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Alterations of cortical excitability and central motor conduction time in Wilson's disease

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HIGHLIGHTS

- In Wilson's disease (WD) there are structural alterations of brain.
- Transcranial magnetic stimulation (TMS) can evaluate neurophysiological changes.
- Thirteen patients with WD were studied using TMS.
- Non-recordable or high RMT and prolonged CMCT were observed in WD.
- Patients with WD have widespread changes of cortical excitability.

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ABSTRACT

Wilson's disease (WD) leads to widespread structural alterations of central nervous system and our objectives were to determine the cortical excitability changes in WD by using transcranial magnetic stimulation (TMS). Thirteen patients with WD, diagnosed by the presence of Kayser–Fleischer ring and biochemical tests, were studied. TMS was performed using a figure-of-eight coil attached to Magstim 200 stimulator. Motor evoked potentials (MEP) were recorded from right first dorsal interosseous at rest. Resting motor threshold (RMT) was determined using standard techniques and central motor conduction time (CMCT) by 'F' wave method. Comparison was made with control data of our laboratory. Dysarthria was the presenting symptom in 5 patients (38.5%) and chorea, tremors, dystonia and abnormal gait in 2 patients each (15.4%). RMT was recordable in 10 patients and not recordable in 3. Compared to controls, patients in whom RMT was recordable, had significantly higher mean RMT (80.9 ± 14.8 vs. 41.1 ± 7, $p < 0.0001$) and CMCT (6.7 ± 0.5 ms vs. 4.8 ± 0.6 ms; $p < 0.0001$). In 2 of the 3 patients with non-recordable RMT, MEP could be obtained with active contraction. CMCT in these 2 patients was also prolonged. Patients with WD have reduced cortical excitability and prolonged CMCT which may be due to the intracortical presynaptic motor dysfunction.

1. Introduction

Wilson's disease (WD) is an autosomal recessive disease associated with heterogeneous mutations in the gene ATP7B [19]. It is characterized by accumulation of intracellular copper in the liver and central nervous system. Nearly 50 percent of the patients presents with neurological symptoms [17]. In a large study of 136 patients, Walsh [18] divided the neurological symptoms in WD patients into four groups namely parkinsonian, tremor and dysarthria predominant ("pseudosclerotic"), dystonic, and choreic. The relative frequencies of these and other phenotypes have been reported in many large case series [13,12]. Neuropathology and MRI studies have found extrapyramidal structures like caudate, putamen and globus pallidus to be predominantly involved followed by thalamus and brainstem [5]. Small number of studies [10,3] has shown the involvement of cortex and pyramidal tract in the patients with WD. Subclinical involvement of the pyramidal tracts has also been reported in patients with WD [10,3]. Perretti et al. [10] with the help of transcranial magnetic stimulation (TMS) and transcranial bifocal electric cortical stimulation (TES) have shown subclinical involvement of the pyramidal tracts in patients with WD. Presently TES is an outdated technique with adverse side effects. There are very few studies which have looked into the cortical excitability changes in patients with WD. We report here our observations on the cortical excitability changes, using TMS, in patients with WD.

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Table 1
Clinical features and TMS findings in patients with Wilson's disease.

Case	Age	Sex	AAO	Duration	Treatment		Symptoms								RMT	CMCT
No			(years)	(years)	Pen	Zinc	Tr	Rig	Br	Pts	Bu	Dy	Cer	Cho	(%)	(ms)
1	20	M	18	2	+	+	–	+	–	–	–	+	–	–	73	7.25
2	15	M	11	4	+	+	+	–	–	–	–	–	+	–	72	5.95
3	44	M	40	4	+	+	+	–	–	–	–	+	–	–	EWAC	8.80
4	31	F	31	0.5	+	+	–	–	+	–	–	+	–	–	54	6.50
5	13	F	12	1	+	+	–	–	+	–	+	–	–	+	85	6.20
6	30	M	30	0.66	+	+	–	–	–	–	–	–	+	+	90	6.55
7	17	M	12	5	+	+	–	–	+	+	–	+	–	–	65	6.37
8	12	M	6	6	+	+	+	–	–	–	–	–	+	–	95	7.20
9	13	M	11	2	+	+	–	–	+	+	–	+	+	–	EWAC	5.57
10	18	M	16	2	+	+	+	–	–	+	–	+	–	–	80	7.00
11	16	M	11	5	+	+	–	+	–	+	–	–	–	–	IE	NR
12	13	F	13	0.5	+	+	–	+	–	+	–	+	–	–	100	6.58
13	12	M	3	9	+	+	+	–	–	–	–	–	+	–	95	7.20

AAO, age of onset of symptoms; Br, bradykinesia; Bu, bulbar signs; Cer, cerebellar signs; Cho, chorea; Dy, dystonia; EWAC, excitable with active contraction; IE, in excitable; NR, non recordable; Rig, rigidity; Pen, penicillamine; Pts, pyramidal tract signs; TMS, transcranial magnetic stimulation; Tr, tremor.

2. Subjects and methods

2.1. Patients

The study was conducted in the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. Thirteen patients (10 men and 3 women; mean age 19.5 ± 9.7 years) with WD were taken up for the study. All patients had undergone biochemical copper studies and ophthalmological evaluation for the presence of Kayser–Fleischer ring. All the patients were clinically evaluated by a Movement Disorder Specialist.

2.2. Assessments

A Magstim 200 stimulator and a figure of eight coil with an inner diameter of 70 mm were used for TMS. Patients were made to sit comfortably on a chair with eyes open. The coil was held in antero-medial direction at an angle of 45° with respect to Cz and the direction of flow of the induced electric field was from posterior to anterior. Surface EMG recordings were done from the first dorsal interossei (FDI) muscle of right hand. The area of left motor cortex which when stimulated, gave optimal MEP was marked over the scalp and subsequently the coil was positioned on the same area for evaluation of resting motor threshold (RMT) and central motor conduction time (CMCT).

RMT was defined as the minimal stimulator output eliciting MEP of at least 50 μV in amplitude in 5 out of 10 trials from FDI muscle at rest. Thirty trials were performed at intensities of 110%, 130% and 150% of the RMT and the shortest latency from all the 30 trials was taken for measuring the RMT. CMCT was calculated using the F wave method. The F wave was obtained after stimulating the ulnar nerve at the wrist with supramaximal strength. A total of 20 F wave recordings were taken and the shortest F wave latency was taken for the measurement of CMCT. The following formula was used to calculate CMCT: CMCT = MEP − (F + M − 1)/2, where MEP – shortest MEP latency, F – shortest F wave latency, M – latency of the direct M response and 1 ms is the turnaround time across anterior horn cell.

MRI brain was done in 11 patients. All the MRIs were seen and reported by neuroradiologist.

The data of the patients were compared with our laboratory control data of 26 healthy subjects (20 men and 6 women; mean age of 31 ± 6.7 years). Statistical significance was assessed at 5% level of significance. Pearson's correlation test was used for determining correlations.

3. Results

The mean age of the patients was 19.5 ± 9.7 years, the mean age of onset of symptoms was 16.5 ± 10.7 years, the mean duration of illness was 2.8 ± 2.5 years and mean duration of treatment was 0.74 ± 1.39 years (Table 1).

3.1. Clinical

Of the 13 patients, 11 patients were on treatment with zinc sulphate and/or penicillamine and 2 patients were not on any medications. Dysarthria was the presenting symptom in 5 patients (38.5%). Chorea, tremors, dystonia and abnormal gait were the presenting symptoms in 2 patients (15.4%) each. A history of jaundice was present in 6 patients (46.2%). Evidence of involvement of pyramidal system (the presence of Babinski's sign with or without brisk reflexes) was present in 5 patients (38.5%) (Table 2).

3.2. MRI

Of the 11 patients who underwent MRI, 9 had abnormal signal intensities of different anatomical regions bilaterally, and 2 had unilateral changes. The structures involved on MRI were: caudate (81.8%), thalamus (63.6%), putamen (54.5%), globus pallidus (45.5%), midbrain (45.5%), and cerebellum (9.1%).

3.3. Transcranial magnetic stimulation

3.3.1. RMT

RMT was recordable in 10 patients and not recordable in three patients. Among these three patients, in two MEP could be obtained with active contraction of the right FDI. Compared to controls, the

Table 2
Clinical characteristics of patients with Wilson's disease.

Clinical features	No of patients (%)
Dystonia	7 (53.9)
Cerebellar signs	5 (38.5)
Tremor	5 (38.5)
Pyramidal signs	
(a) Only Babinski's sign	5 (38.5)
(b) Only hyperreflexia	4 (30.7)
(c) Babinski's sign + hyperreflexia	3 (23.1)
Bradykinesia	4 (30.7)
Rigidity	3 (23.1)
Chorea	2 (15.4)
Bulbar signs	1 (7.7)