ORIGINAL ARTICLE

Cortical Relay Time for Long Latency Reflexes in Patients with Definite Multiple Sclerosis

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ABSTRACT: ***Background:*** Long latency reflexes (LLR) include afferent sensory, efferent motor and central transcortical pathways. It is supposed that the cortical relay time (CRT) reflects the conduction of central transcortical loop of LLR. Recently, evidence related to the cortical involvement in multiple sclerosis (MS) has been reported in some studies. Our aim was to investigate the CRT alterations in patients with MS. ***Methods:*** Upper extremity motor evoked potentials (MEP), somatosensory evoked potentials (SEP) and LLR were tested in 28 patients with MS and control subjects (n=22). The patients with MS were classified according to the clinical form (relapsing-remitting [R-R] and progressive groups). The MS patients with secondary progressive and primary progressive forms were considered as the "progressive" group. CRT for LLR was calculated by subtracting the peak latency of somatosensory evoked potentials (SEP) and that of motor evoked potentials (MEP) by transcranial magnetic stimulation from the onset latency of the second component of LLR (LLR2) (CRT = LLR2 – [MEP latency + N20 latency]) ***Results:*** Cortical relay time was calculated as 7.4 ± 0.9 ms in control subjects. Cortical relay time was prolonged in patients with MS (11.2 ± 2.9 ms) ($p<0.0001$). The latencies of LLR, MEP and SEP were also prolonged in patients with MS. Cortical relay time was not correlated with disease severity and clinical form in contrast to other tests. ***Conclusions:*** Our findings suggested that CRT can be a valuable electrophysiological tool in patients with MS. Involvement of extracortical neural circuits between sensory and motor cortices or cortical involvement due to MS may cause these findings.

RÉSUMÉ: Temps de relais cortical pour les réflexes à latence longue chez les patients atteints de sclérose en plaques dont le diagnostic est certain. ***Introduction***: Les réflexes à latence longue (RLL) possèdent des voies afférentes sensitives, des voies efférentes motrices et des voies transcorticales centrales. On présume que le temps de relais cortical (TRC) reflète la conduction au niveau de la boucle transcorticale centrale des RLL. Des données sur l'atteinte corticale dans la sclérose en plaques (SEP) ont été rapportées récemment. Nous avons étudié les altérations du TRC chez des patients atteints de SEP. ***Méthodes***: Les potentiels évoqués moteurs (PÉM), les potentiels évoqués somesthésiques (PÉS) et les RLLont été évalués chez 28 patients atteints de SEPet chez 22 sujets contrôles. Les patients atteints de SEP ont été classifiés selon la forme clinique de la maladie (rémittente ou chronique progressive) . Les patients étaient classés dans le même groupe, que la forme progressive soit secondaire ou primaire. Le TRC pour les RLLa été calculé en soustrayant la latence maximale des PÉS et des PÉM, obtenues par stimulation magnétique transcrânienne, de la latence du début de la seconde composante du RLL (RLL2) (TRC = RLL2 – [latence PÉM + latence N20]). ***Résultats***: Le temps de relais cortical a été calculé à 7,4 ± 0,9 ms chez les sujets témoins. Il était plus long chez les patients atteints de SÉP(11,2 ± 2,9 ms, $p < 0,0001$). Les latences du RLL, PÉM et PÉS étaient également prolongées chez ces patients. Le temps de relais cortical n'était pas corrélé à la sévérité ou à la forme clinique de la maladie contrairement aux autres tests. ***Conclusions***: Selon nos observations, le TRC peut être un outil électrophysiologique précieux chez les patients atteints de SEP. L'atteinte des circuits nerveux extracorticaux entre les cortex sensitifs et moteurs ou l'atteinte corticale due à la SEP peuvent être responsable de ces anomalies.

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Multiple sclerosis (MS) is a demyelinating disorder affecting periventricular white matter, brainstem, spinal cord and optic nerves. Different neurophysiological tests have been studied in patients with MS and the results obtained from these studies demonstrated that evoked potentials are of limited value in diagnosis of MS.[1,2] However, these tests are useful in the documentation of involved neural pathways in MS.

Motor evoked potentials (MEP) elicited by magnetic cortical stimulation as a noninvasive and painless method has been used to investigate the function of the fast conducting nerve fibers located at the descending motor pathways in patients with MS.[1,3,4] Hess, et al[3] concluded that MEP is useful in demonstrating central motor pathway lesions in MS, especially when physical signs are equivocal. Hess, et al[3] and Mayr, et al[4] demonstrated that prolonged latency of MEP and increased central motor conduction time (CMCT) were frequently

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observed abnormalities in patients with MS. Somatosensory evoked potentials (SEP) elicited by peripheral nerve stimulation has also been investigated many times in patients with MS.[1] This test provides information about the continuity of afferent pathways.

Long latency reflexes (LLR) are reflex responses originating from supraspinal neural pathways.[5,6] These late responses which were observed after a spinal reflex response (H reflex) are mediated by monosynaptic projection of group Ia sensorial afferents onto the alpha motor neurons. This reflex includes three late components. Among these, the second component (LLR2), seen at about 50 ms, is the most stable. First and third components (seen at about 40 and 70 ms respectively) have only been seen in some normal subjects.[7,8] Deuschl, et al[9] and Michels, et al[10] demonstrated that the afferent part of LLR and SEP share the same neural pathway.[9,10] On the other hand, they claimed that the efferent branch of the LLR is identical with MEP. It is thought that LLR is a reflex response originating from supraspinal neural pathways. If the latency of MEP evoked by transcranial magnetic stimulation was used for the efferent conduction time and the latency of N20 potential of the SEP for the afferent conduction time, the cortical relay time (CRT) for LLR in healthy subjects can be considered as a polysynaptic transcortical reflex[9,10] though its exact central pathway has not yet been established.[9-11] This parameter was defined as follows: CRT=onset latency of LLR2 – (peak latency of N20 + onset latency of MEP). Cortical relay time was measured in some studies as between 8.5-11.4 ms for upper extremities in healthy controls.[9-11]

This study was designed to determine the CRT in patients with MS and healthy controls, and to compare the alterations of these electrophysiological parameters in MS patients with different clinical status of MS.

Materials and methods

Subjects

We examined 28 consecutive patients with definite MS (10 men [35.7%], 18 women [64.3%]), whose ages ranged from 17 to 48 years (mean 33.5 ± 8.3). Patients were diagnosed as definite MS according to McDonald, et al[12] Recommended Diagnostic Criteria for MS. All of the patients had demyelinating lesions on their MRI investigations. Subjects had no other neurological or systemic disease. Patients with cognitive dysfunction were excluded from the study. Written informed consent for the study was obtained from each patient and this study was approved by the local ethical committee. The patients were followed up by our outpatient MS clinic and their mean disease duration was 6.4 years (range from 1 to 18 years). Patients were categorized into relapsing-remitting MS (R-R), secondary progressive and primary progressive groups according to Lublin and Reingold.[13] Secondary progressive and primary progressive groups were considered as the "progressive" group. Eighteen patients, with ages ranging from 17 to 44 years (mean 26.4 ± 7.9) were classified as R-R (six men, 12 women) and ten patients aged from 26 to 48 years (mean 40.6 ± 11.4) (four men and six women) were classified as the progressive (secondary progressive and primary progressive) group.[13] Reference values were obtained from 22 healthy volunteers (eight men [36.4%], 14 women [63.6%]) with a mean age of 32.8 ± 5.2 (22-41 years). There was no statistical difference between ages of patients and control groups ($p>0.05$). Normal subjects were chosen from our clinical staff and their relatives. Mean heights of patients and controls (165.2 cm ± 9.6 and 168.4 cm ± 10.7, respectively) also did not show significant difference ($p>0.05$).

Clinical assessment

All patients were evaluated using the Kurtzke Disability scale and expanded disability status scale (EDSS). In addition, Kurtzke's Disability scores for pyramidal, cerebellar and sensorial systems were obtained for every patient[14] (Table 1). Clinical evaluation was made just before electrophysiological investigations. The fatigue complaints of MS patients were analysed by fatigue severity scale in 16 patients with MS.[15] This questionnaire contains nine statements that attempt to explore severity of fatigue symptoms. Subjects are asked to read each statement and circle a number from 1 to 7 depending on how appropriate they feel the statement applies to themselves. The scoring is done by calculating the average response to the questions.

Motor evoked potentials

Motor evoked potentials were performed using a Magstim 200 magnetic stimulator (Magstim Company Ltd. Spring Gardens, Whitland, UK). Stimulation coil of 90 mm diameter was used. The coil was centred over the vertex. The left hemisphere was stimulated with clockwise current flow, and the right hemisphere with a counterclockwise current flow. For cervical root stimulation the center of the inner edge of the coil was placed at the level of C7, 2 cm lateral to the spinous process. For recording, we used Toennies multiliner version 2.0 EMG device. (Toennies, Germany) Filter settings were between 2 Hz-5 kHz and the period for analysis was 50 msec. Gain was set to 500μV/division-2mV/division. Stimulus intensity was supramaximal for cortical and cervical stimulations. At least five compound muscle action potentials were recorded over both thenar muscles. Position of the stimulator coil was Cz for upper extremity, and 2 to 3 cm anterior to Cz for lower extremity. At first, motor threshold was determined in the relaxed muscles then subjects were requested to make a slight thenar contraction during the test. Compound muscle action potentials were recorded with surface electrodes. Latencies were measured to the first negative deflection of potential. Peak to peak amplitudes were measured. Peripheral stimulation was performed by magnetic stimulator from the C7 level. Central motor conduction time (CMCT) was estimated by subtraction of peripheral latency from cortical latency. The absence or delay of MEPlatency or an increase of CMCT was considered abnormal.

Long latency reflexes

Long latency reflexes were recorded from bilateral upper extremity thenar muscles using square wave electrical stimulation of both median nerves at wrist level. Stimulation intensity was adjusted at the threshold for motor fibers (just above of median nerve motor threshold level). The electrical current which can evoke a muscle response of 0.1 mV was determined as the motor threshold level for each muscle. Electrical current was between 5-15 mA and stimulus duration was 0.2 ms. with stimulus frequency of 1Hz. Amplifier filters

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Table 1: The correlations (r values) between clinical status (EDSS) and electrophysiological parameters

r values	LLR2 Latency (ms)	N20 Latency (ms)	MEP Latency (ms)	CRT (ms)
EDSS[1]	0.74**	0.40*	0.79**	0.04
Kurtzke pyramidal[1]	0.36	0.21	0.62**	0.21
Kurtzke cerebellar[1]	0.53**	0.21	0.53**	0.23
Kurtzke Sensory[1]	0.24	0.21	0.18	0.16
FSS[2]	0.38*	0.36*	0.48**	0.09

** Correlation is significant at the .01 level (2-tailed).

* Correlation is significant at the .05 level (2-tailed).

[1] EDSS: expanded disability status scale[14]

[2] FSS: Fatigue severity score[15]

LLR=long latency reflexes; N20=first cortical response of SEP MEP=motor evoked potentials; CRT=cortical relay time

Table 2: The electrophysiological data obtained from MS patients and controls (mean ±SD) and p values.

	MS	Controls	p
LLR2 Latency (ms)	55.8 ± 5.5	45.5± 1.6	<0.0001
HR-LLR2 interval (ms)	33.4 ± 4.8	21.7 ± 1.8	<0.0001
MEPLatency (ms)	25.1 ± 5.0	19.4 ± 1.8	<0.0001
CMCT (ms)	13.6 ± 7.7	6.5 ± 1.1	<0.0001
N20 Latency (ms)	19.7 ± 2.1	18.7 ± 2.1	0.006
CRT*(ms)	11.0 ± 2.5	7.6 ± 1.2	<0.0001

LLR2=second component of LLR; HR=spinal reflex response; MEP=motor evoked potentials; CMCT=central motor conduction time; CRT=cortical relay time

Table 3: Electrophysiological data and EDSS score obtained from MS patients with R-R and progressive group.

	R-R Group	Progressive Group	P value
LLR2 Latency (ms)	54.9 ± 5.4	60.3 ± 7.8	0.018
HR-LLR2 interval (ms)	28.7 ± 3.8	38.1 ± 5.7	<0.0001
N20 Latency (ms)	19.7 ± 2.3	20.5 ± 1.5	0.03
MEPLatency (ms)	23.6 ± 4.4	30.7 ± 6.9	<0.0001
CMCT (ms)	10.8 ± 4.9	18.7 ± 9.3	<0.0001
CRT (ms)	11.3 ± 2.6	10.9 ± 3.7	0.5
EDSS	2.3 ± 0.1	4.9 ± 2.4	<0.0001

LLR2=second component of LLR; HR=spinal reflex response; MEP=motor evoked potentials; CMCT=Central motor conduction time; CRT=Cortical relay time; EDSS=expanded disability status scale

were set between 2Hz-2kHz. The patients were requested to sustain a slight voluntary contraction of their thenar muscle during investigation. All subjects were instructed to apply the same muscle strength during MEP and LLR investigation. The electromyographic (EMG) was recorded with conventional surface electrodes. We averaged approximately 100 to 400 EMG recordings. Toennies multiliner version 2.0 EMG machine was used for averaging and analysing. We evaluated onset latencies of spinal reflex response (HR) and LLR2 and the time of the HR-LLR2 interval. The absence or delay of LLR2 potentials and an increase of the HR-LLR2 interval were considered abnormal.

Somatosensory evoked potentials

Upper extremity SEPs were recorded by C3 and C4 scalp electrodes with a reference Fz. First cortical responses' (N20 potential) peak latency was measured. Stimulation was delivered to the median nerve at the wrist. Electrode position was same for the LLR. Four to eight hundred responses were averaged. Amplifier filters were between 2Hz-2kHz. Prolongation of N20 peak latency was considered abnormal.

All tests were performed twice and recorded on the same day for each patient.

Cortical relay time

Cortical relay time for the thenar muscle was calculated by subtracting the afferent time measured at the peak latency of N20 potential and the efferent time measured at the onset latency of median nerve MEP potential from the onset latency of LLR2. Cortical relay time was calculated by the formula:

CRT = LLR2 – (MEP latency + N20 latency)

Statistical methods

An analysis of covariance test was used to compare the electrophysiological data obtained from patients and controls. Mean values of the latencies of MEP, SEP, LLR and the duration of CRT were corrected by ages and heights of the patients and controls since these variables can affect the electrophysiological parameters. The relations of clinical and electrophysiological examinations were evaluated with Pearson correlation analysis. Two tailed tests were used and $p<0.05$ was considered as significant. Normal ranges had a mean ± 3SD.

Results

Neurological findings included pyramidal dysfunction (weakness and/or spasticity) involving upper and/or lower extremities (22 patients), loss of position or vibration sensation and a Romberg sign (18 patients), extremity and truncal ataxia (seven patients), and optic neuropathy (four patients). The mean EDSS score of MS patients was 2.8 ± 2.0. The EDSS score was correlated with the disease duration (r:0.76, $p<0.05$). Among the electrophysiological parameters investigated in this study, the latencies of MEPand LLR were well correlated with EDSS score (r:0.79 and 0.74, $p<0.05$, respectively). Additionally, Kurtzke cerebellar and Kurtzke pyramidal scores were correlated with the latency of MEP (r:0.62 and r:0.53, respectively, $p<0.05$). The mean fatigue severity score of MS patients was 4.3±1.4 (between 1.5 to 6.5). Cortical relay time was not correlated with disability scores and fatigue severity score. Table 1 shows the relationship between clinical status (EDSS, Kurtzke pyramidal, cerebellar,

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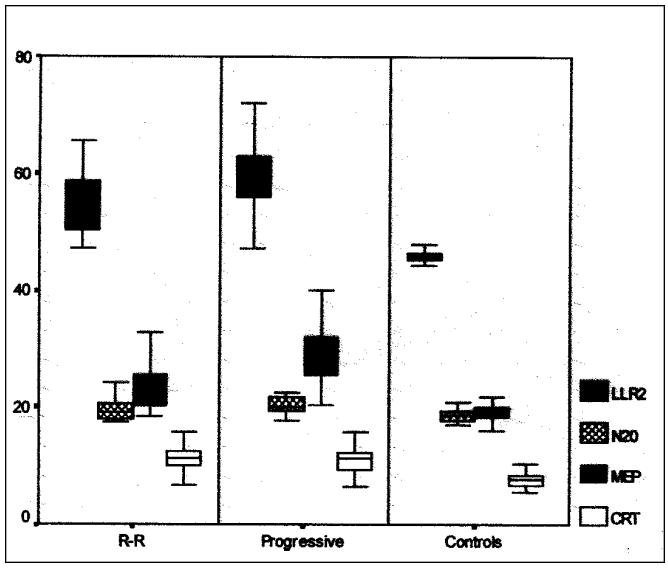

Figure 1: *Electrophysiological parameters in patients with relapsing-remitting (R-R) MS and progressive MS and controls.*

sensory scores and fatigue score) and electrophysiological parameters.

Long latency reflexes were correlated with the latency of MEP, the latency of N20 potential and CRT (r:0.76, p<0.0001, r:0.65, p<0.0001, r:0.50, p:0.001 respectively) in the control group. Cortical relay time showed moderate correlation with LLR2 latency (r:0.44, p:0.001). There was no correlation between CRT and the latencies of N20 and MEP. In patients, the latency of LLR2 was well-correlated with the latencies of MEP and N20 potentials (r:0.66, p<0.0001, r:0.45, p:0.001 respectively). However, there was no correlation between the latency of LLR2 and CRT (r:0.12, p:0.4).

Long latency reflexes 2 could not be evoked in four patients with MS (unilateral in three patients and bilateral in one patient); MEP could not be evoked in one patient with MS; and N20 potential could not be obtained in three patients with MS. Cortical relay time measurement was possible in 24 patients with MS. All electrophysiological parameters could be measured in control subjects. Upper limits of normal values were accepted as 49.7 ms for LLR2 latency, 26.0 ms for HR-LLR2 interval, 24.0 ms for MEPlatency, 9.0 ms for CMCT, 23.7 ms for N20 latency and 11.2 ms for CRT.

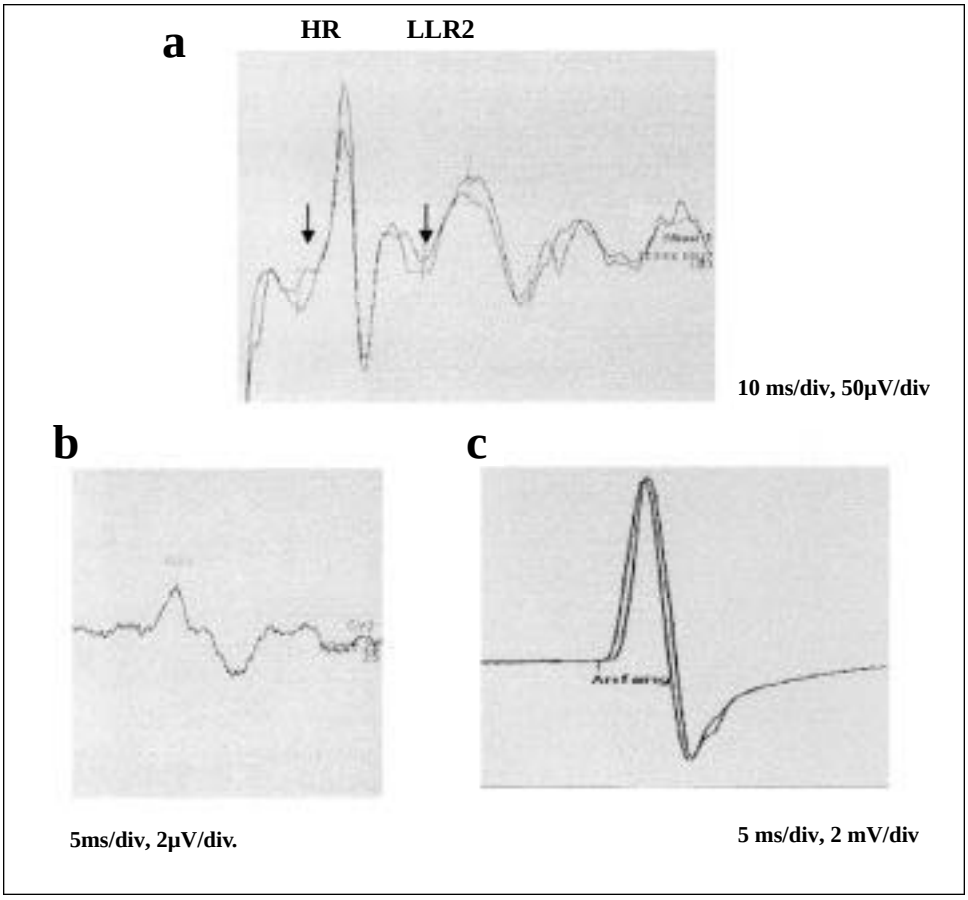

Figure 2: *Long latency reflex (a), somatosensory evoked potential (b) and motor evoked potential (c) obtained from a control subject. Arrows indicate the onset latencies of H reflex (HR) and long latency reflex (LLR2) components.*

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Cortical relay time was between 1.8 to 18.0 ms (11.2 ± 2.9) in patients with MS. A patient with MS showed normal latency of N20 potential and short CRT (1.8 ms). On the other hand, the same patient had apparent prolongation of MEP latency and slightly increased LLR2 latency.

The latencies of LLR2, HR-LLR2 interval, N20, CMCT and median MEP were prolonged in patients with MS ($p<0.05$) (Table 2). Additionally, CRT was increased in patients with MS ($p<0.0001$) (Table 2). The latencies of LLR2, N20 and median MEP obtained from MS patients from the progressive group had the greatest prolongation ($p<0.05$). Nevertheless, CRT was not different between the R-R and progressive groups ($p>0.05$) (Table 3) (Figure 1).

An abnormally prolonged CRT was observed in 19 out of 24 patients with MS (83.3%). Prolonged LLR2 latency was observed in 20 out of 24 patients with MS (79.2%). All patients with prolonged latency of LLR2 potential also showed an increased HR-LLR2 interval time. There was no superiority of increased HR-LLR2 interval time over LLR2 latency in our patient group. Central motor conduction time was also prolonged in 20 out of 27 patients with MS (74.7%). Prolonged latency of median MEP was apparent in 18 patients with MS (66.7%). The prolongation of median nerve N20 latency was seen in only six patients with MS (24.0%). Two patients who had normal latency of LLR2 showed prolonged CMCT. In addition, four patients who had normal CRT, demonstrated prolonged CMCT.

Discussion

In this study, our primary aim was to determine CRT in patients with MS. Cortical relay time was calculated by subtraction of the latencies of the MEPand SEPfrom the latency of LLR2 (Figure 2). Our findings demonstrated that evoked potentials (SEP, MEP) and LLR2 were prolonged in patients with definite MS. Evoked potentials were well-correlated with the disability scores. On the other hand, CRT was increased in patients with MS but it was not related to disability scores (disease severity).

Evoked potentials document neural pathways influenced in patients with MS. Long latency reflexes may provide information about both ascending and descending neural pathways. Additionally, LLR includes a neural arch probably located at the supraspinal level. The time for this supraspinal pathway named as CRT was calculated as about 8 to 11 ms in some studies.[9-11] Michels, et al[10] and Kurusu and Kitamura[11] concluded that this conduction time is compatible with a polysynaptic neural pathway, mediating LLR. Mean CRT values of our control group was in concordance with those obtained from previous studies.

We considered the latency of N20 potential as the afferent part of the LLR arch. Deuschl, et al[9] and Michels, et al[10] concluded that the N20 component of the cortical potential can reflect the first activation of the cortex by peripheral stimulation, and the afferent fibers mediating the SEP are identical to the afferents of the LLR. In addition, Deuschl, et al[16] demonstrated that fast conducting afferent fibers are mainly responsible in the generation of SEP and LLR. We measured the peak latency of N20 potential. There are some reports concluding that N20 onset latency more precisely reflects the afferent conduction time than peak latency.[11,17] Nevertheless, sensitive determination of taking off point of N20 potential is very difficult and controversial.

We used the latency of MEP evoked by TMS as a measure of the efferent part of the LLR. Michels, et al,[10] Deuschl, et al[9] and Kurusu and Kitamura[11] also accepted that MEPlatency reflected the efferent arch of LLR2. Deuschl, et al[9] claimed that transcranial stimulation during contraction would better reflect the conditions of the cortico-motoneural connection during LLR testing. Nevertheless, there are some controversies over whether the MEP latency would be an appropriate reflection of the cortico-motoneuronal transmission of LLR. Cortical relay time was extremely short in one patient with MS. The CMCT and MEPlatency of this patient were prolonged in spite of the normal SEP and LLR latencies. Michels, et al[10] observed the existence of negative CRT values in patients with MS. The sum of the MEP and SEP latency had exceeded that of the latency of LLR in their study. They explained this finding by the conduction of smaller diameter fibers of the pyramidal tract and the utilization of alternative oligosynaptic pathways as a cause of both the prolongation of MEP latency and normal LLR latency. It is thought that a partial lesion of the pyramidal tract might lead to this unexpected result. These findings bring some doubt about consistency and clinical importance of CRT as an electrophysiological parameter. During the contraction of the target muscle, the latency of MEP is shortened by 1-3 ms when compared with a relaxed state. It seems that the level of muscle strength applied during LLR and MEP testing may be an important factor in the present study. Nevertheless, we could not confirm accurately whether the same muscle strength was applied during both tests. This may be a limitation of our study.

Cortical relay time prolongation was independent from the patients' clinical status and disease severity contrary to that of the evoked potentials. There was strong evidence suggesting that LLR was a cortically originated reflex response.[5,18] On the other hand, some evidence involving cortical dysfunction in MS patients with fatigue has been reported previously.[19,20] However, no correlation between fatigue severity scale and CRT was observed in our study. Michels, et al[10] demonstrated that CRT was not changed in patients with MS. They concluded that the CRT was compatible with a polysynaptic intracortical pathway of the LLR. Recently, cortical involvement of MS was observed in some studies.[21,22] It was demonstrated that some of the cortical lesions encompassed both white matter and cortex (leukocortical lesions).[22] Many additional studies have been reported indicating that MS is not limited to the CNS white matter but is a diffuse disorder.[23-26] Additionally, Catalaa, et al[26] demonstrated that cortical involvement was not correlated with disability scores or neurocognitive tests in their patient group. Magnetic resonance imaging evidence of cortical involvement was absent in our patient group. Nevertheless, probable cortical involvement may cause prolongation of CRT. The role of grey matter in the explanation of abnormal prolongation of CRT is not clear because there was no cortical involvement in our patients. It is thought that the polysynaptic reflex arch of LLR may include an extracortical neural circuit probably responsible for the prolongation of CRT. This extracortical neural pathway may include association fibers between sensorial and motor cortical areas. The involvement of this pathway also results in the alterations of CRT.

Our findings demonstrated prolongation of CRT in patients with MS. We think further studies regarding CRT may be of interest in patients with MS and in patients with more localized disorders involving the CNS. While this approach may help the understanding of MS, it is unlikely to help in its diagnosis given present advances in imaging technology.

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