Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): Clinical Features, Diagnosis, and Current Treatment Strategies

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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, 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.

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. 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.

**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 electrodagnostic 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. 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. Other findings that may be seen include nerve edema, nerve fibrosis, and inflammatory infiltrates. 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. 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 neuro-muscular ultrasound techniques are now being investigated for utility in the diagnosis of CIDP, though ultrasound is still experimental in its applications for polynuropathy.

**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. 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. Another small study comparing IV methylprednisolone to oral prednisone and IVIG demonstrated no difference in efficacy and fewer side effects as compared to prednisone. 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 with generally fewer side effects. 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. 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 therapy23 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 NF155.25 Limited data suggests that alemtuzumab may also offer an alternative to traditional therapies for patients with refractory illness26 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


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