Prolongation of Central Motor Conduction Time in Chronic Fatigue Syndrome

Arnold Hilgers
Johannes Frank
Petra Bolte

ABSTRACT. We compared the central motor conduction time (CMCT) obtained by magnetic stimulation of the central nervous system (CNS) of 181 patients who fulfilled the criteria (see Fukuda 1994) for CFS with those of 27 healthy control subjects. A cortical and a cervical stimulation was performed on each person under standardised conditions, and the motor evoked potentials (MEP) either from Musculus Abductor Pollicis Brevis (M. APB) or from Musculus Abductor Digitii Minimi (M. ADM) was recorded.

For the CFS patients a significant prolongation of the central motor conduction time (M. APB right: \( p < 0.0001 \); M. ADP left: \( p < 0.00005 \); M. ADM right: \( p < 0.00005 \); M. ADM left: \( p < 0.005 \)) was observed compared to controls. The results presented in this study suggest a central nervous system dysfunction in CFS.

KEYWORDS. Chronic Fatigue Syndrome (CFS), central motor conduction time (CMCT), magnetic stimulation, motor evoked potential (MEP), central nervous system (CNS)

INTRODUCTION

A variety of somato-psychological symptoms along with longstanding debilitating fatigue are summarized under the term "Chronic Fatigue Syndrome" (CFS). In the 10th revision of the international classification of diseases (ICD-10), the World Health Organization (WHO) listed this syndrome in the category of neurological diseases as "Postviral Fatigue Syndrome" (1). At present it is not clear whether CFS is a disease on its own, or whether various disorders are concealed behind this term. This is largely the consequence of controversial results of research carried out on CFS to date (2,3,4), of the unclear aetiology, and of the disputed pathogenesis of this syndrome. However, there is strong evidence for disturbances of the immune system in this disorder (5,6,7,8).

To facilitate comparability between studies and to achieve uniform diagnostics, the Center for Disease Control (CDC), Atlanta, published diagnostic criteria for the disease (9,10). Single Photon Emission Computed Tomography (SPECT) of the Central Nervous System (CNS) of patients with CFS showed significantly reduced cerebral blood flow in several cerebral areas as compared to healthy controls (11,12). By performing Magnetic Resonance Imaging (MRI) of the brain in CFS patients in comparison with a control group, Buchwald et al. (13) were able to show that punctiform subcortical regions with an elevated signal intensity of T2-weighed images occur significantly more often in CFS patients as compared with controls, which is consistent with a demyelination. In addition, the significance of magnetic stimulation in demyelinising diseases has been demonstrated (14,15,16).

Magnetic stimulation is based on the physical principle of electromagnetic induction (17). Neuronal structures are excited by a monophasic magnetic field impulse (18). The motor-evoked potential produced by cerebral/cervical magnetic stimulation can be recorded by surface standard electromyogram (EMG) disc electrodes or concentric needle electrodes. To evaluate the CMCT a potential has to be obtained after cervical as well as after cortical stimulation.

Taking into account these findings and the observation of prolonged central motor conduction time in patients fulfilling the CFS criteria, the present study investigated the descending motor system of these patients by magnetic stimulation.
PATIENTS AND METHODS

Investigations were carried out on 181 CFS patients who fulfilled the CDC criteria and on 27 healthy control persons (19).

Previous experiments had shown that nerve potentials can be analysed more exactly by deduction of MEP with needle electrodes and therefore the MEP was recorded in this way for 178 of the 181 CFS patients. Due to needle pain in 3 patients as well as in the 27 voluntary control persons, recording with surface electrodes was preferred because the more accurate but painful deduction could not be justified in these cases. Other experiments showed that latency is not influenced by the superficial electrode.

Target muscles were:

Musculus Abductor Pollicis Brevis (M. APB, predominantly supplied by cervical root level 7: C7) in

a. 136 CFS patients (81 female, 55 male) with a mean age of 40.4 years; recording of potential by needle electrodes in 135 patients, by surface electrodes in 1 patient
b. 23 control persons (10 female, 13 male) with a mean age of 29.7 years.

and Musculus Abductor Digiti Minimi (M. ADM, monoradicular supplied by C8) in

a. 45 CFS patients (27 female, 18 male) with a mean age of 40.0 years; recording of potential by needle electrodes in 43 patients, by surface electrodes in 2 patients
b. 13 control persons (6 female, 7 male) with a mean age of 30.2 years.

The measurements were performed under standardised conditions. Every measurement included a transcranial stimulation of the motor cortex and a cervical root stimulation each leading to the excitation of the proximal part of the spinal nerve which is the main nerve to supply the muscle under investigation. Cortical stimulation was achieved by placing the excitation coil above the Vertex while a target muscle contraction of about 30% of maximal voluntary contraction was sustained. The excitation intensity was approximately 1.5 times that required to reach the stimulus threshold in muscular rest.

Cervical excitation and MEP from respective muscles at rest with approximately 1.2 times the threshold stimulus intensity was achieved by placing the excitation coil at C7 (stimulation of M. APB) and at C8 (stimulation of M. ADM).

The stimulation was always performed first on the right and then on the left side of the body. Special attention was paid to the use of the correct side of the coil for the excitation. The magnetic stimulator Magstim 200 used for this investigation induced an impulse with the following properties: voltage 2 – 3 kV, increase 150 µs, decrease 300 – 500 µs, electric flow 5000 A. The magnetic field applied corresponded to 1 – 2 Tesla; the Novamix standard coil had an external diameter of 5.5 cm and contained 19 coils of copper tape.

The muscular potentials were recorded either with Ag/AgCl-surface electrodes (diameter: 9 mm) or with concentric EMG needles (length: 27 mm). For the recording of the potentials an electromyograph, type Ms92a-Medelec, was used. The sweep time was set to 5 ms/cm and a filter-setting of 20 Hz LF and 10 kHz HF was used. The sensitivity was approximately 2 mV.

We mainly took into consideration the central motor conduction time (CMCT), which is the most consistent parameter of the MEP and the criterion best suited for assessing the descending motor system (20). The CMCT is calculated from the difference in latency between cortically and cervically induced muscular sum action potentials. Furthermore, the latency time of the cervically induced MEP was assessed. The CMCT and the latency times were measured in milliseconds (ms).

Height as a measure of the given conduction distance influences the latency time of the cortically and cervically induced muscle (21,22,16). Therefore, to assess the latency time of the cortically evoked potential a group of smaller persons (< 175 cm) and a group of taller persons (= 175 cm) were studied separately.

Because all data were not consistent with a normal distribution and did not show equal variances, we used the two-sided U-Test for comparison of patient and control groups. The significances resulting from the Bonferroni adjustment of the a level were included.
RESULTS

In 14 of the 136 CFS patients no potential of the target muscle M. APB (9 times on the right and 5 times on the left side of the body) could be obtained. Of these 14 patients, no potential could be evoked by cervical stimulation in 13 cases, in only 1 case stimulation was carried out only on one side because the patient showed a tendency to faint. In 5 of the 136 CFS-patients no potential of the target muscle M. ADM could be evoked (one time on the right and 4 times on the left side of the body) and therefore the determination of the CMCT was impossible. Among these 5 patients no potential could be obtained after cervical stimulation in 2 cases. For the remaining 3 patients neither a cortical nor cervical potential could be obtained on one side, because of pain.

For the target muscle M. APB the mean CMCT in the control group was 6.31 ms on the right and 5.56 ms on the left and in the CFS patients it was 8.06 ms on the right and 8.22 ms on the left (Table 1).

For the target muscle M. ADM the mean CMCT in the control group was 5.95 ms on the right and 6.35 ms on the left and in the CFS patients it was 8.30 ms on the right and 8.17 ms on the left (Table 2).

In 41.5 % of the patients, in whom after recording of M. APB the CMCT could be evaluated, the results were above the reference range obtained from the control collective (mean value ± 2 standard deviations). For the target muscle M. ADM in 57.7 % of the patients, in which a cortical and cervical potential could deduced, the results were above the corresponding reference range obtained from the control collective (mean value ± 2 standard deviations).

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The comparison of the CFS patients with the control group showed highly significant prolongation of the CMCT in CFS patients regarding the target muscles M. APB on the right ($p < 0.0001$), M. APB on the left ($p < 0.00005$), M. ADM on the right ($p < 0.00005$) and M. ADM on the left ($p < 0.005$) (see Figure 1).

A comparison of the cervical latency times of the two patient groups with different body height did not reveal any significant differences.

In about 50% of the patients with CFS the CMCT was above the reference range (mean ± 2 standard deviations) obtained from the control group while in less than 10% of the CFS patients the CMCT was below the reference range (Table 3).

The major results are summarized in Table 1-3 and in Figure 1.

**DISCUSSION**

The data obtained for the control group correspond well to previously published results (20,21,22). Because the use of different types of electrodes has no influence on latency of the potentials (23), a comparison between the patient group in which the potential was recorded by surface

![Central Motor Conduction Time (CMCT)](image)

**TABLE 3.** Percentages of CFS patients with a CMCT beyond the reference range obtained from the control group (m: mean value, s: standard deviation). The values are given with respect to the target muscle (M. APB rsp. M. ADM) and body sides (right rsp. left).

<table>
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<tr>
<th>Target Muscle</th>
<th>M. APB right</th>
<th>M. APB left</th>
<th>M. ADM right</th>
<th>M. ADM left</th>
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<td>CMCT</td>
<td>&lt; $m - 2s &gt; m + 2s$</td>
<td>&lt; $m - 2s &gt; m + 2s$</td>
<td>&lt; $m - 2s &gt; m + 2s$</td>
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</tr>
<tr>
<td>P</td>
<td>$&lt; 0.0001$</td>
<td>$&lt; 0.00005$</td>
<td>$&lt; 0.00005$</td>
<td>$&lt; 0.005$</td>
</tr>
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<td>Interval</td>
<td>0.8%</td>
<td>1.5%</td>
<td>0.0%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Percentage</td>
<td>41.7%</td>
<td>41.2%</td>
<td>52.3%</td>
<td>63.4%</td>
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</table>
or needle electrodes and the control group in which potential was recorded by surface electrodes is possible. Our data confirms this for all groups.

The main results of this study provide evidence for the possibility of a neurological disorder, in the region between the motor cortex and the proximal spinal nerve in proximity to the interverbral foramen in CFS patients. A prolongation of the central motor conduction time (CMCT) could result from disturbed conduction by demyelination or inadequate remyelination of the cortico-motoneuronal nerve fibres (14). Furthermore, the conduction could take place along less myelinated, slower-conducting neurons or via polysynaptic connections to the motor neurons (e.g., cortico-cerebrolospinal tract) after destruction of the fast-conducting nerve fibres, thus leading to a prolongation of the CMCT (24). A further cause to be considered for the prolonged CMCT would be a general fibre degeneration (15). Because the CMCT includes the survival time of the -motorneuron, a reduced excitability of the motor neurons could lead to a prolongation of CMCT (25).

The study of Buchwald et al. (13) showed MRI signal alterations in the brain of CFS patients which could also be explained by a demyelinating process in these patients. The prolonged CMCT found in this study could consequently be a further sign of an underlying demyelinating process in CFS patients. This consideration is supported by the widely accepted and proven relevance of magnetic stimulation in demyelinating diseases (14,15,16).

Cortically-evoked potential parameters (amplitude, duration of potential and number of base line passages) suggest a damage of predominantly fast-conducting nerve fibres in CFS. There might be several possible pathophysiological mechanisms leading to this destruction of nerve fibres. In the context of the immune dysfunction associated with CFS influences of cytokines on the central nervous system should be considered, especially the contribution of tumor necrosis factor alpha (TNF-a) (26-28). A possible influence on ionic channels, especially on the sodium channel, has been proposed (29).

From the magnetic stimulation experiments alone, however, we cannot prove one single mechanism. Therefore, all the mechanisms discussed or a combination of these must be considered as causes for the pathological changes found in the central nervous system of CFS patients.

Comparing the results of this study on CFS patients with similar data on patients with Multiple Sclerosis (MS), similarities in magnetic stimulation are obvious (15). In MS patients, however, pathological alterations are more marked. Buchwald et al. (13) also observed similarities of their MRI findings in CFS patients to those from MS patients. Komaroff (5) and Behan et al. (30) recognized the similarities in the clinical symptoms of both diseases. The immunological parameters of CFS patients (7,8,30) also show analogies with those from MS patients. Other diseases such as various hereditary degenerations of the corticospinal tract, cerebrovascular diseases, tumors of the CNS and stenoses of the spinal canal can also lead to alterations in the magnetically evoked potentials, and especially to a prolongation of the CMCT (24).

The manifestations considered above (MRI, clinical symptoms and immunological findings) have only limited specificity for the diagnosis of MS and can also be found in a number of other diseases and conditions.

A further question is how far CFS can be considered as a disease on its own, or whether it might be more a syndrome associated with early stages or manifestations of many chronic diseases.

CONCLUSIONS

The prolongation of CMCT found in CFS patients suggests a manifestation of the disease in the central nervous system. Because magnetic stimulation does not permit an unambiguous explanation of the aetiology of the prolongation of the CMCT, further studies should be carried out to elucidate the aetiology.
REFERENCES


