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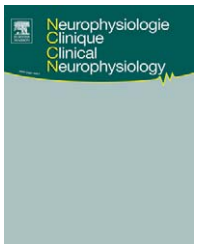

ORIGINAL ARTICLE/ARTICLE ORIGINAL

Cortical excitability of amyotrophic lateral sclerosis: Transcranial magnetic stimulation study

Excitabilité corticale et sclérose latérale amyotrophique : étude des stimulations magnétiques transcrâniennes

E.M. Khedr*, M.A. Ahmed, A. Hamdy, O.A. Shawky

Department of Neurology, Assiut University Hospital, Assiut, Egypt

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KEYWORDS
Transcranial magnetic stimulation (TMS);
Cortical excitability;
Cortical silent period;
Transcallosal inhibition;
Amyotrophic lateral sclerosis;
ALS

Summary
Objective. — The primary purpose of this study was to provide insight into the central changes that occur in amyotrophic lateral sclerosis (ALS) with a view to understanding how these could contribute to symptoms.
Material and methods. — Seventeen patients with definite ALS and 17 control healthy volunteers were included in the study. Clinical examination, amyotrophic lateral sclerosis severity score (ALSSS) and TMS investigations including measurement of resting and active motor threshold (RMT and AMT), motor evoked potential (MEP), input-output curve, contralateral silent period, and transcallosal inhibition (CSP and TI, postulated markers of GABAb function) were measured for each participant.
Results. — There were no significant differences in RMT or AMT in either hemisphere between patients and the control group. Despite this there was a significant negative correlation between ALSSS and RMT and AMT meaning that increased severity was associated with higher thresholds. MEPs were significantly smaller in ALS patients in comparison to the control group ($P = 0.03$). There was a significant decrease in the slope of the I/O relationship of MEP amplitude to TMS intensity in patients group in comparison to controls. ALS patients had a significant prolongation of CSP and TI for both hemispheres. There was a tendency for a significant negative correlation between left TI and ALSSS ($P = 0.051$).
Conclusion. — Measurements of cortical motor excitatory changes in ALS confirm the presence of corticospinal hypoexcitability. Additionally we found increased excitability of presumed intracortical GABAb circuits that correlated with the severity of ALS. We postulate that the disease results in an imbalance between excitation and inhibition in the cortex that can contribute to clinical symptoms.

* Corresponding author.
E-mail address: emankhedr99@yahoo.com (E.M. Khedr).

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MOTS CLÉS
Stimulation magnétique transcrânienne ;
Excitabilité corticale ;
Période de silence cortical ;
Inhibition transcalleuse ;
Sclérose latérale amyotrophique ;
SLA

Résumé
But de l'étude. — Étudier les dysfonctionnements nerveux centraux associés à la SLA et examiner dans quelle mesure ceux-ci peuvent contribuer à ses symptômes.
Patient et méthodes. — Nous avons inclus 17 patients porteurs de SLA et 17 contrôles. Pour chaque sujet, nous avons réalisé : un examen clinique, la mesure du score de sévérité de la SLA (ALSSS) et des stimulations magnétiques transcrânienne avec les mesures suivantes : seuil moteur au repos (SMR) et sous-activation (SMA), potentiels évoqués moteurs (PEM), courbes de relations entrées-sortie (CRES), période de silence controlatéral et inhibition transcalleuse (ITC et IT, constituant des marqueurs probables de la transmission GABAb).
Résultats. — Les SMR et SMA ne différaient significativement dans aucun hémisphère entre les patients et les contrôles. Néanmoins, nous avons retrouvé une corrélation négative significative entre l'ALSSS et les SMR et SMA, un score de sévérité accrue étant associé à des seuils plus élevés. L'amplitude des PEM était significativement plus faible chez les patients que les contrôles. La pente de la relation amplitude du PEM et intensité de stimulation était significativement plus faible chez les patients. Une prolongation de l'ITC et de l'IT fut retrouvée au niveau des deux hémisphères chez les patients porteurs de SLA avec une tendance à une corrélation négative significative entre l'ALSSS et l'IT sur l'hémisphère gauche ($p = 0{,}051$).
Conclusion. — La mesure des modifications de l'excitabilité du cortex moteur confirme l'existence d'une hypoexcitabilité corticospinale dans la SLA. Nous avons également retrouvé une excitabilité accrue de circuits intracorticaux GABAb, corrélée à la sévérité de la maladie. Nous postulons qu'un déséquilibre entre l'excitation et l'inhibition intracorticale pourrait contribuer à la symptomatologie clinique.

Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder of the motor system. Lower motor neuron (LMN) involvement may be detected by electromyography (EMG), whereas clinically, upper motor neuron (UMN) involvement may be elusive. Alteration of cortical excitability and intracortical inhibition (ICI) has been demonstrated in a number of cases, but in the majority of patients there were no significant changes in corticomotor thresholds (MT) and/or central motor conduction time (CMCT) in early stages of the disease [19]. Motor cortex hyperexcitability has been demonstrated in conjunction with a shortened cortical silent period (CSP) after single-pulse TMS [9]. It was suggested that the reduced CSP represents a shift in the balance of excitatory and inhibitory inputs to cortical output neurons responsible for voluntary action, due to degeneration of cortical interneurons. Impairment of short and long interval intracortical inhibition (SICI and LICI) is considered as being due to depletion of specific subpopulations of intracortical GABAergic neurons and can be seen in motor cortex reorganization following progressive neuronal loss [35,36]. However, we cannot exclude that other networks also participate.

Occasionally, mirror movements have been observed in ALS patients, suggesting an involvement of transcallosal fiber tracts in ALS. Additionally, ipsilateral motor evoked potentials (IMEP) have been demonstrated in ALS patients [15]. TMS can evaluate callosal function [17] by measuring the ipsilateral silent period (TI), which reflects transcallosally mediated inhibition of motor cortical output neurons [8,32].

The primary purpose of this study was to provide insight into the central changes that occur in ALS with a view to understanding how these could contribute to symptoms.

Material and methods

Seventeen cases with ALS were recruited according to the El Escorial criteria (El Escorial World Federation of Neurology, 1994) [5], evidence of lower motor neuron (LMN) as well as upper motor neuron (UMN) involvement is essential for the diagnosis of ALS. The mean age was 56.9 ± 9.9 years ranging from 32 to 75 years old, 13 were males. The mean duration of illness was 15.9 ± 8.97 months ranging from 9 to 36 months. Amyotrophic lateral sclerosis functional rating scale (ALS-FRST) [7] and Amyotrophic Lateral Sclerosis Severity Score (ALSSS) [13] were assessed for each patient, the lower the score the more impaired the patient. MRI was performed for each patient to exclude those with cervical spondylosis.

Seventeen age-matched healthy volunteers (61.1 ± 6.7 ranging from 49 to 70 years old), 13 males were studied as control group. All participants or their caregivers (if the patient could not write [illiterate or due to severe hand muscles weakness] gave their written informed consent before participation after full explanation of the study. The local ethical committee of Assiut University Hospital approved the study protocol. Each subject was submitted to the following: clinical examination and battery of electrophysiological examination to measure the cortical excitability as follow.

Electrophysiological investigations

Subjects sat in a comfortable chair. Electromyographic (EMG) recordings from the first dorsal interosseous muscle (FDI) of both hands were acquired with silver-silver chloride surface electrodes, using a muscle belly-tendon set-up, with a 3 cm diameter circular ground electrode placed on the wrist. A Nihon Kohden Machine model 9400 (Japan) was used to collect the signal. EMG parameters included a bandpass of

20—1000 Hz and a recording time window of 200 ms. TMS was performed with a commercially available 90 mm figure of eight coil connected to Magstim super rapid magnetic stimulator (UK). A routine needle EMG procedure was performed in all patients for the diagnosis of ALS (El Escorial Revisited, 1998) to confirm the presence of LMN.

Determination of motor thresholds

First we determined the optimal scalp location of each hemisphere from which TMS evoked motor potentials of greatest amplitude in the FDI. We used constant suprathreshold stimulus intensity and moved the figure of eight coil systematically in 1 cm steps to determine the scalp position from where TMS evoked motor potentials of maximum peak-to-peak amplitude in the target muscle. The coil was positioned tangentially to the scalp and oriented so that the induced electrical currents would flow approximately perpendicular to the central sulcus, at a 45° angle from the mid-sagittal line. Single-pulse TMS was then delivered to the optimal location starting at suprathreshold intensity and decreasing in steps of 1% of the stimulator output. Relaxation and EMG signals were monitored for 20 ms prior to stimulation. The rMT was defined as the minimal intensity required eliciting motor evoked potentials of 50 μV peak-to-peak amplitude in five out of 10 consecutive trials. AMT was determined in the same way while subjects made a mild contraction of about 10% maximum. AMT was defined as the minimal intensity required to elicit an MEP larger than 200 μV in five of 10 consecutive trials. Both the rMT and the aMT were expressed as a percentage of the magnetic stimulator maximal output (equal to 100%).

Contralateral and ipsilateral MEPs (IMEP)

After determination of the optimal scalp location of each hemisphere, from which TMS evoked motor potentials of greatest amplitude in the FDI, stimulus intensity was set at 30% above the threshold level. Peak-to-peak amplitudes and latency (from the onset of stimulus to the onset of MEP) were measured and five consecutive responses averaged. Recordings were done from both FDI after stimulation of each hemisphere. The scalp localization for iMEP presumably was at the hot spot of the contraleral muscle.

The MEP recruitment curve

The MEP recruitment curve was made by increasing the intensity of stimulation using steps of 10% starting from 110% to 150% of RMT. At each intensity, five trials were collected with intertrial intervals of 5 s and averaged. All results were expressed as means $\pm$ SD. The effects of rTMS on the MEP recruitment curve were evaluated using the natural logarithm of the data by two-way repeated measures Anova with intensity of stimulation as within-subject main factors x group Patients vs control group.

Contralateral cortical silent period (CSP)

The duration of the CSP was determined for both hemispheres during isometric voluntary contraction of the contralateral FDI. The participants were asked to perform 50% of the maximum voluntary abduction of the fifth finger as judged by audio-visual feedback. Voluntary contraction started 10 seconds before TMS. Stimuli were delivered not closer than one every 15 second to avoid fatigue. Ten magnetic stimuli were applied at intensity 130% of RMT. The EMG traces were rectified and averaged. The length of the CSP (ms) was determined from the end of the motor evoked potential to the recurrence of at least 50% of EMG background activity.

Transcallosal inhibition (TI)

Approximately five seconds prior to each stimulus, subjects were instructed to make an isometric (approximately 50% of maximal contraction) contraction of the ipsilateral FDI and to maintain it for a similar period after the stimulus. The degree of muscle activation was monitored by an oscilloscope for both the CSP and TI, measurements. Stimulation intensity was 150% RMT of both hemispheres. If RMT was above 65% of maximum stimulator output then maximum intensity TMS was used. The onset and the offset of TI were defined as the points where the EMG trace fell persistently below and where it returned persistently above the base line. The TI duration is calculated as the time of offset of TI minus the onset [12].

Statistics

Mann-Whitney U-test was utilized in order to detect group differences in RMT, AMT, MEP amplitude, CSP and TI latency and duration between patients and healthy subjects. Correlations were done between different clinical rating scales and neurophysiological parameters using Spearman correlation. Association between different clinical presentation of ALS and neurophysiological parameters was also recorded. A repeated measures two-way analysis of variance (Anova) was used to compare changes in amplitude of MEP recruitment curve in patients and control group. Greenhouse Giesser degree of freedom corrections were applied to correct for non-sphericity of the data. Data are given as mean, standard deviation. All significance levels are reported as two-tailed, and the criterion for statistical significance was $P < 0.05$.

Results

The study included 17 patients with ALS, and 17 age and sex matched normal volunteers. ALSFRST was 24.4 ± 4.6 ranging from 18 to 38 points and ALSSS was 31.7 ± 4.9 ranging from 24 to 39 points (Table 1). Fifteen cases had both U- and LMN manifestations. Ten cases had wasting and fasciculation of tongue and seven patients had bulbar manifestation. Two cases had mirror movements during sequential finger-to-thumb movements. Four cases had no evoked potential response that could be obtained from left hand and one from right hand due to severe wasting of the muscles. Three cases recorded ipsilateral MEPs (250—450 μV).

Mann-Whitney tests showed that ALS patients had no significant differences in RMT or AMT of either hemisphere in

Table 1 Demographic and clinical data of studied patients.

	Amyotrophic lateral sclerosis patients (17)	Control (17)
Age, mean ± SD (range) years	56.9 ± 9.9 (32–75)	60.7 ± 6.7 (45–70)
Sex M/F	13/4	14/3
Handedness right/left	16/1	17/0
Duration of illness, range (month)	15.9 ± 8.9 (9 months–36 months)	
ALSSSFRS	24.4 ± 4.6 (18–38)	
Amyotrophic lateral sclerosis severity score	31.7 ± 4.9 (24–39)	

Table 2 Electrophysiological data of the patients with amyotrophic lateral sclerosis (ALS) and the control subjects (all values are expressed as mean ± SD).

	Patients (ALS) n = 17[a]	Control n = 17	P values (Mann-Whitney-test
Right resting motor threshold (RMT)	49.5 ± 17.7	45.3 ± 5.2	0.36
Left resting motor threshold (RMT)	45.5 ± 13.7	44.8 ± 4.1	0.80
Right active motor threshold (AMT)	39.78 ± 14.2	35.5 ± 4.1	0.34
Left active motor threshold (AMT)	38.3 ± 13.4	35.5 ± 4.2	0.45
Right cortical silent period (CSP), ms	129.4 ± 47.1	80.5 ± 26.1	0.001
Left cortical silent period (CSP), ms	117.1 ± 54.3	80.4 ± 25	0.035
Right transcallosal inhibition duration (TI), ms	29.4 ± 6.1	22.9 ± 2.3	0.001
Left transcallosal inhibition duration (TI), ms	30.9 ± 10.2	22.3 ± 2.2	0.014
Onset latency of transcallosal inhibition (TCL) for left hemisphere, (ms)	45.5 ± 11.7	42.7 ± 4.2	0.48
Motor evoked potential latency for left hemisphere (ms)	22.6 ± 1.6	22.2 ± 2.1	0.43
Right motor evoked potential amplitude (μV)	711.6 ± 682	1255.6 ± 723	0.038
Left motor evoked potential amplitude (μV)	721.8 ± 742	1201.5 ± 734	0.050

[a] Four patients had no evoked response recorded from left hand and one from right hand even at 100% of the output of magnetic stimulation.

comparison to the control group. Motor evoked potential latencies were the same but the amplitudes were significantly smaller at 130% of RMT in patients compared with the control group (P = 0.035 for right and 0.05 for left hemispheres for amplitudes) (Table 2).

ALS patients had significantly prolonged CSP in both right and left hemispheres in comparison to the control group (P = 0.001, and 0.035 respectively), as well as a significantly increased duration of TI (P = 0.001 for right, and 0.014 for left hemispheres). There were no significant differences between groups in the onset latency of TI (Table 2).

The input-output curve (I/O) relationship was significantly reduced in patients compared with the control group (F = 5.7, df = 1.29(37.5), P = 0.015) for left hemisphere (Fig. 1), while no such significance was observed in right hemisphere.

There were significant correlations between left RMT and AMT with the ALSSS (r = −0.85, P = 0.007, r = −0.75, P = 0.03 respectively), meaning that the lower score (severe patient's disease status) the higher the thresholds (low cortical excitability (Fig. 2), but there was no such correlation with thresholds in the right hemisphere.

There was a tendency for a significant negative correlation between left TI duration and ALSSS (r = −0.73, P = 0.051) (Fig. 3).

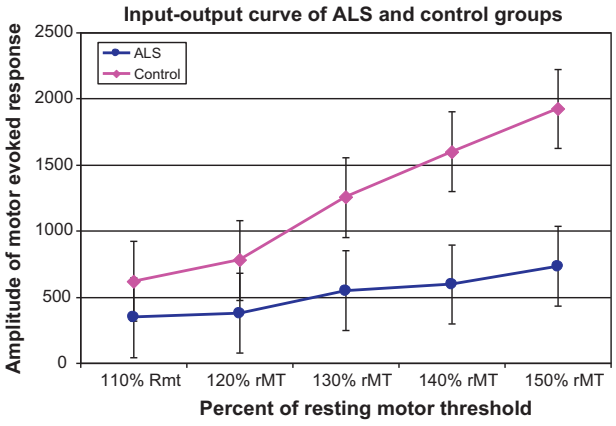

Figure 1 The motor evoked potential (MEP) recruitment curve of ALS patients compared with control group at different intensity of stimulation using steps of 10% starting from 110% to 150% of RMT. The mean values ± SD of amplitude of motor evoked potentials (MEPs) at each intensity was presented in the figure. There was significant decrease of the slope of curve in amyotrophic lateral sclerosis (ALS) in comparison to control group (F = 5.7, df = 1.29(37.5), P = 0.015) for left hemisphere.

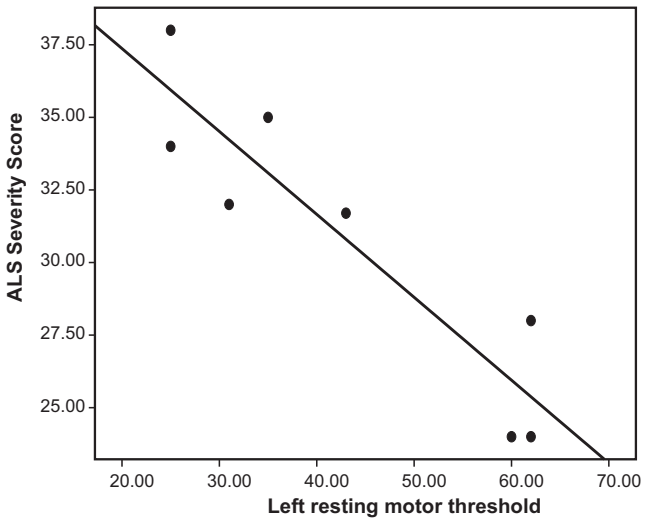

Figure 2 Correlation between amyotrophic lateral sclerosis (ALS) severity scale and resting motor threshold of dominant hemisphere. There is significant negative correlation between the severity of illness and resting motor threshold ($r = -0.85$, $P = 0.007$). Because many patients had the same severity and the same resting motor threshold the number of points are not exactly the number of patients.

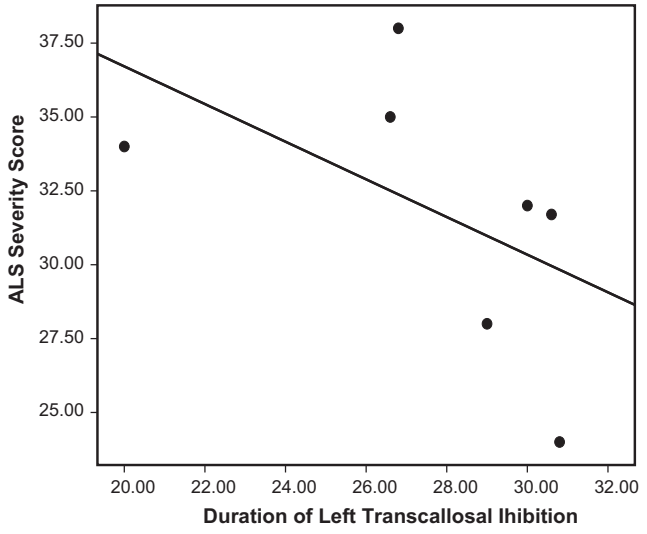

Figure 3 Correlation between amyotrophic lateral sclerosis (ALS) severity scale and duration of transcallosal inhibition of dominant hemisphere. There is tendency to be significant negative correlation between the severity of illness and duration of transcallosal inhibition ($r = -0.73$, $P = 0.05$).

Discussion

Different techniques were utilized in the present series to address several different aspects of cortical excitability and its relation with clinical presentation. Glutamate excitotoxicity is considered to be an important pathogenetic factor in ALS disease. It is believed that overactivity of glutamatergic neurons may cause excitotoxic damage in postsynaptic neurons through inappropriate activation of the glutamate receptors [21]. This study was performed on a group of definite ALS patients while most previous studies investigated patients earlier in the course of the disease.

Motor thresholds (particularly AMT) reflect the stimulus intensity needed to activate the most excitable corticospinal elements and motoneurons. It depends on the membrane excitability of cortical neurons, and synaptic connections in brain and spinal cord. There were no significant differences in RMT or AMT between patients and controls, although there was a significant negative correlation between RMT and AMT in the left hemisphere and severity of illness (ALSSS) meaning that the lower score (severe patient's disease status) the higher the thresholds (low cortical excitability). In addition, MEP amplitudes at all TMS intensities tended to be reduced and the recruitment curve was shallow in comparison to normal volunteers, which would be compatible with reduced cortical excitability in advanced ALS. Others [14,31] also found no evidence of increased corticospinal excitability early in the disease.

A higher RMT associated with decreased motor cortex excitability was seen in advanced ALS, and lower RMTs were recorded in the early stage of ALS by Eisen et al. [10]; Triggs et al. [26]; Eisen and Swash [11]. They hypothesized that patients with lower RMT and a steeper MEP recruitment curve may be in the early stages of the disease, while the subgroup with normal RMT and MEP recruitment may represent patients switching from early hyperexcitability to hypoexcitability. This is consistent with progressive loss of corticospinal fibres, which counteracts the early motor cortex hyperexcitability during the evolution of the disease. The present results on patients with definite ALS would therefore be consistent with development of hypoexcitability of the corticospinal system as disease progresses. Attarian et al. [1] recorded that the mean RMT values were 41, 58, 61.3, 57.5, and 87.5%, respectively along the course of illness. They hypothesized that, in the early stages of ALS, inhibitory responses were increased, as is also the case for excitatory responses [2]. They proposed that spinal reinnervation may occur in the earliest stage in patients in whom intact corticospinal axons lose some of their motoneuronal targets and branch to converge on surviving motoneurons. This may account for both the increase in excitatory and inhibitory responses, which decreased with time and disease progression [2,3]. However most previous studies point to the occurrence of a decrease in the effectiveness of short intracortical inhibition (SICI) a measure commonly attributed to activation of GABAa receptors [6,29,34,36,39]. The late TMS-induced inhibitory effects (late intracortical inhibition [LICI]) attributed to GABAb receptors have been investigated in ALS patients in only two studies, both of which reported a loss of LICI [23,36]. However Attarian et al. [1] reported that TMS-induced inhibitory responses occur more frequently than normal throughout the course of the disease. Inhibitory responses were found to be abnormally strong during the first year after onset, which contrasts strongly with the disruption of TMS-induced inhibitory processes observed in studies based on the paired-pulse paradigm. [6,29,34,36,39]. It is worth noting, however, that a decrease in intracortical inhibitory mechanisms has been reported in patients with various neurological disorders, and these deficits therefore may be somewhat non-specific. Interestingly, motor units tested in

patients with the familial SOD 90A form of ALS showed particularly strong inhibitory responses prior to a late TMS-induced excitatory responses [30].

The strong inhibitory process observed in this study as a significant prolongation of CSP in ALS patients is consistent with the presence of strong GABAb-ergic inhibitory transmission, perhaps contributing to the cortical hypoexcitability. It should be noted that the origin of CSP is predominantly cortical, although the initial part may have a superimposed spinal origin [25,27,37]. Thus the duration of the CSP that we measured in this study thus depends only on the late cortical part. Studies on late intracortical inhibition tested with a paired stimulation protocol [35,36], which corresponds in time course to the silent period, suggest that both phenomena are related to a long inhibitory postsynaptic potential (IPSP) evoked in output cells by GABAb-ergic inhibitory cortical interneurons [24].

In contrast, Desiato and Caramia, [9], Ziemann et al., [40] and Karandreas et al. [14] reported that absolute values of CSP duration did not differ in comparison to controls. This discrepancy may reflect patients selection and duration of illness. A similar explanation may account for our finding that the TI was prolonged in our patients compared to normal. Previous studies in patients studied earlier in the course of the disease with suspected or possible ALS [8,17,18,31] reported reduced or absent TI with prolonged latencies. In contrast this study recorded an increased duration of TI with normal onset latency. The TI is thought to be mediated by activity in excitatory transcallosal fibres that synapse onto local GABAb-ergic inhibitory interneurones. The increased duration we observed would be consistent with an increased excitability of GABAb-ergic inhibitory connections.

Furthermore, several groups have published results in various pathological conditions [4,8,17,18,32], demonstrating that the TI paradigm is a robust paradigm for investigation of callosal function. Occasionally, mirror movements (MM) have been observed in ALS patients of the present study that suggesting an involvement of transcallosal fibre tracts in ALS. Additionally, IMEP were seen in three of our ALS patients. In the present study two cases had mirror movements and three cases had an ipsilateral evoked responses. The assumption of an affected corpus callosum in ALS is also supported by conventional MRI and diffusion tensor MRI findings [22,28,33].

Occurrence of MM, IMEP and pathological TI has been attributed to callosal pathology in other conditions like X-linked Kallmann's syndrome [16] or a genesis of corpus callosum [17]. However, MM are also seen in healthy subjects and have increased incidence in a range of movement disorders such as Parkinsons disease [20]. In these cases, MM are thought to be linked to changes in excitability of the transcallosal inhibitory system [38]. It seems likely that the MM and IMEP seen in ALS may have the same explanation.

Conclusion

The present results support the conclusion of previous authors that during the course of the disease, corticospinal excitability gradually declines from being hyperexcitable to hypoexcitable. In addition we observe here that this is supplemented by an increase in excitability of GABAb-ergic systems within motor cortex. As described by others [8], the GABAb-ergic systems probed by TI and CSP suppress activity in GABAa systems, as measured by the common paired-pulse SICI protocol. Thus increased GABAb excitability here may be directly linked to the reduced GABAa activity reported by others [6,29,34,36,39]. We hypothesize that with progressive degeneration of corticospinal output, there is loss not only of excitatory input to spinal cord, but also, via recurrent collaterals, to cortex itself. This may shift the balance of excitation and inhibition in the cortex towards increased inhibition as we observed. Paradoxically though, since the GABAb and GABAa systems interact, the increased GABAb effect reduces the excitability of GABAa circuits resulting in the loss of SICI noted by others.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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