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Magnetic resonance spectroscopy findings as related to fatigue and cognitive performance in multiple sclerosis patients with mild disability

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ABSTRACT

Background: The origin of fatigue in multiple sclerosis (MS) remains unclear. Magnetic resonance spectroscopy (MRS) provides an insight into metabolic properties of the brain.
Objectives: The aim of the study was to evaluate brain MRS measurements in MS patients, with regard to fatigue and cognition.
Methods: The study comprised 32 MS patients and 43 controls. Fatigue was assessed using the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS) and cognition — using the Brief Repeatable Battery of Neuropsychological Tests (parts of BRBNT). MRS voxels were placed in the parietal white matter (PWM) and the posterior cingulate gyrus (PCG); N-acetyl-aspartate (NAA), choline (Cho) and myoinositol (mI) to creatine (Cr) ratios were determined. Relationships were searched between MRS measurements and fatigue as well as BRBNT results.
Results: MS patients in comparison with controls showed decreased NAA/Cr and increased mI/Cr ratios in PCG and PWM, respectively. No significant relationships between MRS parameters and fatigue measures, BRBNT results or MS-related variables were found.
Conclusions: The decrease of NAA and increase of mI within white and gray matters in MS patients do not show a significant relationship with cognitive performance or fatigue.

1. Introduction

Fatigue is a frequent complaint of patients with multiple sclerosis (MS), which essentially affects their daily functioning and quality of life. Although often discussed in recent years, the etiology of fatigue remains unclear. It remains a matter of debate as to whether fatigue in the course of MS is associated with disability or rather related to cognitive impairment, another non-physical aspect of MS receiving increasing attention in recent years [1]. Occurrence of fatigue and cognitive dysfunction in the early stages of MS, with few or no other signs of neurological deficit, suggests a link between them [2].

Neuro-imaging studies in MS patients, aimed at investigating the inflammatory/demyelinative process as a possible background of fatigue, have failed to find the relationship between its level and total load of lesions shown in magnetic resonance (MR) imaging, their activity (contrast enhancement) or progression in time [3,4]. There was also no evidence of association between fatigue and localization of the lesions within the areas responsible for particular brain functions. MR spectroscopy (MRS) has enabled the in vivo studies of certain metabolites in the brain and offered a unique insight into the biochemical properties of neurons, thus being sensitive to subtle abnormalities of even normal appearing cerebral white and gray matters. The results of MRS in MS patients have been evaluated with respect to early disease recognition, disability and cognitive impairment [5–8]. However, apart from the single report of Tartaglia et al. [9], there have been no studies so far analyzing the relationships between brain MRS parameters and fatigue. Assuming the common background for fatigue and cognitive dysfunction, we had the aim of investigating the relationships between fatigue and metabolic properties of brain areas involved in cognitive processes.

The purpose of our study was therefore to evaluate MRS parameters within cerebral white and gray matters in MS patients, with regard to their level of fatigue and cognitive performance as well as disease-related variables.

2. Material and methods

The study comprised 32 patients with clinically definite, relapsing–remitting MS, according to McDonald's criteria [10]: 8 men and 24 women, aged 20–41 (mean 28.8), all right-handed, as well as 43 healthy controls, matched for age, gender and educational level and without complaints of fatigue.

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The patients included were free from any coexisting diseases and conditions known to be associated with fatigue and had only mild disability (Expanded Disability Status Scale/EDSS/score < 3.5) [11]. Fourteen patients have not been treated with any disease-modifying agents, 18 subjects were undergoing treatment with interferon beta for 6–12 months (such a limitation was made to eliminate fatigue as a side effect of treatment at its onset, as well as the possible influence of long-lasting therapy upon fatigue and neuronal properties and thus MRS results). The patients were followed up in the Department of Neurology, Medical University of Wroclaw. All the subjects gave their informed consent to participate in the study and its project was approved by the Bioethical Committee at Medical University of Wroclaw.

2.1. Clinical assessment

On the basis of medical records and neurological examination duration of the disease and degree of neurological deficit and disability (assessed in EDSS) were determined.

Fatigue was evaluated by means of self-assessment questionnaires: Fatigue Severity Scale (FSS) [12] and Modified Fatigue Impact Scale (MFIS) [13], using their basic versions and the versions modified by Mills et al. [14,15] with the use of Rasch analysis (FSS-5 and MFISmod, respectively, including physical and cognitive subscales of MFISmod). Cognitive performance was assessed using the Brief Repeatable Battery of Neuropsychological Tests, including: Selective Verbal Reminding Test (SVRT), Spatial Recall Test (SpaRT), Symbol Digit Modalities Test (SDMT), Word Generation List (WGL) and Paced Auditory Serial Addition Test (PASAT) [16]. Their results in MS patients were referred to normative values [17].

Neurological examination and assessment of fatigue and cognitive functions were performed during the same day, in morning hours. MR was performed within a week from the remaining tests.

2.2. MR imaging and MRS protocols

The imaging examinations were performed with a 1.5 T unit (Signa HDx, GE Medical System) using a 16-channel coil dedicated for head and spine imaging. Before ^{1}H MRS examination of axial, sagittal and coronal T2-weighted images, axial T1-weighted images and FLAIR (fluid-attenuated inversion recovery sequences) were obtained. The imaging protocol also included diffusion-weighted imaging (DWI).

In each patient a lesion load was assessed as a total number of plaques visible on T2-weighted and FLAIR images counted by two experienced neuroradiologists.

The MRS examinations were performed using the single voxel spectroscopy (SVS) technique (PRESS sequence). The data acquisition parameters were as follows: TR = 1500 ms, TE = 35 ms, number of acquisitions — 128, and time of acquisition — 3 min 45 s. Using the localizing axial T2-weighted images voxels of 2 × 2 × 2 cm (8 cm^3) were placed within the normal appearing gray and white matters. Voxels were located in the following 2 regions: posterior cingulate gyrus — PCG (Fig. 1A) and left parietal white matter — PWM (Fig. 1B). There were no demyelinative lesions within the voxels in any of the patients included in the study. The total acquisition time was 3 min 45 s for each voxel. MRS data were postprocessed using algorithms provided by the manufacturer (GE workstation, ADW 4.4). Each spectrum was automatically fitted to four peaks corresponding to the levels of N-acetylaspartate (NAA) (2.02 ppm), total creatine (Cr) (3.03 ppm), choline-containing compounds (Cho) (3.23 ppm) and myo-inositol (mI) (3.56 ppm). Ratios of NAA, Cho and mI to creatine (NAA/Cr, Cho/Cr, mI/Cr, respectively) were calculated and analyzed.

Radiological measurements (total lesion load, NAA/Cr, Cho/Cr and mI/Cr ratios for white [PWM] and gray [PCG] matters) were compared between MS patients and controls, between fatigued and non-fatigued patients (FSS/FSS-5 > or <3.5), as well as between the patients with impaired (results of at least two parts of BRBNT worse than those obtained in the controls) and normal cognitive performance. Correlations were searched between radiological

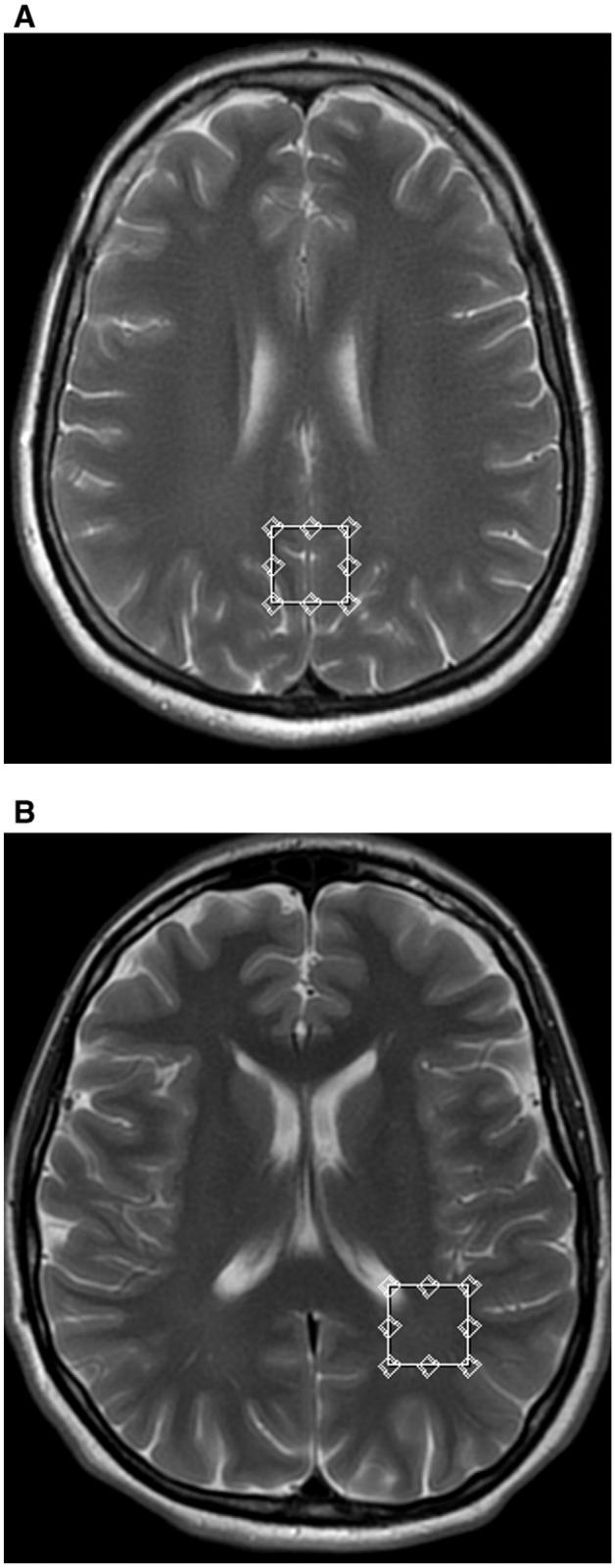

Fig. 1. Representative T2-weighted images (transverse cross-section) indicating voxel locations. Single voxel magnetic resonance spectroscopy was performed in the following regions: in the posterior cingulate gyrus (PCG) (A) and in the white matter of the left parietal region (PWM) (B).