

Motor cortical excitability in peritoneal dialysis: a single-pulse TMS study

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Abstract The aim of this paper is to investigate cortical excitability in patients with end-stage renal disease receiving peritoneal dialysis (PD) without any symptoms suggestive of uremic encephalopathy. We performed transcranial magnetic stimulation for 52 PD patients and 28 normal subjects. We compared the active motor threshold (AMT), resting motor threshold (RMT), root latency, central motor conduction time (CMCT), and cortical silent period (CSP) in PD patients to those in normal subjects. AMT, RMT, CMCT, and CSP were not significantly different between PD patients and normal subjects. However, root latency was significantly prolonged in PD patients compared to normal subjects. The root latency correlated linearly with HbA1c or duration of PD in the patients. The results suggest that the corticospinal tract and the cortical and spinal excitabilities are preserved but the peripheral nerves are disturbed in PD patients. The severity of peripheral neuropathy corresponds to the severity of DM and the duration of PD. We uncovered no evidence suggestive of any subclinical abnormality of the motor cortical excitability in PD patients.

Keywords Chronic renal failure (CRF) · Chronic kidney disease (CKD) · Peritoneal dialysis (PD) · Transcranial magnetic stimulation (TMS) · Central motor conduction time (CMCT) · Cortical silent period (CSP)

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive, painless method of studying human brain function [1, 2]. Motor cortical excitability can be measured using several parameters of motor-evoked potential (MEP) to TMS over the primary motor cortex. The cortical silent period (CSP) following MEPs is one of those parameters. Several studies have shown that CSP is shortened in some patients with cortical positive myoclonus [3–7]. On the other hand, CSP is prolonged in some patients with negative myoclonus, i.e., asterixis [5, 8, 9]. Moreover, it has been reported that CSP is affected by GABAergic medicines [2, 10]. Motor threshold (MT) is a parameter affected by synaptic efficacy at both the motor cortex and the spinal cord and also by corticospinal tract conduction. When corticospinal tract conduction is preserved, the MT can reflect both cortical and spinal excitabilities. The MT may also reflect cortical and spinal glutamatergic function [2, 10]. Corticospinal tract conduction can be evaluated by calculating the central motor conduction time (CMCT), which is the latency difference between MEPs elicited by cortical stimulation and magnetic-motor-root stimulation [2, 11, 12].

Patients with end-stage renal disease (ESRD) who receive a form of continuous dialysis such as hemodialysis (HD) or peritoneal dialysis (PD) often develop uremic encephalopathy and present with positive or negative myoclonus [13–18]. In such patients, the

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cortical excitability is assumed to be abnormal [9], but there are few published TMS studies on patients with ESRD.

We hypothesized that patients supported by PD over long periods might show some subclinical changes in cortical excitability even in the absence of uremic encephalopathy, because abnormal findings have been reported in several neurophysiological studies, such as electroencephalography and visual evoked potential [19–23], and in several imaging studies, such as magnetic resonance spectroscopy, single photon emission computed tomography, and positron emission tomography [24–26] for dialysis patients without uremic encephalopathy. To assess this hypothesis, we studied several factors reflecting motor cortical excitability using TMS in the patients supported by PD.

Methods

Subjects

Totals of 52 PD patients (17 women) and 28 normal subjects (19 women) participated in this study. Thirteen patients were treated with automated PD, 23 with combined therapy, and 16 with continuous ambulatory PD and/or incremental PD. Clinical characteristics of PD patients and normal subjects are shown in Table 1. The mean age of PD patients was 61.0 ± 11.1 (mean \pm SD) years (range 33–83 years) and that of normal subjects was 62.6 ± 12.8 years (38–86 years); these were not significantly different (unpaired *t* test, $P = 0.578$). The body height of PD patients was 164.2 ± 9.1 cm (140–182 cm) and that of normal subjects was 161.1 ± 8.1 cm (145–183 cm); these also did not differ significantly (unpaired *t* test, $P = 0.127$). Eleven PD patients (21.2 %) and three normal subjects (10.8 %) took GABAergic medicines (benzodiazepines) for insomnia or anxiety (Fisher's exact test, $P = 0.358$). No other participants took any other medicines acting on the central nervous system such as anti-epileptic drugs. All participants had normal consciousness. None of the participants had dementia. PD patients had no history of encephalopathy or myoclonus. Ten PD patients had previously undergone brain magnetic resonance imaging (MRI). Brain MRI showed the subclinical lacunar infarctions in one PD patient but no specific lesions in the other nine PD patients. Normal subjects had no history of the disturbance of central or peripheral nervous systems, nor other medical problems including diabetes mellitus (DM). Surface EMG recordings from the wrist extensor muscle during relaxation and contraction revealed neither positive nor negative myoclonus in any participants.

Table 1 Characteristics of PD patients and normal subjects

	PD patients	Normal subjects	<i>P</i> value
Number (female)	52 (17)	28 (19)	
Age (years)			
Mean (SD)	61.0 (11.1)	62.6 (12.8)	NS
Range	33–83	38–86	
Body height (cm)			
Mean (SD)	164.2 (9.1)	161.1 (8.1)	NS
Range	140–182	145–183	
GABAergic medicines	11 (21.2 %)	3 (10.8 %)	NS
Duration of illness (years)			
Mean (SD)	4.7 (3.2)		
Range	1–12		
Causes of ESRD (<i>n</i>)			
Chronic glomerulonephritis	14		
Diabetic nephropathy	13		
IgA nephropathy	6		
Mesangiopathic glomerulonephritis	2		
Nephrosclerosis	1		
Membranous nephropathy	1		
Polycystic kidney disease	1		
Unknown causes	14		
Biochemical data: mean (SD)			
Albumin (g/dL)	3.9 (0.3)		
Hemoglobin (g/dL)	11.4 (1.4)		
Creatinine (mg/dL)	10.8 (3.4)		
BUN (mg/dL)	55.7 (15.0)		
C-reactive protein (mg/dL)	0.6 (1.0)		
Calcium (mg/dL)	8.8 (0.7)		
Phosphorus (mg/dL)	5.1 (1.4)		
Intact PTH (pg/mL)	237.7 (188.8)		
HbA1c (%)	6.0 (1.0)		
Kt/V (weekly)			
Peritoneal	1.5 (0.6)		
Renal	0.7 (1.2)		
Total	2.2 (1.0)		
CCr (weekly)			
Peritoneal	26.7 (11.7)		
Renal	30.8 (57.5)		
Total	56.8 (53.7)		

NS not significant

Informed consent to participate in this study was obtained from all participants. The procedures were approved by the Ethics Committee of the Japanese Red Cross Medical Center, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Single-pulse TMS study

Subjects were seated comfortably on a bed. Surface EMG activities were recorded from the right first dorsal interosseous muscle (FDI) via pairs of Ag/AgCl surface cup electrodes placed in a belly tendon montage. Signals were amplified with filters set at 20 and 3 kHz and recorded by a computer (Neuropack MEB-2306; Nihon Kohden, Tokyo, Japan). Magnetic stimulation was conducted with a monophasic stimulator (Magstim 200²; Magstim, Whitland, UK).

For cortical stimulation, the center of a round coil (9 cm diameter) was placed over the Cz (international 10–20 system), with induced currents flowing in the posterior-anterior direction over the contralateral hand motor area [1, 2, 27]. In cortical stimulation, we measured active motor threshold (AMT), resting motor threshold (RMT), cortical latency, MEP amplitude, and CSP. Whereas RMT was measured in the relaxed condition, AMT, cortical latency, MEP amplitude, and CSP were measured during a continuous voluntary contraction (20 % power of maximal contraction). RMT was defined as the lowest stimulus intensity that elicited a MEP larger than 50 μV in more than half the trials. Similarly, AMT was defined as the lowest stimulus intensity that elicited a MEP (<200 μV) distinguishable from the pre-stimulus background EMG activity in more than half the trials [28]. To measure the cortical latency, stimulus intensity was gradually increased and MEPs were recorded in all stimulations. Then, if reproducible MEPs were obtained, the onset MEP latency was measured as the cortical latency. For motor-root stimulation, the upper edge of a round coil was placed over the C7 spinous process, with induced currents flowing in the direction from muscle to spine [29–32]. In motor-root stimulation, we measured the root latency. Stimulus intensity was gradually increased. Then, if reproducible MEPs were obtained, the onset MEP latency was measured as the root latency. CMCT was obtained by subtracting the root latency from the cortical latency (Fig. 1a).

The MEP amplitude and CSP were measured from MEPs in response to TMS at the three stimulus intensity levels (RMT 120, 130, and 140 %) during voluntary contraction. For each MEP, the peak-to-peak MEP amplitude and duration of CSP were measured (Fig. 1b). To analyze MEP amplitude and CSP, a total of eight MEPs were measured at each stimulus intensity.

Renal function parameters

We studied the relationships between certain neurophysiological parameters and renal function parameters [HbA1c, duration of PD, total dialysis adequacy (total Kt/V), and total creatinine clearance (total CCr)].

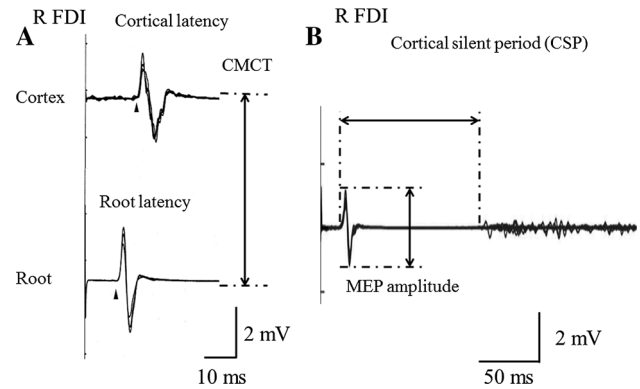


Fig. 1 CMCT and CSP. **a** To calculate central motor conduction time (CMCT), motor-evoked potentials (MEP) elicited by transcranial magnetic stimulation (TMS) and magnetic-motor-root stimulation were analyzed. The onset latency of reproducible MEPs was measured for cortical latency and root latency (*Cortex* and *Root*). CMCT was calculated according to the following formula: CMCT = cortical latency – root latency. **b** To measure the cortical silent period (CSP), MEPs elicited by TMS were analyzed, and the figure shows the superimposed MEPs for demonstration. To analyze CSP, peak-to-peak MEP amplitude and CSP ranging from MEP onset to reappearance of electromyographic activities reflecting voluntary contraction were measured for each MEP. A total of eight MEPs were analyzed at each stimulus intensity. All recordings are from the right first dorsal interosseous (FDI) muscle

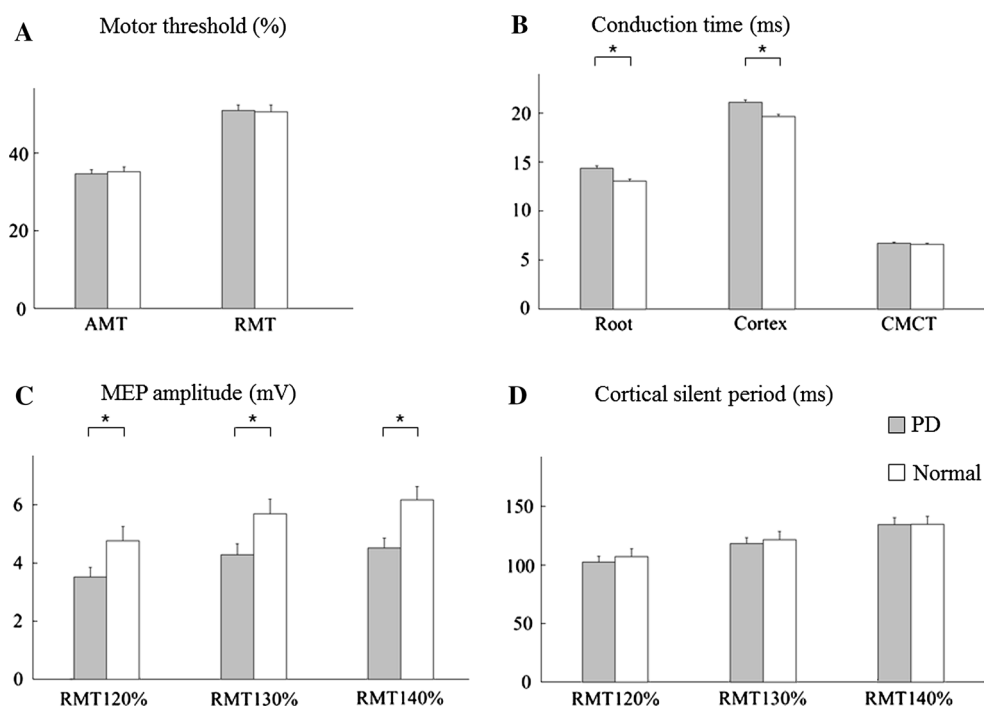
Statistical assessment

The following statistical analyses were performed using SPSS (v.16.0; SPSS, Chicago, IL, USA). To compare MTs (AMT and RMT) between PD patients and normal subjects, and to compare conduction times (root latency, cortical latency, and CMCT) between PD patients and normal subjects, the unpaired *t* test was used. To compare MEP amplitudes and CSPs at each of several stimulus intensities (RMT 120, 130, and 140 %), a two-way analysis of variance (ANOVA) with repeated measures in one factor was used, with stimulus intensity as a within-subject factor and subject group as a between-subject factor. If necessary, the Greenhouse–Geisser correction was used to evaluate non-sphericity. Post-hoc analyses were also conducted, if necessary, using the unpaired *t* test. Finally, to investigate the relationships between selected neurophysiological parameters and renal function parameters, Pearson’s correlation coefficient test was conducted on PD patients. The coefficient of correlation was expressed as *r*. In all analyses, *P* values of less than 0.05 were considered significant.

Results

None of the subjects experienced any side effects. All results are shown in Fig. 2.

Fig. 2 TMS results in PD patients. **a** Active motor threshold (AMT) and resting motor threshold (RMT) did not differ between PD patients and normal subjects. **b** Central motor conduction time (CMCT) did not differ between the two groups. Root latency and cortical latency were prolonged. **c** Amplitude of motor-evoked potential (MEP) was significantly smaller in PD patients than in normal subjects at all stimulus intensities. **d** Cortical silent period (CSP) did not differ between the two groups at any stimulus intensity



Mt

As shown in Fig. 2a, AMT in PD patients was not significantly different from that in normal subjects (PD patients: 34.7 ± 7.7 %; normal subjects: 35.2 ± 6.3 %, $P = 0.760$). RMT was also comparable between the two groups (PD patients: 50.9 ± 10.5 %; normal subjects: 50.6 ± 9.0 %, $P = 0.898$).

Conduction times

As shown in Fig. 2b, in PD patients, both root latency and cortical latency were significantly longer than those in normal subjects (root latency: PD patients: 14.4 ± 1.8 ms; normal subjects: 13.1 ± 1.0 ms, $P < 0.001$; cortical latency: PD patients: 21.1 ± 1.9 ms; normal subjects: 19.7 ± 1.0 ms, $P < 0.001$). On the other hand, CMCT was comparable between the two groups (PD patients: 6.7 ± 0.9 ms; normal subjects: 6.6 ± 0.6 ms, $P = 0.560$).

MEP amplitude

As shown in Fig. 2c, ANOVA revealed a significant effect of subject group on MEP amplitude without any significant interaction between stimulus intensity and subject group (test of within-subject effect: stimulus intensity \times subject group interaction, $F_2 = 1.574$, $P = 0.210$; test of between-subject effect: subject group, $F_1 = 6.087$, $P = 0.016$). Post-hoc analysis showed that MEP amplitude was smaller in PD patients than in normal subjects (RMT 120 %:

$P = 0.035$; RMT 130 %: $P = 0.030$; RMT 140 %: $P = 0.005$).

Csp

As shown in Fig. 2d, ANOVA revealed that subject group had no significant effect on CSP and that there was no significant interaction between stimulus intensity and subject group (test of within-subject effect: stimulus intensity \times subject group interaction, $F_{1,594} = 0.748$, $P = 0.447$; test of between-subject effect: subject group, $F_1 = 0.095$, $P = 0.758$).

Correlation analysis

Root latency was significantly prolonged in PD patients. We studied the relationships between root latency and several parameters of renal function (HbA1c, duration of PD, total Kt/V, and total CCr) (Table 2). Pearson's correlation coefficient test revealed a positive significant correlation between root latency and HbA1c or duration of PD. No significant correlations were observed between average CSPs at any of the three stimulus intensities and renal function parameters (Table 2).

Discussion

AMT, RMT, CMCT, and CSP were comparable between PD patients and normal subjects, suggesting that

Table 2 Correlation analysis between root latency and renal function parameters

	Root latency	CSP
HbA1c	$P = 0.012, r = 0.348$	NS
Duration of PD	$P = 0.041, r = 0.284$	NS
Total Kt/V (weekly)	NS	NS
Total CCr (weekly)	NS	NS

NS not significant, r coefficient of correlation

corticospinal tract conduction is preserved in PD patients and that their motor cortical and spinal motoneuronal excitabilities are normal. On the other hand, root latency and cortical latency were prolonged in PD patients, while MEP amplitude was decreased, indicating that peripheral conduction is disturbed in PD patients. The positive significant correlation between root latency and HbA1c or duration of PD suggests that peripheral neuropathy may progress in parallel with PD duration, becoming more severe in association with DM. The present findings can be summarized as follows: in PD patients, (1) normal MT and CSP suggest that motor cortical excitability is normal, (2) normal CMCT indicates normal conduction of the corticospinal tract, and (3) prolonged root latency suggests peripheral neuropathy, its severity increasing with severity of DM and PD duration. We discuss each of these results separately in the following subsections.

Normal motor cortical excitability

Battaglia et al. [33] reported that MT and CSP were normal in PD patients. However, the number of PD patients in their study was small (eight patients). Additionally, there have been no other papers supporting their results. On the other hand, other studies except for TMS have suggested brain dysfunction in dialysis patients [19–26]. Therefore, a study on the motor cortical excitability including a large number of PD patients has been required. In the present study, we confirmed that our results obtained from a large number of PD patients are compatible with the results reported by Battaglia et al. [33]. MT is considered to reflect the cortical motoneuronal excitability, and CSP the motor cortical GABA-mediated inhibitory interneuronal excitability [2, 10]. The present results indicate that the function of these neurons is certainly normal in PD patients.

In the same paper, Battaglia et al. [33] analyzed two other parameters reflecting motor cortical excitability in eight PD patients, namely, short-interval intracortical inhibition (SICI) and short-interval facilitation (ICF); both were normal. SICI is considered to reflect the motor cortical GABA_A-mediated inhibitory interneuronal excitability, and ICF the motor cortical glutamatergic excitatory

neuronal excitability [2, 10]. These findings indicate that no abnormal neuronal function in the primary motor cortex is involved in PD patients.

Normal corticospinal tract conduction

One previous paper has reported on CMCT in ESRD patients receiving HD [34], but there is no published research on the same topic in patients receiving PD. In regular HD patients, CMCT for the lower extremities was ‘marginally’ prolonged in 3 out of 19 patients, leading the authors to conclude that the central motor pathways are less frequently and less severely affected than the peripheral motor pathways in ESRD patients. Their results and ours both indicate that the corticospinal tract is only slightly affected in ESRD patients. The continuous exposure of these patients to accumulated organic waste products that are not cleared by the kidneys may affect several organs including the nervous systems [35]. We speculate that the blood–brain barrier might protect the corticospinal tract from the effects of this accumulation more effectively than the blood–nerve barrier protects the peripheral nerves.

Peripheral neuropathy as a common concomitant disease in PD

Peripheral nerve involvement is frequently seen concomitantly with ESRD requiring PD, and its severity increases with the severity of DM and PD duration. Nerve conduction studies have often shown some abnormalities in PD patients [36–38]. Peripheral neuropathy is reported to be more severe in PD patients with DM than in those without DM [37], and our results are consistent with this previous finding. The rate of peripheral neuropathy is high in both non-DM and DM patients (77.4 % [36], 95.6 % [37], and 91.7 % [38] for non-DM patients and 100.0 % [37, 38] for DM patients).

The peripheral neuropathy in PD patients without DM is considered to be caused by uremic toxins [39]. Therefore, our results suggesting that peripheral neuropathy may progress in parallel with PD duration are consistent with this hypothesis. However, the nature of the uremic toxin and the underlying mechanism of peripheral neuropathy are unknown [39]. The characteristic is a distal, motor and sensory polyneuropathy in which there is axonal degeneration, segmental demyelination, and segmental remyelination. The typical symptoms are paresthesia, cramps, and fasciculation, beginning in the distal lower extremities and evolving slowly over many months. The peripheral neuropathy is often subclinical and detectable only by electrophysiological studies [37]. Since the aim of the present study was to investigate the motor cortical excitability, motor-root stimulation was performed to record MEPs

from a hand muscle, but not a leg muscle. However, it readily revealed the presence of peripheral neuropathy even in an upper extremity. Therefore, to reveal the pathophysiology of peripheral neuropathy in PD patients, magnetic motor-root stimulation for the lower extremities may be useful [31, 40, 41]. This must be a further issue for research.

Conclusion

In a single-pulse TMS study, we confirmed that motor cortical excitability and the corticospinal tract are normal in a great number of PD patients without any symptoms suggesting uremic encephalopathy, although peripheral neuropathy is more severe in conjunction with DM and is observed in parallel with PD duration. There is no evidence of subclinically abnormal cortical excitability in PD patients.

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Conflict of interest The authors declare they have no conflicts of interest.

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