Central motor conduction time in progressive multiple sclerosis
Correlations with MRI and disease activity

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Summary
The purpose of this study was to relate abnormalities of motor conduction time to the presence of spinal cord MRI lesions in progressive multiple sclerosis and to investigate the relationship between changes in motor conduction over time and clinical and MRI changes. Central motor conduction time (CMCT), serial MRI of the brain and spinal cord, and clinical evaluations were carried out in 20 patients with primary and secondary progressive multiple sclerosis. CMCT was carried out at the beginning and end of the study whilst the clinical and MRI examinations occurred at monthly intervals for 12 months. Median CMCT to abductor pollicis brevis was 14.8 ms (range 8.8–27.4 ms). The response latency to tibialis anterior correlated with disability measured on the Expanded Disability Status Scale. Latencies to upper limb muscles correlated with cervical MRI lesion load and the presence of atrophy of the cervical cord. Over the 12-month study period, 15 of 19 patients deteriorated clinically. However, an increase in motor response latencies occurred only in the four patients who had developed new cord lesions. The results suggest that prolonged CMCT is related to spinal cord lesion load and that, over time, changes in the CMCT occur only when spinal cord lesion load increases. Clinical change in progressive multiple sclerosis may therefore occur without either the development of new lesions on MRI scans or an increase in motor conduction time. This suggests that clinical deterioration in these patients may occur by a mechanism other than increasing demyelination. This may be progressive axonal degeneration.

Keywords: multiple sclerosis; motor conduction time; MRI; pathophysiology

Abbreviations: CMCT = central motor conduction time; EDSS = expanded disability status scale; FS = Functional Score

Introduction
Conduction in nerve fibres is propagated by the activation of sodium channels during the depolarizing phase of the action potential. In myelinated fibres such voltage-sensitive channels are clustered in high concentration within axon membranes at nodes of Ranvier and, at much lower density, within the internodal axolemma beneath the myelin sheath (Ritchie and Rogart, 1977). In a region of demyelination this structural relationship is disrupted and there is conduction block (McDonald, 1963; McDonald and Sears, 1969, 1970; Rasmisky and Sears, 1972). Initially, the density of sodium channels distant from the nodes of Ranvier is too low to support conduction, and the presence of potassium channels holds the membrane potential near to equilibrium potential (Waxman, 1977). In areas in which there is partial demyelination conduction may continue, although transmission is abnormal, being characterized by slowing of conduction velocity across the lesion, a prolonged refractory period of transmission and, importantly, an impaired ability to transmit trains of high frequency impulses faithfully. Following remyelination of an experimental central lesion, secure conduction returns (Smith et al., 1981). Although remyelination occurs in multiple sclerosis, and may be more extensive than previously supposed (Prineas et al., 1993), it is clear that recovery of function can occur despite persistent demyelination, as shown by relatively normal vision in the presence of persistent delays in the visual evoked potential (Halliday et al., 1973).

It has been shown that both continuous and microsaltatory conduction can occur along persistently demyelinated axons (Bostock and Sears, 1976, 1978; Smith et al., 1982) and can be explained by the aggregations of sodium channels which develop along the exposed peripheral axon (Waxman and...
Ritchie, 1985; England et al., 1990). These aggregations can account for the ‘physiological’ (φ) nodes described by Smith et al., (1982). However, the maximum conduction velocity along such axons (~2 m/s) is still much less than normal (~65 m/s).

The electrophysiological effects of demyelination within the human central nervous system may be investigated using stimulation of the motor cortex (Merton and Morton, 1980); responses in multiple sclerosis are characteristically delayed and temporally dispersed (Cowan et al., 1984; Mills and Murray, 1985). Central motor conduction time (CMCT) acts as a reasonable measure of the integrity of myelinated pathways, since, in contrast, experimental studies in surviving fibres running through lesions in which axonal degeneration has occurred have shown that conduction is normal or only slightly prolonged (McDonald and Robertson, 1972). Similar results have been obtained in human studies in disorders such as motor neuron disease (Berardelli et al., 1987) and hereditary spastic paraplegia (Thompson et al., 1987) in which axonal degeneration is the major pathophysiological factor.

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MRI has had a profound impact on the understanding of the pathophysiology of multiple sclerosis, particularly in relation to the development of the progressive phase of the disease (McDonald et al., 1992), which is the most important determinant of clinical disability (Rummark and Andersen, 1993). The MRI results of the present study, which have already been published (Kidd et al., 1996), have provided evidence to suggest that the pathogenesis of clinical impairment in relapse, in which there is a high incidence of new and enhancing MRI lesions, is different from that of progression; there are few new lesions during progression, but there is diminution of spinal cord cross-sectional area, implying progressive atrophy of fibre tracts. This change in cord area was not seen in a similar study of patients with an early relapsing–remitting course (Thorpe et al., 1996).

Therefore, in an attempt to define the nature of progressive multiple sclerosis further, the aims of the second part of this study were (i) to relate abnormalities of motor conduction time to the presence of spinal cord MRI lesions and (ii) to investigate what changes in motor conduction time occur over time and determine their relationship to clinical change and MRI activity in progressive multiple sclerosis.

**Methods**

Twenty patients were recruited from the population of multiple sclerosis patients attending the out-patient department of the National Hospital for Neurology and Neurosurgery. All had definite multiple sclerosis (Poser et al., 1983), 10 had primary progressive multiple sclerosis, defined as a clear history of progressive neurological deterioration from the onset of the disease, without relapse or remission, and 10 had a secondary progressive course, defined as a clear history of progressive neurological deterioration for ≥6 months, following an initial relapsing–remitting course. All had oligoclonal bands in the CSF. All subjects gave written informed consent to participate in the study, which had been approved by the ethics committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery.

A full history was taken from each subject, and it was followed by a detailed neurological examination. Disability was scored using the Functional Scores (FS) and Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Patients were seen at monthly intervals for 12 months, at which times they were re-examined and questioned about new or recurring symptoms, and the disability was scored by a single observer (D.K.).

**MRI protocol**

Sequence parameters have been noted in the previous paper (Kidd et al., 1996). All scans were carried out using a Signa 1.5-T superconducting system (GE Medical Systems, Milwaukee, Wis., USA) at the time of each clinical assessment.

**Brain MRI**

T₂- and proton density-weighted axial images of the brain were acquired using a fast variable echo sequence. T₁-weighted images were acquired 5–10 min following injection of gadolinium–DTPA (0.1 mmol/kg).

**Sagittal spinal cord MRI**

Two sets of 3-mm thick contiguous interleaved sagittal T₂-weighted images were obtained using a multi-array spinal coil (GE Medical Systems). T₁-weighted sagittal images were acquired 15–20 min following injection of gadolinium–DTPA. Brain and sagittal spinal cord scans were analysed by a neuroradiologist (B.E.K.), who was blinded to clinical details. At serial assessment the appearance of new and enlarging lesions on proton density and T₂-weighted images, and the appearance of enhancement on T₁-weighted images was recorded. Active lesions were defined as any new enhancing lesion or any lesion which, although not enhancing, was either new or enlarged on the proton density and T₂-weighted images.

**Axial spinal cord MRI**

Axial slices of the cord were acquired at the beginning and end of the study using a gradient echo sequence at each of four vertebral levels (C₅, T₂, T₇ and T₁₁). The cross-sectional area of the cord at each level was calculated by manually tracing the circumference of the cord images using Dispimage software (Dr D. L. Plummer, Department of Medical Physics, University College London, UK) on a Sun workstation by a blinded observer (D.K.). The change in cord area was calculated by subtracting the mean area at the
beginning of the study from that at the end. Atrophy was considered to be present when the measured area was >2 SD below that of the mean areas obtained for healthy controls at the appropriate level (Thorpe et al., 1993).

In the cross-sectional part of the present study, the appearances of the first scans were used to correlate with results of cortical stimulation, and the changes which had been noted to occur over the 12-month study period were used to investigate any change in motor conduction times over the same period.

**Cortical stimulation**

Stimulation of the motor cortex and the ventral roots at the spinal processes of C7 was undertaken by one observer (D.K.) using a Magstim magnetic stimulator at 80–90% and 40–50% of the stimulating output, respectively. Response latencies were measured in upper limb muscles after stimulation using a 150-mm outer diameter flat surface coil. Each hemisphere was stimulated in turn, by turning the coil over in order to reverse the direction of current flow. The cervical roots were stimulated by placing the edge of the flat coil over the spinous process of C7. Response latencies to tibialis anterior were measured on both sides simultaneously after stimulation using an angled butterfly coil 200 mm in diameter. The lumbar roots were not stimulated. Surface electrodes were placed over the following muscles on each side: biceps, extensor digitorum communis, the first dorsal interosseous, abductor pollicis brevis and tibialis anterior. Muscle responses were obtained at rest and with gentle background muscle activation. The signals produced were amplified using a Digitimer D150 system, and were band-pass filtered (53 Hz to 3 kHz). The data were sampled at 5 kHz.

The CMCT was calculated by subtracting the latency to onset of the EMG response to each muscle for ventral root stimulation from that for cortical stimulation.

Measurements of motor conduction time were then repeated after an interval of 12 months by the same observer, in order to investigate the nature of any possible change.

**Statistical analysis**

Spearman’s rank correlation was used to analyse relationships between variables and the Mann–Whitney U and Kruskal–Wallis tests for group data comparisons. Paired observations were contrasted using the Wilcoxon matched-pairs signed rank sum test.

**Results**

The clinical characteristics and MRI lesion loads for the total patient population and subgroups are summarized in Table 1.

Eleven patients had a moderate paraparesis (FS pyramidal score 2–3) and in nine it was severe (FS pyramidal score 4–5). Upper limb weakness was detectable in 10 subjects, loss of dexterity in only seven, and three had increased reflexes in the upper limbs with normal muscle power.

**MRI**

In the brain, involvement of the brainstem (50 lesions), internal capsules (26 lesions) and corona radiata (286 lesions) was seen.

Sixty-three lesions were detected in the spinal cord, of which eight were anterior, nine posterior and 36 central, and another 10 occupied the full thickness of the cord in sagittal section. Cord atrophy was noted in eight cases (five primary progressive, three secondary progressive).

**CMCT**

Figure 1 shows the CMCT to each upper limb muscle and the minimum latency to response measured at the tibialis anterior in each case. The median (range) CMCT to the right biceps was 7.5 ms (4.6–17.5 ms) and that to the right abductor pollicis brevis was 14.8 ms (8.8–27.4 ms). There was no significant difference between the right and left sides for the median CMCT to any muscle, nor between the primary progressive group [14.9 ms (range 6.6–27.4 ms) to the right abductor pollicis brevis] and the secondary progressive group [16.3 ms (10.4–22.8 ms) to the same muscle] (P > 0.05). This conduction time was significantly greater than from departmental normal control data using the same technique (van der Kamp et al 1991) [median CMCT 7.0 ms (5.0–7.6 ms), P < 0.001].

The median minimum latency of the response at the right and left tibialis anterior was 48.3 ms (27.6–84.6 ms) and
Fig. 1 Scatterplot showing minimum CMCT to right upper limb muscles and minimum response latency of the tibialis anterior (TA) in all 20 patients at the first assessment, and minimum CMCT to the right abductor pollicis brevis (APB) in departmental control subjects. R = right; BI = biceps; EDC = extensor digitorum communis; FDI = first dorsal interosseous.

45.8 ms (26.6–86.1 ms), respectively. Again, there was no significant difference between these values for patients with a primary versus secondary progressive disease course.

**Association between motor conduction and clinical features**

Latencies to tibialis anterior showed a weak correlation with the EDSS ($r = 0.458, P < 0.05$) but not with pyramidal FS score ($r = 0.227$). The CMCT to upper limb muscles did not correlate with any clinical measurement. The CMCT to the abductor pollicis brevis was more prolonged in the nine patients with weakness of the small muscles of the hand (median CMCT 15.4 versus 13.6 ms), but this was not significant.

**Association between motor conduction and MRI lesions**

The CMCT to upper limb muscles correlated with MRI lesion loads in the cervical cord (for the extensor digitorum communis, $r = 0.548, P < 0.05$; for the first dorsal interosseous $r = 0.689, P < 0.01$; and for the abductor pollicis brevis $r = 0.677, P < 0.05$), but the latency to response of the tibialis anterior did not correlate with whole cord lesion load ($r = 0.249, P > 0.05$). This could be due to the fact that there was an unmeasurable muscle response in four (20%) patients, all of whom had severe paraparesis.

There was no difference in latency between patients who had lesions involving the whole transverse section of the cord and those who did not, nor in those who had only anteriorly placed lesions. There was also no correlation between number of brainstem and internal capsular lesions and latency to any muscle tested.

The presence of cord atrophy at C5 was associated with a significantly longer CMCT to the biceps (median 10.6 ms versus 6.5 ms) ($P = 0.01$) but not to hand muscles.

**Change over 1 year**

**Clinical changes**

One patient in the secondary progressive group had to withdraw from the study following a severe relapse, and the electrophysiological measurements could not be repeated. In the primary progressive group, eight subjects (80%) had deteriorated neurologically on examination, resulting in a change in EDSS, and seven subjects (78%) in the secondary progressive group had also worsened on the EDSS, of whom four had had a total of seven superimposed relapses. Overall the median change (± SD) in EDSS was $1.0 ± 0.97$ (range 0–3).

**MRI**

There was a total of 132 active brain lesions, 112 (85%) of which occurred in the secondary progressive patient group; 121 (92%) of the total enhanced.
In the spinal cord there were six active lesions. Four of these were new thoracic lesions and two enlarging cervical lesions, one of which was enhanced; three of the lesions were in the primary progressive group, three in the secondary progressive group.

There was a significant decrease in cord cross-sectional area at C5 overall ($P < 0.05$); the median change in area at C5 was $-2.62$ mm$^2$ (range $-20.45$ to $+6.70$ mm$^2$) (Kidd et al., 1996).

**Motor conduction times**

The CMCTs to upper limb muscles were remarkably unchanged over the course of the study period (Table 2), and there was no correlation with clinical deterioration ($r = 0.06$). Latencies to response at the tibialis anterior increased only in the four patients in whom new cord lesions developed [median increase in latency at the right tibialis anterior was $11.0$ ms (range $10.4$–$30.0$ ms), at the left tibialis anterior $22.2$ ms (range $24$–$30.2$ ms)] ($P < 0.01$), whilst in the 15 patients in whom no new cord lesions were seen, latencies did not change significantly [median increase in latency at the right tibialis anterior $0.9$ ms (range $-7.6$ to $+8.2$ ms), at the left tibialis anterior $-0.5$ ms (range $-7.0$ to $+7.6$ ms) ($P > 0.5$)] (Fig. 2). The presence of enlargement of cord lesions in the sagittal plane was not associated with any significant change in response latency.

There was no significant correlation between the decrease in cord area at C5 and the change in response latency to any muscle tested ($r = 0.19$).

**Discussion**

This is the first study in which motor conduction times have been studied together with spinal cord imaging in both a cross-sectional and a longitudinal fashion. This was facilitated by the use of multi-array coils and fast imaging techniques, which allowed the acquisition of high resolution MRI scans of the whole cord (Thorpe et al., 1993). The CMCT to upper limb muscles correlated significantly with MRI lesion load in the cervical cord, suggesting that, at least in patients with a progressive course, the number of lesions seen and their extent are significantly associated with the resultant disordered conduction.

The presence of cord atrophy at C5 was associated with a significantly longer conduction time at muscles innervated from the C5–C7 segments of the cervical spinal cord, but not at more distal muscles. Lesion load in the cervical cord correlated with upper limb muscle CMCT but not conduction to the legs. In a study of benign multiple sclerosis (Filippi et al., 1995), conduction times were less prolonged than in patients with a secondary progressive course matched for disease duration. This cannot be accounted for by a smaller cord lesion load since this has not been found to be the case (Kidd et al., 1993).

Is conduction delay associated with functional impairment? As previously reported (Ingram et al., 1988) the present study found that latency at the tibialis anterior correlated with EDSS, implying that this is so. However, latencies at muscles of the hand were similar in weak and strong hands, suggesting a more complicated association of CMCT with muscle weakness. The relationship between CMCT measurements and clinical signs in the upper limbs of patients with multiple sclerosis has been discussed by van der Kamp et al. (1991); patients with normal tonic strength assessed on clinical examination may have significant conduction delay in central motor pathways. However, the extent to which conduction delay occurred was inversely correlated with phasic muscle force, reflecting the importance of corticospinal tract function in the fine manipulative aspects of hand and finger movement (van der Kamp et al., 1991). The effects of demyelination on conduction, with conduction block and temporal dispersion of volleys, would distort or interrupt the passage of multiple descending volleys after cortical stimulation to prevent or delay motor neuron depolarization. Conduction failure, longer CMCT and functional impairment are likely to be related, although subtle tests of function may be required to reveal this.

A longitudinal study may provide important information about the nature of change over time. One of the aims of the present study was to investigate the nature of change in motor conduction accompanying increasing neurological impairment; acquisition of new lesions may be associated with conduction block, or increasing conduction time, causing an increase in the temporal dispersion of descending volleys so that summation of responses may not be as likely to elicit motor neuron discharges (Day et al., 1987), or there may be an altogether different mechanism.

### Table 2 Conduction times to right upper limb muscles at first and second assessments

<table>
<thead>
<tr>
<th></th>
<th>Biceps</th>
<th>Extensor digitorum communis</th>
<th>First dorsal interosseous</th>
<th>Abductor pollicis brevis</th>
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<tr>
<td><strong>First assessment (n = 20)</strong></td>
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<tr>
<td>Median CMCT (ms)</td>
<td>7.5</td>
<td>10.8</td>
<td>14.1</td>
<td>14.8</td>
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<tr>
<td>Range</td>
<td>4.6–17.5</td>
<td>5.6–22.3</td>
<td>6.0–28.3</td>
<td>8.8–27.4</td>
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<td><strong>Second assessment (n = 19)</strong></td>
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<tr>
<td>Median CMCT (ms)</td>
<td>7.4</td>
<td>12.5</td>
<td>13.7</td>
<td>14.2</td>
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<tr>
<td>Range</td>
<td>4.6–17.9</td>
<td>4.6–22.7</td>
<td>6.6–32.8</td>
<td>6.0–27.6</td>
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</table>
This study has shown that an increase in response latency occurs only if new lesions are seen to develop. The significant change in the response latency of tibialis anterior in four patients occurred only in association with the development of new lesions within the thoracic cord. Importantly, in the remaining 15 patients in whom no new cord lesions had developed, none of the muscles tested showed changes in response latency over the course of 1 year. This suggests that changes in latency as a result of demyelination do not necessarily occur in patients with progressive disease, despite clear evidence of clinical deterioration. It is likely that small new lesions are beyond the resolution of current imaging techniques. However, experimental studies have shown that lesions as small as 100 µm can induce conduction block (Ochoa et al., 1972), and with some lesions (probably smaller ones), possibly in combination, an appreciable (65%) reduction in conduction velocity can occur (McDonald and Sears, 1970). It may therefore be argued that measurements of motor conduction time, being a sensitive marker of the integrity of central motor pathways, could have identified new lesions which were too small to have been seen on MRI scans. It has already been noted, in the Introduction section, that little or no change in CMCT takes place in patients with diseases in which axonal degeneration occurs; clinical change without any accompanying increase in response latency may therefore be due to axonal loss without increasing demyelination.

Physiological studies on experimental demyelinating lesions (McDonald and Sears, 1970) have shown that conduction in some fibres was associated with conduction block, whilst others retained the ability to conduct, although with considerably increased conduction times. Morphological studies of the same type of lesion showed that, at a given level, some lesions contained completely demyelinated fibres, whilst others showed some fibres which were incompletely demyelinated or not demyelinated at all (Harrison et al., 1970). Evidence from studies of the visual evoked response suggests, however, that it is conduction block rather than slowing which is important in determining visual deficit (Persson and Sachs, 1981). The vision of patients who recover from acute optic neuritis may return to normal, yet they have a very prolonged visual evoked response latency (Halliday et al., 1972, 1973). In contrast, the acute phase, in which there is diminished visual acuity, is associated with absence of visual evoked responses, owing to conduction block (Halliday et al., 1973). If, as has been intimated above, clinical deficit is associated principally with conduction block, rather than simply conduction delay, it may be postulated that the lesions of the progressive phase are associated with a greater proportion of completely demyelinated lesions than those in non-disabled patients. Alternatively, or additionally, there may be a failure of reparative mechanisms; alteration in sodium channel density along naked axons is probably responsible for the return of slow saltatory conduction in experimental demyelinated lesions (Black et al., 1991) and an increase in sodium channels has been shown to occur in demyelinated plaques with many surviving axons (Moll et al., 1991).
entered, the mechanism maintaining the internodal sodium channels fails.

There are, however, other reasons why conduction may fail; the presence of TNF-α (tumour necrosis factor-α) and other cytokines (Brosnan et al., 1988) is thought to affect conduction adversely in inflammatory lesions. This raises the possibility that the electrophysiological differences between benign and progressive multiple sclerosis are contributed to by continuous low grade inflammation in the latter, causing conduction block, whilst there is quiescence in the former (Kidd et al., 1994).

In summary, these studies have increased understanding of the pathophysiology of progressive multiple sclerosis. The lack of change in conduction velocities along with an absence of MRI change and a reduction in spinal cord area suggests that progressive clinical impairment in such patients may be due to fibre tract degeneration in the spinal cord in the absence of the development of new MRI-visible lesions.

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