SHORT REPORT

Changes in motor cortex excitability during muscle fatigue in amyotrophic lateral sclerosis

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To further investigate the pathophysiology of amyotrophic lateral sclerosis (ALS), the silent period (SP) evoked by transcranial magnetic stimulation during a fatiguing muscle contraction was evaluated in 15 patients and in 15 healthy subjects. Physiological lengthening of the SP duration was not observed in patients with disease duration of ≥ 2 years. Decreased intracortical inhibition, probably secondary to dysfunction of the inhibitory interneurons that modulate the corticomotoneuronal firing, appears in later stages of disease. Normal motor cortex adaptation is impaired and cortical hyperexcitability might be unmasked during fatigue in ALS patients with longer disease duration.

During and after muscle fatigue changes occur in the excitatory responses to transcranial magnetic stimulation (TMS) and in the cortical silent period (SP) following these responses. The SP increases during a sustained maximal voluntary contraction (MVC) of an intrinsic hand muscle,¹ of the elbow flexors,² and of the tibialis anterior muscle.³ No study has been reported describing the relationship between corticomotoneuron excitability and fatigue in amyotrophic lateral sclerosis (ALS). The aim of the present study was to compare the changes in SP duration associated with a fatiguing contraction of the first dorsal interosseous (FDI) muscle between ALS patients and healthy controls. TMS studies showed that both increased excitability of corticomotoneurons and reduced intracortical inhibition contribute to motor cortex hyperexcitability in ALS;^{4–7} clarification of the importance of these factors in the pathogenesis may have diagnostic and therapeutic implications.

MATERIALS AND METHODS

Patients

Fifteen patients (ten men and five women; mean age 56 years, range 42–73 years) affected by sporadic ALS were recruited in the study. The patients exhibited a clinically definite form of sporadic ALS assessed according to the revised 'El Escorial Criteria'.⁸ For comparison, 15 healthy age-matched control subjects were investigated. Patients and healthy volunteers gave their informed consent according to the Declaration of Helsinki. Each patient was evaluated on the basis of medical history and complete neurological examination. According to Triggs *et al.*,⁹ the hand function was rated as 0 = normal; 1 = mild to moderate weakness without impairment of dexterity (ten patients); 2 = weakness with significant impairment of performing independent finger movements (five patients); 3 = marked weakness and loss of fine motor control.

Exclusion criteria consisted of severe intrinsic hand muscle weakness (none of the patients scored 3 on the tested side),

or atrophy and abnormal TMS excitability threshold (1.5 SD $\pm$ control mean); evidence of multifocal neuropathy with conduction block; sensorimotor peripheral neuropathies; and pure or severe bulbar involvement (to create a clinically homogeneous group of patients). The ALS patients were divided into two groups: Group A comprised eight patients with a disease duration of ≤ 2 years (mean age 50 years, range 42–68) and Group B comprised seven patients with a disease duration of ≥ 2 years (mean age 59 years, range 46–73 years), because such a time limit neatly divided the patients into two approximately equal subgroups. There were no differences in the clinical features between the two groups of patients.

Patients and control subjects were asked not to take drugs that affect motor cortex excitability at least 1 week before the study. Five patients (two of Group A and three of Group B) were taking gabapentine, seven (three of Group A and four of Group B) benzodiazepine, and all were taking riluzole, which was temporarily discontinued.

Methods

TMS was performed with a high-power Magstim 200 Stimulator (Magstim Co., Whitland, Dyfed). A figure-of-eight coil (external loop diameter 90 mm) was held over the motor cortex at the optimum scalp position to elicit motor responses in the contralateral FDI muscle, usually on the clinically more affected side. The induced current flows in a postero-anterior direction. The central motor conduction time (CMCT) was calculated using the F wave method by subtracting the peripheral conduction time from spinal cord to muscles from the latency of responses evoked by cortical stimulation. The resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 50 μ V in 50% of 10 trials) at rest. The active motor threshold (AMT) was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 200 μ V in 50% of trials) during isometric contraction of the tested muscle at about 10% of maximum force as measured through a manual transducer.

We compared the duration of the SP elicited before exercise and while subjects held a maximal 2 minute voluntary pinch contraction of the index finger and thumb. Each subject was asked to squeeze a mercury sphygmomanometer positioned in front of them with the index finger against the thumb as strongly as possible for 2 minutes to maximally activate the FDI muscle. Feedback of the performance was given during the effort through the height attained by the mercury. Five

Abbreviations: ALS, amyotrophic lateral sclerosis; AMS, active motor threshold; CMCT, central motor conduction time; FDI, first dorsal interosseous; GABA, γ -aminobutyric acid; MVC, maximal voluntary contraction; RMT, resting motor threshold; SP, silent period; TMS, transcranial magnetic stimulation

stimuli at 150% AMT were given during the MCV 1 minute after the starting of the compression.

In addition, supramaximal stimulation (0.2 ms square-wave constant current pulses) of the ulnar nerve at the wrist was used to assess spinal and peripheral motor excitability. While FDI was relaxed, the peak-to-peak amplitude of F waves (average, 20 trials) and compound muscle action potential (CMAP) (maximum, 3 trials) were determined.

Statistical analysis

All data are reported as group means $\pm$ SD. Statistical analysis was performed using the analysis of variance (ANOVA) of repeated measures with subsequent post hoc Student's *t* test. *p* Value <0.05 was taken as the significant threshold for all tests.

The relation between different variables was evaluated with the Spearman's *r* correlation coefficient. Results are considered significant when *p* value was <0.0001 .

RESULTS

The neurophysiological data are summarised in table 1.

CMCT was increased in four patients (two of Group A and two of Group B). There was a tendency for all ALS patients to have an increase in motor threshold, but the differences between patients and controls were not significant ($p>0.05$, unpaired *t* test). Moreover, there were no significant difference of RMT and AMT between patients of Group A and Group B ($p>0.05$).

Before fatigue, there was a significant decrease in SP duration in patients of both Group A and Group B when compared to the controls ($p<0.05$, unpaired *t* test).

During fatigue, the increase in SP duration in the controls and Group A patients was significant ($p<0.05$, paired *t* test) within their respective groups. By contrast, there was no significant change in Group B patients ($p>0.05$).

The increase in SP duration was not significantly different between Group A patients and control subjects ($p>0.05$, unpaired *t* test). The lack of increase in SP duration in patients with longer disease duration (Group B) was significantly different from the controls ($p<0.05$).

There was no statistically significant difference in the prolongation of the SP during fatigue when all ALS patients were considered.

Changes in peripheral and spinal motor excitability were not observed.

The difference between the before and during fatigue SP values correlated strongly with the disease duration

($p<0.0001$, Spearman's *r*), but did not correlate with the hand motor score ($p>0.01$, Spearman's *r*).

DISCUSSION

To our knowledge, this study is the first to demonstrate an abnormal behaviour of the motor cortex during fatigue in ALS patients.

Several previous studies failed to find any significant differences in the absolute SP duration in ALS patients.^{6,7} However, some authors have already reported a decrease in the SP duration,¹⁰ whereas others have described declining SP only with increasing stimulus intensity or early in the disease.^{11,12}

The novel finding of our study was that only in patients with longer disease duration (at least 2 years) did the cortical SP duration not increase during a muscle fatigue. The slight and statistically not significant differences in stimulus intensity (higher in the patients subgroups, but always identical before and during the MVC) could have marginally accounted for the failure of the SP duration to increase with fatigue in the Group B patients. Changes in SP duration reflect changes in intracortical inhibition. Inhibition at spinal level may contribute to the initial electromyograph silence following TMS, but the later part of the SP is because of reduced cortical output.^{13,14} In healthy subjects, the lengthening in SP produced by cortical stimulation during sustained MVC seems to be related to focal changes within the activated motor cortex and reflects a net increase in inhibition to corticospinal cells. Changes in spinal excitability and in afferent input to the cortex appear not to be responsible for the increase in SP duration during fatigue.¹⁵

The SP abnormalities suggest that cortical hyperexcitability, in addition to being the result of excitotoxicity phenomena, might be the manifestation of impaired inhibition in the later stages of disease. The selective abnormality of intracortical inhibition is compatible with an impaired function of inhibitory interneuronal circuits that in turn renders the corticomotoneuron hyperexcitable, or might represent a 'positive' neuroplastic response in an attempt to compensate for the corticomotoneuronal loss. The most powerful inhibitory transmitter in the nervous system is γ -aminobutyric acid (GABA). The impaired inhibitory modulation of the corticomotoneurons, probably because of both depletion of specific subpopulations of intracortical GABAergic interneurons and mechanisms involved in motor cortex reorganisation following progressive neuronal loss, represents likely a secondary event in ALS pathogenesis related to disease progression. Impairment of the GABAergic inhibitory transmission can therefore play a significant role in the later stages of the disease, and a pharmacological reversal might be induced by administration of a drug promoting GABAergic transmission,¹⁶ such as benzodiazepine or gabapentin. Also the glutamate antagonist riluzole may be therapeutic in ALS because of their GABAergic properties rather than their ant glutamate properties.

Our findings provide further evidence of increased motor system excitability due to distinct mechanisms. The demonstration of these excitability changes related to corticomotoneuronal involvement in ALS patients during a fatiguing exercise makes a contribution toward understanding the pathophysiology of the disease; we believe that these measures of central motor function could also be useful for monitoring patients in a clinical trial setting. Furthermore, it will be interesting to study if different fatigue-related cortical abnormalities can be used to identify subgroups of ALS patients, who might respond to different drugs, such as anti-glutamatergic and GABAergic agents.

Table 1 Motor cortex excitability measurements (mean values $\pm$ SD) in the control subjects, in the ALS patients of group A (with disease duration ≤ 2 year), and in the patients of Group B (disease duration ≥ 2 year)

	CMCT (ms)	Motor threshold		Silent period (ms)
		RMT	ATM	
Control subjects	6.6 $\pm$ 1.7	47 $\pm$ 12	39 $\pm$ 15	180 $\pm$ 27† 225 $\pm$ 22‡
Group A	7.2 $\pm$ 1.4	51 $\pm$ 8	42 $\pm$ 13	154 $\pm$ 34† 202 $\pm$ 36‡
Group B	7.3 $\pm$ 2.0	55 $\pm$ 10	48 $\pm$ 14	148 $\pm$ 30† 151 $\pm$ 28*‡

AMT, active motor threshold (percentage of magnetic stimulator output); CMCT, central motor conduction time; RMT, resting motor threshold (percentage of magnetic stimulator output).

* $p>0.05$ when compared with control subject mean value; †before maximal voluntary contraction; ‡during maximal voluntary contraction.

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