REVIEW ARTICLE

MEDICAL PROGRESS

Chronic Inflammatory Demyelinating Polyneuropathy

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CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY IS A COMmon, albeit underdiagnosed, and potentially treatable disease with an estimated prevalence of about 0.5 per 100,000 children[1] and 1 to 2 per 100,000 adults.[2,3] Clinical similarities to the acute variant of inflammatory demyelinating polyneuropathy (the Guillain–Barré syndrome) and the beneficial effects of immunosuppressive therapies suggest an immune-mediated pathogenesis. Since the first descriptions of patients with corticosteroid-responsive chronic polyneuropathies by Austin,[4] Thomas et al.,[5] and Dyck et al.,[6] the spectrum of clinical presentation and the diagnostic armamentarium have enlarged, and further therapeutic options have evolved. The recognition of this disorder as distinct from other common chronic sensorimotor polyneuropathies that accompany diabetes, alcoholism, or malnutrition is important. This review summarizes present knowledge about the clinical features of this condition, diagnostic criteria and diagnostic procedures involved in assessment, and current management strategies based on the results of randomized, controlled trials. Current concepts of immunopathogenesis are also considered.

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CLINICAL PRESENTATION

CLASSIC CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Classic chronic inflammatory demyelinating polyneuropathy is characterized by the occurrence of symmetrical weakness in both proximal and distal muscles that progressively increases for more than two months (setting this condition apart from the Guillain–Barré syndrome, which is self-limited). The condition is associated with impaired sensation, absent or diminished tendon reflexes, an elevated cerebrospinal fluid protein level, demyelinating nerve-conduction studies, and signs of demyelination in nerve-biopsy specimens.[7-9] The course can be relapsing or chronic and progressive, the former being much more common in young adults.

As the disease has become better recognized and clinical trials have been considered, several groups have proposed clinical definitions of this neuropathy (Table 1).[9-15] In all these definitions, the diagnosis is based primarily on clinical features and electrophysiological studies, whereas the requirement for cerebrospinal fluid examination and nerve biopsy varies, depending on the level of clinical diagnostic certainty, which can range from possible to probable to definite. Obtaining both cerebrospinal fluid and a nerve-biopsy specimen is mandatory to make a definitive diagnosis of the disease, according to criteria of the American Academy of Neurology,[9] but not according to the widely used criteria proposed by Saperstein et al.[10] and by the Inflammatory Neuropathy Cause and Treatment (INCAT) group.[11] Classic chronic inflammatory demyelinating polyneuropathy typically responds well to corticosteroid treatment — an ob-

Table 1. Diagnostic Criteria.*

Feature	AAN Criteria	Saperstein Criteria	INCAT Criteria
Clinical involvement	Motor dysfunction, sensory dysfunction of >1 limb, or both	Major: symmetric proximal and distal weakness; minor: exclusively distal weakness or sensory loss	Progressive or relapsing motor and sensory dysfunction of more than 1 limb
Time course (mo)	≥2	≥2	>2
Reflexes	Reduced or absent	Reduced or absent	Reduced or absent
Electrodiagnostic test results	Any 3 of the following 4 criteria: partial conduction block of ≥1 motor nerve, reduced conduction velocity of ≥2 motor nerves, prolonged distal latency of ≥2 motor nerves, or prolonged F-wave latencies of ≥2 motor nerves or the absence of F waves†	2 of the 4 AAN electrodiagnostic criteria	Partial conduction block of ≥2 motor nerves and abnormal conduction velocity or distal latency or F-wave latency in 1 other nerve; or, in the absence of partial conduction block, abnormal conduction velocity, distal latency, or F-wave latency in 3 motor nerves; or electrodiagnostic abnormalities indicating demyelination in 2 nerves and histologic evidence of demyelination
Cerebrospinal fluid	White-cell count <10/mm³, negative VDRL test; elevated protein level (supportive)	Protein >45 mg/dl; white-cell count <10/mm³ (supportive)	Cerebrospinal fluid analysis recommended but not mandatory
Biopsy findings	Evidence of demyelination and remyelination	Predominant features of demyelination; inflammation (not required)	Not mandatory (except in cases with electrodiagnostic abnormalities in only 2 motor nerves)

* The criteria are those proposed by the American Academy of Neurology (AAN),[9] Saperstein et al., [10] and Hughes et al.,[11] for the Inflammatory Neuropathy Cause and Treatment (INCAT) group. VDRL denotes Venereal Disease Research Laboratory.

† According to AAN criteria, a partial conduction block is a drop of 20 percent or more in negative peak area or peak-to-peak amplitude and a change of less than 15 percent in duration between proximal and distal site stimulation. A possible conduction block or temporal dispersion is a drop of 20 percent or more in negative peak area or peak-to-peak amplitude and a change of more than 15 percent in duration between proximal and distal site stimulation. A reduced conduction velocity is a velocity of less than 80 percent of the lower limit of the normal range if the amplitude of the compound muscle action potential (CMAP) is more than 80 percent of the lower limit of the normal range or less than 70 percent of the lower limit if the CMAP amplitude is less than 80 percent of the lower limit. Prolonged distal latency is more than 125 percent of the upper limit of the normal range if the CMAP amplitude is more than 80 percent of the lower limit of the normal range or more than 150 percent of the upper limit if the CMAP amplitude is less than 80 percent of the lower limit. An absent F wave or F-wave latency is more than 125 percent of the upper limit (INCAT criteria, more than 120 percent) if the CMAP amplitude is more than 80 percent of the lower limit or latency is more than 150 percent of the upper limit if the CMAP amplitude is less than 80 percent of the lower limit.

servation that may serve to distinguish it from other forms of acquired demyelinating polyneuropathies.

DEMYELINATING NEUROPATHIES DISTINCT FROM CLASSIC CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Refined clinical analysis has defined other forms of acquired demyelinating polyneuropathies with presumed autoimmune or dysimmune causes that differ from classic chronic inflammatory demyelinating polyneuropathy, both with respect to clinical presentation and to the response to treatment. It is not clear whether these conditions are variants of chronic inflammatory demyelinating polyneuropathy or distinct diseases.

Distal Acquired Demyelinating Symmetric Neuropathy

It has been suggested that distal acquired demyelinating symmetric neuropathy is a distinct acquired demyelinating polyneuropathy.[16] Features of the disorder include an increased prevalence in men and in persons over the age of 50 years, a predominantly distal sensory loss, a mild distal weakness (as opposed to the more generalized motor deficits in classic chronic inflammatory demyelinating polyneuropathy), and an unsteady gait. IgM paraproteinemia is present in nearly two thirds of patients with this condition.[17] IgM-associated distal demyelinating symmetric neuropathy seems to respond poorly to immunosuppressive therapy.[17]

Multifocal Motor Neuropathy

It is important to differentiate multifocal motor neuropathy from motor neuron disease. Multifocal motor neuropathy is characterized by asymmetric weakness without sensory loss, often starting in distal arm muscles. A partial motor-conduction block at multiple sites is a characteristic electrophysiologic feature, although not all patients have this finding. The same holds true for the detection

of circulating antiganglioside antibodies. Cerebrospinal fluid protein levels and cell counts are usually normal. Although corticosteroids and plasmapheresis are ineffective treatments, multifocal motor neuropathy improves with immune globulin[18] or cyclophosphamide[19] therapy.

Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (the Lewis–Sumner Syndrome)

Multifocal acquired demyelinating sensory and motor neuropathy (the Lewis–Sumner syndrome) has similarities to both chronic inflammatory demyelinating polyneuropathy (i.e., motor and sensory deficits, an elevated protein content, and abnormal results on motor-nerve and sensory-nerve conduction studies) and multifocal motor neuropathy (i.e., asymmetrical presentation of symptoms, often starting from the arms and hands, and conduction block).[20-22] Some patients with the condition have antibodies to gangliosides,[23] and these patients have a reasonably good response to treatment with intravenous immune globulin or cyclophosphamide.

OTHER NEUROPATHIES SIMILAR TO CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

A number of other forms of acquired and chronic polyneuropathy share features with chronic inflammatory demyelinating polyneuropathy and have been classified as subgroups. These forms include axonal chronic inflammatory demyelinating polyneuropathy, pure sensory chronic inflammatory demyelinating polyneuropathy,[10] and pure motor and axonal chronic inflammatory demyelinating polyneuropathy (which is also termed multifocal acquired motor axonopathy).[24] Only a small number of patients within each subgroup have been reported. Patients with peripheral-nerve demyelination and a complete or partial response to immunotherapies are best regarded as having a disorder that is part of the larger family of chronic acquired demyelinating polyneuropathies.[10] Depending on the entire picture, some patients' condition may also fit the definition of possible, probable, or definite chronic inflammatory demyelinating polyneuropathy. Chronic idiopathic axonal polyneuropathy is a heterogeneous group of slowly progressing sensorimotor neuropathies with or without pain, causing mild-to-moderate disability.[25]

CONCURRENT DISEASES

Chronic inflammatory demyelinating polyneuropathy may be also associated with concurrent diseases, such as infection with the human immunodeficiency virus or hepatitis C, Sjögren's syndrome, inflammatory bowel disease, melanoma, lymphoma, diabetes mellitus,[26,27] and IgM, IgG, or IgA monoclonal gammopathy of unknown significance.[13,28] The pathogenetic relevance of such concurrent diseases is unclear. Furthermore, in contrast to distal acquired demyelinating symmetric neuropathy with IgM paraproteinemia, the clinical presentation with both proximal and distal muscle weakness is identical to that of classic chronic inflammatory polyneuropathy, and therapeutic guidelines are the same. The association with diabetes mellitus is of special interest because, according to some estimates, chronic inflammatory demyelinating polyneuropathy occurs more commonly among patients with diabetes, generating diagnostic and management challenges.[27] Occasionally, chronic inflammatory demyelinating polyneuropathy may develop in a setting of another polyneuropathy, even one with a hereditary basis, such as Charcot–Marie–Tooth disease.[29]

CENTRAL NERVOUS SYSTEM INVOLVEMENT

Magnetic resonance imaging (MRI) of the brain has revealed demyelinating lesions in the central nervous system in some patients with chronic inflammatory demyelinating polyneuropathy, despite the rarity of cerebral or cerebellar symptoms.[30,31] Demyelination of visual pathways, however, as evidenced by prolonged latencies of visual evoked potentials, were identified in nearly half of the patients with chronic inflammatory demyelinating polyneuropathy in one study.[30] Symptoms that are related to cranial-nerve dysfunction are also seen in 5 to 30 percent of patients with the condition.[30,31] Of interest, clinical symptoms that are based in the central nervous system as well as brain lesions that are visualized on MRI may resolve after treatment with immune globulins.[32]

DIAGNOSTIC APPROACH

The diagnosis of distal acquired demyelinating symmetric neuropathy is based mainly on the clinical presentation and on nerve-conduction findings that are consistent with demyelination (Table 1). Elevation of the protein content of the cerebrospinal fluid, without pleocytosis, and histologic proof of demyelination and remyelination, often with inflammation, in nerve-biopsy specimens provide additional supporting data. When the diagnosis is not clear, we recommend nerve biopsy, given the

various therapeutic implications and the potentially serious adverse effects of long-term treatment with immunomodulatory or immunosuppressive drugs. A list of the most relevant elements of the differential diagnosis is provided in Table 2.

ELECTROPHYSIOLOGICAL DIAGNOSTIC PROCEDURES

Nerve-conduction studies reveal the cardinal features of demyelination. An ad hoc committee of the American Academy of Neurology included mandatory physiological features as the presence of three of the following four criteria for demyelination[9]: partial motor-nerve conduction block (Fig. 1A), reduced motor-nerve conduction velocity, prolonged distal motor latencies, and prolonged F-wave latencies. To define inclusion criteria for clinical studies, the demyelination criteria have been modified.[10,11] Thaisetthawatkul et al. emphasized the dispersion of the distal compound muscle action potential as a very sensitive diagnostic criterion for chronic inflammatory demyelinating polyneuropathy.[33] Although research criteria for enrollment in clinical studies need to have a high specificity, clinical criteria should be more sensitive to allow the identification of patients who may need treatment.[14]

LABORATORY EXAMINATIONS

Most experts recommend cerebrospinal fluid analysis in order to demonstrate the typical findings in this condition: increased protein and a normal or only slightly elevated cell count. However, spinal taps are not mandatory, according to the criteria of the INCAT group (Table 1). More extended laboratory testing may also be necessary in some pa-

Table 2. Differential Diagnosis.

Neuropathy	Examples	Remarks
Guillain–Barré syndrome	—	Muscular weakness progressing over a period of ≤1 mo
Inherited neuropathy	Hereditary motor and sensory neuropathy; hereditary neuropathy with susceptibility to pressure palsies	Family history and DNA analysis needed
	Recessively inherited neuropathies	Family history often negative
Metabolic neuropathy	Diabetic neuropathy and neuropathy associated with impaired glucose tolerance; uremic, hepatic, and acromegalic neuropathy; neuropathy associated with hypothyroidism	Appropriate laboratory testing needed
Paraneoplastic neuropathy	Neuropathy associated with lymphoma or carcinoma	Workup for underlying cancer needed
Neuropathy associated with monoclonal gammopathy	Neuropathy associated with osteosclerotic myeloma, with monoclonal gammopathies of undetermined significance, and with Waldenström's macroglobulinemia	Workup for underlying cancer needed
Neuropathy associated with infectious diseases	Infection with the human immunodeficiency virus	Appropriate laboratory testing needed
	Leprosy	Typically starts with sensory loss; minor weakness in later stages
	Borreliosis (including Lyme disease)	Appropriate laboratory testing needed
	Diphtheria	Microbiologic culture of isolates
Neuropathy associated with systemic inflammatory or immune-mediated diseases	Sarcoidosis; neuropathy associated with acquired amyloidosis; vasculitis, including polyarteritis nodosa, Churg–Strauss syndrome, rheumatoid arthritis, Sjögren's syndrome, Wegener's granulomatosis, systemic lupus erythematosus, systemic sclerosis, giant-cell arteritis, Behçet's syndrome, cryoglobulinemia, Castleman's disease	Appropriate laboratory testing needed and sural-nerve or muscle biopsy if condition is suspected
	Nonsystemic vasculitic neuropathy	Sural-nerve or muscle biopsy needed if condition is suspected
Toxic neuropathies	Alcohol, industrial agents (e.g., acrylamide), metals (e.g., lead), drugs (e.g., platinum-based agents, amiodarone, perhexiline, tacrolimus, chloroquine, and suramin)	Axonal more than demyelinating
Neuropathy due to nutritional deficiency	Deficiency of vitamin B_1, B_6, B_{12}, or E	Appropriate laboratory testing needed
Porphyria-associated neuropathy	—	Appropriate laboratory testing needed
Polyneuropathy associated with critical illness	Polyneuropathy associated with sepsis, multiple-organ failure, or long-term ventilation	—

tients to search for other causes of a demyelinating polyneuropathy, as well as concurrent diseases (Table 2).

NERVE BIOPSY

The diagnostic value of nerve biopsy, usually of the sural nerve, has been extensively debated during the past few years. Some experts believe that nerve biopsy is of no diagnostic value,[34] whereas others view it as essential for diagnosis and management in up to 60 percent of patients with chronic inflammatory demyelinating polyneuropathy.[35] Bosboom et al.[36] compared signs of demyelination, axonal degeneration, regeneration, and inflammation in biopsy specimens from patients with chronic inflammatory demyelinating polyneuropathy with those of patients with chronic idiopathic axonal polyneuropathy. The biopsy specimens from the majority of patients in both groups had similar or overlapping abnormalities. In addition, nerve biopsies may have a low diagnostic yield in chronic inflammatory demyelinating polyneuropathy, for several reasons. The most prominent abnormalities may lie in the proximal segments of the nerves or roots or in motor nerves, which are areas not accessible to biopsy. Moreover, concomitant or secondary axonal changes starting early in the disease processes may over-

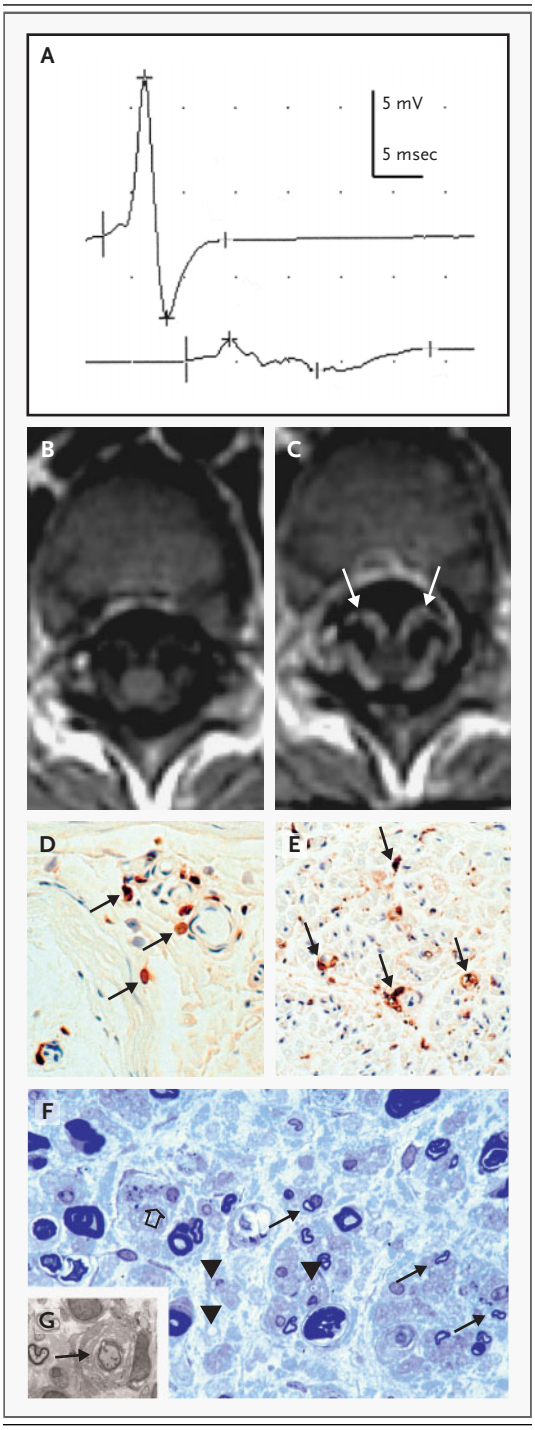

Figure 1. Diagnostic Findings in Chronic Inflammatory Demyelinating Polyneuropathy.

Panel A shows a partial motor-nerve conduction block and abnormal temporal dispersion in a nerve-conduction study, with a reduction of compound muscle action potentials from the abductor digiti minimi muscle after ulnar nerve stimulation at the elbow (bottom), as compared with the amplitude after stimulation at the wrist (top). Axial T_1-weighted MRI scans of the lower thoracic spine, shown before the administration of gadolinium in Panel B and after the administration of gadolinium in Panel C, reveal strong enhancement of ventral and dorsal nerve roots (Panel C, arrows). Cross-sections of a sural nerve in Panels D and E show typical features of chronic inflammatory demyelinating polyneuropathy, with immunohistochemical staining mirroring the distribution pattern of T lymphocytes and macrophages. Invading CD3+ T cells can primarily be localized to perivascular infiltrates (Panel D, arrows) in the epineurium and perineurium, and CD68+ immunoreactive macrophages (Panel E, arrows) can be seen within the endoneurium. Panel F shows a semithin section in which the extent of the inflammatory process is reflected by the loss of myelin (arrowheads indicate demyelinated axons and arrows the remains of thinly myelinated fibers) and the invading macrophages (open arrow). In Panel G, an electron micrograph shows the onion-bulb formation of Schwann cells (arrow) around demyelinated axons. (MRI scans were provided by A. Saleh, Institute for Diagnostic Radiology, Heinrich-Heine University, Düsseldorf; the semithin section by E. Neuen-Jacob, Institute of Neuropathology, University of Düsseldorf; and the electron micrograph by J. Pollard, University of Sydney.)

shadow the initial signs of demyelination and inflammation by the time biopsy is performed.

Despite these limitations, nerve biopsy is still considered useful by many specialists under certain conditions (Fig. 1D to 1G). Haq et al. observed that examination of sural-nerve biopsy specimens had a higher sensitivity than electrophysiological studies.[37] Likewise, Vallat et al. reported that 8 patients in a series of 44 had pathological findings indicative of chronic inflammatory demyelinating polyneuropathy on biopsy even though they did not have electrophysiological evidence of demyelination.[38] It is important to note that five of these patients had a favorable response to therapy.[38]

Biopsy is recommended especially for patients with clinically suspected chronic inflammatory demyelinating polyneuropathy in whom electrophysiological proof of demyelination is absent or vasculitis is suspected. In a series of 100 patients with chronic inflammatory demyelinating polyneuropathy, Bouchard et al.[39] observed that axonal loss on nerve biopsy was the most sensitive prognostic factor, predicting an unfavorable course of the disease. They found demyelinating changes in 71 percent of the patients, mixed axonal and demyelinating changes in 21 percent, and purely axonal changes in only 5 percent. A diagnostic algorithm is shown in Figure 2.

MRI

MRI may be used to demonstrate gadolinium enhancement (Fig. 1B and 1C) and enlargement of proximal nerves or roots, reflecting active inflammation and demyelination in the cauda equina[40] or brachial plexus.[41-43] Abnormalities of the brachial plexus with irregular swelling and increased signal intensity on T_2-weighted images were detected in about 50 percent of patients with chronic inflammatory demyelinating polyneuropathy.[34] Of interest, these changes have also been noted in patients with distal demyelinating polyneuropathy associated with IgM monoclonal gammopathy,[42] pointing to similarly widespread nerve disease in the latter condition.

PATHOGENESIS

A normal, well-balanced network of immunocompetent cells and soluble factors meticulously regulates the immune system within the local tissue compartment of the peripheral nerves, sustaining its integrity. Protection against immune responses to autoantigens is key for the maintenance of self-tolerance. In chronic inflammatory demyelinating polyneuropathy, self-tolerance breaks down, and autoreactive T cells and B cells, which are part of the normal immune repertoire, become activated, causing the organ-specific damage characteristic of autoimmune disease.[44] The concept of molecular mimicry may hold special relevance to the breakdown in tolerance associated with autoimmune neuropathies. Molecular mimicry refers to a process in which the host generates an immune response to an inciting factor, most frequently an infectious organism that shares epitopes with the host's affected tissue. However, in chronic inflammatory demyelinating polyneuropathy, specific targets for such a response have been convincingly identified only in rare instances.

Although chronic inflammatory demyelinating polyneuropathy occurs rarely in the context of cancer, an association with melanoma is of great interest, since both melanoma and Schwann cells derive from neural crest tissues and share antigens. Several cases of chronic inflammatory demyelinating polyneuropathy have been reported in association with melanoma; several carbohydrate epitopes shared by the myelin sheath and the tumor have been implicated as target antigens.[45,46] Nevertheless, the hypothesis of molecular mimicry cannot explain the entire immunopathologic and laboratory spectrum of this complex disorder. On the basis of current data, chronic inflammatory demyelinating polyneuropathy appears to be an organ-specific, immune-mediated disorder emerging from a synergistic interaction of cell-mediated and humoral immune responses directed against incompletely characterized peripheral nerve antigens (Fig. 3).

CELLULAR IMMUNE RESPONSE

Evidence of T-cell activation in the systemic immune compartment in patients with chronic inflammatory demyelinating polyneuropathy exists, although antigen specificity remains largely unknown.[47-49] From studies of nerve-biopsy specimens and animal models, it is known that activated T lymphocytes can invade peripheral-nerve tissue. The T-cell populations that have been identified are heterogeneous, belonging to both the CD4 and CD8 subgroups.[50-54] In order to generate inflammatory lesions in nerves, activated T cells must cross the blood–nerve barrier, a complex process that includes homing, adhesion, and transmigration.[55] Derangement of the blood–nerve barrier has

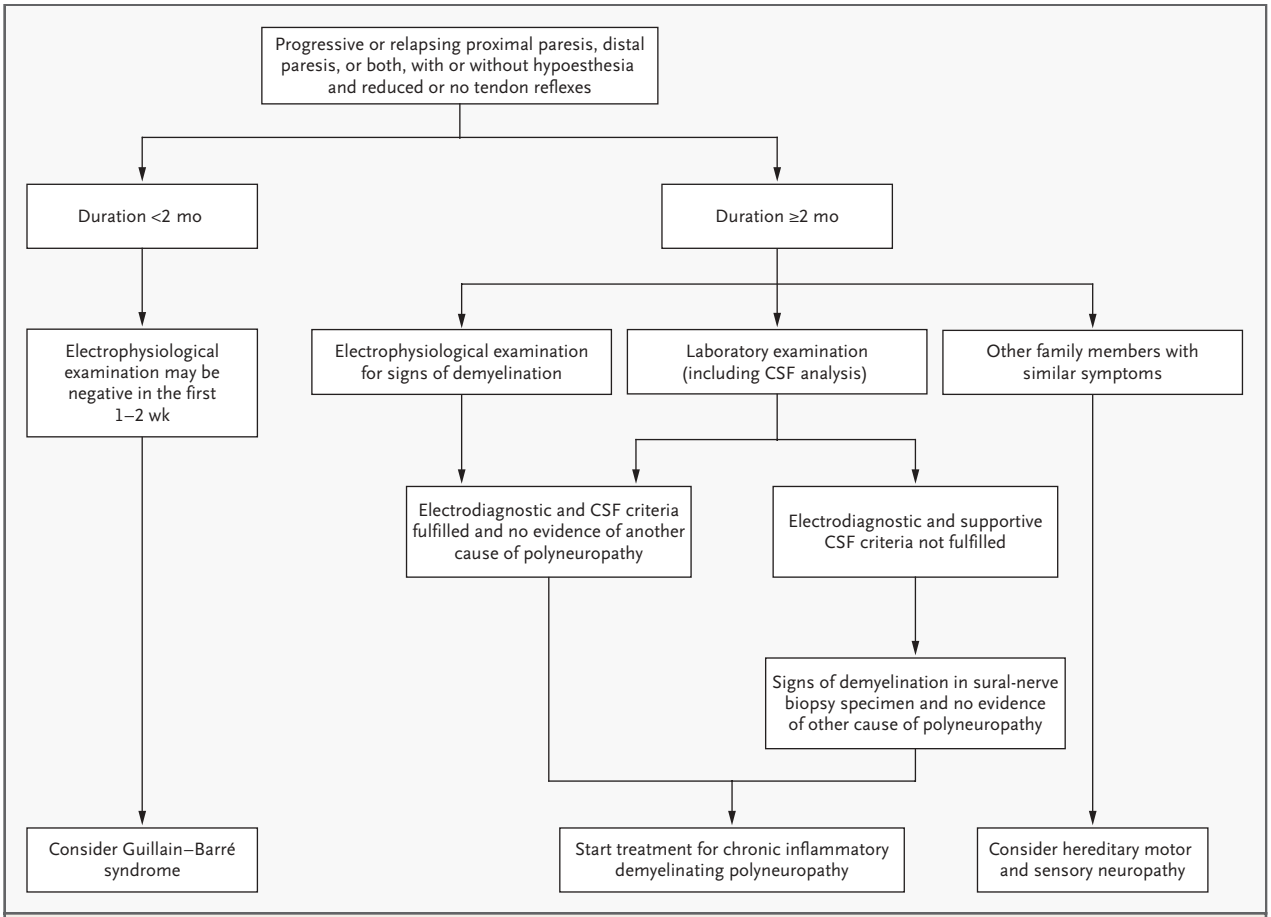

Figure 2. Algorithm of Diagnostic Procedures.

If a patient presents with a history of symptoms suggestive of chronic inflammatory demyelinating polyneuropathy of two months' duration or more, we perform nerve-conduction studies for signs of demyelination — including partial conduction block, reduced motor-nerve conduction velocity, prolonged distal latency of the motor nerve, and the absence of F waves or a prolonged F-wave latency — to differentiate between predominantly demyelinating or axonal disease of peripheral nerves. We also use laboratory tests — including cell-count and protein studies of cerebrospinal fluid (CSF) — to evaluate supportive criteria and to rule out other causes. If these causes have been ruled out and electrodiagnostic and supportive CSF criteria are fulfilled, patients may begin long-term antiinflammatory and immunosuppressive therapy. To confirm the diagnosis, we recommend sural-nerve biopsy.

been shown by demonstrating that the tight-junction proteins claudin-5 and ZO-1 are down-regulated in sural-nerve biopsy specimens.[56] Elevated levels of soluble adhesion molecules,[57,58] chemokines,[59,60] and matrix metalloproteinases[61,62] can be detected in serum, cerebrospinal fluid, or both — findings that are indicative of active T-cell migration across the blood–nerve barrier.

Once within the peripheral nervous system, these T cells may undergo clonal expansion after encountering an antigen presented in the context of appropriate major-histocompatibility-complex molecules and costimulatory signals. Such T cells then express and secrete cytokines such as tumor necrosis factor α, interferon-γ, and interleukin-2.[55,63] T cells thereby activate resident endoneurial or passenger macrophages, which then discharge an array of neurotoxic and immunopotentiating molecules (i.e., oxygen radicals, nitric oxide metabolites, arachidonic acid metabolites, proteases, and complement components)[64,65] or engage in increased phagocytic and cytotoxic activity against myelin or Schwann cells. On the other hand, specialized subpopulations of T cells may terminate the acute immunoinflammatory process by secreting down-regulatory cytokines (e.g., transforming growth factor

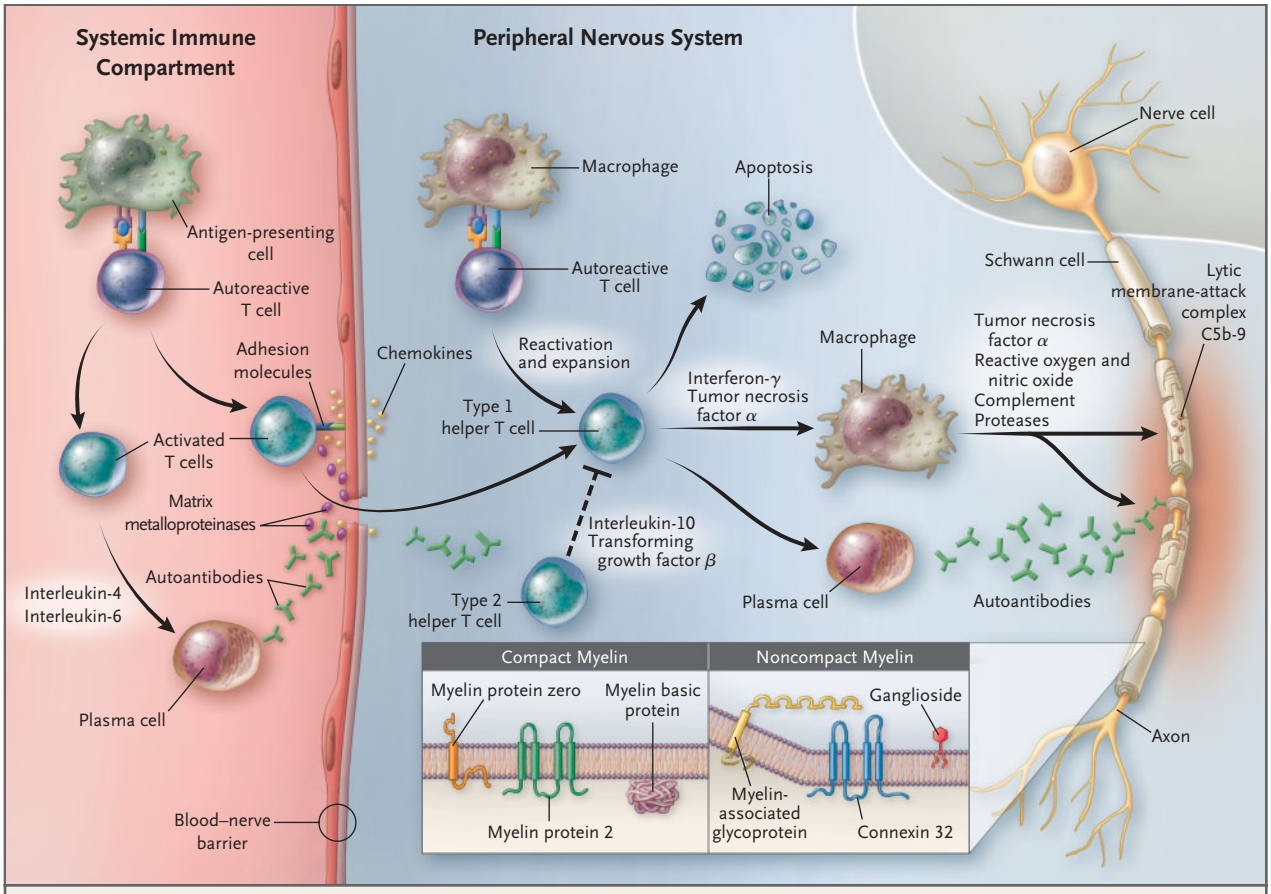

Figure 3. Immunopathogenesis of Chronic Inflammatory Demyelinating Neuropathy.

A schematic illustration of the basic principles of the cellular and humoral immune responses shows that autoreactive T cells recognize a specific autoantigen in the context of major histocompatibility complex class II and costimulatory molecules on the surface of antigen-presenting cells (macrophages) in the systemic immune compartment. An infection might trigger this event through molecular mimicry, a cross-reaction toward epitopes shared between the microbial agent and nerve antigens. These activated T lymphocytes can cross the blood–nerve barrier in a process involving cellular adhesion molecules, matrix metalloproteinases, and chemokines. Within the peripheral nervous system, T cells activate macrophages that enhance phagocytic activity, the production of cytokines, and the release of toxic mediators, including nitric oxide, reactive oxygen intermediates, matrix metalloproteinases, and proinflammatory cytokines, including tumor necrosis factor α and interferon-γ. Autoantibodies crossing the blood–nerve barrier or locally produced by plasma cells contribute to demyelination and axonal damage. Autoantibodies can mediate demyelination by antibody-dependent cellular cytotoxicity, potentially block epitopes that are functionally relevant for nerve conduction, and activate the complement system by the classic pathway, yielding proinflammatory mediators and the lytic membrane-attack complex C5b-9. Termination of the inflammatory response occurs through the induction of T-cell apoptosis and the release of antiinflammatory cytokines, including interleukin-10 and transforming growth factor β. The myelin sheath (inset) is composed of various proteins, such as myelin protein zero, which account for more than 50 percent of the total membrane protein in human peripheral nervous system myelin; myelin protein 2; myelin basic protein; myelin-associated glycoprotein; connexin 32; and gangliosides and related glycolipids. These molecules have been identified as target antigens for antibody responses with varying frequencies in patients with this disease.

β) or other molecules. It is important to note that the local immune environment of the peripheral nerves appears to facilitate the apoptosis of invading autoaggressive T cells,[66] a process augmented by therapeutically administered corticosteroids.[67]

Macrophages also serve as antigen-presenting cells in chronic inflammatory demyelinating polyneuropathy, a finding that is underscored by the observed expression of major-histocompatibility-complex class II molecules and the class I–like molecule CD1a in nerve-biopsy specimens.[68] Costimulatory molecules B7-1 and B7-2 are essential for effective antigen presentation and may determine the differentiation of T lymphocytes into a pheno-

type of type 1 or type 2 helper cells, thus modulating the local immune response and the clinical course of the disease. A spontaneous immune neuropathy with clinical, electrophysiological, and morphologic similarities to chronic inflammatory demyelinating polyneuropathy in humans develops in autoimmune nonobese diabetic mice that are deficient in B7-2 costimulation.[69]

The cellular immune response within the peripheral nervous system is tightly regulated at the transcriptional level. One of its key regulators, the transcription factor nuclear factor-κB, is up-regulated predominantly in macrophages in chronic inflammatory demyelinating polyneuropathy.[70]

HUMORAL IMMUNE RESPONSE

The contribution of autoantibodies to the pathogenesis of chronic inflammatory demyelinating polyneuropathy was suggested more than 20 years ago on the basis of immunoglobulin and complement deposition on myelinated nerve fibers[71] and the presence of oligoclonal IgG bands in the cerebrospinal fluid.[72] Passive transfer experiments have demonstrated that serum or purified IgG from patients with chronic inflammatory demyelinating polyneuropathy induces conduction block and demyelination in rat nerves.[73] In these experiments, the 28-kD myelin protein zero was identified as one of the putative target antigens.[74]

Gangliosides and related glycolipids may also be target antigens (Fig. 3, inset). In a few patients with chronic inflammatory demyelinating polyneuropathy, there is serologic evidence of recent infection with *Campylobacter jejuni*. Given the shared expression of carbohydrate epitopes in nerve glycolipids and microbial lipopolysaccharides, this finding may hint at molecular mimicry as the underlying cause of chronic inflammatory demyelinating polyneuropathy in rare instances.[75] GM_1 antiserum from a patient with chronic inflammatory demyelinating polyneuropathy substantially suppressed sodium currents in single myelinated nerve fibers from rats.[76] Serum reactivity against presumably nonmyelin antigens on Schwann cells has recently been reported in 12 of 46 patients studied.[77] Demyelination and conduction block may also result from serum constituents other than myelin-directed antibodies, such as cytokines, complements, or other inflammatory mediators (e.g., nitric oxide). The low frequency of specific antibodies that is observed in patients with chronic inflammatory demyelinating polyneuropathy suggests that various antibodies and separate mechanisms are involved in individual patients.

AXONAL LOSS

Chronic inflammatory demyelinating polyneuropathy, though a demyelinating polyneuropathy, is associated with a concomitant axonal loss attributed to the primary demyelinating process.[39,48] This finding appears to be important, since the long-term prognosis in chronic inflammatory demyelinating polyneuropathy depends on the magnitude of axonal loss rather than on demyelination. There are questions as to whether the release of neurotoxic cytokines (e.g., tumor necrosis factor α) and noxious mediators (e.g., nitric oxide and metalloproteinases) enhances axonal destruction, but it has become clear that early, effective therapy minimizes axonal loss.

CURRENT TREATMENT

In general, therapies are directed at blocking immune processes to arrest inflammation and demyelination and to prevent secondary axonal degeneration. In patients who have a response, treatment must be continued until maximum improvement or stabilization occurs; thereafter, maintenance therapy is required and must be tailored to the individual patient, with the goal of preventing or diminishing the frequency of relapses or disease progression. A positive response to therapy is determined by a measurable improvement in strength and sensation and the patient's ability to perform activities of daily living. It is important to be aware that infections and febrile conditions may also affect demyelination and thereby worsen the clinical symptoms of chronic inflammatory demyelinating polyneuropathy. Concomitant use of neurotoxic drugs or the presence of systemic conditions known to cause neuropathies may also theoretically influence the clinical symptoms of the condition.

The most widely used treatments for chronic inflammatory demyelinating polyneuropathy (Table 3) consist of intravenous immune globulin,[11,80,81,84-86] plasma exchange,[78,79] and corticosteroids.[11,87,88] Therapy should be initiated early in the course of the disease to prevent continuing demyelination and secondary axonal loss leading to permanent disability. According to published data, there appears to be no difference in efficacy among these three main therapies.[28,85,87] The decision to choose one of them is usually made on

Table 3. Current Therapy Based on the Results of Randomized, Controlled Studies.*

Reference	Year	Therapy	No. of Patients	Duration	Design	Result
Dyck et al.[78]	1994	Plasma exchange vs. intravenous immune globulin	15	42 days	Randomized, observer-blinded, crossover	No significant difference
Hahn et al.[79]	1996	Plasma exchange	15	28 days	Double-blind, sham-controlled, crossover	Improvement in 80% of patients
Hahn et al.[80]	1996	Intravenous immune globulin	30	28 days	Double-blind, placebo-controlled, crossover	Improvement in 63% of patients
Mendell et al.[81]	2001	Intravenous immune globulin	53	42 days	Double-blind, randomized, placebo-controlled	Improvement in 76% of patients
Hughes et al.[11]	2001	Intravenous immune globulin vs. oral prednisolone	32	14 days	Double-blind, randomized, crossover	No significant difference
Dyck et al.[82]	1985	Azathioprine in combination with prednisone vs. prednisone alone	30	9 mo	Open, parallel-group, randomized	No significant difference
Hadden et al.[83]	1999	Interferon beta-1a in treatment-resistant disease	20	28 wk	Double-blind, randomized, placebo-controlled, crossover	No significant benefit of treatment

* Most of the clinical trials in chronic inflammatory demyelinating polyneuropathy have been limited to several weeks, which is a rather short time period for a disease that typically spans months or years.

the basis of cost, availability (e.g., plasmapheresis and venous access), and side effects (most important, the serious long-term side effects of corticosteroids).[87] All these factors should be considered when cost–utility analyses are performed.[89] In some 60 to 80 percent of patients with classic chronic inflammatory demyelinating polyneuropathy, the condition improves while they are receiving one of the three therapies, but the long-term prognosis appears to vary according to the time at which therapy is initiated and the degree of associated axonal loss. Azathioprine,[82] cyclophosphamide, and cyclosporine have long been used mainly as secondary agents in the therapy of chronic inflammatory demyelinating polyneuropathy, but reliable data on their efficacy from randomized, controlled trials are not available.[90] For unknown reasons, the efficacy of these latter treatments is clearly less favorable in patients who have a neuropathy accompanied by antibodies to myelin-associated glycoprotein.[91,92]

Given the presumed autoimmune cause of this condition and its suggested pathogenetic similarities to multiple sclerosis, immunomodulatory therapies that are considered effective in that disorder have been investigated. Twenty patients with treatment-resistant chronic inflammatory demyelinating polyneuropathy were enrolled in a prospective, multicenter, open-label study that evaluated intramuscular interferon beta-1a at a dose of 30 μg once a week for six months.[93] Thirty-five percent of the patients had an improvement, and the disease stabilized in 50 percent, prompting the authors to recommend a larger, placebo-controlled trial. However, another study, in which four patients with chronic inflammatory demyelinating polyneuropathy were treated, showed that treatment with interferon beta-1a was effective only in combination with intravenous immune globulin.[94] Furthermore, a small, randomized, double-blind, placebo-controlled, crossover study involving 10 patients with treatment-resistant chronic inflammatory demyelinating polyneuropathy and evaluating interferon beta-1a (3 million IU for 2 weeks and 6 million IU for 10 weeks, administered subcutaneously three times per week) failed to show a significant treatment effect.[83] The role of interferon alfa in the condition is also uncertain. Some case reports[95,96] and an open-label prospective pilot study[97] suggested that interferon alfa was effective.

Of concern, chronic inflammatory demyelinating polyneuropathy has been reported to develop during treatment with interferon alfa[98-100] or interferon beta.[101] Furthermore, interferon was ineffective in patients with IgM monoclonal gammopathy[102] and the Guillain–Barré syndrome.[103] These disturbing observations raise the provocative question of whether interferons are causally related to the onset of chronic inflammatory demyelinating

polyneuropathy, as opposed to being capable of suppressing the disease.[104] Hughes et al. concluded that there is currently no adequate evidence to decide whether interferons are beneficial in the treatment of this condition.[90]

Other forms of treatment have been tested in open-label studies with a small number of patients or in individual patients. Beneficial effects in patients with previously treatment-resistant chronic inflammatory demyelinating polyneuropathy were reported for the combination of plasmapheresis and intravenous immune globulin,[105] mycophenolate mofetil,[106-108] cyclosporine,[109-111] etanercept,[112] cyclophosphamide,[113,114] and autologous hematopoietic stem-cell transplantation.[115] In patients with multifocal motor neuropathy or chronic inflammatory demyelinating polyneuropathy, the combination of intravenous immune globulin and mycophenolate mofetil may permit a reduction in the dose of immune globulin or corticosteroids, a finding that was recently suggested by an open-label study of 6 patients[116] and a retrospective analysis of the efficacy of mycophenolate mofetil in 21 patients with chronic inflammatory demyelinating polyneuropathy.[108] Two recent open-label studies involving 30 patients found improvement in those with IgM-associated demyelinating polyneuropathy who were receiving treatment with rituximab, a chimeric humanized monoclonal antibody against CD20 antigen that reduces B-lymphocyte counts.[117,118] However, no data that have been collected on the basis of randomized, controlled studies with a sufficient number of patients are available to allow conclusive recommendations about treatment with any of these agents. Furthermore, controlled trials providing long-term data are lacking. The evidence concerning the efficacy of plasma exchange, intravenous immune globulin, and corticosteroids derives only from short-term studies. Plasma exchange and intravenous immune globulin are expensive therapies and must be continued over the long term to maintain benefit. Anecdotal experience suggests that the use of immunosuppressive agents may allow therapy with plasma exchange or intravenous immune globulin to be administered less frequently or even phased out, with subsequent substantial financial savings. There is clearly a need for controlled studies to assess this long-term aspect of therapy for chronic inflammatory demyelinating polyneuropathy.

CONCLUSIONS

It is important to recognize chronic inflammatory demyelinating polyneuropathy in a patient with a chronic progressive or chronic relapsing neuropathy, since therapies that are at least partially effective — including corticosteroids, intravenous immune globulin, plasma exchange, and immunosuppressants — are available for this crippling disease. Sets of diagnostic criteria have been developed. The disorder appears to be heterogeneous in terms of clinical presentation and immunopathogenesis. Further research should provide further insight into the underlying mechanisms of nerve damage and may facilitate the development of more effective treatments.

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