

PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS OF RHEUMATOLOGICAL AND SYSTEMIC INFLAMMATORY DISEASE: VASCULITIC NEUROPATHIES, SMALL FIBER NEUROPATHIES, SENSORY NEUROPATHIES

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Patients with rheumatologic disease often have peripheral nervous system involvement typically in the form of peripheral neuropathies. As a neurologist, it is of utmost importance to identify underlying autoimmune etiologies as they may lead to successful treatment and early identification can prevent irreversible neurologic deficits. Many patients without an established diagnosis of rheumatologic disease will present first to the neurologist and it is his evaluation that will ultimately lead to a diagnosis. Additionally many of the current treatments for rheumatologic disease will result in unwanted peripheral nervous system side effects, which will also be covered briefly here.

1. Vasculitic Neuropathies

Vasculitis is a disease state in which there is inflammation and destruction of blood vessels of different sizes. This in turn results in ischemic injury to the involved tissue. Vasculitis may be systemic or confined to a single organ. Vasculitis can also affect the vessels that feed the nerves resulting in vasculitic neuropathies. In 2010, the Peripheral Nerve Society issued a guideline classifying vasculitic neuropathies into primary systemic vasculitides, secondary systemic vasculitides, and non-systemic/localized vasculitis. Only the small vessels feed the nerves, so in a sense all vasculitic neuropathies are small vessel vasculitides. Vasculitic neuropathies, by convention, can be divided into large arteriole vasculitis which affects epineurial and perineurial vessels and microvasculitis which affects the endoneurial microvessels and venules.

a. Clinical presentation of vasculitic neuropathies

Clinically vasculitic neuropathies most commonly present with acute to subacute multifocal mononeuropathies (also called mononeuritis multiplex) or an asymmetric polyneuropathy. Nerve conduction studies and electromyography will help demonstrate asymmetry and acuity. Most often tissue diagnosis is necessary, unless a patient with systemic vasculitis has already had another involved organ biopsied. The nerve biopsy will help confirm the diagnosis and differentiate nerve large arteriole vasculitis from microvasculitis. Physicians should determine whether or not the vasculitis is localized to the peripheral nervous system, such as in non-systemic vasculitic neuropathy, or is systemic and involves other organs such as the lungs, kidneys, gastrointestinal tract and skin. The presence of specific antibodies will also support the diagnosis.

b. Specific types of vasculitis

Specific types of systemic vasculitis include the small vessel vasculitides: anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis such as microscopic polyangiitis (MPA), eosinophilic granulomatosis polyangiitis (EGPA, previously Churg-Strauss syndrome,) and granulomatosis with polyangiitis (GPA, previously Wegener's granulomatosis). Microscopic polyangiitis is associated with perinuclear ANCA 50-70% of the time. The major clinical features include renal impairment (rapidly progressive glomerulonephritis), pulmonary involvement, skin lesions, and abdominal pain. Eosinophilic granulomatosis with polyangiitis presents with asthma, peripheral eosinophilia, fleeting pulmonary infiltrates, neuropathy, and paranasal sinus abnormalities. Granulomatosis with polyangiitis is characterized by granulomatous inflammation of the upper and lower respiratory tracts and involvement of the lungs and kidneys. The predominately medium vessel vasculitis, polyarteritis nodosa affects the small and medium arteries of the skin, kidneys, GI tract and rarely the heart and testes.

c. Secondary systemic vasculitic neuropathy and non-systemic vasculitic neuropathy

The secondary systemic vasculitides occur as the result of rheumatologic diseases such as rheumatoid arthritis and Sjögren's syndrome or may occur in the setting of infection such as hepatitis C and cryoglobulinemia and HIV. Most of the secondary systemic vasculitides are nerve large arteriole with the notable exception of Sjögren's syndrome. Non-systemic vasculitic neuropathy, which is primarily a nerve microvasculitis, presents similarly to systemic vasculitic neuropathy. It is more gradually progressive and patients will have milder systemic symptoms such as weight loss and fevers. Thus there is usually a delay in diagnosis. Unlike systemic vasculitic neuropathies, non-systemic vasculitic neuropathy is not fatal. Non-systemic vasculitic neuropathy has the potential to evolve into systemic vasculitic neuropathy.

d. Treatment of vasculitic neuropathy

Treatment of vasculitic neuropathies almost universally includes corticosteroids either high dose oral prednisone (60-80 mg/day) or even intravenous methylprednisolone initially. Cyclophosphamide is added in refractory cases. For patients needing long term immunosuppression, other therapies such as rituximab, azathioprine, methotrexate, and mycophenolate mofetil can be used. Intravenous immunoglobulins (IVIG) and plasma exchange are additional therapeutic options in refractory patients.

e. Specific forms of localized microvasculitis

Specific forms of localized microvasculitis include diabetic and non-diabetic lumbosacral radiculoplexus neuropathies (DLRPN and RLPN respectively), diabetic cervical radiculoplexus neuropathy, and painless diabetic motor neuropathy. In all of these entities, the lumbosacral roots, plexus, and individual peripheral nerves are affected. The clinical hallmark of DLRPN and RLPN is acute to subacute onset of severe pain in the proximal thigh that spreads to involve the distal lower extremity and spreads contralaterally. Pain gives way to weakness and to a lesser extent numbness. Autonomic dysfunction occurs in the form of bowel and bladder dysfunction and orthostatic hypotension. Weight loss is a common accompanying symptom. In DLRPN, the diabetics are typically type 2 without poor control and without evidence of other organ involvement. Given this is a monophasic disease, some degree of improvement is expected, though full recovery is often not achieved. Other forms of localized microvasculitis include diabetic cervical radiculoplexus neuropathy which is upper extremity equivalent to DLRPN. A painless diabetic motor neuropathy has also been described. Unlike other forms of vasculitic neuropathies, tissue biopsy is often unnecessary in straight-forward cases. There is no consensus on treatment of these patients; IVIG, plasma exchange and pulse intravenous methylprednisolone have been tried with varying degrees of success.

2. Sensory Neuronopathies (Dorsal Root Ganglionopathies)

The sensory neuronopathies are a group of neuropathies that result from destruction of the dorsal root ganglia and trigeminal ganglion sensory neurons. The differential diagnosis for autoimmune sensory neuronopathies is short and includes paraneoplastic disease, Sjögren's syndrome, systemic lupus erythematosus, autoimmune hepatitis and celiac disease. Patients with sensory neuronopathies classically present with early onset ataxia due prominent large fiber involvement. When proprioceptive loss is severe, pseudoathetosis, or involuntary writing of the fingers and toes, will be appreciated. Patients report multifocal, asymmetric impaired sensation with positive sensory symptoms (burning pain, hyperesthesia, and allodynia). Electrodiagnostic studies will demonstrate reduced or absent sensory responses with relatively preserved motor responses. The recommended evaluation for sensory neuronopathies includes laboratory testing for anti-Hu and anti-CV2/CRMP-5 paraneoplastic antibodies, antinuclear antibodies, anti-SSA/SSB antibodies (anti-Ro and anti-La respectively), pyridoxine, and HIV. Treatment of the paraneoplastic sensory neuronopathies includes treatment of the underlying malignancy, immunomodulatory therapy (with corticosteroids, IVIG, plasma exchange and others) and symptomatic management. For the non-paraneoplastic sensory neuronopathies, a variety of treatments have been tried including IVIG, plasma exchange, corticosteroids, rituximab, cyclophosphamide, and azathioprine.

3. Small Fiber Neuropathies

The small fiber neuropathies are the result of damage to the small-diameter unmyelinated C-fiber nerves. These nerves mediate pain and temperature sensation. Given that routine nerve conduction studies are usually normal, additional studies such as skin biopsies and autonomic function testing are often required. The autoimmune causes of small fiber neuropathy are primarily sarcoidosis and Sjögren's syndrome.

A. Small fiber neuropathy in sarcoidosis

Small fiber neuropathy symptoms have been reported in up to two-thirds of patients with sarcoidosis. Patients present with pain and paresthesia in stocking-glove pattern or non-length-dependent pattern. Autonomic dysfunction may also be present. Small fiber involvement in sarcoidosis is thought to be systemic cytokine-mediated and not the direct result of granulomatous disease.

B. Small fiber neuropathy in Sjögren's syndrome

Sjögren's syndrome can also manifest with small fiber neuropathy. In a large study of neuropathies in Sjögren's patients, Mori et al. classified small fiber neuropathy as sensory neuropathy without ataxia. These patients had primarily small fiber symptoms with retained sensory responses on nerve conduction studies. The small fiber neuropathy in Sjögren's may be acute onset or slowly progressive, and the pattern may be length-dependent, generalized or multifocal. Trigeminal nerve involvement is often present. Autonomic involvement manifests as pupillary changes, anhidrosis/hypohidrosis, and orthostasis. Pure autonomic neuropathies without sensory nerve involvement can occur as well in the context of Sjögren's. Treatment for Sjögren's-associated neuropathies, regardless of the pattern, includes IVIG and corticosteroids.

C. Other autoimmune forms of small fiber neuropathy

There is emerging evidence that some forms of previously considered idiopathic small fiber neuropathy may be due to acute or chronic tissue-specific dysimmunity, similar to Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. This has been described in childhood-onset, unexplained, widespread pain syndromes. Consideration of this diagnosis is important, as both corticosteroids and IVIG have been used with some success. Celiac disease has also been implicated as a cause of small fiber neuropathy, or sensory predominant neuropathy.

4. Trigeminal Neuropathies

Trigeminal neuropathies present with numbness of the face in a trigeminal distribution, facial pain and masticatory weakness. Trigeminal neuropathies are different than trigeminal neuralgia in which sensation and strength are spared. There are a spectrum of etiologies for trigeminal neuropathies including autoimmune conditions such as mixed connective tissue disease, scleroderma, Sjögren's syndrome, and sarcoidosis. If there is no clinical deficit (facial numbness, atrophy of the temporalis and masseter muscles, weakness of the jaw), additional studies such as blink reflexes in the electrophysiological lab are helpful. Imaging with an MRI, with and without gadolinium contrast, visualizing the complete trajectory of the trigeminal nerve should be performed to exclude a mass lesion. Recommended laboratory studies include a complete blood count, erythrocyte sedimentation rate, extractable nuclear antigen antibodies and other autoimmune markers of connective disease. Undifferentiated and mixed connective tissue diseases are most commonly associated with trigeminal neuropathy, followed by scleroderma and Sjögren's. In general patients with connective tissue disease often do not respond to corticosteroids. There is limited data regarding the response in Sjögren's associated trigeminal neuropathy, and corticosteroids have been used with variable success.

5. Neuromuscular Side Effects of Rheumatological Drugs

Certain drugs used to treat rheumatologic diseases are associated with significant peripheral nervous system manifestations. Colchicine, a treatment for gout, causes a relatively painless myoneuropathy often in the setting of kidney dysfunction. Cytokine inhibitors such as etanercept and infliximab which are used for rheumatoid arthritis and psoriatic arthritis can cause chronic inflammatory demyelinating polyneuropathy. Leflunomide, which is a treatment for rheumatoid arthritis, can cause a severe axonal, sensorimotor neuropathy. Rheumatologic diseases and their treatments are associated with a wide array of peripheral nervous system manifestations, many of which are treatable and reversible. The neurologist must be aware of this possibility to allow for prompt diagnosis and initiation of therapy.

Suggested References:

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