Chronic Immune-Mediated Polyneuropathies

Stephen Zachary Cox, DO, Kelly G. Gwathmey, MD*

KEYWORDS

• CIDP • Multifocal motor neuropathy
• Multifocal acquired sensory and motor polyneuropathy • Vasculitic neuropathy

KEY POINTS

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) typically presents with progressive generalized weakness and large fiber sensory deficit.
- CIDP is a treatable neuropathy and responds to intravenous immune globulins, subcutaneous immune globulins, corticosteroids, and plasma exchange in most cases.
- Vasculitic neuropathies present with painful, progressive, sensory, and motor mononeuropathies.
- Failure to identify and treat chronic immune-mediated polyneuropathies may result in significant disability and even death.

INTRODUCTION

Immune-mediated chronic polyneuropathies include a diverse group of diseases that can vary widely in clinical presentation and pathophysiology. For those patients affected, these diseases represent a significant source of disability, often requiring lifelong therapy to prevent significant complications. This article focuses first on chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and its variants, followed by vasculitic neuropathies, both systemic and nonsystemic with attention to clinical presentation, initial workup, pathophysiology, and treatment options. This discussion does not include other microvasculitic processes such as diabetic and nondiabetic lumbosacral radiculoplexus neuropathies. Other chronic inflammatory neuropathies associated with rheumatological disorders and systemic inflammatory diseases are briefly highlighted in **Table 1**.

Department of Neurology, Virginia Commonwealth University, 1101 East Marshall Street, PO Box 980599, Richmond, VA 23298, USA
* Corresponding author.
E-mail address: Kelly.gwathmey@vcuhealth.org

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Table 1
Other causes of chronic immune-mediated polyneuropathies

Connective Tissue Diseases			
• Sjögren Syndrome	• SFN • Sensory ataxic neuropathy (ie, sensory neuronopathy or dorsal root ganglionopathy) • Sensorimotor axonal polyneuropathy • Demyelinating polyneuropathy • Vasculitic neuropathy • Polyradiculoneuropathy • Autonomic neuropathy	• ANA • Anti-SSA, anti-SSB antibodies • Anticentromere antibodies • Schirmer test, Rose Bengal testing (ocular surface staining), salivary flow study, labial salivary gland biopsy if indicated	• Consider IVIg for SFN,[60,61] sensory ataxic neuropathy,[62] demyelinating neuropathy, sensorimotor neuropathy, and autonomic neuropathy[63] • Corticosteroid benefit unclear although may be helpful in large fiber neuropathies, sensory ataxic neuropathies (with IVIg)[62] • Rituximab often considered if IVIg refractory[63–65] • Other treatments used: mycophenolate mofetil, azathioprine, cyclophosphamide, tacrolimus, plasma exchange
• Systemic Lupus Erythematosus	• Large fiber sensory polyneuropathy • SFN • Vasculitic neuropathy	• ANA • Anti–double stranded DNA • Anti-Smith antibodies • Antiphospholipid antibodies • C3 and C4 or CH50 complement levels • ESR • CRP • Urine protein-to-creatinine ratio	• Corticosteroids for large fiber neuropathy[66,67] • Other agents used: azathioprine, cyclophosphamide, mycophenolate mofetil • Treatment of SFN unknown
• Rheumatoid Arthritis	• Large fiber sensory or sensorimotor polyneuropathy • Mononeuropathy (eg, carpal tunnel syndrome) • Vasculitic neuropathy	• Joint involvement as per 2010 ACR/EULAR criteria[68] • Rheumatoid factor • Anticitrullinated peptide/protein antibody • ESR • CRP	• Unknown treatment of large fiber polyneuropathy • Splinting, corticosteroid injection, surgical decompression for median mononeuropathy at the wrist (carpal tunnel syndrome) • Glucocorticoids and cyclophosphamide

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Table 1
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			for vasculitic neuropathy[69,70]
• Scleroderma (Systemic Sclerosis)	• Large fiber sensory or sensorimotor polyneuropathy • Mononeuropathy	• ANA • Anti-DNA topoisomerase I (Scl-70) • Anticentromere antibody • Anti-RNA polymerase III antibody	• Unknown treatment of large fiber polyneuropathy • Splinting, corticosteroid injection, surgical decompression for median mononeuropathy
Sarcoidosis	• SFN • Large fiber sensory and sensorimotor polyneuropathy • Polyradiculoneuropathy • Mononeuropathy • Vasculitic neuropathy	• Angiotensin-converting enzyme • Soluble interleukin-2 receptor level • Chest radiograph • Pulmonary function testing • Ophthalmic evaluation with slit lamp • Skin examination and referral to dermatology as needed • Occasionally FDG-PET, Gallium 67 scanning • Tissue biopsy demonstrating noncaseating granulomas	• For SFN, response to standard immunomodulating therapies such as methotrexate and corticosteroids is often poor[71] • IVIg and infliximab may be helpful • For large fiber and multiple mononeuropathies likely corticosteroids are helpful[72–74]
Behcet Disease	• Large fiber sensory or sensorimotor polyneuropathy • Vasculitic neuropathy	• Diagnosis relies on presences of recurrent oral and genital ulcers, anterior or posterior uveitis, retinal vasculitis, skin lesions (pseudofolliculitis, erythema nodosum, papulopustular lesions, acneiform nodules) and positive pathergy test	• Unclear, given the rarity of peripheral nervous system manifestations. • Extrapolating from therapies used in parenchymal involvement, corticosteroids, interferon-α, azathioprine, methotrexate, TNF-α antagonists, and cyclophosphamide could be considered.[75]
Immune-mediated Gastrointestinal Disorders			
• Inflammatory Bowel Disease (Crohn Disease and Ulcerative Colitis)	• Demyelinating polyneuropathy • SFN • Large fiber sensorimotor polyneuropathy	• Small bowel imaging with MRI (Crohn disease) • Endoscopy with mucosal biopsies	• Corticosteroids[76] • IVIg • Plasma exchange

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Table 1
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	• Radiculoplexus neuropathy		
• Celiac Disease	• SFN • Large fiber sensorimotor polyneuropathy	• Antigliadin, antitissue transglutaminase, antiendomysial antibodies • Villous atrophy on small bowel biopsy	• Gluten avoidance[76] • Exclude other causes (vitamin deficiencies) • Mixed results with immunomodulatory therapy

Abbreviations: ANA, antinuclear antibody; anti-SSA, anti-Sjogren syndrome antibody A; anti-SSB, anti-Sjogren syndrome antibody B; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET, fluorodeoxyglucose positron emission tomography; IVIg, intravenous immune globulins; SFN, small fiber neuropathy.

*Although not explicitly stated in Table 1, basic laboratory studies (see **Box 1**) and electrodiagnostic studies should be performed in all patients. Should electrodiagnostic studies be normal, then a skin biopsy looking for reduced intraepidermal nerve fiber density supporting a small fiber neuropathy should be performed. On occasion, autonomic testing is pursued in those with significant dysautonomia or to support a diagnosis of small fiber neuropathy.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

History/Background

CIDP was first described in 1890 by Eichhorst as episodes of "recurrent neuritis" although the term chronic immune demyelinating polyradiculoneuropathy would not be coined until almost a century later.[1] Current estimates of the incidence rate of CIDP is at 0.33 per 100,000 and the prevalence rate at 2.81 per 100,000.[2] Despite its relative rarity it is the most common chronic autoimmune neuropathy. The age of onset of CIDP is variable occurring from childhood to late in adulthood. Even when symptoms do begin at an early age, many patients experience a relapsing/remitting or progressive course that requires lifelong therapy and results in significant disability.

Pathophysiology

CIDP is the result of the immune-mediated destruction of peripheral nerve myelin. The exact mechanisms by which this occurs are not yet fully understood but likely comprise a mixture of cellular and humoral immunity.[3] T-cell and macrophage infiltration is seen on biopsy with phagocytosis of peripheral nerve myelin.[4,5] Consequently, heavily myelinated peripheral nerves are the most affected in this condition.

Presentation and Examination Findings

CIDP is characterized by insidious onset, symmetric, generalized weakness, and large fiber sensory dysfunction. Patients often develop a sensory ataxia due to the involvement of proprioceptive fibers. Other symptoms include neuropathic pain, postural tremor as well as significant fatigue although weakness should be the predominate feature of the disease.[6,7] Examination reveals symmetric weakness, both proximal and distal, diminished vibratory and proprioceptive sensation, and perhaps most importantly the depression or altogether absence of deep tendon reflexes. Patients may have a monophasic, relapsing/remitting, or chronically progressive course.

Several characteristics help distinguish CIDP from Guillain-Barré syndrome (GBS), a condition similar in pathogenesis and presentation. Unlike GBS, a prodromal illness is

Box 1
Recommended laboratory studies for those with suspected immune-mediated polyneuropathies

Initial Serum Laboratory Studies
- Complete blood count with differential
- Basic metabolic panel
- Liver function tests
- Hemoglobin A1c or glucose tolerance test
- Thyroid function tests
- B12, methylmalonic acid
- Serum and urine electrophoresis
- Immunofixation
- Serum light chains
- ESR and CRP
- Hepatitis serologies
- Antinuclear antibodies
- Antineutrophil cytoplasmic antibodies
- Rheumatoid factor

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

not a defining feature of CIDP. The timing surrounding onset and nadir of symptoms is a key factor in differentiating CIDP from GBS. Patients with CIDP reach the nadir of their sensory and motor symptoms at or after 8 weeks following symptom onset. The initiation of symptoms tends to be more gradual as well, although a subset of patients will have an abrupt onset and are termed acute-onset CIDP or A-CIDP.[8] Cranial nerve, bulbar involvement, and autonomic disturbance are more common in GBS as opposed to CIDP.

Evaluation

Although the clinical presentation and examination should strongly support the diagnosis of CIDP, further investigation may be warranted, including serum, cerebrospinal fluid (CSF), electrodiagnostic, imaging, and rarely histopathology. Initial serum laboratories should be performed to exclude alternative causes. For a list of appropriate initial laboratory testing in all suspected immune-mediated polyneuropathies please refer to **Box 1**. The presence of a monoclonal gammopathy or other paraprotein disorder may prompt further testing, which is discussed in Leavell and Shin's article, "Paraproteinemias and Peripheral Nerve Disease," in this issue.

CSF studies can often be deferred in straightforward cases of CIDP. If obtained, the most common finding is albuminocytological dissociation (elevated protein in setting of a normal leukocyte count). The sensitivity of this finding is traditionally quite high at 95%, although there is recent evidence to suggest that increasing the protein upper limit of normal value may improve specificity at a modest cost to sensitivity[9]. Alternative diagnoses should be considered if CSF studies reveal a pleocytosis.

Electrodiagnostic studies including nerve conduction studies and electromyography are mandatory to confirm a diagnosis of CIDP. Electrodiagnostic studies show evidence of slowed conduction velocities, conduction block, temporal dispersion, prolonged distal latencies, as well as prolonged or absent F waves and H reflexes. All of these findings are consistent with a peripheral demyelinating process. CIDP variants may have unique electrodiagnostic features. **Table 2** reviews the clinical presentation, diagnosis, and treatment of the CIDP variants.

Table 2
Chronic inflammatory demyelinating polyradiculoneuropathy variants

	Clinical Features	Electrodiagnostic Studies	Treatment	Other
Sensory CIDP	Symmetric sensory loss without clinical weakness, early upper extremity involvement, cranial nerve involvement[77]	• Studies typically show evidence of motor nerve involvement[78]	• Corticosteroids • IVIg • Plasma exchange	• May go on to develop weakness and typical CIDP
Motor CIDP	Symmetric weakness with absence of sensory symptoms	• Can completely spare sensory nerves or may have mild evidence of sensory nerve involvement	• Poor response to steroids[79] • Can use IVIg or plasma exchange	• May represent a spectrum including multifocal motor neuropathy
Distal Acquired Demyelinating Sensory Neuropathy (DADS)	Distal sensory loss resulting in ataxia and mild distal motor involvement May have action tremor	• Disproportionate slowing of distal motor conduction velocity, no conduction block, and absent sural responses[80]	• Poor response to IVIg, plasma exchange, and corticosteroids in the presence of MAG antibodies • Possibly responsive to rituximab[19]	• Often associated with IgM monoclonal gammopathy and MAG antibodies
Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM)	Multifocal, asymmetrical motor and sensory involvement, which may include cranial neuropathies[20]	• Similar to typical CIDP	• Corticosteroids • IVIg • Plasma exchange	• Almost 50% will progress to typical CIDP • Also known as Lewis-Sumner syndrome
Chronic Immune Sensory Polyneuropathy (CISP)	Similar presentation to sensory CIDP with prominent sensory ataxia	• Normal nerve conduction studies[81] • Somatosensory evoked potentials will be abnormal	• Corticosteroids • IVIg	• MRI may demonstrate enlarged, contrast-enhancing nerve roots • CSF analysis may demonstrate elevated protein • Considered a subclassification of sensory CIDP

Abbreviations: CISP, chronic immune sensory polyneuropathy; DADS, distal acquired demyelinating sensory neuropathy; IVIg, intravenous immune globulins; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MAG, myelin-associated glycoprotein.

Imaging is not routinely performed in the evaluation of CIDP although certain abnormalities may support the diagnosis. Enlargement of peripheral nerves, nerve roots, and plexuses with contrast enhancement may be seen on MRI.[10] Focal enlargement of peripheral nerves, particularly in the early stages of disease, may appear on ultrasound.

Nerve biopsy is very rarely undertaken if the suspected diagnosis is CIDP, as the clinical presentation and electrodiagnostic testing are usually sufficient to make the diagnosis. However, in atypical presentations that do not clearly fit into established categories, biopsy may be required. The hallmark histopathologic findings on nerve biopsy are evidence of chronic demyelination and remyelination resulting in an onion bulb appearance along with epineurial, endoneurial, or perivascular macrophage and T cell infiltration (**Fig. 1**).[4]

Treatment

First-line therapy for CIDP includes intravenous or subcutaneous immunoglobulin (IVIg and SCIg, respectively), plasma exchange, and corticosteroids. Treatment is generally conducted in a 2-fold approach with an induction phase followed by maintenance therapy. Response varies individually particularly between CIDP variants as discussed in **Table 2**. Overall response rate is 50% to 70%.[11] Medical comorbidities, severity of disease, patient preferences, and response to treatment help guide therapeutic choices. Response can be measured in a variety of ways. Muscle strength, particularly grip strength, as measured on examination is a useful metric commonly used. There exist standardized scales such as the Inflammatory Neuropathy Cause and Treatment disability score as well as the more recent Inflammatory Rasch-built Overall Disability Scale. These measures, coupled with patient-reported quality of life measures, help build a more comprehensive picture for providers to judge success of therapies.

IVIg is a mainstay of CIDP treatment both for induction and maintenance therapy and received Food and Drug Administration (FDA) approval for this indication in 2008. Induction therapy is dosed at 2 g/kg divided over 2 to 5 days. There is currently no clear evidence for optimal maintenance dosing but typically a dose of 1 g/kg every 3 weeks is used after initial induction.[12] A full 6 weeks should be given to assess response to therapy before alternative therapies are considered.[13] Dosing considerations for continued maintenance should be made with treatment response in mind and weaning the frequency of administration as well as the dose received with each infusion is reasonable provided symptoms remain stable. A recent alternative to IVIg was approved by the FDA in 2018 in the form of SCIg, which offers patients the option of self-administering the subcutaneous form on a weekly basis rather than having to go to an infusion center. SCIg has been found to be comparable to IV formulation in prevention of relapses although onset of improvement may lag in treatment-naïve patients.[14,15] Side effects of Ig therapy include headache, nausea, fatigue, and increased risk of thrombotic events. Many of these side effects can be mitigated simply by slowing the infusion rate or decreasing the concentration of the agent being used. If necessary, premedication based on the type and severity of the reaction can be considered and may include acetaminophen, diphenhydramine, or IV corticosteroids.

Plasma exchange has shown equal efficacy when compared with IVIg, and therapy is carried out in a similar fashion with induction phase followed by maintenance dosing.[16] Induction is carried out in 5 to 10 exchanges of 50 mL/kg alternating days during the first 2 to 4 weeks, followed by 1 to 2 exchanges monthly or even as frequent as every 3 weeks. Because there is no active medication being administered, it is generally well tolerated. However, as dialysis, patients can have complications based around the large amount of fluid shifts with treatments. Permanent central venous

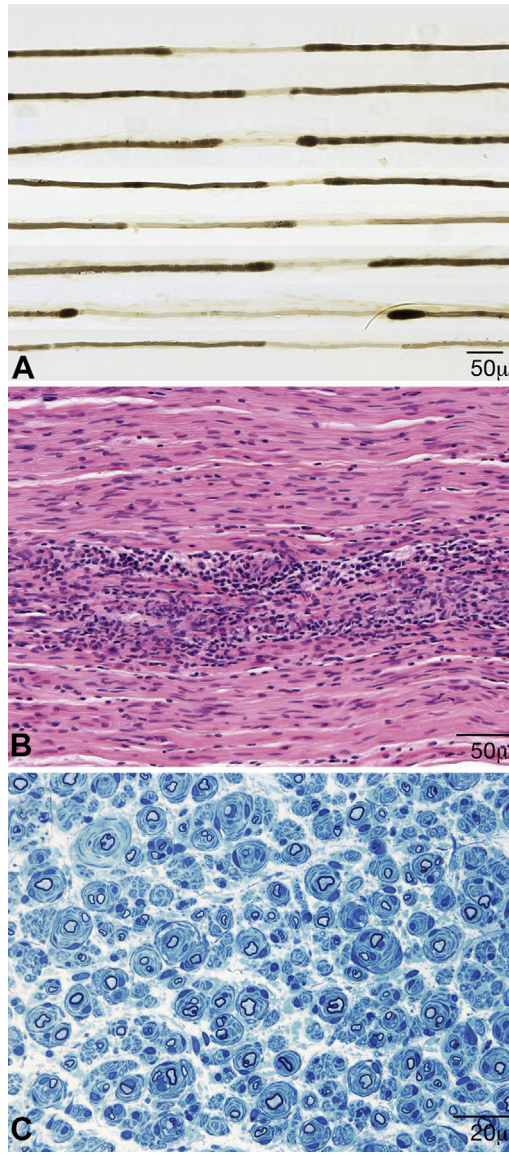

Fig. 1. Chronic inflammatory demyelinating polyradiculoneuropathy. (*A*) Teased fiber preparations from a sural nerve showing multiple segments of segmental demyelination. (*B*) Longitudinal paraffin section (stained with hematoxylin and eosin) from a sciatic biopsy showing large endoneurial perivascular mononuclear cell infiltration. (*C*) Epoxy cross-section (stained with methylene blue) from the sural nerve showing widespread hypertrophic neuropathy with onion-bulb formation (stacks of Schwann cell cytoplasmic processes) and thin myelin. (Reused with permission from Mayo Clin Proc. 2018 Jun;93(6):777-793.)

access is required and can present its own set of challenges and complications. These issues, coupled with the frequency of maintenance therapy, tend to relegate plasma exchange to those patients who have failed or could not tolerate therapy with Ig.

Corticosteroids are used as induction therapy and, if possible, avoided for maintenance given the significant adverse effects associated with chronic use. Multiple options both in dosing and agent can be considered. Oral prednisone at a dose of 1 to 1.5 mg/kg every 24 to 48 hours, IV methylprednisolone weekly, or oral dexamethasone, 40 mg, for 4 days repeated every 4 weeks can all be considered and have been shown to have equal efficacy and safety.[17] Patients with refractory disease or who cannot tolerate other therapies may require long-term steroid treatment. Steroid-sparing agents are often considered in these cases; unfortunately, data backing the efficacy of many of these medications are lacking.[18]

If a patient is refractory to these 3 therapeutic options, reevaluation is warranted to exclude another diagnosis provided they have received an adequate trial. As mentioned earlier IVIg should be allowed 6 weeks to assess response. Plasma exchange and corticosteroids tend to have more rapid onset although again induction for plasma exchange may take place over 4 weeks. The decision to switch therapy should also be weighed with the clinical picture of the patient in mind. More aggressive disease may require more frequent reconsideration of therapeutic options.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy Variants

Distal acquired demyelinating symmetric neuropathy (DADS) is a CIDP variant characterized by, as the name implies, a distally predominant, symmetric sensory and motor neuropathy. Sensory symptoms tend to predominant often resulting in an ataxia, and when motor symptoms are present, they are typically mild and involve the distal lower extremities. DADS is associated with anti–myelin-associated glycoprotein antibodies and a high rate of IgM monoclonal gammopathy (reference paraprotein disorders and peripheral nerve disease). This may correspond to its relative refractory nature to traditional first-line agents. Rituximab may offer benefit.[19]

Multifocal acquired demyelinating sensory and motor neuropathy, otherwise known as Lewis-Sumner syndrome, is another CIDP variant distinct in its asymmetric presentation. Similar to traditional CIDP, both motor and sensory nerve involvement is present although symptoms predominate in upper extremities.[20] Cranial nerve involvement can also be seen. Nearly half of the patients will progress to CIDP.

There are many other variants of CIDP, including those with varying degrees of sensory or motor symptoms. Treatment approach is overall similar to traditional CIDP with some notable exceptions. Although treatment is the same, response to therapy can differ between variants. Please refer to **Table 2** for a list of variants along with associated presentations, electrophysiologic findings, and treatment options.

Multifocal Motor Neuropathy and Nodo-Paranodopathies

Nodo-paranodopathies may present similarly to CIDP, but underlying pathophysiology is not a demyelinating process but rather the production of antibodies to targets on or near the Nodes of Ranvier.[21] One such entity is multifocal motor neuropathy (MMN), a disorder that until recently was characterized as a CIDP variant until its pathophysiology was more clearly understood.[22] MMN is a result of autoantibodies to ganglioside GM1, which tends to be concentrated at peripheral motor nerve nodes.[23] It is characterized by the presence of multiple motor mononeuropathies in an asymmetric, distal-predominant pattern with the presence of fasciculations and cramping. First-line treatment is IVIG, and MMN is known for its poor response to plasma exchange and corticosteroids.[12] There exist now multiple other identified antigens that serve as autoimmune targets at or adjacent to peripheral nerve nodes. These include contactin-1, contactin-associated protein-1, and neurofascin-155.[24] As with MMN,

treatment response differs from traditional CIDP, and other therapeutic options such as rituximab or cyclophosphamide may be considered.[25,26]

VASCULITIC NEUROPATHIES

Background/Definitions

Regardless of the underlying cause, vasculitic neuropathies result from inflammatory infiltration of the vasa nervorum, the blood vessels that supply the peripheral nerves. The resulting ischemic injury of the peripheral nerves results in pain, weakness, and numbness. Several vasculitic neuropathy classification systems exist, which catalog these disorders in terms of size of the affected vessels and underlying cause.[27] These neuropathies may be associated with primary systemic vasculitis, in which vasculitis affects multiple organs without alternative autoimmune cause (eg, eosinophilic granulomatosis with polyangiitis). Vasculitic neuropathies may also be secondary to underlying rheumatological conditions, malignancy, infections, or rarely drug exposure. When the inflammation is restricted to the peripheral nerves it is considered nonsystemic vasculitic neuropathy (NSVN). Please see **Table 3** for a list of the underlying causes of vasculitic neuropathies.

Presentation and Examination Findings

The archetypal presentation with vasculitic neuropathies is that of mononeuritis multiplex characterized by acute to subacute painful sensorimotor mononeuropathies (eg, painful wrist drop due to radial mononeuropathy, followed by painful foot drop from common fibular mononeuropathy). These mononeuropathies occur in a nonlength-dependent, asymmetrical pattern, although often eventually overlap, conforming to a distal symmetric or asymmetrical polyneuropathy pattern. Taking a careful history and obtaining an account of multiple painful mononeuropathies is imperative. Those with systemic vasculitic neuropathy typically have a stepwise progression, whereas those with NSVN may progress more slowly, resulting in diagnostic delay. In those with systemic vasculitis, involvement of other organs, such as the lungs, skin, kidneys, and gastrointestinal tract, is expected. In addition, constitutional symptoms are commonplace, including weight loss, fatigue, arthralgias, and myalgias. These symptoms, however, are rarely encountered when the vasculitis is isolated to the peripheral nerves.

Evaluation

In any patient with suspected vasculitic neuropathy, a comprehensive panel of laboratory studies must be completed (see **Box 1**). If the patient has an erythrocyte sedimentation rate (ESR) greater than 100 mm/h and antineutrophil cytoplasmic antibody (ANCA) positivity, this highly suggests primary systemic vasculitic neuropathy.[28] Mildly elevated ESR may also be encountered in NSVN in approximately 70% of cases.[29]

Electrodiagnostic testing serves several important roles in the evaluation of those with suspected vasculitic neuropathy. Identification of a multiple mononeuropathies or asymmetrical axonal sensorimotor polyneuropathy is highly consistent with vasculitic neuropathy in the appropriate clinical setting.[30] Also, electrodiagnostic studies may guide nerve and muscle biopsy.

A clinical suspicion of vasculitic neuropathy is one of the few indications for cutaneous nerve biopsy, and it is often mandatory in this context. Any affected cutaneous sensory nerve can be biopsied, although the sural, superficial radial, and superficial fibular are the most common. It is generally recommended to concurrently biopsy a

Table 3
Common vasculitic neuropathies

Cause of Vasculitic Neuropathy	Comments
Primary Systemic Vasculitides	
Predominantly Small Vessel Vasculitis	
Microscopic polyangiitis	• Organs involved include lungs, kidneys, skin, and abdominal pain • Commonly associated with ANCAs (MPO > PR3) • Neuropathy prevalence 40%–50%[34]
Granulomatosis with polyangiitis	• Granulomatous infiltration of the upper and lower respiratory tracts • May have kidney involvement • Commonly associated with ANCAs (PR3> MPO) • Neuropathy prevalence 15%–25%[82]
Eosinophilic granulomatosis with polyangiitis	• Associated with asthma, blood eosinophilia, paranasal sinus abnormalities, extranasal eosinophil infiltration, fleeting pulmonary infiltrates • Commonly associated with ANCAs (MPO > PR3) • Neuropathy prevalence 60%–70%[83–85]
Predominantly Medium Vessel Vasculitis	
Polyarteritis nodosa	• Frequently triggered by hepatitis B • Often skin involvement, renal involvement (renal artery aneurysms, hypertension), abdominal pain • Prevalence of neuropathy 75%[86]
Secondary Systemic Vasculitides	
Connective Tissue Disease	
Rheumatoid arthritis	• Late manifestation of severe seropositive rheumatoid arthritis • Neuropathy present in 40%–50% of rheumatoid vasculitis[69,87]
Systemic lupus erythematosus	
Sjögren syndrome	• Associated with sicca symptoms • Associated with positive anti-SSA or anti-SSB antibodies, positive antinuclear antibody • Evidence of lymphocytic infiltrates on salivary gland biopsy • Vasculitis is only one of many peripheral nerve manifestations in Sjögren
Infection	
Hepatitis C and cryoglobulinemia	• Associated symptoms include purpura, glomerulonephritis, ulceration, arthritis, and sicca symptoms[54] • Incidence of neuropathy is 65%[58,88–92]
Hepatitis B and polyarteritis nodosa	• Relatively rare with advent of hepatitis B vaccine
HIV	• Rare cause of vasculitic neuropathy
Drugs	• Associated with tumor necrosis factor inhibitors, minocycline, checkpoint inhibitors, and cocaine[93]
Malignancy	• Relatively rare • Associated with anti-Hu antibodies • Associated with lymphoma and small cell lung cancer

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Table 3
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Cause of Vasculitic Neuropathy	Comments
Nonsystemic vasculitic neuropathy	• Likely the most common form of vasculitic neuropathy • May be more gradually progressive • Not fatal

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; HIV, human immunodeficiency virus; MPO, myeloperoxidase; PR3, proteinase 3; SSA, Sjögren syndrome–associated A; SSB, Sjögren syndrome–associated B.

piece of muscle, as it increases diagnostic yield to 60% to 70%.[31,32] Nerve biopsy is vital to secure the diagnosis in NSVN, whereas it can be avoided in primary systemic vasculitides if diagnostic biopsy of another organ has already occurred.

Some experts classify vasculitic neuropathies by the size of the involved vessels into either nerve large arteriole vasculitis or microvasculitis.[33] Nerve large arteriole vasculitis is present in most primary systemic and secondary systemic vasculitic neuropathies, whereas microvasculitis is often associated with NSVN and occasionally Sjögren syndrome–associated vasculitic neuropathy. Nerve large arteriole vasculitis affects vessels ranging from 75 to 300 μm and is characterized by fibrinoid necrosis of the tunica media and intima (**Fig. 2**).[34] In contrast, microvasculitis targets smaller vessels, typically less than 40 μm in diameter, including the small arterioles, capillaries, and venules. Other common histopathological features, regardless of the underlying cause, include Wallerian degeneration, perineurial thickening, neovascularization, hemosiderin-laden macrophages, and deposits of complement, fibrinogen, and IgM in the vessel walls.[28,35–40]

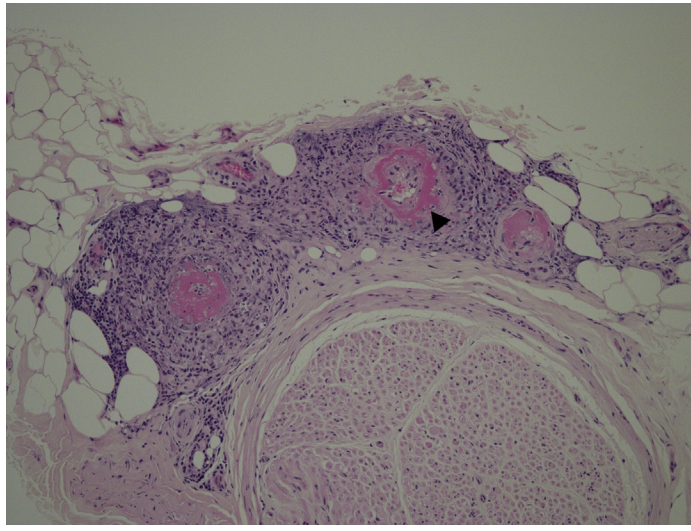

Fig. 2. Vasculitic neuropathy. Transverse paraffin section of the sural nerve demonstrating large arteriole vasculitis (hematoxylin and eosin stain). Fibrinoid necrosis is appreciated in all 3 vessels (*arrowhead*) as well as transmural inflammatory infiltration.

Treatment

The treatment approach to vasculitic neuropathy is dictated by the underlying cause. As systemic vasculitis can be deadly, aggressive treatment should be initiated promptly. Induction therapy with corticosteroids (1 mg/kg day of prednisone, occasionally preceded by several days of 1 g of IV methylprednisolone) is used for 6 to 8 weeks before a tapering.[41,42] To supplement corticosteroids, cyclophosphamide or rituximab (especially with ANCA-associated vasculitis [AAV]) may be used.[43–45] In those with AAV and milder symptoms, methotrexate may be used with corticosteroids.[46,47] Following induction therapy, maintenance therapy is achieved with oral, steroid sparing immunosuppressants such as azathioprine or methotrexate for 18 to 24 months.[48]

NSVN, although not fatal, still carries risk of permanent neurologic deficits. Experts now recommend combination therapy (corticosteroids with either cyclophosphamide or methotrexate). Rituximab may be used as the first-line alternative therapy for severe NSVN.[49]

The virus-associated vasculitic neuropathies (hepatitis C–associated cryoglobulinemia, hepatitis B–associated polyarteritis nodosa, and human immunodeficiency virus) have historically been managed with antiviral therapy. There is emerging evidence, however, that concomitant immunosuppressant or immunomodulatory therapies such as plasma exchange, rituximab, and corticosteroids may be indicated in advanced disease.[50–59]

Although addressing the neuropathic pain in vasculitic neuropathies does not alter disease trajectory, it is a cornerstone of comprehensive management. Please see Pedowitz and colleagues' article, "Management of Neuropathic Pain in the Geriatric Population," in this issue for details.

SUMMARY

The chronic immune-mediated polyneuropathies are a wide spectrum of autoimmune conditions ranging from those solely affecting the peripheral nervous system (ie, CIDP and NSVN) to those associated with systemic inflammatory conditions (eg, ANCA-associated vasculitis, sarcoidosis, or Sjögren syndrome). Much is still being discovered about these conditions and, as a result, classifications remain somewhat fluid. These polyneuropathies are characterized by their varied, unique clinical presentations. A familiarity with these disorders enables the provider to initiate the appropriate diagnostic evaluation and treatment, whereas failure to identify these conditions may result in permanent disability and even death.

CLINICS CARE POINTS

- CIDP is a demyelinating polyneuropathy characterized by symmetric, generalized sensory and motor dysfunction with areflexia on examination often with relapsing, remitting, or progressive course.
- Diagnosis is made from careful history, neurologic examination, electrodiagnostic studies, and rarely nerve biopsy.
- First-line treatment of CIDP includes corticosteroids, IVIg, and plasma exchange.
- There are many CIDP variants and closely associated conditions such as nodoparanodopathies. Making the correct diagnosis is important for selection of appropriate therapies.
- Vasculitic neuropathies present with painful, progressive sensory and motor mononeuropathies or "mononeuritis multiplex."

- The vasculitic neuropathies may be associated with systemic vasculitis, be secondary to rheumatological conditions, infections, malignancy, or drug exposure, or isolated to the peripheral nervous system (NSVN).
- Diagnosis of vasculitic neuropathies requires taking a thorough history, the neurologic examination, extensive serum studies, electrodiagnostic studies, and often nerve biopsy.
- Treatment of the vasculitic neuropathies is primarily corticosteroids. Often cyclophosphamide, rituximab, and occasionally methotrexate are also used for induction therapy. Maintenance therapy consists of transitioning the patients to oral steroid-sparing agents.

DISCLOSURE

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