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Prolonged intracortical delay of long-latency reflexes: Electrophysiological evidence for a cortical dysfunction in multiple sclerosis

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Abstract

Convincing evidence suggests that long-latency reflexes (LLRs) are capable of testing the transcortical sensorimotor reflex arch. By subtracting the sum of the latencies of N20 (afferent branch) and transcranially elicited motor evoked potentials (MEP; efferent branch) from the LLR II latency, the cortical relay time (CRT) can also be obtained, which is alleged to represent the time required for the cortical sensorimotor integration. The aim of the present study was to investigate if a cortical dysfunction occurs in multiple sclerosis (MS).

Median nerve somatosensory evoked potentials (SEPs), MEPs and LLRs were recorded from the upper limbs of 23, not severely disabled MS patients in acute phases of the disease. Eighteen age and sex matched healthy volunteers served as controls. N20, MEP, LLR II latencies were measured, and the CRT was calculated for each limb.

The statistical comparison between patients and controls was only weakly significant by taking into account conduction times along either the afferent (N20) or the efferent (MEP) pathways. On the contrary, it turned out to be considerably significant if both branches of the transcortical sensorimotor reflex arch, together with the intracortical pathway, were simultaneously tested by means of the LLRs. Moreover, the patients showed a significantly higher CRT compared with that found in the control subjects.

These findings are consistent with a prolonged intracortical delay of LLRs in the MS group and suggest the occurrence of conduction velocity slowing and/or synaptic transmission impairment along the sensorimotor intracortical pathway in MS.

Keywords: Long-latency reflexes; Cortical relay time; Multiple sclerosis; Sensorimotor integration; Fatigue; Manual dexterity

1. Introduction

Multiple sclerosis (MS) is traditionally described as an idiopathic inflammatory demyelinating disease of the central nervous system (CNS), characterized by focal lesions that are mostly disseminated in the white matter [36]. Nevertheless, in spite of the focal character of the lesions, the causal relationships between pathological and clinical findings are quite often difficult to reconstruct. Cases with minimal or no neurological deficits with an extensive white matter lesion load and vice versa are rather common in clinical practice. Likewise, multimodal evoked potential (EP) abnormalities are sometimes not easily explained in terms of the lesion site [8,48,50]. Although axonal injury has been described since 1868 [9], it has been progressively highlighted only recently by either neuropathological [18,65] or imaging studies [11,20,63]. Nevertheless, axonal damage does not seem to adequately explain those EP alterations that appear to be independent of both location and extension of the lesions, since at the present moment it is not believed to provoke relevant conduction defects [28,31,44].

Despite the fact that MS is considered a white matter disease, the probability that cortical grey matter involvement might play a role both in clinical deficits and in electrophysiological abnormalities has been known for a long time [7,36]. Recent studies have stressed the importance of cortical damage [5,10,27,56], even if over the decades it has been considered irrelevant in comparison to the global white matter lesion load and the apparently poor relationship with clinical symptoms. From a functional point of view, the first indications for the possible role of cortical involvement date back to the early 1980s. Both orientation-

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specific visual contrast sensitivity losses [53] and orientation-dependent visual evoked potential (VEP) abnormalities [8] were found in MS patients and thought to be of cortical origin, since neural sensitivity for oriented visual stimuli is a merely cortical phenomenon. These suggestions were subsequently resumed to explain colour-VEP delays following stimulation of fellow eyes in clinically monolateral optic neuritis with no chiasmatic or post-chiasmatic demyelinating lesions in magnetic resonance images (MRI) [50]. Finally, cortical functional impairment has been proposed recently to explain pathological fatigue in MS patients [33,34,60,61].

Long-latency reflexes (LLRs) represent a clinical neurophysiological test that has been employed to assess cortical function [24,32]. LLRs are muscular responses that can be elicited by a simple electrical stimulation of mixed nerves (the median nerve in this instance) and recorded from target muscles during a slight isometric voluntary contraction. They consist in three main muscular responses beyond the H reflex (HR), the most reliable of which – the LLR II [25] – is thought to be a transcortical reflex [15,37,38,45,54,62]. A good correlation exists between the LLR latencies and the sum of somatosensory evoked potential (SEP) and transcranially elicited motor evoked potential (MEP) latencies, suggesting that LLRs, MEPs and SEPs are mostly conducted along the same fibres [45]. Moreover, the afferent branch probably coincides with the proprioceptive fibres "Ia" eliciting the N20, since both LLRs and SEPs can be recorded simultaneously. On the contrary, the efferent branch is probably the same, descending from pyramidal cells, excited by transcranial magnetic stimulation (TMS). Therefore, LLRs allow testing both sensory and motor pathways simultaneously, separately assessable by SEPs and MEPs, respectively. Moreover, by subtracting the sum of the latencies of N20 and MEP from the LLR II onset latency [LLR II − (N20 + MEP)], the so-called 'cortical relay time' (CRT) can be calculated, the length of which is considered to be consistent with a polysynaptic [45] or an oligosynaptic [57] intracortical pathway.

In recent years, LLRs have been employed besides EPs in the diagnostic assessment of MS and have revealed to be more useful than SEPs alone [16,39,45,64], in virtue of their ability to assess the central motor pathways at the same time. Purpose of the present study was to investigate the nature of the pathophysiological mechanisms underlying the observed LLRs abnormalities, regardless of the diagnostic power offered by the neurophysiological methods employed. In particular, assuming the hypothesis of an intracortical reflex arch for LLRs to be correct, the aim of this study was to verify the possibility of a cortical functional disorder in MS.

2. Materials and Methods

Patients were enrolled from a group of 38 with definite or suspected MS who were consecutively admitted for treatment of acute episodes. The inclusion criteria in the patient group were: (i) a diagnosis of definite MS, according to the criteria by McDonald et al. [43] and (ii) LLRs, MEPs and SEPs all elicitable (so as to be able to calculate the CRT) at least for one hand. The exclusion criteria were: (i) clinical or electrophysiological evidence of peripheral neuropathy and (ii) severe paresis of hand muscles that prevented patients from performing a slight sustained voluntary contraction of the target muscle. Twenty-three patients (18 females and 5 males), ranging in age from 22 to 55 yrs (mean age ± S.D.: 36.7 ± 9.3 yrs), fulfilled the above mentioned criteria and were therefore included. Disease duration ranged from 2 to 25 yrs (mean duration ± S.D.: 7.9 ± 6.0 yrs). All patients had a preserved walking performance. Eighteen healthy subjects (12 females and 6 males), ranging in age from 28 to 43 yrs (mean age ± S.D.: 34.4 ± 4.1 yrs), served as controls.

A Medelec (Vickers Ltd.) ER 94a neuroaverager was employed in all recordings. Raw EMG [57] from the opponens pollicis brevis muscle, evoked either by repetitive median nerve electrical stimulation (for LLRs) or by TMS (for MEPs), was recorded by surface Ag/AgCl electrodes placed in a belly-tendon montage. In both cases, the subjects had to maintain a slight voluntary activation of the target muscle by bringing together the thumb and little finger of the same hand so that the fingertips just touched each other (about 5–10% of the maximum force). Filter setting was 1 Hz–3 kHz [13].

For LLRs, rectangular wave pulses (100 μs duration) with a frequency of 5 Hz and intensity adjusted at threshold for motor fibres were delivered to the median nerve at the wrist [57]. A total of 256 sweeps was averaged. Two traces were superimposed in order to ensure reproducibility of the waveforms. The onset latencies of both HR and LLR II and the HR–LLR II interval (central sensorimotor conduction time, CSmCT) were taken into account.

Magnetic stimulation was carried out by using a Novametrix Magstim 200, with a 9 cm diameter coil, producing a monophasic waveform stimulus with a pulse width of less than 1 ms, a rise time of 0.1 ms and a maximum magnetic field of 1.5 T. For TMS, the coil was tangentially placed over the skull and centred at the vertex (Cz of the International 10–20 system); in this way, a clockwise current flow excited the right cerebral hemisphere, whereas a counter-clockwise flow excited the left one. Since the primary goal of the study was to calculate the CRT, the accuracy of the latency measurements was given utmost attention. Therefore, the stimulus intensity was adjusted for the individual subjects to obtain reliably distinguishable MEPs from the electromyographic voluntary background, so that latencies could be more precisely detectable. In this way, the stimulation strength was, on average, about 30% above the previously determined threshold. Four consecutive stimuli were given, and the shortest latency was used for analysis. For cervical root magnetic stimulation (CMS), the coil was placed parallel to the vertebral column and centred over the spinous process of the seventh cervical vertebra (C7). The stimulation strength was increased until stable potentials could be recorded [59]. The onset latency of the MEPs and the central motor conduction time (CMCT; calculated as the difference between TMS- and CMS-MEP latencies) were considered.

Finally, the same stimulation modalities and filter setting used for the LLRs were also employed for SEP recordings. Cortical evoked responses were recorded with surface Ag/AgCl electrodes fixed with collodion over the scalp at C3′ and C4′ points (2 cm back to C3 and C4 positions). Cervical cord responses were also recorded over the spinous process of C7 with an anterior neck (thyroid cartilage) reference. Usually, 1024 responses were averaged. All the recordings were reproduced at least twice. The peak latencies of both N13 and N20 and the N13–N20 interpeak interval (central somatosensory conduction time, CSsCT) were considered. All the experiments followed the tenets of the declaration of Helsinki. Informed consent was obtained after the aims and the experimental techniques were fully explained. The experiments had the approval of the local ethics committee.

2.1. Statistical analysis

Analysis of the data was both qualitative and quantitative. In the case of the former, the parameters considered were central motor (CMCT), somatosensory (CSsCT) and sensorimotor (CSmCT) conduction times. The data were judged to be abnormal if they resulted at least 2.5 S.D. above the mean values found in the group of healthy subjects or if they were not calculable due to the unevocability of either MEP, N20 or LLR II. Then the relative distribution frequencies (percentages) of the abnormal results were calculated, in relation to the number of both limbs and patients, for every neurophysiological test employed. The percentages of abnormal results in terms of limbs were compared by the chi-square test, in the case of expected frequencies over 5 in the 2×2 contingency table, otherwise by Fischer's exact test.

As far as the quantitative aspect was concerned, the absolute latencies of MEP, N20, LLR II and the CRT values were considered over and above the aforementioned parameters. Since the distribution of the data was non-parametric, the