated with methotrexate or rituximab. About half of patients with typical CIDP had a complete remission, while about one-third improved, but required continued treatment. Clinicians with pediatric neuromuscular training are not common, but all neuromuscular clinicians may be called upon to evaluate children. Although a hereditary neuropathy is more likely, CIDP does occur, and the EFN/PNS criteria are important to apply.

PROPRIOCEPTIVE NERVE INVOLVEMENT

In addition to weakness and cutaneous sensory loss, patients with CIDP frequently describe reduced balance, and ataxic gait is observed. Peripheral aspects of balance require both muscle strength and proprioceptive input. A study of posturography as a potential treatment response biomarker highlights the importance of group II muscle afferent fibers in CIDP.[11] This study found that the sway path (how much body movement regain balance when perturbed) was increased in patients with CIDP over control subjects, especially when eyes were closed and feet together, and improved after treatment with IVIG. In patients with CIDP with poor balance, compared with patients with better balance, more electrodiagnostic abnormalities were noted, and in particular, sensory responses were likely to be absent. Muscle afferent fibers are not easily studied and do not contribute to cutaneous sensory nerve conduction studies, but the improvement in posturography with treatment supports their clinical role.

AXONAL DAMAGE IN CIDP

The EFNS/PNS and EFN/PNS criteria focus on demyelination and conduction block for diagnosis of CIDP and variants, leading to treatment.[1,2] The primary goal of treatment is improved strength and function, but a secondary goal is timely treatment to reduce secondary axonal damage. A measure of axonal loss is reduced distal sensory nerve action potential and compound muscle action potential (CMAP) amplitudes, but the former has a floor effect (absent response when ~60% of fibers are lost) while the latter is buoyed up by collateral reinnervation (the response can be above the lower limit of normal when up to 80% of fibers are lost). A study assessed the relative effect of axonal loss and demyelination on patient disability.[12] Ninety-five patients with CIDP according to ENFS/PNS criteria 20433600 included 48% with CIDP, 29% with DADS, and 14% with MADSAM forms.[1] Twenty-six percent were assessed within 6 months of diagnosis, and the remainder was diagnosed at an early time with a mean disease duration of ~6 years. Markers of axonal loss were amplitudes below the limits of normal for distal CMAP and sensory nerve action potential from sural, peroneal motor, tibial, median motor/sensory, ulnar motor/sensory, and superficial radial nerves. The degree of axonal damage was scaled in ordinal numbers: "0" was no damage with normal nerve metrics, "1" was mild damage with sensory nerve involvement in leg nerves, "2" was moderate damage with sensory and motor involvement in leg nerves, "3" was severe involvement with sensory and motor involvement in leg nerves plus sensory involvement in arm nerves, and "4" was very severe with sensory and motor nerve involvement in both leg and arm nerves. Demyelination was based on the number of limbs that fulfilled EFNS/PNS criteria for demyelination elements. Markers of disability were Inflammatory Neuropathy Cause and Treatment-Overall

Disability Sum Scale (INCAT-ODSS), INCAT sensory score and summed Medical Research Counsel strength scores.

There was a correlation between the presence of abnormal spontaneous activity during needle electromyography in the tibialis anterior muscle and low CMAP amplitudes and elevated creatine kinase levels, thus establishing CMAP amplitude as a marker of axonal loss in the setting of a demyelinating neuropathy. No patients, including the short-duration patients, had only "0" or "1-mild" axonal loss scores; by contrast, all 95 patients had "4-very severe" loss, and the short-duration patients had "3-severe" axonal loss scores. Higher NCAT-ODSS scores correlated with patients with "3-severe" and "4-very severe" axonal loss, and reduced CMAP amplitudes in arm nerves had the highest correlations with disability. By contrast, there was no correlation between the number of limbs with demyelinating metrics and INCAT-ODSS scores.

Another approach to assessing the degree of nerve-based damage to muscles in CIDP is magnetic resonance imaging studies assessing muscle volume and quantifying the amount of noncontractile tissue (adipose and connective tissue) infiltration. An MRI study compared 5 patients with CIDP to 7 age-matched control subjects.[13] The study assessed muscles innervated by a long nerve (sciatic) comparing proximal (hamstring) with distal (triceps surae) muscles, and also a shorter proximal nerve (femoral) innervating the anterior quadriceps muscles compared with posterior hamstring muscles. There was no difference in muscle volume of proximal muscles (quadriceps or hamstring) in patients with CIDP compared with control subjects, but there was a 17% reduction in volume for triceps surae muscles. Importantly, there were reductions in contractile tissue in CIDP versus control subjects; 11.5% less in quadriceps, 15.6% less in hamstring, and 35.9% in triceps surae. Thus, there was a length-dependent loss of contractile tissue in the setting of treated CIDP. These 2 studies document the damaging effect of axonal loss in patients with CIDP despite effective treatment, including those with treatment within 6 months of diagnosis.

NONMOTOR SYMPTOMS

The main clinical focus in diagnosing and managing patients with CIDP is on weakness and sensory abnormalities, but once a diagnosis is made there are nonmotor symptoms to address. From a cohort of 84 patients who fulfilled EFNS/PNS criteria for CIDP, 45% with typical and 55% with atypical (DADS, MADSAM/LSS) pain was assessed by the Pain Detect Questionnaire, fatigue by the Krupp Fatigue Severity Scale, depression by the Beck Depression Inventory II, and quality of life by the SF-36.[14] Pain was described in 62% of patients with 52% as moderate in severity and 33% as severe, and neuropathic type pain was described in 46%, with no differences in frequency and type of pain between typical and atypical forms of CIDP. Factors related to the prevalence of pain were more sensory abnormalities but not degree of weakness; factors associated with pain were worse physical quality of life domain of the SF-36, greater fatigue scores, and more common depressive symptoms. Although the study population was from a tertiary medical center, only 40% received medication for pain; there was no comment on the percentage receiving medication for depression.

This study emphasizes the importance of asking specific questions regarding the presence of pain, both neuropathic and nociceptive, and altered mood. Commonly used clinical disability scales for monitoring CIDP (INCAT-ODSS, Rasch-built Overall Disability Scale [iRODS]) do not query pain or mood. Chronic illness such as CIDP cause a "burden" on a patient, separate from weakness and sensory loss, in the form of pain, fatigue, mood and anxiety, and financial. These topics are usually assessed individually, and a literature research compiled data on these burdens.[15] First, epidemiologic data varied in the literature, with incidence 0.2–1.6/100,00 and prevalence 0.8–10.3/100,000; however, other

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data support a prevalence of 1.6–3.7/100,000 fulfilling EFNS/PNS criteria 20433600 raising questions of overdiagnosis. Fatigue was reported 3 times more than pain. Depression and anxiety occurred in ~10% of patients. Treatment costs, likely linked to the use of IVIG, varied among countries, but annual cost in the United States (2016) was $116,330. In the United States, it seems that drug costs represented 57% of total costs, with much of the balance from clinic and hospital visits. Other nondrug costs include impaired productivity, sick leave, and overall disability/unemployment. Although the above findings from a literature search represent packets of data, it supports CIDP as an expensive disease (treatment and lost productivity) and has a psychologic burden. Asking patients about these issues is important.

WITHDRAWAL OF IVIG

A major clinical question with patients with CIDP is whether, or when, to withdraw maintenance IVIG treatment, because it has been found that among patients in formal CIDP trials, >50% randomized to placebo do well. A multicenter randomized trial was conducted to assess withdrawal of IVIG (29 patients) versus continuing treatment (31 patients) in patients fulfilling EFNS/PNS criteria for CIDP and who received maintenance IVIG for >6 months.[1,16] Infusions were blinded, and IVIG dose in the placebo arm followed a 75%, 50%, 25%, and 0% taper schedule of prestudy dose and interval. Patients were followed for 24 weeks with periodic assessment for relapse for end point assessment and for a total of 52 weeks. Relapses were treated with 2 g/kg followed by the previous maintenance doses. The primary end point was assessment by the iRODS. This study showed a lower iRODS score at end point (24 weeks or earlier if relapse) for both groups, and thus, the end point was inconclusive for whether withdrawal was inferior to maintenance IVIG (the authors believed the study was underpowered due to higher than expected clinical variability). In the placebo group, 41% remained stable at 24 weeks follow-up, compared with 58% in the continuing treatment group. During the extension, from 24 to 52 weeks, among the 12 patients (41%) who remained stable off of IVIG at 24 weeks, 8 remained stable, but 4 relapsed. Patients who relapsed were successfully retreated.

The Discussion section raised a number of uncertain issues within the trial that are considerations in the clinic when reducing or stopping IVIG in a patient. One is how to stop IVIG treatment, whether abruptly or by tapering? It is not known immunologically whether there is a benefit to tapering, but patients may be more comfortable with tapering. Another question is the type of measurement for clinical status and degree of change in the measurement to identify a relapse needing to be treated. In this study, iRODS and a preset deterioration level was used, and 42% of patients on stable IVIG reached the deterioration level. Reasons for the high number are not clear, but were not explained by the end of IVIG dose wearing off. Patient-reported disability scales (iRODS) may have limitations based on the threshold for considering a relapse. In the clinic, incorporating quantitative measures (grip strength) may be useful. A third issue is whether patients believed they were in the placebo group, as they were queried at the end of this study; interestingly, 70% of patients in the maintenance group believed they were in the withdrawal group. Negative feelings about randomization in the trial could have led to a nocebo effect, negative expectations leading to negative effects on iRODS score the outcome measure. In this study, reluctance about this study was high, and 30% of eligible patients did not want to participate. In the clinic, a patient on maintenance dosing may have anxiety about reducing and stopping IVIG which may lead to heightened vigilance and over reporting; it may be worthwhile at the start of IVIG treatment to state that at some time, a dose reduction will be considered.

REFERENCES

1. Joint Task Force of the E and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic

inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—First Revision. *J Peripher Nerv Syst.* 2010;15:185–95.

2. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint Task Force-Second revision. *J Peripher Nerv Syst.* 2021;26:242–268.
3. Athanasopoulos D, Motte J, Gruter T, et al. Evaluation of the EFNS/PNS diagnostic criteria in a cohort of CIDP patients. *Ann Clin Transl Neurol.* 2021;8:1110–1121.
4. Querol LA, Hartung HP, Lewis RA, et al. The role of the complement system in chronic inflammatory demyelinating polyneuropathy: implications for complement-targeted therapies. *Neurotherapeutics*. 2022;19:864–873.
5. Liberatore G, De Lorenzo A, Giannotta C, et al. Frequency and clinical correlates of anti-nerve antibodies in a large population of CIDP patients included in the Italian database. *Neurol Sci.* 2022;43:3939–3947.
6. Shelly S, Klein CJ, Dyck PJB, et al. Neurofascin-155 immunoglobulin subtypes: clinicopathologic associations and Neurologic outcomes. *Neurology*. 2021;97:e2392–e2403.
7. Doneddu PE, Dentoni M, Nobile-Orazio E. Atypical chronic inflammatory demyelinating polyradiculoneuropathy: recent advances on classification, diagnosis, and pathogenesis. *Curr Opin Neurol.* 2021;34:613–624.
8. Menon D, Katzberg HD, Bril V. Treatment approaches for atypical CIDP. *Front Neurol.* 2021;12:653734.
9. Hauw F, Fargeot G, Adams D, et al. Charcot-Marie-Tooth disease misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy: an international multicentric retrospective study. *Eur J Neurol.* 2021;28:2846–2854.
10. Lukawska M, Potulska-Chromik A, Lipowska M, et al. Pediatric CIDP: diagnosis and management. A single-center experience. *Front Neurol.* 2021;12:667378.
11. Silsby M, Yiannikas C, Ng K, et al. Posturography as a biomarker of intravenous immunoglobulin efficacy in chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve*. 2022;65:43–50.
12. Gruter T, Motte J, Bulut Y, et al. Axonal damage determines clinical disability in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): a prospective cohort study of different CIDP subtypes and disease stages. *Eur J Neurol.* 2022;29:583–592.
13. Fanous J, Zero AM, Gilmore KJ, et al. Length-dependent changes of lower limb muscle morphology in Chronic Inflammatory Demyelinating Polyneuropathy assessed with magnetic resonance imaging. *Eur J Transl Myol*. 2021;31:10200.
14. Mork H, Motte J, Fisse AL, et al. Prevalence and determinants of pain in chronic inflammatory demyelinating polyneuropathy: results from the German INHIBIT registry. *Eur J Neurol.* 2022;29:2109–2120.
15. Querol L, Crabtree M, Herepath M, et al. Systematic literature review of burden of illness in chronic inflammatory demyelinating polyneuropathy (CIDP). *J Neurol.* 2021;268:3706–3716.
16. Adrichem ME, Lucke IM, Vrancken A, et al. Withdrawal of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *Brain*. 2022;145:1641–1652.