Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP): Clinical Features, Diagnosis, and Current Treatment Strategies

JACQUES REYNOLDS, DO; GEORGE SACHS, MD, PhD; KARA STAVROS, MD

ABSTRACT

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated disorder characterized by weakness and sensory deficits that can lead to significant neurological disability. The diagnosis is based on a combination of clinical examination findings, electrodiagnostic studies, and other supportive evidence. Recognizing CIDP and distinguishing it from other chronic polyneuropathies is important because many patients with CIDP are highly responsive to treatment with immunosuppressive or immunomodulatory therapies. This review summarizes the clinical features, diagnosis, and current treatment strategies for CIDP.

KEYWORDS: chronic inflammatory demyelinating polyradiculoneuropathy, CIDP, polyneuropathy, immune-mediated neuropathy

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated disorder characterized by progressive symptoms of proximal and distal muscle weakness, often accompanied by sensory deficits. CIDP is a common, albeit frequently underdiagnosed condition with an estimated prevalence of 1 to 2 per 100,000 adults.[1] Distinguishing CIDP from other chronic sensorimotor polyneuropathies is imperative as numerous therapeutic options are now available.

CLINICAL FEATURES

In adults, peak incidence occurs at 40-60 years of age with a slight male predominance.[2] Classic presentation of CIDP is slow progression of both proximal and distal muscle weakness. Predominantly distal weakness may occur but this finding should prompt further investigation to exclude other types of neuropathy (as discussed below). Although weakness predominates in CIDP, the majority of patients also have sensory symptoms such as numbness or paresthesias, classically in a stocking-glove pattern. On examination, there may be diminished sensation to multiple modalities. Deep tendon reflexes are absent or reduced. Gait may be wide based and unsteady. Cranial nerve and bulbar involvement is rare, occurring in only 10-20% of patients.[3] Autonomic involvement is also rare and typically mild.[4] Symptoms follow either a progressive or relapsing course, with a relapsing course being more likely in younger individuals.[5]

CIDP VERSUS GUILLAIN-BARRE SYNDROME

CIDP and acute inflammatory demyelinating polyradiculoneuropathy (AIDP or Guillain-Barre Syndrome) may share many clinical features but can be distinguished primarily based on the time from onset to peak of clinical symptoms. AIDP is a monophasic illness that typically occurs with acute onset and progresses to a clinical nadir over a period of less than four weeks.[6] It is often associated with an antecedent event such as vaccination or diarrheal illness. By comparison, CIDP symptoms typically progress for a period greater than 8 weeks. Unlike in AIDP, patients with CIDP may experience a relapsing course of symptoms and onset is only rarely preceded by vaccination or illness.[7] Additionally, in CIDP involvement of the cranial nerves, respiratory muscles, and autonomic nervous system is more rare than in AIDP. In some cases the temporal delineation outlined above may be difficult and only observation over time can clarify whether the clinical course is that of AIDP or CIDP. Another consideration is that of treatment-related fluctuation of symptoms. Approximately 8-16% of AIDP patients can show a clinical deterioration within 8-9 weeks after their initial improvement or stabilization following immunotherapy.[8]

PATHOGENESIS

CIDP is an immune-mediated disorder generated from both cellular and humoral immune responses that are directed against peripheral nerve antigens, leading to demyelination and often secondary axonal loss.[9] Studies of the pathogenesis of CIDP suggest that activated T lymphocytes invade the peripheral nervous system through derangement of the blood-nerve barrier. Once within the peripheral nervous system these activated T cells generate pro-inflammatory cytokines and produce cytotoxic activity against myelin.[9] The myelin sheath is composed of numerous proteins, many of which are being investigated as possible targets for antibody responses in CIDP. Potential auto-antigens include myelin protein zero, myelin basic protein, connexin 32, and

gangliosides.[9] Overall, the mechanisms for these immune responses and the precise peripheral nerve antigens that are targeted have not been fully elucidated. Further research may assist in defining subtypes of disease and how they respond to particular treatments. For example, recent research has demonstrated that patients with antibodies against paranodal proteins contactin-1 (CNTN1) and neurofascin-155 (NF155) comprise a specific phenotype of CIDP that is refractory to first line therapies.[10]

DIAGNOSTIC WORK-UP

Diagnostic criteria

As CIDP has become better recognized, researchers and professional societies have proposed various diagnostic criteria based on clinical features, specific electrodiagnostic criteria, and ancillary studies including nerve biopsy or lumbar puncture. Unfortunately, consensus is lacking. Review of the details of the various diagnostic criteria and their differences is outside the scope of this review. In general, the diagnosis of CIDP is primarily based on clinical presentation and electrodiagnostic studies, whereas CSF analysis and histologic studies provide additional supportive data in selected cases.

Nerve conduction studies and Electromyography (EMG)

Electrodiagnostic studies are key for determining if the underlying pathology is demyelinating or axonal. Hallmark findings of a demyelinating disorder in a nerve conduction study may include evidence of conduction block, prolonged distal latencies, slowing of conduction velocity, or absent/delayed F responses. [2] The pattern of demyelination seen on these studies may be patchy or multifocal, in contrast to hereditary demyelinating polyneuropathies such as Charcot-Marie-Tooth disease, where demyelination is more uniform and conduction block is not seen. The needle EMG may reveal signs of secondary axonal loss.

Lumbar Puncture

Similar to AIDP, in CIDP there may be elevation of CSF protein with a normal cell count (albuminocytologic dissociation). Sampling of the CSF is not necessary in every patient suspected to have CIDP but may help further support the diagnosis in certain cases. Finding a pleocytosis in the CSF should prompt consideration of alternative diagnoses.

Nerve biopsy

A nerve biopsy may be considered in the workup of CIDP; however the diagnostic value is controversial. In patients with classic CIDP, the hallmark pathology includes demyelination and re-myelination changes, however this is only seen in about one-half to two-thirds of biopsies.[11] Other findings that may be seen include nerve edema, nerve fibrosis, and inflammatory infiltrates.[11] Unfortunately, the most prominent abnormalities in CIDP may lie in the proximal nerve segments or roots, which are not amenable to biopsy, and secondary axonal changes may obscure the underlying demyelinating process.[9] However, nerve biopsies can be useful to identify or exclude other etiologies including amyloid or vasculitic, toxic, or hereditary neuropathies.

Imaging findings

MRI studies of CIDP patients may show gadolinium enhancement or enlargement of the nerve roots or the lumbosacral/brachial plexi, thought to reflect chronic inflammation and demyelination/re-myelination. In addition, advanced neuromuscular ultrasound techniques are now being investigated for utility in the diagnosis of CIDP,[12] though ultrasound is still experimental in its applications for polyneuropathy.

Other laboratory workup

The differential diagnosis of CIDP is broad. Depending on the clinical scenario, a variety of laboratory studies may be considered to rule out neuropathy from other causes, including (but not limited to) toxicology screen, hemoglobin A1c, thyroid function studies, hepatitis profile, HIV antibody, serum immunofixation, Lyme titers, vasculitic markers, and angiotensin converting enzyme. Hereditary neuropathies, in particular the demyelinating forms of Charcot-Marie-Tooth disease, must also be considered in the differential diagnosis, especially in cases where there is a family history of neuropathy.

TREATMENT

Treatment is aimed at stopping the inflammatory response to prevent further demyelination and secondary axonal injury. The mainstays of treatment for CIDP include corticosteroids (CS), intravenous immunoglobulin (IVIg), and plasma exchange.

CS have been used in the treatment of CIDP for many years. While there is no strong evidence from controlled trials for oral CS, they are used commonly in practice and with good effect. Initial treatment with oral prednisone is typically high dose at 60-100 mg per day.[13] Once the patient is stabilized clinically the dose is slowly tapered. Unfortunately, CS cause many undesirable systemic side effects so alternative dosing regimens have been considered. Trials comparing pulsed dexamethasone to standard daily prednisolone therapy show no significant difference in efficacy.[14] Another small study comparing IV methylprednisolone to oral prednisone and IVIG demonstrated no difference in efficacy and fewer side effects as compared to prednisone.[15] Alternate day dosing of oral prednisone may also be considered. There is no clearly preferred regimen for CS administration in CIDP.

IVIg has proven to be an effective alternative to CS[16] with generally fewer side effects.[17] There are no strong guidelines regarding dosing and frequency of IVIG. Typically a loading dose of 2 g/kg is given over 2-5 days but subsequent maintenance therapy is variable and dependent upon how rapidly

the patient relapses. Maintenance doses may range from 0.4-2 g/kg given as frequently as every 3-4 weeks.[13] Patients can be maintained on IVIg long-term but weaning or discontinuing IVIg may be considered after a period of clinical stability of about six months or more. As with the dosing, there are no universal guidelines for tapering or discontinuing the medication and it is done on an individual basis. Side effects of IVIg include increased risk of thromboembolic events, renal dysfunction, and aseptic meningitis. Subcutaneous immunoglobulin, administered weekly, is more cost-effective and may be a consideration for patients who do not tolerate IVIg well but more data is needed to establish whether it provides the same efficacy as the IV formulation.[18]

Plasmapheresis is another treatment modality that has demonstrated efficacy in small trials.[19, 20] However, it is more time consuming and invasive than IVIg, requiring the placement of a central venous catheter rather than a peripheral intravenous line. It can be used as initial therapy in a patient with prominent weakness followed by other, less invasive immunotherapy, or in some cases may be used for long-term treatment.

REFRACTORY CASES

First line therapy for CIDP typically consists of IVIG, CS, plasmapheresis, or some combination of these agents. Other treatments may be considered in patients with refractory disease but strong supportive data for their efficacy is generally lacking. Additionally, many of these second- and third-line agents pose the risk of rare but serious side effects and should be considered with caution.

Cyclophosphamide and cyclosporine A have both shown positive results in small case series.[21, 22] Unfortunately they also pose the risk of significant side effects and use should be considered with caution. A small study of azathioprine showed no benefit in patients on oral prednisone therapy[23] though there may be anecdotal support for its use. Methotrexate has been reported to yield some benefit in case reports, but a randomized, placebo-controlled trial of oral methotrexate (adjuvant to IVIg or corticosteroid maintenance) demonstrated no significant clinical benefit.[24]

Rituximab is another consideration in patients not responsive to traditional therapies but more research is needed to establish its potential benefit; so far a significant treatment effect has not been proven in CIDP. However, as described above, recent data may suggest that rituximab is beneficial in a subset of treatment-resistant patients with antibodies against node of Ranvier proteins CNTN1 and NF155.[10] Limited data suggests that alemtuzumab may also offer an alternative to traditional therapies for patients with refractory illness[25] but further studies are needed and its use is experimental at this time. There have been several trials of interferons (interferon-alfa 2a and interferon beta 1a) that did not demonstrate efficacy.[26,27]

Experimental treatments such as peripheral blood stem cell transplantation, have not demonstrated safety or efficacy to date.[28] There is little data regarding non-pharmacological interventions such as regular exercise but physical therapy referral should be considered for patients with CIDP for gait training and fall prevention when clinically indicated.

CONCLUSIONS

Recognition of CIDP in a patient presenting with chronic neuropathy is crucial because treatments such as CS, IVIg, plasmapheresis, and other alternative agents may yield significant benefit with increased quality of life and reduction in disability. Future directions include advancing our understanding of the underlying pathogenesis of CIDP and honing the diagnostic criteria. Further research is needed to establish the optimum treatment doses and durations for established therapies and to further investigate the utility of the alternative, less well-studied agents.

References

1. Mcleod J, Pollard J, Macaskill P, et al. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. *Ann Neurol.* 1999; 46: 910-913.
2. Dimachkie M, Saperstein D, Lewis S. Acquired Immune Demyelinating Neuropathies. *Continuum.* 2014; 20: 1241-1260.
3. Saperstein D, Katz J, Amato A, Barohn R. Clinical spectrum of chronic acquired demyelinating polyneuropathies. *Muscle Nerve*. 2001; 24(3):311.
4. Figueroa J, Dyck P, Laughlin R, et al. Autonomic dysfunction in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology.* 2012;78(10):702.
5. McCombe P, Pollard J, McLeod, J. Chronic inflammatory demyelinating polyradiculopathy. A clinical and electrophysiological study of 92 cases. *Brain.* 1987; 110(6): 1617-1630.
6. Hughes R, Sanders E, Hall S, et al. Subacute idiopathic demyelinating polyradiculoneuropathy. *Arch Neurol.* 1992; 49 (6):612.
7. Hahn A. Guillain-Barré Syndrome. *Lancet.* 1998; 352 (9128): 635.
8. Ruts L, van Konigsveld R, van Doorn P. Distinguishing acute-onset CIDP from Guillain-Barre syndrome with treatment related fluctuations. *Neurology.* 2005; 65: 138-140.
9. Koller H, Kieseier B, Jander S, Hartung H. Chronic inflammatory demyelinating polyneuropathy. *N Engl J Med.* 2005; 352: 1343-1356.
10. Querol L, Rojas-Garcia R, Diaz-Manera J, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neurol Neuroimmunol Neuroinflamm* 2015; 2: e149.
11. Dyck P, Lais A, Ohta M, et al. Chronic inflammatory polyradiculoneuropathy. *Mayo Clin Proc.* 1975; 50 (11); 621-637.
12. Kerasnoudis A. The Role of Neuromuscular Ultrasound in the Diagnostic of the Chronic Inflammatory Demyelinating Polyneuropathy. *European Neurological Review.* 2013;8(1):62–4.
13. Dalaskas M. Clinical trials in CIDP and chronic autoimmune demyelinating polyneuropathies. *J Periph Nerv Syst.* 2012 May; 17 Suppl 2: 34-9.
14. Van Schaik I, Eftimov F, van Doorn P, et al. Pulse high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind randomized, controlled trial. *Lancet Neurol.* 2010; 9(3): 245-253.

15. Lopate G, Pestronk A, Al-Lozi M. Treatment of chronic inflammatory demyelinating polyneuropathy with high-dose intermittent intravenous methylprednisolone. *Arch Neurol.* 2005; 62(2): 249-254.
16. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polradiculoneuropathy (ICE study): a randomized placebo-controlled trial. *Lancet Neurol.* 2008; 7: 136-144.
17. Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomized controlled trial. *Lancet Neurol.* 2012; 11(6): 493-502.
18. Lee D, Linker R, Paulus W, et al. Subcutaneous immunoglobulin infusion: a new therapeutic option in chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve.* 2008; 37(3): 406-409.
19. Dyck P, Litchy W, Kratz K et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuraopthy. *Ann Neurol.* 1994; 36: 838-45.
20. Hahn A, Bolton C, Pillay N, et al. Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy: a double-blind, sham-controlled, cross-over study. *Brain.* 1996; 119: 1055-1066.
21. Good J, Chehrenama M, Mayer R, Koski C. Pulse cyclophosphamide therapy in chronic inflammatory demyelinating polyneuropathy. *Neurology.* 1998; 51(6): 1735-1739.
22. Matsuda M, Hoshi K, Gono T, et al. Cyclosporin A in treatment of refractory patients with chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Sci.* 2004; 224(1-2): 29-35.
23. Dyck P, O'Brien P, Swanson C, et al. Combined azathioprine and prednisone in chronic inflammatory demyelinating polyneuropathy. *Neurology.* 1985; 35(8): 1173-1176.
24. RMC Trial Group. Randomised controlled trial of methotrexate for chronic, inflammatory demyelinating polyradiculoneuropathy (RMC trial): a pilot, multicenter study. *Lancet Neurol.* 2009; 8(2): 158-164.
25. Marsh E, Hirst C, Llewelyn J, Cossburn M, et al. Alemtuzumab in the treatment of IVIG-dependent chronic inflammatory demyelinating polyneuropathy. *J Neurol.* 2010; 257(6): 913-919.
26. Gorson K, Ropper A, Clark B, et al. Treatment of chronic inflammatory demyelinating polyneuropathy with interferon-alpha 2a. *Neurology* 1998; 50(1): 84-87.
27. Hadden R, Sharrack B, Bensa S, et al. Randomized trial of interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology.* 1999; 53(1): 57-61.
28. Mahdi-Rogers M, Kazmi M, Ferner R, et al. Autologous peripheral blood stem cell transplantation for chronic acquired demyelinating neuropathy. *J Peripher Nerv Syst.* 2009; 14(2): 118-124.

Authors

Jacques Reynolds, DO, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI.

George Sachs, MD, PhD, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI.

Kara Stavros, MD, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI.

Correspondence

Kara Stavros, MD
Assistant Professor, Department of Neurology
Rhode Island Hospital
593 Eddy Street APC 5
Providence, RI 02903
401-444-2596
Fax 401-444-3205
kstavros@lifespan.org