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Triple stimulation technique (TST) in amyotrophic lateral sclerosis☆

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Abstract

Objective: The authors studied amyotrophic lateral sclerosis (ALS) patients using triple stimulation technique (TST) to detect upper motor neuron (UMN) involvement.

Methods: Nineteen ALS patients (aged 45–72 years) were enrolled in the study. According to the El Escorial criteria, 6 diagnoses were suspected or possible, 6 probable, and 7 definite. Patients were examined clinically, with conventional (single-pulse) transcranial magnetic stimulation (TMS), and with TST (on one side only).

Results: Among the whole group of patients, TST appeared to be more sensitive than conventional TMS techniques. In particular among suspected/possible ALS patients, TST area ratio was pathologic in 100%, while single-pulse TMS was abnormal only in 50% of cases. Overall, the use of TST area ratio was more sensitive than the analysis of TST amplitude ratio.

Conclusions: The results suggest that TST might be more sensitive and useful in the diagnosis of subclinical UMN involvement than conventional TMS techniques, even if TST is performed on one side only.

Keywords: Transcranial magnetic stimulation; Amyotrophic lateral sclerosis; Triple stimulation technique

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease, mainly involving the upper (UMN) and lower motor neuron (LMN). Transcranial magnetic stimulation (TMS) of the motor cortex may be useful to reveal upper motor neuron involvement (Miscio et al., 1999; Triggs et al., 1999). Along with increased motor evoked potential (MEP) thresholds (reflecting progressive inexcitability of central motor pathways), a reduction of the normal inhibitory cortical stimulation silent period, and a prolongation of central motor conduction times (CMCT) may be observed (Caramia et al., 1991; Miscio et al., 1999; Siciliano et al., 1999; Triggs et al., 1999). In addition, paired-pulse TMS has been used to evaluate corticocortical inhibitory or facilitatory mechanisms in ALS patients suggesting an alteration of intracortical inhibition (Caramia et al., 2000; Desiato et al., 1999; Sommer et al., 1999).

Sensitivity of single-pulse TMS to detect UMN involvement is discussed controversively. Miscio et al. (1999) found abnormalities (MEP latency, CMCT, absence of MEPs) in 95.4% of ALS patients with UMN signs while only 72.2% of patients with probable UMN signs showed pathologies. Thus, sensitivity in patients with clinical UMN symptoms may be regarded as high, but the diagnostic value of TMS appears to be poor in this subgroup of patients (since clinical examination delivers enough evidence for UMN involvement).

Recently, a new collision technique has been introduced, the so-called triple stimulation technique (TST; Magistris et al., 1998). TST links central to peripheral conduction (through two collisions) suppressing desynchronization of MEPs (Magistris et al., 1998). It has been suggested that TST may be more sensitive to detect UMN diseases

☆ This article is dedicated to the memory of Leonid Komissarow who passed away shortly after acceptance of this paper.

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(Magistris et al., 1999). Among other diseases, 9 ALS patients with predominantly UMN syndrome and 6 with predominantly LMN signs were enrolled in a TST study (Magistris et al., 1999). TST appeared to be 2.75 times more sensitive than conventional TMS in detecting a conduction failure.

The present study is devoted to the question whether TST may be a more useful and sensitive tool than conventional TMS in the diagnosis of UMN involvement in ALS.

2. Subjects and methods

2.1. Subjects

We studied 19 right-handed patients with definite ($n = 7$), probable ($n = 6$), or suspected/possible ALS ($n = 6$) according to the El Escorial criteria (Brooks, 1994) and 7 healthy controls. The ALS patients were 39–72 years of age (mean 59.6 ± 9.6), 13 were males, mean duration of symptoms was 2.4 years (± 1.2) (Table 1). Eleven patients were treated with riluzole, 8 were drug-free at study entry. Mean ALS Functional Rating Scale (The ALS CNTF treatment study (ACTS) phase I–II Study Group, 1996) was 33.3 (± 5.2).

Subjects were informed on the research purpose of the experiments and gave written informed consent to the experimental procedure. The study was approved by the local ethics committee.

2.2. Experimental procedure

2.2.1. Conventional (single-pulse) TMS

Subjects were seated with both arms in slight abduction from the trunk (20°) and with flexion in the elbow (110°). TMS was carried out using a MagStim200 stimulator (MagStim Co., Whitland, UK). The circular coil (diameter 9 cm) was adjusted over vertex to evoke optimal responses in the abductor digiti minimi muscle (ADM). Stimulus intensity was 120% of threshold at rest which was defined as the intensity eliciting 3 responses at least 50 μV amplitude in 4 stimuli (Däuper et al., 2002). Mean MT among patients was 79.7% (± 10.6) of maximal stimulator output. MEPs were recorded from the right and then from the left ADM using conventional surface electromyographic techniques. Signals were amplified (bandpass 10 Hz to 5 kHz) and digitized (sampling rate 10 kHz). Epochs of 300 ms duration (100 ms prior to the stimulus and 200 ms after) were stored on disk. The myoelectrical activity was continuously monitored to ensure absence of

Table 1
Sample characteristics

Pat.	Age	Sex	Disease duration (years)	El Escorial criteria	ALSFRS	UMN signs	LMN signs	Bulbar signs	EMG	Riluzole treatment (−/+)	Pathologic TMS (−/+)	Pathologic TST amplitude ratio (−/+)	Pathologic TST area ratio (−/+)
JA	45	M	2.0	Suspected	38	−	+++	−	++	−	+[a]	+	+
EK	72	F	1.0	Suspected	37	−	+	+	−	−	−	−	+
HDK	59	M	1.5	Suspected	34	−	++	+	++	−	−	+	+
RR	65	F	2.5	Suspected	35	−	++	−	++	−	+[b]	−	+
JW	67	M	2.0	Suspected	33	−	++	−	+++	+	−	+	+
HE	65	M	1.5	Possible	38	+	+	−	++	+	+[a]	+	+
DH	63	M	4.0	Probable	34	++	+	+	−	+	+[a]	+	+
JL	53	F	–	Probable	34	+	++	+	+++	+	−	−	−
HZ	66	M	3.0	Probable	38	++	++	−	++	+	+[c]	+	+
HK	39	M	3.0	Probable	36	++	++	−	++	+	+[b]	+	+
KH	59	M	3.0	Probable	41	++	++	−	++	+	+[c]	+	+
MS	56	F	2.0	Probable	34	++	+	+	−	+	+[c]	+	+
VB	44	M	2.0	Definite	27	+++	+++	+	+++	−	+[b]	+	+
HD	63	M	2.5	Definite	31	+++	+++	+	+++	−	−	+	+
ED	66	F	6.0	Definite	18	+++	+++	+	+++	+	+[b]	+	+
FE	71	M	2.5	Definite	28	+++	+++	+	+++	−	−	+	+
IH	53	F	1.0	Definite	30	+++	+++	−	+++	+	+[b]	+	+
HM	72	M	2.0	Definite	31	+++	+++	+	+++	−	+[c]	+	+
MS	54	M	2.0	Definite	36	+++	+++	−	+++	+	+[a]	+	+

ALSFRS = ALS Functional Rating Scale; UMN signs = clinical upper motor neuron signs (− = no; +++ = evident); LMN signs = clinical lower motor neuron signs (− = no; +++ = evident); Bulbar signs = clinical bulbar signs like dysphagia, atrophy of tongue, etc. (− = no; +++ = evident); EMG = typical EMG findings like acute denervation (− = no; +++ = evident in all extremities); Riluzole treatment = Riluzole treatment at study entry (− = no; + = yes); pathologic TMS = absence of MEPs or prolongation of CMCT in conventional TMS examination (− = no; + = yes). Pathologic TST amplitude ratio = TST amplitude ratio <0.93 (− = no; + = yes). Pathologic TST area ratio = TST area ratio <0.92 (− = no; + = yes).

[a] Pathologic prolongation of CMCT (>8.0 ms), at least on one side.

[b] Absence of MEPs, at least on one side.

[c] Pathologic MEPamplitude/$CMAP_{Erb}$ (<0.33), at least on one side.

voluntary background activity. MEP latencies, amplitudes, and areas of rectified MEPs were analyzed off-line. CMCT was computed using the F-wave method. Formula for calculation of CMCT was: CMCT = MEP latency − (F latency ± M latency-1)/2. Conventional TMS examination was regarded as pathologic (Miscio et al., 1999; Magistris et al., 1999) if no MEPs could be evoked, MEP amplitude ratio was decreased (MEPamplitude/$CMAP_{Erb}$ < 0.33) or CMCT was prolonged (CMCT > 8.0 ms), at least on one side.

2.2.2. Triple stimulation technique (TST)

Details of this method are described elsewhere (Magistris et al., 1998, 1999). TST is performed using two peripheral electrical stimulations (wrist and Erb's point), and one TMS-pulse, leading to two collisions. By means of this technique desynchronization (leading to phase cancellation) of MEPs may be suppressed. Thus, detection and quantification of central motor conduction failures can be improved. As additional equipment, an external electrical stimulator (Dantec Keypoint II, Dantec, Skovlunde, Denmark) and an external timer (Digitimer D4030, Digitimer Ltd., Hertfordshire, UK) were used. Three stimuli were given leading to two collisions (Magistris et al., 1998): the first stimulus is applied to the scalp overlying the motor cortex (TMS, vertex, intensity 120% of MT). After a delay (delay I, equal to the minimal latency of the MEP minus the latency of the potential evoked at the wrist), a second stimulus (supramaximal intensity) is given to the ulnar nerve at the wrist. After another delay, a third stimulus is applied at Erb's point (delay II, equal to the compound muscle action potential (CMAP) latency after Erb stimulation minus the latency of the M-response after wrist stimulation). The response to this third stimulus was recorded. Amplitude and area of this test response was measured off-line. Further, a control response was recorded and analyzed in which the first stimulus was replaced by electrical Erb stimulation (Erb – wrist – Erb) (Fig. 1). Then a TST amplitude/area ratio was computed using the formula: $TST_{ratio} = TST_{test}/TST_{control}$. As demonstrated in a previous study, amplitude ratios ≥0.93 and area ratios ≥0.92 may be regarded as normal (Magistris et al., 1998). We have used these normal values based on 2.5 SD limits (Magistris et al., 1998). Due to painfulness of triple stimulation (in particular Erb stimulation), TST was performed for the right side, only.

2.3. Statistics

Sensitivity was expressed as percent of pathologic findings (computed for each subgroup of patients). To compare the number of pathologic and normal findings determined through TMS and TST, cross-tabulations were done.

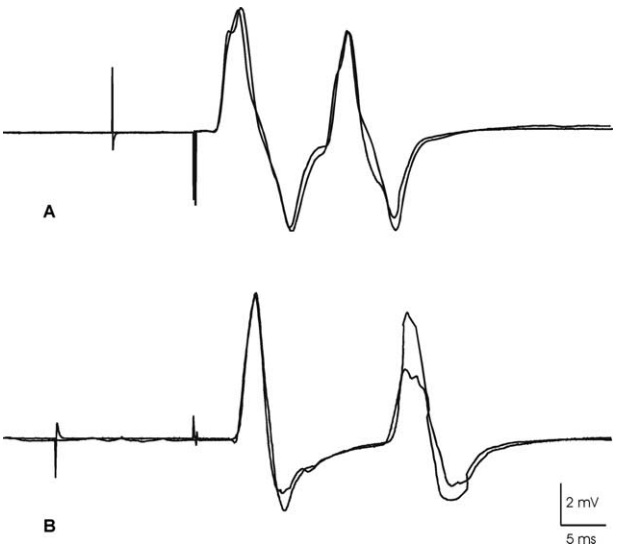

Fig. 1. Demonstration of normal (A); and pathologic (B) TST findings. The first large negative deflection of the curves are M-responses after wrist stimulation. The second negative deflection is the TST test resp. control response. In this figure, test and control traces are superimposed. In (A), TST test and control amplitude are nearly the same, TST ratio is close to 1 (healthy control). In (B), a conduction failure is demonstrated, test amplitude is smaller than control, TST amplitude ratio equals approx. 0.57. In addition, latencies of the second deflection are prolonged (due to a prolongation of CMCT).

3. Results

3.1. Healthy controls

In our sample of healthy control subjects, mean TST amplitude ratio was 0.96 (±0.02) and mean area ratio 0.98 (±0.02). No abnormalities of CMCT or MEPamplitude/$CMAP_{Erb}$-ratio were observed, MEPs could be evoked in 7 out of 7 participants. Among controls, mean MEPamplitude/$CMAP_{Erb}$-ratio was 0.68 (±0.08), and mean CMCT was 3.68 ms (±0.92).

3.2. Suspected/possible ALS

In the subgroup of suspected/possible ALS patients, mean CMCT equaled 5.6 ms (±3.2). Mean MEPamplitude/$CMAP_{Erb}$-ratio was 0.51 (±0.18) and was normal among all subjects with suspected/possible ALS. MEPs could not be evoked only in one subject (on one side only), CMCT was pathologic only in two patients (33%). This means that conventional TMS detected abnormalities in 3 out of 6 patients (50%). Mean TST amplitude ratio was 0.93 (±0.03), and mean TST area ratio 0.73 (±0.2). TST amplitude ratio was pathologic in 4/6 (67%) while TST area ratio was abnormal in 6/6 (100%) of suspected/possible ALS patients (Fig. 2). Thus, TST was 1.3–2 times more sensitive than single-pulse TMS. It has to be mentioned that none of the suspected ALS patients had clinical UMN signs,

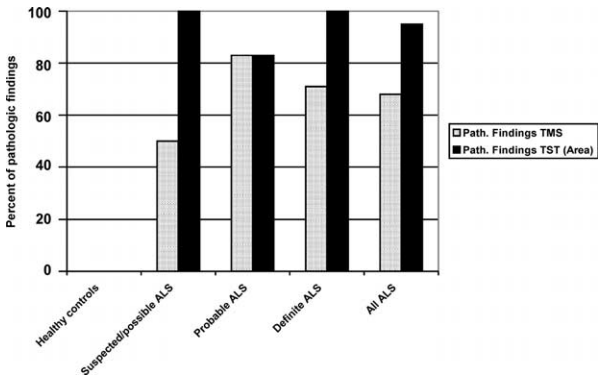

Fig. 2. Percent of pathologic findings (sensitivity) using conventional TMS and TST (area ratio).

but TST area ratio was abnormal in all cases indicating subclinical UMN involvement.

3.3. Probable ALS

Among probable ALS patients, mean CMCT was 3.9 ms (±1.4). Mean MEPamplitude/$CMAP_{Erb}$-ratio was 0.39 (±0.32) and was abnormal in 3 subjects with probable ALS. No MEPs could be evoked in one subject (on both sides), CMCT was abnormal only in one probable ALS patients (only on the right side). Thus, conventional TMS detected abnormalities in 5 out of 6 patients (83%) with MEPamplitude/$CMAP_{Erb}$-ratio being most sensitive. Mean TST amplitude ratio was 0.49 (±0.38), mean area ratio 0.50 (±0.40). Both, TST amplitude and area ratio were pathologic in 5 out of 6 probable ALS patients (83%).

3.4. Definite ALS

Among definite ALS patients, mean CMCT was 5.7 ms (±3.7). Mean MEPamplitude/$CMAP_{Erb}$-ratio was 0.39 (±0.15) and was abnormal in one subject with definite ALS. No MEPs could be evoked in 3 subjects (one patient unilateral, two cases bilateral absence of MEPs) and CMCT was abnormal in one case (only on the left side). Thus, conventional TMS detected abnormalities only in 5 out of 7 patients (71%). Mean TST amplitude ratio was 0.66 (±0.24), mean area ratio 0.66 (±0.23). Both, TST amplitude and area ratio were pathologic among all definite ALS patients (100%) demonstrating a 1.4 times higher sensitivity than conventional TMS techniques.

3.5. Whole group of ALS patients

Among all ALS patients, mean CMCT was 5.4 ms (±3.0), mean MEPamplitude/$CMAP_{Erb}$-ratio was 0.43 (±0.22), mean TST amplitude ratio was 0.71 (±0.30), and mean TST area ratio was 0.64 (±0.28). Absence of MEPs, decrease of MEPamplitude/$CMAP_{Erb}$-ratio, or prolongation of CMCT occurred in 13 out of 19 patients (overall sensitivity 68%) while pathologies – through TST area ratio – were detected in 18 out of 19 patients (overall sensitivity 95%). Using the TST amplitude ratio, abnormalities were found in 16 out of 19 patients (overall sensitivity 84%). This means that sensitivity using TST was 1.2–1.4 times higher than conventional TMS for the whole group of patients. When clinical UMN signs were evident, conventional TMS was found to be abnormal in 11 out of 14 cases (79%), while TST amplitude and ratio were pathologic in 13 cases (93%).

4. Conclusions

TMS may be used to detect UMN involvement in ALS patients (Caramia et al., 2000; Desiato et al., 1999; Miscio et al., 1999; Sommer et al., 1999). However, sensitivity may be poor, in particular in patients with subclinical UMN impairment (Miscio et al., 1999). Recently, a new collision technique has been introduced, the so-called triple TST (Magistris et al., 1998, 1999). This technique has proved to be 2.75 times more sensitive than conventional TMS in the detection of UMN lesions (Magistris et al., 1999).

Among all ALS patients, TST appeared to be 1.2–1.4 times more sensitive than conventional TMS to detect pathologies. This sensitivity is lower than reported in previous studies (Magistris et al., 1999), but it has to be taken into account that only one side was examined using TST technique in the present study. In particular in the subgroup of suspected ALS, TST was two times more sensitive revealing subclinical UMN impairment in all cases, while conventional TMS showed abnormal results only in 50%. It has to be mentioned that this subgroup of patients constitutes a huge diagnostic challenge since clinical UMN signs are absent very frequently. In our sample, none of the suspected ALS sufferers had clinical signs of UMN involvement. TST may help to improve diagnosis in these patients – through higher sensitivity, even when TST is examined only on one side.

The question whether to prefer the analysis of TST amplitude or area ratio can be answered as follows: the use of area ratio appeared to be superior since it showed higher sensitivity, in particular among suspected/possible ALS patients. While 4 out of 6 tests were pathological with TST amplitude ratio, 6/6 were positive using TST area ratio.

In summary, we could reproduce a higher sensitivity of TST in the diagnosis of subclinical UMN impairment, in particular among suspected/possible ALS patients (Miscio et al., 1999). However, the technique has some limitations: first, TST is really painful, and some patients may refuse to undergo this diagnostic procedure. Second, it is technically difficult to perform and affords specialized, well trained staff, and machinery. Thus, only a limited number of clinical neurophysiology labs might be able to establish this technique in routine diagnostics. Third, TST is by far more time consuming than conventional TMS. Besides these limitations, TST might offer a diagnostic benefit in

the diagnosis of ALS, in particular among suspected/possible ALS patients. Therefore, TST could be used in this subgroup of patients offering higher sensitivity than conventional TMS techniques. We believe that TST examination of one side only would be sufficient to reveal UMN involvement.

It should be pointed out that the significance of our findings may be improved by clinical and electrophysiological follow-up examinations, in particular among suspected/possible ALS patients. On the basis of a large Outpatients' Department specialized in the diagnosis and treatment of ALS, we are in the position to re-evaluate our patients very frequently. The results will be published in the near future.

While the findings of our study defy ready summary, the authors do believe that TST is an interesting and innovative technique to increase diagnostic sensitivity of UMN involvement in ALS, even when performed on one side only. Prospective studies enrolling larger numbers of ALS patients are strongly encouraged.

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