Original Article

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Long-latency Reflexes and Area Measurements of Corpus Callosum in Patients with Multiple Sclerosis

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ABSTRACT

Objective: We aimed to establish the utility of long-latency reflex (LLR) examinations and area measurements of corpus callosum (CC) in the assessment of multiple sclerosis (MS) and determination of disability caused by axonal degeneration.

Methods: This study was prospectively conducted with 23 MS patients with "definite MS" and a control group of 15 healthy individuals. Neurologic examination of the control group and MS patients were performed, and Expanded Disability Status Scale (EDSS) scores were estimated. LLR examination and callosal area measurements were performed for all individuals.

Results: In the MS group, LLR latencies were longer and callosum areas were smaller than that in the control group. There were no significant correlations between CC area and latency, latency difference, or amplitude in the MS group (p=0.606, p=0.736, and p=0.757, respectively). In the MS group, we found a significant correlation between EDSS and CC area. There was a significant negative correlation between the duration of disease and corpus callosum area (p=0.016). Only patients with mild deficits were included in this study, and nearly half the patients had normal LLR tests and corpus callosum area measurements. Therefore, the probability of finding a significant correlation between them was low. These findings revealed the need for other studies that would be performed with more patients.

Conclusion: Long-latency reflex examination and CC area measurements may be used together or alone for the evaluation of patients with MS and for the estimation of disability as safe and easy tests.

Keywords: Multiple sclerosis, evoked potentials, corpus callosum, magnetic resonance imaging

Introduction

Multiple sclerosis (MS) is a demyelinating disease that affects periventricular white matter, brain stem, spinal cord, and optic nerves in adults (1). Magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) examination, and some neurophysiological (NP) tests are widely used investigations in the diagnosis of MS. These NP tests provide useful information about sensory and motor pathways in MS. The investigation of long-latency reflexes (LLR) I-II-III are thought to include afferent sensory, efferent motor, and central transcortical pathways (2). LLR has three late components. The second component (LLR II) is the most stable component. The first and the third components (LLR I and LLR III) may be seen in some normal subjects (3). It is known that the latency of LLR II is prolonged or the response is absent in patients with MS (4). The visual evoked potentials (VEPs) test is another neurophysiological test that is used in the evaluation of visual pathways in patients diagnosed with MS (5).

Magnetic resonance imaging is used to detect the demyelinating lesion in the periventricular white matter, optic nerves, periaqueductal area, pons, and spinal cord. In addition, MRI provides useful information about the atrophy or demyelination of the corpus callosum (CC) (6-11). The CC can be quantified through a number of radiological methods. It has

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been proposed that CC atrophy is an accurate predictor of future disability accumulation, and it has a correlation with the duration and severity of the disease (11-13).

There is not a single diagnostic test or a single clinical feature for the diagnosis of MS. Although VEP was considered to be the most useful neurophysiological test for the evaluation of MS patients in the past, there have been studies about LLR examinations in the diagnosis of MS after the early 1990s (3, 14-18).

In spite of a limited number of studies that compared neuroimaging modalities with evoked potentials in the management of patients with MS, there are no studies that have evaluated the LLR examination and CC area measurements together in this patient group. In this study, we aimed to evaluate the diagnostic usefulness of LLR examination and CC area measurements in MS and evaluate whether there was any relationship between these techniques.

Material and Methods

We prospectively evaluated 23 patients diagnosed with definite MS and 15 healthy individuals as the control group. Written informed consent was obtained from patients who participated in this study. Ethics committee approval was received for this study from the ethics committee of Şişli Etfal Training and Research Hospital. The data, which had been collected over a 2-year period, were evaluated and analyzed retrospectively after the termination of the study. The inclusion criteria for the patient group were as follows: (i) a diagnosis of definite MS according to the criteria by Poser et al. (19) and McDonald et al. (20) and (ii) absence of an acute attack. The exclusion criteria were: (i) clinical or electrophysiological evidence of peripheral neuropathy and (ii) severe paresis of the thumb, which could prevent patients from performing sustained contraction during LLR examination. The inclusion criteria for the control group were as follows: (i) normal neurological examination and (ii) absence of any complaints.

Twenty-three patients (17 females and 6 males), ranging in age from 22 to 44 years (mean age±SD: 30.5±6.5 years), were included in the study. Fifteen healthy subjects (7 females and 8 males), ranging in age from 23 to 41 years (mean age±SD: 30.9±4.6 years) served as controls.

Neurological examination of the patients and the control group who fulfilled the above mentioned criteria were conducted. All patients were evaluated using the Expanded Disability Status Scale (EDSS). EDSS of MS patients varied between 0.0 and 3.5 (mean 1.28±0.25). Mean duration of MS diagnosis was 4.52±0.57 (range 2–12 years). In our patient group, 19 patients had relapsing–remitting MS (82.6%). Three patients had clinically isolated syndrome, whereas 1 patient had primary progressive MS.

The area measurements of CC were performed on T_1-weighted sagittal MRI sequences for the assessment of corpus callosum atrophy. LLRs investigation was carried on bilaterally for both the patient and control group.

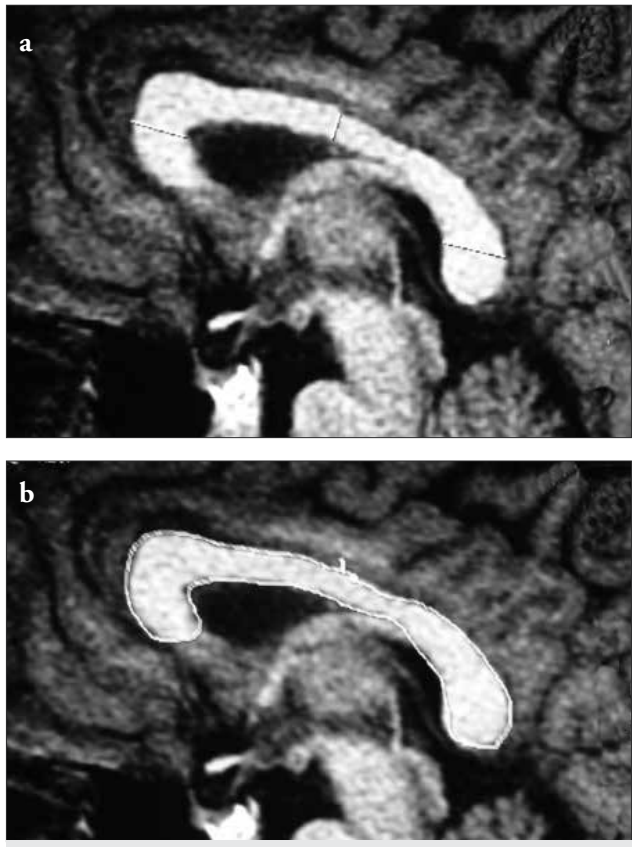

Figure 1. a, b. Measurement of corpus callosum (CC) area. (a) Measurement of the AP lengths of the genu, corpus, and splenium. (b) Manual outlining of CC for the measurements of CC area

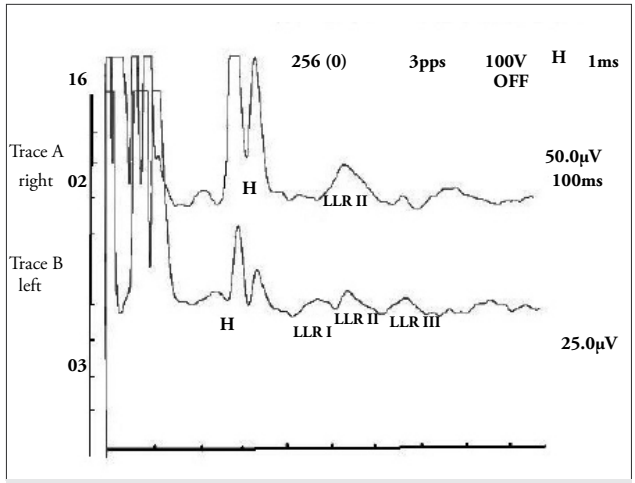

Figure 2. Normal long-latency reflex (LLR) examination of one of the MS patients. Trace A (top) shows only LLR II component following HR, whereas Trace B (bottom) shows all components of LLR (LLR I-II-III)
LLR: Long-latency reflex; MS: multiple sclerosis

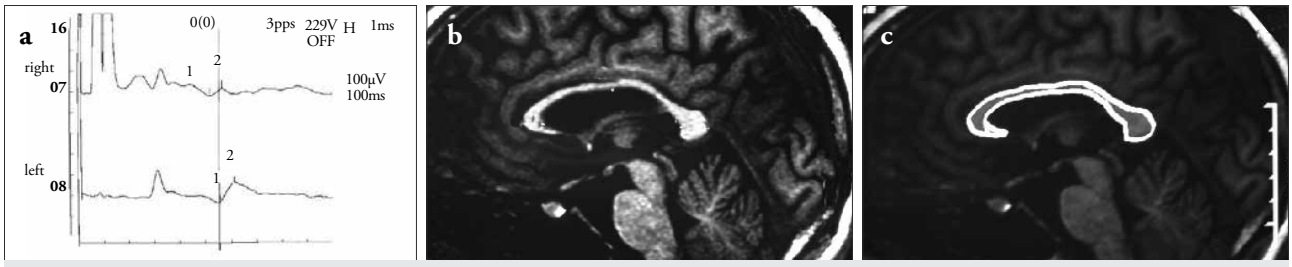

Figure 3. a-c. (a) Long-latency reflex (LLR) examination of the MS patient with the smallest corpus callosum (CC) area. The LLR 2 latencies, which were 51.6 ms on the right side (top) and 55.4 ms on the left side (bottom), were both considered to be within normal limits. (b) and (c) Measurements of the CC area of the same patient

Magnetic resonance imaging protocol

Magnetic resonance imaging was performed at 1.5T Magnet (General Electric, Signa Excite, Millwaukee, USA) using a standard head coil. Spoiled Gradient (SPGR) 3D sequences were used for the area measurements of CC on sagittal series. A uniform protocol consisting of sagittal sequence (time to echo 4.2 ms, time to repetition 12.5 ms, field of view (FOV) 22 cm, matrix 256 × 256, and slice thickness 4.0 mm) was followed. The maximum anteroposterior (AP) length of CC was defined by using the intercomissural line on T_1-weighted (3D) SPGR sequences. The height of corpus was calculated by drawing a straight line on the long axis of CC, which divided it into two equal parts. The maximum AP lengths of genu and splenium were manually measured on the intercomissural line using the midsagittal image. The area of the CC was manually outlined on the slice representing the midsagittal plane and the area values (in mm^2) were calculated automatically. These measurements were performed by the same radiology technician. The lengths of genu, corpus, and splenium were not used in the statistical analysis. They were only used for the area measurements of CC. Normal values of area measurements were determined by the mean values ±3 SD of the measurements of healthy individuals in the control group. The area measurements on MRI are shown in Figure 1a and b.

LLR protocol

Long-latency reflexes were recorded on bilateral upper extremity thenar muscles using electrical stimulation of median nerve at wrist level by a Medelec Sapphire 4 ME EMG-EP machine. Three consecutive recordings were obtained on one side and then the same procedure was repeated on the other side. Stimulus duration was 1 ms and stimulus frequency was 3 Hz. Amplifier filters were set between 1.5 and 3 kHz. The potentials were filtered, rectified, and averaged. A total of 128–256 sweeps was averaged. The patients were requested to sustain a slight voluntary contraction of their thenar muscle during examination. The evoked potentials were recorded via conventional surface electrodes, which had been placed on m.abductor pollicis brevis. Onset latencies of Hoffman Reflex (HR), LLR I-II-III, and the amplitude of LLR II were evaluated. HR and LLR II potentials were recorded in all healthy individuals (Figure 2). While evaluating the onset latencies, delay of LLR II potentials were considered abnormal. In the evaluation of amplitude values, only the absence of LLR II was considered abnormal because of the variability in amplitudes. For LLR II, difference of onset latencies and the amplitude ratios of both sides were evaluated. Normal values for LLR II latencies were determined as the mean values ±3 SD of the latencies of healthy individuals in the control group. LLR parameters of both sides were included in the statistical analysis as joint data.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) statistics 15.0 version. The correlation between the LLR parameters, CC area, corpus, splenium, age, the period of disease duration, and EDSS were analyzed by Pearson correlation test. The differences between the data of two groups were estimated by the Mann–Whitney U test. A value of $p \leq 0.05$ was considered significant.

Results

Mean and standard measurements of LLR and MRI parameters of the patient and control groups are summarized in Table 1 and Table 2, respectively. Table 2 reveals the latency, difference of onset latencies (between both sides), amplitudes, and the amplitude ratios of both sides regarding only LLR II.

The mean latencies of LLR II and the mean latency difference (of both sides) in the MS group were higher than those of the control group (p=0.014 and p=0.013, respectively).

The mean genu, corpus, splenium, and area values in MS group were smaller than those of the control group (p=0.016, p=0.01, p=0.04, and p=0.04, respectively).

In the MS group, there was not a significant correlation between age and the CC area, genu, corpus, or splenium (p=0.083, r=–0.259; p=0.391, r=0.130; p=0.095, r=–0.249; and p=0.229, r=–0.181 respectively). We did not find a significant correlation between age and the latency, latency difference, amplitude, or amplitude ratio (p=0.094, r=0.306;

Table 1. LLR II parameters of the MS patients and control groups (A value of p≤0.05 was considered significant)

LLR II parameters Mean±SD (min–max)	MS (n=23)	Control (n=15)	p
Latency	54.50 ±4.67 (47.7–70.10)	51.21±2.25 (46.3–55.4)	0.014*
Latency difference (of both sides)	3.20±3.08 (0.20–11.50)	1.29±1.49 (0.0–5.2)	0.013*
Amplitude	0.065±0.046 (0.00–0.225)	0.049±0.024 (0.003–0.091)	0.374
Amplitude ratio (of both sides)	0.55±0.29 (0.00–1.00)	0.61±0.24 (0.21–0.97)	0.174

LLR: long-latency reflexes; MS: multiple sclerosis; SD: standard deviation

Table 2. MRI parameters of the patient and control groups (A value of p≤0.05 was considered significant)

MRI parameters Mean±SD (min–max)	MS (n=23)	Control (n=15)	p
Genu	9.35±1.90 (6.0–14.0)	10.47±0.97 (9.0–12.0)	0.016*
Corpus	4.78±1.03 (3.0–7.0)	6.0±0.74 (5.0–7.0)	0.01*
Splenium	11.13±0.97 (9.0–13.0)	9.78±1.46 (6.0–12.0)	0.04*
Area	549.27±80.27 (397.00–668.25)	646.18±76.49 (538.69–792.00)	0.04*

MRI: magnetic resonance imaging; MS: multiple sclerosis ; SD: standard deviation

p=0,192, r=0.240; p=0.109, r=0.278, and p=0.85, r=0.041 respectively).

Duration of MS diagnosis in our patient group ranged between 2 and 12 years (mean 4.52±0.57). There was a significant negative correlation between the duration of disease and CC area (p=0.016, r=–0.496). There was no significant correlation between the duration of disease and EDSS, latency, amplitude, latency difference, or amplitude ratio (p=0.176, r=0.292; p=0.731, r=–0.076; p=0.792, r=–0.058; p=0. 424, r=–0.180, and p=0.294, r=–0.229, respectively).

In the control group, a significant correlation was not identified between CC area and latency, amplitude, latency difference, or amplitude ratio (p=0.229, r=–0.226; p=0.401, r=0.159; p=0.071, r=–0.479; and p=0.058, r=0.500, respectively).

There was not a significant correlation between CC area and latency, latency difference, amplitude, or amplitude ratio in MS group as shown in Table 3 (p=0.606, r=0.079; p=0.736, r=–0.051; p=0.757, r=0.068 and p=0.690, r=0.088, respectively).

Table 3. Correlations between CC area and latency, latency difference, amplitude, and amplitude ratio in MS group (A value of p≤0.05 was considered significant)

		Latency	Latency difference	Amplitude	Amplitude ratio
CC area	p	0.606	0.736	0.757	0.690
	r	0.079	–0.051	0.068	0.088

CC: corpus callosum; MS: multiple sclerosis

Table 4. Distribution of MS patients according to LLR and MRI values

	LLR normal	LLR pathologic	Total
Area normal	**10**	**4**	**14**
Area pathologic	**4**	**5**	**9**
Total	**14**	**9**	**23**

MS: multiple sclerosis; LLR: long latency reflexes; MRI: magnetic resonance imaging

Expanded Disability Status Scale of the MS patients varied between 0.0 and 3.5 (mean 1.28±0.25). Mean EDSS of the patients who had small (pathologic) CC area was 0.72±0.28 (range 0–2.0). EDSS of the patients with pathologic LLR values varied between 0.0 and 3.5 (mean 1.11±0.40).

In the MS group, we found a significant negative correlation between EDSS and CC area (p=0.013, r=–0.362).

We did not find a significant difference in the comparison of the number of MS patients with normal or pathologic CC area values with the number of patients with abnormal LLR values (at least one parameter) (p=0.38).

Table 4 shows that nearly half of the MS patients had normal LLR and CC area values.

Parameters of LLR examination have wide variable ranges (similar to that of other electrophysiological investigations). LLR test of the patient who had the smallest CC area was accepted normal despite the nearly pathologic values of amplitude and latency difference. Figures 3a, b, and c show the LLR examination and MRI of the MS patient with the smallest CC area whose LLR values were considered in normal limits.

Discussion

There have been previous studies that compare the diagnostic usefulness of evoked potentials with each other and with neuroimaging techniques in MS (2, 5, 15, 21). In addition, CC atrophy in patients with MS has been the

subject of various studies (6-8, 11, 12). As LLRs are capable of testing the transcortical sensorimotor reflex arch, they might be regarded as useful tools in the diagnosis of MS (2, 14). In our study, we aimed to evaluate the usefulness of both LLRs and CC area measurements in MS and investigate whether there is any correlation between these techniques.

Latencies of LLR II of healthy individuals detected in our study were consistent with that of previous studies (2, 4, 15). Latency values were prolonged in MS patients in comparison with the individuals in the control group. Abnormal responses were detected in 39.3% of our patients. Among a limited number of studies in which LLR tests in MS were evaluated, Deuschl et al. (4) reported abnormal LLR latencies in 79% of the patients, whereas Michels et al. (2) reported abnormal values in 45.9% of the patients. The delay in latency may be due to the slowing of conduction in the central part of the reflex arch (14). In our study, latencies, the latency difference of both sides, amplitudes, and amplitude ratios of both sides were evaluated in contrast to previous studies in which only the latencies of LLR were considered. The finding that the LLR abnormalities detected in our study were less than that of the other studies might be related to the fact that most of the patients included in our study had mild deficits. Nevertheless, clinical status of the patients, EDSS values, or the period of disease duration were not analyzed in the above mentioned studies. This might suggest the need for further studies in which the clinical features, EDSS, MS types, and the duration of MS diagnosis are taken into consideration.

There are several studies on the role of MRI in the clinical management of MS (20, 22-29). MRI has been used not only to detect demyelinating lesions in MS but also to determine the existence of CC atrophy (6, 7, 11, 13). Area measurements of CC on computerized tomography were found to be not practical and morphometric techniques have been utilized with the advent of MRI.

The technique used to measure CC area in our study seems to be similar to the techniques used in the studies by Simon et al. (6) and Jäncke et al. (30). In the study of Jäncke et al. (30), the total midsagittal CC area was subdivided into four subareas (anterior third, middle third, isthmus, and splenium) and absolute CC measurements. In addition, CC subareas relative to the total CC or forebrain volume were further analyzed with regard to possible effects of handedness, gender, and handedness by gender interaction. Simon et al. (6) analyzed the relationship of CC area measurements with age, gender, and periventricular high signal lesions. Contrary to these reports, CC was divided into two parts in our study and genu, splenium lengths, and corpus height were used only in the measurements of CC area. CC areas of MS patients were smaller than that of control group. The values of CC area detected in our study were consistent with the values reported in other studies (6, 30).

In our study, the mean genu, corpus, splenium, and area values in the MS group were smaller than that of the control group. We did not find a significant correlation between the CC area and age in the MS group. In addition, Simon et al. (6) reported that the MS group in their study exhibited a statistically significant decrease in mean CC area, which was independent of age and sex. In the MS population, CC atrophy paralleled the extent of periventricular and callosal high-signal lesions. Their data indicated that age can be an important variable in the earliest age groups but after adolescence, no obvious relationship could be seen between age and callosal area (6).

To the best of our knowledge, this is the first work that evaluates the relationship of CC area and LLR in MS patients. In our study, CC area was not correlated with LLR parameters (latency, latency difference, amplitude, and amplitude ratio of both sides). Previous studies mostly aimed to compare LLR with other NP tests such as SEP and MEP in MS (2, 15, 16). In addition, the CC has been a promising candidate in various studies because of its sensitivity to demyelination and axonal loss. With the advent of MRI, the measurements of CC size have been performed practically in patients with MS (6, 7, 11, 12). In a limited number of studies in which the relationship of the NP tests (other than LLR) and MRI was evaluated in MS patients, it was concluded that NP tests and MRI were complementary techniques for the detection of MS lesions (5).

We detected a significant negative correlation between CC areas and EDSS in MS patients. In addition, there was a significant negative correlation between the duration of disease and CC area in our patients. Clinical correlations of CC lesions have been studied in various studies. Previous studies have suggested that CC atrophy may be a predictor of disability and intellectual impairment of patients with MS, which may support the findings of our study (6, 25-28).

Only 5 of the 23 MS patients had abnormal values for both CC areas and LLR parameters. LLR values of the MS patient with the smallest CC area were nearly in normal limits. Our finding that the CC area was not correlated with LLR parameters might be explained by the following factors: (i) the increased number of patients included in the study might enhance the probability of finding abnormal values for CC areas and LLR and (ii) a wide range of variability in LLR parameters might decrease the probability of obtaining abnormal LLR values. Therefore, the first limitation of our study is the small sample size. Second, inclusion of patients with more severe clinical features (besides the patients with mild deficits) may strengthen the data, which has wide variability. Further studies with larger sample size

and with homogeneity in terms of disease severity and duration are required.

Conclusion

Both LLR examination and CC area measurements should be considered in the evaluation of patients with MS. LLR examination, which provides useful information about afferent sensory, efferent motor, and central transcortical pathways, may be used to support the diagnosis of MS. CC atrophy, which may be detected via CC area measurements on MRI, may be used as a predictor of disability. These non-invasive, safe, and easy investigations can be used together or alone in the assessment of patients with MS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Şişli Etfal Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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