Chronic Neuropathies – Chronic Inflammatory Demyelinating Neuropathy and Its Variants

Sindhu Ramchandren · Richard A. Lewis
Detroit Medical Center Department of Neurology, Wayne State University, Detroit, Mich., USA

Abstract
Background: Chronic neuropathy is a highly prevalent condition, and an enormous burden to society, from a health, social and financial standpoint. Identifying new therapeutic strategies that have a significant impact on the neuropathy patients’ quality of life has been difficult. Objective: This review presents a brief perspective on clinical evaluation of chronic neuropathies, with a focus on chronic inflammatory demyelinating neuropathy (CIDP) and its variants. Methods: The diagnosis of CIDP is based on a careful history and examination, with evidence of peripheral nerve demyelination established. Disorders with unique characteristics but similar clinical, electrophysiologic, laboratory and therapeutic aspects to CIDP, such as Lewis-Sumner syndrome, are considered variants. Conclusion: Although defined diagnostic criteria for CIDP are now increasingly sensitive and specific, there is still significant overlap among CIDP and other neuropathies. Further research into the underlying pathophysiology of CIDP, its variants, and other immune-mediated demyelinating neuropathies will help us eventually develop targeted therapies that are less toxic and more beneficial than those currently available. Copyright © 2009 S. Karger AG, Basel

Chronic neuropathy is a common affliction of the peripheral nervous system, affecting over 10% of the older adult population and approximately 20 million people in the United States alone [1, 2]. Clinically, chronic neuropathy can manifest positive symptoms, such as painful dysesthesias, or negative symptoms, such as numbness, and can lead to varying levels of functional weakness and associated morbidity. Socially, peripheral neuropathy is well known to decrease the affected individual’s overall quality of life [3, 4]. The financial cost of peripheral neuropathy is difficult to assess, as chronic neuropathies can be caused by a myriad of etiologies, with each having its own costs. However, since diabetic neuropathy is the most common cause of chronic neuropathy in the United States [5] and diabetic neuropathy alone has annual costs of between 4 and 14 billion dollars in the United States [6], it is reasonable to conclude...
that the costs of chronic neuropathy are enormous to our society. Despite the enormous burden to society from a health, social, and financial standpoint, identifying new therapeutic strategies to manage chronic neuropathies has been difficult. This review will present a brief perspective on clinical evaluation of chronic neuropathies, and then focus on chronic inflammatory demyelinating neuropathy (CIDP) and its variants.

Clinical Evaluation of Chronic Neuropathies

The differential diagnosis one considers when someone presents with an acute or subacute neuropathy is relatively small, consisting mainly of Guillain-Barré syndrome (GBS), vasculitis, acute toxic neuropathies, porphyria and neuropathy related to an underlying malignancy [7]. The acute neuropathies often manifest within 4 weeks, with most clinical evaluations being completed within the same time frame. Defining subacute neuropathies is slightly more difficult: their course can range between 4 and 12 weeks [8]. For the purpose of this review, ‘chronic neuropathy’ will be defined as those with a clinical course beyond 2 months.

The evaluation of chronic neuropathies, as with any neurologic complaint, should begin with localization based on history and physical examination. Chronic neuropathies can be classified as acquired versus inherited, and demyelinating versus axonal. Inherited neuropathies typically evolve over decades and are slowly progressive. Needle electromyography and nerve conduction studies (EMG/NCS) are needed to determine whether a neuropathy is active or chronic, and if the underlying mechanism is predominantly axonal or demyelinating. Electrodiagnostic evidence for polyneuropathy is defined as a nerve conduction abnormality of the sural sensory nerve and an abnormality in one other separate nerve [9].

One of the biggest concerns in evaluating patients with chronic neuropathy is determining the extent of the diagnostic workup, given the ever-growing number of possible etiologies [10, 11]. While some patients are tested only for underlying diabetes or vitamin deficiencies, others receive more elaborate panels of tests, sometimes including expensive and often inappropriate genetic testing. The heterogeneity of etiologies causing chronic neuropathy necessitates some physician autonomy in the choice of laboratory tests ordered. However, recently published guidelines may provide a basis for rational test selection [12, 13]. The evidence-based review on the role of laboratory investigation of polyneuropathy noted that the tests that are most likely to find an abnormality pertinent to the neuropathy are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis. The report also mentioned the potential usefulness of looking for impaired glucose tolerance with a 2-hour glucose tolerance test [12].
Chronic Inflammatory Demyelinating Polyneuropathy

CIDP or polyradiculoneuropathy was first described in 1958 [14], and by 1975, its clinical, electrodiagnostic, and pathologic features had been delineated [15]. Disorders with unique characteristics but similar clinical, electrophysiologic, laboratory and therapeutic aspects to CIDP, are considered variants.

Epidemiology

CIDP has an estimated prevalence of 0.8–1.9 per 100,000 in adults [16, 17]. Although childhood prevalence rates are unknown, one study reported a prevalence of 0.48 per 100,000 among patients under age 20 [17]. No clear genetic predisposition has been identified.

Clinical Characteristics

The temporal distinction between acute inflammatory demyelinating polyneuropathy, one of the forms of GBS, and CIDP is a somewhat arbitrary one. Acute inflammatory demyelinating polyneuropathy is a monophasic disorder with disease progression of less than 4 weeks. CIDP is a chronic progressive or relapsing disorder that can cause new symptoms for years if left untreated. Most diagnostic criteria for CIDP arbitrarily use progression or recurrent relapses that occur more than 8 weeks from onset as the minimum length of time required to diagnose CIDP. There is a gray zone between 4 and 8 weeks which has been designated as subacute inflammatory demyelinating polyneuropathy; most of these patients end up having CIDP [18, 19]. The importance of these distinctions is that GBS, being a monophasic illness, does not require ongoing immunomodulating therapy after the initial 4 weeks. CIDP, on the other hand, frequently requires long-term immune treatment. Complicating this issue is that some patients with GBS who are treated with either plasmapheresis or intravenous immunoglobulin (IVIg) can relapse requiring a repeated treatment. Whether these patients really have GBS or CIDP with an initial GBS-like onset is frequently difficult to determine during the 4- to 8-week period [20]. In general, any relapse that occurs after 4 weeks is most likely CIDP.

Clinically, CIDP typically presents symmetrically in the arms and legs, with predominantly motor symptoms and reduced or absent deep tendon reflexes. Unlike other chronic length-dependent neuropathies, CIDP affects proximal as well as distal muscles of both upper and lower extremities, and is more aggressive in course, pointing to a multifocal pathophysiology even at early stages of the disease. Cranial nerve and bulbar involvement is seen in 10–20% of patients. Vibration and proprioception are more often affected than pain and temperature sensation, reflecting preferential
involvement of large myelinated fibers. Autonomic symptoms may be seen, including constipation and urinary retention. Rarely, patients can develop lumbar spinal stenosis and cauda equina syndrome secondary to marked nerve root hypertrophy [21]. Compared with adults, children present earlier and progress faster; they commonly present with gait instability and falls, but up to a third may present with sensory symptoms. Cranial nerve palsy or autonomic dysfunction is not typically seen. One third to a half of all children with CIDP have a prodromal upper respiratory infection [22–26].

**Immunopathogenesis**

CIDP is an autoimmune inflammatory disorder mediated by the cellular and humoral immune system. Crossing of the blood-nerve barrier by activated T cells has been demonstrated along with expression of cytokines, tumor necrosis factor, interferon and interleukins. Immunoglobulin and complement deposition has been seen on myelinated nerve fibers. Passive transfer of serum or purified IgG from patients who have CIDP have induced conduction block and demyelination when injected into rats. However, the immunologic causes of CIDP remain unclear. Although there is evidence implicating gangliosides and other glycoproteins as target antigens in GBS, multifocal motor neuropathy (MMN), anti-myelin-associated glycoprotein, and other neuropathies, specific antigens have not been identified in CIDP [27–29].

**Diagnostic Studies**

Demyelination is the sine qua non of CIDP, proven by EMG/NCS or by nerve biopsy. Cerebrospinal fluid (CSF) analysis, neuroimaging and appropriate laboratory studies can support the clinical diagnosis and exclude other possibilities. MRI of the spine can reveal enhancement of the nerve roots, likely due to disruption of the blood-brain barrier secondary to inflammation [26, 30].

**Electrophysiologic Studies**

EMG/NCS show segmental or nonuniform demyelination of multiple nerves. Nonuniform features include conduction block (amplitude reduction needed depends on the distance between stimuli) and temporal dispersion of the duration of the compound motor action potential (CMAP) on proximal stimulation compared with distal stimulation. Features of demyelination include prolonged distal motor latencies, prolonged duration of the distal CMAP, and prolonged F wave and H reflex latencies. Slowed conduction velocities greater than can be explained by axon loss are also seen;
normal conduction velocities of motor fibers range from 30 to 70 m/s in the arms and from 25 to 60 m/s in the legs. Velocities less than 30 m/s in the arm and 25 m/s in the leg can only be due to demyelination. Problems with interpretation arise when velocities range between 30 and 45 m/s in which careful comparison of velocity and amplitude, supplemented with needle EMG, is needed. Given these issues, many criteria explicitly stating the parameters of conduction changes have been developed to assist physicians in diagnosing demyelination [31, 32]. Studying several segments in all four limbs can improve the diagnostic yield of the EMG/NCS [33].

**Laboratory Investigations**

Albuminocytologic dissociation in CSF analysis is seen in more than 90% of patients with CIDP [34]. Although there are no serum markers of CIDP, it is appropriate to obtain a serum immunofixation electrophoresis to look for an associated paraprotein. Studies to look for associated disorders such as systemic lupus, HIV, hepatitis B or C are appropriate.

**Pathology**

Nerve biopsy is not a routine procedure for the diagnosis of CIDP, but can be helpful in ruling out diseases with similar findings such as amyloidosis, sarcoidosis and vasculitis, as well as in finding demyelination when the NCS were equivocal. Unfortunately, the yield is not high since CIDP is a multifocal disorder and motor nerves are more affected than the typically biopsied sural sensory nerve [35–37]. The characteristic finding is segmental demyelination and remyelination at any portion from the proximal nerve root to the distal nerve ends, as well as onion bulb formation. Inflammatory infiltrates, including lymphocytes and macrophages, and subperineurial edema can also be seen rarely [34]. Disease severity and functional impairment is related to axon loss [24]. Although demyelination and conduction block are often equated, they differ pathologically: block is determined by changes at the paranodes and nodes of Ranvier [38–41].

**Diagnostic Criteria**

Much effort has been directed towards developing a set of valid diagnostic criteria for CIDP, since improved recognition of the disease will help not only in understanding the underlying immunopathogenesis, but also towards enrollment in future trials of less toxic, more efficacious immunomodulative therapies. Over the past 20 years, several different criteria have been published for diagnosing CIDP (definite, probable
and possible categories), based on specific clinical, laboratory and electrodiagnostic criteria [42–46]. Some are considered specific but not sensitive enough for clinical use, such as the American Academy of Neurology criteria, developed for research purposes. The European Federation of Neurological Societies/Peripheral Nerve Society guideline is more clinically relevant and extends the diagnostic criteria to include other supportive evidence such as neuroimaging.

While some of the classifications of CIDP variants and disorders distinct from CIDP could be questioned, it remains a useful approach to the disease. Recently, a novel approach based on blinded retrospective review of 300 cases from 13 investigators, developed criteria which had 83% sensitivity and 97% specificity in diagnosing CIDP [47]. The diagnostic rule is that in a patient with a chronic polyneuropathy that is progressive for more than 8 weeks, who does not have a serum paraprotein or a genetic neuropathy, the diagnosis of CIDP requires one of the following: (1) at least 75% of the motor nerves studied electrophysiologically have a recordable CMAP and an abnormal distal motor latency in >50% of nerves or an abnormal motor conduction velocity in >50% of nerves or an abnormal F wave latency in >50% of nerves; OR (2) there is a symmetrical onset of motor symptoms and symmetrical weakness of all four limbs with proximal weakness in at least one limb. The implication is that the diagnosis of CIDP can be made without electrodiagnostic evidence of segmental demyelination if the patient presents with a classic clinical picture. Whether this rule will be utilized appropriately and successfully remains to be determined.

Treatment

Immunomodulation is the treatment of choice for CIDP. Three treatments have been shown to be effective, IVIg, plasmapheresis, and corticosteroids [48–50]. IVIg is a first-line therapy, based on randomized controlled trials in adults [51–54], and case series in children showing clinical improvement after treatment [30, 55–57]. The initial dose is usually 2 g/kg divided over 2–5 days with maintenance therapy of up to 1 g/kg/day given over 1–2 days every 2–6 weeks [56, 58]. Risks and drawbacks of IVIg include cost, aseptic meningitis, flu-like symptoms (headaches, nausea, fever, chills) due to infusion, anaphylaxis in IgA-deficient individuals when non-IgA-depleted IVIg is used, hemolytic anemia, and thromboembolism.

Plasmapheresis has been shown to be equivalent in efficacy to IVIg [59–61], but the timing of subsequent courses of pheresis is not as well established as for IVIg, especially in children [62]. Drawbacks include availability of pheresis centers, venous access, coagulopathy, hypotension and anemia in those requiring chronic treatment.

Corticosteroids have been shown to be equivalent to IVIg [63]. Other studies have reported benefit in both adults and children, and shown that corticosteroids are more likely to produce clinical remission than IVIg or plasmapheresis [23, 55]. The dosing
regimen in adults is not agreed upon. There is recent interest in using high-dose pulse therapy instead of daily or alternate day dosing. The hope is that the pulse therapy may have less side effects and more benefit. Dosing in children, based on several recent studies, is 1–2 mg/kg daily or on alternate days followed by a gradual wean as symptoms improve [25, 55].

Several immunosuppressive therapies have been beneficial in case series. These include azathioprine, mycophenolate mofetil, methotrexate (MTX), cyclosporine, tacrolimus and cyclophosphamide. A randomized trial of MTX as a steroid-sparing agent was negative but there was a remarkably high placebo effect suggesting that many patients may be taking more corticosteroids than necessary. The role of MTX in CIDP remains unclear. High-dose cyclophosphamide without stem cell rescue was helpful in a small series of patients who were refractory to other treatments [64]. However, it is unclear whether this high-dose regimen is superior to lower dose cyclophosphamide which may carry less risk. Interferon-α and etanercept are considered potential treatments for CIDP, but they can also reportedly cause the disorder [65–69]. The potential role of other monoclonal antibodies such as rituximab (directed against B cells) and eculizumab (complement inhibitor) is exciting but untested. Multicenter randomized controlled trials need to be done to prove the safety and efficacy of these therapies [70].

As we learn more about the immunopathogenesis of CIDP, many of these classification schemes may become redundant. While the above-mentioned guidelines are an excellent point of reference, clinicians must ultimately convince themselves of the diagnosis based on their clinical and diagnostic findings. In some cases, a treatment trial may be warranted; however, it is important to bear in mind that while response to immunomodulation is suggestive of an inflammatory or immunologic disease, it is not diagnostic of a specific disorder. Below, we describe some CIDP variants, defined as disorders with unique characteristics but similar clinical, electrophysiologic, laboratory and therapeutic aspects to CIDP.

**Lewis-Sumner Syndrome**

Lewis-Sumner syndrome (LSS) or multifocal acquired demyelinating sensory and motor neuropathy varies from classic CIDP by its striking multifocal picture. LSS was originally described as a mononeuropathy multiplex with sensory or motor symptoms in named nerve distributions [71]. Several subsequent case series have helped distinguish LSS from MMN [72–76]; these differences are summarized in table 1. NCS show sensory abnormalities in LSS, particularly if proximal stimulation is used; distal sensory responses may be abnormal if the conduction block is distal, or if secondary Wallerian degeneration has occurred [77]. Except for the multifocal presentation, LSS is identical to CIDP, including its response to treatments, and can therefore be reasonably considered a variant of CIDP.
Fifteen percent of patients with CIDP have sensory signs and ataxia as the predominant feature [78]. Distal acquired demyelinating sensory (DADS) neuropathy, despite lack of or minimal weakness, shows significant motor conduction slowing and other demyelinating features [78–80]. DADS neuropathy is frequently associated with an IgM paraprotein; half of these patients have anti-myelin-associated glycoprotein antibodies. The presence of IgM paraprotein correlates with poor response to standard CIDP immunomodulatory treatments [81]. DADS neuropathy without IgM paraprotein, however, differs from CIDP mainly in its sensory predominant presentation and responds favorably to standard CIDP treatment, and therefore can be considered a variant of CIDP.

Other Chronic Inflammatory Demyelinating Neuropathy Variants

Patients with demyelinating neuropathies and IgG or IgA paraproteins are identical to patients with CIDP in terms of presentation and response to treatment, and are therefore considered variants. Demyelinating neuropathies with IgM paraproteins, on the other hand, are distinct from CIDP, in terms of unresponsiveness to standard treatments. Clinical and electromyographic findings of CIDP have been reported in patients with central nervous system demyelination of unknown etiology as well as due to multiple sclerosis, but the true association remains unclear [82–84]. Demyelinating neuropathies have also been reported in association with systemic disorders such as hepatitis B or C, HIV, lymphoma, diabetes, systemic lupus erythematosus and other collagen vascular disorders, thyrotoxicosis, organ or bone marrow transplants, nephrotic syndrome and inflammatory bowel disease [21] and are usually considered to be CIDP associated with other immune-mediated disorders.
The relationship of CIDP and diabetes mellitus is particularly controversial. Although some authors have noted a high incidence of CIDP in diabetics [85–87], it is particularly difficult to differentiate the conduction slowing seen in some diabetics with the demyelinating features that are an important component of the diagnostic criteria for CIDP; elevated CSF protein can also be seen in diabetes alone [88]. In our view, concomitant CIDP may be considered in diabetics who (1) display a significant motor component to their neuropathy, (2) have a more rapid or aggressive evolution, (3) exhibit both a proximal and distal neuropathy, (4) have CSF protein levels >150 mg/dl, and (5) unequivocally respond to immunomodulatory treatment.

Some cases of inherited neuropathy can mimic CIDP [89], some patients with inherited neuropathy have a steroid responsive neuropathy [90], and some patients have CIDP superimposed on their underlying inherited disorder. It is essential to emphasize the importance of obtaining a careful family history, but one should be aware that many patients with genetic mutations have no family history either because their disorder is recessive, due to a de novo mutation or because of variable expression of the gene [91].

**Immune-Mediated Demyelinating Neuropathies Distinct from Chronic Inflammatory Demyelinating Neuropathy**

Certain demyelinating neuropathies that are immune mediated have distinct properties such that it is important to distinguish them from CIDP. Most importantly, treatment response is clearly different in these disorders than in CIDP. MMN does not respond to corticosteroids or plasmapheresis and may actually worsen with steroids. DADS neuropathy with IgM paraprotein, with or without anti-myelin-associated glycoprotein antibodies, does not usually respond to any of the immunosuppressant or immunomodulatory treatments but does respond to rituximab [92]. POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) is related to osteosclerotic myeloma and/or Castleman's syndrome and responds only to treatment of the underlying disease.

**Conclusions**

The diagnosis of CIDP is based on a careful history and examination, with evidence of peripheral nerve demyelination established by EMG/NCS or nerve biopsy. Supportive studies include albuminocytologic dissociation in the CSF, and laboratory tests to exclude other etiologies of neuropathy. Although defined diagnostic criteria for CIDP are now increasingly sensitive and specific, there is still significant overlap among CIDP and its variants due to our uncertainty regarding the underlying immunopathophysiology. We have provided one way of classifying CIDP and its associated
variants, summarized in Table 2, based on typical disease progression, electrophysiological findings and response to therapy. While this and other published criteria may serve as a point of reference, clinicians must ultimately convince themselves of the diagnosis based on their exam and diagnostic findings. Future efforts need to be directed towards developing therapies that are more specific, less toxic, and more beneficial than those currently available.

Table 2. Classification of the immune-mediated demyelinating neuropathies

(A) CIDP

(B) CIDP variants
   Multifocal sensorimotor demyelinating neuropathy with persistent conduction block
   LSS or MADSAM
   Sensory variants
   DADS without IgM paraprotein
   CIDP associated with systemic disorders
   SLE and other collagen vascular disorders
   Hepatitis B and/or C
   Inflammatory bowel disease
   HIV
   Lymphoma
   Inherited neuropathies (Charcot-Marie-Tooth disease)
   Diabetes mellitus
   IgG or IgA paraprotein (not POEMS)
   Thyrotoxicosis
   Organ or bone marrow transplants
   Nephrotic syndrome

(C) Immune-mediated neuropathies distinct from CIDP
   IgM-related demyelinating neuropathy with or without anti-myelin-associated glycoprotein antibody
   POEMS
   MMN

MADSAM = Multifocal acquired demyelinating sensory and motor neuropathy; SLE = systemic lupus erythematosus.
References


