Abnormal corticospinal tract modulation of the soleus H reflex in patients with pure spastic paraparesis

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A B S T R A C T

Central motor conduction time (CMCT) is usually abnormally prolonged in leg muscles of patients with pure hereditary spastic paraparesis (PHSP). One consequence of such abnormality should be an abnormal timing in the modulation of segmental reflexes, which might be more relevant for the pathophysiology of spasticity-related gait disturbances than just the CMCT delay. We examined the effects of transcranial magnetic stimulation (TMS) on the soleus H reflex in 13 control subjects and 11 PHSP patients using a conditioning (TMS) and test (H reflex) paradigm. Interstimulus interval (ISI) was 0–100 ms in steps of 10 ms. The amplitude of the H reflex at each interval was expressed as percentage of the control H reflex and the conditioned curves were compared between control subjects and patients. In control subjects, TMS-induced facilitation of the H reflex with two well-defined phases: early (ISIs 10 and 20 ms) and late (ISIs 70–90 ms). In patients, the early phase of facilitation was significantly reduced, while there was facilitation at 40 ms that was not present in control subjects. However, neither the characteristics of the MEP nor the differential modulation of the H reflex correlated significantly with clinical measures of motor dysfunction. Our results indicate an abnormal effect of TMS on the H reflex in PHSP patients. This suggests that the excitability of interneurons and soleus motoneurons is not modified in tune with the arrival of descending inputs. Desynchronization of the descending volley may contribute to both the lack of early facilitation and the presence of abnormal facilitatory phases.

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Pure hereditary spastic paraparesis (PHSP) constitutes a heterogeneous group of disorders in which the main clinical feature is progressive gait disorder and lower limb spasticity [26]. Central motor conduction time (CMCT) is usually abnormally prolonged in patients with PHSP [3,6,13,20,22,32,34–36,38,41,42,45]. The abnormalities in corticospinal tract conduction of descending impulses may cause a disordered control of segmental leg reflexes that may be functionally relevant. The H reflex of the soleus muscle is the electrophysiological counterpart of the monosynaptic ankle reflex. Variations in its size are considered to reflect segmental motor excitability changes when other influencing factors are kept unchanged [28,44]. Therefore, we examined the effects of transcranial magnetic stimulation (TMS) on the size of the soleus H reflex in control subjects and PHSP patients.

We examined 13 control subjects (8 men and 5 women) and 11 patients (4 men and 7 women) with PHSP. The controls were healthy volunteers without history of nervous system disease. Their mean age was 43.7 ± 14.6 years. The diagnosis was made according to McDermott et al. [26] on the basis of a well-documented family history, characteristic clinical findings and gradually progressive evolution. The mean age of the patients finally selected for the study was 36.7 ± 15.3 years. The mean disease duration was 19.8 ± 14.1 years.

All patients had pure spastic paraparesis with no other disorders except for impaired vibration sense in eight and urinary problems in four patients. The severity of spasticity and paraparesis was assessed by using the modified Ashworth scale of muscle spasticity (ASH) and the Medical Research Council Scale (MRC) for the proximal (quadriceps femoris muscle) and distal muscles (gastrocnemius and soleus muscles) on upper and lower extremities of each side. A three-point functional grading scale was adopted for the study, modified from Behan and Maia [2]. Grade 1 was assigned to asymptomatic patients who had pyramidal signs in the lower
limbs with normal or only slightly spastic gait; grade 2 to patients with spasticity that were able to walk independently with or without support; and grade 3 to chairbound or bedridden patients. To further divide the patients of grade 2, we evaluated their subjective walking disability as the patient’s own estimation of how many meters he or she were able to walk before having to rest. All clinical and demographic information was obtained by an examiner blinded to the analysis of neurophysiological data.

The soleus H reflex was recorded by surface electrodes attached 2 cm apart over the muscle belly. Electrical stimuli were applied to the posterior tibial nerve at the popliteal fossa. The knee and ankle joints were carefully maintained in the same position (ankle joint at an angle of 105–110° and knee joint at an angle of 160–170°) using cushions and sand bags, and elastic bands wrapped around the leg. Stimulus duration was 1 ms. TMS was performed with a MagStim 200 magnetic stimulator (maximum intensity of 1.7 T). A double cone coil, appropriate to activate the interhemispheric area, was used in the study of soleus H reflex modulation. Cortical and spinal stimulation over the cervical and lumbar spine were applied to determine the CMCT to upper and lower limbs, by subtracting the latency of the MEPs elicited by spinal stimulation from the latency of those elicited by cortical TMS. Recordings were done in the thenar muscles for the upper limb and in the tibialis anterior for the lower limb. The TMS intensity used to calculate CMCT was 120% of motor threshold for each muscle. We determined motor threshold for the MEP as the lowest stimulus intensity needed to elicit an MEP of at least 50 μV in half the stimuli of a series of 8 or 100% of the stimulus output at rest. For the soleus H reflex modulation, we used 90% of threshold.

The intensity of the electrical stimulus applied to the posterior tibial nerve was adjusted to elicit a baseline H reflex of an amplitude about 10% of the supramaximal M response. If necessary, little adjustments of the stimulus intensity were done in order to maintain the amplitude of the control H reflex about the same along the whole test. We synchronized the triggering of both the magnetic and electrical stimulators at interstimuli intervals (ISI) of 0–100 ms in steps of 10 ms. In control trials, we applied only the posterior tibial nerve electrical stimulus and obtained the soleus H reflex. In test trials, TMS preceded the posterior tibial nerve electrical stimulus by predetermined ISIs. The ISI was chosen at random and control trials were interspersed between test trials also at random. To avoid habituation or sensitization of the H reflex, the inter trial time interval always exceeded 10 s. Two test trials were obtained for each time interval.

We measured the peak-to-peak amplitude and calculated the average between the two test trials for each interval. For interindividual normalization, the mean value obtained for the control H reflex was assigned 100% and that of the test trials for each interval were represented as percentages of that value. The SPSS 11.5 software was used for statistical analysis. We used the one-factor ANOVA for the analysis of the effects of interval on the modulation of the H reflex for control subjects and patients. Unpaired t-tests were used for the statistical analysis of differences between groups on each interval, with the Bonferroni’s correction for multiple comparisons. The unpaired t-test was also used for comparison of data on the MEPs between control subjects and patients. Correlation between neurophysiological data and clinical variables was examined with the Spearman’s correlation test.

All patients except 1 were classified as grade 2 of the Behan–Maia modified scale. The mean value of ASH was 1.9 ± 1.1 points, ranging from 0 to 3 in both proximal (quadriceps femoris muscle) and distal muscles (gastrocnemius and soleus muscle) in lower limbs. The mean value of MRC was 4.3 ± 0.5 points ranging from 3.5 to 5. Their subjective walking dyscapacity ranged between 100 and 5000 m.

Table 1 shows the mean data gathered after TMS in patients and control subjects. Differences between control subjects and patients were significant for all parameters of the MEPs recorded in leg muscles to cortical stimulation, but for none to spinal stimulation. In arm muscles the significant difference was only for the amplitude and duration of MEPs recorded to cortical stimulation. To note is the longer duration and lower amplitude of the MEP in PHSP patients with respect to control subjects. Individual CMCT was longer than the mean ± 2.5 S.D. of the control subjects in nine patients for the lower limbs and in two patients for the upper limbs.

Mean motor threshold for the soleus muscle was significantly higher in patients than in control subjects (68.2 ± 11.7% for patients vs. 51.8 ± 12.3% for control subjects; p < 0.01). The mean intensity for the stimulus used as conditioning for the modulation of the H reflex was 62.7 ± 12.3% in the patient group and 46.7 ± 11%.

In control subjects, ANOVA showed that interval had a significant effect on the size of the H reflex (F[10, 132] = 4.4; p < 0.01).

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Upper limbs (APB)</th>
<th>Lower limbs (TA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Patients</td>
</tr>
<tr>
<td>Motor threshold (%)</td>
<td>39.9 ± 5.8</td>
<td>41.0 ± 6.3</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>22.6 ± 1.7</td>
<td>23.0 ± 2.3</td>
</tr>
<tr>
<td>Spinal</td>
<td>14.2 ± 1.6</td>
<td>13.9 ± 1.2</td>
</tr>
<tr>
<td>Duration (ms)</td>
<td>22.6 ± 1.7</td>
<td>23.0 ± 2.3</td>
</tr>
<tr>
<td>Spinal</td>
<td>14.2 ± 1.6</td>
<td>13.9 ± 1.2</td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>2.3 ± 1.5</td>
<td>1.4 ± 0.8</td>
</tr>
<tr>
<td>Spinal</td>
<td>1.2 ± 1.9</td>
<td>2.5 ± 3.4</td>
</tr>
<tr>
<td>Area (mV ms)</td>
<td>41.3 ± 30.9</td>
<td>23.7 ± 18.6</td>
</tr>
<tr>
<td>Spinal</td>
<td>14.9 ± 24.4</td>
<td>33.5 ± 56.3</td>
</tr>
<tr>
<td>CMCT (ms)</td>
<td>8.5 ± 0.8</td>
<td>9.2 ± 2.1</td>
</tr>
</tbody>
</table>

The p values correspond to the statistical comparison to control subjects, unpaired t-test was used. APB: abductor pollicis brevis; TA: tibialis anterior; NS: not significant.
There was a significant facilitation of the H reflex in test trials at intervals 10, 20, 30, 70, 80 and 90 ms $(p < 0.05$ for all intervals). Similarly, there was a significant effect of interval in patients $(F(10, 110) = 2.1; p < 0.05)$. However, in this case, the post hoc analysis indicated larger H reflex at intervals 40, 50, 60, 70, 80 and 90 ms. Direct comparison of the percentage H reflex facilitation seen at each interval showed significant differences between control subjects and patients at ISIs 10 and 20 ms $(p < 0.01$ for both intervals). The figure shows examples taken from representative subjects of each group and the mean amplitude of the H reflex for each interval expressed as percentage of the control H reflex. Note the absence of the first phase of facilitation in patients. ISI = interstimulus interval; * significant changes at given ISI $(p < 0.05)$.

![Fig. 1. Representative examples of the TMS-induced H reflex modulation in a healthy subject (A) and a patient with PHSP (B). Individual traces for individual interstimulus intervals from 0 to 90 ms are superimposed. The graph (C) shows the mean amplitude of the soleus muscle H reflex for each interval for the control subjects and the patients expressed as percentage of the control H reflex. Note the absence of the first phase of facilitation in patients. ISI = interstimulus interval; * significant changes at given ISI $(p < 0.05)$.](image)

The results of our study have shown abnormally prolonged CMCT to lower limbs in a significant number of PHSP patients, which is in line with many other previous studies [6,22,34,38,42,45]. Also, we have found other abnormalities in the analysis such as a longer duration and a lower amplitude and smaller area than in control subjects. A new finding of our study is that TMS modulation of the soleus H reflex was abnormal in PHSP patients. However, none of these abnormalities correlated with the results of the scales used to evaluate motor dysfunction, including the subjective rating of walking disability. Probably, subjective appraisal of motor dysfunction results from the evaluation of multiple aspects of the disorder, including physiological abnormalities in motor pathways, compensatory mechanisms as well as social and personal factors.

Prolonged CMCT has been attributed to demyelination and functional loss of the fastest axons. However, this would not necessarily give rise to motor deficit if a sufficient number of conducting axons are preserved [19,24]. It has been already reported that the prolonged CMCT in PHSP patients does not correlate with clinical deficits [22,34,41,45] and does not match with the main finding of the very few pathological studies available in the literature, i.e., axonal loss and degeneration of the corticospinal tract [41,11]. No autopsy study has provided evidence for demyelination in the corticospinal tract in PHSP patients with prolonged CMCT.

The size and shape of the MEP vary from one stimulus to another and among subjects and, usually, these measures are considered not reliable enough for clinical evaluation. Reduced MEP sizes can physiologically result from central axonal lesions, central conduction block or decreased excitability of corticospinal or spinal motor neurons. Its variability is mostly due to varying degrees of desynchronization of the TMS induced spinal motor discharges [25]. Changes in MEP duration are not systematically documented in the assessment of MEPS but abnormally prolonged MEP duration has been indeed reported by Boensch et al. [3] in members of one SPG4 positive family in comparison to control subjects but also to members of other SPG4 positive family with different spastin mutation. Klebe et al. [22] reported the observation of abnormal polyphasic MEPS in all 22 patients of their study. This included 10 patients who did not have abnormalities in CMCT[22]. MEP duration could reflect the chronodispersion of the descending volley, which may be an important aspect of the pathophysiology of PHSP. In our patients, MEP duration, which is likely to reflect the degree of desynchronization of the descending corticospinal volley, correlated positively and significantly with the decrease of facilitation of the H reflex at the interval 10 ms.

The size of the H reflex is considered a measure of segmental motor excitability, which is under control by descending pathways. The excitability of the H reflex arc has been seen to change in a patterned fashion during walking [5,12,14,37,43], reflecting the mechanism by which the central nervous system controls segmental reflexes during motor actions involving leg muscles. The
patterned modulation of the H reflex seems to be a necessary aspect for adequate control of motor activities during bipedal gait. The effects of experimental activation of descending motor tracts on the soleus H reflex has been studied before, either using auditory stimuli intended to activate the reticulospinal tract [9,39], or cortical stimuli, intended to activate the corticospinal tract [7,16]. However, the modulation of the H reflex by descending inputs has been used only scarcely in clinical practice [10,47]. The pattern of TMS modulation of the H reflex [16,47] was that of two facilitatory phases, the first one occurring at about 10–20 ms and the second at about 60–70 ms. The origin of the two phases is unclear. However, the first phase has a time course and shape compatible with those described in the generation of an excitatory postsynaptic potential (EPSP) in alpha motoneurones by cortical stimuli [23]. Our TMS was subthreshold for a soleus MEP, but the transient increase in motoneuronal excitability induced by the subthreshold EPSP would lead the motoneurones to fire when the afferent excitatory volley generated in the posterior tibial nerve stimulus arrives. Our results suggest that PHSP patients cannot generate the same EPSP in lumbar motoneurones as control subjects. However, the mechanisms responsible for the second phase seem to be preserved. Although the exact origin of the second facilitatory phase of the H reflex is not known, the differences with respect to the first phase in PHSP patients suggests that the mechanisms for the two facilitatory phases are different. It is likely that some of the sources of late H reflex facilitation are reflex after activation of other, non-monitored, muscles. TMS might also have activated unimpaired slow conducting descending fibres. Further studies in this subject would be welcomed.

Klebe et al. [22] performed a complete quantitative gait analysis of PHSP patients, and reported a broad-based gait with increased variability of step length and step height and reduction of the temporal, spatial and kinematic gait parameters. The gait velocity, the step height, the step width and the cadence were significantly correlated with the results of Ashworth scale of muscle spasticity whereas no correlations of quantitative gait parameters with MRC were reported. In our study we found a positive correlation between the clinical parameters of MRC score for both lower limbs and the value referring meters the patient is able to walk. This suggests that the walking capacities are related to the preserved muscular power in lower limbs in PHSP patients.

Abnormal modulation of spinal reflexes in patients with spasticity has been already reported [8,18,21,29,30,33]. One important mechanism of modulation of segmental reflexes is presynaptic inhibition [31,40]. It has been shown that TMS transiently decreases presynaptic inhibition of soleus H reflex in healthy subjects at rest and during voluntary movements [17,27,46]. Therefore, the early facilitatory phase of the H reflex found in our subjects might result also from TMS reducing the amount of presynaptic inhibition of la afferents. Abnormal presynaptic inhibition has been reported in spastic patients at rest [1,15,33]. Abnormalities have been found also during tonic plantar flexion using vibration [18] or heteronymous inputs from the femoral nerve [29]. Our findings suggest that such abnormality may in part depend on a reduced strength of the descending corticospinal input, which may not be able to reduce presynaptic inhibition to the same level as in healthy controls. The failure of the patients with spasticity to increase segmental reflex facilitation to the same extent as healthy subjects may contribute to their motor dysfunction.

The abnormal TMS effect on the H reflex is a complementary finding to the results of previous studies in patients with spasticity that provide evidence of abnormal modulation of the spinal reflexes in spasticity. This is the first study demonstrating directly a disorder of the descending modulatory action of the central nervous system in spastic patients.

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References