Mononeuritis multiplex

Jun Kimura, MD

Polyneuropathy consists of a triad of sensory changes in a glove and stocking distribution, distal weakness and hyporeflexia. Certain types of neuropathy may show widespread sensory symptoms, and others may begin with more prominent proximal weakness. Positive sensory symptoms result from ectopic impulse generation and auto excitation of myelinated afferent fibers. Generally, but not always, normal muscle stretch reflexes speak against peripheral neuropathy. Acute pandysautonomic neuropathy characteristically shows severe postganglionic sympathetic and parasympathetic dysfunction, with a relatively or complete sparing of motor and sensory function. Milder autonomic dysfunction also accompanies most peripheral neuropathies, but manifests clinically detectable symptoms only in a few conditions, such as diabetes, amyloidosis, Guillain-Barré syndrome, porphyria, and familial dysautonomia. Such autonomic disturbances usually result from acute demyelination or damage to small myelinated and unmyelinated fibers.

A detailed history often reveals general medical conditions such as diabetes, alcoholism, renal disease, malignancies, sarcoidosis, periarteritis nodosa, amyloidosis and infectious processes such as diphtheria and leprosy. Inflammatory neuropathies include Guillain-Barré syndrome and chronic inflammatory demyelinating neuropathy. Metabolic neuropathies result from nutritional deficiencies or the toxic effects of drugs or chemicals. The family history is essential in establishing the type of inherited conditions associated with polyneuropathy. Sometimes a patient's own account may not provide sufficient information, necessitating independent examination of family members. For some patients with an unequivocal diagnosis of polyneuropathy, extensive studies may fail to uncover the exact etiology. Hereditary and immune mediated polyneuropathy account for most cases. In one study, intensive evaluation permitted classification of 76% of 205 patients with initially undiagnosed neuropathy; the final diagnoses included inherited disorders in 42%, inflammatory-demyelinating polyradiculoneuropathy in 21%, and neuropathies associated with systemic disorders in 13%.

Anatomic diagnosis depends on clinical and electrodagnostic evaluation, but few specific patterns of peripheral nerve involvement characterize a given disorder. Nerve conduction and electromyographic studies delineate the extent and distribution of the lesions, and differentiate 2 major pathologic changes in the nerve, which are the axonal degeneration and demyelination. An index based on multiple electrophysiologic measures against standard norms may provide a better overall estimation as reported in the assessment of diabetic polyneuropathy. Electrical studies alone rarely distinguish clinical types of neuropathies or establish the exact etiology in a given case. Arriving at a specific diagnosis and establishing a course of therapy depend heavily on clinical, electrophysiologic and histologic assessments.

Clinical classifications of neuropathies are comprised of 1) polyneuropathy, length dependent and symmetrical; 2) mononeuropathy, either entrapment or compressive and 3) mononeuropathy multiplex, which may be seen as complication of other system disorders such as diabetes mellitus or as the primary manifestation of the disease as in necrotizing angiopathy and multifocal motor neuropathy and related disease. This paper reviews the essential characteristics of the last 2 entities as they relate to electrophysiologic abnormalities.

Necrotizing angiopathy and diabetic mononeuropathy. In necrotizing angiopathy, which is probably related to autoimmune hypersensitivity, patients have systemic or non-systemic vasculitic neuropathy. The inflammatory process, possibly through endothelial cell activation, involves the small and medium-sized arteries in multiple organ systems, including the thoracic and abdominal viscera, the joints and muscles, and the nervous system. Necrosis of the media gives rise to small aneurysms and thrombosis of
the vessels, with palpable nodules along the affected arteries. This type of neuropathy also occurs in association with known or suspected connective tissue disease such as rheumatoid arthritis, systemic sclerosis, nonvasculitic, steroid-responsive mononeuritis multiplex, and Sjögren’s syndrome, or other multisystem diseases such as Wegener's granulomatosis and cryoglobulinemia with an IgM Kappa M protein.

The clinical symptoms and signs, which may appear either abruptly or insidiously, consist of malaise, fever, sweating, tachycardia, and abdominal and joint pain. Approximately one half of the patients develops neuronal disturbances such as diffuse polyneuropathy and mononeuritis multiplex. Neuropathy presumably results from ischemia caused by thrombosis of the nutrient arteries heavily infiltrated with inflammatory cells. The disease may remit spontaneously despite a generally poor prognosis, with survival of only a few months to a few years after the onset of clinical symptoms. In one series, 10 of 16 patients had features of mononeuritis multiplex and the remaining 6 had a distal symmetric sensory motor polyneuropathy. In another study of 23 patients with giant cell arteritis, 11 had generalized neuropathy, 9 had mononeuritis multiplex, and 3 had a mononeuropathy. Nerve conduction studies shows a slow velocity in proportion to reduced amplitude of the compound muscle and sensory potentials in the affected limbs. A conduction block may result from sub infarctive nerve ischemia affecting the segment outside the usual sites of compression mimicking demyelinating neuropathy. In series of studies, however, usually demonstrate conversion of the electrophysiologic findings to those most consistent with severe axonal loss. Electromyography reveals spontaneous activities in atrophic muscles as expected in acute or subacute axonal neuropathy.

Patients with diabetes mellitus may develop mononeuropathy multiplex often, though not always, affecting the ulnar, peroneal, or femoral nerve. Similar to diabetic truncal neuropathy, the entity probably constitutes parts of the spectrum of diabetic amyotrophy, sharing vasculitic changes as the common pathogenesis. Compared to the entrapment mononeuropathies, the disease evolves more rapidly. The patients complain of pain and respond poorly to decompression. Although a prednisone therapy may help suppress vasculitis, the loss of axons makes the prognosis guarded for recovery of muscle strength.

**Multifocal motor neuropathy with conduction block.** As a unique variant of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) is a potentially treatable condition that needs to be distinguished from atrophic poliomyelitis (ALS) and other motor neuron syndromes. Affected patients develop chronic asymmetric predominantly motor neuropathy with multifocal conduction delay and persistent conduction block. Although MMN typically causes distal upper limb weakness and atrophy, proximal muscles, biceps brachii in particular, may show hypertrophy possibly associated with continuous motor unit activity. Similar to earlier reported cases with sensory and motor involvements, the long-lasting conduction block suggests chronic demyelination as the pathological basis. The patient often has normal or occasionally even increased stretch reflexes with a normal or only slightly elevated cerebrospinal fluid (CSF) protein. Some patients develop cranial nerve involvement and others, central demyelination. These features make it difficult to diagnose the condition solely/mm² in the control. Axonal diameter and myelin thickness had a linear relationship in the normal subjects. In contrast, the patient had numerous large-diameter axons with thinner myelin, although some normally myelinated large axons remained.

The underlying pathogenic mechanism centers on elevated titters of anti-GM1 antibodies found in a wide variety of neuromuscular conditions, but more commonly in some lower motor neuron disorders and in MMN. Antibodies may have a predilection for the GM1 component of motor fibers, which have a longer carbon chain than sensory fibers. Autoantibodies may exert their effect, partly, by binding to GM1 on the surface of motor neurons. Anti-GM1 antibodies may or may not cause motor dysfunction by binding to the nodal and para nodal regions. In one study, sera of patients with MMN induced conduction block in rat tibial nerves, but sera of patients with progressive spinal muscular atrophy did not, despite a similar elevation of anti-GM1 titers. These antibodies however, may not have a causal relationship with MMN, as evidenced by many patients without raised levels. Surface-bound antibodies directed against major axoplasmic antigen might be interfering with demyelination rather than causing demyelination. In some cases, nerve ischemia may play a role in the pathogenesis.

In an extraordinary case, a patient had received a duck embryo rabies vaccine 3 months before the onset of the motor neuron disorder. She had a multifocal conduction block, elevated levels of anti-GM1 IgM antibodies, and deposits of IgM at nodes of Ranvier. Aside from attacking motor neurons guided by the abundant GM1 on the cell surface, anti-GM1 antibodies may cause conduction block in peripheral nerves by binding to the nodes of Ranvier. An autopsy study in another patient showed findings consistent with both ALS and MMN. It is necessary to clarify the exact pathogenesis underlying these findings to properly classify the motor neuron disease and MMN.

A mononeuropathy multiplex may be seen as complication of other system disorders or as the primary manifestation of a disease. Previously, necrotizing angiopathy results in sensory and motor axonal degeneration, whereas MMN mainly causes segmental demyelination selectively affecting the
motor fibers. Nerve conduction studies, and electromyography help confirms the diagnosis by documenting the typical physiologic abnormalities and characteristic distribution of involvement in these entities, on the basis of clinical examination.

Conduction blocks typically involve unusual sites such as the median nerve in the forearm or brachial plexus rather than the common sites of compression seen in multiple entrapment neuropathies. Most patients have selective involvement of motor fibers with normal sensory conduction through the sites of motor conduction block. Both motor conduction block and abnormally increased threshold probably reflect a chronic focal demyelinating lesion that for yet undetermined reasons becomes persistent without repair. Some patients with features indistinguishable from ALS have multifocal motor nerve conduction abnormalities. In one series, 17 of 169 patients clinically diagnosed as having motor neuron disease had some abnormalities in motor nerve studies, including 10 with conduction block. A demonstration of motor conduction block at multiple sites differentiates this potentially treatable clinical entity from the small subgroup of ALS patients with only lower motor neuron involvement.

Electrophysiologic studies must confirm the diagnosis before initiating therapeutic trials, for example, immunosuppressants such as cyclophosphamide. Several authors have documented a successful treatment with intravenous immunoglobulin. Outcomes of therapy with either immunosuppressants or immunoglobulin vary, considerably among different reported cases. Some patients improve but do not return to normal, others stabilize, some require long term therapy and still others become refractory to any form of treatment. Most studies suggest better results with cyclophosphamide or human immunoglobulin therapy compared to prednisone or plasmapheresis.

In our series, 2 patients with MMN had focal conduction block involving motor but not sensory fibers at the site of nerve swelling. A nerve biopsy taken adjacent to the enlargement in one patient revealed subperineurial edema and slight thickening of the perineurium under low-power light micrographs. The perivascular area at the center contained scattered large-diameter axons almost devoid of myelin or with very thin myelin. These thinly myelinated axons usually had small onion bulbs. The presence of cytoplasmic processes covered with basement membrane suggested their Schwann cell origin. A nerve biopsy specimen from another patient also revealed a perivascular area containing scattered demyelinated axons surrounded by small "onion bulbs" morphometric studies with high-power light micrographs showed a fiber density of 6458 fibers/mm², compared with 7906 fibers.

Further Reading


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