



Research Article

**Single-pulse Transcranial Magnetic Stimulation in Amyotrophic Lateral Sclerosis:
Experience of a single institution**

F.Gökçem YILDIZ¹, Can Ebru Bekircan-KURT², Kubilay VARLI²

¹*Hacettepe University, The Institute of Neurological Sciences and Psychiatry, Ankara, Turkey*

²*Hacettepe University School of Medicine, Department of Neurology, Ankara, Turkey*

Summary

Objective: To investigate the assessment of cortical function changes and intrinsic circuitry in Amyotrophic Lateral Sclerosis (ALS) by transcranial magnetic stimulation (TMS).

Methods: We studied 16 ALS and 11 healthy controls by single pulse TMS from abductor digiti minimi muscle (ADM). We evaluated cortical excitability parameters including, resting motor evoked potentials (MEPs) amplitude, resting MEPs threshold, central motor conduction time (CMCT), cortical silent period duration (CSPD) and cortical silent period threshold (CSPT) in ALS.

Results: Resting MEPs threshold, CMCT, CSPT were increased in ALS patients compared to controls. CSPD was significantly shortened in ALS group.

Conclusions: TMS findings reflect the cortical hyperexcitability in ALS.

Key words: Cortical excitability, ALS, Transcranial magnetic stimulation, cortical silent period

**ALS Hastalığında Tek Uyarımlı Transkraniyal Manyetik Uyarım Çalışması: Tek
Merkez Hastane Tecrübesi**

Özet

Giriş: Bu çalışmada ALS hastalığında kortikal fonksiyon değişikliklerinin değerlendirmesi ve iç bağlantılarının değerlendirilmesi hedeflenmiştir.

Yöntem: Abduktör digiti minimi kasından kayıtlarla tek uyarımlı TMS kullanılarak 16 ALS hastası ve 11 sağlıklı kontrol çalışıldı. İstirahat motor uyarılmış potansiyel amplitüdü, istirahat motor potansiyel eşik, santral motor iletim zamanı, kortikal sessiz süre zamanı, kortikal sessiz süre eşığının dahil olduğu kortikal uyarılabilirlik parametrelerini değerlendirdik.

Sonuçlar: İstirahat motor potansiyel eşik, santral motor iletim zamanı, kortikal sessiz süre eşığı ALS hastalarında sağlıklı kontrollere göre daha yüksek düzeyde saptandı. Kortikal sessiz süre zamanı ise ALS hastalarında istatistiksel olarak anlamlı şekilde düşük olarak saptandı. TMS bulguları ALS de kortikal artmış uyarılabilirliği yansıtabilir.

Anahtar Kelimeler: Kortikal uyarılabilirlik, ALS,Transkraniyal manyetik uyarım,kortikal sessiz süre

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, fatal neurodegenerative disease of both upper and lower motor neurons. The clinical

presentation of ALS may vary according to the combination of dysfunction in the upper and lower limbs (1). Although ALS is a well-known disease, its underlying pathophysiologic mechanisms remain to be elucidated. The diagnosis is confirmed

with clinical and neurophysiologic demonstration of both lower motor neuron and upper neuron involvement. Transcranial magnetic stimulation (TMS) is a kind of non-invasive technique used to assess central motor pathways, networks, and its connections. TMS may trigger both upper and lower motor neuron pathways after activating the motor cortex. Central motor conduction time (CMCT), motor-evoked potential (MEP) thresholds, and silent period measures are the most useful parameters for identifying cortical excitability (2,3). However, silent period threshold detection has not been studied in ALS. In this study, we used TMS measurements as clinical correlates for the assessment of cortical function in patients with ALS.

MATERIAL AND METHODS

1. Subjects:

Sixteen individuals who were diagnosed as having certain sporadic ALS and 11 healthy controls were enrolled in the study. All ALS patients fulfilled the revised Escorial criteria for definite ALS(4). The Amyotrophic Lateral Sclerosis Severity Score (ALSSS) and ALS Functional Rating Scale (ALSFR) were used in the assessments (5,6). A clinical evaluation was performed to all patients for detecting the mean disease duration. None of the patients was under medication. The exclusion criteria included the following: pure upper motor neuron disease, Kennedy's disease, neuroimaging studies showing diagnoses other than definite ALS, and patients receiving medication.

2. Cortical excitability parameters:

Subjects sat in a comfortable chair. Electromyography (EMG) recordings from bilateral abductor digiti minimi (ADM) muscles were acquired using silver-silver chloride surface electrodes, with a muscle belly-tendon set-up. A Keypoint (Denmark) activity monitor was used to collect the signal. Routine needle EMG was performed in all patients for the

diagnosis of ALS to detect the lower motor neuron dysfunction.

Cortical excitability was assessed using a 90-mm circular coil oriented to induce current flow in a posterior anterior direction. The current was generated by a Mag Pro (Denmark) stimulator. The single-pulse TMS technique was used to determine the MEP amplitude (mV), MEP onset latency (ms), central motor conduction time (CMCT) (ms), the resting motor-evoked threshold (RMT) (%), cortical silent period duration (CSPD) (ms), and cortical silent period threshold (CSPT) (%).

Resting motor-evoked threshold (RMT):

The coil was positioned at the vertex (Cz position) and adjusted in the anterior-posterior position until the optimal position for an evoked response was obtained from the ADM muscle. Records of MEPs were filtered (3Hz - 3 kHz) and amplified using a Keypoint, Denmark activity monitor. The threshold detection TMS technique was used as previously described (7). A target response of 0.2 mV (20%) MEPs were tracked. Resting motor-evoked potential (MEP) was defined as the stimulus intensity required to produce the target MEPs.

Central motor conduction time (CMCT):

Central motor conduction time was calculated by subtracting the minimal cervical spinal root stimulation latency of the upper spine from the minimal latency achieved by cortical stimulation.

MEPs amplitudes: Amplitudes were calculated from baseline to the highest negative peak of the MEP responses at each visit for TMS.

Cortical silent period duration: The cortical silent period (CSP) was recorded whilst performing a weak voluntary contraction, and was calculated from the average 5 stimulus of 150% MEP response to the return of electromyography activity (8). The CSP duration was measured from

onset of MEP to the return of EMG activity.

Cortical silent period threshold (CSPT):

The cortical silent period threshold detection was elucidated by single-pulse TMS delivered to the optimal location starting at suprathreshold intensity and then decreasing in steps of 3% of the stimulator output. The cortical silent period threshold was defined as the minimal intensity required to elicit a visible silent period duration in five out of 10 consecutive trials. To achieve sufficient muscle activation, EMG was continuously observed, and the subject was provided with visual feedback. Stimulation intensity influenced the appearance of the silent period. The strength of the muscle contraction was adjusted by EMG monitoring to approximately 1 mV peak-to-peak.

3. Statistical analysis: Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 16.0). Demographic data and neurophysiologic data were compared between the two groups using the independent sample t-test for normally distributed data. The Mann-Whitney U test was used to detect group differences in RMT, CSP duration, CSP threshold, CMCT, and CSP between patients and healthy subjects. All significance levels are reported as two-tailed, and the criterion for statistical significance was accepted as $P < .05$.

RESULTS

1.1. Clinical Characteristics:

Sixteen patients with ALS (4 female, 12 male), with a mean age of 54.1 ± 12.2 years (range, 31-79 years) and 11 (6 female, 5 male) healthy subjects with a mean age of

46.9 ± 8.4 years (range, 33-57 years) with no known history of a neurologic disorder were included in the study. The median disease duration was 15.8 ± 11.9 months (range, 6-48 months). Limb-onset disease was evident in 13 (81.3%) patients, and bulbar-onset disease was evident in 3 (18.7%) patients. The median ALSFRS-R score was 38.8 ± 3.2 , and the median ALSSS was 33.6 ± 3.3 (Table 1).

1.2. Cortical excitability parameters:

All cortical excitability measures are summarized in Table 2.

Resting motor-evoked threshold: The resting motor threshold in patients with ALS was significantly greater than in the control group (56.7 ± 14.3 ; 40.2 ± 3.5 , respectively; $p < 0.001$).

Cortical silent period duration: Patients with ALS had significantly reduced CSP duration compared with the control group (139.3 ± 50.9 ; 200.6 ± 28.5 , respectively; $p < 0.001$).

Cortical silent period threshold: CSPT was significantly increased in patients with ALS (55.5 ± 13.7 ; 40.9 ± 2.4 , respectively; $p < 0.001$).

Central motor conduction time (CMCT): There were no significant differences in onset latency (20.2 ± 6.8 ; 21.01 ± 1.2 respectively; $p = 0.62$) between the groups. CMCT was significantly prolonged in patients with ALS compared with the controls (9.3 ± 1.8 ; 7.9 ± 1.8 , respectively; $p = 0.019$).

MEPs amplitudes: The CMAP amplitude was 1.06 ± 0.8 mV in patients with ALS and 1.2 ± 0.5 mV in the controls ($p = 0.064$). Cortical MEPs were absent in two patients with ALS.

Table 1: Demographic and clinical data of individuals

	ALS	Controls
Age SD (years)	54.1±12.2	46.9±8.4
Gender (M/F)	12/4	5/6
Duration of illness (months)	15.8± 11.9	
Site of onset (bulber / limb)	3/ 16	
ALSFRS-R	38.8±3.2	
ALSSS	33.6±3.3	

Abbreviations: SD: Standard deviation, ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-revised, ALSSS: Amyotrophic Lateral Sclerosis Severity Scale

Table 2: Electrophysiological data of the patients and controls

	Patients	Controls	p value
Resting motor threshold (%)	56.7±14.3	40.2±3.5	p<0.0001
Motor evoked potential amplitude (mV)	1.06±0.8	1.2±0.5	p=0.064
Cortical silent period duration (ms)	139.3±50.9	200.6±28.5	P <0.0001
Cortical silent period threshold (%)	55.5±13.7	40.9±2.4	p<0.0001
Cortical MEP latency (ms)	20.2±6.8	21.01±1.2	p=0.62
C8 root minimal latency (ms)	12.7±0.6	12.6±0.8	p=0.44
CMCT (ms)	9.3±1.8	7.9±1.8	P=0.019

Abbreviations: MEP: Motor evoked potential, C8: Cervical root 8, CMCT: Central motor conduction time, ms: millisecond

DISCUSSION

Corticomotoneuronal system involvement in ALS seems to have positive signs of cortical hyperexcitability, which may be assessed using TMS techniques (9,2). The novel finding in the present study is that cortical silent period threshold measurements were at lower levels in patients with ALS than in healthy controls. However, previous studies did not use these measurements, which were not designed for cortical silent period threshold detection. Defining this neurophysiologic parameter may be useful for detecting ALS

in early stages of the disease and may contribute to diagnostic success. In agreement with previous studies, the most prevalent excitability impairment was the resting MEP threshold, which showed significantly increased intensity in patients with ALS compared with the controls (7). It reflects the excitability of a central core of cortical neurons, and it also depends on the integrity of the corticospinal tract and spinal motor neurons (10). To the best of our knowledge, cortical silent period is absent or shortened in sporadic and familial ALS (11). Although the silent

period is mediated by cortical inhibitory neurons, spinal mechanisms also suggested a major role of GABA b receptors in the generation of the silent period (12-16). GABA b receptor agonists and GABA reuptake inhibitors are believed to increase the cortical silent period duration (17,18). Accordingly, CMCT is typically prolonged in ALS (19,3). The attenuation or absence of cortical MEPs has been previously reported in patients with ALS (7). We also found that cortical MEPs were absent in two patients, and CMCT was significantly prolonged when compared with the healthy controls.

A potential limitation of our study is the sample size and disease heterogeneity. Future studies with larger series may demonstrate the specificity and sensitivity of this technique as a diagnostic tool in the early stages of the disease, its implication for the prognosis of the disease, and it may provide diagnostic biomarkers or function as a monitoring tool for physicians.

Correspondence to:

F. Gökçem Yıldız

E-mail: gokcemyildiz@hotmail.com

Received by: 28 July 2016

Revised by: 08 September 2016

Accepted: 13 October 2016

The Online Journal of Neurological Sciences (Turkish) 1984-2017

This e-journal is run by Ege University
Faculty of Medicine,

Dept. of Neurological Surgery, Bornova,
Izmir-35100TR

as part of the Ege Neurological Surgery
World Wide Web service.

Comments and feedback:

E-mail: editor@jns.dergisi.org

URL: <http://www.jns.dergisi.org>

Journal of Neurological Sciences (Turkish)

Abbr: J. Neurol. Sci.[Turk]

ISSNe 1302-1664

REFERENCES

1. *Sabatelli M, Conte A, Zollino M Clinical and genetic heterogeneity of amyotrophic lateral sclerosis. Clin Genet 2013,83:408-416.*
2. *Khedr EM, Ahmed MA, Hamdy A, Shawky OA. Cortical excitability of amyotrophic lateral sclerosis: transcranial magnetic stimulation study. Neurophysiologie clinique = Neurophysiol Clin. 2011,41:73-79.*
3. *Eisen A, Shytbel W, Murphy K, Hoirch M. Cortical magnetic stimulation in amyotrophic lateral sclerosis. Muscle Nerve 1990,13:146-151.*
4. *Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron D.El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis and other motor neuron disorders : official publication of the World Federation of Neurology, Research Group on Motor Neuron Diseases 2010,1:293-299.*
5. *Hillel AD, Miller RM, Yorkston K, McDonald E, Norris FH, Konikow N . Amyotrophic lateral sclerosis severity scale. Neuroepidemiology 1989,8:142-150.*
6. *Cedarbaum JM, Stambler N. Performance of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFERS) in multicenter clinical trials. Journal of the J Neurol Sci 1997,152 Suppl 1:S1-9.*
7. *Vucic S, Howells J, Trevillion L, Kiernan MC. Assessment of cortical excitability using threshold tracking techniques. Muscle Nerve 2006,33:477-486.*
8. *Cantello R, Gianelli M, Civardi C, Mutani R. Magnetic brain stimulation: the silent period after the motor evoked potential. Neurology 1992,42:1951-1959.*
9. *Floyd AG, Yu QP, Piboolnurak P. et al. Transcranial magnetic stimulation in ALS: utility of central motor conduction tests. Neurology 2009,72:498-504.*
10. *Groppa S, Oliviero A, Eisen A. et al A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol official journal of the International Federation of Clinical Neurophysiology 2012,123:858-882.*
11. *Vucic S, Cheah BC, Yiannikas C, Kiernan MC. Cortical excitability distinguishes ALS from mimic disorders. Clin Neurophysiol official journal of the International Federation of Clinical Neurophysiology 2011,122:1860-1866.*
12. *Chen R, Lozano AM, Ashby P. Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. Exp Brain Res 1999,128:539-542.*

13. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol. official publication of the American Electroencephalographic Society* 1998,15:333-343.
14. Ziemann U, Winter M, Reimers CD, Reimers K, Tergau F, Paulus W. Impaired motor cortex inhibition in patients with amyotrophic lateral sclerosis. Evidence from paired transcranial magnetic stimulation. *Neurology* 1997,49:1292-1298.
15. Ziemann U, Netz J, Szelenyi A, Homberg V Spinal and supraspinal mechanisms contribute to the silent period in the contracting soleus muscle after transcranial magnetic stimulation of human motor cortex. *Neuroscience letters* 1993,156:167-171.
16. Avoli M, Hwa G, Neurosci Lett, Kurcewicz I, Pumain R, Lacaille JC. Functional and pharmacological properties of GABA-mediated inhibition in the human neocortex. *Can J Physiol Pharmacol.* 1997,75:526-534.
17. Siebner HR, Willoch F, Peller M et al. Imaging brain activation induced by long trains of repetitive transcranial magnetic stimulation. *Neuroreport* 1998,9:943-948.
18. Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *The J Physiol.* 1999,517:591-597.
19. Rossini PM, Pauri F. Central motor conduction time studies. *Electroencephalogr Clin Neurophysiol Suppl.* 1999, Supplement 51:199-211.