Inflammatory Neuropathies: An Update on Evaluation and Treatment

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Inflammatory neuropathies are a diverse group of illnesses sharing the pathologic characteristic of inflammation surrounding nerve fibers. They may be autoimmune, granulomatous, infectious, paraneoplastic, or paraproteinemic in origin. All can result in significant morbidity and rarely, death. It is critical to correctly diagnose these illnesses, as many respond well to treatment. In this paper, the diagnosis and latest developments in the treatment of the most common inflammatory neuropathies (Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, neurosarcoidosis, anti–myelin-associated glycoprotein neuropathy, Sjögren's syndrome, paraneoplastic neuronopathy, and vasculitic neuropathies) will be discussed.

Introduction

Inflammatory neuropathies encompass a unique set of acquired conditions often occurring sporadically in adulthood. Inflammatory neuropathies fall into four major categories: autoimmune, granulomatous, infectious, and paraneoplastic/paraproteinemic. These neuropathies include familiar disorders such as Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and lesser known diseases such as paraneoplastic sensory neuronopathy and neuropathies associated with monoclonal proteins. These diverse pathologic conditions are united by the pathologic characteristic of inflammatory cells visualized on nerve biopsy. It is important for physicians to recognize and diagnose these disorders, as many are treatable. The authors report the latest advances in diagnosis and treatment of these disorders.

Autoimmune Neuropathies

Guillain-Barré syndrome

Guillain-Barré syndrome is the most common cause of acute flaccid paralysis, affecting 1-2 of 100,000 people worldwide. GBS refers to the clinical presentation of disease and the name does not imply the underlying pathology or electrophysiologic findings. The most common presentation in North America and Europe is acute inflammatory demyelinating polyneuropathy (AIDP). Axonal variants exist and include acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), as well as Miller Fisher syndrome. This section will focus on AIDP, but the treatments for the other variants are the same.

Acute inflammatory demyelinating polyneuropathy typically presents with predominantly motor symptoms that can worsen over a period of up to 4 weeks before reaching a plateau. The condition classically presents with a rapidly ascending paralysis and hyporeflexia/areflexia. The weakness is symmetric with concurrent loss of deep tendon reflexes. Thirty percent of patients develop diaphragmatic weakness requiring ventilatory support. Sensory involvement is absent or much less impressive than the motor involvement. The disease is often preceded by a respiratory or gastrointestinal illness 1 to 2 weeks prior to the onset of weakness. Autonomic dysfunction occurs in more than 50% of patients and contributes to the 1.5% to 5% mortality rate still seen today.

Diagnosis of AIDP is largely by history and clinical examination. Nerve conduction studies are often unrevealing during the first few days of the disease. Cerebrospinal fluid (CSF) is helpful at days 5 to 7 and usually shows elevated protein in the absence of pleocytosis (cytoalbuminologic dissociation). No other serum or CSF reliable markers exist.

Acute inflammatory demyelinating polyneuropathy remains a sometimes fatal and often disabling condition. Early recognition and treatment is critical to minimize progression of disease and hasten recovery. Plasma exchange (PEX) and intravenous immunoglobulin (IVIg) are the current standards of care. PEX was established as an effective treatment in 1985 when the GBS study group found that treatment within 7 days of onset resulted in less disability at 4 weeks and 6 months [1]. The optimal number of exchanges is not well established but is generally accepted to be 200 to 250 mL/kg over 7 to 10 days (4–5 exchanges) [1,2]. However, since PEX is not available at all medical centers, IVIg offers a more widely available alternative treatment of equal efficacy [3]. IVIg is usually infused at 0.4 gm/kg/day on 5 consecutive days. Treatment

with IVIg or PEX improves time to walking and clinical outcomes at 4 weeks and 6 months [1,4]. Even so, nearly 20% of patients are left with some disability at 1 year [5]. PEX and IVIg are not without hazards. PEX has been associated with cardiovascular complications including arrhythmias and hypotension, as well as catheter-related sepsis and bleeding. IVIg is known to cause headache, aseptic meningitis, and rarely, thrombotic events. Presently PEX and IVIg are considered equivalent standards of treatment for GBS.

Other treatments have been attempted in GBS. In 1991, Hughes [6] reported that corticosteroids were no more effective than placebo for the treatment of AIDP, but this view was not shared by all investigators. In 1994, scientists in Holland proposed that IVIg combined with steroids resulted in improved outcomes [7]. Ten years later, a study by the Dutch GBS group described the use of methylprednisolone as an adjunct to IVIg [8•]. Over 200 patients were enrolled; 50% were treated with IVIg monotherapy and 50% were given IVIg plus 500 mg/day of methylprednisolone. No statistical difference was noted in any outcome measure between the two groups [8•].

Interferon-beta 1a has been studied in GBS, as it ameliorates experimental autoimmune neuritis, the animal model of AIDP. In a recent study, 13 patients were treated with interferon for 24 weeks after receiving standard infusions of IVIg and compared with six placebo patients [9]. Four patients receiving interferon developed adverse reactions and stopped treatment early. No statistical difference was noted in outcomes between the two groups.

Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy presents with some features similar to AIDP, but with a more protracted course. It affects 1-2 of 100,000 people with a peak incidence in the 5th and 6th decades of life. CIDP is characterized by a symmetrical motor and sensory illness and hyporeflexia/areflexia progressing for greater than 8 weeks. The diagnosis is often suggested by the results of nerve conduction studies, which commonly show conduction block, temporal dispersion, or slowing of conduction velocity. A definite diagnosis requires motor nerve conduction velocities to be less than 70% to 80% of the lower limit of normal [10•]. CIDP is not always idiopathic and is often diagnosed in association with other conditions including HIV infection, systemic lupus erythematous (SLE), diabetes mellitus, and malignancy [11].

Since CIDP often has a progressive course plagued by relapses and remissions, chronic medical management is required. Other presentations of CIDP include monophasic, chronic progressive, and stepwise progressive courses. Unlike AIDP, corticosteroid therapy can be useful in the treatment of CIDP. Steroids decrease the expression of proinflammatory cytokines and inhibit T-cell proliferation and immunity. The initial studies of corticosteroids in the treatment of CIDP were performed in the early 1980s and described that 120 mg of prednisone tapered over 12 weeks was beneficial when compared with placebo [12]. Other authors have used smaller doses (60 mg) with similar effect.

Other treatments for CIDP include plasma exchange [13] and IVIg [14]. Dosing is the same as with AIDP, but retreatment is usually required every 1 to 3 months until the patient reaches remission. Both treatments are equally effective and approximately two-thirds of patients will respond favorably.

Recent literature has described the use of intermittent intravenous steroid therapy to reduce the risk for corticosteroid associated side effects. Lopate *et al*. [15••] looked at 39 patients receiving IVIg, oral immunosuppressants, or intermittent methylprednisolone as long-term maintenance therapy for CIDP. Sixteen patients received intermittent methylprednisolone at a dose of 1000 mg/day for 3 to 5 consecutive days, then one dose per week for the next month. The period between subsequent treatments was 2 to 12 weeks. The patients were followed for up to 10 years with 13 of 16 patients demonstrating improved strength compared with baseline [15••]. Far fewer side effects were experienced compared with patients taking daily oral corticosteroids.

Other immunosuppressants are useful in CIDP, especially in those patients who cannot tolerate the effects of chronic corticosteroid use. Although current practice parameters state that inadequate evidence exists to recommend the use of these adjunctive agents, clinical experience suggests that many patients benefit from alternative immunosuppressants. Several case series and case reports can be cited to support their use. These agents include azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, rituximab, and interferon beta 1-a.

Mycophenolate mofetil is one of the most promising new treatments for CIDP. The drug inhibits inosine monophosphate, interrupting a key metabolic pathway in lymphocytes. It has been useful in the management of another autoimmune disorder, myasthenia gravis, and the low incidence of side effects makes it an attractive drug. Limited experience and literature exists to support the use of mycophenolate mofetil in CIDP, but the outlook is favorable [16,17]. In recent studies, 30% to 100% of treatment resistant patients have improved on doses of 1000 mg twice a day [16,17]. Its use as a first-line agent has not been explored.

Azathioprine has been utilized for the treatment of CIDP for over 20 years. Surprisingly, there is little data to support its use. Dyck *et al*. [18] compared azathioprine with prednisone. No difference between the two therapies was observed. Despite the lack of evidence, azathioprine is commonly prescribed with success for management of CIDP, often to reduce patient dependency on corticosteroids.

Cyclosporin A is another oral immunosuppressant used in the treatment of CIDP. Cyclosporin A is a fungal

metabolite first used to prevent rejection of transplanted organs; it is believed to selectively inhibit T-cell function. The drug has been used since the 1980s for treatment of autoimmune neurologic disease, including CIDP. Cyclosporin A is dosed orally at 3 to 7mg/kg/day divided into two doses. Multiple studies have consistently shown cyclosporin A to be an effective treatment for patients with refractory CIDP [19,20]. The main side effect is a dose-dependent nephrotoxicity that can be prevented by careful monitoring of serum levels.

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen. The agent was initially designed to treat B-cell lymphoma, but its use is being extended to treat neurologic conditions such as multifocal motor neuropathy and CIDP. Evidence for the use of rituximab in CIDP is limited and anecdotal. A report in 2004 described the successful use of rituximab 375 mg/m^2 in a single treatment-resistant patient [21].

Interferons are also being investigated as potential therapies for CIDP based on evidence that they inhibit tumor necrosis factor-α (TNF-α) [22]. One group of investigators found that 5 of 16 patients responded to treatment with interferon alpha 2a [23].

Rheumatologic Disorders

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder resulting from a T-cell inflammatory response and granuloma formation [24••]. The etiology of the disease is unknown, but is believed to be triggered by environmental factors (bacterial infection, pollen, talc). In the United States, it is most prevalent in the Southeast and disproportionately affects black women. Prevalence estimates range from 1 to 50 per 100,000 depending on the population sampled [24••]. Pulmonary involvement is common and the disease is often diagnosed when hilar adenopathy is observed on a chest radiograph. Other involved organs include the skin, eyes, liver, and lymph nodes.

Neurologic involvement occurs in up to 5% of patients, but is the initial presentation of sarcoidosis in 50% of those affected by neurosarcoidosis [24••]. Manifestations include aseptic meningitis, a GBS-like syndrome, hypothalamic dysfunction, myopathy, and seizures [25]. Cranial neuropathy secondary to chronic basal meningitis is the most common neurologic presentation, with bilateral facial nerve palsies being the classic presentation [24••]. Optic neuropathy is also common and neurosarcoidosis should be considered in the differential diagnosis whenever optic neuritis appears [24••].

Peripheral neuropathy is a complication of sarcoidosis and may present as an asymmetrical mononeuritis multiplex, symmetrical axonal polyneuropathy, or a polyradiculopathy [26]. The neuropathy is rare and occurs in only 5% to 18% of patients with neurosarcoidosis [24••]. Neuropathy results from epineural and perineural granuloma formation and vasculitis within the nerve. The nerves undergo ischemic axonal loss and demyelination in the regions adjacent to the granulomas. Diagnosis is often difficult as sarcoid neuropathy may occur in patients without known disease [27]. Electromyography and nerve conductions studies may show a variety of neuropathic abnormalities, but an axonal sensorimotor neuropathy is most common [26]. Confirmation of sarcoidosis is made through correlation of chest radiography, elevated serum angiotensin converting enzyme (ACE) levels, liver function studies, pulmonary function studies, calcium levels and examination of the CSF for elevated protein and ACE levels. Unfortunately, these tests lack sensitivity and the most reliable diagnostic test remains pathologic examination of affected tissues. Whole-body gallium or positron emission tomography (PET) scanning is often useful in selecting an extraneural biopsy site [24••]. Biopsy of the nerve itself may be helpful for finding granulomas and other features of neurosarcoidosis: inflammation, multinucleated giant cell, and necrotizing vasculitis [28].

No large randomized controlled trials exist for the treatment of sarcoid-related neuropathies. The disease is typically treated with the same medications used for systemic disease and evidence for efficacy is largely anecdotal. Corticosteroids are a mainstay of treatment for systemic sarcoid disease, but the complications of long-term use limit their utility. Alternative agents include azathioprine, methotrexate [29], cyclophosphamide [30], cyclosporine, infliximab [29,31], thalidomide, IVIg [32], and radiation therapy.

Corticosteroid therapy for neurosarcoidosis is initiated with prednisone 1 mg/kg/day (higher than the 40 mg/day used for isolated pulmonary disease) [24••]. If the patient's condition is poor, many physicians recommend starting with 3 to 5 days of intravenous methylprednisolone (500–1000 mg/day) prior to initiating an oral agent. If the patient responds to treatment, the dose is tapered over a period of weeks to months until symptoms recur or the patient remains in remission. The patient is maintained on the lowest dose possible. Some patients experience complete remission of their symptoms and are able to stop treatment.

For patients who do not respond to steroids or are unable to tolerate the side effects, other immunosuppressants can be prescribed. Methotrexate, azathioprine and cyclosporin are commonly used. Methotrexate is dosed at 10 to 25 mg/week and commonly induces a 60% response rate in neurosarcoidosis [29]. Folic acid (1 mg/day) is given concurrently to prevent anemia. Other side effects of methotrexate include hepatic dysfunction, neutropenia and pneumonitis. Azathioprine is another agent that has been reported to halt progression of neurosarcoidosis when used at a dose of 100 to 200 mg/day, although the results are not as impressive as those achieved with other agents. Cyclophosphamide is considered a third-line treatment, largely because of its toxicity (hemorrhagic cystitis, hair loss,

neutropenia). At doses of 50 to 200 mg per day, approximately 75% percent of patients will improve [29,33].

Infliximab has recently received attention for the treatment of sarcoidosis [34]. It is a monoclonal antibody that inhibits production of TNF-α and is presently used in the treatment of rheumatoid arthritis and Crohn's disease. The drug is commonly administered as an intravenous infusion of 3 to 5 mg/kg in week 1, week 3, and week 5 followed-up by 3 to 5 mg/kg every 6 weeks [29,31]. Experience at this time is largely in the form of case studies and series, but those reports describe a favorable response in patients refractory to other treatments. Potential side effects include infection (particularly reactivation of latent tuberculosis), possible induction of anti-phospholipid antibodies (more likely in those receiving concurrent methotrexate), hypercoagulability, and deep venous thrombosis.

Other less commonly used agents for the management of sarcoid neuropathies include hydroxychloroquine (200 mg/day), an antimalarial drug associated with the adverse effects of retinopathy, cardiomyopathy, and neuropathy [29,35]. Thalidomide has also resurfaced as a treatment, given its ability to inhibit the production of TNF, but thalidomide can cause an iatrogenic neuropathy [24••]. Radiation therapy is reserved for those patients with a focal central nervous system (CNS) or peripheral nerve lesion and can be highly effective in select cases [36].

Sjögren syndrome neuronopathy and neuropathy

Sjögren syndrome is an autoimmune disease characterized by mononuclear cell infiltration of the salivary and lacrimal glands as well as involvement of other organs. The disorder may be primary or associated with conditions such as rheumatoid arthritis, scleroderma, and SLE. Diagnosis of the disorder is suggested by characteristic clinical examination findings and confirmed by salivary gland biopsy and if detected, Ro/SSA and La/SSB autoantibodies (present in only 30% to 50% of patients) [37•].

Approximately 76% of patients with Sjögren syndrome suffer from neurologic symptoms of the peripheral and CNS. Sensory ganglionopathy is one of the most common neurologic manifestations of Sjögren syndrome and usually presents before the diagnosis of Sjögren syndrome is made. Asymmetric onset of symptoms is common with paresthesias and pain presenting initially in the fingers. The upper body tends to be involved first followed by the face and lower limbs. Autonomic symptoms including orthostatic hypotension and anhidrosis may occur. Strength is usually preserved; although isolated cases of motor neuropathy have been reported [37•]. Other less common manifestations of Sjögren syndrome include a diffuse sensorimotor neuropathy, sensory ataxia, mononeuritis multiplex, autonomic neuropathy, and recurrent cranial neuropathies [38••].

The diagnosis of Sjögren syndrome neuronopathy or neuropathy is suggested by clinical examination and the detection of Sjögren syndrome-A and Sjögren syndrome-B antibodies. If no antibody is detected, a minor salivary gland or nerve biopsy may be necessary to confirm the diagnosis. Nerve biopsy yields findings of necrotizing vasculitis. The salivary gland biopsy is considered positive when greater than two foci of lymphocytic infiltrates are seen in 4 mm^2 of tissue [39]. When a pre-existing diagnosis of Sjögren's syndrome is not known, verifying Sjögren's neuropathy can be challenging and elusive.

Treatment of Sjögren syndrome-related peripheral nerve disease is frustrating. Most patients do not respond to traditional immunotherapy, including oral corticosteroids and cyclosporine A [40]. Responses to several forms of treatment have been reported in isolated case studies. IVIg has been successful in the treatment of Sjögren's-related motor neuropathy and peripheral neuropathy [41,42]. Plasma exchange has also been reported to improve patients with chronic ataxic sensory neuropathy [43]. D-penicillamine has been used with limited success [44]. Yamada *et al.* [45] recently reported three cases of Sjögren syndrome neuropathy/gangliopathy responding to interferon-alpha treatment [45].

Paraneoplastic/Paraproteinemic Neuropathy

Anti–myelin-associated glycoprotein neuropathy

Antibodies against myelin-associated glycoprotein (anti-MAG) are directed against an antigen located on peripheral nerve. This antibody is present in about 50% of patients with an IgM monoclonal protein (monoclonal gammopathy of undetermined significance [MGUS]) and most often results in a slowly progressive predominantly sensory demyelinating polyneuropathy [46]. As the neuropathy is believed to be secondary to the presence of the antibody, treatment focuses on reducing titers by at least 50% [47].

Anti–myelin-associated glycoprotein neuropathy is more common in men and has a later age of onset (the sixth decade) compared with idiopathic CIDP [48]. It can present with pure sensory involvement, sensory ataxia, or an action tremor of the upper extremities. The process is slowly progressive, rather than relapsing-remitting.

The diagnosis is usually suggested by the detection of a monoclonal protein on laboratory testing. Any patient with signs of neuropathy in late life should have a serum protein electrophoresis, immunofixation studies, and urine protein electrophoresis. The presence of a monoclonal protein warrants evaluation for multiple myeloma and Western blot testing for anti-MAG. Electrophysiologic studies in anti-MAG neuropathy typically show a sensory much greater than motor demyelinating process.

Anti–myelin-associated glycoprotein neuropathy is also known for its lack of responsiveness to immunotherapy. Patients with mild anti-MAG sensory neuropathy rarely need immunosuppressive therapy since the treatment is often worse than the clinical manifestations of the disease. Those who present with a more CIDP-like process, however, are more likely to respond to treatments.

Multiple therapeutic agents have been used, but controlled trials confirming efficacy are lacking. Treatments include plasma exchange, IVIg, corticosteroids, rituximab, cyclophosphamide, and chlorambucil. Corticosteroids and IVIg have been largely ineffective against anti-MAG neuropathy [49••].

Cyclophosphamide in combination with plasma exchange is a popular choice for the treatment of anti-MAG neuropathy. Monthly infusions of cyclophosphamide at 1 g/m^2 preceded by two plasma exchanges for 6 consecutive months are recommended [47]. Approximately 60% to 80% of patients will experience sustained reduction in their anti-MAG titers for up to 6 years after treatment. The neuropathy will improve or stabilize in a smaller percentage of patients (as low as 20%) [47].

Chlorambucil was previously the most commonly used chemotherapeutic agent for anti-MAG neuropathy [50]. Studies have shown this alkylating agent to be effective in about one-third to one-half of patients when used as monotherapy. The drug has serious side effects, including myelosuppression and secondary leukemia, [51] and should not be used in mild disease. Similar response rates are seen in patients treated with purine analogues such as fludarabine given monthly at 25 mg/m^2 intravenous daily for 5 days [52].

One analysis compared the outcomes of 24 patients with anti-MAG neuropathy treated with different therapies [49••]. Twelve patients responded to treatment (50%), but only four patients demonstrated a sustained response. Plasma exchange lead to improvement in three of eight patients and cyclophosphamide was effective in two of three. Patients treated with prednisone, chlorambucil, and azathioprine did not improve.

Rituximab is emerging as a promising treatment for patients with anti-MAG neuropathy. Data are limited and long-term outcomes are not known, but recent literature supports its use [53,54]. In one case series, nine patients with anti-MAG IgM polyneuropathy were treated with rituximab (375 mg/m^2) once weekly for 4 weeks. Eight of nine patients responded with a reduction of anti-MAG titers of greater than 52%. Over the next 12 months, six patients clinically improved and two remained stable; seven showed improvement in nerve conduction velocities [54].

Thus far, no therapy is universally accepted as first-line treatment for anti-MAG neuropathy. Plasma exchange, cyclophosphamide, rituximab, and chlorambucil seem to be the best options for moderate-to-severe disease. However, it also seems reasonable to use those treatments thought to be effective in CIDP until controlled trials are performed.

Sensory Neuronopathy

Sensory neuronopathies reflect pathology at the level of the dorsal root ganglion. They are frequently associated with malignancy, dysimmune conditions, and exposure to toxins. Anti-Hu neuropathy and Sjögren's disease are the most common associations. The disorder is characterized by early onset of ataxia, areflexia, and distal sensory loss.

Paraneoplastic subacute sensory neuronopathy

Anti-Hu antibody neuronopathy was first described clinically in 1948 by Denny-Brown, prior to the discovery of the antibody. It is associated with malignancy, particularly small-cell lung cancer (85%) and neuroendocrine tumors [55••]. The symptoms are rapidly progressive over the course of days to weeks. Patients report pain, paresthesias and numbness typically affecting the upper extremities first. Physical examination often shows pseudoathetoid movements of the hands, lost deep tendon reflexes, and distal gradient sensory loss. Autonomic neuropathy, cerebellar degeneration, and limbic encephalitis may also occur in association with the disorder [55••].

The onset of anti-Hu sensory neuronopathy typically predates the diagnosis of malignancy by several months, so clinical suspicion must be high to diagnose early in the disease [56]. Conventional radiologic exams are often normal and whole-body PET scans are sometimes utilized to locate the neoplasm. Electrophysiologic studies reveal loss of sensory nerve action potentials (SNAPs) or a severe reduction in their amplitude in the presence of normal motor nerve parameters. The detection of serum anti-Hu antibodies confirms the diagnosis; specificity is 99% and sensitivity is 82% [57]. Therefore, the absence of the antibody does not preclude the disorder.

The disease is the result of cross-reactivity between tumor cells and the nervous system. Anti-Hu antibodies represent the immune system's reaction to the underlying malignancy. Because of the cross-reactivity, the antibody binds to cells in the dorsal root ganglia, resulting in inflammation and degeneration.

Anti-Hu neuronopathy is commonly disabling and patients may die from complications of a bedridden state. Older age at onset (> 60 years) and involvement of the CNS are associated with increased mortality. Treatment of the tumor can improve or stabilize the condition. In a 2002 study of 73 patients with anti-Hu syndrome, 53% of patients stabilized or improved after treatment of the malignancy [56].

No immunotherapy (IVIG, corticosteroids, azathioprine, plasma exchange, or cyclophosphamide) has been demonstrated to improve outcomes in paraneoplastic sensory neuronopathy. Isolated case reports of improvement or stabilization after treatment with various agents can be found in the literature [58]. In the 2002 study previously mentioned, 14% of patients improved after immunotherapy alone, compared with 27% of those who received no treatment, implying immunotherapy may actually worsen the condition [56]. Despite the pessimistic outlook for immunosuppressants in the treatment of anti-Hu neuronopathy, further research is being performed.

As the neuronopathy is characterized by widespread inflammation and neuronal loss, one focus is identifying the disease early so that treatment begins prior to cell death [58]. A series of 17 patients were treated with a combination of IVIg, cyclophosphamide, and methylprednisolone in an attempt to study the effects of aggressive immunotherapy on paraneoplastic syndromes. The authors found that such therapy had little effect on those with advanced disease, but stabilized those in the early stage of disease [59].

Vasculitic Neuropathies in Connective Tissue Disease

Systemic lupus erythematosus and rheumatoid arthritis

Vasculitic neuropathies are relatively uncommon. They may be primary or secondary in origin. The primary disorders include Churg-Strauss syndrome, Wegener's granulomatosis, polyarteritis nodosa, and most connective tissue disorders (SLE and rheumatoid arthritis). Secondary vasculitic neuropathies may be associated with many etiologies, including hepatitis C infection, HIV infection, and diabetes mellitus [60]. This discussion will focus on the connective tissue disorders. By definition, vasculitic neuropathies result from nerve ischemia and infarction, which produce axonal loss. Although the pathophysiology is not well defined, it is hypothesized that circulating immune complexes initiate the process [60]. The resulting inflammatory response affects the epineurial arteries and vasa nervorum, eventually causing ischemic damage to the nerve [61]. The characteristic pattern of nerve involvement is considered to be mononeuritis multiplex, a step-wise involvement of individual sensory and motor nerves. Although this is often described as the "typical pattern" of vasculitic neuropathy, a symmetric, length-dependent sensorimotor polyneuropathy is found in up to 40% of cases [60].

The diagnosis of vasculitic neuropathy is suggested by characteristic clinical examination findings, such as livedo reticularis, cutaneous necrosis, and patchy sensorimotor changes. Laboratory studies may reveal an elevated erythrocyte sedimentation rate, C-reactive protein, or other serum markers (rheumatoid factor, cANCA, pANCA). Nerve conduction studies are compatible with an axonal neuropathy that may be asymmetric (mononeuritis multiplex) or a symmetric length-dependent polyneuropathy. The diagnosis is confirmed by nerve, skin, or muscle biopsy findings of epineurial and perineurial inflammatory infiltrates [60].

The exact incidence of neuropathy in SLE or rheumatoid arthritis is unknown, but an estimated 14% of all vasculitic neuropathies are associated with connective tissue disease [62]. Of this group, almost one-fifth is associated with rheumatoid arthritis [62]. The prevalence in SLE is less well defined, but neuropathy is estimated to occur in 5% to 27% of affected patients [63]. These percentages may underestimate the prevalence of neuropathy in SLE, as the CNS manifestations usually dominate the clinical picture. The presence of a vasculitic neuropathy in rheumatoid arthritis carries a particularly poor prognosis, with survival rates of only 57% at 5 years [64].

The treatment and prognosis of primary and secondary vasculitic neuropathies is founded in immunosuppressive therapies. The accepted standard for treatment is prednisone 1 to 2 mg/kg/day [60,61]. However, corticosteroid monotherapy often does not improve the patient's condition and is associated with many undesirable side effects. When faced with these difficulties, many physicians add cyclophosphamide as a second line agent (2 mg/kg/day orally or 0.5–0.7g/m^2 intravenously every 2–3 weeks) [60,61,65]. The patient's erythrocyte sedimentation rate and C-reactive protein are used to monitor therapy, if abnormal prior to treatment. This practice allows for laboratory-supported reductions in medication over the course of weeks to months, based upon the patient's response [60].

Conclusions

In summary, many disease processes can produce an inflammatory neuropathy. Some, such as AIDP and CIDP, have well-established treatment protocols. Others (sarcoidosis and paraneoplastic syndromes) suffer from rarity and treatment is largely an individualized trial-and-error approach. Most physicians will encounter patients with these disorders throughout their careers and it is important to remain abreast of the latest developments in diagnosis and treatment.

References and Recommended Reading

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

- • Of importance
- •• Of major importance

1. Guillain-Barré Syndrome Study Group: **Plasmapheresis and acute Guillain-Barré syndrome.** *Neurology* 1985, **35:**1096–1104.
2. Esperou H, Jars-Guincestre MC, Bolgert F, *et al.*: **Cost-analysis of plasma exchange therapy for the treatment of Guillain-Barré syndrome. French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome.** *Intensive Care Med* 2000, **26:**1094–1100.
3. Hughes RAC, Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group: **Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome.** *Lancet* 1997, **349:**225–230.
4. French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome: **Efficacy of plasma exchange in Guillain-Barré syndrome: role of replacement fluids.** *Ann Neurol* 1987, **2:**753–761.
5. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group: **Randomised trial of plasma exchange, intravenous immunoglobulin and combined treatments in Guillian-Barré syndrome.** *Lancet* 1997, **349:**225–230.

6. Hughes RA: **Ineffectiveness of high dose intravenous methylprednisolone in Guillain-Barré syndrome.** *Lancet* 1991, **338:**1142.
7. The Dutch Guillain-Barré Study Group: **Treatment of Guillain-Barré syndrome with high-dose immune globulins combined with methylprednisolone: a pilot study.** *Ann Neurol* 1994, **35:**749–752.
8.• Van Koningsveld R, Schmitz PIM, van der Meche FGA, *et al.*: **Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barré syndrome: randomized trial.** *Lancet* 2004, **363:**192–196.

A randomized controlled trial demonstrating that IVIg plus methylprednisolone is no better than IVIg monotherapy.

9. Pritchard J, Gray IA, Idrissova ZR, *et al.*: **A randomized controlled trial of recombinant interferon-beta 1a in Guillain-Barré syndrome.** *Neurology* 2003, **61:**1282–1284.
10.• Köller H, Kieseier BC, Jander S, Hartung H-P: **Chronic inflammatory demyelinating polyneuropathy.** *N Engl J Med* 2005, **352:**1343–1356.

Excellent review of CIDP representing the latest knowledge in the field.

11. Kissel JT: **The treatment of chronic inflammatory demyelinating polyneuropathy.** *Semin Neurol* 2003, **23:**169–179.
12. Dyck PJ, O'Brien PC, Oviatt KF, *et al.*: **Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment.** *Ann Neurol* 1982, **11:**136–141.
13. Dyck PJ, Daube J, O'Brien P, *et al.*: **Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy.** *N Engl J Med* 1986, **314:**461–465.
14. Van Doorn PA, Vermeulen M, Brand A, *et al.*: **Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy.** *Arch Neurol* 1991, **48:**217–220.
15.•• Lopate G, Pestronk A, Al-Lozi M: **Treatment of chronic inflammatory demyelinating polyneuropathy with high-dose intermittent intravenous methylprednisolone.** *Arch Neurol* 2005, **62:**249–254.

This 2005 study provides evidence that intermittent intravenous corticosteroids are as effective as daily oral corticosteroids, but result in fewer complications. This article has the potential to change current treatment of CIDP.

16. Gorson KC, Amato AA, Ropper AH: **Efficacy of mycophenolate mofetil in patients with chronic immune demyelinating polyneuropathy.** *Neurology* 2004, **63:**715–717.
17. Mowzoon N, Sussman A, Bradley WG: **Mycophenolate (CellCept) treatment of myasthenia gravis, chronic inflammatory polyneuropathy and inclusion body myositis.** *J Neurol Sci* 2001, **185:**119–122.
18. Dyck PJ, O'Brien P, Swanson C, *et al.*: **Combined azathioprine and prednisone in chronic inflammatory demyelinating polyneuropathy.** *Neurology* 1985, **35:**1173–1176.
19. Barnett MH, Pollard JD, Davies L, McLeod JG: **Cyclosporin A in resistant chronic inflammatory demyelinating polyradiculoneuropathy.** *Muscle Nerve* 1998, **21:**454–460.
20. Mahattanakul W, Crawford TO, Griffin JW, *et al.*: **Treatment of chronic inflammatory demyelinating polyneuropathy with cyclosporine-A.** *J Neurol Neurosurg Psychiatry* 1996, **60:**185–187.
21. Briani C, Zara G, Zambello R, *et al.*: **Rituximab-responsive CIDP.** *Euro J Neurol* 2004, **11:**788–791.
22. Meriggioli MN, Rowin J: **Chronic inflammatory demyelinating polyneuropathy after treatment with interferon-alpha.** *Muscle Nerve* 2000, **23:**433–435.
23. Hadden RD, Sharrack B, Bensa S, *et al.*: **Randomized trial of interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy.** *Neurology* 1999, **53:**57–61.
24.•• Stern BJ: **Neurological complications of sarcoidosis.** *Curr Opin Neurol* 2004, **17:**311–316.

A comprehensive, yet succinct, review of neurosarcoidosis, its presentation, and treatment.

25. Shah JR, Lewis RA: **Sarcoidosis of the cauda equina mimicking Guillain-Barré syndrome.** *J Neurol Sci* 2003, **208:**113–117.
26. Zuniga G, Ropper AH, Frank J: **Sarcoid peripheral neuropathy.** *Neurology* 1991, **41:**1558–1561.
27. Ferriby D, de Seze J, Stojkovic T, *et al.*: **Long-term follow-up of neurosarcoidosis.** *Neurology* 2001, **57:**927–929.
28. Said G, Lacroix C, Planté-Bordeneuve V, *et al.*: **Nerve granulomas and vasculitis in sarcoid peripheral neuropathy: a clinicopathological study of 11 patients.** *Brain* 2002, **125:**264–275.
29. Hoitsma E, Faber CG, Drent M, Sharma OP: **Neurosarcoidosis: a clinical dilemma.** *Lancet Neurol* 2004, **3:**397–407.
30. Doty JD, Mazur JE, Judson MA: **Treatment of corticosteroid-resistant neurosarcoidosis with a short course cyclophosphamide regimen.** *Chest* 2003, **124:**2023–2026.
31. Sollberger M, Fluri F, Baumann T, *et al.*: **Successful treatment of steroid-refractory neurosarcoidosis with infliximab.** *J Neurol* 2004, **251:**760–761.
32. Heaney D, Geddes JF, Nagendren K, Swash M: **Sarcoid polyneuropathy responsive to intravenous immunoglobulin.** *Muscle Nerve* 2004, **29:**447–450.
33. Stern BJ, Schofeld SA, Sewell C, *et al.*: **The treatment of neurosarcoidosis with cyclosporine.** *Arch Neurol* 1992, **49:**1065–1072.
34. Pettersen JA, Zochodne DW, Bell RB, *et al.*: **Refractory neurosarcoidosis responding to infliximab.** *Neurology* 2002, **59:**1660–1661.
35. Sharma OP: **Effectiveness of chloroquine and hydroxychloroquine in treating selected patients with sarcoidosis with neurological involvement.** *Arch Neurol* 1998, **55:**1248–1254.
36. Bruns F, Pruemer B, Haverkamp U, Fischedick AR: **Neurosarcoidosis: an unusual indication for radiotherapy.** *Br J Radiol* 2004, **77:**777–779.
37.• Kuntzer T, Antoine J-C, Steck AJ: **Clinical features and pathophysiological basis of sensory neuronopathies (ganglionopathies).** *Muscle Nerve* 2004, **30:**255–268.

A detailed presentation of the ganglionopathies useful for anyone treating patients with these disorders.

38.•• Donofrio PD: **Immunotherapy of idiopathic inflammatory neuropathies.** *Muscle Nerve* 2003, **28:**273–292.

A detailed, comprehensive review of the inflammatory neuropathies with information on the history, pathophysiology, clinical findings, and treatment of each disorder.

39. Gorson KC, Ropper AH: **Positive salivary gland biopsy, Sjögren syndrome, and neuropathy: clinical implications.** *Muscle Nerve* 2003, **28:**553–560.
40. Font J, Ramos-Casals M, de la Red G, *et al.*: **Pure sensory neuropathy in primary Sjögren's syndrome. Long-term prospective followup and review of the literature.** *J Rheumatol* 2003, **30:**1552–1557.
41. Molina JA, Benito-Leon J, Bermejo F, *et al.*: **Intravenous immunoglobulin therapy in sensory neuropathy associated with Sjögren's syndrome.** *J Neurol Neurosurg Psychiatry* 1996, **60:**699.
42. Pascual J, Cid C, Berciano J: **High-dose IV immunoglobulin for peripheral neuropathy associated with Sjögren's syndrome.** *Neurology* 1998, **51:**650–651.
43. Chen WH, Yeh JH, Chiu HC: **Plasmapheresis in the treatment of ataxic sensory neuropathy associated with Sjögren's syndrome.** *Eur Neurol* 2001, **45:**270–274.
44. Asahina M, Kuwabara S, Asahina M, *et al.*: **D-Penicillamine treatment for chronic sensory ataxic neuropathy associated with Sjögren's syndrome.** *Neurology* 1998, **51:**1451–1453.
45. Yamada S, Mori K, Matsuo K, *et al.*: **Interferon alfa treatment for Sjögren's syndrome associated neuropathy.** *J Neurol Neurosurg Psychiatry* 2005, **76:**576–578.
46. Latov N, Hays AP, Sherman WH: **Peripheral neuropathy and anti-MAG antibodies.** *Crit Rev Neurobiol* 1988, **3:**301–332.
47. Blume G, Pestronk A, Goodnough LT: **Anti-MAG neuropathy associated polyneuropathies: improvement following immunotherapy with monthly plasma exchange and IV cyclophosphamide.** *Neurology* 1995, **45:**1577–1580.

48. Isoardo G, Migliaretti G, Ciaramitaro P, *et al.*: **Differential diagnosis of chronic dysimmune demyelinating polyneuropathies with and without anti-MAG antibodies.** *Muscle Nerve* 2005, **31:**52–58.

49.•• Gorson KC, Ropper AH, Weinberg DH, Weinstein R: **Treatment experience in patients with anti-myelin-associated glycoprotein neuropathy.** *Muscle Nerve* 2001, **24:**778–786.

Noteworthy case series of 24 patients that reports patients' responses to various immunotherapies.

50. Czaplinski A, Steck AJ: **Immune mediated neuropathies: an update on therapeutic strategies.** *J Neurol* 2004, **251:**127–137.

51. Rodriguez JN, Fernandez-Jurado A, Martino ML, Prados D: **Waldenström's macroglobulinemia complicated with acute myeloid leukemia. Report of a case and review of the literature.** *Haemetologica* 1998, **83:**91–92.

52. Wilson HC, Lunn MP, Schey S, Hughes RA: **Successful treatement of IgM paraproteinemic neuropathy with fludarabine.** *J Neurol Neurosurg Psychiatry* 1999, **66:**575–580.

53. Dimopoulos MA, Zervas C, Zomas A, *et al.*: **Treatment of Waldenström's macroglobulinemia with rituximab.** *J Clin Oncol* 2002, **20:**2037–2333.

54. Renaud S, Gregor M, Fuhr P, *et al.*: **Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies.** *Muscle Nerve* 2003, **27:**611–615.

55.•• Oh SJ, Gürtekin Y, Dropcho EJ, *et al.*: **Anti-Hu antibody neuropathy: a clinical, electrophysiological, and pathological study.** *Clin Neurophys* 2005, **116:**28–34.

This clinical and electrophysiological study of 16 patients with anti-Hu antibody neuropathy provides the latest information on the presentation and outcome of anti-Hu neuropathy.

56. Smitt PS, Grefkens J, de Leeuw B, *et al.*: **Survival and outcome in 73 anti-Hu positive patients with paraneoplastic encephalomyelitis/sensory neuronopathy.** *J Neurol* 2002, **249:**745–753.

57. Molinuevo JL, Graus F, Serrano C, *et al.*: **Utility of anti-Hu antibodies in the diagnosis of paraneoplastic sensory neuropathy.** *Ann Neurol* 1998, **44:**976–980.

58. Oh SJ, Dropcho EJ, Claussen GC: **Anti-Hu associated paraneoplastic sensory neuronopathy responding to early aggressive immunotherapy: report of two cases and review of literature.** *Muscle Nerve* 1997, **20:**1576–1582.

59. Keime-Gubert F, Grgaus F, Fleury A, *et al.*: **Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (anti-Hu, Anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone.** *J Neurol Neurosurg Psychiatry* 2000, **68:**479–482.

60. Said G, Lacroix C: **Primary and secondary vasculitic neuropathy.** *J Neurol* 2005, **252:**633–641.

61. Pagnoux C, Guillevin L: **Peripheral neuropathy in systemic vasculitides.** *Curr Opin Rheumatol* 2004, **17:**41–48.

62. Olney RK: **Neuropathies associated with connective tissue disease.** *Semin Neurol* 1998, **18:**63–72.

63. Omdal R, Løseth S, Torbergsen T, *et al.*: **Peripheral neuropathy in systemic lupus erythematosus – a longitudinal study.** *Acta Neurol Scand* 2001, **103:**386–391.

64. Puechal X, Said G, Hilliquin P, *et al.*: **Peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis A clinicopathologic and prognostic study of thirty-two patients.** *Arthritis Rheum* 1995, **38:**1618–1629.

65. Guillevin L, Cohen P, Mahr A, *et al.*: **Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognostic factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients.** *Arthritis Rheum* 2003, **49:**93–100.