Unusual Peripheral Neuropathies. Part II: Intrinsic Reactive Causes

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ABSTRACT

Peripheral neuropathy is common with many different etiologies. This is the second of three articles to review the less-common causes of peripheral neuropathy. Part II reviews the intrinsic “reactive” causes of peripheral neuropathy, including those related to connective tissue, vasculitis, sarcoid, organ failure, and inflammatory bowel disease. The extrinsic causes of neuropathy and the induced or inherited causes of neuropathy are covered in separate articles in this issue of Seminars in Neurology, Part I and Part III, respectively. The brief series of reviews of causes of neuropathy describe common presentations and constellation of clinical findings. The goal is to help the practicing clinician increase the diagnostic yield when sorting out the unusual causes of peripheral neuropathy.

KEYWORDS: Peripheral neuropathy, neuropathy, connective tissue disease, sarcoid, vasculitis, inflammatory bowel disease, organ failure

Peripheral neuropathy is a common diagnosis for the neurologist and primary care physician to make in the clinical setting. Population studies suggest 7% of elderly adults are afflicted by neuropathies.¹ Besides the common causes of neuropathy due to diabetes or trauma, the less-obvious etiologies can be frustrating or expensive to work-up. The aim of this article, in addition to the preceding and following articles, is to aid in the identification of less-common peripheral neuropathic causes and identify when it is appropriate to consider a less-common cause of neuropathy in the differential diagnosis and work-up.

Unusual peripheral neuropathies Part II is a continuation of a review of the vast etiologic spectrum of less-common causes of peripheral neuropathy. This part covers the diverse causes of intrinsic peripheral neuropathy, ranging from connective tissue disease, vasculitis, sarcoid, organ failure, to inflammatory bowel disease. These disorders cause neuropathy through the patient’s own immune response or inflammation cascade. For this reason, they are considered “reactive” causes of peripheral neuropathy. Some disorders, such as polyarteritis nodosa, cause neuropathy solely due to inflammation and neuronal infarction. Other etiologies, such as Sjogren disease, cause neuropathy through numerous pathways including a vasculitic component. For clarity, the peripheral neuropathy causes will first be reviewed as attributed by the primary cause and then later reviewed under a separate section on vasculitic neuropathy. For either extrinsic or gene product etiologies of unusual peripheral neuropathies, please refer to Part I or Part III, respectively (Table 1).

HOW TO USE THIS REVIEW

Over 200 causes of peripheral neuropathy exist. The epidemiology of peripheral neuropathy is a difficult endeavor given the wide range of etiologies in a

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geographically disparate, heterogeneous population.\textsuperscript{2} As set forth and described in Part I, a horse to zebra continuum pictograph will appear next to each neuropathy etiologic agent. The more rare the neuropathy etiology, the more stripes will appear on the zebra (Fig. 1). Also as described in greater detail in the When to Think of Toxin-Related Neuropathy section in Part I, denotes clinical features that will increase the pretest probability when attempting to diagnose an unusual peripheral neuropathy. The goal is to reinforce a thoughtful approach to aid in the etiologic determination of a patient’s unusual neuropathy.

**CONNECTIVE TISSUE DISEASE-RELATED NEUROPATHY**

Rheumatologic connective tissue diseases encompass a heterogeneous group of disorders with autoimmune or inflammatory pathways. As a whole, 2\% of the population (more women than men) has one of these disorders, with up to 10\% of these individuals developing a neuropathy.\textsuperscript{3} Further investigation of the pathologic connective disease processes also implicates specific antineuronal autoantibodies, such as anti-GM1 and antilsulfatide, in the destructive process.\textsuperscript{4}

Many of these diseases affect multiple organs. The nonvasculitic peripheral neuropathy component of connective tissue diseases including systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Sjögren syndrome, and scleroderma, is briefly reviewed below. The vasculitic component of connective tissue disorders is discussed separately under the Vasculitic Neuropathy subsection.

**Systemic lupus erythematosus:** Systemic lupus erythematosus (SLE) is a disorder of numerous organs and has a higher prevalence in young African American women. Constitutional symptoms include fatigue, malaise, and fever with weight loss. Systemic features include a facial malar rash or discoid rash, arthritis, serositis, nephropathy, and Libman-Sacks endocarditis. The effects on the central nervous system (CNS) are varied, from seizures to behavioral changes to movement disorders. The incidence of neuropathy in SLE patients ranges from 25 to 50\% based on electrodiagnostic studies.\textsuperscript{5} Curiously, the incidence drops to only 5\% based on clinical criteria.\textsuperscript{5,6} Peripheral neuropathy does not commonly accompany the initial manifestations of SLE. Peripheral neuropathy manifestations are variable, but commonly include a late-onset, symmetric distal axonal sensorimotor or sensory neuropathy.\textsuperscript{5,7} Other less-common neuropathies include autonomic neuropathy, cranial nerve III–VI mononeuropathies, multiple mononeuropathy, acute or chronic inflammatory demyelinating neuropathies (including the Miller-Fisher syndrome), mononeuritis multiplex, and trigeminal sensory neuropathy.\textsuperscript{5,7} Trigeminal neuropathy usually does not improve and is marked by unilateral or bilateral numbness paresthesias in at least two divisions with associated pain in a majority of patients. Electrodiagnostic results are equally as variable as the presentation, but are straightforward as one would predict given their presentations. The best treatment is with steroids or immunosuppressant agents, depending on the severity of disease.

**Rheumatoid arthritis:** Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joint...
synovium with a typical onset age between 20 to 40 years. Patients commonly note significant morning stiffness and joint pain with predilection of the proximal interphalangeal, metacarpophalangeal, and wrist joints. Systemic manifestations may also involve the skin, eyes, lungs, heart, and, more rarely, vasculitis. Over the disease course, peripheral sensory neuropathy may occur in approximately two-thirds of patients and carpal tunnel in at least one-fifth of patients.5 The neuropathy manifests with stocking distribution paresthesias. Many patients may be asymptomatic until clinically diagnosed through impaired foot vibration and pin prick sensation, even though Achilles reflexes are relatively preserved. Nerve conduction abnormalities and biopsies of the lower limb show the presence of axonal neuropathy with slightly impaired motor nerve conduction in the peroneal nerve and abnormal sensory conduction in the superficial peroneal or sural nerve.5,8 In electrodiagnostic studies, rheumatoid arthritis may initially appear similar to mononeuropathy multiplex with mild, asymmetric abnormalities of nerve conduction. The distinguishing factor is that the RA patient may be asymptomatic and is not as severely affected as a patient with true mononeuropathy multiplex. Focal nerve conduction slowing across common entrapment points, such as the carpal or tarsal tunnel, may indicate active tenosynovitis or carpal/tarsal deformities.5 Further, compression mononeuropathies of the femoral, plantar, peroneal, posterior tibial, radial, posterior interosseous, saphenous, and ulnar nerves may occur.3,5 When symptoms of compressive neuropathy occur, treatment of the RA usually helps reduce the neuropathies. The occurrence of vasculitis should be reconsidered when a mononeuropathy outside the common entrapment sites is present or when there is an unusual progression of the distal neuropathy, which indicates the need for more aggressive immunosuppressive therapy.

**Sjögren syndrome:** Sjögren syndrome is an autoimmune disease of the exocrine glands with lymphocytic infiltration and destruction of the lacrimal and salivary glands. Many other organs may also be affected including the skin, lungs, thyroid, blood vessels, and liver. Patients often note dry eyes (xerophthalmia) and mouth (xerostomia), as well as arthralgias and fatigue. The incidence of peripheral neuropathy is 10 to 60% and many (40–93%) of these patients present with neuropathy as the sentinel symptom.5,9,10 Women are more likely to get Sjögren syndrome and display neuropathy. Sjögren syndrome has the most varied neuropathy presentations of all the connective tissue disorders. Patients often note numbness or burning type paresthesias of their feet. More commonly encountered neuropathies ranging from more to less frequent include trigeminal sensory neuropathy, symmetric distal sensory or sensorimotor neuropathy, sensory neuronopathy (loss of proprioception), autonomic neuropathy, carpal tunnel syndrome, other entrapment neuropathies, mononeuritis multiplex, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and motor neuropathy.9,10 The majority of patients have more than one type of neuropathy; for example, many patients with peripheral neuropathy demonstrate autonomic dysfunction with a tonic pupil (Adie pupil), as well as other evidence of autonomic nervous system involvement after thorough analysis.11 Treatment is symptomatic, but in severe forms includes immunomodulatory medications.

**Scleroderma:** Scleroderma or systemic sclerosis is a chronic connective tissue disorder that can lead to widespread fibrosis due to abnormally large amounts of collagen deposition. Common early findings include Raynaud phenomenon; cutaneous fibrosis (e.g., sclerodactyly) and gastrointestinal, pulmonary, renal, and cardiac involvement are later effects. The CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) occurs in some patients with retrospective studies suggesting peripheral neuropathy in ~1% of patients.7 In general, associated peripheral neuropathies are rare with infrequent cases of carpal tunnel syndrome, mononeuropathy multiplex, distal axonal sensory neuropathy, trigeminal sensory neuropathy, brachial neuropathy, and lumbar sacral neuropathy.5 Asymptomatic patients frequently have distal motor and sensory latencies and action potential amplitudes consistently at the lower limits of normal. Systemic sclerosis is associated with an increased incidence of inflammatory muscle disease, occurring in 13% of patients.5 Treatment is generally symptomatic with immunomodulatory measures needed when pulmonary and renal effects occur.

**Mixed connective tissue diseases:** Mixed connective tissue diseases represent an “overlap” syndrome with features similar to any of the above in addition to polymyositis. Diagnosis is challenging as the clinical features do not always simultaneously occur and may include myopathy. Patients will normally have Raynaud phenomenon. CNS manifestations include aseptic meningitis, seizures, or psychosis. Neurologic complications are less common in general than other connective tissue diseases. The main peripheral neuropathy involvement includes trigeminal sensory neuropathy, autonomic neuropathy, distal sensorimotor polyneuropathy, or CIDP-type picture. Patients usually respond robustly to corticosteroids and many patients do quite well.

**WHEN TO THINK OF CONNECTIVE TISSUE DISEASE-RELATED NEUROPATHY**

1. Neuropathy in a patient with prior diagnosis of a connective tissue disease or evidence of multiple organ involvement
2. Patient with significant proprioceptive loss and ataxic sensory neuropathy (neuropathy)
3. Electrodiagnostic evidence of axonal sensory neuropathy without another underlying diagnosis

**ORGAN FAILURE-RELATED NEUROPATHY**

Failure of a specific organ may cause multifactorial remote nerve dysfunction. It is well known that critical illness is a predisposing factor for myopathy and poly-neuropathy. Several organ derangements provide examples of a local organ process that extends to cause systemic effects.

**Renal failure:** Renal failure as a cause of neuropathy was recognized in dialysis patients and severe chronic renal failure patients as early as the 1960s. The factors contributing to neuropathy and kidney failure appear to be independent from those typically associated with diabetes. In a study with children, asymptomatic uremic–polyneuropathy was identified in ~60% of children on chronic dialysis. More recent trials implicate subclinical values of hypovitaminosis, such as vitamin B6, with subsequent replacement improving neuropathy symptoms. Autonomic neuropathy is common in advanced renal failure with chronic hemodialysis. Cases of acute inflammatory demyelinating polyradiculopathy (AIDP) temporally related to initiation of hemodialysis are present in the hemodialysis literature but are overall uncommon. Common electrodiagnostic findings demonstrate prolonged H reflex, distal and F-wave latency, as well as slower conduction velocities. These adverse effects are largely unaffected by the type of hemodialysis, continuous ambulatory peritoneal hemodialysis, or maintenance hemodialysis, and are avoided by preservation of native kidney function.

**Hepatic disease:** Hepatic disease and neuropathy are commonly associated together although the causality is controversial. Typically, hepatic neuropathy only presents in a length–dependent pattern with severe liver disease. Generally, 20 to 100% of liver failure patients may have clinical findings of neuropathy with distal loss of pain, vibration, and reflexes. Nerve conduction studies commonly identify an axonal process with greater sensory than motor involvement. Autonomic involvement may be detected with tilt table testing and heart rate variability with deep breathing and the Valsalva maneuver. Viral hepatitis, especially hepatitis C, is described in the Vasculitic Neuropathy section due to its common relationship to mixed cryoglobulinemia and mononeuritis multiplex. More recent work makes the case that antineuronal myelin antibodies produce a mixed axonal and demyelinating peripheral neuropathy picture.

**Pulmonary disease:** Neuropathy can be found in nearly half of pulmonary failure patients. Pulmonary failure patients are often affected with distal sensory deficiencies and clinically may present with absent Achilles reflexes. The severity of the polyneuropathy is generally related to patient age, severity of hypoxia/hypercapnia, cachexia/nutritional deficiency, and smoking history. Electrodiagnostic studies reveal a length–dependent axonal polyneuropathy. Histologic evidence of neuropathy in pulmonary failure patients suggests a hypoxic/ischemic distal axonal process with secondary demyelination and remyelination.

**Organ transplantation:** Organ transplantation incurs damage to peripheral nerves in numerous ways. Causes of neuropathy may be related to the pathologic process necessitating the organ transplant, graft versus host disease, neurotoxicity of immunosuppressants, or focal mechanical injury from retraction. Electrodiagnostic testing may reveal either axonal or demyelinating nerve disruption, or a mixed picture. Sensorimotor polyneuropathies such as Guillain–Barré or CIDP are known to present following kidney, liver, bone marrow, heart, or lung transplantation; however, cases are rare.

**Critical illness polyneuropathy:** Critical illness polyneuropathy (CIP) is a major complication of severe critical illness and is related to the systemic inflammatory response (SIRS) as well as organ failure. It sometimes is accompanied by critical illness myopathy (CIM); however, this will not be discussed in this review. Patients with critical illness neuropathy have increased mortality, longer hospitalizations, and prolonged ventilator weaning. One-third of severe CIP cases have persistent tetraplegia, tetraparesis, or paraplegia, and mortality from the underlying medical conditions is very high. Since CIP was first recognized in the mid 1980s, the list of known risk factors has grown to include female gender, severity and duration of organ dysfunction, renal failure, hyperosmolarity, parenteral nutrition, low serum albumin, vasopressor and catecholamine support, and central neurologic failure. Although controversial, some studies indicate additional risk factors for CIP/CIM including corticosteroids, aminoglycosides, and paralytic nerve blocking agents. Electrodiagnostic evidence of CIP is apparent in 70 to 100% of cases depending on whether SIRS or sepsis is compounded by multiorgan failure. The pathogenesis of CIP involves a noninflammatory distal axonal sensorimotor polyneuropathy likely due to abnormal microvascular autoregulation. The initial electrodiagnostic sign, reduction in nerve conduction potentials, may occur within 2 to 5 days of the onset of the critical illness. Further electrodiagnostic changes due to CIP, namely fibrillation potentials and positive sharp waves, may not occur until the second or third week of the critical illness. In a multicenter prospective trial, screening with peroneal compound muscle action potentials below two standard deviations of normal accurately identified patients with CIP/CIM. Abnormal sensory nerve action potentials combined with reduced compound muscle action potentials suggest CIP, although local effects such
as edema may interfere with a proper analysis. Still, the differentiation between CIP and CIM may be difficult to ascertain even in cooperative patients and may require muscle biopsy. Prevention of CIP with strict normoglycemia is controversial with only some studies linking strict blood sugar control to decreased morbidity and improved outcomes. Physical therapy is the only known treatment. In severe cases, patient sensory and motor improvement is linked to axonal regeneration, requiring weeks to months for recovery.

**WHEN TO THINK OF ORGAN FAILURE-RELATED PERIPHERAL NEUROPATHY**

1. Evidence of neuropathy in the setting of isolated acute or chronic organ failure
2. Patients with significant systemic inflammatory response or sepsis in addition to organ failure with reduction of nerve conduction potentials
3. Examination findings of flaccid extremity weakness and hypo/areflexia in the critical care unit support critical illness neuropathy.

**CELIAC DISEASE/INFLAMMATORY BOWEL DISEASE**

Celiac disease and inflammatory bowel disease (IBD) are associated with an axonal distal sensorimotor neuropathy. Neuropathy prevalence in celiac disease diagnosed by gastric biopsy is ~2 to 5%. Depending on the case series, upwards of 30% of these patients had sensory neuropathy or weakness prior to being diagnosed with celiac disease. However, case series differ in diagnostic methods. When only antigliadin and antitransglutaminase antibodies are tested, more celiac-related neuropathies are detected. But without a gastric tissue biopsy to confirm villous atrophy, the elevated antibody levels could be due to other autoimmune disorders. Patients are likely to report paresthesias or dysesthesias of tingling, burning, heavy or numb extremities, hypersensitivity, or chills. Occasionally, patients demonstrate gait instability or foot drop. Commonly there are few abnormal electrodiagnostic findings; however, some demonstrate axonal processes with sensorimotor involvement. The neuropathy symptoms generally, but not always, improve on a gluten-free diet, yet a gluten-free diet may not be protective from celiac disease-related neuropathy.

Inflammatory bowel disease exemplified by Crohn disease (CD) and ulcerative colitis (UC) cause effects within the gastrointestinal system and systemically. Historically, IBD-associated peripheral neuropathies occurred in 0.3 to 30% of patients and was attributed to vitamin B₁₂ absorption deficiency, and was assumed to be induced from metronidazole treatment. Observations in the 1980s, however, independently linked IBD with axonal sensory polyneuropathy that fluctuated with Crohn disease activity. IBD-affected patients may note any combination of asymmetric numbness, burning, hyperhidrosis, fatigue, cramping, and eventually weakness and gait instability. More recently, an IBD neuropathy series implicated sensorimotor polyneuropathy and demyelinating subtypes. In a series of 33 individuals with IBD and peripheral neuropathy (18 with CD, 15 with UC), 30% had demyelinating features consistent with multifocal motor neuropathy (MMN) or CIDP, 30% had axonal sensory polyneuropathy, and 40% had axonal sensorimotor polyneuropathy. Electrophysiology reveals diverse asymmetric derangements such as conduction block with preserved sensory nerve action potentials, prolongation of distal latencies and F-waves (findings consistent with AAN criteria for CIDP), or reduced amplitude of sensory or compound muscle action potentials. In nearly all cases, IBD presents first, followed by axonal polyneuropathy with demyelinating features occurring at anytime. In rare cases neuropathy can precede UC or CD diagnosis. Immunotherapy treatment with intravenous immune globulin (IVIG), plasmapheresis, or cytotoxic agents improved symptoms in nearly all patients that were treated; however, improvement was also observed with only pain management.

**WHEN TO THINK OF CELIAC OR INFLAMMATORY BOWEL DISEASE-RELATED NEUROPATHY**

1. Neuropathy in a patient with family history or suggestive signs or symptoms of celiac sprue or inflammatory bowel disease
2. Demyelinating or axonal features on electrodiagnostic studies with intestinal symptoms is suggestive of an inflammatory bowel-associated neuropathy.

**SARCOID**

Sarcoidosis can present with multisystemic disease including myopathy and peripheral neuropathy. Sarcoidosis is most prevalent in patients of African American descent and pulmonary disease is by far the most common manifestation. Neurosarcoidosis is relatively rare, only affecting ~5% of sarcoid patients. Isolated neurologic symptoms rarely occur, but are possible. Sarcoid-associated neuropathy may have several patterns: chronic distal symmetric sensorimotor axonal polyneuropathy, vasculitic mononeuritis multiplex manifestation including cranial neuropathies (most frequently bilateral facial nerve palsies), and an AIDP-like polyradiculoneuropathy. A review of sarcoid neuropathy cases found that there is often associated involvement in another system, such as muscle. The diagnosis of
sarcoid neuropathy can be difficult. A chest x-ray or computed tomography (CT) scan may be negative for pathologic changes. Serum or CSF angiotensin converting enzyme (ACE) level and serum calcium is insensitive with false-negatives in 60% of cases. The diagnosis is often made by nerve or muscle biopsy showing non-specific inflammation or ideally noncaseating granulomas. In the case of non-specific inflammation on nerve biopsy, other inflammatory causes are likely excluded first before a search for other systemic manifestations of sarcoidosis by imaging and biopsy. Therefore, routine chest x-ray or serum ACE levels are of low yield, and the clinical setting and nerve biopsy are likely helpful in specific cases of high suspicion. Treatment with corticosteroids is beneficial, although some mild cases will go untreated and improve without intervention.

**VASCULITIC NEUROPATHY**

Vasculitis is the inflammation of blood vessels. Certain types of vasculitis cause local fibrinoid necrosis in the walls of the vasa nervorum causing an ischemic infarction of the nerve fascicle. The infarction produces a neuropathy. Since the description of vasculitis in the mid 1800s, neuropathy has been a prominent feature of many types of vasculitis. For example, polyarteritis nodosa (incidence of 5–10 per million per year) will cause clinical neuropathy in 50 to 75% of patients.

Vasculitis is divided into two types: nonsystemic, if only muscle and nerves are involved, or systemic. Systemic vasculitis is further divided into primary and secondary causes. Primary vasculitis is mainly caused by necrosis of precapillary vessels surrounding nerves and is generally defined based on the size of blood vessels involved. Examples of primary vasculitis are immune modulated, blood vessel directed disorders. Secondary vasculitis is reserved for etiologies such as infection, malignancy, or connective tissue diseases that may induce vascular inflammation by a secondary process, not considered being the disease defining quality.

There are many potential mechanisms that may precipitate a vasculitis. Interestingly, endothelial cells' intrinsic properties predispose them to inflammation when activated to present antigen and interact with immune surveillance mechanisms. Of course, there must be other abnormal changes of expression, function of adhesion molecules, and leukocyte and endothelial cell activation that makes the process pathologic. Histologically, primary vasculitis is associated with polymorphonuclear cell infiltrates, whereas predominantly mononuclear infiltrates signify secondary vasculitis. Common pathophysiology is based on humoral versus cellular autoimmunity. Examples of humoral mediated response include (1) the deposition of circulating antigen–antibody complexes that target specific blood vessel antigens with the activation of complement, (2) antineutrophil cytoplasmic antibody (ANCA–) mediated effects against neutrophil and monocyte cytoplasmic proteins. Cellular autoimmunity of vasculitis is exemplified by T-cell mediated cytotoxic effect on endothelial cells.

Specific causes of systemic and nonsystemic vasculitic conditions are briefly described below. Commonly, the vasculitis-related neuropathy is painful with an acute to subacute onset of both sensory and motor manifestations. It is often asymmetric as varied lengths of distinct nerves are involved; however, overlapping of involved nerves may form a picture of mononeuropathy multiplex. Nearly unanimously, electromyography (EMG) demonstrates evidence of axonal loss with low amplitude compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) responses, fibrillation potentials, and reduced recruitment.

**Primary Systemic Vasculitis**

- **Polyarteritis nodosa (PAN)**—is a focal and segmental disorder affecting small to medium-sized arteries with associated gastrointestinal pain or neurologic symptoms. It can be associated with HIV, hepatitis B, and drug reactions. The patient may present with weight loss, fever, weakness, myalgias, arthralgias, and gastrointestinal ischemic pain. Treatment is with corticosteroids, and if severe, with cyclophosphamide.

- **Microscopic polyangiitis**—is a disorder that involves smaller vessels than in PAN, and more commonly involves the lungs and a rapidly progressive glomerulonephritis. The prevalence of neuropathy is low.

- **Churg-Strauss syndrome**—is a disorder of medium- to capillary-sized blood vessels with multiple organ involvement (respiratory, cardiac, gastrointestinal, skin, renal, peripheral nervous system) strong association with asthma, and eosinophilia. Patients often have a fever and experience fatigue and weight loss. Neuropathy is common, 65 to 80% of patients, and is the sentinel symptom in 20% of cases. Treatment is with glucocorticoids.

- **Wegener’s granulomatosi**—is a disorder of capillaries, arterioles, and venules with upper and lower pulmonary airway and kidney involvement. Peripheral neuropathy is noted in 10 to 40% of patients, usually within 2 years of diagnosis. Patients present with painful multiple mononeuropathies or asymmetric polyneuropathy with rare cranial neuropathies. Life expectancy may be limited to a few years, although treatment with cyclophosphamide and corticosteroids may induce remission with unknown time of reoccurrence.

- **Giant cell arteritis**—is composed of Takayasu arteritis and temporal arteritis, and involves the inflammation of large and medium-sized arteries. Rarely, temporal arteritis is associated with a distal
Peripheral neuropathy or mononeuritis multiplex, although other causes may also be found.  

**Hypersensitivity vasculitis**—includes a series of causes of vasculitis with prominent cutaneous findings or a leukocytoclastic reaction, classically involving arterioles, capillaries, and venules. The precipitating factor usually resolves within 1 to 3 weeks. There appears to be cases of neuropathy associated with the following hypersensitivity vasculitis causes:

- **Henoch-Schönlein purpura** is characterized by palpable purpura commonly involving the legs and buttocks with rare associated peripheral neuropathy.  
- **Malignancy** may cause a paraneoplastic process of vessels with rare peripheral nerve involvement.  
- **Drug-induced vasculitis** is more commonly related to central nervous system vasculitis, although peripheral vasculitis and rare resulting neuropathy may occur.  
- **Infection** generally causes large vessel involvement, although vessel wall antigens may also be involved causing more discrete neuropathies. Infectious etiologies may include viral, bacterial, mycobacterial, fungal, or parasitic.  
- **Cryoglobulins** in mixed cryoglobulinemia is described usually resolves within 1 to 3 weeks. There appears to be cases of neuropathy associated with the following hypersensitivity vasculitis causes:

### Secondary Systemic Vasculitis

- **Systemic lupus erythematosus (SLE)**—involves small to medium-sized vessels in the context of a systemic inflammatory disorder with autoantibody production, deposition, and complement activation. Vasculitis is not the main pathologic cause of peripheral neuropathy in SLE, but can be seen on biopsy with epineural vasculitis.  
- **Rheumatoid arthritis (RA)**—is a small vessel vasculitis in the setting of systemic disease with joint destruction, pleuritis, pericarditis, interstitial lung disease, vasculitic organ infarction, and glomerulonephritis. A vasculitic neuropathy occurs in less than 7% of patients with RA.  
- **Sjögren syndrome**—is a small vessel vasculitis in the setting of autoimmune disease exocrine gland disruption. Vasculitic neuropathy may present with mononeuritis multiplex, sensory or sensorimotor distal symmetric neuropathy with slowly progressive numbness, cranial nerve neuropathies (III, V–VII, IX–X), and paresthesias or rarely as CIDP.  
- **Scleroderma/systemic sclerosis**—is a disorder of small-sized vessels in the setting of progressive systemic fibrosis from the overabundance and deposition of normal collagen. Scleroderma rarely causes clinically evident vasculitic mononeuritis multiplex–type neuropathy.  
- **Mixed connective tissue disease**—is a disorder capable of small to medium-sized blood vessel disruption. It is a rare cause of mononeuritis multiplex.  
- **Sarcoidosis**—is associated with small vessel inflammation with instances of epineurial and perineural granulomatous angiitis. Isolated peripheral neuropathies and myopathy are possible and often present together.  
- **Type II cryoglobulinemia** secondary to hepatitis C—involves a bystander effect to arterioles, capillaries, and venules. Hepatitis C is associated in 73 to 90% of cases. As described in the Paraproteinemias/Monoclonal Gammopathy section in Part III, the neuropathy is generally painful and asymmetric, with evidence of sensorimotor polyneuropathy or multiple mononeuropathies.  
- **Viral** (for example, HIV or cytomegalovirus)—involves immune complex deposition in blood vessels rather than a specific targeted effect.  
- **Paraneoplastic vasculitic neuropathy**—is most commonly associated with small-cell lung cancer, but can be seen in leukemia, lymphoma, renal-cell carcinoma, and other adenocarcinomas. Serological detection is difficult, but cases have been correlated with ANNA–1 or anti–Hu autoantibodies.  
- **Behçet’s syndrome**—is a multisystem inflammatory disorder that is rare and poorly characterized but that may have vessel involvement. Most reports are of patients from Eastern Mediterranean countries or Japan. The clinical features are oral or genital ulcerations and uveitis. Nervous system involvement occurs in likely less than 20% of cases with meningoencephalitis and/or transverse myelitis far more common than peripheral involvement, which is rare. Steroids are effective treatment.

### Nonsystemic Vasculitis

- **Diabetic and nondiabetic lumbosacral radiculoplexus neuropathy**—Diabetic and nondiabetic lumbosacral radiculoplexus neuropathy is a nonsystemic vasculitic neuropathy that has a stereotyped monophasic pattern with subacute or acute onset of pain and weakness. It often begins unilaterally and can spread bilaterally. Interestingly, a more mild cervicobrachialplexus neuropathy can complexify the picture in 15% of cases. Although it is considered “nonsystemic” there is frequently concomitant weight loss with decreased appetite.

### When to Think of a Vasculitic Neuropathy

1. Large myelinated fibers are involved first even though the process is axonal.
2. More likely in polyarteritis nodosa or rheumatoid arthritis
3. Acute to subacute course of a painful, multifocal sensory and/or motor deficit tracing the distribution of one or more nerves
4. In the lower extremity, the predilection for involvement is common peroneal >tibial >sural nerve, whereas the upper extremity is notable for the ulnar nerve >median >radial involvement.
5. Consider in asymmetric cases of neuropathy with upper extremity involvement prior to lower extremity or in varying severity within the same nerve or dermatome.

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