MOTOR EVOKED POTENTIALS IN MOTOR NEURON DISEASE: PARAMETERS OF EVALUATION AND ITS RELATION TO DISEASE SEVERITY

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ABSTRACT

Background: *Transcranial magnetic stimulation (TMS) is a technique that can activate cortical motor areas and the corticospinal tract without causing discomfort to the patients.*

Objective*: To evaluate the parameters of MEP induced by TMS in MND and its relation to the severity of the disease.*

Methodology: *Twenty five subjects with motor neuron disease (MND) who had been diagnosed as MND using the standard clinical and electrophysiological studies (nerve conduction studies, EMG and the somatosensory evoked potential studies) had been subjected to TMS and the MEP parameters {threshold, central motor conduction time (CMCT), amplitude percentage quotient, phases and duration of the MEPs} were determined. Matched healthy persons were selected as control. Functional evaluation and disease severity assessment had been scored using the ALS Functional Rating Scale (ALSFRS) and the ALS Severity Score (ALSSS) respectively and compared to the control group.*

Results: *A statistical significant difference of all the motor evoked potentials (MEP) parameters of the studied patients and the scale measurements were present when compared with the control group. The mean central conduction time (CMCT) was correlated with the severity of the disease while the amplitude changes were evident in late stages especially when associated with bulbar manifestations whereas*

there was no correlation between MEP parameters and the functional rating scale.

Conclusions & Recommendations: *From these findings it would be recommended to use the TMS as a useful tool to determine the extent of the disease as well as to predict severity of motor neuron disease (MND).*

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a technique that can activate cortical motor areas and the corticospinal tract without causing discomfort to the patients *(Curra et al., 2002).* Since TMS has been introduced, numerous applications of the technique have been developed for the evaluation of neurological diseases. Standard TMS applications (central motor conduction time, threshold and amplitude of motor evoked potentials) allow the evaluation of motor conduction in the CNS *(Curra et al., 2002).*

Motor evoked potentials (MEP) induced by TMS provide specific information in neurological conditions characterized by clinical and subclinical upper motor neuron (UMN) involvement. In addition, they have proved useful in monitoring motor abnormalities and the recovery of motor function. TMS also gives information about the pathophysiology of the processes underlying the various clinical conditions *(Curra et al., 2002).*

The MEP recorded from various muscles in response to magnetic stimulation probably result from either direct or indirect presynaptic activation of the large more rapidly conducting pyramidal tract neurons *(Day et al., 1987 and Day et al., 1989)* as well as the direct cortico-motoneuronal component of the pyramidal system (Brown et al., 1992) with subsequent production of descending corticospinal volleys *(Murray, 1999).*

Motor neuron disease (MND) is a disorder characterized clinically by progressive wasting of the muscles combined with evidence of pyramidal dysfunction and pathologically by degenerative changes of the anterior horn cells of the spinal cord and motor nuclei of the brain *(Harding, 1993).* This group of diseases comprises progressive bulbar palsy, progressive muscular atrophy, amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis *(Kimura, 2001).*

ALS or *Lou Gehrig disease* is a progressive neurodegenerative disease of adult onset characterized by a loss of motor neurons in the spinal cord and motor cortex *(Simpson et al., 2003).* It is by far the most common variant of MND *(Preston and Shapiro, 1998).* Its annual incidence lies

between 0.4 to 2/ 100000 and usually starts between 50 and 75 years *(Miller, 2001).* It is a fatal disease with no approved curative management *(Dilazzaro et al., 2004).* The cause of death is usually due to respiratory insufficiency or problems of prolonged inactivity as pulmonary embolism, sepsis or pneumonia *(Preston & Shapiro, 1998).* Therefore, owing to its grave prognosis compared to other MND variants it is essential that the correct diagnosis be reached *(Preston & Shapiro, 1998).* From the practical point of view, ALS can be diagnosed with great certainty based on clinical data supported by electrodiagnostic investigations including nerve conduction studies and needle electromyography (EMG) *(Wiechers, 1988).* However, owing to the low sensitivity of the clinical signs in assessing the UMN involvement in ALS, there is a need for investigative tools capable of detecting abnormal function of the pyramidal tracts *(Pouget et al., 2000).*

The involvement of UMN is often difficult to assess in early stage of the disease (it may be very mild or subclinical) *(Sach et al., 2004*) or in patients in whom LMN lesion is so severe that an associated UMN lesion may have been masked *(Murray, 1999).* Central motor conduction (CMC) abnormalities detected using TMS are presumed to reflect UMN dysfunction *(Osei-Lah & Mills, 2004)* TMS helped also in diagnosis of ALS among the lower motor neuron diseases (LMND). It had diagnostic sensitivity up to 85.7% and its specificity was 93.9% *(Attrian et al., 2005).*

Moreover, some clinical and laboratory data are associated with severe MND and hence a poor prognosis. These data include early bulbar involvement, advanced age at onset, recent weight loss, low forced vital capacity and low serum chloride *(Miller, 2001).* At the electrophysiological level, some researches have correlated the electrophysiological findings to the stage of the disease or the prognosis as low CMAP, decrement on repetitive supramaximal stimulation; in addition to markedly increased jitter and low fiber density in single fiber EMG *(Magnus et al., 2002).*

Moreover, on routine EMG, the number and the location of the affected muscles, their number of active motor units, the presence or absence of reinnervation, the percentage of unstable motor units, the density and extent of fibrillation potentials, all are helpful prognostic indicators *(Wiechers, 1988).* On the other hand, the relationship between MEP induced by TMS and the clinical findings has been demonstrated in some studies *(Cruz-Martinez & Trejo, 1999).* Study of the parameters of the MEPs in patients with MND had shown various changes. The slow progression and dominant upper motor neuron features of primary lateral sclerosis (PLS) are associated with a high threshold to cortical magnetic stimulation and

sometimes slow central motor conduction. In ALS the cortical threshold may be reduced early in the disease and central conduction is usually normal. Thus, the corticomotoneuronal function appears to be impaired differently in PLS and ALS. Higher threshold and longer duration of the primary peak in PLS probably reflect lower excitability and greater loss of corticomotoneuronal connections than in ALS *(Weber et al., 2002).* Nevertheless, further elaboration on this issue is still needed aiming at demonstrating the relationship between the MEP parameters and MND severity (assessed clinically) and hence whether changes in MEP can reflect disease severity or not.

Aim of the study:

The aim of this work was to evaluate the parameters of MEP induced by TMS in MND and its relation to the severity of the disease.

SUBJECTS AND METHODS

Twenty five patients with clinically definite MND who attended the Neurology as well as the Physical Medicine, Rheumatology &Rehabilitation departments were included in this study. Patients were diagnosed according to El Esocorial World Federation of Neurology (WFN) criteria for the diagnosis of ALS *(Brooks, 1994)* and using the standard electrophysiological studies (nerve conduction studies and EMG) *(Preston and Shapiro, 1998 and Wiechers, 1988).* Patients were excluded from the study if they had one or more of the following:

1- An associated metabolic, endocrinal or collagen disease.

2- Associated neurological or neuromuscular disorders.

3- Any contraindication to TMS as presence of epilepsy, metal implants within the neck, skull defects, cochlear implants cardiac pacemakers or patients receiving medications which interfere with cortical excitability (e.g. drugs that affect Ca++ and Na+ channels) *(Hallet, 2000).*

Patients were subjected to thorough clinical, functional and neurophysiological evaluation.

Clinical and functional evaluation:

After history taking, patients were clinically examined with emphasis on the different neurological items. Spasticity was assessed by Modified Acworth's scale *(Bohannon & Smith, 1987).* The degree of the underlying functional status had been assessed using the ALS Functional Rating Scale (ALSFRS) *(ALS CNIF, 1996).* This is used to monitor

functional changes in patients with ALS over time. It includes measures for speech, salivation, swallowing, hand writing, handling objects, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs and breathing. It includes sum of points of ten measures, with a minimum score of zero to a maximum score of forty. The higher the score the more function is retained. On the other hand, the severity of the ALS had been assessed by using the ALS Severity Score (ALSSS) *(Hallet & Miller, 1989).* This score includes measures for evaluating the speech, swallowing, lower extremity function including walking and the upper extremity function and hygiene. Further analysis is achieved by obtaining data from the ALSSS and calculating further score measurements such as the bulbar score (speech subscore+ swallowing subscore) and the spinal score (lower extremity subscore+ upper extremity subscore). Previous results had shown reliability of the test to the extent that the estimated reliability coefficient between examiners reached up to 0.95 and the correlation between the speech rating and objective speech measures >0.80 *(Hallet & Miller, 1989).*

Neurophysiological evaluation:

Using TMS, MEP were recorded from the tibialis anterior muscle bilaterally for each patient as well as for 10 healthy control subjects. Magnetic stimulation had been applied using single pulse stimulator, Magstim 200 (Magstim company, Whitland, Wales, UK), equipped with a high power 90 mm circular coil, capable of generating 2-tesla maximum field intensity *(Escudero et al., 1998).* The patient was laying supine on a wooden bed in a quite room *(Escudero et al., 1998).* For the left hemisphere stimulation, the coil was held with face A of the coil visible from above (current anticlockwise) and for stimulation of the right hemisphere, the coil was held with face B of the coil visible from above (current clockwise) *(Escudero et al., 1998).* The coil was positioned tangentially over the skull (forward and 2 inches from the vertex and contra lateral to the side of the tested muscle) *(Escudero et al., 1998),* with center of the coil placed over the cortex and the handle parallel to the sagittal plane. The coil position had to be slightly adapted in every case to achieve optimal excitation. The muscle responses were recorded on a Nihon Kohden electrophysiological apparatus (Neuropack 2), using 7 mm surface disk electrodes filled with electrode jelly. The active electrode was placed over the belly of the tibialis anterior (TA) and the reference electrode was placed distally on the shin of the tibia *(Preston & Shapiro, 1998).* Filter settings were set with a low filter setting of 3 Hz and a high frequency filter 3 KHz. Responses were amplified, gain set was set at a 0.5-2mV/ division and adjusted according to

the amplitude of the response, so that the responses produces a deflection that is at least 50% of the maximal excursion but does not go off scale. The time base was set with a sweep speed of 10ms/ division.

The following data were determined:

1- Threshold level determination:

The motor threshold was determined *(Noordhout, 1999).* To establish the threshold, the stimulus strength (given in percentage of the maximum output of the stimulator) was increased in 5% increment with the target muscle (TA) in completed relaxation until a compound muscle action potential (CMAP) was seen. Threshold defined as a lowest intensity, which give three reproducible responses.

2- MEP recording:

The procedure was performed while the patient was at complete rest and with facilitation by asking the patient to do a mild voluntary contraction of the TA (MEP amplitude is not affected significantly if the voluntary contraction was maintained between 15% - 75% of its maximum) *(Eisen & Shtybel, 1990).* Stimulus intensity was set at 20% above threshold value. For each side muscle, three reproducible cortical MEPs were elicited and superimposed. Absent MEPs was defined when it failed to appear after three successive discharges with maximum output.

The following were recorded:

(a) The shortest MEP cortical latency was determined to the onset of the negative peak. The central motor conduction time (CMCT) was calculated as the difference between the cortical latency (CL) and the peripheral latency (PL) *(Eisen & Shtybel, 1990).* The peripheral latency was calculated by the following formula:

PL (ms) = (minimal F wave latency in ms+ M wave latency in ms)- 1/2 *(Kimura, 1983).*

(b) The amplitude percentage quotient was also determined by determining the maximal amplitude of the MEPs (peak to peak) and expressed as a ratio of the amplitude of the M wave (peak to peak) using the following formula:

- Maximum MEP amplitude in mV/ M response maximum amplitude in mV % *(Murray, 1999 and Eisen & Shtybel, 1990).*

(c) The duration percentage quotient of the MEP was measured from the onset of the negative deflection to the return to the base line and it was

also expressed as a ratio of the duration of the M wave using the following formula:

- Duration of the MEP/M response duration % *(Noordhout, 1999).*

(d) Lastly the number of phases of the MEPs was counted as the number of base line crosses +1 *(Noordhout, 1999).*

3- The M wave and F wave evaluation *(Preston & Shapiro, 1998):*

- In order to judge the MEP waveform, it is necessary to obtain an M wave and F wave recordings from respective muscle of study by mean of conventional neurographary. They were obtained with unchanged recording electrode positions.

The M wave was obtained by supra maximal electrical stimulation of the peroneal nerve above the neck fibula, gain setting was set at 2-5mV/ division and a sweep speed of 5ms/division. The distal latency, peak-to-peak amplitude of the M wave and it duration from the initial to the terminal deflection back to baseline were recorded for each side muscle.

The F wave was obtained by supramaximal stimulation of the peroneal nerve above the neck fibula with the cathode proximal to avoid anodal block. Gain was set at 200 microvolt and a sweep speed at 5ms/division. At least 10 waves per muscle were recorded. Minimal F wave latency was chosen. The PL was calculated using the previously mentioned formula *(Kimura, 1983).*

Ten healthy control subjects had been subjected to TMS with recording of MEP.

Statistical Analysis:

Student t test was used to compare the quantitative data expressed as mean ± standard deviation (X±SD). While Chi square (X^2) test was used to compare the qualitative data between the studied groups. Pearson correlation was used to correlate between the different parameters. A level of $p<0.05$ had been defined as a statistically significant.

RESULTS

The examined patients had a mean age of 53.7±5.8 years and a mean duration of MND of 4.4± 2.1 years compared with10 control subjects with a mean age of 53.95±7.19 years. There was no statistically significant difference between both groups. Males exceeded female at both groups. In patients group, there was 22 males (88%) and 3 females (12%), as for the control group there was 9 males (90%) and 1 female (10%).

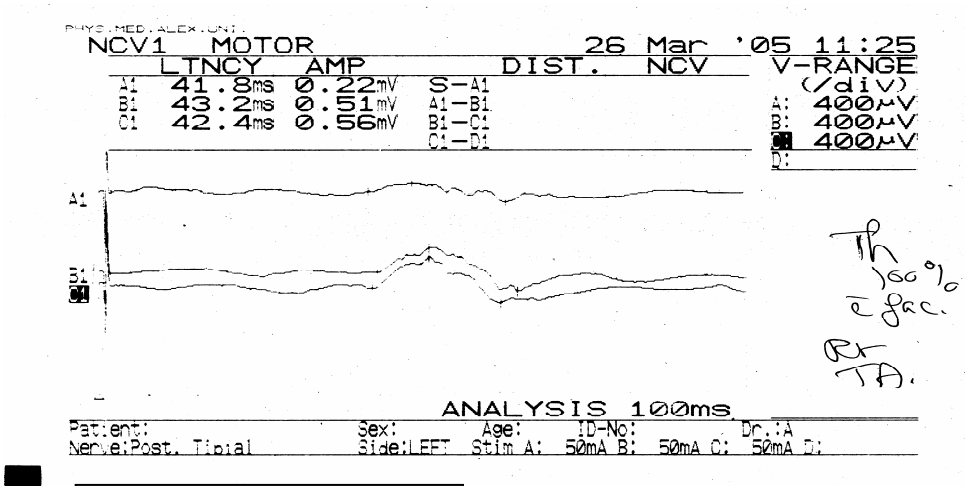
Table (1) shows the frequency of the clinical features among the examined patients. Fasciculations were the most common clinical findings present in the examined patients (100%) while anarthria was the least demonstrated (8%). Moreover, 3 patients (12%) had no clinical features of UMN involvement.

Table (1): Clinical findings in the patients' group.

Clinical findings	Patients number	Percentage
Fasciculations	25	100
Cramps	16	64
UMN manifestations	22	88
Spasicticty	18	78
Anarathria	2	8
Dysphagia	6	24
Dysarathria	4	16
Wasting	18	72
Weakness	18	72

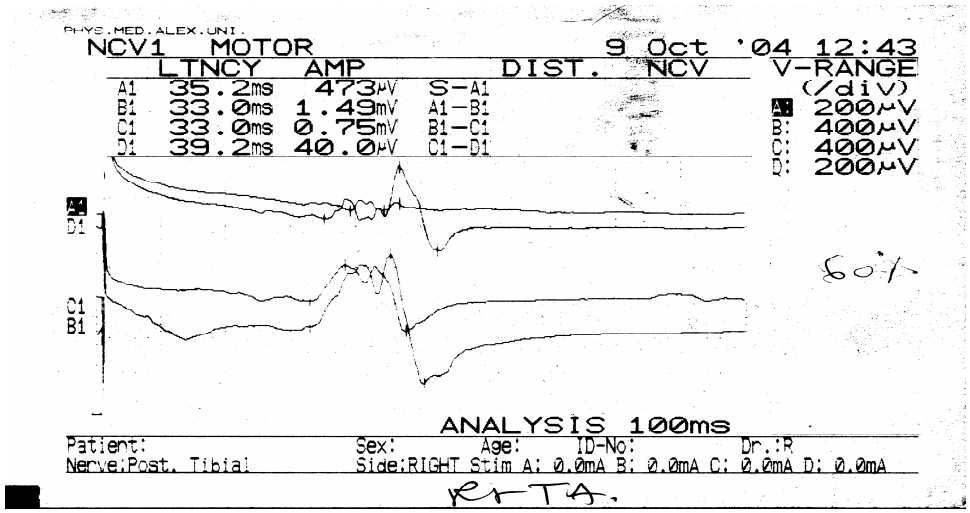
Table (2): The MEP parameters in the two studied groups.

	Patients (Mean +SD)	Controls (Mean +SD)	t- test	p value
RT threshold Percentage	57.96 ± 22.2	31.4 ± 10.1	5.048	0.001*
LT threshold Percentage	65.64 ± 17.6	31.4 ± 10.1	7.906	0.039*
Mean threshold Percentage	60 ± 20.9	31.4 ± 10.1	5.725	0.028*
RT CMCT	16.7 ± 11.5	13.8 ± 2.59	1.1	0.003*
LT CMCT	15.6 ± 9.1	13.8 ± 2.59	0.91	0.001*
Mean CMCT	15.8 ± 9.3	13.8 ± 2.59	0.94	0.008*
RT amplitude Percentage	5.62 ± 2.6	14.5 ± 9	-4.67	0.000*
LT amplitude Percentage	5.65 ± 2.4	14.5 ± 9	-4.69	0.000*
Mean amplitude Percentage	5.67 ± 2.2	14.5 ± 9	-4.7	0.000*
MEPs phases at the Rt side	3.8 ± 0.91	2.3 ± 0.58	6.12	0.017*
MEPs phases at the Lt side	3.1 ± 0.91	2.3 ± 0.58	3.03	0.06
Mean MEPs phases	3.4 ± 0.56	2.3 ± 0.58	5.95	0.836
RT MEPs duration	20.2 ± 7.12	10.1 ± 2.36	6.241	0.007*
LT MEPs duration (Mean ±SD)	20.4 ± 6.92	10.1 ± 2.36	6.503	0.006*
Mean MEPs duration (Mean ±SD)	20.7 ± 6.39	10.1 ± 2.36	7.215	0.001*



Abnormal MEPs

Fig. (1):



Normal MEPs

Fig. (2):

The MEP studied parameters included the determination of the threshold value, central motor conduction time (CMCT), amplitude percentage quotient, number of phases of the MEPs response and their duration at both sides. Comparison between the MEP parameters of the examined patients and control is demonstrated in table (2). There was a statistically significant difference between patients and control regarding MEP parameters at both sides in the form of increased threshold intensity, prolonged CMCT as well as increased duration of the response. However, the number of phases was significantly increased compared to the control group at the right side only.

Clinical evaluation of the degree of the underlying functional status had been assessed using the ALS Functional Rating Scale (ALSFRS). On the other hand the severity of the ALS had been assessed using the ALS severity score (ALSSS). Further score measurements such as the bulbar and the spinal sub scores were determined for further differential evaluation of the bulbar and spinal affection in the examined patients. Statistical significant difference had been detected in all the examined patients when compared with control group table (3).

Table (3): ALSFRS, ASLSSS, bulbar and spinal sub scores in the 2 studied groups.

	Patients	Controls	t- test	p value
ALSFRS (Mean +SD)	28.96 ± 4.67	40 ± 0.00	-10.82	0.000*
ALSSS (Mean +SD)	31.68 ± 3.88	40 ± 0.00	-9.8	0.000*
Bulbar sub score	1.094 ± 0.143	1 ± 0.00	3.013	0.000*
Spinal sub score	1.183 ± 0.182	1 ± 0.00	4.598	0.000*

The correlation between the ALS rating scales including the ALSFRS, ALSSS, bulbar sub score and the spinal sub score and the MEP parameters reveals a statistically significant negative correlations between the ALSSS and the CMCT (r :- 0.412, P:0. 041) as well as the bulbar sub-score and the amplitude percentage quotient at the Lt side (r: -0.430, P:0. 032). Table (4)

Table (4): correlation between ALSFRS, ALSSS, bulbar and spinal sub scores; and different parameters of MEP.

	ALSFRS	ALSSS	Bulbar sub score	Spinal sub score
RT threshold Percentage	0.087 0.678	-0.085 0.687	0.101 0.631	0.247 0.235
LT threshold Percentage	-.333 0.104	0.119 0.57	-0.119 0.619	0.104 0.619
Mean threshold Percentage	-0.017 0.935	0.021 0.922	-0.063 0.766	0.118 0.576
RT CMCT	0.071 0.734	-0.379 0.062	-0.282 0.172	-0.122 0.56
LT CMCT	0.101 0.630	-0.339 0.098	-0.240 0.247	-0.192 0.357
Mean CMCT	0.095 0.651	-0.412 0.041*	-0.295 0.152	-0.164 0.433
RT amplitude Percentage	-0.072 0.732	0.060 0.775	-0.218 0.296	-0.199 0.340
LT amplitude Percentage	-0.049 0.815	0.092 0.662	-0.430 0.032*	-0.051 0.809
Mean amplitude Percentage	-0063 0.765	0.095 0.653	-0.346 0.091	-0.126 0.547
MEPs phases at the Rt side	0.135 0.520	0.087 0.679	-0.200 0.338	-0.146 0.485
MEPs phases at the Lt side	-0.78 0.712	-0.276 0.182	0.122 0.562	0.157 0.454
Mean MEPs phases	0.006 0.976	-0.085 0.688	-0.038 0.858	-0.038 0.858
RT MEPs duration	-0.141 0.500	-0.153 0.466	0.234 0.261	-0.314 0.126
LT MEPs duration	0.158 0.452	-0.098 0.642	0.175 0.403	-0.339 0.098
Mean MEPs duration	0.077 0.714	-0.150 0.475	0.364 0.073	-0.342 0.094

DISCUSSION

Single pulse TMS is easy to employ because it is non invasive, non painful and safe. It can probe the function of many different parts of the cerebral cortex i.e. excite, inhibit and assess aspects of excitability *(Hallet, 2000).* This is achieved through analysis of many MEP parameters which are useful in understanding the changes in brain physiology seen in the setting of cortical plasticity and brain disorders *(Hallet, 2000).*

In the present study, there was a statistically significant difference of nearly all the parameters of MEP when compared with the control group (table 3). This included increased threshold, prolonged central conduction time, reduction of the amplitude, increased phases and prolonged duration of the MEP response of the patients' group.

The threshold for producing an MEP in a resting muscle reflects the excitability of a central core of neurons as a result of the excitability of the individual neurons and their local density *(Hallet, 2000).* On the other hand, MEP amplitude is supposed to result from a complex interaction between the upper and lower motor neurons. However, it is the upper motor neurons that are the dominant responsible constituents of MEP amplitude *(Eisen & Shtybel, 1990).* Their loss will have proportionally a much greater effect on the MEP amplitude as the size of the maximum MEP amplitude is a reflection of the number of large diameter and fast conducting upper motor neurons. These cells account for < 5% of the total population of the pyramidal cells among which only 2% of the myelinated axons has a diameter >4 μm and are capable of reaching a conduction velocity of 60-70 m/s. These are the cells that are responsible for the shortest latency and the largest amplitude component of MEP *(Eisen & Shtybel, 1990).*

In pathological conditions, the amplitude of the MEP response to TMS may be reduced due to block or degeneration of the corticospinal fibers. Moreover, temporal dispersion of MEP may also occur with increased polyphasicity and duration of the response *(Murray, 1999).* In ALS, the above-mentioned cells which are one type of pyramidal cells are the major excitatory cortical neurons involved in the disease *(Enterzari-Taher et al., 1997).* In normal conditions they are subjected to modulation by several different classes of cortical interneurons.

The discharge of the local interneurons results in the release of gamma amino butyric acid (GABA) onto the cortical pyramidal cells leading to generation of fast inhibitory potentials *(Enterzari-Taher et al., 1997).* In ALS there is an abnormal balance between intracortical inhibitory and excitatory mechanisms *(Mills, 2003).* The inhibitory functions linked to multiple neurotransmitter systems decline with disease progression. Both depletion of specific subpopulations of intracortical GABA ergic neurons and mechanisms involved in motor cortex reorganization following progressive neuronal loss have been considered to account for the impaired inhibition *(Zanette et al., 2002).* This in turn leads to chronic excitotoxicity which is strongly implicated in the final cascade of events which cause cell death in ALS *(Enterzari-Taher et al., 1997).*

Thus, in the early stage of ALS i.e. excitotoxicity without loss of corticomotoneurons, the MEP may be large with decreased threshold possibly due to the associated spinal disinhibition *(Eisen & Shtybel, 1990).* Another suggestion proposed by *Ziemann et al. (1998)* was that the selective abnormality of the intracortical inhibition is best compatible with an impaired function of inhibitory interneuronal circuits in the motor cortex that renders the corticomotoneuron hyperexcitable *(Ziemann et al., 1998).* In the contrary, another view suggested that there is no evidence of increased corticomotor hyperexcitability at any stage of the disease. The early lowering of threshold, however, probably represents a shift in the balance of excitatory and inhibitory inputs to the cortical output cells responsible for the voluntary action and could be a reflection of degeneration of the cortical interneurons(usually inhibitory) *(Mills, 2003).*

As the disease progressed, most of the changes are attributed to the degeneration of the motor neurons and the connecting interneurons *(Mills, 2003),* and hence the deterioration of the MEP parameters induced by TMS. In 1999 Kohara et al studied the pattern of corticospinal tract involvement in patients with ALS by analyzing MEP waveforms and their relationship to the behavior of the single motor units using the peristimulus time histogram technique. They concluded that in ALS there is preferential involvement of the fast conducting direct corticospinal tracts sparing the slower polysynaptic projection *(Kohara et al., 1999).* In the present work the overall deterioration of MEP parameters among the studied patients indicate that the study sample has approached the late stage of ALS. Several studies yielded almost similar results as the current one regarding the abnormalities of MEP in MND *(Mills, 2003, Osei-Lah & Mills, 2004, Domzal-stryga and Bojakowski, 2001),* although most of them did not consider all MEP parameters at a time especially MEP duration and phasicity. In one study, central motor conduction (CMC) abnormalities were measured in patients with ALS.

The commonest finding was the absent MEP in 44% of the patients. The degree of muscle weakness as well as selecting distal muscles for examination was significantly associated with an abnormal CMC *(Osei-Lah & Mills, 2004).* Another study compared the results of MEP in 79 patients with ALS to those of healthy control. M and F responses were evoked by peripheral stimulation of ulnar and peroneal nerves to abductor digiti minimi and tibialis anterior muscles respectively followed by recording of MEP. There was significant prolongation of CMCT and an increase in the MEP/M amplitude ratio in patients compared to control. However, a

subpopulation of patients with predominant upper motor neuron lesion had significant increase of CMCT but not the amplitude ratio *(Domzal-stryga & Bojakowski, 2001).* In another study the central motor pathways were unexcitable by TMS in 10 patients out of 21, while CMCT of the tibialis anterior muscle was prolonged in 14 sides *(Mirsa et al., 1995).* Therefore it appears that MEP parameters including the CMCT can be used for assessment of the pyramidal dysfunction in ALS. However, Eisen et al had argued about the validity of using CMCT as a reflection of pyramidal dysfunction. They found that the overall abnormalities of MEP approached 100% while the CMCT was not significantly different in ALS patients compared to healthy control *(Eisen et al., 1990).*

It remains in this context to comment on the contribution of the lower motor neuron lesion, namely the weakness and the wasting of the examined muscle to the abnormality of the MEP parameters. In fact, the loss of anterior horn cells (AHC) alone might theoretically cause prolongation of the CMCT because of reduced temporospatial summation of the descending volley, but it was proved that MEP in patients with pure muscular atrophy and patients with AHC loss from poliomyelitis have revealed normal CMCTs *(Murray, 1999)*. Moreover, although the amplitude represents as previously mentioned a complex interaction between the upper and lower motor neurons, yet the upper motor neuron has a greater contribution to MEP *(Eisen & Shtybel, 1990).* In addition, between the second and ninth decades, cortical neuronal loss is in the order of 36-60% while for the AHC is only 25%. Besides, another important fact is that AHC can compensate for their loss by enlargement of their peripheral field *(Eisen & Shtybel, 1990).*

The principal sequence of MND is the loss of motor function. Evaluation of such motor deficits implies assessment of the resulting incapacity and the final disability. In the present study, patients with MND had significantly severe disease and significant functional disability as well (table 4) In spite of this, there was no significant correlations between the functional and severity indices used in this study and most of MEP parameters. Exceptionally, there was a significant inverse correlation between the mean CMCT and the ALSSS as well as between the left amplitude % and the bulbar subscore. The first correlation denotes that if the disease severity is great (as indicated by a low score of ALSSS) the CMCT will be prolonged assuming that the more the disease is severe the more the pyramidal tracts are degenerated.

The second correlation reflects almost the same concept i.e. the more the bulbar subscore is (as a feature of severity), the less is the amplitude ratio, supporting the assumption that the severity is correlated with pyramidal tracts degeneration. In support of this view is that among the studied patients 48% had bulbar manifestations which are known to be associated with severe illness *(Eisen & Shtybel 1990).* Most of the studies have correlated some MEP parameters to the disease duration *(Zanette et al., 2002 & Zanette et al., 2002 and De Carvalho et al., 2002).* as well as the clinical features (where no correlation had been proved) *(Zanette et al., 2002 & Zanette et al., 2002).* On the other hand, the lack of correlation between the MEP parameters and the ALSFRS could be explained on the fact that the function is the outcome of the contribution of many areas in the central nervous system including the pyramidal tracts which are excited by TMS. Hence, the dysfunction of the pyramidal tracts can be partially compensated by the uninvolved areas of the brain leading to a relatively better overall functional outcome in relation to the severity of the pyramidal tracts involvement.

Conclusion And Recommendations:

Motor evoked potentials induced by TMS were collectively found to be abnormal in MND (irrespective to its variant) compared to healthy control subjects. The pattern of abnormality indicated a relatively later stage of the disease. In spite of this none of MEP parameters was correlated to the Functional Rating Scale, denoting that the functional performance is influenced by many areas of the brain other than the pyramidal tracts (which are typically involved in MND and tested by TMS). On the other hand, CMCT and MEP amplitude % were significantly correlated with disease severity indicating that the magnitude of pyramidal tract degeneration is intimately matching with the disease severity at any stage of the disease. Therefore, it could be recommended to use MEPs as one of the diagnostic tools for MND (to determine the extent of the disease) and as one of the measures for assessment of disease severity especially CMCT and the MEP amplitude percentage.

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الملخص العربي

النظرية: التنبيه المغناطيسي عبر القحف طريقة يمكن أن تنشّط الباحات الحركيّة القشريّة و السّبيل القشريّ النّخاعيّ بدون أن تسبب عدم الرّاحة للمرضى .

الطريقة: اجريت الدراسة على خمسة و عشرين مواطنًا بمرض العصب الحركيّ الّذين قد شُخِّصُوا إكلينيكيًّا بالإضافة إلى دراسات اليكتروفيسيولوجيا (دراسات التّوصيل العصبيّ، رسم العضلات) و قدتم تقييم الاتى {عتبة و زمن التوصيل الحركى المركزي، ناتج نسبة مئويّة مدى التّردّد، مراحل و مدّة الجهد المستحث الحركى}. بالإضافة إلى عشرة أشخاص أصحاء ملاءمون أُخْتِيرُوا كمجموعة ضابطة. وقد تم تقييم شدة المرض بالإضافة للتقييم الوظيفى بإستخدام مقياس قسوة المرض ومقياس الفرز الوظيفى لمرض العصب الحركى تباعابالمقارنة بالمجموعة الضابطة .

النتائج: أسفرت عن وجود فرق ذو دلالة إحصائية لكلّ مقاييس الجهد المستحث الحركى تقريبا مقارنة بالمجموعة الضابطة. و قد وجد أن متوسط زمن التوصيل الحركى المركزي وناتج نسبة مئويّة مدى التّردّد، الأكثر إرتباطًا بقسوة المرض.

التوصيات: وبناء على هذه النّتائج سيُوصَى أن يستخدم التنبيه مغناطيسي عبر القحف كأداة مفيدة في تشخيص المرض وقياس قسوة المرض و خاصة زمن التوصيل الحركى المركزي وناتج نسبة مئويّة مدى التّردّد.