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Vasculitic Neuropathies

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The various forms of vasculitis comprise a heterogenous group of disorders that can affect different organ systems and different blood vessel calibers. Many forms of vasculitis share the common feature of frequently affecting the peripheral nervous system. Several schemes aimed at classifying the vasculitides are offered. The purpose of this review is to bring neurologists up to date on the current classification and treatment of the most common forms of vasculitic neuropathy.

Classification

The classification of the vasculitides has become increasingly sophisticated over the past half-century [1–4]. The classification, however, remains complex and still is unsettled. For neurologists, it is helpful to conceptualize the classification in terms of (1) clinical characteristics (eg, systemic or nonsystemic, chronic or acute, or monophasic) and (2) histopathologic features (nerve large arteriole vasculitis or nerve microvasculitis). This construct has limits, however, because any binary classification scheme of vasculitis necessitates dividing what likely is actually a continuum. For example, it is proposed that some cases of nonsystemic vasculitic neuropathy (NSVN) actually are a relatively localized form of (systemic) microscopic polyangiitis (MPA) [5]. With regard to classification based on vessel size, the marked overlap in vessel size involvement among the various vasculitides also must be considered. Nonetheless, the authors believe classification based on clinical and histopathologic features has merit because it allows for a characterization of an individual's vasculitic neuropathy that provides

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information about prognosis and provides a blueprint for treatment and other management.

From a clinical standpoint, vasculitis of nerve needs to be thought of as systemic or nonsystemic. The systemic vasculitides commonly are divided into primary systemic vasculitis, of which there is no known cause, and secondary systemic vasculitis, in which a virus, drug, or connective tissue disease is responsible for vessel wall inflammation [6–8]. Vasculitides are classified further by the kind and size of blood vessels involved, organ involvement, disease associations, underlying mechanisms, and, sometimes, autoantibody profiles [9]. The primary systemic vasculitides most likely to cause vasculitic neuropathy include polyarteritis nodosa (PAN), Wegener's granulomatosis, Churg-Strauss syndrome, and MPA [1,2,7,10]. Of these, MPA is perhaps the one that causes vasculitic neuropathy most commonly [10]. Secondary causes of systemic vasculitis involving peripheral nerves include connective tissue diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosis, and Sjögren's syndrome. For example, RA, which affects 1% to 2% of the population, may evolve into rheumatoid vasculitis in 2% to 15% of patients who have RA, and half of these patients develop neuropathy on a vasculitic basis [11–14]. Mixed type II cryoglobulinemic vasculitis associated with hepatitis C infection is another secondary form of vasculitis. Other viruses associated with vasculitis are HIV and cytomegalovirus. Sarcoidosis affecting nerve also may cause an angiitis [15,16]. Vasculitis that seems confined to the nerve and muscle classically is termed NSVN [5,17–19]. An important distinction between systemic vasculitic neuropathy (SVN) and NSVN is that NSVN usually is not fatal, whereas untreated SVN often is fatal. Early on, it may be difficult to distinguish NSVN from SVN; approximately 10% of cases of initially what seems to be NSVN ultimately become systemic vasculitis [19,20]. For this reason, the evaluation in the early phase for what seems to be NSVN should be no different than that for SVN. Some investigators suggest, however, that NSVN simply is part of a continuum in the spectrum of systemic vasculitis. In favor of this view is the demonstration of clinicopathologic and pathologic similarities between NSVN and MPA. Alternatively, NSVN and MPA differ in age of onset, severity, and presence of antineutrophil cytoplasmic antibody (ANCA) with perinuclear immunofluorescence pattern directed against myeloperoxidase (MPO) (p-ANCA), which is absent in NSVN [5].

From the perspective of peripheral nerve histopathology, the authors favor a separation of necrotizing vasculitis of nerve into two groups, nerve large arteriole vasculitis (Fig. 1) and nerve microvasculitis (Fig. 2) [4]. The separation is based on differences in the size and kind of vessels involved, disease associations, and, perhaps, course, outlook, and treatment considerations. Again, classification based on vessel size must acknowledge the overlap of vessel involvement [9]. Large arteriole vasculitis of nerve has involvement of small arteries, large arterioles, and a varying degree of smaller vessels [4]. In large arteriole SVN, pathologic changes typically are found in epineural and perineural vessels 75 to 200 microns in diameter

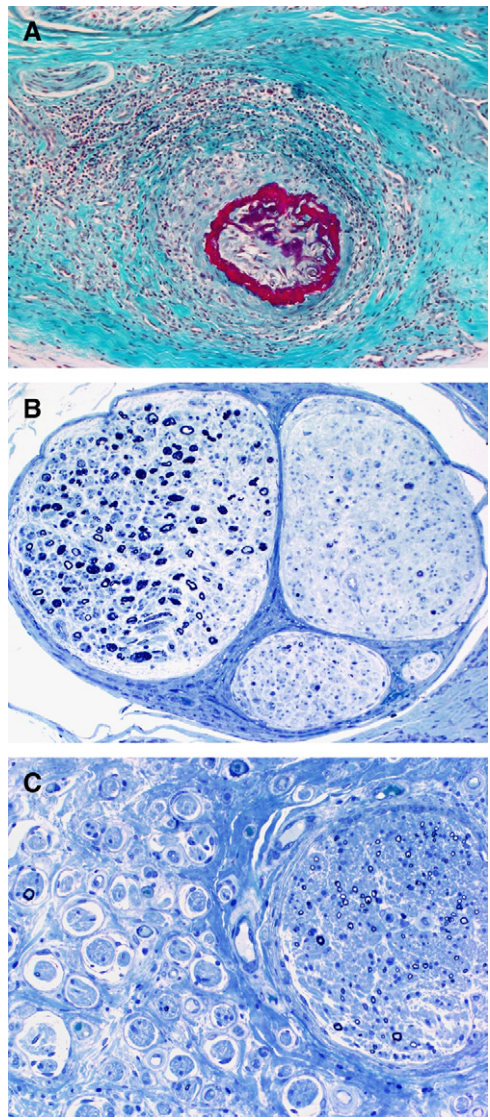

Fig. 1. Nerves from patients who have large nerve vessel necrotizing vasculitis demonstrating changes typically seen in chronic ischemic damage. (*A*) A cross-section of sural nerve in paraffin showing an arteriole with an inflammatory mononuclear cell infiltrate and fibrinoid necrosis of a sector of the wall (red) (trichrome stain). (*B*) Transverse semithin epoxy sections stained with methylene blue demonstrating multifocal fiber loss. The fascicle on the left shows relative preservation of myelinated fibers, whereas the fascicles on the right are devoid of myelinated fibers. (*C*) Transverse semithin epoxy section showing the injury neuroma and microfascicular (*left*). Note the parent fascicle on the right. These ischemic changes (multifocal fibers loss at injury neuroma) are found frequently in nerves of patients who have either large nerve vessel (arteriole) or small nerve vessel (microvessel) vasculitis.

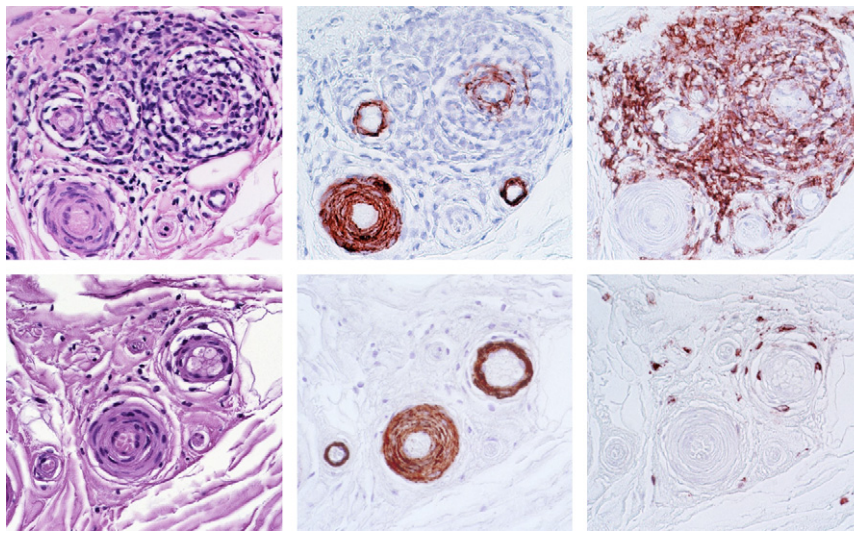

Fig. 2. Serial skip paraffin sections of a microvessel at (*upper row*) and below (*lower row*) regions of microvasculitis in the sural nerve of a patient who has LRPN. The sections in the left column are stained with hematoxylin and eosin; the sections in the middle column are reacted with antihuman smooth muscle actin; and the sections in the right column are reacted with CD45 (lymphocytes). The smooth muscle of the tunica media in the regions of the microvasculitis (*upper row, middle panel*) are separated by mononuclear cells, fragmented, and decreased in amount. The changes are those of a focal microvasculitis. These changes are seen in the diabetic and the nondiabetic conditions.

[17,21]. Almost all nerve vessels are small vessels, so nerve large arteriole vasculitis still is a "small vessel" vasculitis, but the nerve vessels involved—although small—are larger than those in nerve microvasculitis. Nerve large arteriole vasculitis usually is associated with RA, PAN, Churg-Strauss syndrome, or Wegener's granulomatosis. Nerve microvasculitis is less well defined but involves a different spectrum of vessels—the smallest arterioles (<40 μm), microvessels, venules, and not the large arterioles [4]. Nerve microvasculitis occurs in NSVN, MPA, immune sensorimotor polyneuropathies sometimes associated with sicca, classic Sjögren's syndrome, paraneoplastic neuropathies, and virus-associated neuropathies (some cases of HIV, cytomegalic, hepatitis C, and perhaps others).

The authors also believe that many autoimmune, monophasic, or relapsing plexopathies—or, more accurately, radiculoplexus neuropathies (RPNs)—also should be classified as nerve microvasculitis. These include diabetic lumbosacral RPN (DLRPN) (also known by diabetic amyotrophy, proximal diabetic neuropathy, and other names), nondiabetic LRPN, and immune and inherited brachial plexus neuropathies (BPNs) (also called neuralgic amyotrophy and hereditary neuralgic amyotrophy). Histopathologic study of LRPN has demonstrated features suggesting nerve microvasculitis (see Fig. 2). The pathology of BPN (eg, cervical RPN) has not been

studied as extensively as LRPN but nerve microvasculitis is demonstrated in some cases [22–24]. With respect to clinical classification, RPN is interesting because it does not fall clearly on one side of the systemic versus nonsystemic scheme. RPN probably has more features in common with NSVN: vessel involvement seems to be confined primarily to nerves and does not evolve to involve other organs (nonetheless, the unexplained weight loss of RPN indicates at least some effects outside of the peripheral nervous system); vessels involved in NSVN and RPN are similar in size; and NSVN and RPN are not fatal disorders. But it must be recognized that RPN differs from NSVN in the distribution of nerve involvement and by being monophasic. This unique temporal profile places the focus of RPN (and BPN) treatment on acute intervention rather than on relapse prevention. Thus, treatment of RPN (and BPN) differs from treatment of more typical NSVN or SVN. Nonetheless, the authors believe that the RPNs probably are stereotypical, monophasic forms of NSVN.

Clinical and diagnostic features of vasculitic neuropathy

The typical clinical features of vasculitic neuropathy are acute to subacute onset of painful sensory or sensorimotor deficits [8,25]. The most common presentations are of multiple mononeuropathies or an asymmetric polyneuropathy [12,17,21,26–33]. Commonly, the progression of mononeuropathies is so rapid that on presentation the deficits seem confluent. For this reason, it is imperative that patients are queried in detail about the clinical course of the initial and all subsequent deficits. Although any nerve may be affected, most patients who have SVN or NSVN experience their initial symptoms in the lower extremities, typically the peroneal or tibial divisions of the sciatic nerve (the distribution of nerve involvement is different for RPN and BPN). A distal, symmetric polyneuropathy is less common, but vasculitic neuropathy infrequently may present in this manner [10,27,30,31]. Accompanying constitutional symptoms may include myalgias, arthralgias, weight loss, respiratory symptoms, hematuria, abdominal pain, rash, or night sweats. These systemic symptoms infrequently may be minimal or absent early [12,17,21,26–33].

Electrodiagnostic studies help reveal characteristic vasculitic neuropathy findings, including acute-to-subacute axonal loss of sensory and motor nerve fibers, often in a patchy, multifocal distribution. In contrast, studies that show only conduction slowing or block at common entrapment sites (such as median neuropathy at the wrist or peroneal neuropathy across the fibular head) should lead clinicians to consider other causes that increase the likelihood for compression neuropathies, such as some forms of diabetic neuropathies (carpal tunnel syndrome and ulnar neuropathy at the elbow), nonvasculitic RA, or hereditary neuropathy with liability to pressure palsies [18].

Laboratory evaluation of suspected cases of vasculitic neuropathy should include a complete blood count (CBC), metabolic panel (electrolytes, blood urea nitrogen, creatinine, and glucose), erythrocyte sedimentation rate (ESR), C-reactive protein, antinuclear antibody, rheumatoid factor, ANCA with cytoplasmic immunofluorescence pattern directed against the neutrophil serine protease proteinase 3 (PR3/c-ANCA) and MPO/p-ANCA, hepatitis B and C panel, and cryoglobulins [34]. Serum complement determinations are appropriate in suspected mixed cryoglobulinemia or systemic lupus syndromes. In many cases, it also is appropriate to check extractable nuclear antigen, serum angiotensin-converting enzyme level, serum protein electrophoresis, and HIV. Cerebrospinal fluid analysis usually is not helpful, except to aid in the investigation of mimickers, including infectious (eg, Lyme disease) or other inflammatory causes (eg, carcinomatous root involvement). In SVN, serologic testing is abnormal and helps define the cause or syndrome further (Table 1). In NSVN, the ESR or C-reactive protein may be elevated slightly, but other markers of inflammation or systemic disease usually are normal.

Because of the need for long-term treatment with potentially toxic medications, the diagnosis of vasculitis usually requires histologic confirmation. This is so especially for Churg-Strauss syndrome, Wegener's granulomatosis, and MPA. Alternatively, because PAN affects larger vessels, diagnostic confirmation sometimes can be achieved by angiography. In general, the sensitivity of a nerve or nerve and muscle biopsy is believed to be approximately 60% for vasculitis if inflammation and vessel wall destruction are mandatory criteria [30,35]. Sensitivity of nerve biopsy increases but specificity decreases if other features, such as ischemic injury (multifocal nerve fiber loss) with inflammation but without vessel wall destruction [30,32,35], are considered sufficient for diagnosis. Some investigators recommend biopsy of nerve and muscle, for example the superficial peroneal nerve and ipsilateral peroneus brevis muscle [30,35]. The sensitivity of a nerve biopsy depends on several factors, including patient selection, which nerve is biopsied, timing in relation to symptoms, and the histologic criteria required for diagnosis.

In large arteriole SVN, pathologic changes typically are found in epineural and perineural vessels 75 to 200 microns in diameter [17,21]. The vessels involved in microvasculitis usually are smaller arterioles without an internal elastic lamina (ie, <40 μm), microvessels, and venules [4]. Whereas in nerve large arteriole vasculitis, fibrinoid necrosis of the tunica media often is prominent and characteristic, obvious fibrinoid necrosis usually is not found in nerve microvasculitis. In microvasculitis, there is inflammation of the vessel wall with separation, fragmentation, and necrosis of the thin tunica media (see Fig. 2). In both groups of necrotizing vasculitis, evidence of ischemic injury or repair (multifocal fiber loss, injury neuroma, neovascularization, and perineurial thickening) often is found [36–39]. Inflammatory cells separate muscle layers. With increased severity there is separation of the muscle

leaflets, which become fragmented and separated from the microvessel. Obvious occlusion of vessels usually is not encountered but recent or previous bleeding (hemosiderin in macrophages) is typical. Hemosiderin typically is found adjacent to affected microvessels. Typical of vessel inflammation is angioneogenesis—closely spaced, thin-walled microvessels in regions of previously ischemic areas. The authors have found all stages of perineurial injury associated with microvasculitis—from acute fibrinoid degeneration to thickening and scarring and regrowth of microfasciculi through the perineurium into the epineurium (injury neuroma). Although segmental demyelination may be found in acute ischemic injury, it usually is at borders of ischemic injury and may relate to axonal atrophy (distal to sites of axonal stasis) or to sites of axonal enlargement. Immune complex deposition in vessel walls is seen commonly in SVN and NSVN.

Clinical features of the primary systemic vasculitides

Microscopic polyangiitis

MPA is perhaps the form of systemic vasculitis associated most commonly with vasculitic neuropathy [10]. In MPA, arterioles, capillaries, and venules are affected. Many of these patients present with systemic, renal, or cutaneous manifestations of vasculitis (see Table 1). More than half of patients who have MPA develop neuropathy.

Polyarteritis nodosa

PAN is a primary vasculitis affecting vessels larger than those affected by the other vasculitides that affect nerves, namely the medium and small muscular arteries (typically not arterioles, capillaries, and venules) [40,41]. PAN is distinct from and less common than the ANCA-related systemic vasculitides. In one analysis of systemic vasculitis, only 2% of the patients could be classified as true PAN [42]. Vasculitic neuropathy occurs in up to 75% of patients who have PAN [28]. Other clinical features of PAN are listed in Table 1. PAN commonly is associated with hepatitis B (one third to one half of patients) and may behave more aggressively in cases where it is associated with hepatitis B [28,43].

Churg-Strauss syndrome

Churg-Strauss syndrome affects small- to medium-sized vessels (arterioles, venules, capillaries, and small arteries). The presentation usually is of asthma, pulmonary infiltrates, fever, and eosinophilia (see Table 1). Neuropathy is common, occurring in 65% to 80% of patients [27,32,42,44]. Of the ANCA-related syndromes, Churg-Strauss syndrome is most likely to present as a vasculitic neuropathy, occurring in more than 20% of cases [42].

Table 1
A partial list of clinical characteristics and treatments for six common forms of systemic vasculitis affecting small or medium-sized vessels of nerve

Characteristic	Wegener's Granulomatosis	Churg-Strauss syndrome	Polyarteritis nodosa	Microscopic polyangiitis	Rheumatoid vasculitis	Mixed cryoglobulinemia
Peripheral nerve disease	40%–50%	65%–80%	35%–75%	60%–70%	50% (of cases of rheumatoid vasculitis—a secondary vasculitis that occurs in 5%–15% of cases of RA)	20%–90%
Upper airway disease	95%	50%–60%	No	No		No
Pulmonary disease, radiographic nodule/infiltrates	70%–85%	40%–70%	No	15%–70%	5%–30%	No
Glomerulonephritis	70%–80%	10%–40%	No	75%–90%	10%–25%	33%–55%
Gastrointestinal	<5%	30%–50%	15%–55%	30%	10%–30%	<20%
Arthralgia/arthritis	60%–70%	40%–50%	50%–75%	40%–60%	90%–100%	20%–90%
Cardiac	10%–25%	10%–40%	5%–30%	10%–15%	10%–30%	No
Skin	40%–50%	50%–55%	25%–60%	50%–65%	30%–90%	60%–100% (eg, palpable purpura)
Central nervous system	5%–10%	5%–30%	3%–30%	10%–15%	5%–15%	No
c-ANCA (PR3)	75%–90%	3%–35%	Rare	10%–50%		No
p-ANCA (MPO)	5%–20%	2%–50%	Rare	50%–80%		No

Vessel size involved	Small to medium vessels (eg, capillaries, venules, arterioles, arteries)	Small to medium vessels	Medium to small arteries (not arterioles, capillaries or venules)	Small vessels (eg, capillaries, arterioles, venules)	Medium to small arteries (histologically indistinguishable from polyarteritis nodosa)	Small (eg, capillaries, arterioles, venules)
Other features		Asthma, fever, hypereosinophilia	Fever, hypertension	Fever	Elevated serum rheumatoid factor and ESR, extraarticular disease (eg, nodules) fever, weight loss, scleritis	Hepatitis C infection, mixed cryoglobulins, fatigue, Raynaud's phenomenon, leg ulcers, sicca syndrome
Treatment	Glucocorticoid plus cytotoxic agent	Glucocorticoid. Add cyclophosphamide if life-threatening disease.	Glucocorticoid. Add cyclophosphamide if life-threatening disease	Glucocorticoid plus cytotoxic agent, such as cyclophosphamide	Glucocorticoid. Add cyclophosphamide if life-threatening vasculitis or if not responsive to steroids alone.	Pegylated interferon-α +/− ribavirin. Plasma exchange in fulminent cases. Monitor for interferon alpha-associated exacerbation of vasculitis.
Viral association?			Sometimes associated with hepatitis B, hepatitis C, or HIV. If so, antiviral agent or plasmapheresis should be considered.			Hepatitis C >80%

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Wegener's granulomatosis

Classically a disease of the upper and lower airways, Wegener's granulomatosis involves mainly capillaries, arterioles, and venules. Peripheral nerve involvement is reported in 14% to 40% of cases [45,46] (see Table 1), usually presenting as painful multiple mononeuropathies or asymmetric polyneuropathy, although cranial neuropathies may occur less commonly [31].

Clinical features of secondary systemic vasculitis

The following are examples of vasculitis triggered by a known underlying cause, such as collagen vascular disease, viral infection, or paraneoplastic disorder.

Rheumatoid vasculitis

As in PAN, rheumatoid vasculitis affects small- to medium-sized arteries, usually sparing the arterioles, capillaries, and venules [47]. Rheumatoid vasculitis usually occurs as a late manifestation of severe seropositive disease. With more modern rheumatoid therapies, the incidence of rheumatoid vasculitis is declining and is less common than the ANCA-related syndromes (see Table 1). Because this complication of RA is seen primarily in established disease, physicians should consider other causes of vasculitis in patients who are positive for rheumatoid factor who do not have an established RA diagnosis, such as cryoglobulinemia, Wegener's granulomatosis, or extraglandular Sjögren's syndrome.

In contradistinction to rheumatoid vasculitic neuropathy, many patients who have RA develop an insidious, mild, symmetric, distal sensory, or sensorimotor polyneuropathy that is not caused by vasculitis [48]. Median neuropathy at the wrist (carpal tunnel syndrome) and other compression neuropathies also are common in RA, and electrophysiologic studies in patients who have RA often are abnormal even without clinical symptoms [49]. When present at multiple sites, these compression neuropathies rarely, at least superficially, can mimic a mononeuritis multiplex [50,51].

Much of the understanding about the pathologic damage of nerve in large arteriole necrotizing vasculitis stems from a detailed autopsy case of a patient who died from vasculitis from RA [36]. More than 10,000 serial skip peripheral nerve sections were performed from her root level, through the lumbosacral plexus, and sciatic nerves distally to her peroneal and tibial nerves. Necrotizing vasculitis of small arteries and large arterioles was found at all levels. Nerve infarction was not observed, however, until the mid thigh (mid sciatic nerve) level, the level that was the end of two vascular distributions (the watershed zone). Initially, central fascicular fiber degeneration was seen. As the nerve was examined progressively more distally, greater degrees of axonal fiber degeneration and multifocal fiber loss were observed.

Hepatitis C and mixed cryoglobulinemia

Elevated serum cryoglobulins may be secondary to chronic infection or autoimmune or hematologic diseases. Type II cryoglobulinemia, containing monoclonal and polyclonal immunoglobulins, shows a strong association with hepatitis C virus infection [52–54]. Neuropathy occurs in type II cryoglobulinemia and is observed in 30% to 70% of cryoglobulinemic vasculitis [55,56]. Arterioles, capillaries, and venules are affected [57,58]. The neuropathy typically presents as a painful, asymmetric, sensorimotor polyneuropathy or multiple mononeuropathies [54,59–62].

HIV and cytomegalovirus

SVN secondary to HIV infection is believed to occur in less than 1% of patients who have HIV and typically occurs in those who have CD4 cell counts between 200 and 500 cells/μl [63]. The inflammatory process is believed the result of immune-complex deposition rather than direct HIV infection. Moreover, HIV infection increases the risk of other forms of secondary vasculitis, including hepatitis B–associated PAN and MPA [64]. SVN also can occur in patients who have HIV in association with lymphoma [41]. In more advanced stages of HIV, particularly in patients who have CD4 counts below 50 cells/μL, a cytomegalovirus-associated vasculitic neuropathy may occur [65].

Paraneoplastic vasculitic neuropathy

Paraneoplastic vasculitic neuropathy is reported. The tumors associated most commonly with vasculitic neuropathy are small cell lung cancer, lymphoma, leukemia, renal cell carcinoma, and other adenocarcinomas. Serum antineuronal nuclear antigen (ANNA-1 or anti-Hu) and anti–CRMP-5 (also known as anti-CV2) autoantibodies are reported in some patients who have cancer, in particular small cell lung cancer and SVN [66].

Clinical features of nonsystemic vasculitic neuropathy

As with SVN, NSVN presents most commonly as multiple mononeuropathies, and an asymmetric neuropathy or sensory/sensorimotor polyneuropathy presentation is less common [17,67,68]. In general, the overall tempo of disease progression in NSVN is slower than in SVN in that the individual attacks of mononeuropathy are less frequent. After a static period, a slow, gradual return of function typically occurs for a given nerve, with most nerves eventually making a good recovery. In general, there are fewer attacks of mononeuropathy in NSVN compared with SVN. Unlike SVN, untreated NSVN usually is not fatal, and long-term follow-up studies show most patients ambulate without assistance and are independent in activities of daily living [17,68].

Clinical features of lumbosacral and cervical radiculoplexus neuropathies

Diabetic and nondiabetic LRPN are unique forms of vasculitic neuropathy because of the stereotypic presentation, relatively confined distribution of nerve injury, frequent weight loss, and monophasic course. Both forms of LRPN present with acute or subacute pain followed by weakness in the lower extremities (proximal and distal segments), typically beginning unilaterally but often spreading to the other lower extremity. Pain is severe and includes aching, sharp stabbing, burning, and contact allodynia. A concomitant thoracic radiculopathy is common, which presents with a band and pain in the abdomen or chest and weakness of abdominal wall musculature. A cervical BPN may accompany LRPN in up to 15% of cases, although upper-extremity manifestations are overshadowed by the lower-extremity neuropathic symptoms, impairments, and disability [69]. The LRPNs are monophasic illnesses—in contrast to most other cases of NSVN—with progression lasting weeks, months, and, rarely, years and with slow but incomplete recovery of motor function. Although it seems that this disorder is more prevalent in diabetes mellitus, glycemic exposure does not seem to be the direct metabolic cause. The frequently associated weight loss may perhaps provide an indication of systemic involvement. The authors question whether or not circulating cytokines might be the possible explanation for the weight loss and have shown that they are increased in this disorder [70]. Although motor predominant, the LRPNs also involve sensory and autonomic nerves and symptoms, and findings in these systems are frequent. The pathologic findings of DLRPN and LRPN are ischemic injury (multifocal fiber loss, injury neuroma, neovascularization, perineurial thickening, and hemosiderin laden macrophages) from microvasculitis (focal disruption of the muscle layers of small epineurial blood vessels by mononuclear inflammatory cells) (see Fig. 2). In contrast, the pathologic basis of noninherited and inherited immune BPN (a cervical RPN) has not been studied as extensively as LRPN, but inflammation and nerve microvasculitis are demonstrated in some cases [23]. Some cases of hereditary BPN (also called hereditary neuralgic amyotrophy) are caused by a mutation in the SEPT9 gene [71]. It is of considerable interest that this inherited neuropathy seems to be triggered by endocrine or immune-mediated factors. Within hours of parturition, when the immune system changes to a less tolerant state, patients who have the mutant gene may develop an acute BPN. Biopsy of a superficial radial nerve during an attack has shown changes suggestive of microvasculitis [72].

Treatment—general comments

An important role of neurologists in vasculitic neuropathy management is the assessment of clinical response, especially in terms of neuropathic impairment. For the assessment of response to treatment, it is important to

follow predetermined neurologic endpoints. Reliable endpoints include routine examination of muscle power, deep-tendon reflexes, and sensory thresholds, functional rating scores, and electrodiagnostic testing, whereas worsening pain seems to be a less reliable endpoint. If, in the course of treatment, new neurologic deficits develop, more aggressive therapy is indicated. Treatment decisions should be made in consultation with a rheumatologist or internist and are based, in part, on the form of systemic vasculitis, extent and degree of organ involvement, prior responsiveness to any treatments, and presence or absence of viral infection [8]. For example, chronic immunosuppressive agents, which may be first-line therapy for nonviral vasculitis, often are relatively contraindicated in viral-associated SVN.

Treatment of systemic vasculitic neuropathy

Vasculitic neuropathy not associated with virus

For nonviral SVN, corticosteroids are the initial therapy. Damage from systemic vasculitis appears and accumulates early. Treatment strategies have been developed to stop inflammatory damage (induction) rapidly, followed by safer long-term suppression (maintenance). Corticosteroids plus an additional immunosuppressant, such as cyclophosphamide, usually are required to treat MPA or Wegener's granulomatosis [73]. In PAN and Churg-Strauss syndrome, cyclophosphamide should be added in life-threatening cases (Table 2), such as those with cardiac, gastrointestinal, or CNS involvement. The addition of plasma exchange in severe cases does not seem to improve survival [43]. Some patients who have Wegener's granulomatosis or MPA require long-term immunosuppression because of relapsing disease [74,75].

Corticosteroids

In general, corticosteroids remain first-line therapy for systemic vasculitis (see Table 2), either alone or combined with other immunosuppressants [74,75]. Steroids have been used for systemic vasculitis since the 1960s, yet controlled trials and consensus statements on dosing regimens are lacking. Dosage titration should be based on patients' disease severity and response to treatment [34]. Most investigators recommend starting oral prednisone (1 to 2 mg/kg per day) [7,20,34,73,74]. In severe cases, intravenous (IV) methylprednisolone may be appropriate for initial therapy (eg, 1000 mg IV daily for 3 to 5 days followed by daily oral prednisone). Daily oral steroids should be continued until patients show a clear response. During the subacute phase of treatment, usually after 6 to 8 weeks [20], patients may be transitioned to alternate-day dosing, either at the same or at a lower averaged daily dose. At this time or after another 1 to 2 months of observation, physicians should begin tapering the steroid dose, for example by 5 to 10 mg per day per month, perhaps with lesser decrements occurring near the end of the taper. Table 2 lists the potential adverse effects of steroid therapy.

Table 2
Treatment options, potential side effects, and suggested measures to monitor for and manage side effects for nonviral systemic vasculitic neuropathy

Drug	Partial list of potential side effects	Management of potential side effects
Steroids (Prednisone)		
Initially daily 1–1.5 mg/kg, subsequent transition to alternate day dosing and gradual taper	Acute: Increased susceptibility to infections, hyperglycemia, increased appetite and weight gain, anxiety, confusion, insomnia, impaired wound healing, electrolyte disturbances. Chronic: Avascular necrosis of the femoral heads, hyperlipoproteinemia, accelerated atherosclerosis, osteoporosis, myopathy, alteration in fat deposition, peptic ulcer disease, cataracts.	Patients should start or continue an exercise program, monitoring their diet and weight. Blood glucose monitoring periodically during treatment. Bone mineral density testing baseline and annually. Consider bisphosphonates for prophylaxis of steroid-induced osteoporosis (avoid during pregnancy).
Cyclophosphamide		
Oral cyclophosphamide at 2 mg/kg as a once-daily dose	Hemorrhagic cystitis, TCCA of the bladder, oncogenicity, bone marrow suppression, gonadal toxicity, teratogenicity. Approximately one half of patients develop hematuria, usually resulting from cystitis.	Hematuria is a sensitive marker for cyclophosphamide-induced bladder injury. Injury is due to acrolein, a toxic metabolite, which is excreted into the urine. Shortening the duration of acrolein exposure to the bladder epithelium may minimize the risk of toxicity. Hence, oral administration should be every day, usually in the morning, followed by a large amount of fluids. TCCA, when it develops, almost always does so after episodes of hematuria. Urinalyses every 3 to 6 months, even after discontinuation, as TCCA may develop decades after cyclophosphamide is stopped. In cases of hematuria, discontinuation and referral to a urologist is necessary.

	Dose-related bone marrow suppression is common, with an increased risk of infection associated with leucopenia.	CBC with platelets weekly the irst month, then every month while on treatment. Total leukocyte counts below 3500/mL or absolute neutrophil counts below 1500/mL mandate titration or suspension of the drug. Lower neutrophil counts may warrant admission to the hospital and perhaps treatment with broad-spectrum antibiotics. A precipitous drop in cell counts also warrants more aggressive intervention, including cessation of cyclophosphamide.
	Nausea and vomiting.	Taking oral cyclophosphamide with or after a meal lessons the likelihood of nausea and vomiting. Consider anti-nausea medications. IV monthly cyclophosphamide also shortens the time patients experience nausea.
	Increased risk of Pneumocystis carinii pneumonia, especially with combined steroids and cytotoxic therapy.	Patients not allergic to sulfa who are on combination therapy may be treated with "low-dose" oral trimethoprim (160 mg) and sulfamethoxazole (800 mg) 3 times per week.
	Potential increased risk of other malignancies, including myelo- and lymphoproliferative disorders, years after its discontinuation. Permanent infertility may also occur because of its ability to interfere with spermatogenesis and oogenesis, which is related to its cumulative dose. Teratogenicity may occur.	Counseling and birth-control measures.
Methotrexate Often used for maintenance therapy, once SVN is in remission.	Bone marrow toxicity	Baseline CBC with platelets should be obtained prior to initiation (usually done as part of vasculitic neuropathy evaluation) and every 3 months thereafter. Repeat testing with fever, rash, or mouth ulcers.

(*continued on next page*)

Table 2 (*continued*)

Drug	Partial list of potential side effects	Management of potential side effects
In patients who have SVN, starting dose is 0.3 mg/kg orally (not exceeding 15 mg orally) per week. If tolerated, the dose can be increased gradually to 20–25 mg/week.	Hepatic fibrosis and cirrhosis; elevated LFTs	Baseline LFTs should be obtained prior to initiation of therapy and at least every 3 months. Repeat testing with fever, rash, or jaundice, especially within the first 3 months of treatment. Consider other adjuvant therapy in patients who have hepatitis or frequent alcohol consumption.
	Nephrotoxicity	Relatively uncommon, but extra caution should be used in patients who have baseline renal impairment. A baseline serum urea nitrogen and creatinine probably is sufficient, provided the vasculitis itself does not involve the kidneys.
	Increased risk for opportunistic infections	Prophylactic trimethoprim/ sulfamethoxazole (160 mg/800 mg) 3 times per week is recommended.
	Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis	Discontinue the drug in suspected rash secondary to methotrexate.
	Pulmonary fibrosis (rare)	Baseline PFTs in those who have rheumatoid vasculopathy may be helpful for comparison if symptoms develop; PFTs not helpful for subclinical detection. Discontinue drug in cases of new or worsening pulmonary function.
	Lowers seizure threshold	Consider other adjuvant therapies in patients who have seizures.
Azathioprine May be used for maintenance, once SVN is in remission.		

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Immunosuppressant adjuvant therapies

An important decision in the treatment of SVN is whether or not to add a cytotoxic or corticosteroid-sparing agent, such as cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, or leflunomide. Most investigators recommend starting a cytotoxic agent, such as cyclophosphamide, in cases of Wegener's granulomatosis or MPA [7,74]. Cytotoxic agents also are indicated in patients who have other forms of systemic vasculitis who progress despite corticosteroid therapy or who have severe multiorgan involvement, such as pulmonary-renal syndrome, rapidly progressive necrotizing glomerulonephritis, central nervous system involvement, or other life-threatening organ involvement. Physicians must keep in mind that adjuvant therapies have a delayed onset of action, often weeks to months.

Regardless of the treatment, it is important that physicians monitor for and promptly identify any life-threatening organ involvement, including of the gastrointestinal tract, heart, or central nervous system [7,74,75]. The involvement of these systems should prompt physicians to add an adjuvant therapy, if not yet done, or to escalate the doses of existing therapy. Worsening subjective constitutional symptoms may not signify relapse reliably, however, so objective clinical and laboratory parameters must be followed closely. This includes a thorough general and neurologic examination and surveillance CBC, chemistries, ESR, and urinalysis at least every 3 months and chest radiograph at least annually [75]. Physicians also must monitor for potential drug side effects; recommendations for each therapy are in Table 2.

Cyclophosphamide seems to be the most effective drug for remission induction and prolonging survival in the nonviral systemic vasculitides [74,76]. Patients usually require between 3 and 12 months of cyclophosphomide induction therapy before they can be switched to a maintenance immunosuppressant [7,73]. Oral cyclophosphamide typically is dosed at 2 mg/kg per day. There is debate as to whether or not IV pulse-dose cyclophosphamide with prednisone is as safe and effective as the oral continuous-dose combination. Current available data do suggest that pulse-dosing cyclophosphamide results in fewer adverse effects but carries an increased risk for relapses compared with oral cyclophosphamide [29].

Cyclophosphamide is known to cause hemorrhagic cystitis and transitional cell carcinoma (TCCA) of the bladder (see Table 2). Hydration and frequent voiding should be emphasized. A urinalysis is indicated every 3 to 6 months. The development of hematuria should prompt discontinuation of the drug and patient referral to a urologist. Recommendations for surveillance and prophylaxis of other potential cyclophosphamide-associated complications are listed in Table 2.

Methotrexate has been used most commonly for remission maintenance after cyclophosphamide induction [75]. A common approach is to use cyclophosphamide as the adjuvant agent until remission, then to switch to methotrexate or azathioprine for maintenance. Once the vasculitis is in remission,

it is reasonable to continue maintenance therapy for at least a year before attempting to taper the methotrexate or azathioprine. Methotrexate dosing, in the range of 15 to 25 mg once weekly, is used for systemic vasculitis [7,73,74]. Methotrexate also is associated with an acute interstitial pneumonitis, and checking pulmonary function tests (PFTs) is indicated in patients who are symptomatic (see Table 2).

Azathioprine may be considered for patients unable to tolerate cyclophosphamide therapy [7,74]. Azathioprine is a purine derivative that inhibits T-cell activation and antibody-mediated responses. Azathioprine may be as effective as cyclophosphamide in maintaining remission in Wegener's granulomatosis or MPA [77]. Azathioprine initially is dosed at 50 to 100 mg or 1 mg/kg orally, usually divided into two daily doses. The dose then is increased, by 50 mg per day every 4 weeks, to a goal dose, 2 to 2.5 mg/kg per day divided into two daily doses. An idiosyncratic hypersensitivity reaction can occur, usually within the first few weeks of therapy (see Table 2); symptoms often include nausea, diarrhea, malaise, myalgias, and rash. Liver function tests (LFTs) may be elevated. The symptoms are reversible with discontinuation, but even a single-dose rechallenge can reinitiate the syndrome.

Mycophenolate mofetil and leflunomide are reported in pilot studies as potentially useful for maintaining remission after cyclophosphamide induction in Wegener's granulomatosis [78,79].

Other agents

IV immunoglobulin (IVIg) has been used in nonvasculitic, immune-mediated neuropathies and generally has a benign safety profile, making it an attractive consideration as adjuvant therapy. Small, open-label trials of IVIg in SVN suggest clinical benefit, although randomized, controlled trials have not been performed [80–82]. Rituximab, a chimeric anti-CD20 antibody, shows promise in the treatment of cryoglobulinemic vasculitis and RA [83,84]. Randomized controlled trials of rituximab for vasculitis, however, have not been performed.

Vasculitic neuropathy associated with hepatitis B or hepatitis C

It is necessary to determine whether or not the vasculitic neuropathy is associated with a virus, such as hepatitis B or C or HIV. A detailed discussion of treatment of viral-associated vasculitis is beyond the scope of this review. Physicians experienced in treating viral hepatitis, for example, hepatologists, should make the treatment decisions and manage such patients. In general, chronic immunosuppression is relatively contraindicated in viral-associated vasculitides because such treatment may increase viremia. Shorter courses of immunosuppression, however, still are used for PAN associated with hepatitis B. Corticosteroids typically are followed by a 6-month course of an antiviral agent (either interferon-α2b or the

nucleoside analog lamivudine), often with concomitant plasma exchange [85–90]. Treatment of hepatitis C typically involves pegylated interferon (pegIFN)-α2a or -α2b, often with ribavirin [91,92]. Interferon-α treatment is associated with clinical improvement in patients who have hepatitis C–cryoglobulinemic vasculitic neuropathy [93–96]. Neurologists must be aware, however, that exacerbation of vasculitic neuropathy subsequent to initiation of pegIFN-α is an infrequent but well-reported complication of treatment [95,97,98]. In such cases, drug discontinuation may lead to improvement and should be considered [97]. Rituximab may hold promise for treatment of patients who have hepatitis C–cryoglobulinemic vasculitic neuropathy, although randomized, controlled trials are needed [99,100]. Plasma exchange should be considered in fulminant cases, although no randomized, controlled trials have been performed.

Treatment of nonsystemic vasculitic neuropathy, diabetic lumbosacral radiculoplexus neuropathy, and lumbosacral radiculoplexus neuropathy

NSVN, DLRPN, and LRPN generally are not fatal and, thus, differ from that of untreated systemic vasculitis. DLRPN and LRPN usually are monophasic, whereas other forms of NSVN often are chronic. Furthermore, the neurologic deficits seen with NSVN often resolve gradually without treatment and NSVN disease activity may remit for years or even decades before relapsing. All of these factors should be considered when arriving at treatment decisions for these microvasculitides. Immunosuppressive treatment may not be indicated for patients who have NSVN and who have either mild or improving neuropathy. For more fulminant disease, treatment clearly is indicated. Patients who have active and severe DLRPN or LRPN often are treated with either IV immunoglobulin or IV methylprednisolone. As in SVN, when immunotherapy is initiated, objective endpoints should be predetermined and followed.

Corticosteroids for nonsystemic vasculitic neuropathy

For cases of NSVN warranting treatment, oral prednisone therapy is the usual first-line agent. Most investigators recommend either 40 to 60 mg per day or 1 mg/kg per day [19,34] for 2 to 3 months followed by steroid taper and transition to alternate-day dosing if patients respond clinically, although others believe that smaller doses suffice [8,34]. See Table 2 for a list of potential side effects.

Cytotoxic adjuvant therapies for nonsystemic vasculitic neuropathy

A detailed discussion of cyclophosphamide dosing and side effects is discussed previously (see Table 2). A recent retrospective study [68] for NSVN (not DLRPN or LRPN) argues for both corticosteroids and cytotoxic

adjuvant therapy, based on statistically significant better response rates and disability scores. Patients exposed to immunosuppressant therapy, however, also experience significantly more episodes of pneumonia, *Varicella zoster*, and sepsis. A prospective, randomized trial would be ideal but seems impractical given the infrequency of NSVN.

Another option in the adjuvant treatment of NSVN is weekly methotrexate [8,34]. It probably is not necessary to use the higher doses often required in SVN. A starting dose (7.5 mg orally per week), increasing gradually (to 15to 20 mg per week), is one option. See Table 2 for more details.

Azathioprine is another option in the adjuvant therapy of NSVN, one probably better suited for patients who have infrequent mononeuropathies, as its therapeutic onset is delayed up to 8 months after initiating therapy [8]. Delayed onset should be considered when tapering corticosteroids. For dosing, side effect, and management details, see Table 2.

Treatment of diabetic lumbosacral radiculoplexus neuropathy and lumbosacral radiculoplexus neuropathy

There is no proved course-altering therapy for DLRPN or LRPN and only one randomized, controlled trial [24,69]. Based on anecdotal case reports, however, patients who have DLRPN or LRPN often are treated with IV corticosteroids or IVIg [101,102]. One noncontrolled study of a series of patients who had LRPN and were treated with IV corticosteroids showed that they all improved, many to a marked degree, but the investigators warn that the results should be viewed with caution, because the disease improves spontaneously [103]. Treatment should be considered for patients in the acute phase or for those in the subacute phase who do not seem to be improving. The authors tend to treat with IV methylprednisolone because steroids have been first-line therapy for other forms of microvasculitis. Patients treated with steroids—especially patients who have DLRPN—must be monitored closely for hyperglycemia. A randomized, controlled trial comparing IV methylprednisolone with IV placebo in DLRPN is completed but all of the data have not yet been analyzed [24]. Preliminary results suggest that sensory symptoms and pain are helped by IV methylprednisolone [24].

Summary

Because neurologists play an integral role in the diagnosis and management of patients who have vasculitis involving the peripheral nerves, they need to understand the classification and treatment options and indications for these diseases. Provision of care for patients who have vasculitic neuropathy also includes patient counseling, monitoring for potential complications of treatments, and response to treatments. Corticosteroids remain the mainstay of therapy for SVN unassociated with virus, often with adjuvant

immunosuppressive therapy. In many instances (eg, systemic vasculitis), neurologists should team up with a rheumatologist or internist to provide care. For the microvasculitides of nerve, such as NSVN, DLRPN, and LRPN, treatment decisions and management often are performed solely by a neurologist.

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