CHAPTER 19

Motor Neuropathy and Monoclonal Gammopathy

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Motor neuropathy is manifested by weakness, wasting, fasciculation, and normal sensations; thus, it resembles motor neuron disease (MND) clinically (1–3). It can be generalized or involve one or more individual nerves, with acute, subacute, or slowly progressive onset. Motor nerve axons are primarily affected, not the perikaryon. Motor neuropathy is often immunologically mediated and, in contrast to MND, may respond to immunosuppressive therapy.

Laboratory investigations can aid in the diagnosis of motor neuropathy and provide clues as to its etiology. Electrophysiologic studies often reveal conduction abnormalities, including conduction block. Serologic studies may reveal high titers of anti-GM1 or GD1a ganglioside autoantibodies often in association with an IgM paraprotein. This chapter reviews aspects of motor neuropathy due to monoclonal gammopathy.

CLINICAL FEATURES

Motor neuropathy begins at almost any age from the second to eighth decade, with a predilection for men. The neuropathy can be generalized or involve only one or several nerves, and is frequently asymmetric. The arms are more frequently involved than the legs (4,5), and unlike MND, bulbar involvement and respiratory failure rarely if ever occur (6,7). It is usually slowly progressive, sometimes over 20 years or more (7,8). Deep tendon reflexes may be absent or hypoactive but are sometimes active in weak and wasted limbs (9–11); Babinski signs are never a feature of motor neuropathy, and myokymia rarely occurs (12,13).

ELECTRODIAGNOSTIC STUDIES

In both motor neuropathy and MND, electrophysiologic studies show reduced compound motor action potentials (CMAP) amplitudes, with fibrillation and fasciculation activity, and long duration neurogenic motor unit potentials on needle electromyography consistent with axonal degeneration and denervation. There may be associated demyelinating features that help distinguish it from MND, including slowing of motor nerve conduction velocities, prolongation of distal motor and F-wave latencies (into a demyelinating range), temporal dispersion, or motor conduction block. Some patients with motor neuropathy exhibit minimal electrical abnormalities in life and thus may be difficult to diagnose.

Multifocal demyelinating neuropathy with persistent conduction block was first described electrophysiologically in 1982 by Lewis et al. (14) among several patients with chronic sensorimotor demyelinating polyneuropathy characterized clinically by mononeuritis multiples and electrophysiologically by persistent multifocal conduction block. In 1985, Parry and Clark (15,16) described several patients with a syndrome resembling MND, but with multifocal motor conduction block and normal sensory conduction. Persistent motor conduction block is one feature that unequivocally identifies a patient as having a neuropathy, although its demonstration may be technically difficult. Paranodal and internodal demyelination increases the transverse capacitance and reduces the resistance at the internode. This increases outward leakage current, increasing the time the internal longitudinal current must flow to generate an impulse at the next node of Ranvier. If the transverse current leakage is excessive, not enough current may be available to depolarize the next node of Ranvier and the impulse blocks (17,18). The demonstration of a drop in the CMAP amplitude from proximal to distal stimulation is insufficient by itself to


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conclude the presence of conduction block because similar findings can result from submaximal stimulation along sites where the nerve trunk is deep to the skin such as at Erb's point (19). Interphase shift and cancellation of the negative phase of the motor unit action potential with the positive phase of another motor unit potential also results in significant drops in amplitude, particularly with chronic partial denervation. There is no definitive consensus as to the required amplitude or area loss for the block in multifocal motor neuropathy (MMN), with published figures ranging from 20 to 50% (4,5,13,20–26). However, an amplitude loss of up to 41% and area loss of 29% can be seen in normal subjects (27). Computer modeling indicates that temporal dispersion can result in a drop in amplitude of greater than 50%, but a drop in the area of greater than 50% is due to conduction block (28). The analysis of short nerve segments is most helpful in demonstrating conduction block because a gradual change in amplitude is also likely to be caused by temporal dispersion (29).

Motor conduction block may be verified by comparing the partially blocked CMAP with the surface-recorded potential obtained during maximal volitional effort. This is accomplished by triggering on the largest peak of the recruitment pattern during maximal effort (30). If the volitional summed potential is larger than the proximal CMAP, than true conduction block has not occurred and the reduced proximal amplitude may be due to submaximal stimulation.

Patients with motor neuropathies, diagnosed by presence of conduction block or elevated titers of anti-GM1 antibodies, frequently exhibit other conduction abnormalities. In nine patients with motor conduction block, the only features of demyelination were seen in the same or other nerves: temporal dispersion in five, slowed motor conduction velocity in seven, and prolonged distal motor latencies in four; all had prolonged F waves in at least one nerve (21). In a study of 16 patients with MMN including 9 with elevated anti-GM1 antibodies and 5 with motor conduction block, 15 patients had other features of demyelination: 5 had prolonged distal latencies, 7 had abnormal temporal dispersion, 8 had prolonged F waves not explained by distal slowing, and 13 had conduction velocity slowing. Eight patients had at least one nerve with pure axonal features but had other nerves meeting demyelinating criteria. The one patient that did not meet formal criteria for demyelinating neuropathy instead had a prolonged F-wave latency and a 31% drop in the median CMAP area across the forearm. Two thirds each of patients treated with intravenous immunoglobulin (IVIg) with or without conduction block improved (31).

Sensory conduction across the site of motor conduction block should be normal (16,26), but that generally requires special techniques to ensure that pure motor conduction is present (32,33).

PATHOLOGIC STUDIES

Nerve biopsy can be helpful in supporting the diagnosis of motor neuropathy. Noninflammatory demyelination was seen at the site of conduction block in two patients with anti-GM1 antibodies (34). Similar findings were seen in the peripheral nerves of other patients, although not at the site of conduction block (22,35). IgM deposits at the nodes of Ranvier were seen in the neural nerve of a patient with MMN and anti-GM1 antibodies (23); however, other reported cases were normal (25,36) or showed minimal abnormalities (36,37). Obturator motor nerve biopsy shows increased regenerative clusters of small myelinated fibers in comparison with those with MND (35).

There is limited postmortem data of patients with motor neuropathy; however, four patients (24,38–40) with a lower motor neuron syndrome resembling spinal muscular atrophy (SMA) were studied at postmortem examination. One patient with motor neuropathy and an IgM monoclonal gammopathy without known conduction block or elevated GM1 titers was reported by Rolland et al. (38). There was central chromatolysis of anterior horn cells accompanied by severe loss of nerve fibers in the ventral roots. Another patient with motor neuropathy and an IgM polyclonal gammopathy, in addition, showed endoneurial perivascular lymphocytic infiltration (39). A third patient with elevated anti-GM1 antibodies revealed immunoglobulin deposits on myelin sheaths with predominant involvement of the anterior roots, explaining the lack of correlation between the presence of distal conduction block and the distribution or severity of weakness (24). A fourth patient with motor neuropathy without anti-GM1 antibodies or conduction block had perineurial perivascular mononuclear inflammation in peripheral motor nerves (40).

Nonetheless, the differentiation of motor neuropathy from MND may be difficult even after extensive evaluation. Clinical features that may distinguish motor neuropathy from MND include the multifocal or asymmetric involvement, and prolonged time course. Electrophysiological may show persistent multifocal conduction block (16) or other signs of demyelination on electrophysiological studies (21,31). High titers of anti-GM1 and anti-GD1a antibodies often seen in motor neuropathy are rarely found in MND (11,41).

Motor neuropathy may also be difficult to distinguish from motor forms of CIDP and, as discussed in Chapter 15, both respond to immunsuppressive therapy (42). Unlike CIDP, however, motor nerve velocities in motor neuropathy are normal between regions of block as are sensory conduction studies, and the cerebrospinal fluid (CSF) protein is not commonly elevated. Corticosteroids are frequently helpful in CIDP but not in MMN (43–45).
MOTOR NEUROPATHY AND MONOCLONAL GAMMOPATHY

Monoclonal gammopathy results from the abnormal proliferation of monoclonal B cells that secrete excessive IgM, IgG, or IgA antibodies (46). The monoclonal antibodies are detected and characterized by serum protein immunoelectrophoresis or immunofixation electrophoresis and are called M-proteins or paraproteins. They may be autoreactive and cause autoimmune disease; however, 1% of normal adults have serum M-proteins, and the monoclonal gammopathy may be coincidental and unrelated to the motor neuropathy.

The incidence of peripheral neuropathy in patients with IgM monoclonal gammopathies is 5 to 50% (47–50). In most patients with peripheral neuropathy and IgM M-proteins, the monoclonal gammopathy is nonmalignant, and the M-proteins have autoantibody activity and react with oligosaccharide determinants of glycolipids or glycoproteins or glycoconjugates concentrated in peripheral nerve. Occasionally, it is sometimes associated with Waldenström’s macroglobulinemia, B-cell lymphoma, or chronic lymphocytic leukemia.

Structure of Glycolipids

Glycosphingolipids are composed of the long-chain aliphatic amine sphingosine, an acylated ceramide attached to one or more sugars. Gangliosides are complex glycosphingolipids containing sialic acid. Sialic acid is a generic term for N-acetylneuraminic acid. Gangliosides are designated G for ganglioside followed by M, D, T, or Q for mono, di, tri, or quad, respectively, referring to the number of sialic acids. Arabic numbers and lowercase letters follow and refer to the sequence of migration by thin-layer chromatography (51,52).

IGM MONOCLONAL GAMMOPATHIES

In 1968, Peters and Clatanoff (53) described a patient with SMA and IgM monoclonal gammopathy who improved with chlorambucil treatment. However, that patient probably had a motor neuropathy rather than MND. The first documented case of a patient with motor neuropathy and an IgM monoclonal gammopathy was reported by Rowland et al. in 1982 (38). That patient presented with progressive weakness, wasting, and fasciculation and had an IgM-k monoclonal gammopathy. Motor conduction velocities were slow, with normal sensory conduction.

Motor Neuropathy and Anti-GMI Antibodies

In 1986, Freddo et al. (54) described a patient with SMA clinically, anti-GMI antibodies, and an IgM monoclonal gammopathy. A second similar patient improved with intravenous cyclophosphamide therapy (55). In 1988, Pestronk et al. (20) demonstrated that patients with MMN and conduction block had high titers of IgM anti-GMI antibodies. In 1990, Yuki et al. (56) reported IgG anti-GMI antibodies in patients with acute motor axonal neuropathy, a variant of the Guillain-Barré syndrome (GBS). Estimates of the frequency of increased IgM anti-GMI antibody titers in patients with MMN range from 18 to 84% (11). In most patients, they are polyclonal, but some are monoclonal, and the total serum IgM concentration is often increased.

In a review of 14 patients chosen for the presence of highly elevated anti-GMI antibody titers, 5 had a single site of conduction block, 4 had multiple conduction blocks, 1 had diffusely slowed motor conductions, and the remaining had normal motor conductions.

In most patients, the anti-GMI antibodies recognize the Gal(B1-3)GalNAc determinant that is shared by asialo GM1 (AGM1) and the ganglioside GDLB. The same determinant is also present on some glycoproteins and is recognized by the lectin peanut agglutinin. Some of the antibodies, however, are highly specific for GM1 or recognize internal determinants shared by GM2 (57–60). Although GM1 and other Gal(B1-3)GalNAc-bearing glycoconjugates are highly concentrated and widely distributed in the central and peripheral nervous systems, they are generally cryptic and unavailable to the antibodies. However, anti-GMI antibodies bind to spinal cord gray matter and to GM1 on the surface of isolated bovine spinal motor neurons but not to dorsal root ganglia neurons (61). In peripheral nerve, GM1 ganglioside and Gal(B1-3) GalNAc–bearing glycoproteins are expressed at the nodes of Ranvier (62). Two glycoproteins have been identified as the oligodendroglial-myelin glycoprotein in paranodal myelin and a versican-like glycoprotein in the nodal gap (63). The antibodies also bind to the presynaptic terminals at the motor end-plate in skeletal muscle, where the antibodies might also exert an effect (55,64).

It is not known whether the anti-GMI antibodies cause or contribute to the disease or whether they are only an associated abnormality. The binding to motor but not sensory neurons correlates with the clinical syndrome. GM1 is highly enriched in myelin sheaths of motor nerves and differs in its ceramides in comparison with sensory nerves (65,66). This might render the anterior roots more susceptible to the autoantibody effects. In one study, rabbits immunized with GM1 or Gal(1-3)GalNAc-BSA developed conduction abnormalities with immunoglobulin deposits at the nodes of Ranvier (67), and in another, serum from a patient with increased titers of anti-GMI antibodies and IgM deposits at the nodes of Ranvier produced demyelination and conduction block when injected into rat sciatic nerve (68). The human anti-GMI antibodies have also been shown to bind to, and kill, mammalian spinal motor neurons in culture (69) and at the motor end-plate (70). Serum from patients with MMN both with and
without anti-GM1 antibodies block nerve conduction in the mouse phrenic nerve-diaphragm preparation (71). Anti-GM1 antibodies alter potassium current and, in the presence of complement, block sodium channels in rat myelinated nerve fibers (72). Based on the persistence of the motor conduction block and the pathologic findings of axons devoid of myelin and only minimal onion bulbs, Kaji et al. (73) suggested that anti-GM1 antibodies impair remyelination. The variable regions of anti-GM1 antibodies from normal individuals or patients with neuropathy exhibit multiple somatic mutations in their hypervariable regions, suggesting that they have been derived from a process of antigenic stimulation (74,75).

In contrast to the IgM anti-GM1 antibodies in patients with chronic motor neuropathies, increased titers of polyclonal IgG or IgA anti-GM1 antibodies are associated with acute motor axonal neuropathy. These have been reported to occur after infection with Campylobacter jejuni (56,76–79), which bears GM1-like oligosaccharides (80–82), or after parenteral injection of GM1-containing gangliosides (83–85a). Postmortem studies in some of the patients who died of GBS after C. jejuni infection showed noninflammatory degeneration of the anterior roots and chromatolytic changes in spinal motor neurons (78) similar to the chronic disease associated with IgM anti-GM1 antibodies.

**IgM Anti-GD1a Autoantibodies**

Several patients with motor neuropathy and anti-GD1a antibodies have been described. The first patient was a 73-year-old man with 3 years of lower limb weakness and an IgM-k monoclonal gammopathy. He had absent leg and reduced arm reflexes. CSF examination was normal, and nerve conduction velocity was slow. During 2 years of treatment with melphalan and corticosteroids, he did not progress (86). The other two patients had high titers of anti-GD1a IgM antibodies. One was a 66-year-old woman with 8 months of progressive weakness and wasting in distal muscles in the arms and legs. The second was a 63-year-old woman with 6 months of asymmetric weakness who was unable to walk or use her upper limbs. Sensation was normal in both, and reflexes were absent except for reduced ankle reflexes in the second patient. CSF revealed one to three white blood cells, and the protein content was between 60 and 78 mg/dL. CMAP amplitudes and motor conduction velocities were reduced, the latter into a demyelinating range. Some sensory responses were abnormal in the first patient, although they were normal in the other. The first patient did not respond to IV Ig or oral cyclophosphamide. There was a slight but progressive improvement with prednisone leading to the ability to stand and walk with a cane. The other patient improved with IV Ig and later rapidly deteriorated despite prednisone and plasma exchange, but reinitiation of IV Ig and oral cyclophosphamide led to improvement. In two other patients with IgG anti-GD1a antibodies and GBS, the clinical improvement was accompanied by a corresponding decline in anti-GD1a titers (87).

**IgG AND IgA MONOCLONAL GAMMOPATHIES**

Patients with motor neuropathies and nonmalignant IgA monoclonal gammopathies have also been reported (88,89) including several with IgA-δ monoclonal gammopathies (90–92). One patient had motor neuropathy with an IgG-k paraprotein and the Crow-Fukase syndrome of gynecomastia, hypertrichosis, leg edema, impotence, and a raised CSF protein (93). It is not known whether the monoclonal gammopathy in these patients were coincidental or related to the neuropathy.

**TREATMENT OF MOTOR NEUROPATHY**

The treatment of choice for motor neuropathy is IV Ig, which has been shown effective in placebo-controlled trials (4,94). A favorable response of IV Ig was reported in 67 to 100% of patients (95,96), including reduction of the degree of conduction block and an increase in the amplitude of the CMAP (21). However, its effect is transient, and prolonged therapy is often required. Frank remissions with (95) or without therapy (97) have also been reported, with benefit lasting up to 4 years (95). Patients can occasionally have a diminished response after prolonged treatment (95,98), but responsiveness to IV Ig can sometimes be restored with plasmapheresis, similarly to that of CIDP (99). Of the patients with motor neuropathy and anti-GM1 antibodies, those with conduction block have the best response to IV Ig (4), and of those with MMN, the presence of anti-GM1 antibodies is associated with a better therapeutic response (95). Patients without anti-GM1 antibodies or conduction block also respond to IV Ig (31,35).

The mode of action of IV Ig in motor neuropathy is probably multifactorial. Although titers of anti-GM1 antibodies remain unchanged after IV Ig treatment, it probably exerts anti-idiotypic activity (100,101) or blocks Fc-receptor-mediated recruitment of macrophages and inhibits complement activation and the action of various cytokines, as suggested in other autoimmune diseases (102–104).

Motor neuropathy is also responsive to the chemotherapeutic agents chlorambucil (55), cyclophosphamide (20, 32,43), and fludarabine (105), which lower autoantibody titers and serum IgM concentrations and lessen dependency on IV Ig. Oral cyclophosphamide or plasmapheresis have generally been ineffective (6,34). Corticosteroids are rarely beneficial and have been associated with disease exacerbations (43–45).

Rare patients with motor neuropathy without nerve conduction abnormalities suggesting demyelination also respond to immunosuppressive medications, including