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Chronic Inflammatory Demyelinating Polyradiculoneuropathy: From Bench to Bedside

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Abstract

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is the most common treatable chronic autoimmune neuropathy. Multiple diagnostic criteria have been established, with the primary goal of identifying neurophysiologic hallmarks of acquired demyelination. Treatment modalities have expanded to include numerous immuno-modulatory therapies, although the best evidence continues to be for corticosteroids, plasma exchange, and intravenous immunoglobulins (IVIg). This review describes the pathology, epidemiology, pathogenesis, diagnosis, and treatment of CIDP.

Keywords

CIDP; demyelination; inflammatory neuropathy

Introduction

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is the most common automimmune polyneuropathy in adults. The term CIDP was coined in 1975 by Peter Dyck and colleagues (1), although similar remitting disorders were described by Eichhorst in 1890 and Henrikson in 1956 (2) and Austin in 1958 (3). The key features, weakness (both proximal and distal), sub-acute to chronic onset (greater than 8 weeks), and areflexia were associated with electrodiagnostic features of conduction block and asymmetric conduction velocity slowing and cyto-albuminologic association (eleveated CSF protein without a pleocytosis)(1). Since that time, CIDP has been broadened to include multiple variants including distal acquired demyelinating symmetric (DADS)(4), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM or Lewis-Sumner syndrome)(5), and sensory predominant CIDP(6), in addition to recognition of similar but pathologically distinct disorders of multifocal motor neuropathy (MMN)(7) and CIDP associated with monoclonal gammopathy(8;9). In this article, we will review the salient features, current evidence of pathogenesis, diagnostic testing, and treatment options, focusing on typical CIDP.

Pathogenesis

The pathologic features in CIDP described by Dyck (1) were “onion bulb” formations, perivascular inflammatory infiltrates and segmental demyelination in teased fibers. These have led to two assumptions: 1) that CIDP is a primarily demyelinating disorder, and 2) that inflammation or autoimmunity is a key feature of the pathogenesis. The exact cause of CIDP is still unknown. Humoral immune factors have been presumed to be involved given the

response of most patients to corticosteroids, intravenous immunoglobulins (IVIg) or plasma exchange.

Segmental demyelination and remyelination are hallmarks of CIDP and repetitively over time lead to onion bulb formations by proliferation of Schwann cell processes. Thinly myelinated large axons are also frequently observed in nerve biopsy sections(10). Myelin itself is thought to be the source of antigenic epitopes, as immunization of animals with peripheral nerve myelin proteins and glycolipids can produce experimental autoimmune neuritis (EAN) which has similar physical and pathologic features to CIDP (11;12). Antibodies to peripheral nerve components such as protein zero, peripheral myelin protein 22, sulfated glucuronyl paragloboside (SGPG), LM1, GM1, and GD1a have also been found (13). However, none of these antibodies have been found in a majority of patients, suggesting a heterogenous cause of CIDP unlike myasthenia gravis where the vast majority of patients display acetylcholine receptor antibodies.

Cellular immune mechanisms are also a key feature of CIDP. Perivascular inflammation and infiltrates in nerves of macrophages and T cells suggest a cell-mediated mechanism of damage which may cause the actual demyelination. Elevated T helper cells have been found in the CSF of CIDP patients (14). EAN can also be induced by infusing auto-reactive T cells into naïve animals(15). Cytokines produced by auto-reactive T cells have been shown to be elevated in serum from CIDP patients (16-18). Elevated serum IL-2 and tumor necrosis factor (TNF)-α have been demonstrated in CIDP patients and correlate with longer distal latencies although this observation has not been reproduced (19). However, in patients' biopsies, T cells infiltrates are much less prevalent than in macrophages (20). Because of the similarity to multiple sclerosis, a CNS demyelinating disease, investigation into activation of T cells and induction of macrophages also show B7/CD28 pathway activation, which is involved in co-stimulation of antigen presenting cells (macrophages) in CIDP (21). Schwann cells may also be involved in the process by upregulating CD58 , an adhesion molecule which interacts with T cells and natural killer cells (22). Upregulation of B7-1 and B7-2 molecules has been demonstrated in Schwann cells from CIDP patients and treatment with an antiCD28 monoclonal antibody improves the disease course of EAN (23).

Presentation/Symptomatology

CIDP is distinguished from acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the most common form of Guillain-Barré Syndrome (GBS), by time course and steroid responsiveness. Unlike AIDP, CIDP typically has a more indolent course and all of the published criteria for CIDP recognize time to greatest weakness of longer than 8 weeks to differentiate CIDP from AIDP (which reaches nadir in 4 weeks or less). Some CIDP patients may have a more acute onset and may present as multiple occurrences of AIDP with ventilator failure (24). Typically most patients present with weakness, both proximal and distal, paresthesias, and sensory loss that may be slowly progressive or have a more relapsing/remitting course. Unlike AIDP, back pain and autonomic symptoms are less common although autonomic abnormalities are frequently present on testing (25). While some patients may identify a preceding infection or injury, most patients with CIDP do not. In addition, CIDP may also present in patients with hereditary or diabetic neuropathy

(although the extent to which these underyling disorders increase CIDP risk remains controversial), making diagnosis more difficult. Another differentiation between AIDP and CIDP is the less common occurrence of bulbar involvement or respiratory compromise in CIDP. CIDP typically responds to corticosteroid therapy, whereas AIDP does not.

CIDP occurs slightly more often in men in all ages, and has its highest prevalence in middle age (ages 30-60). CIDP has been recognized world-wide, with varying prevalence (partly due to diagnostic criteria) from 1.0 to 8.9 per 100,000 persons (24;26-29). Prevalence is lowest in the United Kingdom (30), with the highest rate in Olmstead County, MN (26). CIDP has also been recognized to have a higher prevalence in patients with HIV infection (31;32). Whether the prevalence of CIDP is increased in diabetes mellitus has been under debate (26).

The prognosis of CIDP is variable and is reminiscent of multiple sclerosis in its heterogeneity. Some patients (20-65%) follow a relapsing remitting course, others a more progressive course . Over time, most patients with CIDP without associated conditions respond to treatment, especially if CSF protein is elevated . Presence of monoclonal proteins portend poor prognosis and lack of response to immuno-modulatory treatment, causing some to suggest this should not be categorized with idiopathic CIDP (33-35). Predominantly distal weakness also has poorer prognosis. It is not clear if this is related to presence of associated monoclonal protein-patients with DADS more likely to have an IgM monoclonal protein than CIDP patients (36;37). Respiratory failure requiring ventilator support is rare, but can occur (24). CNS lesions can also occur, varying from T2 hyperintense white matter lesions, atrophic cervical cord, and abnormal brainstem evoked potentials, although prominent upper motor neuron features would be atypical and suggest an alternative diagnosis (38-41).

Other CIDP Variants

Pure Sensory CIDP: Pure sensory CIDP has been reported by several authors as a CIDP variant with purely or predominantly sensory involvement, which is unlike typical CIDP where weakness is a required symptom. Patients with sensory CIDP often have findings in motor nerves despite their lack of motor symptoms and may progress to develop motor symptoms over time (6;42). Patients who have sensory CIDP typically respond as well to immune-modulating treatment (43). Sensory CIDP is to be differentiated from demyelinating neuropathies with monoclonal gammopathy, as these neuropathies, while sensory predominant in symptoms, have a much different prognosis and respond poorly to standard treatments for CIDP.

Multifocal Motor and Sensory Demyelinating Neuropathy/Lewis-Sumner Syndrome: Typical CIDP has asymmetric conduction velocity slowing, but clinically patients have symmetric weakness and sensory loss on exam. Five patients who had a presentation resembling mononeuritis multiplex were reported by Lewis and colleagues with primarily upper limb symptoms in the distribution of single nerves (5). Patients had elevated CSF protein and demyelination on nerve biopsy, further confirming a demyelinating process

rather than a mononeuritis multiplex(5). Patients had a favorable response to corticosteroids as well as IVIG.

Distal Acquired Demyelinating Neuropathy (DADS) was first coined by Katz and colleagues to describe patients with distal weakness and demyelinating features on electrophysiological studies (44). However, subsequent articles have suggested that DADS with monoclonal paraproteinemia, which is often a typical presentation of neuropathy associated with IgM paraproteinemias, not be included as a CIDP variant because of the poor response to treatment (45-47).

Diagnostic Criteria

Electrodiagnostic Criteria—There are currently seventeen published sets of electrodiagnostic criteria for acquired demyelinating disorders (GBS/AIDP and CIDP). Many criteria were established for research study patient inclusion such as the INCAT criteria and AAN criteria (48;49). Features observed in both CIDP and AIDP/GBS which have been carried forward by Dyck's publication and in most criteria include asymmetric conduction velocity slowing to distinguish CIDP from uniform conduction velocity slowing observed in dysmyelinating inherited neuropathies (50). Prolonged distal latency and F-wave latencies have also been included in most criteria. However, the electrodiagnostic hallmark of acquired demyelination has been conduction block (decrease in amplitude of the compound muscle action potential - CMAP - at more proximal stimulation sites) and temporal dispersion (prolonged CMAP duration after proximal stimulation compared to distal stimulation). (figure 1)

The first criteria were put forth were by Kelly in 1983 to distinguish neuropathies associated with monoclonal protein as axonal or demyelinating (8). These criteria were further refined by Albers et al. in 1985 for AIDP(51) . Albers and Kelly in 1989(52) revised the initial Kelly criteria and specified conduction velocity slowing, prolonged distal latency, prolonged F-wave latency or temporal dispersion in 2 or more nerves with specificity CMAP amplitude. A third set was proposed by an AAN Ad Hoc Committee Task Force for research criteria (49) but this criterion has been criticized in multiple publications for low sensitivity (53-55); spurring further sets of criteria including other metrics such as distal CMAP duration (56), CSF protein elevation (see further next section)(57), or conduction block (58).

Wilson et al. compared electrodiagnostic features of patients with CIDP (biopsy proven), diabetes and monoclonal gammopathy and found that F-wave latency was best able to distinguish CIDP from other neuropathies with demyelinating features (59;60). Variability in severity of conduction block (20-50%) and number of motor nerves displaying abnormalities also significantly affects sensitivity and specificity. Other authors have suggested using a treatment responsive approach (61) which may be helpful in practice but is not practical for research purposes and may generate significantly increased health care costs.

Cytoalbuminologic Dissociation and cerebrospinal fluid analysis—
Approximately 90 % of patients with CIDP demonstrate elevated CSF protein (greater than 45 mg/dL) (62-64). CSF pleocytosis is not typically seen, and often suggests a co-infection, such as HIV (65). The AAN Ad Hoc criteria specifically exclude patients with CSF cell

count >10/mm^3. This is one of the distinguishing factors that separate CIDP from MMN, as MMN patients typically have normal CSF protein (66). Patients with CIDP and diabetes have higher CSF protein than patients with CIDP alone(67), although diabetics tend to have baseline higher CSF protein without the presence of CIDP.

Nerve Pathology—As previously mentioned, peripheral nerve pathology was included in the initial Dyck review in 1975. Paranodal and intermodal segmental demyelination on teased fibers, edema, onion bulb formation, epineurial and endoneurial inflammation and axonal degeneration were observed (1). Biopsies performed for research purposes have also identified activated Cd4 or CD8 T cells and elevated soluble adhesion molecules, chemokines and matrix metalloproteinases (68). Macrophages are the most common inflammatory cell in biopsies although T cells are also highly abundant in subgroups of CIDP patients (69;70).

However, there is not a specific pathologic finding for CIDP. Sural nerve biopsy is not commonly performed for diagnostic confirmation of CIDP as characteristic features are often absent and there is considerable overlap between demyelinating findings observed by Dyck et al (1) and findings in biopsies from patients without clinical CIDP (1). This may be in line with the asymmetric process and “sural sparing” which is observed electrophysiologically (71). Skin biopsy, especially of glabrous skin may also demonstrate segmental demyelination and could be used as an alternative in future studies of CIDP(72). Fascicular nerve biopsy of motor nerves may prove to be more sensitive than traditional sensory nerve biopsies (73) especially in multifocal motor neuropathy.

The diagnosis of CIDP is based primarily on recognition of a characteristic history and typical clinical features. Electrophsyiological studies, CSF examination, and rarely nerve biopsy are useful confirmatory tests and are often used to exclude other disorders. Because diagnostic criteria have largely been devised for research settings, and are thus meant to have high specificity, the absence of typical electrophysiological or pathologic features in a patient with otherwise typical clinical features of CIDP should not necessarily exclude the diagnosis. Similarly, the observation of demyelinating features on nerve conduction studies or nerve biopsy in a patient lacking clinical features of CIDP should be interpreted with caution.

Treatment of CIDP

Treatments for CIDP are similar to those for GBS, except they are broader and more varied. In controlled studies, corticosteroids, intravenous immune globulin and plasma exchange (plasmapheresis) have been shown to have similar efficacy, improving strength and function in approximately 65 to 70% of patients (74) Other therapies directed against the presumed autoimmune basis of CIDP have been tried with success in case reports and small series, but high quality randomized controlled trials have yet to be performed(74)

Corticosteroids—Corticosteroids have been used to treat CIDP for more than 60 years. One of the first reports of CIDP discussed its recurrence and response to corticosteroids treatments, implying that this previously unreported type of neuropathy could be treated, a rare expectation in 1958 (Austin)(3) Since this first report, corticosteroids became the

benchmark treatment for CIDP until other forms of immune therapy were tried. In a small study of 28 patients who completed a controlled 3 month trial of prednisone in CIDP, prednisone led to a small, but significant improvement over no treatment in several measures of strength, sensation, and some attributes of nerve conduction(75) No difference was noted in the response rate in those patients with progressive compared to recurrent CIDP (75).

Corticosteroids are usually given in high daily doses initially to produce a rapid response, followed by tapering over months to years to low dose daily or alternate day treatment. A popular treatment regimen was proposed by Dalakas and Engel in 1981(76). Patients are started on 80-100 mg of prednisone per day for 1-2 months. This dose is tapered over time with many patients remaining on low dose prednisone (10-20 mg every other day) to sustain remission (76). Improvement may occur over several weeks, but is often lower with gradual recovery over months to years. Many neurologists prefer to use a somewhat lower dose of corticosteroids and taper more rapidly, hoping to avoid side effects.

An alternative to daily oral prednisone or prednisolone is administration of high dose corticosteroids over several, in the hopes of avoiding long term side effects. Van Schaik and colleagues compared the response rate of patients with definite or probable CIDP to pulsed high dose dexamethasone every 4 weeks to daily oral prednisolone (77). After one year, there was no difference between the two groups in the percentage of patients who achieved remission. A substantial proportion of patients in both groups were in remission at one year. Adverse events did not differ statistically between the two treatment groups. In a follow up study of those patients, the authors reported that a cure or long term remission could be achieved in about one quarter of patients with CIDP after 1-2 courses of pulse dexamethasone or 8 month treatment with daily oral prednisolone(78).

Intravenous Immunoglobulin—Intravenous immunoglobulin (IVIG) has many immune modulatory effects which may underlie its reported benefit for CIDP. Immunoglobulin blocks antibody production via negative feedback on the bone marrow, inhibition of complement activation, and downregulation of cytokines, adhesion molecules and Fc receptors on macrophages(74). IVIG has been shown to be beneficial in CIDP in numerous studies. A randomized, double-blind placebo controlled multicenter study compared IVIG at a dose of 1 gm/kg on days 1, 2 and 21 placebo. Patients were followed for 42 days.(79) The average muscle score improved in the IVIG group compared to the placebo group at day 42 ($p=0.019$) and 11 subjects in the IVIG group showed improvement in the functional disability scale (79). Parallel improvement was also observed in 3 nerve conduction parameters. The longest evidenced-based clinical trial of IVIG in CIDP was reported by Hughes et al in 2008(80). The ICE trial randmozied117 CIDP patients in a double-blind, placebo-controlled, response-conditional crossover trial of proprietary IVIG (Gamunex). Patients in the treatment arm received 1g/kg of IVIG every 3 weeks for up to 24 weeks in an initial blinded treatment period. Patients who did not improve were moved to the alternate treatment regimen. Patients who completed the 24 weeks period and improved were re-randomized to a blinded 24 week extension phase. Fifty-four percent of patients receiving IVIG improved by at least one point on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) compared to 21% of patients receiving placebo ($p>0.0002$)(80). Statistically significant improvement was also observed in grip strength in the dominant and

non-dominant hand. In the second phase of the study, subjects receiving IVIG experienced a longer time to relapse. Side effects did not limit the completion of the trial. In a follow up publication, the most common drug-related adverse events were headache and fever(81)

A recent Cochrane Review analyzed 7 randomized controlled trials of IVIG versus placebo, plasma exchange, or corticosteroids in cases of definite or probable CIDP(82). The authors found a significantly higher proportion of participants improved in disability within one month after receiving IVIG compared to placebo. There was no significant difference between IVIG and plasma exchange at 6 weeks and between IVIG and prednisolone at 2 to 6 weeks(82). One study suggested that IVIG responsiveness may relate to a specific haplotype of a single nucleotide polymorphisms (SNPs) of TAG-1(83).

Given the constraints of infusing IVIG in the hospital, an infusion center, or at home, interest has developed in the infusion of immunglobulin subcutaneously. This preparation of immunoglobulin can be administered using 2-4 small subcutaneous needles connected to a line attached to a small battery powered infusion pump. Patients or care takers can be taught to perform the infusion without nursing assistance. A small case series suggests that subcutaneous IVIG is well tolerated at a similar monthly dose to intravenous delivery with similar efficacy. Four of 5 patients preferred subcutaneous delivery(84). Over time, SQ infusion of immune globulin may become the preferred method of treating CIDP long term with immunoglobulin.

Plasma Exchange—Plasma exchange (PEx) has been used to treat GBS for decades and in a large controlled study was shown to be more beneficial than best medical management in GBS in 1985(85). Dyck and colleagues performed a randomized sham controlled trial of PEx in 15 patients with CIDP (86). After 3 weeks of treatment, there was a statistically significant improvement of nerve conduction parameters favoring patients who had received PEx, and in the neurologic disability score in 5 patients and in subset scores for weakness and reflexes in 4 patients. The authors concluded that PEx helps some, but not all patients with CIDP(86). Similar benefit was reported in another double-blind, sham-controlled , cross-over study(87). In this study, 80% of patients improved after undergoing plasma exchange. The improvement in motor functions correlated with the electrophysiologic data. Of interest, all but 2 patients required long term immunosuppressive drug therapy to achieve stabilization of disease(88). A Cochrane Review noted short term benefit in about two-thirds of patients with CIDP, but cautioned that rapid deterioration may occur afterwards. They reinforced the potential for adverse events such as difficulty with venous access, use of citrate and hemodynamic changes during or after exchange(89).

Immunoadsorption (IA) is a process that uses an immunosorbent to purify a substance. One study of tryptophan-immune adsorbers in14 patients with CIDPdemonstrated significant improvement in INCAT scores in 10 after one treatment series(90). IA was considered safe and well-tolerated.

Several studies have compared IVIG to PEx. One carefully-designed crossover study of IVIG versus PEx, found no statistical differences between the two treatments(91). For most patients, the benefits were short lived and required continued intermittent treatment with the

same agent. Another study examined the benefit of various treatments in 67 consecutive patients with CIDP over 4 years(92). Although the response rate was similar to IVIG, steroids and PEx, the functional improvement as measured by the Rankin Score was greatest after PEx. Of patients who did not respond to initial therapy with one of the 3 agents, 35% responded to the second tand of those who failed to improve after 2 modalities, 27% responded to the third (92). The overall response rate to one of the 3 therapies was 66%. In a larger study from 11 centers in Italy, the percentage of responders to first-line therapy (steroids, IVIG or PEx) was 69%(93). This percentage increased to 81% after a change to another therapy. There was a better response to steroids or IVIG than to PEx. Adverse effects were the highest after receiving PEx. In a randomized controlled trial of IVIG versus oral prednisolone in CIDP, both treatments produced a significant improvement in the primary outcome(48). Non-statistically significant changes in secondary outcomes favored the IVIG group.

Immunosuppessants—Many oral and intravenous immunosuppressants have been used to treat CIDP including azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenylate mofetil, rituximab, interferon, and alemtuzumab(74). Many have reported in case reports or small series, and there have been few randomized trials.

Azathioprine: A single small randomized 9 month trial of alternate day dosing of prednisone therapy alone or with azathioprine given as 2 mg/kg found no treatment benefit(94). The lack of response may have been due to the short duration of treatment (9 months) or the dosing of azathioprine. Many neuromuscular experts routinely use azathioprine as a steroid sparing agent based on clinical experience despite the lack of strong evidence from the literature.

Cyclophosphamide: Pulse cyclophosphamide, infused once per month for 6 months, was used in 15 patients with CIDP(95). The dosing was 1 g/M^2 given over 1.5 -2 hours. Eleven patients achieved complete remission and one patient improved in his functional scale. Three patients did not improve and only one person worsened. Adverse effects included nausea, vomiting, anemia and hair loss. High dose cyclophosphamide (200 mg/kg) has also been used to good effect in refractory patients (96)

Cyclosporin: Four studies (including one of two children) suggest cyclosporine may be beneficial for CIDP(97-100). In the largest study, patients with both progressive and relapsing CIDP improved after receiving cyclosporin(97). The initial dosing was 8-11 mg/kg in 8 patients and 3-7 mg/kg in 10 patients. The dosing was reduced stepwise over 6 months. All of the patients with progressive CIDP improved and the incidence of relapses declined in the group with recurrent worsening CIDP. In a second study of 6 patients with CIDP and two with IgG monoclonal gammopathies who were treated with cyclosporine in a dose of 3-5 mg/kg, improvement was recorded in 3 patients and no change in 5 patients(98).

Mycophenylate mofetil: Mycophenylate mofetil induces immune suppression by selectively blocking purine synthesis in lymphocytes and inhibiting the proliferation of B and T cells(101). Studies of mycophenylate in CIDP have shown benefit in several patients, but the results are not as impressive as in other illnesses or when compared to other immune

suppressants. In one report, almost 75% of patients with myasthenia gravis improved after the initiation of mycophenylate 33% for CIDP and inflammatory myopathy. Favorable results were reported in 2 patients with CIDP treated with mycophenylate(102). In a study of 21 patients there was a modest improvement in 30%, permitting a reduction of steroids or IVIG therapy(103). Another study found no clinically significant benefit or reduction in the dosing of corticosteroids or other immunosuppressants in 5 patients with treatment-resistent CIDP who were taking mycophenylate(104).

Methotrexate: Methotrexate has been used for decades to treat inflammatory myopathies such as polymyositis and dermatomyosities. A 40 week study of methotrexate compared to placebo did not demonstrate a reduction in the dosing of corticosteroids or IVIG of 20% (the primary outcome) in patients taking methotrexate (15 mg weekly) compared to placebo(105). In addition, there was no clinically or statistically significant difference in secondary outcomes.

Rituximab: Rituximab is a chimeric anti-CD20 monoclonal protein that is approved for the treatment of B-cell lymphoproliferative diseases and which is now used to treat B-cell mediated disorders. A retrospective, observational study of 13 patients with treatment refractory CIDP demonstrated a response in 9 patients, 6 of whom improved clinically(106). Three patients maintained the improvement they had achieved from treatment with IVIG or plasma exchange. Seven of the patients who responded had associated hematologic diseases. The response occurred as early as 2 months in some patients. In an early study of the use of rituximab in patients with IVIG-dependent immune polyneuropathy, two patients with CIDP who were given rituximab (375mg/M^2 IV weekly for 4 weeks) did not experience a reduction in IVIG requirements(107). In single case reports, rituximab was effective in a patient with CIDP and idiopathic thrombocytopenic purpura and another who had CIDP and SLE(108;109). Rituximab has been described as useful in childhood onset CIDP (110).

Alemtuzumab: Alemtuzumab is a recombinant, humanized monoclonal protein that is directed against the CD52 antigen(111). CD 52 is expressed on most B and T lymphocytes, macrophages and monocytes. Because of its mechanism of action, alemtuzumab became an attractive choice as a possible therapeutic agent for the treatment of CIDP. Seven patients with CIDP, who were refractory to conventional immunosuppression, were treated with 9 courses of alemtruzumab, the dose ranging from 60-150 mg(112). Two patients experienced a prolonged remission, two patients a partial remission, and three no clear benefit from alemtuzumab. Three patients developed an autoimmune disease after treatment with alemtruzumab. Thus, alemtruzumab may have a future in the treatment of refractory CIDP, but a concern over the development autoimmune disease may limit its utility.

Interferon: The interferons were developed decades ago to treat demyelinating diseases of the central nervous system. Because of the role of various interferons in the inflammatory process, they have also been considered as potential treatments in CIDP. Sabatelli and colleagues reported two patients with treatment refractory CIDP who achieved complete and sustained recovery after treatment with interferon alpha-2a(113). Nine of 16 patients in another study experienced improved strength and sensation after receiving interferon-alpha

2a for 6 weeks(114). All patients who were studied had failed to respond to at least one conventional treatment for CIDP(114).

Individual case reports have suggested efficacy of interferon beta in CIDP (115) (116;117). In some cases, improvement was observed in electrophysiologic parameters(116). However, several studies have failed to demonstrate treatment efficacy of interferon –beta 1a as primary therapy of CIDP (118;119) or in patients who were IVIG dependent(120).

Cocito et al reviewed the clinical and electrophysiologic data of 110 patients with CIDP followed at 10 Italian centers to assess the response rate to immunosuppressive and immunomodulatory therapies prescribed in patients who were non-responders to conventional treatments (corticosteroids, IVIG, and plasma exchange)(121). Approximately one fourth of patients experienced benefit when given one of the immunosuppressive or immunomodulatory therapies. None of the 3 patients who received interferon-beta 1a improved. The response rate to each drug is as follows: azathioprine 27%, rituximab 33%, cyclosporine 25%, cyclophosphamide 38%, methotrexate 17%, mycophenylate mofetil 25%, and alpha interferon 36%(121). A Cochrane Review examined randomized and quasi-randomized trials of immunosuppressive agents for the treatment of CIDP and concluded the evidence is inadequate to decide whether azathioprine, interferon beta, or any other immunosuppressive drug or interferon is beneficial in CIDP(122).

Stem Cell Transplantation—Autologous peripheral blood stem cell transplantation (PBSCT) is an attractive treatment for autoimmune inflammatory conditions as it offers the potential for restructuring the immune system and reaction to antigens. Mahdi-Rogers and colleagues treated 3 patients with CIDP, two patients with POEMS Syndrome, and one with a neuropathy from an IgM paraprotein with (PBSCT). Two of the three patients with CIDP improved, but one relapsed after 18 months. Four of the 6 patients developed neutrophenic septicemia and pneumonia(123). Thus, PBSCT may offer improvement in a highly select cadre of patients with CIDP, but its serious adverse effects will preclude its use for all but the most refractory patients.

Conclusions

Despite significant advancements in treatment options for CIDP, further work on elucidating the pathogenesis is needed. While there is substantial evidence for an immune dysregulation etiology, better understanding may improve selection of therapeutic agents for interventional studies rather than the current “shotgun” approach in which all immunosuppressive therapies are tried. In addition, more specific biomarkers are needed to guide therapeutic decisions and improve interventional trials, however no biomarkers have met sufficient sensitivity and specificity for clinical use (124-126).

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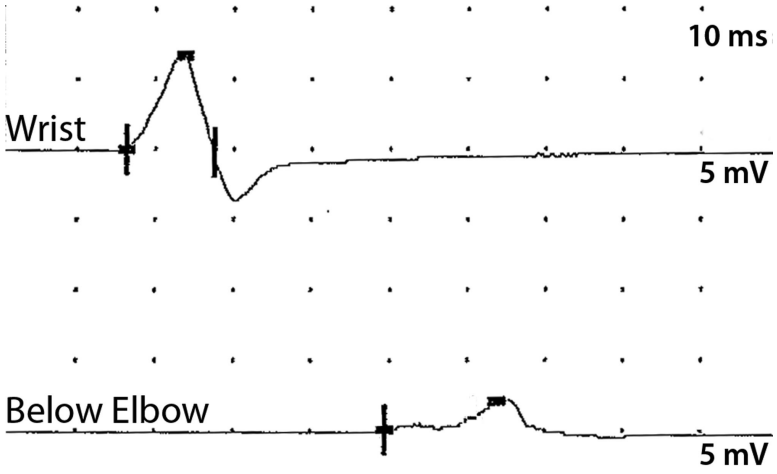

Figure 1.

Temporal dispersion and conduction block observed recording from the ulnar nerve at the abductor digiti minimi in a patient with CIDP. The proximal amplitude is lower with longer duration typical of temporal dispersion.

Table 1

Characteristics of CIDP

Equal prevalence in men and women
Time course of 2 months or more
Disease Evolution: Chronic progressive, stepwise progressive, relapsing and remitting
Symmetric proximal and distal weakness
Large fiber more than small fiber involvement
Hyporeflexia or areflexia
Cranial nerve involvement rare
Respiratory failure rare
Nerve conduction abnormalities: slowing of conduction velocities, prolonged distal latencies, conduction block, temporal dispersion
CSF protein: greater than 45 mg/dl, fewer than 10 WBCs
Nerve biopsy: may show inflammation, demyelination, and axon loss
Responsive to immunotherapy.

Table 2

Treatment Options for CIDP

Treatments with Class B or higher efficacy	Other Treatments
Corticosteroids	Azathioprine
Intravenous Immunoglobulin (IVIg)	Methotrexate
Plasma Exchange	Cyclosporin A
	Cyclophosphomide (pulse IV)
	Mycophenolate
	Interferons
	Rituximab
	Alemtuzumab
	Stem Cell Transplantation
	Immunoadsorption