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Motor disability in patients with multiple sclerosis: transcranial magnetic stimulation study

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Abstract

Background: Transcranial magnetic stimulation (TMS) is a non-invasive procedure used in a small targeted region of the brain via electromagnetic induction and used diagnostically to measure the connection between the central nervous system (CNS) and skeletal muscle to evaluate the damage that occurs in MS.

Objectives: The study aims to investigate whether single-pulse TMS measures differ between patients with MS and healthy controls and to consider if these measures are associated with clinical disability.

Patients and methods: Single-pulse TMS was performed in 26 patients with MS who hand an Expanded Disability Status Scale (EDSS) score between 0 and 9.5 and in 26 normal subjects. Different TMS parameters from upper and lower limbs were investigated.

Results: TMS disclosed no difference in all MEP parameters between the right and left side of the upper and lower limbs in patients with MS and controls. In all patients, TMS parameters were different from the control group. Upper limb central motor conduction time (CMCT) was prolonged in MS patients with pyramidal signs. Upper and lower limb CMCT and CMCT-f wave (CMCT-f) were prolonged in patients with ataxia. Moreover, CMCT and CMCT-f were prolonged in MS patients with EDSS of 5–9.5 as compared to those with a score of 0–4.5. EDSS correlated with upper and lower limb cortical latency (CL), CMCT, and CMCT-f whereas motor evoked potential (MEP) amplitude not.

Conclusion: TMS yields objective data to evaluate clinical disability and its parameters correlated well with EDSS.

Keywords: Multiple sclerosis, TMS, Disability, EDSS

Introduction

Multiple sclerosis (MS) is an autoimmune, progressive chronic central nervous system (CNS) disease of unknown etiology. Over time, the symptoms will get worse and more debilitating and, eventually, loss of functions will be noted often leading to substantial disability [1, 2].

The clinical disability of MS has a progressive course with eventual individual and societal impacts [3]. Several studies have demonstrated increased Expanded Disability Status Scale (EDSS) scores with time [4, 5] and a deterioration in the physical aspects [5, 6] with the progressiveness of MS.

The diagnosis of MS is primarily clinical and relies on the demonstration of symptoms and signs attributable to white matter lesions on magnetic resonance imaging (MRI). The signs and symptoms are disseminated in time (i.e., the disease course) and space (i.e., the affected areas in the CNS), along with the exclusion of other conditions that may resemble MS [7].

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Table 1 Baseline clinical data of patients with multiple sclerosis

	Disease duration (years)	EDSS	Pyramidal sign		Cerebellar signs		Incoordination	
			UL	LL	UL	LL	UL	LL
1	5	4	+	+	−	−	+	+
2	2	3	−	−	+	+	+	+
3	5	0	−	−	−	−	−	−
4	18	3.5	−	−	+	+	+	+
5	12	1	−	−	−	−	−	−
6	5	1	−	−	−	−	−	−
7	3	4	+	+	+	+	+	+
8	6	1.5	−	−	+	+	+	+
9	1	5	+	+	+	+	−	−
10	15	1	−	−	−	−	−	+
11	8	4.5	−	−	−	−	+	+
12	2	1	−	−	−	−	−	−
13	10	5	+	+	−	−	−	−
14	19	3	+	+	−	−	−	−
15	1	1	+	+	−	−	−	−
16	13	0	+	+	−	−	−	−
17	2	0	+	+	−	−	−	−
18	3	1	+	+	−	−	−	−
19	9	6.5	+	+	−	+	+	+
20	1	2.5	+	+	−	−	−	−
21	14	8	+	+	+	−	−	−
22	7	7.5	+	+	+	+	+	+
23	16	6.5	+	+	−	+	+	+
24	5	6.5	+	+	+	+	+	+
25	18	6.5	+	+	+	+	+	+
26	20	6	+	+	−	−	+	+
27	5	4	+	+	−	−	+	+
28	2	3	−	−	+	+	+	+
29	5	0	−	−	−	−	−	−
30	18	3.5	+	+	+	+	+	+
31	12	1	−	−	−	−	−	−
32	5	1	−	−	−	−	−	−
33	3	4	−	−	+	+	+	+
34	6	1.5	−	−	+	+	+	+
35	1	5	+	+	−	−	−	−
36	15	1	−	−	−	−	−	+
37	8	4.5	+	+	−	−	+	+
38	2	1	−	−	−	−	−	−
39	10	5	+	+	−	−	−	−
40	19	3	+	+	+	−	−	−
41	1	1	−	−	−	−	−	−
42	13	0	−	−	−	−	−	−
43	2	0	−	−	−	−	−	−

Table 1 Baseline clinical data of patients with multiple sclerosis *(Continued)*

	Disease duration (years)	EDSS	Pyramidal sign		Cerebellar signs		Incoordination	
			UL	LL	UL	LL	UL	LL
44	3	1	+	+	+	−	−	−
45	9	6.5	+	+	+	+	+	+
46	1	2.5	+	+	−	−	−	−
47	14	8	+	+	−	−	−	−
48	7	7.5	+	+	+	+	+	+
49	16	6.5	+	+	+	+	+	+
50	5	6.5	+	+	+	+	+	+
51	18	6.5	+	+	+	+	+	+
52	20	6	+	+	−	−	+	+

"−" indicates negative, and "+" positive

The presence or absence of dysfunction in the sensory or motor pathways in patients with MS can be ascertained by evoked potentials (EPs) especially in detecting clinically silent lesions where unclear symptoms are present. So EPs can be used as a paraclinical tool for MS evaluation [8, 9]. These EPs are generated by stimulation of a peripheral nerve or its receptors and reflect orchestrated activity by neuronal and axonal groups in the CNS. The motor evoked potentials (MEPs) occur when the brain's motor area is stimulated [10].

MEPs can be elicited either by transcranial electrical stimulation which is not widely used in daily clinical practice or by transcranial magnetic stimulation (TMS) technique as an alternative method. In the latter process, a high-voltage capacitor discharges into a coil of copper wire placed on the subject's head. The resulting

Table 2 TMS parameters of patients with multiple sclerosis and controls

Parameters		Right side	Left side	*p* value
UL CL (ms)	Controls	20.18 ± 1.84	19.79 ± 1.73	0.441
	Patients	24.65 ± 3.94	25.28 ± 5.41	0.604
UL MEP amplitude (mV)	Controls	4.34 ± 2.89	4.03 ± 2.81	0.695
	Patients	1.76 ± 1.92	1.39 ± 1.04	0.393
UL RL (ms)	Controls	12.18 ± 1.53	12.28 ± 1.4	0.807
	Patients	13.05 ± 2.2	12.76 ± 1.76	0.504
UL CMCT (ms)	Controls	7.99 ± 1.64	7.53 ± 1.4	0.218
	Patients	11.53 ± 3.6	12.2 ± 5.0	0.58
UL CMCT-f (ms)	Controls	6.8 ± 1.35	6.82 ± 1.9	0.96
	Patients	10.56 ± 3.6	11.23 ± 4.82	0.52
LL CL (ms)	Controls	37.32 ± 4.04	37.31 ± 3.47	0.997
	Patients	49.51 ± 15.1	50.51 ± 11.04	0.80
LL MEP amplitude (mV)	Controls	1.13 ± 0.23	1.61 ± 1.12	0.132
	Patients	0.68 ± 0.55	0.8 ± 0.47	0.432
LL RL (ms)	Controls	22.34 ± 2.95	22.03 ± 2.7	0.696
	Patients	24.28 ± 4.05	23.33 ± 2.96	0.364
LL CMCT (ms)	Controls	14.88 ± 3.1	15.19 ± 2.91	0.714
	Patients	27.4 ± 11.44	27.57 ± 10.33	0.966
LL CMCT-f (ms)	Controls	12.09 ± 2.51	12.54 ± 2.66	0.534
	Patients	25.51 ± 10.69	22.36 ± 11.08	0.333

UL upper limb, *CL* cortical latency, *MEP* motor evoked potential amplitude, *RL* radicular latency, *CMCT* central motor conduction time, *CMCT-f* central motor conduction time-F, *LL* lower limb

Table 3 TMS parameters of patents with multiple sclerosis and control subjects

Parameters	Patients (n = 52)	Controls (n = 52)	p value
UL CL (ms)	24.94 ± 4.7	19.98 ± 1.78	< 0.001
UL MEP amplitude (mV)	1.57 ± 1.5	1.18 ± 2.83	< 0.001
UL RL (ms)	12.91 ± 1.98	12.23 ± 1.45	0.049
UL CMCT (ms)	11.87 ± 4.33	7.76 ± 1.53	< 0.001
UL CMCT-f (ms)	10.94 ± 4.23	6.81 ± 1.64	< 0.001
LL CL (ms)	50 ± 13.17	37.31 ± 3.73	< 0.001
LL MEP amplitude (mV)	0.73 ± 0.51	1.37 ± 1.15	0.001
LL RL (ms)	23.82 ± 3.56	22.19 ± 2.8	0.012
LL CMCT (ms)	27.42 ± 10.8	15.04 ± 2.98	< 0.001
LL CMCT-f (ms)	24.0 ± 10.87	12.32 ± 2.57	< 0.001

UL upper limb, *CL* cortical latency, *MEP* motor evoked potential, *RL* radicular latency, *CMCT* central motor conduction time, *CMCT-f* central motor conduction time-F, *LL* lower limb

magnetic field perpendicular to that coil induces an electrical current in motor neurons [11].

Even though the diagnostic relevance of EPs has been decreased after MRI which can establish an early diagnosis of the disease, they still maintain direct functional assessment of myelin, axon, and synapses in multisynaptic sensorimotor pathways, a prognostic significance and better correlate with neurological disability [8, 9, 12]. Using EP scales including MEP have a good diagnostic utility in MS and can assess neurodegeneration, predict future disability, and monitor the effects of disease-modifying drugs [13, 14].

Many pieces of research recommend MEPs as a useful test for predicting the clinical course of early demyelinating episodes [15], a priority for patients experiencing an initial episode of probable demyelinating disease, especially if symptoms include medullary syndrome [16], or in combination with brain MRI to confirm the diagnosis and possible clinical correlations in relapsing-remitting MS [17].

EPs have long been studied as a diagnostic and prognostic biomarker. In recent years, they were shown to help in differentiating early between possibly effective and unsuccessful interventions in phase-II trials and thus may serve as response biomarkers [18, 19].

In this study, we aimed to assess the motor disability using MEPs by TMS and to investigate the associations between EDSS score and MEP parameters.

Methods

A randomized prospective study was conducted at the Department of Neurophysiology/Ghazi Al-Hariri Hospital, Baghdad, Iraq, for the period from May 2019 till October 2019. The study was performed following the Declaration of Helsinki (2008) and was approved by the Iraqi Council of Medical Specialization (decision No. 1257; date, 20 March 2019). Each participant in the study ensured written informed consent.

The eligible 26 patients were ten males and 16 females (39.19 ± 9.67 years) with a definite diagnosis of MS according to the revised McDonald criteria [20]. The duration of illness ranged from 1 year to more than 10 years. Those patients with relapsing-remitting (17 patients) and secondary progressive type (9 patients) were studied. We excluded any patient with a history of seizure, having a pacemaker, or with ferromagnetic material in the head area and other types of MS. Another 26 healthy subjects comprised of 6 males and 20 females aged 34.38 ± 11.83 years serve as the control group.

A thorough neurological examination and an assessment of disability status were done by a senior neurologist, including Kurtzke EDSS [21] which is used to evaluate the degree of disability of MS patients. The scale ranges from 0 (normal) to 10 (death due to MS) in 20-step scale scores (with 0.5-unit increments). EDSS

Table 4 CMCT in patients with multiple sclerosis with and without upper limb pyramidal signs, incoordination, and ataxia

Parameters		Number	Yes	No	p value
Pyramidal signs	UL CMCT (ms)	58	12.64 ± 4.52	10.89 ± 3.96	0.148
	UL CMCT-f (ms)	46	12.39 ± 4.31	9.12 ± 3.42	0.005
Incoordination	UL CMCT (ms)	24	13.36 ± 4.75	10.6 ± 3.54	0.020
	UL CMCT-f (ms)	26	12.77 ± 4.31	9.37 ± 3.53	0.003
Ataxia	UL CMCT (ms)	24	34.66 ± 10.61	20.79 ± 5.44	< 0.001
	UL CMCT-f (ms)	26	30.97 ± 10.67	17.62 ± 6.2	< 0.001

UL upper limb, *CMCT* central motor conduction time, *CMCT-f* central motor conduction time-F

steps 1.0–4.5 refer to fully ambulatory patients, and the precise step number is defined by the functional system score(s), while EDSS steps 5.0–9.5 are mostly described by impairment of ambulation [22].

Considering the pyramidal signs (spasticity, increased deep tendon reflex), 58 limbs with and 46 without were studied. Besides, the presence of ataxia and incoordination in upper extremities, 24 limbs with, and 26 without were examined.

A single-pulse stimulus of the cortex was delivered using a circular stimulator coil with a 90-mm diameter (type 9784, UK) placed tangentially to the scalp (handle pointing backward) and connected to a Magstim 200 stimulator (The Magstim Company Ltd., Spring Gardens, Whitland, UK). The signals were recorded with an EMG machine (Micromed, 8-channel electromyography, B, model 1715, Italy) from the abductor pollicis brevis (APB) in the upper limbs and the tibialis anterior (TA) in the lower limbs by disk surface electrodes in a belly-tendon montage.

Patients were seated comfortably with the arms at rest. The stimulus was delivered at intensity approximately 15–20% above threshold until at least two reproducible responses were obtained to reduce the variability. MEPs with the shortest latency and largest amplitude were evaluated. The filter setting used was 30-Hz low filter and 30-kHz high filter. The coil center positioned over or slightly anterior to the vertex for cortical stimulation of upper or lower limbs, respectively. For the spinal roots, the magnetic stimulation was done by placing the center of the circular coil over the 7th cervical and 5th lumbar vertebrae.

The parameters evaluated were the following: cortical-APB/TA latencies (CL) and spinal cord (cervical/LS spine)-APB/TA latencies correspond to radicular latency (RL); MEP amplitude from peak to baseline; central motor conduction time (CMCT); and central motor conduction time-f wave (CMCT-f). The CMCT was measured by subtracting the latency resulting from spinal stimulation from that on cortical stimulation. CMCT-f was measured with the following equation:

$$\mathrm{CMCT-f\ (ms)} = \frac{\mathrm{TMCT} - (\mathrm{F\ \ min.} + \mathrm{DML}) - 1}{2}$$

where CMCT-f = central motor conduction time using F wave latency, TMCT = total motor conduction time (cortical latency), F min. = minimum F wave latency, and DML = distal motor latency [23]

Statistical analysis

Statistical analysis was performed using IBM-SPSS (Statistical Package for Social Sciences) version 25 (IBM incorporation, USA). Normal distribution of the data was assessed with the Kolmogorov-Smirnov test, and variance homogeneity was evaluated with the Levene test. Pearson correlation coefficient was used to analyze the relationship between EDSS and MEP parameters.

An independent *t* test was used to analyze the difference between right and left side in the control group and MS patients and between controls and MS patients concerning MEP parameters and clinical data. A *p* value of ≤ 0.05 was considered significant.

Table 5 CMCT in patients with multiple sclerosis with different EDSS

Parameters	EDSS		*p* value
	0–4.5 (*n* = 32)	5–9.5 (*n* = 20)	
UL CMCT (ms)	10.87 ± 3.88	13.47 ± 4.62	0.034
UL CMCT-f (ms)	9.68 ± 3.75	12.96 ± 4.26	0.005
LL CMCT (ms)	24.7 ± 9.49	33.74 ± 11.35	0.007
LL CMCT-f (ms)	21.1 ± 9.45	30.64 ± 11.32	0.005

EDSS expanded disability status scale, *UL* upper limb, *CMCT* central motor conduction time, *CMCT-f* central motor conduction time-F, *LL* lower limb

Results

The pyramidal and cerebellar signs and incoordination in the upper and lower limbs, disease duration, and EDSS for all patients with MS were presented in Table 1.

MEPs were elicited in all the four limbs in controls and patients with MS. In both groups, no significant difference was demonstrated between the right and left side of the upper and lower limbs considering all MEP parameters (Table 2). Thus, they were tabulated as one group for the upper limbs and another one for the lower limbs for further statistics.

The upper limb and lower limb CL, RL, CMCT, CMCT-f, and upper limb MEP amplitude were significantly higher in patients with MS. In contrast, the lower limb MEP amplitude was significantly lower in patients with MS when compared to the control group (Table 3).

Table 6 Correlation of CMCT and CMCT-f with disease duration

Parameters	Disease duration	
	Correlation coefficient	*p* value
UL CMCT (ms)	0.092	0.515
UL CMCT-f (ms)	0.044	0.756
LL CMCT (ms)	0.097	0.522
LL CMCT-f (ms)	0.078	0.606

UL upper limb, *CMCT* central motor conduction time, *CMCT-f* central motor conduction time with F wave, *LL* lower limb

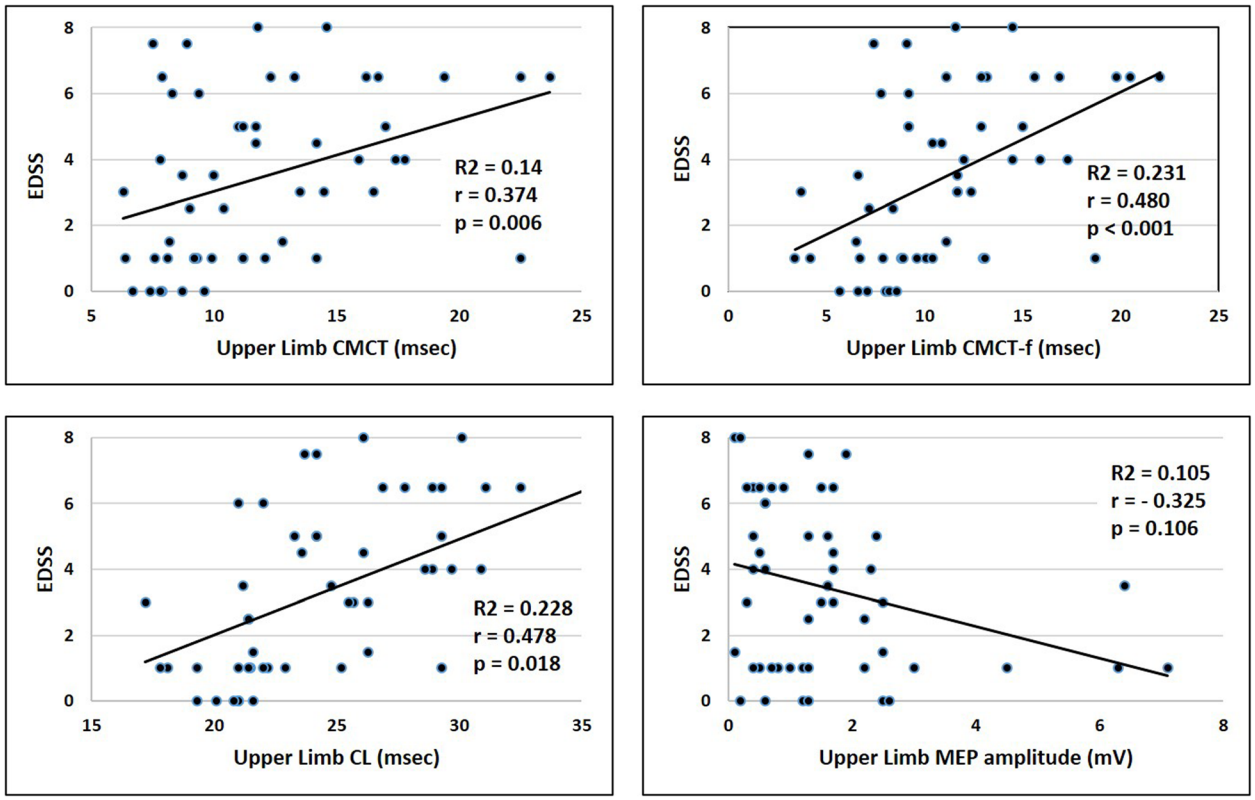

Fig. 1 Relationship of EDSS and upper limb CMCT (upper left), CMCT-f (upper right), CL (lower left), and MEP amplitude (lower right)

Table 4 illustrates that the upper limb CMCT was the only parameter that is significantly prolonged ($p = 0.005$) in patients with pyramidal signs (12.39 ± 4.31 ms) as compared to patients without (9.12 ± 3.42 ms). Also, upper limb CMCT and CMCT-f were significantly prolonged in those patients with ataxia and incoordination.

Upper and lower limb CMCT and CMCT-f were significantly prolonged in those patients with EDSS of 5–9.5 as compared to those with a score of 0–4.5 (Table 5).

Table 6 illustrated no significant correlation between either CMCT or CMCT-f and the duration of disease in MS patients.

In the upper limb, a significant positive correlation was observed between EDSS and CL ($r = 0.636$, $p < 0.001$), EDSS and CMCT ($r = 0.374$, $p = 0.006$), and EDSS and CMCT-f ($r = 0.480$, $p < 0.001$). On the contrary, a non-significant negative correlation was observed between EDSS and MEP amplitude ($r = -0.325$, $p = 0.106$) as shown in Fig. 1.

Similarly, in the lower limb, a significant positive correlation was observed between EDSS and CL ($r = 0.478$, $p = 0.018$), EDSS and CMCT ($r = 0.588$, $p < 0.001$), and EDSS and CMCT-f ($r = 0.553$, $p < 0.001$). On the reverse, a non-significant negative correlation was observed between EDSS and MEP amplitude ($r = -0.397$, $p = 0.067$) as shown in Fig. 2.

Discussion

In our study, both the healthy controls and patients with MS showed no hemispheric difference. Caramia et al. [24], Neva et al. [25], and Zipser et al. [26] also demonstrated such findings but with contradictory results which could be due to the sample size difference, stimulus, and stimulation coil types.

TMS of our patients with MS revealed abnormal corticospinal excitability which could be due to central or peripheral neuronal demyelination or to peripheral corticospinal axonal damage. Neva et al. [25], Gagliardo et al. [27], Udupa and Chen [28], Bridoux et al. [29], Conte et al. [30], Nantes et al. [31], and Nantes et al. [32] relate this hyperexcitability to neuronal demyelination. On the contrary, Ziemann et al. [9], Groppa et al. [33], and Simpson and Macdonell [34] demonstrate axonal damage of corticospinal tracts as a cause for the hyperexcitability of patients with MS.

MEP amplitude variability between the upper and lower limbs in this study could be explained by that the motor thresholds vary according to the muscle being assessed. Fernández et al. [10] denoted that thresholds

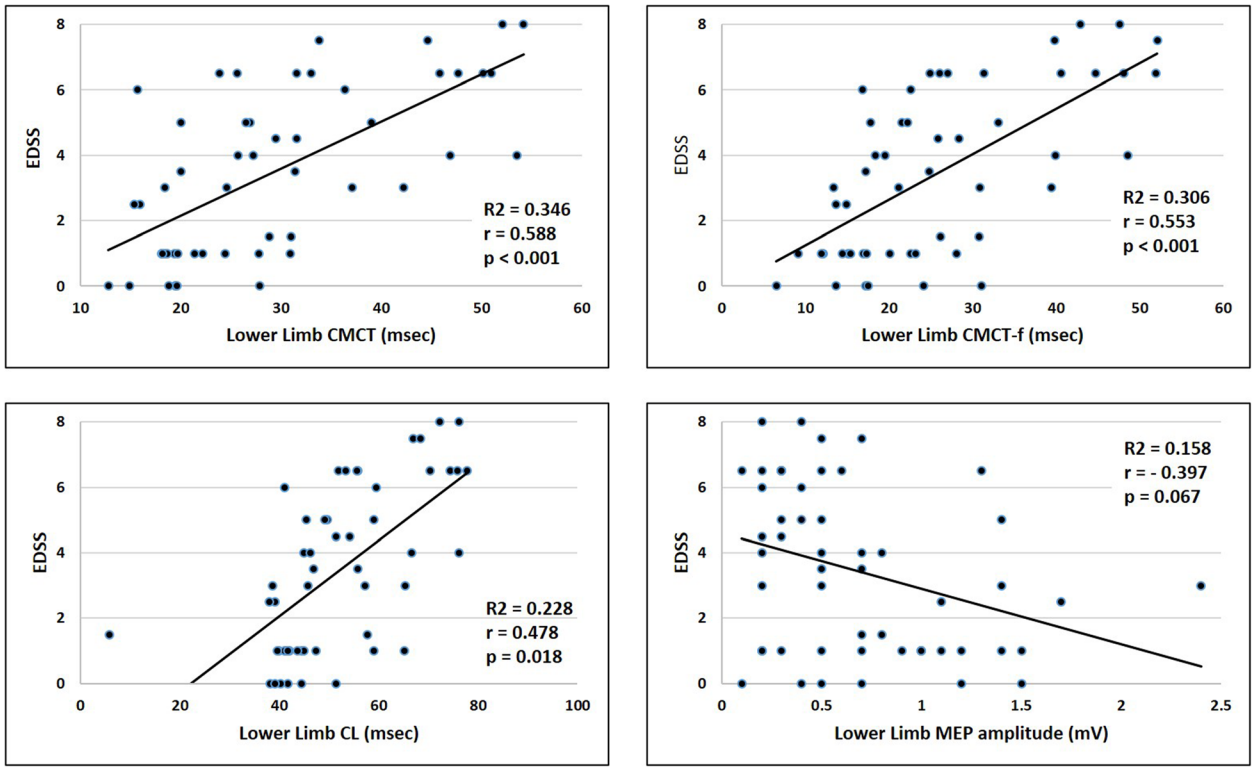

Fig. 2 Relationship of EDSS and lower limb CMCT (upper left), CMCT-f (upper right), CL (lower left), and MEP amplitude (lower right)

are lower for hand muscles than for axial muscles or proximal muscles of the arms or legs. Furthermore, MEP amplitude depends on several factors, including coil position, subject's attention, and tonic facilitation of the muscle in question. Thus, this measurement has little value in clinical practice.

Our patients with MS who have a clinical picture of incoordination, ataxia, and pyramidal signs demonstrate typical CMCT and CMCT-f abnormalities. CMC abnormality was known to be closely correlated with clinical signs of upper motor neuron disturbance, and the Babinski sign when measured from LL [35–37].

EDSS of the present study is well correlated with CL, CMCT, and CMCT-f but not with MEP amplitude. Zeller et al. [38], Vucic et al. [39], and Schlaeger et al. [40] found the same results. On the contrary, Neva et al. [25] found no relationship between CL and EDSS. A potential explanation for that as they proposed is that their work only included patients with relapsing-remitting MS. In contrast, previous studies included individuals with relapsing-remitting MS as well as individuals with primary and secondary progressive MS. Moreover, Sahota et al. [37] demonstrate a lack of correlation between EDSS and CMCT abnormalities. On the other hand, Zeller et al. [38], Schlaeger et al. [40], and Kale et al. [41] found EDSS to be negatively related to MEP amplitude.

EDSS is a standard measure to assess motor, sensory, and cognitive disability levels and is informative as a measure of neurological impairment and MS progression. An increased disability may indicate that the neurons are spastially farther away from the central target muscle representation. Besides, intrinsically less excitable neurons have a greater degree of dysfunction because of advanced cortical damage and demyelination of corticospinal output. These data provide further insights into the potential neural dysfunction associated with clinical disability in MS. Generally, such abnormalities might be due to abnormal propagation of central or peripheral neural signals throughout the corticospinal system [42, 43].

Conclusion

TMS yields objective data to monitor clinical disability in patients with MS, owing to the significant correlation observed between the abnormalities in CMCT and the degree of motor disability. MEP latency and CMCT have the most evidence for use as biomarkers in the clinical approach to MS. To further correlate MEP parameters with EDSS of patients with MS following drug monitoring disease progression, extensive prospective serial studies are required.

Abbreviations
APB: Abductor pollicis brevis; CL: Cortical latency; CMCT: Central motor conduction time; CNS: Central nervous system; EDSS: Expanded Disability Status Scale; EPs: Evoked potentials; MEPs: Motor EPs; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; RL: Radicular latency; TA: Tibialis anterior; TMS: Tanscranial magnetic stimulation

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Settings
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Authors' contributions
Concept—FBH and AKH. Design—ABM and HGK. Supervision—FBH and AKH. Resources—ABM and HGK. Materials—AMB and AKH. Data collection and/or processing—FBH and HGK. Analysis and/or interpretation—FBH and ABM. Literature search—ABM and FBH. Writing manuscript—FBH and HGK. All authors have read and approved the manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study design was approved by the Iraqi Council of Medical Specialization (decision No. 1257; date, 20 March 2019).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

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