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Neurol Clin 25 (2007) 71–87

NEUROLOGIC
CLINICS

Chronic Inflammatory Demyelinating Polyneuropathy

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In 1958, as part of a review of 32 patients who had recurrent polyneuropathies, James Austin presented a patient who, over a 5-year period, repeatedly responded to steroids during relapses of the illness. He made the observation that this disorder most likely was related to segmental demyelination and it is clear that he was describing the disorder now recognized as chronic inflammatory demyelinating polyneuropathy (CIDP) [1]. In 1975, the clinical, electrodiagnostic, and pathologic features of 53 patients seen at the Mayo Clinic defined the disorder. That description did not include ''demyelinating'' in the title but subsequent reports have made it clear that demyelination is a cardinal feature of the disorder [2]. Over the past 30 years, different variants have been described and associated systemic disorders identified. Despite this, there continues to be discussion as to how best to define CIDP and classify the various disorders that are chronic, acquired, immune mediated, and demyelinating. Understanding the different disorders and their similarities, differences, and characteristic features allows clinicians to make appropriate treatment decisions. Box 1 considers CIDP as a symmetric disorder with proximal and distal weakness. The disorders, which have some characteristics that are unique but otherwise have clinical, electrophysiologic, laboratory, and therapeutic aspects similar to CIDP, are considered variants. Some disorders, however, originally considered as variants, now are shown to have characteristic features that make them distinct from CIDP. In particular, these disorders have distinctive clinical, eletrophysiologic or laboratory features and respond differently to therapies. As such, it is imperative to recognize the differences between these disorders.

The reason to consider multifocal motor neuropathy (MMN), the neuropathies associated with IgM paraproteins (IgM neuropathies), and the neuropathy involved in POEMS (polyneuropathy, organomegaly,

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doi:10.1016/j.ncl.2006.11.003

Box 1. Chronic acquired demyelinating polyneuropathies

I. CIDP and variants
  A. Symmetric proximal and distal motor predominant CIDP
  B. Lewis-Sumner syndrome (LSS) (or multifocal acquired demyelinating sensory and motor neuropathy)
  C. Demyelinating neuropathy with IgG or IgA paraprotein
  D. Sensory predominant demyelinating neuropathy
  E. CIDP neuropathy with central nervous system (CNS) demyelination
  F. Demyelinating neuropathy associated with systemic disorders
    1. Hepatitis B or C
    2. HIV
    3. Lymphoma
    4. Diabetes mellitus
    5. Systemic lupus erythematosus or other collagen vascular disorders
    6. Thyrotoxicosis
    7. Organ or bone marrow transplants
    8. Nephrotic syndrome
    9. Inflammatory bowel disease
  G. CIDP in patients who have inherited neuropathy

II. Distinct from CIDP
  A. Multifocal motor neuropathy (MMN)
  B. IgM paraprotein–related neuropathies
    1. Distal demyelinating neuropathy
      a. With anti–myelin-associated glycoprotein (MAG) antibodies
      b. Without anti-MAG antibodies
    2. Chronic ataxic neuropathy ophthalmoplegia M-protein agglutination disialosyl antibodies (CANOMAD)
    3. Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome (POEMS)

endocrinopathy, M-protein, and skin changes) as distinct is because they all have features that are unique or not found in CIDP. MMN does not respond to corticosteroids in the same manner as CIDP. POEMS also does not respond to CIDP treatments and the relationship with osteosclerotic myeloma, or Castleman's syndrome, points to the unique pathophysiology of this disorder. The IgM neuropathy associated with antibodies directed

against myelin-associated-glycoprotein (anti-MAG) typically is a distal sensory predominant disorder with the distinctive electrodiagnostic featue of distal accentuated slowing and does not usually respond to CIDP treatments. This and the other IgM-related neuropathies, therefore, are clearly distinct from CIDP. The relationship of IgA and IgG paraproteins to demyelinating neuropathies is less clear, however. Patients who have demyelinating neuropathies and IgG or IgA paraproteins have features identical to those of patients who have CIDP. Thus patients with CIDP and IgG or IgA paraproteins are considered as CIDP variants.

Epidemiology

The prevalence of CIDP is difficult to ascertain but estimates range from 0.8 to 1.9 per 100,000 [3,4]. The disorder can affect all ages but is more common in older males. The disease is believed more likely to be progressive in the older age group and relapsing-remitting in younger patients. No specific predisposing factors have been identified. There are conflicting studies on HLA-type associations but no clear genetic predisposition is identified.

The temporal continuum of Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy

The distinction between the demyelinating form of Guillain-Barré syndrome (GBS), acute inflammatory demyelinating polyneuropathy (AIDP), and CIDP is a somewhat arbitrary one based on the time of progression. Acute inflammatory demyelinating polyneuropathy is a monophasic subacute illness that reaches its nadir within 3 to 4 weeks. CIDP is defined as a disorder that continues to progress or has relapses for more than 8 weeks. Patients who have presentations in-between these two time periods are designated as having subacute inflammatory demyelinating polyneuropathy [5,6]. This delineation is complicated in practice, because depending on when physicians see patients, therapeutic interventions likely are initiated before patients reach a specific time point that distinguishes between these entities. Some patients who have CIDP have a subacute, GBS-like onset and the only way to recognize that patients have CIDP is when relapses or progression occurs over the ensuing few months.

The onset of GBS usually is identified easily whereas this is less clear with CIDP. Antecedent events are recognized more clearly in GBS than in CIDP, with more than 70% of patients who have GBS having an identifiable infectious illness, vaccination, or surgery preceding, by 3 to 4 weeks, the onset of symptoms. Most studies, however, find an antecedent event in less than 30% of patients who have CIDP. There are other differences between GBS and

CIDP. The IgG antibodies are found primarily in the axonal form of GBS, acute motor axonal neuropathy, which has some parallels with MMN. Table 1 shows some of the similarities and differences between GBS and CIDP.

Clinical manifestations

The initial description of CIDP in 1975 [2] pointed out the major cardinal features of the disorder. Since then, the following aspects have been emphasized:

1. Progression over at least 2 months
2. Predominant motor symptoms
3. Symmetric involvement of arms and legs
4. Proximal muscles involved along with distal muscles
5. Deep tendon reflexes reduction or absence
6. Cerebrospinal fluid (CSF) protein elevation without pleocytosis
7. Nerve conduction evidence of a primary demyelinating neuropathy

CIDP can be distinguished from chronic length-dependent peripheral neuropathies by the more global muscle weakness of upper and lower extremities (proximally and distally), the general reduction or absence of deep tendon reflexes, and the more aggressive course of the disease. These features point to the multifocal or generalized nature of the disease even at early stages of the illness. Typical cases of CIDP are fairly symmetric, and motor involvement is greater than sensory. Cranial nerve involvement and bulbar involvement occur in 10% to 20% and painful dysesthesias

Table 1
Parallels and differences between Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy GBS and CIDP

Parallels	
Acute	Chronic
AIDP: no antibody	CIDP: no antibody
AMAN: IgG anti-GM1	MMN: IgM anti-GM1
Fisher syndrome: IgG anti-GQ1B	CANOMAD: IgM anti-GQ1B and GT1A
Differences	
Acute	Chronic
Antecedent event in 70%	No antecedent event
Monophasic	Requires continued Rx
Steroids ineffective	Steroids effective in CIDP
IgG antibodies	IgM antibodies
Both axonal and demyelinating forms	Axonal forms not as well described

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CANOMAD, chronic ataxic neuropathy ophthalmoplegia M-protein agglutination disialosyl antibodies; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain Barre syndrome; MMN, multifocal motor neuropathy.

are described in a similar minority of patients. The course is slowly progressive in the majority but a relapsing-remitting course is noted in at least one third, more commonly in younger patients. This latter issue is more difficult to characterize now that treatments are initiated early in the disease, making it difficult to tell whether or not remissions are treatment related rather than the natural course of the disease. The sensory involvement usually is greater for vibration and position sense than for pain and temperature, reflecting the involvement of larger myelinated fibers. As opposed to the motor involvement, the sensory involvement tends to follow a distal to proximal gradient, although finger involvement frequently is as early as toe/foot involvement. Constipation and urinary retention can occur but usually is not an early symptom. Back pain may be present and, rarely, if there is marked nerve root hypertrophy, symptoms of lumbar spinal stenosis and cauda equina syndrome can occur, which may be considered for surgical intervention.

Clinical variants

Lewis-Sumner syndrome

The LSS variant is distinguished by its striking multifocal picture. Originally described in 1982 as a true mononeuropathy multiplex with sensory or motor symptoms in individual nerve distributions [7], the disorder became confused with MMN. There now are several series with more than 100 patients described [8–12] and it has become clear that there are important differences between LSS and MMN (Table 2). The increased incidence of MMN in men is not noted as consistently as in LSS. Pain, paresthesias, and Tinel's signs are seen only in patients who have sensory symptoms. Sural nerve biopsies of patients who have LSS reveal significantly more abnormalities consistent with a demyelinating neuropathy than do biopsies of patients who have MMN. High titers of GM1 antibodies are not reported in LSS, although Oh and colleagues [10] note one patient out of 16 who had mildly elevated titers. CSF protein, although not very elevated, tends to be higher than in patients who have MMN, suggesting

Table 2
Multifocal motor neuropathy versus Lewis-Sumner syndrome

Factors	Multifocal motor neuropathy	Lewis-Sumner syndrome
Gender	Male > female (.2:1)	Male = female
Sensory symptoms	No	Yes
Pain and Tinel's	No	Yes
Sensory conduction	Normal	Abnormal
Anti-GM1 Abs	High titers in 35%–80%	Normal in all patients
CSF protein	Minimal increase	Mild to moderate increase
Nerve biopsy	Normal	90% with demyelination
Prednisone	Poor response	Good response
Plasmapheresis	No response	Some respond

that nerve roots may be more involved in LSS. A significant number of patients who have LSS respond to corticosteroids; 50% (3 of 6) in Saperstein and coworkers' series [8] and 79% (11 of 14) in Oh and colleagues' series [10]. This is in distinct contrast to patients who have MMN, in whom corticosteroids have been remarkably ineffective and possibly deleterious [13]. Most patients who had MMN, who were reported to respond to corticosteroids, at closer view had sensory signs or symptoms that more likely indicated LSS [14,15].

The findings on motor conduction studies in LSS are indistinguishable from those found in MMN. Sensory abnormalities usually are seen, however, particularly if proximal stimulation is used. Whether or not the distal sensory response is abnormal depends on whether or not the conduction block lesion is distal or whether or not secondary wallerian degeneration has occurred. Most patients tend to show some distal sensory amplitude reduction, however. In contradistinction to MMN, in which many reports show normal sensory conduction through areas of motor block, there now is at least one case of LSS demonstrating sensory conduction block that improved with treatment [16].

The pathology of LSS has become more clear. Sural nerve biopsies of patients who have LSS show demyelination in a remarkably high number of patients. An autopsy study of two patients who had LSS showed multifocal inflammatory demyelinating changes as seen in CIDP [17].

Although there are compelling reasons to differentiate LSS from MMN, there seems to be a "gray zone" in which occasional patients cannot be labeled easily as MMN or LSS. There are anecdotal reports of patients who present with a pure motor syndrome but then develop sensory symptoms years later. It also is apparent that some patients have a few sensory symptoms or minor changes on sensory conduction studies and it becomes difficult to decide whether or not these changes are significant enough to warrant a diagnosis of LSS. LSS responds to treatments virtually identically to patients who have typical CIDP and except for the persistent multifocal pattern, there are no other features to distinguish LSS from CIDP. It, therefore, is reasonable to consider LSS as a CIDP variant.

Sensory variants

The sensory predominant form of CIDP may have only clinical sensory symptoms and signs with balance problems, pain, paresthesias, and dysesthesias. As many as 15% of patients who have CIDP may have sensory signs and ataxia as the predominant or only feature [18]. Despite the lack of weakness, the nerve conduction studies demonstrate significant motor conduction slowing and other demyelinating features [18–20]. Some patients may present with sensory symptoms, then develop weakness, and then behave as with the motor predominant form. Some patients only have sensory symptoms, however, despite the motor conduction abnormalities.

The distal acquired demyelinating sensory (DADS) neuropathy frequently is associated with an IgM paraprotein and usually has a more slowly progressive course [21,22]. There are patients, however, who have DADS without a paraprotein. Although half of the patients who have DADS and IgM paraprotein have anti-MAG antibodies, it is not clear that the presence of anti-MAG antibodies distinguishes these patients clinically. With or without anti-MAG antibodies, patients who have IgM neuropathy tend to be resistant to standard CIDP immunosuppressant/immunomodulatory therapies. DADS with an IgM paraprotein with or without anti-MAG antibodies is usually considered distinct from CIDP. The response to treatment of patients who have DADS without IgM parparotein, however, may be more favorable and is considered a variant of CIDP.

CIDP and central nervous system (CNS) disease

The disorders with associated CNS involvement may have optic nerve disorders, hyperreflexia, Babinski's signs, and MRI abnormalities of CNS demyelination but whether or not there is a true association or just coincidental problems remains unclear [23].

Immunopathogenesis

Although the cause of CIDP and its variants is unknown, there is strong evidence to support the concept that the disorders are immunologically based. The cellular and humoral components of the immune system seem to be involved. T-cell activation and crossing of the blood-nerve barrier by activated T cells have been demonstrated along with expression of cytokines, tumor necrosis factor, and interferon and interleukins. As for humoral immunity, immunoglobulin and complement deposition on myelinated nerve fibers have been seen and passive transfer experiments using serum or purified IgG from patients who have CIDP have induced conduction block and demyelination when injected into rats. Despite awareness of the role of gangliosides as target antigens in GBS, anti-MAG, and other neuropathies, however, specific antigens are not identified clearly in CIDP. As such, the immunologic causes of CIDP remain unclear and the disorder likely has multiple triggers [24–26].

Electrodiagnostic features

The cardinal pathophysiologic feature of CIDP is demyelination, which must be determined by electrodiagnostic findings (Box 2) [27] or by nerve biopsy. Nerve conduction studies, therefore, are a critical component of the evaluation. Demyelination causes conduction slowing and conduction block, which can be detected in different segments using different techniques.

Box 2. Electrodiagnostic findings suggestive of demyelination

1. Conduction block
2. Conduction velocity slowing greater than can be explained by axonal loss
   A. Prolonged distal motor latencies
   B. Slow conduction velocity
   C. Prolonged F-wave latency
   D. Prolonged H-reflex latency
3. Temporal dispersion of the duration of the compound motor action potential (CMAP) on proximal stimulation compared with distal stimulation
4. Prolongation of the duration of the distal CMAP

Electromyographers must be able to determine if the latencies and velocities observed are too slow to be accounted for by axonal loss alone. The diameters of motor nerve fibers are between 6 and 14 microns, with longer fibers tapering such that the diameters of the peroneal and tibial nerve fibers in the lower leg are thinner than the median and ulnar nerve fibers at the wrist. The corresponding conduction velocities for motor fibers, dependent on the diameter of the fibers, range from 30 to 70 m/sec in the arms and 25 to 60 m/sec in the leg. When velocities are less than 30 m/sec in the arm (or 25 m/sec in the lower leg), then no normal motor fiber could be involved and a demyelinating lesion is apparent. The problem arises when the velocities are between 30 and 40 m/sec. To determine whether or not that degree of slowing is secondary to demyelination or axonal loss requires a careful comparison of velocity and amplitude. The lower the amplitude, the more likely axonal loss is playing a significant role. With higher amplitudes, axonal loss is less likely to be involved. Electromyographers must be careful, however, because in chronic neuropathies, amplitudes can be normal despite severe axonal loss as a result of collateral sprouting and large motor units. Although needle EMG can help sort this out, it can be difficult to determine whether or not the conduction studies point clearly to demyelination. In addition, the determination of conduction block is problematic. How much amplitude reduction on proximal stimulation should be used as the criteria for block varies depending on the distance between stimuli. There also are several potential technical pitfalls that can confuse electromyographers. In CIDP, it is less crucial than in other disorders to differentiate block from amplitude reduction as a result of temporal dispersion, because both suggest segmental demyelination. Although it is customary to equate conduction block with demyelination, in actuality block is determined by changes at the nodes of Ranvier and paranode and is not exclusively the result of demeyelinating lesions.

Because of all these issues, there has been a great deal of interest in developing criteria to assist clinicians in determining whether or not a neuropathy is demyelinating. There are more than 10 published criteria designed to explicitly define the parameters of conduction changes that reflect a demyelinating neuropathy, not only for CIDP but also for GBS, MMN, and other demyelinating neuropathies. They differ in the degree of slowing, the number of abnormalities required, and the definition of conduction block to determine definite, probable, and possible demyelination. A comparison study of 10 criteria in patients who had GBS, CIDP, ALS, and or diabetic neuropathy revealed sensitivities ranging from 39% to 89% for CIDP. One set identified a patient who had ALS and demyelinating features, and eight of the criteria overlapped with diabetic neuropathy. The three most sensitive criteria to CIDP each overlapped with diabetic neuropathy in more than 50%, which is not surprising because diabetic neuropathies frequently have slowing greater than can be accounted for by axonal loss. Based on these findings, the investigators devised another set of criteria but could come up with only 75% sensitivity while avoiding overlaps with diabetic neuropathy [28]. Despite the inability to obtain ideal sensitivity and specificity, these criteria can be helpful to clinicians and are important for clinical trials when uniformity of diagnosis is critical. Expert electromyographers sometimes can recognize subtle changes in conduction that are beyond the scope of most of these criteria. Prolongation of the distal CMAP duration recently has been shown to be helpful in determining demyelinating disorders and is included in more recent diagnostic criteria [27]. A retrospective analysis of six published criteria with and without prolongation of the duration of the distal CMAP concludes that the addition improved sensitivity and that extensive studies of the upper extremities or all four limbs is important to improve diagnostic yield [29]. This point cannot be overemphasized. To determine whether or not a conduction study points to a demyelinating neuropathy, electromyographers must be confident that the findings are not the result of axonal loss, compression, or technical issues. Enough segments need to be studied to overcome some of these issues. They should be suspect if only one or two segmental changes are found and four limbs should be studied if need be.

Pathologic findings

Sural nerve biopsy has been used to determine demyelination and was a mandatory component of some of the earlier criteria for diagnosing CIDP. It has been shown occasionally to find other abnormalities that occasionally may mimic CIDP (amyloidosis, sarcoidosis, and vasculitis). Because CIDP is a multifocal disorder, and motor nerve fibers tend to be more affected than sensory nerves (the usual nerves used for biopsy), the biopsy sample may not demonstrate the demyelination. In addition, although

there is an inflammatory component to CIDP, this may not be prominent and may not be apparent on biopsy. The necessity of nerve biopsy in the diagnosis of CIDP remains controversial. The more recent diagnostic criteria no longer require biopsy for diagnosis, but others argue the importance of biopsy in finding unsuspected disorders or in finding demyelination when electrophysiologic criteria are not met [30,31,68].

The characteristic pathologic features of CIDP are segmental demyelination and remyelination and onion bulb formation [32], usually with some degree of axonal degeneration. Although axonal loss is considered a secondary, bystander product of the inflammatory demyelinating process, the exact mechanism of axonal degeneration is not determined completely. There are varying degrees of interstitial edema and endoneurial inflammatory cell infiltrates, including lymphocytes and macrophages. The macrophages are believed to initiate the demyelination by unraveling and degrading the myelin [33]. Unfortunately, this is not found commonly on most biopsy specimens.

Diagnosing chronic inflammatory demyelinating polyneuropathy

The work-up of any neuropathy includes the electrodiagnostic study to determine if there is demyelination and laboratory studies to look for disorders that either are associated with neuropathy or cause the disorder. If CIDP is suspected, then laboratory studies that are important in helping define or exclude the disorder include serum glucose, glycated hemoglobin, thyroid function studies, hepatitis profiles, HIV testing, and serum immunofixation electropheresis. A lumbar puncture is helpful in that the classic albuminocytologic dissociation is present in more than 90% [33]. A cellular CSF ($>10/\mu L$) suggests that other disorders may be present except when patients are HIV positive, in which case more cells may be seen in the CSF. Nerve biopsy no longer is considered a necessary and required procedure, but is used when the other studies fail to establish the diagnosis clearly. It is recognized that certain genetic disorders of peripheral nerve myelin have characteristics that can mimic the clinical or electrodiagnostic features of CIDP or its variants. A careful family history and appropriate genetic testing should be considered. In particular, Charcot-Marie-Tooth (CMT)-1A, adult-onset CMT-1B, CMT-1X, and hereditary neuropathy with liability to pressure palsies on occasion may be confused with CIDP. In children and patients who have hypertrophic neuropathy, other genetic disorders, including recessive disorders, should be considered.

Diagnostic criteria of chronic inflammatory demyelinating polyneuropathy

During the past 20 years, there have been at least eight different published criteria for CIDP [21,34–38] and there still is no consensus as to the optimal

approach to the diagnosis. They all give clinical, laboratory, and electrodiagnostic criteria and most describe definite, probable, and possible categories. The differences between them are related to definitions of the clinical picture, the requirements for nerve biopsy, electrodiagnostic criteria for demyelination, and the number of features required to make the diagnosis. The American Academy of Neurology criteria, designed for research purposes, are considered specific but not sensitive enough for clinical use. Others are sensitive but less specific and may overdiagnose the disorder. The most recent European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline attempts to provide criteria and recommended practice guidelines based on the currently available literature plus expert consensus [38]. This carefully considered report defines CIDP as typical or atypical, with or without concomitant diseases. MRI with gadolinium of the cauda equina, brachial and lumbar plexus, and other nerve regions to look for enlarged or enhancing nerves may assist in diagnosis, and response to immunotherapy is considered supportive evidence. The diagnostic categories are determined by clinical, electrodiagnostic, and supportive criteria. For definite CIDP, there must be a typical or atypical clinical picture, with clear-cut demyelinating electrodiagnostic changes in two nerves or probable demyelinating features in two nerves plus at least one supportive feature (CSF, biopsy, MRI, or treatment response). CIDP with concomitant disease is relegated to a possible category. Without explanation, these guidelines consider IgM paraprotein–related neuropathies with anti-MAG antibodies as distinct from CIDP but IgM disorders without anti-MAG as a CIDP variant.

The large number of criteria for the electrophysiologic identification of demyelination and conduction block and for the clinical diagnosis of CIDP, with continuing attempts to develop more specific and yet sensitive criteria, point to the difficulties in trying to develop strict criteria for problems that have multiple variations. The EFNS/PNS guidelines have much to recommend them and are an excellent point of reference. Clinicians must assess all patients carefully and individually and convince themselves that patients have a clinical picture that is consistent with the diagnosis and that the electrophysiology or other studies (CSF, nerve biopsy, or MRI) have features suggesting a demyelinating neuropathy. In those instances in which the diagnosis remains unclear, a treatment trial may be indicated and the response to therapy may add clarity to the situation. Although a conclusion may be that response to immunotherapy suggests an inflammatory or immunologic disease, it does not point to a specific disorder.

Treatment

Although there are many treatments available for CIDP, there still is a need for new therapies that are more specific, less toxic, and more

beneficial than those currently available. Intravenous immunogolobulin (IVIg) and plasmapheresis (PE) are shown to be effective in double-blind trials and, along with corticosteroids, are the mainstays of treatment. Several immunosuppressive agents are reported to be beneficial (Box 3) but none has been studied rigorously in randomized controlled trials with enough power to provide convincing evidence of efficacy [39]. Many of these remain promising, however.

The use of high-dose cyclophosphamide without stem cell rescue is shown in small series as effective in patients unresponsive to other treatments [40]. The potential benefits must be weighed against potentially life-threatening complications. More experience is needed before strongly recommending this approach.

Azathioprine was tested in 14 patients and not found to have added benefit to prednisone [59].

Although interferon-α and etanercept are considered potential treatments for CIDP, they also are reported potentially to cause the disorder [51–53,55,56]. This points to the potential concerns as treatments are targeted to different cytokines, and neurotrophic factors may have beneficial and injurious immunologic effects.

The strongest evidence of efficacy is for IVIg; four double-blind trials show evidence of benefit in more than 100 patients [60–63]. The benefit of IVIg is not found to be greater than that of PE [64] or prednisone [36]. The problems with IVIg are that the treatment does not, by itself, usually lead to remission and it requires repeated expensive treatments every 2 to 6 weeks. In a 20-year review of 95 patients treated with IVIg, van Doorn and colleagues [65] found that more than 75% improved with IVIg. Of these, however, 85% required repeated treatment but some were able to discontinue treatment at a mean of 3.5 years (median 2 years). Severity at onset and residual deficit were negative predictors of discontinuation. Therefore,

Box 3. Immunosuppressants considered for chronic inflammatory demyelinating polyneuropathy

1. Cyclophosphamide [40,41]
2. Cyclosporine [42–46]
3. Mycophenolate mofetil [47,48]
4. Interferon-β [49,50]
5. Interferon-α [51–53]
6. Methotrexate [54]
7. Etanercept [55,56]
8. Rituximab (anti-CD 20) [14,57]
9. FK-506 [15,58]
10. Azathioprine

although IVIg can control the disorder, unless other treatments are added, many patients may require infusions for many years.

PE also is shown to be efficacious in double-blind trials [66,67] and is equally effective as IVIg [64]. Like IVIg, it is unlikely, by itself, to lead to remission and has the added concerns of venous access, somewhat more complications, and lack of availability in many locales.

Corticosteroids have been reported to be beneficial for more than 20 years, but no large double-blind study has been performed. One randomized controlled study of 14 patients placed on high-dose prednisone (120 mg/day) compared with 14 patients treated with placebo showed clinically meaningful improvement over 12 weeks. Despite the lack of large trials, there have been years of clinical use of oral prednisone and the overwhelming consensus is that corticosteroids, despite the significant side effects, are effective in CIDP. It is more likely than either IVIg or PE to produce a clinical remission. Dosing of corticosteroids, however, is not agreed upon, with different suggested regimens, including daily and alternate-day oral prednisone and monthly or weekly pulse methylprednisolone.

Corticosteroids are compared with IVIg in a double-blind, crossover study of 32 patients and no significant difference is identified with the two treatment modalities [37].

Therapeutic regimens

There are some patients who have CIDP who, at certain times have mild disease with minimal impact on function and quality of life. Treatment might not be initiated in these cases. Most patients are impaired significantly, however, by the disorder and some treatment should be considered. If severe and fulminant, then treatment with an agent with rapid improvement should be considered. This has the advantage potentially of helping patients quickly, reducing the chance for axonal degeneration, and allowing clinicians to determine effectiveness in a short period of time. Either IVIg or PE could be used. Although studies tend to favor IVIg because of fewer side effects, this is somewhat dependent on the center providing the treatment. The major problems with pheresis are related to the use of indwelling catheters. If these can be avoided, then pheresis may, in some instances, be a better choice. If the disorder is more insidious and the goal is to put patients in remission, then corticosteroids might be initiated without IVIg. If IVIg is used, then the optimal regimen is 2 gms/kg divided into 2 to 5 doses. The trial conducted by Mendell and colleagues [63] added a second treatment, 1 gm/kg at 3 weeks, and treatment response was evident within 6 weeks. If patients have a response but then relapse after a few weeks, repeated treatments are considered. A small portion of patients ($<20\%$) may respond to one treatment and not require further therapy. The other patients who respond require treatment at intervals, usually ranging from 2 to 6 weeks. The timing and dosing is titrated to avoid relapses. If patients continue to

require high doses of IVIg for many months, then the addition of corticosteroids or other immunosuppressants might be considered. Failure to respond to IVIg triggers intervention with PE or immunosuppression.

If treatments other than corticosteroids, IVIg, or PE are considered, the choice of immunosuppressant depends on several factors and must be individualized. These factors include the severity of the disease, which may indicate more aggressive but more risky treatments; the age and gender of patients, which might limit the use of agents that lead to infertility; and coincident medical problems, which may be complicated by certain treatments. Although most patients respond to one or a combination of treatments, there is a significant minority that continue to progress despite all attempts. This seems to be the appropriate time to consider the high-dose cyclophosphamide regimen [40].

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