NEUROIMMUNOLOGY (RP LISAK, SECTION EDITOR)

Chronic Inflammatory Demyelinating Polyneuropathy

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Opinion statement

Chronic Inflammatory polyneuropathies are an important group of neuromuscular disorders that present chronically and progress over more than 8 weeks, being referred to as chronic inflammatory demyelinating polyneuropathy (CIDP). Despite tremendous progress in elucidating disease pathogenesis, the exact triggering event remains unknown. Our knowledge regarding diagnosis and management of CIDP and its variants continues to expand, resulting in improved opportunities for identification and treatment. Most clinical neurologists will be involved in the management of patients with these disorders, and should be familiar with available therapies for CIDP. We review the distinctive clinical, laboratory, and electro-diagnostic features that aid in diagnosis. We emphasize the importance of clinical patterns that define treatment responsiveness and the most appropriate therapies in order to improve prognosis.

Introduction

It is important to recognize CIDP because it represents 21 % of initially undiagnosed neuropathy cases evaluated at the Mayo Clinic and it is responsive to immune system suppression or modulation [1]. In our series from large academic centers in Dallas and San Antonio, CIDP affected 13 % of 402 neuropathy cases referred to our neuromuscular clinic [2]. Academic center data derived from more than 1000 cases in North America (The University of Kansas Medical Center and The University of Texas Southwestern) and 1034 cases from South America (Federal Fluminense University, Brazil) demonstrates a similar proportion of immune-mediated neuropathies ranging from 18 % to 20 % [3, 4]. Other forms of chronic acquired demyelinating neuropathies are described in Table 1.

Table 1. Comparison of the chronic acquired immune-mediated demyelinating polyneuropathies

	CIDP	DADS neuropathy	MADSAM neuropathy	MMN
Clinical features				
Weakness	Symmetric; proximal + distal	Symmetric; distal only; mild or no weakness	Asymmetric; distal > proximal; upper limbs > lower limbs	Asymmetric; distal > proximal; upper limbs > lower limbs
Sensory deficits	Yes; symmetric	Yes; Symmetric	Yes; multifocal (distribution of individual nerves)	No
Reflexes	Reduced or absent symmetrically	Reduced or absent symmetrically	Reduced or absent (multifocal or diffuse)	Reduced or absent (multifocal or diffuse)
Electrophysiology				
Abnormal CMAPs:				
Demyelinating features	Usually symmetric	Usually symmetric Prolonged distal latencies	Asymmetric (multifocal)	Asymmetric (multifocal)
Conduction block	Frequent	Uncommon	Frequent	Frequent
Abnormal SNAPs	Usually symmetric	Usually symmetric	Asymmetric (multifocal)	SNAPs are normal
Laboratory findings				
CSF Protein	Usually elevated	Usually elevated	Usually elevated	Usually normal
Monoclonal protein	Occasionally present; Usually IgG or IgA	IgM-κ present in the majority; 50 %–70 % are MAG positive	Rarely present	Rarely present
Anti-GM1 Antibodies	Rarely present	Not present	Rarely present	Frequently present (50 %)
Sensory nerve biopsy:				
Demyelination/ remyelination	Frequent	Frequent	Frequent; Sometimes asymmetrical	Occasional; Minimal findings
Treatment response				
Prednisone	Yes	Poor[a]	Yes	No
Plasma exchange	Yes	Poor[a]	Possible (more study needed)	No
IVIg	Yes	Poor[a]	Yes	Yes
Cyclophosphamide	Yes	Poor[a]	Possible (more study needed)	Yes

CIDP chronic inflammatory demyelinating polyneuropathy, *CMAPs* compound motor action potentials, *CSF* cerebrospinal fluid, *DADS* distal acquired demyelinating symmetrical, *IVIg* intravenous immunoglobulin, *MADSAM* multifocal acquired demyelinating sensory and motor, *MAG* myelin associated glycoprotein, *MMN* multifocal motor neuropathy, *SNAPs* sensory nerve action potentials.
[a] When associated with an IgM-MGUS.
Treatment responses in DADS neuropathy patients without a MGUS are more similar to those with CIDP.

Epidemiology

Earlier reported prevalence has ranged from 1 to 7.7 per 100,000, and increased with advancing age with a peak incidence at 40–60 years of age [5–7]. In Olmstead County, the incidence of CIDP was more recent-

ly estimated to be 1.6/100,000/year with a prevalence of 8.9/100,000 [5]. The disease can occur at virtually any age with 47.6 years mean age of onset and with a higher prevalence in men than women [6]. Although a relapsing course seems more common between the second and fourth decade; a chronic nonrelapsing course is more common between the fifth and the seventh decade [6].

CIDP

Clinical features

CIDP patients typically present with chronic progressive, stepwise progressive or relapsing weakness [1–3, 8]. The overwhelming majority of patients over the age of 65 have a chronic progressive course for two or more months [1]. Weakness is typically symmetric and characteristically involves proximal and distal muscles [9], occasionally affecting face or neck flexor muscles, and typically sparing of extraocular muscles. Except in pure motor presentation, which affects up to 10 % of cases [10], sensory symptoms include numbness, tingling, gait imbalance, and at times painful parasthesias [10–12]. The sensory variant affects 35 % of cases while classic sensorimotor presentation occurs in 51 % [10]. While muscle stretch reflexes are depressed or absent, autonomic and respiratory insufficiency are uncommon.

The 18 % of CIDP patients who present with the relapsing form are difficult to distinguish from GBS [10, 13, 14]. CIDP cases were more likely than GBS to demonstrate prominent sensory signs and less likely to have autonomic involvement, facial weakness, a preceding infectious illness, or need mechanical for ventilation [13]. The first treatment-related fluctuation (TRF) in GBS always occurred within 8 weeks from onset of weakness and none experienced more than two TRFs [14]. Acute CIDP patients were more likely to maintain independent ambulation, normal cranial nerves, and to display marked demyelination on nerve conduction studies.

Another temporal variant group labeled subacute inflammatory demyelinating polyneuropathy (SIDP) consists of patients who progress for longer than weeks but less than 8 weeks, and therefore do not fall neatly into either the acute or chronic acquired demyelinating neuropathy groups [15–17]. An antecedent infection is found in 38 % of cases with cranial nerve deficits and respiratory failure being rare. CSF protein is elevated in 93 % of cases and demyelination is documented on motor nerve conduction in 88 % of cases. Up to 17 % of cases classified as probable SIDP will relapse when immunosuppressive therapy is discontinued, and these patients ultimately are diagnosed with CIDP. The bottom line is a tincture of time will help distinguish those with future attacks indicative of relapsing CIDP from those with SIDP.

In addition to classic CIDP, other phenotypes sharing some clinical and pathologic features, laboratory findings, and in most cases response to immunomodulatory therapies have been described the rubric of chronic acquired demyelinating polyneuropathies (CADP) (Table 1) [18, 19]. The four categories of CADP are largely based on the phenotypic differences. Symmetrical proximal and distal weakness with or without sensory loss is highly suggestive of CIDP. The pattern of symmetrical distal weakness and sensory loss should raise suspicion of distal acquired demyelinating symmetric

(DADS) neuropathy [20]. When weakness is asymmetric, further classification hinges around the presence or absence of sensory signs. Asymmetric distal weakness without sensory loss is indicative of multifocal motor neuropathy (MMN) whereas sensory loss would suggest multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy (Lewis-Sumner syndrome) [21–24]. Up to half of the MMN patients also have serum GM-1 antibodies and most DADS patients have an IgM monoclonal protein in the serum, often accompanied by antibodies to myelin-associated glycoprotein (MAG). Multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy patients have a chronic sensorimotor mononeuropathy multiplex with typically an insidious onset and slow progression. Initial involvement is usually in the arms, with later spread to distal legs. Unlike MMN, MADSAM neuropathy is not associated with anti-GM1 antibodies [21, 25–27]. As in MMN and CIDP, nerve conduction studies in MADSAM neuropathy shows conduction block, temporal dispersion, prolonged distal latencies, slow conduction velocities, and delayed or absent F-waves in one or more motor nerves. In contrast to MMN, sensory NCS are also abnormal at the outset. Though prospective randomized controlled studies have not been performed, retrospective series have demonstrated improvement in response to IVIg in treatment more than 70 % of MADSAM neuropathy patients [21, 25–30]. In contrast to MMN, most patients with MADSAM neuropathy have also shown response to corticosteroid treatment. Therefore it is important to distinguish MADSAM neuropathy from MMN since the former is steroid-responsive while the latter is not.

Preceding viral infections are less common in CIDP compared with GBS. In 2007, a cluster of patients experiencing a polyradiculoneuropathy mimicking CIDP was identified in a swine abattoir table primarily processing severed heads [7]. Workers removed brains by using compressed air that liquefied brain and generated aerosolized droplets, exposing themselves and nearby workers to porcine neural antigens. An immune-mediated pathophysiology was supported by increased levels of interferon-gamma expression.

Laboratory features

The most important laboratory studies that support of the diagnosis of CIDP are the cerebrospinal fluid (CSF) examination, NCS, and nerve biopsy. Of these three, the CSF evaluation is the most sensitive as protein is elevated in up to 94 % of cases with normal white cells [31, 32]. A CSF white blood cell count exceeding 10/mm3 should lead to suspicion for HIV infection, Lyme disease, sarcoidosis, and lymphomatous, or leukemic nerve root infiltration. Oligoclonal bands are identified in the CSF up to 65 % of CIDP patients [33]. If a paraprotein is detected on serum immunofixation or serum kappa lambda free light chain ratio, a search for a lymphoproliferative disorder, such as osteosclerotic myeloma or lymphoma, should be initiated. Magnetic resonance imaging (MRI) demonstrates an enlargement on T2 sequences of the spinal nerve roots and contrast enhancement.

Nerve conduction studies

Nerve conduction studies demonstrate demyelination including slowed motor nerve conduction velocities, prolonged distal motor latencies, delayed

F wave latencies (Table 2), and partial motor conduction block (at least 30 % to 50 % reduction in proximal amplitude) or abnormal temporal dispersion (prolongation of proximal motor response duration by 30 % or more). Though highly specific to CIDP [34], the AAN research criteria have suboptimal sensitivity of 39 %–43 % as they require abnormalities in three of the above four parameters, with the first three measures affecting two or more nerves [35, 36]. We compared several published criteria and found all had similar sensitivities ranging from 52 % to 76 % [37]. More recently, derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy simplified the electrodiagnostic criteria, in cases of progressive neuropathy for more than 8 weeks without monoclonal protein or genetic neuropathy, to more than one-half of studied nerves demonstrating abnormality in either distal latency, conduction velocity or F wave latency as in Table 2 [38••]. This rule, which applies when 75 % or more of the studied nerves have recordable potentials, had 83 % sensitivity and 97 % specificity in a validation cohort and performed better than published criteria. The EFNS 2010 criteria added prolonged distal CMAP duration from onset of first negative peak to return to baseline of last negative peak in one nerve with one or more other demyelinating parameter in another nerve as supportive of definite CIDP(median ≥6.6 ms, ulnar ≥6.7 ms, peroneal ≥7.6 ms and tibial ≥8.8 ms) [39].

Though the 2010 EFNS guidelines recommend a normal sural with abnormal median or radial SNAP pattern as a supportive good practice point [39], there is controversy around the utility of sensory nerve conduction studies in supporting the diagnosis of CIDP. We retrospectively compared 52 CIDP cases with 35 cryptogenic sensory neuropathy cases and found a lower frequency of sural nerve sparing (8 %) in CIDP with poor specificity [37]. Sensory conduction velocity <80 % of lower limit of normal (<70 % if SNAP amplitude <80 % of lower limit of normal) is also supportive of CIDP according to the 2010 EFNS revision. However, Rajabally and Samarasekera found that SNAP conduction velocities were significantly slower for median and sural nerves in 19 CIDP patients, but ROC curves did not demonstrate

Table 2. Nerve conduction study values needed to be considered "demyelinating"

	NCV (m/s)			DL (ms)			F WAVES (ms)		
	LLN	<80%[a]	<70%[b]	ULN	> 125%[a]	>150%[b]	ULN	>120%[a]	>150%[b]
Median	49	39.2	34.3	4.5	5.6	6.7	31.0	37.2	46.5
Ulnar	50	40.0	35.0	3.6	4.5	5.4	32.0	38.4	48.0
Peroneal	41	32.8	28.7	6.6	8.2	9.9	58.0	69.6	87.0
Tibial	41	32.8	28.7	6.0	7.5	9.0	58.0	69.6	87.0

[a] If Amp >80 % LLN
[b] If Amp <80 % LLN
If: Median CMAP LLN 4.5 mV; then 80 % LLN = 3.6 mV
Ulnar CMAP LLN 5.0 mV; then 80 % LLN = 4 mV
Peroneal CMAP LLN 2.0 mV; then 80 % LLN = 1.6 mV
Tibial CMAP LLN 4.0 mV; then 80 % LLN = 3.2 mV
NCV nerve conduction velocity
DL distal latency
CMAP compound muscle action potential
LLN lower limit of normal

cut-offs with useful sensitivities/specificities when compared with control cases with distal large fiber sensory axonal neuropathy [40]. The 2010 EFNS guidelines also suggest that somatosensory evoked potentials can support the diagnosis of CIDP by demonstrating abnormal proximal sensory conduction, particularly in sensory CIDP cases with normal sensory nerve action potentials and without central nervous system disease.

An important limitation is that almost all of the proposed criteria focus on NCS, and meeting NCS criteria is a necessary component for most. The derivation and validation study included symmetrical onset of motor symptoms, symmetrical weakness of four limbs, and proximal weakness in one or more limbs as a separate criterion for definite CIDP besides the above noted electrophysiologic criteria [38••]. Out of 48 CIDP consensus patients in the validation sample, 63 % satisfied the electrophysiologic and clinical criteria, 20 % only the clinical criteria, and 18 % only the electrophysiologic criteria. Most of the patients who met only the clinical criteria for CIDP had a prolonged course and secondary axonal loss electrophysiologically.

Histology

Of the three main laboratory studies, sural nerve biopsy is probably the least useful [41, 42]. Sensory nerve pathology demonstrates foci of endoneurial or perivascular inflammation in only 11 % of 60 cases [32]. The presence of macrophages clusters, namely three or more macrophages, around endoneurial vessels in sural nerve biopsies may serve as a useful additional marker for establishing the pathologic diagnosis of CIDP [43]. Pathologic evidence of demyelination and remyelination is present on teased nerve fiber analysis in only 48 % to 68 % of CIDP cases and up to 21 % had mixed demyelinating and axonal changes [32]. There was considerable overlap in features of demyelination, axonal degeneration, and inflammation in 21 CIDP and 13 chronic idiopathic axonal polyneuropathy patients [42]. As indicated by the 2009 AAN practice parameter, nerve biopsy is of limited diagnostic value in CIDP but may be useful to exclude in atypical CIDP cases mimics such as amyloidosis, vasculitis, sarcoidosis, and lymphomatous infiltration [44].

Pathophysiology

CIDP is a complex autoimmune disease with evidence in support of both cellular and humoral autoimmunity to an unknown antigen. The main cellular components of inflammatory peripheral nerve infiltrates are epineurial and endoneurial T cells and macrophages with macrophage-mediated myelin stripping [45]. Myelin sheets may at times be surrounded by macrophages invading the basement membrane and actively stripping myelin lamellae [46]. The T cells express increased activation markers and inflammatory chemokine receptors, especially CXCR-3 [47], and secrete matrix metalloproteinase 2 and 9 [48]. In support of humoral immune factors, passive sera, and immunoglobulin G antibodies transfer from patients with CIDP induce peripheral demyelination in recipient animals [49]. Although plasma exchange supports the role humoral factors, autoantibodies to components of peripheral nerve myelin or to neuronal antigens have been inconsistently found in CIDP sera. Antibody-mediated complement attack against peripheral nerve myelin, with resultant myelin stripping and

phagocytosis, is supported by the increase in serum levels of complement terminal attack complex [50] and expression of in C3d products on peripheral myelin sheaths [51]. The strongest evidence incriminates P0, to which antibodies have been found in only 20 % of CIDP cases [52].

CIDP is caused by loss of regulation of immune reaction in response to unknown antigens. Suppressor cell function is defective in CIDP but can be enhanced in vivo by prednisone and plasma exchange in conjunction with clinical improvement [53]. The percentage of circulating regulatory T cells is reduced in CIDP compared with normal controls [54]. The inhibitory Fc-gamma receptor (FcγR) IIB, expressed on myeloid and B cells, plays a critical role in the balance of tolerance and auto-immunity in various murine disease models [55]. Treatment-naive active CIDP patients showed a lower expression of FcγIIB levels on B cells. Furthermore, CIDP and systemic lupus erythematosus patients share an increased representation of a polymorphism in the promoter for the gene that controls expression of Fcγ receptor IIB [56]. CIDP cells displayed lower Fas function, a death receptor on activated lymphocytes involved in switching-off the immune response, than both AIDP patients and controls [57]. Fas function was lower in CIDP patients with progressive course or axonal damage than in those with relapsing-remitting course or pure demyelination respectively.

CIDP with concurrent illness

CIDP can occur in the setting of a number of systemic disorders [58–64]. This group has been termed "CIDP with concurrent illness" [32, 65], although the exact relationship of the underlying illness to the development of CIDP differs from case to case. For example, in Charcot-Marie-Tooth disease, the underlying systemic disorder might increase susceptibility to the development of an acquired demyelinating polyneuropathy resulting in acute or subacute deterioration following a long asymptomatic or stable course [66]. In other cases, such as hepatitis C, the concurrent illness may be part of a systemic dysimmune process, polyneuropathy being one of its manifestations. Therefore, these patients should probably be treated no differently from those with idiopathic CIDP.

An Olmsted County epidemiologic study showed that diabetes mellitus occurred no more frequently in CIDP when compared with normal controls [5]. There are patients with diabetes that develop the classic phenotype of CIDP and most respond with stable and prolonged remissions over several years to IVIg administration [67]. In another report, most diabetic CIDP patients fulfilling the AAN criteria improved in the clinical disability grade at 6 months in response to prednisone therapy but to a lesser extent than nondiabetic CIDP cases [68]. TNF-α antagonists administered for various autoimmune diseases have been reported in association with a variety of immune-mediated neuropathies including GBS, MFS, CIDP, MMN and mononeuropathy multiplex [69]. We [70] and others reported cases of tacrolimus-associated CIDP [71–73].

Ten to 20 % of CIDP cases may have a monoclonal gammopathy of undetermined significance (MGUS) [20, 32, 74]. The level of the monoclonal protein is typically reduced and can be missed with serum protein electrophoresis without serum immunofixation [75, 76]. Though most CIDP-MGUS cases generally do not have an underlying lymphoma, osteosclerotic

myeoloma, or other lymphoproliferative disorder, they should have radiographic skeletal survey, undergo a hematologic evaluation and in some cases a bone marrow biopsy. Those that have an IgG- or IgA-MGUS frequently respond to immunomodulatory therapy. Patients with an IgM-MGUS usually, but not invariably, have exclusively distal involvement of DADS neuropathy and are less responsive to therapy [20]. Osteosclerotic myeloma can be associated with other system manifestations in the POEMS syndrome of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes. The pathogenesis is related to vasoactive endothelial growth factor (VEGF) production, which can be used as a diagnostic marker [77, 78]. Patients with monoclonal gammopathy, osteosclerotic myeloma, and demyelinating neuropathy should undergo evaluation by skeletal survey, which is more sensitive than nuclear bone scan to detect osteoslerotic lesions [76].

Treatment

Randomized controlled trials have confirmed the efficacy of corticosteroids (CS) [79], plasma exchange [80, 81], and intravenous immunoglobulin (IVIg) [82–84] for the treatment of CIDP. Each of these is an acceptable first-line therapy, although the need for specialized facilities for providing outpatient plasma exchange and prolonged intravenous access makes plasma exchange less appealing. Due to the long-term side effect profile of corticosteroids, there is a trend towards using IVIg as the initial therapy for CIDP. A multicenter, randomized, double-blind, crossover trial compared a 6-week course of oral prednisolone tapering from 60 mg to 10 mg daily with IVIg 2.0 g/kg given over 1 to 2 days for treating CIDP [85]. Twenty-four of the 32 randomized patients completed both treatment periods. Though treatment with IVIg did bring about more rapid improvement, there was little difference between the two therapies.

Prednisone therapy is initiated with 100 mg orally once daily in the morning. When improvement begins, usually within 2 to 4 weeks, patients can be switched to alternate day therapy. When strength has returned to normal or improvement has plateaued, usually within three-six months, prednisone dose is slowly tapered by 5 mg every 2 to 3 weeks. Although a minority of patients can eventually be tapered completely off of prednisone, many patients relapse. It is important for both the patient and physician to realize CIDP is a chronic disorder and may require immunosuppressive therapy for one or more years. Some patients will require a steroid-sparing agent to facilitate a downward prednisone taper (see below).

Because the risks of long-term CS therapy are numerous, discussing those with the patient as well as establishing a monitoring plan in collaboration with the primary care physician is integral to the management plan. Before CS initiation we place a PPD skin test to identify the need for isoniazid in previously exposed cases. As we start CS, we obtain a baseline bone DEXA scan and request the patient to seek an ophthalmologic examination, with yearly follow-up for both. We maintain patients on oral calcium 500 to 600 mg two to three times daily with vitamin D 400–800 IU daily. If there is osteopenia or osteoporosis, or there are fractures, we recommend starting an antiresorptive agent such as alendronate. If patients develop gastric irritation, we instruct them to use H2-blockers or proton pump inhibitors. We ask

patients and their family to be alert about personality changes and psychiatric side effects. We inform our patients to reduce the salt and carbohydrate in their diet and visit regularly with the primary care physician for blood pressure, serum glucose, and potassium and measurements. We advocate the pneumococcal vaccine and yearly flu shots but caution against live vaccines.

A recent retrospective chart review from the Washington University neuromuscular group suggests that intravenous high-dose methylprednisolone may be an effective treatment for CIDP [86]. To further investigate the potential to reduce CS side effects, an open-label prospective study of pulse oral weekly methylprednisolone was recently conducted [87]. Steroid-induced osteoporosis was however noted in five/nine cases.

The study by Mendell and colleagues established that intravenous immunoglobulin (IVIg) improves strength and functional score more than placebo in newly diagnosed CIDP patients who had not received any other forms of immunosuppressive therapy [83]. The pharmacodynamic effects of IVIg in CIDP are rapid with onset of isokinetic muscle strength improvement on day 5 after of IVIg reinitiation and peaking by day 10 in association with gait velocity and hand function response [88]. The INCAT group reported that both IVIg and prednisolone were essentially equally effective when compared in a head-to-head trial [85]. The recently published ICE trial [84] was a randomized, double-blind, placebo-controlled, response-conditional crossover trial included 117 patients with CIDP. Caprylate-chromatography purified 10 % immune globulin intravenous or placebo was given every 3 weeks for up to 24 weeks in an initial treatment period. Fifty-four percent of patients treated with IVIg had an improvement in the adjusted INCAT disability score through week 24 compared with 21 % of subjects who received placebo (P=0.0002). Improvements were also recorded for grip strength and in CMAP amplitudes of proximal and most severely affected nerves [89]. During the 24-week extension phase, participants who continued to receive IVIg had a longer time to relapse than did patients treated with placebo (P=0.011). This study led to the first FDA-approved therapy in CIDP.

We recommend an IVIg induction dose of 2 gm/kg over 2 to 5 days, followed by monthly maintenance doses of 0.4 gm/kg. Based on the ICE study, the suggested maintenance dose may be as high as 1 gram per kilogram every 3 weeks. The range of maintenance dose of 0.2 gram per kilogram weekly to 1.0 gram per kilogram every 3 to 4 weeks with adjustments made on an individual basis. We usually plan to treat patients for 6 months, and then re-evaluate to determine if further therapy is needed. We treat with repeated courses for to months before concluding lack of efficacy. While we generally infuse IVIg no faster than 150 to 200 cc/h, a recent report described infusion rates of up to 800 cc/h in 50 patients, which was reasonably well tolerated [83]. Lee and colleagues treated two CIDP patients with subcutaneous infusion of immunoglobulins (SCIg) after IVIg therapy was shown to be effective. Application of SCIg was well tolerated and led to stabilization of the disease course [90].

Intravenous immunoglobulin (IVIG), a pooled gammaglobulin product from several thousand blood donors, has a complex immunomodulatory mechanism of action. It is thought to involve pathogenic autoantibodies production modulation and binding inhibition, pro-inflammatory cytokine

suppression, Fc receptor blockade, macrophage colony stimulating factor and monocyte chemotactant protein-1 increase, alteration in T cell function, decreased in circulating CD54 lymphocytes, and inhibition of cell transmigration into the muscle. More recently, investigators from the Rockefeller found that Fc core polysaccharide 2,6-sialylation mediates the anti-inflammatory properties the IVIg [91].

Plasma exchange (PE) was demonstrated to be more effective than "sham" pheresis for CIDP in two important studies with up to 80 % response rate [80, 81]. PE is typically used if patients are severely weak, if they relapse on prednisone or IVIg, or they are unresponsive to these therapies. However, IVIg may also be effective in severely weak patients. Risks of PE include those of central venous indwelling catheter, hypotension, allergic reaction to albumin, hypocalcemia, anemia, thrombocytopenia, and citrate toxicity. The response obtained with plasma exchange is faster than that from prednisone or IVIg. Five to ten treatments are usually performed over 2 to 4 weeks at the initiation of therapy. Unlike the situation in GBS, there is no benchmark goal of how much total fluid to remove. The effects of plasma exchange are transient, usually lasting 4 to 8 weeks, but sometimes only 1 to 2 weeks. Therefore, unless another immunomodulatory treatment such as prednisone is given, PE will need to be performed indefinitely, something not typically pursued because of cost, risk to the patient, and often the need for a long-term indwelling vascular access device.

When a patient does not respond to or cannot tolerate the first-line agents, other medications may prove beneficial. Azathioprine, cyclophosphamide, cyclosporine, interferon-alpha, interferon-beta, mycophenolate mofetil, and methotrexate have all been reported to be beneficial in CIDP patients not responsive to initial therapies [92–108]. For the most part, these studies were not prospective, randomized, or blinded. In a small controlled trial, patients randomly assigned to azathioprine 2 mg/kg and prednisone did no better than those assigned to glucocorticoids alone [92]. Besides azathioprine, mycophenolate mofetil, cyclosporine, and methotrexate are often used as steroid sparing agents. A negative randomized controlled trial of oral methotrexate 15 mg weekly was reported in CIDP [109]. A recent studied evaluating the effects of intramuscular interferon-beta-1a (Avonex) at low (30 micrograms weekly), intermediate (30 micrograms twice weekly or 60 micrograms weekly) and high dose (60 micrograms twice weekly) on IVIg dose in CIDP did not show a significant benefit [104, 105, 110]. High dose cyclophosphamide without stem cell rescue can lead to long-term remission with refractory CIDP [97] with improved quality of life [112]. In progressive demyelinating neuropathy patients with IgM monoclonal gammopathy of unknown significance, oral treatment with fludarabine was well-tolerated and induced stabilization and improvement in modified Rankin scale at 1one year follow-up in 5/16 patients [111].

Targeted therapies have yet to be fully studied in CIDP. Rituximab is a chimeric monoclonal antibody that specifically binds to CD20 antigen, expressed from pre-B-cell stage to mature B-cell stage, on normal and malignant B-lymphocytes. In a retrospective observational study of rituximab in 13 Italian CIDP patients eight of whom had hematologic malignancy (*n*=4) or MGUS (*n*=4), most cases improved with seven/nine responders having an associated hematologic disorder [113]. Response began after a median of

2.0 months (range 1–6) and lasted for a median period of one year (range 1–5). Effects of antibodies directed against CD52 on circulating T lymphocytes and monocytes following infusion are rapid, with a single dose of alemtuzumab causing depletion of CD8+ T cells for 30 months and CD4+ T cells for 60 months on average. Alemtuzumab was administered in seven severe IVIG-dependent CIDP cases refractory to conventional immunosuppression [114]. Mean monthly IVIG use fell by 26 %; two patients had prolonged remission, two patients had a partial response, and no clear benefit was observed in the remaining three patients. However, three patients developed autoimmune disease following alemtuzumab treatment.

Radiation and surgical removal of the plasmacytoma is an effective treatment regimen of osteosclerotic myeloma and neuropathy [115]. Omaya and colleagues published the first case report of successful nonmyeloablative autologous stem cell transplant in refractory CIDP [116]. Autologous peripheral blood stem cell transplantation improved refractory CIDP and POEMS syndrome cases with additional normalization of serum VEGF levels [117, 118]. Thalidomide treatment may be a treatment option for POEMS cases in whom stem cell transplantation is not indicated. In nine POEMS syndrome cases treated with thalidomide, all had treatment-induced reduction in serum VEGF levels and six substantially improved in their peripheral neuropathy while three clinically stabilized [119].

In comparison with the 2006 EFNS/PNS joint task force report [120], the 2010 treatment recommendation upgrades the use of IVIg in CIDP to a Level A recommendation, while downgrading corticosteroids therapy in sensory and motor CIDP to Level C and retaining the Level A recommendation for PE when IVIg and corticosteroids are ineffective [39]. Good practice points include IVIg as the initial treatment in pure motor CIDP as well as combination therapy or adding an immunosuppressant drug if the therapeutic response is inadequate or the maintenance dose of the initial treatment are high. This is in addition to symptomatic treatment and multidisciplinary management.

Prognosis

In one retrospective series, greater than 90 % of patients with CIDP initially improved with immunosuppressive treatment; however, the relapse rate was approximately 50 % [32]. Only 30 % of patients in this series achieved a complete remission off medication. Two of the patients (3 %) died. It appears the longer patients are followed, the more likely they will relapse [32]. In the Mayo Clinic series, 60 % of patients were improved and able to return to work, another 4 % were in remission, 8 % were ambulatory but unable to work, 11 % were bedridden or wheelchair bound, and six (11)% died of the disease while three (6 %) died from other diseases [31]. The 2007 GBS/CIDP Outcomes Survey indicated that over the last three decades the care of CIDP has improved the overall outcome. The mortality rate has decreased to 1.3 % and patients are less likely to be confined to a wheelchair (7 %). The proportion of patients who recovered or are independent while on treatment has increased remarkably to 31 %. Despite these improvements due to immunotherapy, the majority of cases remain to have some degree of disability with 28 % requiring an assistive device to ambulate (Koski L, 2007 CIDP Outcomes Survey, personal communication).

Several, more recent prospective studies may provide more reliable numbers regarding how often patients respond to treatment. In controlled trials of IVIg in CIDP patients, 63 % to 76 % of patients responded [82, 83]. Symptoms present for less than one year, and an acute relapse at time of IVIg treatment predicted a beneficial response to therapy [82]. Progressive course, CNS involvement (as in 5 % of cases), high proportion of fibers showing active demyelination on nerve biopsy, and axonal loss overall correlated with higher disability. Early and aggressive therapy may prevent secondary axon loss and improve prognosis [121].

Conflict of interest

Mazen M. Dimachkie declares that he has no conflict of interest.
Richard J. Barohn declares that he has no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:
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