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Are the neurophysiological techniques useful for the diagnosis of diaphragmatic impairment in multiple sclerosis (MS)?

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Abstract

Objective: To characterize cortico-diaphragmatic pathway involvement in multiple sclerosis (MS) by means of transcranial magnetic stimulation (TMS), and verify its clinical impact.

Methods: TMS from diaphragm (Dia), and abductor digiti minimi (AbdV°) was performed in 26 MS patients. Phrenic nerve (PN) conduction study was also performed. Expanded disability status scale (EDSS) and fatigue descriptive scale (FDS) were measured. Forced vital capacity (FVC), forced expiratory volume at the first second (FEV1), peak expiratory flow (PEF) were tested: the predicted percentage value (% pred) was considered.

Results: Cortical motor evoked potential (Cx-MEP) latency and central motor conduction time (CMCT) were prolonged, respectively, in 31 and 23% of patients from Dia, in 76 and 79% from AbdV°. PN-compound motor action potential (CMAP) was normal. EDSS correlated to Cx-MEP from AbdV° ($P < 0.01$), and PN-CMAP amplitude ($P < 0.05$), FEV1 % pred ($P < 0.01$), PEF % pred ($P < 0.01$). PN-CMAP amplitude correlated to FVC % pred $P = 0.05$, FEV1 % pred $P < 0.01$, PEF % pred $P < 0.01$. Fatigue was related to AbdV° Cx-MEP and CMCT ($P < 0.05$ and $P < 0.01$).

Conclusions: Cortico-diaphragmatic pathway is impaired only in a minority of MS patients. Lack of correlation between TMS findings from Dia and respiratory tests argues against its routinary use to detect subclinical respiratory alterations. Fatigue seems to be related to the motor impairment rather than to respiratory distress. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Multiple sclerosis; Diaphragm; Phrenic nerve; Transcranial magnetic stimulation; Respiratory function

1. Introduction

Respiratory muscle weakness in multiple sclerosis (MS) is usually described in the advanced phase of the disease, and accounts for the majority of the fatal events in such patients (Mc Alpine and Compston, 1952). However, in some cases respiratory involvement may occur earlier in the course of the disease, particularly during relapses (Guthrie et al., 1952). Respiratory muscle weakness could also contribute to fatigue and increased sense of effort experienced by MS patients.

MS has been the first neurological condition to be studied by both electrical (Cowan et al., 1984) and magnetic (Hess et al., 1986) stimulation of the brain.

Several studies have reported prolonged central motor conduction time (CMCT) to different muscle groups in patients with definite MS (Cowan et al., 1984; Mills and Murray, 1985; Ingram et al., 1988). Recently this technique has been successfully proposed for the non-invasive study of the diaphragm (Dia) (Zifko et al., 1996, Similowski et al., 1996) and phrenic roots (Chokroverty et al., 1995; Similowski et al., 1997). There are only few studies which addressed the diaphragmatic impairment in MS by means of transcranial magnetic stimulation (TMS) (Garland et al., 1996; Lagueny et al., 1998).

Garland et al. (1996) found Dia alterations in CMCT in 70% of their cohort, while Lagueny et al. (1998) demonstrated altered MEP latencies from Dia in 41% of the patients studied. The latter claimed also the usefulness of TMS for revealing infraclinical demyelinating lesions on central motor pathways down to the Dia.

However, the evidence of a poor correlation between central motor conduction abnormalities and clinical signs (Hess et al., 1987) questions a reliable prognostic value of this technique to detect respiratory subclinical involvement.

Thus we aimed to characterize the TMS findings,

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concerning the Dia muscle, in MS patients without severe impairment of respiratory function, and to verify the clinical impact of a likely subclinical cortico-diaphragmatic impairment, namely on fatigue.

2. Methods

Twenty-six patients (16 females and 10 males), mean age 44.1 ± 9.8 years (range 26–61), were recruited. The patients were selected on the basis of a good compliance and tolerability to the respiratory or neurophysiological tests. None of them showed dyspnea. The inclusion criterion was a diagnosis of definite or probable MS, according to Poser's criteria (Poser et al., 1983), and the exclusion criteria were the absence of history for epilepsy, cranial surgery or pacemaker use. Moreover none of the patients showed signs of peripheral neuropathy. Nine of them presented as primary progressive (PP), 12 as secondary progressive (SP) and 5 as relapsing remitting (RR) clinical form of the disease; all patients had been in stable clinical conditions for at least 2 months prior to the study. The severity of the disease was measured by the expanded disability status scale (EDSS) (Kurtzke, 1983).

Subjective fatigue was evaluated using the fatigue descriptive scale (FDS) (Iriarte and De Castro, 1994). Fifteen normal control subjects (9 females and 6 males), aged between 26 and 58 years (mean 38.2 years old) were examined as controls. All patients and volunteers gave their informed consent to the investigation, which was approved by the local ethical committee. All subjects were studied sitting in a chair equipped with head rest and with their abdomen unbound.

2.1. Neurophysiological tests

The recordings were carried out from hemidiaphragm (Dia), and from abductor digiti minimi (AbdV°) for comparison. The recording electrodes were placed over the muscle belly. For the Dia, the surface recording electrodes were applied 5 cm superior to the tip of the xyphoid process (G1) and on the costal margin 16 cm from the G1 electrode ipsilaterally (G2) (Zifko et al., 1996); the ground electrode was positioned on the ipsilateral upper arm (G3) (Fig. 1).

Magnetic stimulation of the motor cortex was carried out by a MAGSTIM 200 stimulator, producing a maximal magnetic field of 2.0 Tesla. A standard stimulation procedure was performed using a round coil of 9 cm diameter. The coil was applied to the scalp region, overlying the vertex in the mid-sagittal line, to evoke a cortical motor response (Cx-MEP) from Dia to C3–C4, according to the International 10–20 system, and to evoke a Cx-MEP from Abd V°. For the root stimulation (spinal motor evoked potentials–Sp-MEP), the round coil was kept flat against the upper cervical vertebral column with the handle pointing towards the feet, and the head of the patients was slightly bent forward. The largest amplitude was obtained generally 1–2 cm above the C5 spine.

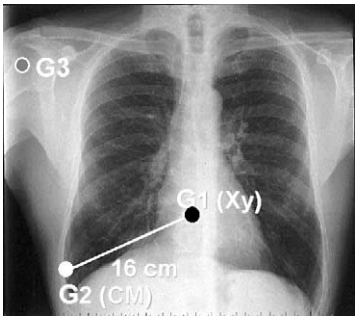

Fig. 1. Positioning of surface electrodes for recording from Dia. G1 indicates the active electrode, 5 cm from the tip of the xyphoid (Xy); G2 indicates the reference electrode, 16 cm from G1 on the costal margin (CM), G3 indicates the ground electrode.

The stimulus intensity was adjusted to obtain the largest reproducible responses (range 65–100% stimulator output). The magnetic pulse was monophasic; thus the coil's orientation was selected according to the cortical site under examination (Claus et al., 1990). During TMS, the patient was required to perform a slight contraction according to the muscle group under study; the level of contraction was defined for each subject, in order to obtain the largest amplitude of the evoked responses among 5 waves recorded for each muscle site. For the Dia, the patient had to perform a quiet inspiratory effort; recordings were rejected if electrocardiogram artifacts were encountered and the stimuli were repeated.

For all the patients, the neurophysiological recording was carried out bilaterally. The CMCT was calculated by subtracting latencies of the spinal evoked potentials from those obtained after cortical stimulation (CMCT = (Cx-MEP − Sp-MEP) latency).

Three conventional parameters of abnormality in response to TMS were considered: (1) prolongation of the Cx-MEP latency; (2) prolongation of CMCT, and (3) absence of Cx-MEP. Cx-MEP latency was measured at the onset of the first negative deflection of the evoked response. Cx-MEP amplitude was not considered because of the large variability even in normal conditions (Amassian et al., 1989; Eisen, 1992).

In all subjects, phrenic nerve (PN) conduction studies were performed bilaterally with percutaneous electrical stimulation at the border of the sternocleidomastoideus muscle. The stimulus duration ranged from 200 to 500 μs.

2.2. Respiratory tests

The respiratory function was studied by means of the routinary respiratory tests to evaluate the maximal voluntary effort: values of forced vital capacity (FVC), forced expiratory volume at the first second (FEV1) and peak expiratory flow (PEF) expressed as percentage of the predicted values. Maximal flow–volume curve was recorded using a spirom-

Table 1
TMS findings from Diaphragm and Abductor Digiti Minimi muscles[a]

	Cx-MEP (ms)	*P*	Sp-MEP (ms)	*P*	CMCT (ms)	*P*
Diaphragm						
Controls	13.6 ± 1.4 (11.3–16)		7.6 ± 0.7 (6.7–9)		6.0 ± 1.3 (4.4–8.5)	
MS patients	15.4 ± 2.6 (11.7–24.7)	0.025	8 ± 1.4 (5.0–11.5)	0.75	7.0 ± 2.0 (4.4–13.2)	0.039
Abductor Digiti Minimi						
Controls	19.6 ± 1.4 (17.2–22.2)		12.7 ± 1.0 (11.3–16.3)		6.7 ± 2.1 (5–8.9)	
MS patients	25.3 ± 5.6 (16–40)	< 0.0001	13.1 ± 1.5 (10.0–15.7)	0.49	12.2 ± 5.3 (4.7–26.8)	0.0004

[a] TMS, transcranial magnetic stimulation; MS, multiple sclerosis; Cx-MEP, cortical motor evoked potential; Sp-MEP, spinal motor evoked potential; CMCT, central motor conduction time.

eter (Sensormedics). Values exceeding 80% of predicted values were considered as normal (FVC % pred; FEV1 % pred, PEF % pred). Nocturnal mean PO_2 saturation was measured and 80% was considered the lower limit; the minimum PO_2 value was also included as well as the number of desaturation events longer than 10 s in 1 h (Des Index).

2.3. Statistics

Results were expressed as mean ± SD. Differences between MS patients and controls were calculated by means of unpaired Student's *t* test. Correlations between respiratory and neurophysiological finding were measured by means of parametric (simple regression line). Non-parametric statistical analysis (Spearman rank correlation coefficient) was applied to correlate clinical score to respiratory and neurophysiological measures. Probability values less than 0.05 were considered significant. The statistical software Statview SaS was used.

3. Results

Patients' duration of the disease was 12.8 ± 6.5 years and clinical conditions ranged from minimal to severe disability (EDSS score 5.5 ± 2.1, range 1.5–8.5). Mean FDS score was 6.5 ± 3.1 (range 3–14).

3.1. Neurophysiological tests

The results obtained from TMS were compared with the normal values of the age-matched controls. The upper limits of MEP latency and CMCT were set at the mean value obtained in the controls ± 2.5 SD.

TMS findings from Dia and Abd V° are reported in Table 1. The Cx-MEP and CMCT from Dia were slightly significantly longer in MS patients, with respect to controls (respectively, $P = 0.025$ and $P = 0.039$). The Cx-MEP latency and CMCT from AbdV° were significantly longer with respect to controls (respectively, $P < 0.0001$ and $P = 0.0004$). No significant differences were found in Sp-MEP latency between controls and MS patients in either recording from Dia or from AbdV°. In the recording from Dia, about 31% of MS patients showed alterations in Cx-MEP latency and 23% in CMCT on at least one side, while in the recording from AbdV° 76% of the patients showed alterations in Cx-MEP latency and 79% in CMCT on at least one side. Conversely, none of the patients from AbdV° and only two patients from Dia (7%) showed prolonged Sp-MEP latency recording. Dia and AbdV° Cx-MEP was could not be obtained in only one patient (patient nr. 20).

The percentage of abnormal Cx-MEP latency and CMCT, when both sides were combined, was even lower for the hemidiaphragms (19% of prolonged Cx-MEP latency and 18% for slowed CMCT), in respect to the upper limbs (64 and 54%, respectively).

Fig. 2 shows 3 patterns of Cx-MEP and Sp-MEP from ABD V° and DIA recorded in MS patients.

The values of latency and amplitude of PN-CMAP are reported in Table 2. On the basis of the mean ± 2.5 SD of the CMAP latency values of the controls, latencies over 9 ms were considered pathological. Only one patient (no. 2) showed prolonged CMAP latency value on one side (10.2 ms). The mean value of both CMAP latency and amplitude did not differ between MS patients and controls.

The comparison among the 3 clinical forms of MS showed significant differences only in Cx-MEP latency and CCT from Abd V° between PP (respectively, 27.1 ± 2.3 and 14.0 ± 3,2) and RR (respectively, 20.3 ± 3.4 and 7.1 ± 2.1) ($P < 0.01$**) and in CCT from Abd V° between RR and SP (12.5 ± 5.2) ($P < 0.05$*). This is likely due to the more severe clinical conditions of the PP and SP patients in our sample (mean EDSS-PP: 5.7; mean EDSS-SP: 5.9; mean EDSS-RR: 3.7).

3.2. Respiratory tests

All patients were able to perform the spirometric and oximetric tests. Four patients (15%) showed values of FEV1 % pred and PEF % pred under 80%; one patient (4%) showed reduced values only of FEV1 % pred and 6 patients (23%) only of PEF % pred.

The minimum values of nocturnal PO_2 saturation decreased below 80% in 6 patients (23%); conversely the mean O_2 saturation value and Des Index were still in the normal range. The findings are reported in Table 3.

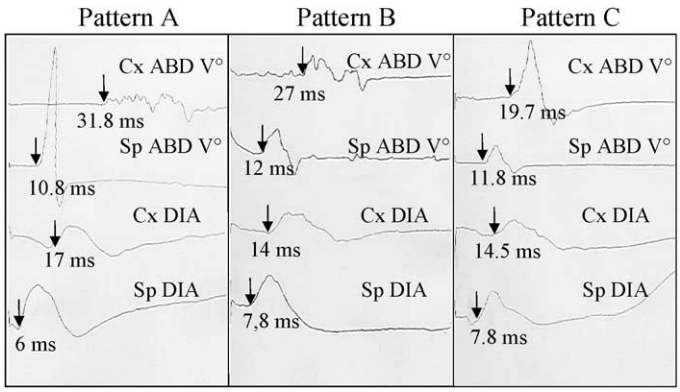

Fig. 2. Three patterns of Cx-MEP and Sp-MEP from Abd V° and Dia. Pattern A: prolonged Cx-MEP and normal Sp-MEP either from Abd V° or Dia; pattern B: prolonged Cx-MEP and normal Sp-MEP from Abd V°, normal Cx-MEP and Sp-MEP from Dia; pattern C: normal Cx-MEP and Sp-MEP either from Abd V° or Dia.

3.3. Correlations

Disease duration was not correlated to neurophysiological parameters. Disease duration was correlated to FEV1% ($r = 0.56$, $P = 0.0001$), but not to other respiratory parameters.

EDSS correlated to the Cx-MEP latency from AbdV° ($r = 0.39$, $P = 0.008$) (Fig. 3). EDSS was also correlated to FVC % pred ($r = -0.60$, $P < .0001$), FEV 1 % pred ($r = -0.55$, $P = 0.0002$) and PEF % pred ($r = -0.49$, $P = 0.001$).

Among the neurophysiological parameters, TMS findings did not show any significant correlations with the respiratory tests; only PN-CMAP amplitude significantly correlated to FEV 1 % pred ($r = 0.40$, $P = 0.008$) and to PEF % pred ($r = 0.42$, $P = 0.005$).

FDS was correlated to EDSS ($r = 0.44$, $P = 0.004$) and the duration of the disease ($r = 0.4$; $P = 0.01$). FDS score significantly correlated only to Cx-MEP latency and CMCT from AbdV° (respectively, $r = 0.52$, $P = 0.005$; $r = 0.52$, $P = 0.004$). FDS score did not correlate either to TMS findings from Dia or to respiratory tests.

3.4. Differences between groups

If we subdivide the MS patients into those presenting mild subclinical respiratory dysfunction and those who do not, the former have the most long-lasting duration of the disease ($P < 0.0001$), and a more severe clinical pattern, expressed by a higher EDSS score ($P < 0.0001$).

The neurophysiological parameters obtained by TMS and electrical stimulation of the PN did not differ in the two groups. Conversely the group with mild respiratory dysfunction showed significantly lower values of FVC % pred, FEV1 % pred, PEF % pred ($P < 0.0001$).

A chi-square test, performed to evaluate the validity of TMS, both from Dia and AbdV°, to discriminate patients with or without respiratory distress, did not show significant result (chi-square 0.19, *P*-value 0.89; chi-square 0.68, *P*-value 0.40, respectively). In fact, in 8 patients showing altered respiratory parameters, TMS from Dia was normal; TMS from AbdV° was normal only in two patients (8%). Conversely, only in 4 patients, TMS from Dia revealed subclinical alterations of diaphragmatic cortical drive, but in 9 patients (36%) TMS from AbdV° showed pyramidal alterations.

4. Conclusions

Respiratory alterations may occur in advanced MS, but it may also complicate relapses earlier in the disease. In paraparetic MS patients, expiratory muscle weakness increases as the upper extremities become involved; the presence of concomitant bulbar dysfunction enhances the likelihood of aspiration pneumonia (Smeltzer et al., 1988). However, the incidence of respiratory muscle involvement in MS is probably underestimated because patients with restricted motor activity usually do not complain of dyspnea. On the other hand, even in the milder form of the disease, impaired motor conduction in the respiratory pathway may contribute to

Table 2
Nerve conduction study from the phrenic nerve[a]

	PN-CMAP latency (ms)	*P*	PN-CMAP amplitude (mV)	*P*
Controls	7.2 ± 0.8 (6.3–9)		0.9 ± 0.4 (0.4–1.6)	
MS patients	7.2 ± 1 (5.4–10.2)	0.8	0.7 ± 0.4 (0.3–1.9)	0.1

[a] PN-CMAP, compound motor action potential of the Phrenic nerve; MS, multiple sclerosis.

Table 3
Respiratory tests of the MS patients[a]

FVC % pred	FEV1% pred	PEF % pred	Mean $SatO_2$	Min $SatO_2$	Des index
83 ± 15 (54–107)	96 ± 17.5 (59–120)	79 ± 22 (27–124)	93.2 ± 2.6 (85.6–98)	79 ± 11.8 (36–89)	5.2 ± 4.7 (0.7–16.3)

[a] FVC % pred: percentage of the predicted values of forced vital capacity; FEV 1 % pred: percentage of the predicted values of forced expiratory volume at the first second; PEF % pred: percentage of the predicted values of peak expiratory flow; Mean Sat O_2: mean oxygen saturation; Min Sat O_2: minimum oxygen saturation; Des Index: desaturation index.

fatigue and to the increased sense of effort experienced by MS patients (Foglio et al., 1994; Olgiati et al., 1988, 1989).

The activity of Dia is controlled by non-volitional mechanisms originating in the brainstem nuclei, which also regulate respiratory homeostasis (Khedr and Trakhan, 2001; Similowski et al., 1996). The voluntary respiratory pathway operates during wakefulness, allows behavioural modulation of respiration and the performance of volitional respiratory movement (Plum, 1970; Newson-Davis, 1974). The system depends on willed activity from the cerebral cortex through the corticospinal tracts and descending in the dorsolateral columns of the spinal cord (Plum, 1970; Aminoff and Sears, 1971; Howard et al., 1992).

In humans, the neurophysiological basis of the voluntary control of breathing appears to reside in the motor cortex (Foerster, 1936; Maskill et al., 1991), more precisely anterior to the thoracic muscle site of representation. Previous studies seem to confirm that cortical representation of each hemidiaphragm is predominantly contralateral (Maskill et al., 1991, Similowski et al., 1996), although some other findings are suggestive of a bilateral cortical representation (Khedr and Trakhan , 2001).

The study by Corfield et al. (1998) demonstrated that motor cortical excitation of the diaphragm is not mediated via brainstem respiratory neurons but, most likely, via the more direct corticospinal tract, fast conducting and oligosynaptic (Gandevia and Rothwell, 1987).

TMS represents a valid tool for a non-invasive investigation of the cortico-diaphragmatic pathway and is a high reliable measure in the diagnosis of MS (Ravnborg et al., 1992; Di Lazzaro et al., 1999). TMS seems to be useful also for revealing infraclinical demyelinating lesions on the central motor pathways down to the Dia (Lagueny et al., 1998).

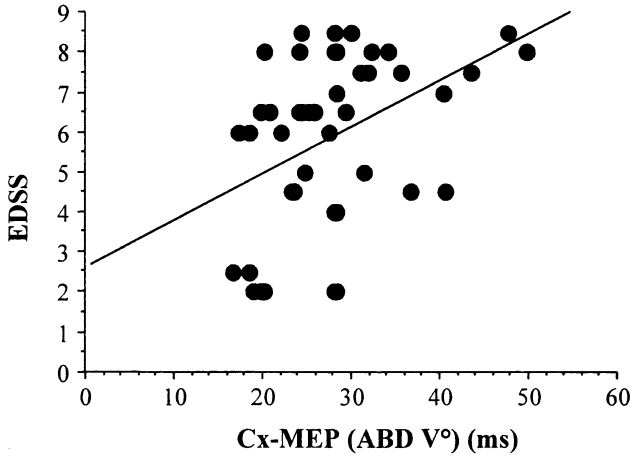

Fig. 3. Correlation between EDSS and Cx-MEP latency from Abd V°.

About 30 % out of our MS patients showed CMCT alterations from Dia. However, the mean value of Cx-MEP latency of our patients was slightly longer with respect to controls. Our Cx-MEP latency values from Dia are comparable with those reported by Gandevia and Rothwell (1987) and Zifko et al. (1996), although 1.5 ms longer than those reported by Khedr and Trakhan (2001). Such a discrepancy can be due to methodological differences with regard to the site of cortical stimulation and of the recording electrodes.

In the study by Lagueny et al. (1998), the percentage of abnormal MEP latency and CMCT was higher for the hemidiaphragms than for the upper limbs and was roughly the same for the hemidiaphragms and the lower limbs. Conversely, in our study we found a higher percentage (76%) of MS patients with CMCT alterations recording from AbdV° as compared to the percentage of patients with Dia TMS alterations. Furthermore the Cx-MEP latency recorded from AbdV° was significantly longer than that recorded from Dia when compared to controls. These findings support the evidence that in normal subjects the CMCT of different muscles is compatible with the craniocaudal distribution of the motor nuclei and therefore with the conduction distance along the corticospinal pathway. Our observations are also in agreement with previous studies (Buyse et al., 1997; Smeltzer et al., 1988) on the respiratory involvement in MS, which found that the involvement of expiratory muscles appeared to be more pronounced than that of the inspiratory muscles. The authors explained that paralysis in advanced MS tended to ascend slowly from lower extremities to upper extremities, as a result, the first respiratory muscles to be affected should be the abdominal muscles followed by the intercostal muscles. Dia, innervated by the phrenic nerve, may be expected to be the last to be affected.

In our study, none of the MS patients showed prolonged Sp-MEP latency, varying from other reports (Lagueny et al., 1998). Furthermore, in only one MS patient PN-CMAP latency was prolonged. Such findings do not allow the confirmation of a peripheral involvement in MS (Waxmann, 1993).

Disease duration was not correlated to neurophysiological parameters, and, among the respiratory parameters, only to FEV1 % pred ($P = 0.0001$). We found a correlation between neurological disability and pulmonary dysfunction,

in fact in the neurologically more disabled group, significantly worse pulmonary function tests (FVC % pred, FEV1 % pred, PEF % pred) were measured, as described by others (Smeltzer et al., 1988). This is probably due to the difficulty of some of these patients with a more severe motor impairment, to control the inspiratory and expiratory muscles when utilized during maximal effort. In fact, performing a pulmonary function test can be quite stressful for MS patients who often show poor tolerance and complain of fatigue (Olgiati et al., 1988).

EDSS was correlated to TMS findings from AbdV°, generally involved in the pyramidal impairment. Conversely, EDSS, expressing the degree of neurological disability, was not correlated to TMS findings from Dia; this can be due to the lack of items specific to test the respiratory function within such a score. All the more reason that we did not find any correlations among TMS findings from Dia and the respiratory tests. However, it should be considered that the use of other techniques, such as the transdiaphragmatic twich tensions, could improve these correlations.

We used FDS score to evaluate the severity and quality of fatigue. It is apparent that the FDS provides a global evaluation of the sensation of fatigue. We found that FDS score was directly related to EDSS and duration of the disease, as expected, this could mean that greater fatigue developed in weaker subjects and with longer history of disease. FDS was also directly related to TMS findings from AbdV°; previous reports found that the degree of symptomatic fatigue was proportional to that of pyramidal tract involvement (De Castro et al., 1994), but this was not confirmed by others (Sheean et al., 1997). Conversely, the score of fatigue did not significantly correlate to TMS findings from Dia and any of the respiratory parameters. The lack of a direct relationship between peripheral and central motor conduction abnormalities to the Dia and fatigue seems to question the possible role of the cortico-diaphragmatic pathway involvement as contributing factor for the respiratory muscle weakness and consequently to a symptomatic fatigue in these patients.

In conclusion, TMS from Dia shows subclinical cortico-diaphragmatic impairment in a minority of MS patients without pulmonary symptoms and with still fairly normal spirometric values. Nevertheless, the lack of correlation between TMS findings from Dia and respiratory tests argues against the routinary use of TMS from Dia, to detect subclinical respiratory alterations. Moreover, fatigue seems to be related to the motor impairment rather than to respiratory distress. However, subclinical TMS alteration from Dia could represent a predictor of the respiratory evolution in MS patients but to confirm such an issue, a longitudinal follow-up study is needed.

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