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Excitatory and inhibitory mechanisms in Wilson's disease: investigation with magnetic motor cortex stimulation

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Abstract

We have evaluated cortical excitability in nine patients affected by Wilson's disease (WD) using transcranial magnetic (TMS) and electric (TES) cortical stimulation and central silent period (CSP) data. A clinical score was derived from the sum of scores assigned to extrapyramidal, pyramidal and cerebellar signs. All patients underwent TMS. Motor evoked potentials (MEPs) from abductor pollicis brevis (APB) and tibialis anterior (TA) muscles were recorded. MEP threshold and amplitude, central motor conduction time (CMCT), CSP threshold, CSP and peripheral silent period (PSP) duration were measured. Three patients also underwent transcranial bifocal electric cortical stimulation (TES) and MEPs were recorded from the APB muscle, and CMCT, MEP threshold and amplitude were measured. TMS MEPs were absent from relaxed muscles in six patients and from contracted muscles in three. CMCT was prolonged in six patients. APB CMCT correlated with clinical score. In three patients in whom TMS revealed abnormal or no MEP, TES MEPs were of normal threshold and amplitude. The CSP threshold was increased in seven patients, and CSP was absent in one. These results suggest an intracortical presynaptic motor dysfunction in WD.

Keywords: Wilson's disease; Transcranial magnetic electric cortical stimulation

1. Introduction

Wilson's disease (WD) is a treatable autosomal recessive disorder of copper metabolism. Extrapyramidal dysfunction is the most frequent neurological feature in WD. Cerebellar dysfunction is seen in approximately 25% of patients, while upper motor neuron syndrome is more rare [1]. Neuropathological and brain magnetic resonance imaging (MRI) studies demonstrated that basal ganglia are more frequently affected, followed by thalamus and brainstem [2,3].

Transcranial magnetic stimulation (TMS) of the motor cortex reveals subclinical pyramidal tract impairment in WD, but its use in monitoring treatment efficacy is controversial [4,5]. Besides motor evoked potentials (MEPs), TMS evokes a central silent period (CSP) attributed, at least during its late part, to intracortical inhibitory mechanisms [6–13]. CSP abnormalities may reflect a derangement of the intracortical inhibitory pathway in patients with basal ganglia dysfunction [14–17].

The aim of this study was to evaluate motor cortical excitability in WD using TMS and transcranial bifocal electric stimulation (TES). To our knowledge, this is the first study to investigate WD using TMS and TES, and to evaluate central silent period in WD.

2. Patients and methods

The clinical and MRI findings observed in our patients are shown in Table 1. TMS was performed in nine WD patients (four men and five women) aged 32.4 ± 11 years (range: 19–55 years). Diagnosis was established by low levels of plasma ceruloplasmin, increased levels of urinary copper and increased liver copper concentrations on needle biopsy. Seven of the nine patients were treated with D-penicillamine (daily dosage range: 600–1650 mg; mean dosage: 1071 ± 329 mg) and six of these patients also received zinc sulphate (daily dosage: 600 mg). Two patients were untreated at the time of the study. Treatment duration ranged from 3 months to 18 years (mean: $6.2 \pm$

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Table 1
Clinical and MRI findings in nine patients with Wilson's disease

Patient no.	Age (years)	Sex	Disease duration (years)	Treatment duration (years)	Extrapyramidal score[a]	Cerebellar score[a]	Pyramidal score[a]	Child–Pugh Class[b]	Hepatic encephalopathy stage[c]	MRI findings
1	19	M	3	3	1	1	0	A	0	BG
2a	33	M	21	10	0	1	0	A	0	Normal
2b	35	M	23	12	0	1	0	A	0	Normal
3	31	F	6	4	0	0	0	A	0	Normal
4	55	F	25	18	2	0	1	C	I	BG, A
5	20	F	13	0	3	0	0	A	0	BG
6a	33	F	12	0.25	2	3	0	A	0	BG, T, PM, A
6b	33	F	12.5	0.75	1	2	0	A	0	BG, T, PM, A
6c	35	F	13.75	2	1	1	0	A	0	BG, A
7	33	F	3	3	0	0	0	A	0	BG
8	35	M	16	4	3	2	0	A	0	BG, A
9a	24	M	4	0	2	1	0	A	0	BG, T, PM
9b	24	M	4.5	0.5	1	1	0	A	0	BG, T, PM
9c	26	M	6	2	1	1	0	A	0	BG, T, PM

BG = Basal ganglia alterations, PM = pons and midbrain white matter alterations, A = cerebral atrophy, T = thalamic alterations.
Patient no. 2 was examined twice, patient nos. 6 and 9 were examined three times (see text for details).
[a] Clinical scores: 0 = normal finding, 1 = mild, 2 = moderate, 3 = severe affection.
[b] Classes A, B and C correspond to mild, moderate and severe hepatic changes, respectively.
[c] Kaiser scale scored from 0 (absence of hepatic encephalopathy) to V, according to the severeness of hepatic encephalopathy.

6.2). Time-to-diagnosis was obtained by subtracting treatment duration from disease duration.

Neurological examination showed extrapyramidal signs in six patients: all had rigidity, and four also had segmental dystonia. Five patients had cerebellar signs: three presented dysarthria, one had upper limb kinetic tremor, and one lower limb dysmetria. One patient had a monolateral extensor plantar response. Extrapyramidal (bradykinesia, dystonia, rigidity and rest tremor), pyramidal (weakness, spasticity, hyperreflexia and extensor plantar response) and cerebellar signs (gait ataxia, limb dysmetria, kinetic tremor and dysarthria) were scored according to clinical severity: 0 = normal finding, 1 = mild, 2 = moderate, 3 = severe (Table 1). The most severe sign in each system (pyramidal, extrapyramidal and cerebellar) determined the score. The total clinical score was the sum of the individual scores. Neurological ratings were determined independently by two experienced neurologists, and the average score was used in this study. All patients underwent brain MRI. According to the Child–Pugh score [18], liver disease was mild in eight patients and severe in one who also had mild hepatic encephalopathy (Kaiser scale stage I) [19] (see Table 1).

A magnetic stimulator (Dantec Mag Pro) producing a monophasic transient magnetic field of 1.9 T at maximum field strength was used for TMS. The circular coil (outer diameter: 14 cm) was placed tangentially on the skull, centred over the vertex for hand muscles and about 3 cm anteriorly for leg muscles; an anti-clockwise current circulation in the coil was used to stimulate the left hemisphere for right hand muscles. The stimulus intensity used to obtain MEPs in contracted muscles was 20% above MEP threshold. However, eight patients were stimulated at 100% of the stimulator output, because the MEP threshold at rest was 80% of the maximum output in two, and MEPs were absent at rest even at 100% of the maximum output in the other six. MEPs were recorded from right abductor pollicis brevis (APB) and left tibialis anterior (TA) muscles (the active electrode was placed on the muscle belly and the reference electrode on tendon), with surface disc electrodes (Dantec 13L29) filled with electrogel. Electrode impedance was below 5000 Ω. The signals were amplified by an electromyograph Dantec Counterpoint with band pass filtering between 20 Hz and 5 kHz and a sampling rate of 20 kHz. MEPs were recorded: (1) in relaxed muscles to measure the excitability threshold (MEP threshold), defined as the stimulus intensity required to produce an MEP of at least 100 μV amplitude in about 50% of 10 consecutive stimuli [20]; and (2) during active muscle contraction (20% of maximum voluntary contraction, maintained with the help of auditory and visual electromyographic feedback). The shortest onset latency and the largest peak-to-peak amplitude of four consecutive MEPs, obtained during active muscle contraction, were measured. Cervical roots were stimulated by positioning the magnetic coil in the midline over the lower cervical and along lumbar vertebrae until the longest latency was obtained. Central motor conduction time (CMCT) was obtained from the latency difference between MEPs and radicular responses. To evoke the central silent period, TMS was delivered after instructing the patient to maintain a sustained voluntary contraction of the APB muscle (70% of maximum strength). The CSP threshold was defined as the minimum intensity required to obtain a pause of the voluntary motor activity equal to or longer than 20 ms. The stimulus intensity used to obtain the CSP in patients and controls was 20% above

the CSP threshold. In patients with a threshold higher than 80%, the CSP was obtained at maximum stimulator output. The CSP duration was measured from the end of the MEP to the reappearance of EMG activity. The peripheral silent period (PSP) was obtained by electrical stimulation (stimulus intensity twice the supramaximal intensity required to obtain the maximum M-response) of the median nerve at the wrist. The PSP duration was measured from the end of the M-response to the reappearance of EMG activity. Three patients also underwent TES by pulses with decay time of 100 μs, delivered by a Digitimer stimulator Model D180. The cortical stimulating anode was placed on the left side of the scalp, 6 cm lateral to the vertex and 2 cm in front of the interaural line, referred to the cathode positioned on the vertex. Motor evoked potentials were recorded from the right APB muscle at rest at threshold intensity, and during active voluntary contraction at 20% above the threshold intensity. Radicular responses in the same muscle were obtained by TES, with cervical electrodes placed over the spinous processes, the cathode on T1 and the anode on C4. CMCT was obtained from the latency difference between MEPs and radicular responses. The TMS MEP findings were compared with the MEP findings of 20 age-matched healthy volunteers (10 men and 10 women) aged 28.5 ± 5.7 years (range: 20–38 years) examined in our laboratory with the same technique. The TES MEP findings were compared with the MEP findings of 10 age-matched healthy volunteers (five men and five women) aged 34.14 ± 3.5 years (range: 32–40 years) examined in our laboratory with the same technique. MEP latency and CMCT values deviating by more than 2.5 SD from the mean control values, as well as a PSP duration below the minimum control value, and MEP and PSP threshold values above the maximum control value were considered abnormal.

Patient 2 was examined with TMS, and then with TMS and TES 2 years later. Patient 6 underwent TMS after 3 and 9 months of penicillamine treatment, and TMS and TES after 2 years of treatment. Patient 9 underwent TMS at the time of diagnosis and after 6 months of penicillamine treatment, and TMS and TES after 2 years of treatment.

Pearson's r regression coefficient was used to analyse parametric data. Non parametric data were studied by Spearman's ρ coefficient. Patients and controls gave their informed consent to the study that was approved by the local Ethics Committee.

3. Results

We will not comment on MEP amplitude and CSP duration findings, because MEP and CSP thresholds were

Table 2
TMS and TES MEP findings in nine patients with Wilson's disease

APB muscle				TA muscle		
Patient no.	MEP threshold (%)	MEP amplitude (mV)	CMCT (ms)	MEP threshold (%)	MEP amplitude (mV)	CMCT (ms)
1	80	4.4	6.2	100	1.8	18.6
2a	nd	1.8	7.6	nd	0.1	24.8
2b	nd	0.4	10.6	np	np	np
2b[TES]	50	6.1	7.8			
3	65	6.8	6.2	80	2.4	15.6
4	nd	0.25	14.7	nd	0.1	25
5	nd	3.2	8	90	1.8	14.4
6a	nd	nd	nd	np	np	np
6b	nd	0.6	15.5	nd	1.9	17.8
6c	nd	nd	nd	np	np	np
6c[TES]	80	3.3	7.1			
7	80	5.9	7.0	nd	0.5	11.7
8	nd	0.28	9.8	nd	nd	nd
9a	nd	0.3	20	nd	nd	nd
9b	nd	0.8	20	nd	0.2	17.2
9c	nd	0.3	9.0	np	np	np
9c[TES]	70	1.5	7.8			
Normal values						
Mean ± SD (TMS)	57.3 ± 10.5	7.1 ± 2.9	6.1 ± 0.7	89.3 ± 8.4	0.88 ± 0.56	14 ± 2.1
(TES)	65 ± 10.4	4.3 ± 2.4	4.0 ± 0.5			
Range (TMS)	40–80	2.6–15	5.4–7.1	75–100[a]	0.35–1.9	11–16.8
(TES)	40–80	1.4–7.7	3.3–4.7			

nd = Not detectable, np = not performed, APB = abductor pollicis brevis, TA = tibialis anterior, MEP = motor evoked potential, CMCT = central motor conduction time, TMS = transcranial magnetic stimulation, TES = transcranial electric stimulation; abnormal values are underlined.
Patient no. 2 was examined twice, patient nos. 6 and 9 were examined three times (see text for details).
[a] Some controls had absent MEPs in relaxed TA muscle.

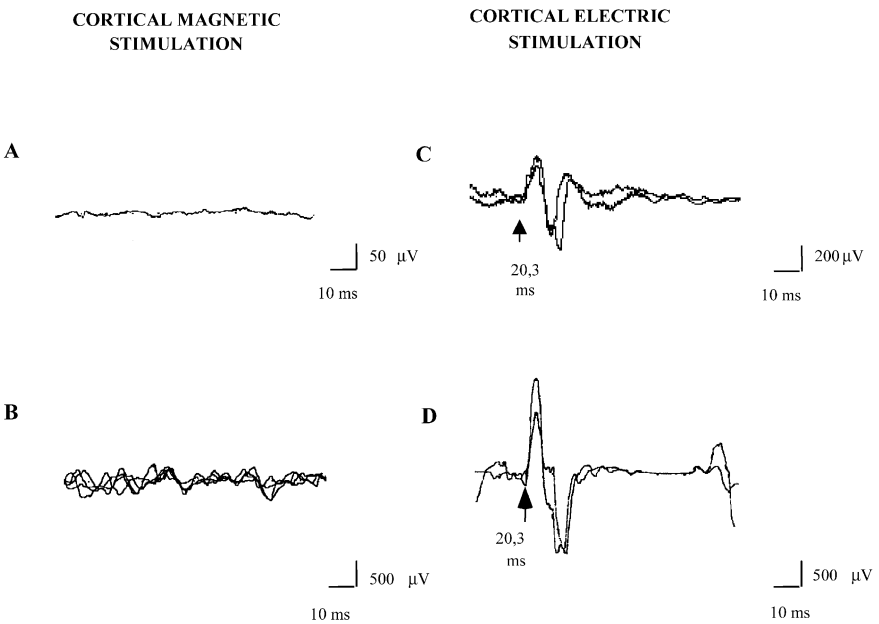

Fig. 1. TMS MEP in relaxed (A) and in contracted (B) right APB muscle at maximum output intensity, and TES MEP in relaxed (C) right APB muscle at 80% of maximum output (threshold intensity), and in contracted (D) right APB muscle at 100% of output intensity in patient 6. Note the absence of a reproducible MEP by TMS.

much higher in most patients than in controls. Consequently, MEP amplitude reduction and CSP duration shortening could be due to insufficient stimulus intensity.

3.1. Motor evoked potentials in APB and TA muscles to transcranial magnetic stimulation

TMS and TES MEP findings are shown in Table 2. Motor responses were undetectable, even at maximum output intensity, in the relaxed APB muscle in six patients (2, 4, 5, 6, 8, 9). In all six patients, APB MEPs showed a prolonged CMCT when recorded during voluntary APB muscle contraction. Of the three patients who underwent follow-up, CMCT was increased at the second examination in patient 2. MEPs were undetectable in patient 6 at the first and third examinations, while CMCT was prolonged at the second examination. There was a progressive shortening of CMCT in patient 9.

The absence of motor responses in relaxed TA muscle at maximum TMS was not considered abnormal, because it was also observed in 20% of our controls. Patients 2, 4, 8, and 9 had MEP abnormalities during TA muscle contraction. No cortical MEP were recorded in patients 8 and 9. MEP CMCT was prolonged in patients 2 and 4. Patient 9 underwent TMS for the TA muscle twice and an MEP with normal CMCT was observed at the second examination after 6 months of penicillamine treatment. Clinical pyramidal signs were found in only one of the six patients with abnormal MEPs, even though MRI white matter alterations in the pons and midbrain suggested corticospinal tract involvement in two. Upper limb CMCT correlated with total clinical score ($\rho = 0.72$, $p < 0.05$); no correlation was found between CMCT and disease duration, therapy duration and liver disease severity.

3.2. Motor evoked potentials in APB muscle to transcranial electric stimulation

TES and TMS MEP findings in the same patients and during the same session are shown in Table 2. TES induced a MEP in the relaxed APB muscle of all the examined patients (2, 6 and 9). During active muscle contraction, MEP amplitude was normal, while the CMCT was prolonged. In patient 6, it was not possible to record a TMS MEP in either relaxed or contracted ABP muscle, while an MEP of normal amplitude was obtained by TES (Fig. 1).

Table 3
Upper limb central silent period in nine patients with Wilson's disease

Patients	1	2a	2b	3	4	5	6a	6b	6c	7	8	9a	9b	9c	Controls mean ± SD (range)
CSP threshold	70	100	100	60	100	90	nd	nd	nd	70	90	100	100	100	52.4 ± 9.9 (30–65)
CSP duration	61	94	23	133	54	47	nd	nd	nd	86	49	61	60	58	107.3 ± 37.3 (52–164)

nd = Not detectable, CSP = central silent period; abnormal values are underlined.

3.3. Central silent period to transcranial magnetic stimulation and peripheral silent period

The CSP results are summarized in Table 3. PSP was normal in all patients. The CSP threshold was increased in seven patients (1, 2, 4, 5, 7, 8 and 9), and normal in patient 3. The CSP could not be elicited in patient 6 even after 2 years of penicillamine treatment. Six of the eight patients with CSP abnormalities also had an increased MEP threshold.

4. Discussion

This is the first study in which transcranial magnetic and electric cortical stimulation have been used to study WD. Moreover, we provide the first CSP data for WD. As found previously [21], in most patients it was difficult to elicit MEPs by TMS in relaxed muscles. Ill-defined MEPs were recorded during active contraction in 60% of our patients. Conversely, better-defined MEPs with normal amplitude were obtained by TES both in relaxed and contracted APB muscle in three patients with abnormal TMS MEPs. The CSP threshold was increased in about 80% of patients, and the CSP could not be elicited in one patient. PSP was normal in all patients.

Abnormal MEPs after electric or magnetic brain stimulation have been described in WD patients [4,5,21,22], but the underlying structural and/or functional disturbances responsible for the MEP abnormalities remain unclear. Meyer et al. [4] found abnormal motor responses in six of their eight WD patients, which they variously attributed to axonal degeneration in the corticospinal pathways, reversible axonal dysfunction, reversible demyelination in corticospinal fibers, or reduction in cortical excitability due to basal ganglia dysfunction. They did not report their MEP threshold results.

In an attempt to define better the level of the corticospinal system dysfunction, we compared TMS and TES findings in three patients: when TES was applied, we observed MEPs with a normal threshold and amplitude, while MEPs were abnormal or undetectable by TMS. This experiment provided the demonstration that the TMS MEP abnormalities found in our patients could be related to intracortical presynaptic impairment leading to reduced cortical excitability. In fact, magnetic stimulation preferentially activates motor cortical cells transynaptically, resulting in a descending excitatory volley in the fast components of the pyramidal tracts [23]. Vice versa, direct electric stimulation of the cortex with a focal anode preferentially activates the proximal nodes of the axons of large corticospinal tract cells in animal models [24], and probably in humans [25]. Thus, the MEP threshold abnormalities found in our patients by TMS, and not confirmed by TES, are suggestive of intracortical excitatory motor dysfunction. Similarly, the increased CSP threshold in most of our patients suggests an intracortical inhibitory neuron dysfunction, since the CSP is attributed, at least during its late part, to intracortical inhibitory mechanisms [6–13].

The reduced excitability of the motor cortex could depend on primary intracortical damage. Our patients were not affected by cortical atrophy or hepatic encephalopathy, and reduced excitability could be due to intracortical accumulation of copper. Alternatively, the reduced excitability of the motor cortex could result from basal ganglia dysfunction [4]. Seven of our nine patients had basal ganglia involvement at MRI; in addition, the clinical score, which was mostly based on extrapyramidal signs, correlated with CMCT findings. Moreover, loss of nerve cells in the putamen, caudate nucleus, globus pallidus and thalamus, and loss of striatal D2 receptors with 123-I-iodobenzamide SPECT have been reported in WD [3,26]. This could indicate reduced inhibitory transmission over the indirect pathway from the putamen to globus pallidus, resulting in increased inhibition on the ventrolateral thalamic nucleus and reduced activating thalamic drive on the motor cortex.

We confirm, by TMS and TES, the finding of a prolonged CMCT, already observed in previous studies, which suggests pyramidal tract involvement, besides motor cortex involvement [4,5,22]. The improvement of MEP findings in one of our patients after penicillamine treatment indicates that corticospinal dysfunction can be reversible. However, the lack of a correlation between CMCT and therapy duration [5, our study] indicates that corticospinal tract fibers may be irreversibly damaged in WD if diagnosis and treatment are delayed.

In conclusion, our study confirms previous results, and provides new insights into the pathophysiology of WD. In fact, by comparing TMS and TES findings we provide the first demonstration of an intracortical presynaptic motor disturbance in WD patients.

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