Magnetic stimulation study in patients with myotonic dystrophy

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Abstract

To further define motor nervous system alterations in myotonic dystrophy (MD), motor potentials to transcranial and cervical magnetic stimulation (MEPs) were recorded from the right abductor pollicis brevis muscle in 10 patients with MD and in 10 healthy controls. Cortical and cervical latencies, central motor conduction time (CMCT), stimulus threshold intensity and cortical MEP amplitudes expressed both as absolute values and as %M were analysed. MEP cervical latency, absolute or relative amplitude and excitability threshold did not significantly differ in patients and controls. The mean cortical motor latency and CMCT were significantly prolonged in MD patients with respect to normal subjects. Moreover, CMCTs were found to be significantly related to stimulus threshold intensity ($P = 0.03$) and only marginally related to absolute cortical amplitude ($P = 0.06$). These findings are indicative of a central motor delay, also related to decreased excitability of motor neurons, in patients with MD. No correlations were found between individual neurophysiological parameters and age, duration of disease and clinical impairment. Our results suggest that magnetic stimulation studies can detect subclinical dysfunctions of the central motor system in MD patients, as one of the multisystemic manifestations of the disease, rather independent of the primitive muscle damage. © 1997 Elsevier Science Ireland Ltd.

Keywords: Magnetic stimulation; Motor evoked potential; Myotonic dystrophy

1. Introduction

Myotonic dystrophy (MD), the most common adult form of muscular dystrophy, is a multisystemic disease inherited with an autosomal dominant trait, with the gene located on chromosome 19. It is characterised by a high heterogeneity and clinical variability, with large individual variation in the clinical severity and the target organs affected. In addition to the characteristic signs of myotonia, weakness and muscle wasting, the disorder shows the occurrence of dystrophic changes in non-muscular tissues, i.e. alterations in the eye lens, testicular atrophy, cardiovascular abnormalities and changes in the pulmonary, endocrine, immune and central nervous systems (Harper, 1986).

Classical signs of nervous system involvement include neuropathic changes, as evidenced by several reports on peripheral motor and sensory conduction slowing (Mongia and Lundervold, 1975; Panayiotopoulos and Scarpalezos, 1976; Mechlér et al., 1982; Mondelli et al., 1993). In addition, multimodal evoked potential studies have shown signs of CNS involvement in patients with MD. In particular, abnormal findings in brain auditory (Thompson et al., 1983) and visual evoked (Ganes and Kerty, 1988) responses have evidenced impairment of the auditory and visual systems. Delays in central conduction times along the somatosensory pathway have also been reported by some authors (Streib, 1983; Gott and Karnaze, 1985; Ganes and Kerty, 1988), although not confirmed by others (Thompson et al., 1983; Bartel et al., 1984). In spite of the large number of SEP, VEP and BAEP investigations, we are not aware of previous motor evoked potential studies in MD.

In the present work we investigated the function of central motor pathways in MD patients by transcranial and cervical magnetic stimulation to further define motor nervous system involvement in this disease and the possible relationships with age, disease duration and muscular impairment.

2. Patients and methods

Ten patients (8 males, 2 females) with clinical and electromyographic evidence of myotonic dystrophy were examined. The mean age was 36.27 ± 11.80 years, the mean age...
at onset was 26.53 ± 8.59 years and the mean duration of disease was 11.47 ± 11.17 years.

They included 8 hereditary cases (belonging to 4 families) and 2 apparently sporadic cases. Four patients had cataract, and no patients presented abnormal thyroid function or glucose intolerance.

The clinical muscular weakness was classified as follows and arbitrarily scored for statistical analysis: (1) presence of myotonia and/or mild functional weakness without functional impairment; (2) moderate muscle weakness leading to some degree of functional impairment; (3) muscle weakness with severe functional impairment and in some cases resulting in the subjects being bound to a wheelchair; and (4) bedridden.

There was no clinical or laboratory evidence of other neurological disorders or diseases giving rise to peripheral neuropathy. There was no malignancy and none of the patients were on drugs known to be toxic for the nervous system.

The controls were 10 healthy subjects (7 males, 3 females) with a mean age of 34.18 ± 10.73 years. All subjects gave informed consent for the study.

Transcranial magnetic stimulation (TMS) of motor cortex was carried out using an Esaote stimulator with a 9 cm circular coil centered over the vertex. The current direction in the coil was counterclockwise for preferential activation of the left hemisphere (Rossini et al., 1994). During the procedure subjects were seated comfortably on a chair, maintaining a state of relaxation of the tested muscle. We first determined resting motor threshold by increasing stimulus intensity progressively in 5% steps until reaching a level which induced at least three MEPs in six consecutive stimulations (Macdonnell et al., 1991). Cortical stimulation was performed at 20% above each subject’s resting motor threshold and 10 responses were recorded.

To evaluate peripheral motor conduction from the spinal cord to the muscles, we stimulated over the cervical spine. The coil was placed with the lower edge over the C7 spinous process. A clockwise inducing current, as viewed from behind, was used for the right side stimulation.

Motor evoked potentials (MEPs) were recorded using surface electrodes placed over the right abductor pollicis brevis in a belly tendon montage, with filter settings of 10 Hz–10 kHz and a gain of 100 μV/cm.

We measured the latency of cortical and cervical MEPs and the amplitude of cortical MEPs. The shortest reproducible latency of the responses (from the first deflection of the baseline) and the largest peak-to-peak amplitude were selected. The amplitude of cortical MEPs was expressed both as absolute values (μV) and as a percentage of maximal M response to distal median nerve stimulation. In this way we obtained an approximation of the percentage of the motoneuron pool activated by scalp stimulation.

Central motor conduction time (CMCT) from the cortex to C7 was evaluated by the difference of cortical and cervical latencies.

Neurophysiological data were compared using Student’s t-test; linear regression analysis was used to test statistical correlations between any of the neurophysiological parameters and between individual abnormal values and muscular impairment, age, age at onset and disease duration. The observed values were considered abnormal when they were beyond ±2 SD of the normal mean.

3. Results

Table 1 shows mean values of MEP latencies, amplitudes, CMCT and stimulation threshold in patients and controls. Cortical motor latency and CMCT were significantly prolonged in MD patients with respect to the control group. The mean cervical motor latency and the mean amplitudes of MEPs, as well as stimulus threshold intensity, however, did not differ in patients and controls. Nevertheless, stimulus threshold intensity correlated significantly with CMCT (R = 0.69, P = 0.03) (Fig. 1). A negative relation was observed between CMCT and amplitude measures, expressed as a percentage of M (R = -0.64, P = 0.05), while only a marginally significant relationship was found between CMCT and absolute amplitude (R = -0.61, P = 0.06).

When analysed individually (Table 2) cortical latency was prolonged in 3 patients while cervical latency was prolonged only in 1 patient. An increase in CMCT was observed in 2 patients, 1 of which having an associated delay of cortical motor latency. Elevation of threshold was detected in 1 patient, who also showed a prolonged CMCT.

No abnormal amplitude values or absent transcranial or cervical responses were detected in the patients. Four patients (40%) showed at least one abnormal parameter of MEPs, while coexisting abnormalities were observed in 3 patients (Table 2).

Age at onset significantly correlated with CMCT (R = -0.72, P = 0.01), stimulus threshold intensity (R = -0.75, P = 0.01) and absolute MEP amplitude (R = 0.64, P = 0.05). No correlations were found between individual electrophysiological parameters and age, duration of disease and clinical impairment.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>MEP values in MD patients and controls (mean ± SD)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>Latency after cortical stimulation (ms)</td>
<td>23.16 ± 2.17*</td>
</tr>
<tr>
<td>Latency after spinal (C7) stimulation (ms)</td>
<td>13.70 ± 2.09</td>
</tr>
<tr>
<td>CMCT (ms)</td>
<td>9.46 ± 2.23*</td>
</tr>
<tr>
<td>Absolute amplitude (μV)</td>
<td>455.04 ± 278.66</td>
</tr>
<tr>
<td>%M</td>
<td>5.81 ± 4.77</td>
</tr>
<tr>
<td>Threshold (%MOS)</td>
<td>61.5 ± 9.73</td>
</tr>
</tbody>
</table>

*P < 0.05.
4. Discussion

Initially seen as a tool to measure conduction velocity in central motor pathways, similar to peripheral nerve conduction studies, transcranial magnetic cortical stimulation is now an essential addition to the standard neurophysiologic tests, as many parameters were found to provide useful insights into the function of the motor system (Caramia et al., 1988; Rossini and Caramia, 1988; Murray, 1992).

Our results are suggestive of a functional involvement of the motor system in MD patients, as revealed by the significantly prolonged cortical motor latency and CMCT.

Conventional peripheral motor nerve conduction studies have already demonstrated an involvement of the motor system in MD, the rostral limit of these studies, however, being confined to the proximal parts of the peripheral axons (Panayiotopoulos and Scarpalezos, 1976; Mechler et al., 1982; Mondelli et al., 1993).

Peripheral nerve slowing should be reflected in the prolongation of absolute latencies of centrally evoked MEPs, but the present investigation revealed that MD patients group differed from an age- and sex-matched control group for cortical motor latency, but not for cervical values. If we assume that latency on cervical stimulation is indicative of peripheral conduction, our findings appear to suggest that in our patients peripheral nerves in the upper limbs are only marginally affected. Indeed neuropathological changes are more frequently reported in the lower limbs (Panayiotopoulos and Scarpalezos, 1976; Mechler et al., 1982).

In our patients a central motor delay was evidenced by the CMCT mean value prolongation. This conduction time in fact is a result of the time taken to depolarise the intracortical neurons, transmission of the volleys along corticospinal tracts, depolarisation of the alpha motor neuron, and transmission along the lower motor neuron axon to the

Table 2

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical rating (1–4)a</th>
<th>Cortical latency (ms)</th>
<th>Cervical latency (ms)</th>
<th>CMCT (ms)</th>
<th>Amplitude (µV)</th>
<th>Amplitude (%M)</th>
<th>Threshold (%MOS)</th>
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<tr>
<td>1</td>
<td>51</td>
<td>M</td>
<td>3</td>
<td>21.6</td>
<td>16.2</td>
<td>5.4</td>
<td>1100.0</td>
<td>31.3</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>M</td>
<td>2</td>
<td>22.2</td>
<td>13.0</td>
<td>9.2</td>
<td>172.4</td>
<td>1.91</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>M</td>
<td>3</td>
<td>26.8b</td>
<td>16.8b</td>
<td>10.0</td>
<td>671.0</td>
<td>9.21</td>
<td>65</td>
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<tr>
<td>4</td>
<td>34</td>
<td>M</td>
<td>2</td>
<td>26.2b</td>
<td>13.4</td>
<td>12.8b</td>
<td>397.6</td>
<td>1.98</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>M</td>
<td>2</td>
<td>25.0b</td>
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<td>10.2</td>
<td>468.7</td>
<td>4.46</td>
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</tr>
<tr>
<td>6</td>
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<td>M</td>
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<td>22.2</td>
<td>16.0</td>
<td>6.2</td>
<td>438.7</td>
<td>3.35</td>
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<tr>
<td>8</td>
<td>16</td>
<td>M</td>
<td>1</td>
<td>23.4</td>
<td>12.0</td>
<td>11.4b</td>
<td>140.6</td>
<td>0.72</td>
<td>75b</td>
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<tr>
<td>9</td>
<td>20</td>
<td>M</td>
<td>1</td>
<td>22.2</td>
<td>11.8</td>
<td>10.4</td>
<td>422.0</td>
<td>10.79</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>F</td>
<td>1</td>
<td>20.0</td>
<td>11.2</td>
<td>8.8</td>
<td>507.7</td>
<td>13.15</td>
<td>60</td>
</tr>
</tbody>
</table>

Upper normal limits (+ 2 SD) 23.8 16.52 10.72

MOS, maximum output of the stimulator.

a Score of muscular weakness.

b Abnormal value (+ 2 SD of normal mean).
of identical intensity makes the amplitude values less variable of MEP amplitude to consecutive stimulations. Additionally, the number of descending volleys could be insufficient or require a longer time to achieve the temporal summation necessary for activation of spinal alpha-motor neurons. This mechanism could account in some measure for delays in CMCT observed in our patients and also explain the marginally significant correlation between CMCT and absolute MEP amplitude. In fact, when a low density of corticospinal neurons is activated, fewer fibres contribute to the generation of MEPs.

Various neurological diseases affecting the upper motor neuron, including stroke and demyelinating diseases, have been shown to be associated with abnormalities of the central motor conduction time (Thompson et al., 1985; Hugon et al., 1987; Murray, 1992). In our series, patients did not have other pathologies or risk factors (e.g. cerebrovascular disease) that could account for motor system dysfunction, but showed an incidence of CMCT abnormalities of 20%. This value may be considered relatively low compared to those generally encountered in such diseases as MS or ALS, where the clinical involvement of motor system is a rule (Hess et al., 1987; Schriefer et al., 1989), but it is comparable to the reported frequency of prolonged central conduction time along the somatosensory pathways in MD (Ganes and Kerty, 1988).

Other indices of upper motor neuron dysfunction, such as mean MEP amplitude or mean stimulus threshold intensity, did not show significant abnormalities in our patients compared to the controls.

Analysis of absolute amplitudes revealed a trend to lower values in MD patients, although the results failed to reach statistical significance ($P = 0.08$). Considering amplitude as %M, values were higher in the patient group without significant differences with controls. This is not surprising, being the consequence of lower mean M amplitudes in MD patients ($10.7 \pm 6.9$ mV versus $16.1 \pm 5.4$ mV, $P = 0.07$) as a result of muscular atrophy.

It must therefore be considered that absolute amplitudes in our series varied from $140 \mu$V to 1.1 mV; this large variability of MEP amplitude to consecutive stimulations of identical intensity makes the amplitude values less suitable for quantification than the latencies (Kiers et al., 1993).

Although considerable individual variation in clinical severity is encountered at any age, muscular impairment generally progresses with age, and it is worse in patients with earlier onset. Parallel to this, our data reveal a clear statistical relation between CMCT, threshold, absolute amplitude and age at onset of the patients. However, we did not find any correlation between neurophysiological parameters and degree of clinical impairment. This finding suggests that motor involvement did not run parallel to the clinical evidence of muscular impairment in our patients, as observed by other authors (Panayiotopoulos and Scarpalezos, 1976), that have evidenced how the severity of the neuropathic changes did not correlate with the degree of muscular atrophy and weakness in MD. Similarly, multimodal evoked potential studies have also revealed the presence of subclinical involvement of the afferent sensory and auditory system in MD, independent of the age, duration or clinical severity of the disease (Bartel et al., 1984; Fierro et al., personal communication). Lack of correlation between motor dysfunction and duration or severity of the disease, in our results, suggests that it is rather independent of the primitive muscle damage and probably is one of the multi-systemic manifestations of the disease.

Taken together, our findings lead to the conclusion that patients with MD present subclinical involvement of motor descending pathways, confirming that different functional systems may be affected as a part of this diffuse disease. Genetically determined abnormalities may be the basis of the multisystem involvement in myotonic dystrophy syndromes.

References


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