Original Article

Transcranial magnetic stimulation: Role in the evaluation of disability in multiple sclerosis

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Background: In patients with multiple sclerosis (MS), transcranial magnetic stimulation (TMS) has shown significant prolongation of central motor conduction time (CMCT). Abnormal CMCT may reflect sub-clinical involvement of motor pathways and correlate with clinical motor disability. **Objective:** To determine the diagnostic yield of TMS in MS and the possible correlation of TMS abnormalities with clinical disability. **Materials and Methods:** Thirty patients with clinically definite MS presenting in acute relapse or with progressive disease course and 30 healthy controls were evaluated. TMS parameters evaluated included threshold intensity, motor evoked potentials (MEP) amplitudes and latencies and CMCT. Reassessment studies were done after three months. **Statistical analysis:** Student t-test, Mann-Whitney U test and Spearman's rank correlation test were used to assess the relationships. **Results:** Patients with MS had significantly higher threshold intensities, prolonged CMCT and reduced MEP amplitudes as compared to controls. Abnormalities in at least one parameter were observed in 86.7% of patients. When inter-side asymmetries in MEP latency and/or in CMCT were considered, the diagnostic yield increased to 96.7%. The diagnostic yield was 74.7% for visual evoked potentials, 13.3% for brainstem auditory evoked response and 10% for cerebrospinal fluid oligoclonal band. One MS patient without pyramidal or cerebellar dysfunction had prolonged CMCT. CMCT abnormalities correlated significantly with the degree of pyramidal signs, limb ataxia, intention tremor, dysdiadokokinesia and overall cerebellar score. In patients who had clinical improvement, follow-up studies showed improvement in CMCT parameters. **Conclusion:** TMS is a highly sensitive technique to evaluate cortico-spinal conduction abnormalities in MS that may have no clinical correlate and in monitoring the course of the disease. The effects of cerebellar dysfunction on TMS results need further evaluation.

Key Words: Magnetic stimulation, central motor conduction, motor evoked potential, pyramidal dysfunction

Over the past few years, interest in evoked potentials (EP) in patients with multiple sclerosis (MS) has shifted from diagnostic applications to their validity as objective parameters of the disease course.[1-3] Among the EPs, transcranial magnetic stimulation (TMS) has been shown to be the single most sensitive diagnostic test among the evoked potentials in patients with MS.[4-7] In these patients, TMS has revealed significant prolongation of central motor conduction time (CMCT).[8-10] It may also detect sub-clinical lesions and CMCT abnormalities may be related to clinical motor disability.[11-13] The possible role of cerebellar dysfunction with regards to TMS abnormalities in MS is not clear although increased threshold intensities and/or abnormal CMCT have been reported in late onset cerebellar atrophies and cerebellar stroke.[14,15]

The present study was undertaken to determine the diagnostic yield of TMS in clinically definite MS besides other methods, to assess the strength of the correlation between clinical disability and TMS abnormalities and to evaluate the possibility that TMS may be used to monitor clinical response in MS over time.

Materials and Methods

The present study was done on 30 consecutive patients of clinically definite MS,[16] admitted between January 2002 and June 2003. Patients included both patients in acute relapse and patients with progressive course. Patients with the history of epilepsy, neurosurgery or pacemaker implants were excluded. A relapse was defined as an increase in the neurological symptoms at least lasting for more than 24 hours, starting within at least two months prior to the evaluation. Ethical clearance was obtained from the local review board and written, informed consent was taken from all the subjects.

All the subjects underwent detailed history taking, systemic and neurological examination. The patients were clinically examined using the following scales:

1) Kurtzke's Expanded Disability status scale (EDSS) and complementary system of grades within 8 "functional systems".[17]

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2) Pyramidal tract function was assessed by muscle strength and reflex grading. Muscle strength was assessed and scored according to the Medical Research Council scale. Deep tendon reflexes (DTR) were classified as normal (0), increased but not necessarily to a pathological degree (1), and markedly hyperactive, often with associated clonus (2); Hoffmann sign was scored as incomplete (1) if only thumb or index finger responded, and complete (2) when definitely positive; Babinski sign was scored as incomplete (1), characteristic (2), or with pathologic shortening reflex present (3).[13]
3) Cerebellar symptoms were rated on a scale ranging from 0 (absent) to 35 (most severe).[18] All the scores were analyzed as percentage of the most severe scale range and an adequate knowledge of the individual limb function was obtained.

A single pulse TMS of the motor cortex was performed with a circular coil of 90 mm diameter of MAGSTIM 200 (2 Tesla version, Magstim Co., Dyfed, UK) stimulator pulsed with a very brief (less than 200 microsecond) current and generating maximum magnetic field of 2 Tesla. The center of the coil was positioned over the vertex for cortical stimulation of the upper limbs, and slightly anterior to the vertex for stimulation of the lower limbs. Since the motor cortex is more sensitive to current flowing from posterior to anterior, a clockwise current flow (side B up) was used for right motor cortex activation, and a counter-clockwise flow (side A up) for the left cortex activation.[19] The filter setting used was 100 Hz low filter and 10 KHz high filter. The signals were recorded with a conventional EMG machine (Nicolet Biomedical Inc., Madison, USA) bilaterally from the abductor pollicis brevis (APB) in the upper limbs and from the tibialis anterior (TA) in the lower limbs by surface silver/silver chloride electrodes in a belly-tendon montage. The nerve conduction studies by electrical stimulation were also performed for median and deep peroneal nerves in all the subjects using the same EMG machine.

The subjects were seated in a chair and threshold intensity (TI) was recorded in a relaxed target muscle. TI was taken as the minimum stimulus intensity (measured as a percentage of maximum output intensity of the stimulator) needed to evoke a response >20 mV in three out of five trials.[20] If no response was recorded even at maximum coil output (100%), the subjects were asked to contract target muscle and if still no response was recorded, then TI was considered as 100%.[21] The subjects were then asked to maintain mild isometric contraction (10-20% of maximal effort) of the target muscles and stimuli were given at intensities at least 30% above TI and 6-10 motor evoked potentials (MEP) were recorded; those with shortest latency and largest amplitude were evaluated. The magnetic stimulation of the spinal roots was done by placing the rim of the same coil over the seventh cervical and fifth lumbar vertebrae. CMCT was measured by subtracting the latency resulting from spinal stimulation from that on cortical stimulation. The parameters evaluated were: TI; cortical-APB/TA latencies (CL) and spinal cord (cervical/LS spine)-APB/TA latencies; amplitude (A_M) of MEP; CMCT and inter-side differences in CL and CMCT between the hemispheres.

All patients also underwent cerebrospinal fluid (CSF) analysis for oligoclonal bands (OCB) by polyacrylamide gel electrophoresis (PAGE), visual (VEP) and auditory (BAER) evoked potentials and MRI of brain and/or spinal cord. Follow-up clinical and electrophysiological evaluation was performed in all the patients at three months after the initial TMS study.

Normal ranges were established from a group of 30 age and sex-matched healthy controls. The upper limits of normality for CL and CMCT were taken as 2 SD above the mean and the lower limit of normality for the A_M as 2 SD below the mean values of controls (Table 1). The latencies and CMCT were considered abnormal when the responses were either absent or the value of the parameter exceeded the upper limits of the normality. In case of MEP abnormality in one limb, we considered this finding as a sign of sub-clinical pyramidal tract involvement if there were no signs of corticospinal involvement in all other limbs.

Statistical analysis between the patient and control results was performed using t-test. The clinical and electrophysiological findings were correlated using Mann-Whitney U-Wilcoxon rank sum test for group data comparisons and Spearman Rank correlation test.

Results

Thirty patients of MS, 17 females, 13 males (age range 12-50 years; mean 30.4±10.8), and 30 healthy controls, 13 females and 17 males (age range 14-45 years; mean 29.7±7.02), were evaluated. The grades of pyramidal and cerebellar dysfunction and the degree of abnormal motor signs in both the upper and lower limbs are summarized in Table 2. At inclusion, five patients had normal pyramidal function; out of these, two patients had normal cerebellar function also. The interval from the first onset of symptoms to the first electrophysiological examination was 32.03±44.6 months (range 5 days to 18 years).

TMS was well tolerated by all the subjects without any immediate or delayed untoward side effects. In total, 119 limbs were studied; MEPs could be elicited in all the four limbs in controls and 57/60 upper limbs and 36/59 lower limbs in the study group (Table 1).

The mean TI, CMCT and CL were significantly prolonged in all the limbs ($P<0.001$) and the mean A_M on cortical stimulation was significantly reduced in the upper limbs ($P<0.001$) in MS patients as compared to the controls. At least one parameter was found to be abnormal in 40% right upper limbs, 50% left upper limbs, 70% right lower limbs and 72.4% left lower limbs. Overall, at least one parameter was abnormal in 68/119 (57.1%) of the total limbs studied. Diagnostic yield of TMS was found to be 76.7% in the upper limbs and 93.3% in the lower limbs. Thus, 28/30 (86.7%) patients had one parameter abnormal in at least one of their limbs. Additional abnormal inter-side asymmetries in either CL and/or CMCT were found in 3(10%) patients. Hence, the diagnostic yield of TMS in our study was 96.7%. In comparison, the diagnostic yield of VEP was 74.7%, BAER 13.3% and CSF OCB 10%.

In the upper limbs, the mean CMCT correlated significantly with the degree of hypereflexia ($r=0.34$, $P=0.01$), Hoffmann score ($r=0.34$, $P=0.01$), limb ataxia ($r=0.32$, $P=0.017$), dysdiadokokinesia ($r=0.33$, $P=0.012$) and intention tremor ($r=0.33$, $P=0.012$). In the lower limbs, mean CMCT correlated significantly with the degree of hyperreflexia ($r=0.49$, $P=0.002$) and in the left lower limbs with pyramidal dysfunction ($r=0.65$, $P=0.05$). No correlation was found in EDSS and CMCT abnormalities in any of the limbs (Table 3).

Table 1: Incidence of limbs with abnormalities of TMS parameters in clinically definite multiple sclerosis patients

TMS parameter	Upper limbs		Lower limbs	
	Cases	Controls (limits of normality)	Cases	Controls (limits of normality)
Threshold (%)				
- Range	70-100%	70-100%	70-100%	70-100%
- Mean ± SD	92.8±9.8	83.8±12.1 (Rt-0.7,Lt>92.3)	98.3±24.8	97.3±6.9 (Rt-100, Lt-100)
- Abnormal (n, %)	36 (62.1%)	-	0	-
Amplitude of MEP On cortical stimulation				
- Range	0.2-11.7	1.1-15.6	0.3-7.0	0.5-5.4
- Mean ± SD	2.8±1.3	5.2±2.4 (Rt<0.24,Lt<0.17)	1.6±0.78	2.2±1.16 (Rt0, Lt<0.05)
- Abnormal (n, %)	1 (1.8%)	-	0	-
Latency of MEP on cortical stimulation				
- Range	15.4-46.2	8.4-27.3	11.6-78.4	10-29.8
- Mean ± SD	24.8±6.5	19.0±3.3 (Rt>26.2,Lt>24.8)	33.2±12.9	25.3±3.2 (Rt>31.9,Lt>30.2)
- Abnormal (n, %)	26 (45.6%)	-	17 (42.5%)	-
Central motor conduction time				
- Range	4.3-31.5	5-16.8	6.7-67.1	6.5±18.8
- Mean ± SD	12.6±6.2	7.7±2.2 (Rt->13.6,Lt->10.7)	21.6±13.1	
- Abnormal (n, %)	21 (36.8%)		16 (40%)	13.5±2.3 (Rt->17.9,Lt>18.1)
Non-stimulable responses	3	0	23	0

TMS- Transcranial magnetic stimulation; MEP- Motor evoked potential; Rt- Right; Lt- Left; n = Number

Table 2: Incidence of limbs with pyramidal and/or cerebellar dysfunction in 30 clinically definite Multiple Sclerosis patients at inclusion

Parameter	Upper limbs	Lower limbs
No. of limbs tested	60	59
No. of limbs clinically weak (N, %)	12 (20%)	25 (42.4%)
Pyramidal dysfunction (N=30)		
- Range*	0-50%	0-66.7%
- Mean ± SD*	15.46±15-11	27.77±17.68
- Abnormal (N, %)	25 (83.3%)	25 (83.3%)
Cerebellar dysfunction (N=30)		
- Range*	0-80%	0-80%
- Mean ± SD*	28.0 ± 30.45	28.0 ± 30.45
- Abnormal (N, %)	16 (53.3%)	16 (53.3%)
Motor scores		
a) Hoffmann / Babinski score		
- N	60	59
- Range*	0-100%	0-100%
- Mean ± SD*	35.83 ± 42.28	48.03 ± 32.92
- Abnormal (N, %)	28 (46.77%)	45 (76.3%)
b) DTR score		
- N	60	59
- Range*	0-100%	0-100%
- Mean ± SD*	39 (65%)	61.67±36.09
- Abnormal (N, %)	42.5 ± 36.62	49 (83.1%)

* - % of the most severe scale range; N- Number

On follow-up, 17(56.7%) patients improved clinically, 11(36.7%) worsened clinically and 2(6.6%) remained clinically stable. Clinical improvement or worsening on follow-up was considered as change in EDSS by one or more points. For follow-up analysis, only the limbs that had abnormal CMCT at inclusion were studied. In total, 24 upper limbs and 12 lower limbs could be evaluated. In patients who improved clinically (n=12), CMCT showed a corresponding reduction in 14/15(93.3%) upper and 9/9(100%) lower limbs; mean CMCT improved significantly from 17.07 msec. to 14.53 msec. ($P<0.001$) [paired t-test] in the upper limbs and from 34.7 msec. to 25.9 msec. ($P<0.001$) in the lower limbs. On the other hand, in patients who remained clinically stable or worsened (n=13), CMCT showed a corresponding worsening in 7/9(77.8%) upper and 1/3(33.3%) lower limbs; mean CMCT worsened from 19.18 msec. to 24.98 msec. in the upper limbs ($P>0.05$) and from 24.5 msec. to 27.13 msec. in the lower limbs ($P>0.05$) (Figure 1).

Discussion

The results of the present study show that TMS parameters are significantly altered in clinically definite MS patients as compared to the controls. The diagnostic yield of TMS was higher than that of VEP, BAER and CSF OCB, akin to previous reports.[9,13,20,22-29] There are no Indian studies available on the role of TMS in MS patients. The diagnostic yield of CSF OCB in our patients was low similar to other Asian studies. The reported CSF OCB positivity in Asian studies varied between 27% and 45%.[23-25] Since we do not have the methodology to assess lesion volume and lesion load, we have not correlated MRI findings and TMS parameters.

The diagnostic yield of TMS increases whenever more than one limb is tested and abnormal asymmetries between the limbs are taken into consideration.[9,13] In our study 96.7% of the patients had at least one abnormal parameter or abnormal inter-side asymmetries in the parameters. This incidence of abnormalities in our study was higher than that previously reported in MS.[8,9,13] This could be have resulted from the evaluation of both the upper and lower limbs, thus a larger segment of spinal cord. In our study examination of the upper limbs alone had resulted in a diagnostic yield of 76.7%, similar to the other studies that evaluated upper limbs only.[9,22] We found a higher incidence of abnormal MEP in the lower limbs when compared to the upper limbs. Recording from the lower limbs allows the efferent volley to traverse a longer path through the cranio-spinal axis. We considered all the non-stimulable responses to be abnormal because MEP could eas-

Table 3: Correlation of CMCT in upper and lower limbs of multiple sclerosis patients with clinical scores at time of inclusion

Parameter CMCT – correlation with:	CMCT – Upper limbs (n=58)			CMCT – Lower limbs (n=36)		
	N	Spearman rank co-efficient (r)	*P* value	N	Spearman rank co-efficient (r)	*P* value
Pyramidal dysfunction	30	0.14	NS	30	0.30	NS°
Hoffmann/ Babinski score	60	0.34	0.01*	60	0.14	NS
DTR score	60	0.34	0.01*	60	0.49	0.002*
Cerebellar dysfunction	30	0.24	NS	30	-0.19	NS
Cerebellar scale score						
a) Total score	30	0.26	NS	30	-0.09	NS
b) Upper limb ataxia	60	0.32	0.017*	29	-0.10	NS
c) Dysdiadokoki-nesia	60	0.33	0.012*	29	-0.09	NS
d) Intention tremor	60	0.33	0.012*	58	-0.12	NS
e) Dysarthria	30	0.27	NS	30	0.09	NS
EDSS	30	0.07	NS	30	0.06	NS

CMCT- Central motor conduction time; EDSS- Expanded disability status score; *Significant *P* value <0.05; NS- Not significant; r = Correlation; °Correlation of pyramidal dysfunction with CMCT in left lower limbs was significant using paired group statistics (r=0.65, *P*=0.05)

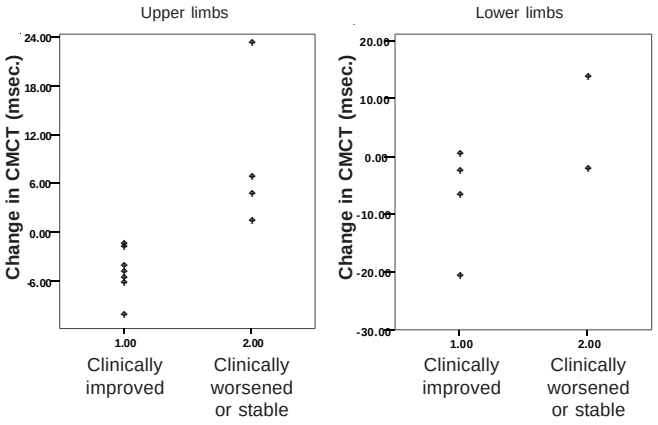

Figure 1: Change in CMCT in upper and lower limbs of MS patients on follow-up

ily be elicited in all the four limbs of the healthy controls. Silent lesions were detected in one patient (3.3%) who had no clinical evidence of pyramidal and cerebellar dysfunction. Similar findings were observed in the earlier studies.[9,11-13]

The present study confirms the observation that CMCT measurements correlate positively with motor disability.[12,13] The lack of correlation between CMCT abnormalities and EDSS is possibly because EDSS takes into account overall clinical disability, i.e., both pyramidal and non-pyramidal tract lesions. The effects of cerebellar dysfunction on TMS results are not well known. We found a significant positive relation between CMCT abnormalities in the upper limbs and limb ataxia, intention tremor, dysdiadokokinesia and overall cerebellar scale score. Previous observations point that cerebellar dysfunction might play a role in the CMCT abnormalities by TMS.[13,14] It however, might be over-represented due to co-incidental pyramidal tract involvement.

In our patients, there was improvement in CMCT parameters corresponding with clinical improvement, although the number of patients evaluated was small. Mean CMCT of the total group studied, improved significantly in patients who had improved clinically, whereas the mean CMCT of the total group worsened in patients who worsened clinically or remained stable. Similar results have been reported previously after steroid therapy[12,21,26,27] and physiotherapy.[28]

TI is a measure of the cortico-cortical excitability of pyramidal neurons. The increased TI and reduced A_M may occur due to temporal dispersion of descending volleys or conduction blocks in the descending motor pathways. The CMCT prolongation in MS occurs secondary to delayed supra-threshold stimulation of smaller and slower conducting motor neurons and a compromise in the stimulus conduction in large diameter demyelinated or incompletely remyelinated corticospinal fibers, resulting in lack of temporal summation.[21,22,26,29] The absence of MEP elicitation results from conduction failure secondary to demyelination across the zone of pathology.[26]

In conclusion, the present study suggests that TMS should be taken into account as a tool in monitoring motor disability in patients with MS, owing to the frequency of lesions in cortico-spinal pathways and the significant correlation observed between the abnormalities in CMCT and the degree of motor disability. In order to further define the potential role of TMS in the characterization of MS-related disability, especially in patients with primary or secondary progressive disease course, large prospective serial studies are required.

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Invited Comments

The pyramidal tract is frequently affected in multiple sclerosis (MS) and impaired motor performance is a major cause of disability in MS. Pyramidal tract function can be assessed using transcranial magnetic stimulation (TMS), yielding motor-evoked potentials in cranial nerve innervated, arm and leg muscles. Among the evoked potentials, TMS has been shown to be the single most sensitive parameter in patients with MS for diagnostic purposes.[1] The most sensitive parameter in single pulse stimulation is the delayed central motor conduction time (CMCT). The chance of obtaining pathological results increases continually from the cranial nerves to the upper and lower limbs, parallel to the increasing length of the examined corticobulbar and corticospinal tracts. The sensitivity further increases when the interhemispheric inhibition between the motor cortices (transcallosal inhibition) is taken into account[2] or when a triple stimulation paradigm is applied.[3]

The authors of the present study summarize their experience of investigating 30 patients with clinically definite MS and 30 healthy controls using TMS. They found abnormalities in at least one of several TMS parameters in 86.7% of the patients, confirming the results of previous studies.[4,5] They also demonstrated a significant correlation between CMCT and the degree of pyramidal signs. On follow up, mean CMCT improved significantly in MS patients who improved clinically. Thus, the authors conclude correctly that TMS is a highly sensitive technique to evaluate corticospinal conduction abnormalities in MS that may have no clinical correlate and may monitor pyramidal function during the course of the disease. In future studies, it would be of interest to monitor short-term and long-term treatment effects (steroids and immunomodulating drugs) by TMS.

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