CHAPTER 15

Multifocal Motor Neuropathy

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In 1985, Parry and Clarke (1) described a predominantly motor disorder with weakness, atrophy, cramps, fasciculations, and preserved tendon reflexes. Sensory symptoms were minimal without objective sensory loss. On the surface, these findings resembled motor neuron disease (MND), but the similarity was superficial; certainly the disorder should not have been mistaken for amyotrophic lateral sclerosis (ALS). The disorder differed from MND in the electrodagnostic finding of multifocal motor conduction block (MCM). Multifocal motor neuropathy (MMN), as it is now known, is rare but has stimulated considerable discussion because it is treatable, whereas most cases of MND are not. It has also highlighted the difficulty in defining conduction block, particularly in chronic denervation, and has resulted in attempts to establish better criteria for the definition of conduction block. Parry and Clarke (1,2) first emphasized the striking motor predominance and pointed out the resemblance to MND, but Lewis et al. (3) had previously described a similar disorder with strikingly multifocal slowly evolving neuropathy that differed from MMN in the finding of significant sensory abnormalities. It is likely that these disorders are pathogenetically identical and may both be variants of chronic inflammatory demyelinating polyneuropathy (CIDP).

CLINICAL FEATURES OF MULTIFOCAL MOTOR NEUROPATHY

The essential clinical feature of MMN is slowly progressive weakness that is strikingly multifocal. It is localized to individual peripheral nerves, which is in contrast to the pattern in MND that is myotomal. It is nearly always accompanied by muscle wasting that may be severe with other muscles normal in bulk despite severe weakness, another feature that distinguishes MMN from MND. Cramps, fasciculations, and myokymia also occur (4). MMN has a predilection for the arms whether it begins there or spreads there from the legs. Weakness of cranial muscles has been rarely reported: One patient had widespread bulbar weakness after almost 20 years of slowly progressive limb weakness (5) and the other presented with hemiatrophy of the tongue (6). Respiratory muscle involvement is equally rare. One patient had tachypnea after several months of severe quadriplegia without overt respiratory failure (7), whereas another died of respiratory failure (5). Although conduction block may be found at almost any site along the length of an affected nerve, the resulting weakness is usually most severe distally. There can be palpable enlargement or tumorlike swellings of the nerve corresponding to sites of conduction block (8–10), which appears on magnetic resonance imaging as areas of high T2 signal and gadolinium enhancement (10,11).

Subtle clinical sensory abnormalities are common. Patients with MMN (2,7,12–14) can have sensory abnormality, such as numbness or paresthesia, with or without objective sensory loss, especially late in their course. Hypo- or areflexia in severely weak atrophic muscles is common, but reflex loss in normal or minimally weak muscles also occurs, suggesting involvement of afferent fibers from muscle spindles. The sensory abnormalities suggest that MMN is a predominantly motor form of CIDP.

MMN typically begins in the third to fourth decade; however, childhood and elderly cases also occur. The progression is typically so slow that patients may not recall when the weakness first began. (One personal patient was unaware of biceps involvement despite profound weakness and wasting, and he unwittingly used trick movements to flex his elbow.) Patients usually remain ambulatory and functional even after years of progression. Another personal patient had weakness for 20 years at the time of diagnosis of MMN and remained functional 10 years later. Progression may be subacute (7), resulting in quadriplegia (4,7). Two fatal cases, including one reported in

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the literature (5) and one personal patient, died after more than two decades of progressive weakness.

The similarities of MMN and MND have been exaggerated with resulting uncertainty as to the number of ALS patients that prove to have MMN. Lange et al. (15) found MMN in 6% of patients with the clinical diagnosis of MND, but in my experience it is far less common. The differences between the two disorders outweigh their similarities. MMN should never be mistaken for ALS, even on purely clinical grounds for five reasons. First, bulbar involvement, which is common in ALS, is extremely rare in MMN. Second, Babinski and Hoffman signs, clonus, and frank spasticity are not encountered in MMN, although the finding of preserved tendon reflexes in limbs with weak, atrophic, and fasciculating muscles certainly raises the specter of upper motor neuron involvement. Third, severe weakness without wasting is a feature of MMN but never MND. Fourth, the weakness progresses slowly over years and decades in MMN and is rarely fatal, as compared with ALS in which death supervenes usually within 3 to 5 years of diagnosis. Fifth, weakness in MMN conforms to the distribution of individual peripheral nerves, whereas in ALS it is myotomal or upper motor neuron in type. Despite these substantive differences, weakness, atrophy, fasciculations, cramps, preserved reflexes, and a paucity of sensory abnormalities are common to both disorders. In addition, rare cases involve bulbar muscles and progress rapidly and individual deficits may become confluent, masking the conformity to a peripheral nerve distribution. Such cases require detailed electrodiagnostic studies to distinguish MND from MMN.

**ELECTROPHYSIOLOGIC STUDIES**

**Electrodiagnosis in Multifocal Motor Neuropathy**

**Motor Nerve Conduction Studies**

The diagnosis of MMN relies on the findings of motor nerve conduction studies (Fig. 1). The electrophysiologic sine qua non is focal or multifocal conduction block, confined to motor axons (2,13). Sensory conduction is normal, both distal to and through nerve segments with severe or complete MCB. The latter is most often found in forearm and distal nerve segments but can occur at any level (2,12–14,16). It can be seen at multiple sites along the length of a single nerve (7). Distal motor latency and F-wave latencies may be normal or prolonged (17). Conduction block is usually severe (11) and may be complete (14). Maximal conduction velocity through blocked segments is severely slowed when measured over short segments. However, conduction slowing over longer lengths of nerve when evaluated by conventional nerve conduction studies is less severe, and the velocity may even be normal (2,7), suggesting that the slowing is highly focal. Krarup et al. (14) confirmed this by stimulating at multiple closely spaced sites along the nerve, showing that conduction slowing and block was confined to segments of 3 to 10 cm in length.

**Sensory Nerve Conduction Studies**

Sensory conduction is normal in MMN. Parry and Clarke (2) evaluated sensory conduction by means of ascending compound sensory nerve action potentials and somatosensory evoked potentials, which were normal despite more than 90% MCB; however, others found somatosensory evoked potential abnormalities in the face of normal distal sensory conduction (18). Krarup et al. (14) showed that the decline of the sensory nerve action potential amplitude across segments of severe motor block was no different from controls. In one case, sensory conduction proceeded normally despite complete motor block. Abnormalities of quantitative sensory testing have also been seen (19).

**Electromyography**

Needle electromyography shows denervation in weak and wasted muscles in MMN. Fibrillation activity is
invariable and fasciculation is common. Weak nonwasted muscles can have a paucity of spontaneous activity, but voluntary motor unit potential (MUP) recruitment is reduced. Myokymia is occasionally seen and is an important clue to demyelination. In comparison with MND, denervation in MMN is confined to clinically weak muscles, whereas in MND and especially ALS, widespread denervation is invariably seen in clinically normal muscles.

**Definition of Conduction Block**

*Conduction Block in Acute Demyelination*

Normally only a small drop in the amplitude of the compound muscle action potential (CMAP) occurs along adjacent segments due to temporal dispersion. This amplitude drop should not exceed 15 to 20% along the wrist-to-elbow segment (20–22). In acute neuropathies, negative peak amplitude and duration criteria are sufficient to define conduction block. An amplitude drop of more than 20% is strongly suggestive of conduction block provided that temporal dispersion does not exceed 15%. When a demyelinating neuropathy progresses for more than a few days, the range of conduction velocities increases and abnormal temporal dispersion develops, resulting in decreased amplitudes and increased negative peak duration. Therefore, amplitude reduction alone is insufficient to define conduction block unless the negative peak duration increases by less than 15%.

The electrophysiologic features of acute conduction block due to pure demyelination can be examined by injecting antibodies to galactocerebroside, a component of myelin, into rat sciatic nerve (23,24). In the beginning, the distal response remains entirely normal. The proximal amplitude progressively falls to a nadir in 3 hours, but there is no temporal dispersion, and conduction remains normal using conventional techniques. Hence, a characteristic feature of acute demyelination is conduction block without slowing or temporal dispersion.

*Conduction Block in Chronic Neuropathies*

Changes in CMAP amplitude may be erroneously attributed to conduction block and can occur when the range of conduction velocities is increased or with chronic axon loss. As demyelinated axons remyelinate, there is an increased range of conduction velocities resulting in abnormal temporal dispersion and reduced CMAP amplitudes with proximal stimulation. The increased negative peak duration of the dispersed proximal response distinguishes this amplitude change from conduction block. However, amplitude reduction without an obvious increase in negative peak duration may occur due to interphase cancellation. The CMAP is comprised of summated MUP, and when there is a narrow range of conduction velocities and electrical impulses traverse a short distance, synchronous firing results in little opportunity for cancellation of the negative phase by the positive phase of other motor units. With longer nerve segments, desynchronization leads to some phase interactions and cancellation is inevitable, resulting in loss of CMAP amplitude out of proportion to the increased negative peak duration. In normal motor nerves, this effect is negligible because the long duration of normal MUPs (5 to 15 msec) necessitates a large phase shift before significant phase interaction occurs (25). In hereditary demyelinating neuropathy, there is equal slowing in all fibers and the range of conduction velocities is minimally increased, so that amplitude loss due to interphase cancellation rarely occurs despite severe slowing (26). In acquired demyelinating neuropathies there is a marked increase in the range of conduction velocities with major phase shifts, and the CMAP amplitudes are often reduced out of proportion to the increased negative peak duration and thus mistaken for conduction block.

Amplitude changes due to phase cancellation also occur with chronic denervation. When motor units are lost, terminal collateral sprouting of remaining units causes polyphasia, increasing the likelihood of phase interaction and cancellation (27). With fewer motor units, phase cancellation has a larger effect on the CMAP amplitude. Therefore, patients with MND or chronic axonal neuropathies may have significant amplitude reductions that may be interpreted as conduction block. Apparent conduction block in ALS results from phase cancellation in partially denervated muscles. Computer simulation studies show that interphase cancellation can reduce the CMAP amplitude by 50% (28). However, the amplitude and waveform changes occur smoothly along the nerve as more distant sites are stimulated, whereas in focal demyelination they are confined to restricted nerve segments.

The difficulties wrought by dispersion and phase interaction leading to changes in amplitude alone should be interpreted with caution (29). Three steps should be undertaken to determine whether there is true conduction block. First, amplitude changes should occur over a short nerve segment rather than gradually along the length of the nerve. This can be demonstrated by incrementally stimulating short segments percutaneously or by a monopolar needle. Second, individual motor units may be present with distal stimulation, but not upon proximal stimulation or with volitional activation. Third, the waveform of the electrically evoked CMAP should resemble the summed individual surface recorded MUP, elicited by maximal volitional contraction. There is conduction block if the electrically elicited CMAP cannot be resynthesized from the surface recorded unitary volitional responses, especially if the patient is cooperative. Amplitude, and even area, changes should be interpreted with caution unless these criteria are met. From a diagnostic perspective, amplitude, waveform, and velocity changes have the same implication as conduction block provided they are focal or multifocal because both indicate acquired demyelination. Conduction block causes loss of
function, whereas focal slowing and dispersion have negligible functional consequences.

**Pathogenesis of Pure Motor Block**

It is not known why conduction block in MMN is confined to motor axons. It may indicate a difference between the antigenic properties of the myelin of motor and sensory axons. The ceramide composition of gangliosides in human sensory and motor nerves is different, and that could impart antigenic differences to the myelin (30). There could be comparable demyelination in motor and sensory axons with a greater safety factor for impulse transmission in sensory axons, leading to conduction block in motor fiber alone (27). However, this is unlikely because the largest diameter axons have the most secure conduction and sensory axons are the largest. Demyelination could also be confined to motor fascicles within the nerve trunk, whereas the sensory fascicles are spared. Variation in the extent of the demyelination seen in different fascicles is common in CIDP, and the differences may occasionally be striking (31). On rare occasions, random demyelination may strike only motor fascicles, resulting in the clinical picture of MMN.

**LABORATORY INVESTIGATION IN MULTIFOCAL MOTOR NEUROPATHY**

The laboratory investigation of patients with MMN is seldom helpful. There is typically no associated systemic illness. Serum protein electrophoresis and immunolectrophoresis are usually normal; however, some patients have antibodies to a variety of glycolipid determinants (see below). Cerebrospinal fluid protein is usually normal.

**RELATIONSHIP OF MULTIFOCAL MOTOR NEUROPATHY TO ANTIGLYCOLIPID ANTIBODIES**

Pestronk et al. (13) first described two patients with MMN that had IgG and IgM GM1 antibodies. Of 500 patients with various motor syndromes so studied (32), 74 had a progressive, asymmetric, pure lower motor neuron disorder, sparing bulbar muscles; 77% had antibodies to gangliosides, a much higher proportion than normal individuals or in those with neurologic or nonneurologic disorders. Three clinically distinct groups were identified as follows. Twenty-five patients had MMN with distal weakness and proximal conduction block, 21 of whom had elevated or very high anti-GM1 antibody titers. In 28 patients, the weakness was distal without conduction block, 64% of whom had elevated anti-GM1 antibodies. In a third group, the weakness was proximal without conduction block. Only 2 of 18 patients so studied had anti-GM1 antibodies, but some had antibodies to other gangliosides. On the basis of these observations, anti-GM1 antibodies were assigned a critical pathogenetic role in MMN. However, others have been unable to confirm these results. Nobile-Orazio et al. (33) studied sera from 232 patients with MND; 23% had anti-GM1 antibodies, regardless of whether they had ALS, progressive bulbar palsy, or pure lower motor neuron disease. In addition, 19% of patients with other neuropathies had elevated antibodies. Others have also found antibodies to GM1 and other gangliosides in disorders of the lower motor neuron (34–36) and in ALS (37–39). Overall, about 70% of MMN patients have elevated GM1 antibody titers. The highest titers are found in MMN; however, a 10-fold elevation or more is characteristic of MMN. Lower titers are suggestive but nonspecific. Nonetheless, MMN should not be diagnosed on the basis of an elevated GM1 antibody titer nor excluded when normal or minimally elevated.

**PATHOLOGY**

**Motor Nerve Pathology**

Descriptions of the presumptive motor nerve pathology are derived from biopsies of mixed nerves in patients with MMN. One patient underwent biopsy of the right ulnar nerve in the axilla, along a site of documented MCB (40). More than half of the cross-sectional area of the nerve was normal, but there were patches of demyelination (Fig. 2). Many axons were thinly myelinated in relation to their diameter and some showed onion bulb formation, a feature of repeated demyelination and remyelination. Inflammatory cells were absent. A second patient had a biopsy of the medial pectoral nerve (10). At surgery, multifocal enlargements of the brachial plexus were seen and intraoperative nerve conduction studies across the site of enlargement in the medial cord documented severe MCB. The medial pectoral nerve, arising from the proximal medial cord at the site of focal enlargement, was removed. The low power light photomicrograph showed a patch.

**FIG. 2.** Ulnar nerve biopsy from the axilla at a site of conduction block. There is an area of demyelination in the center, but adjacent fascicles are spared. (From Ref. 40, with permission.)