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Cognitive performance, fatigue and event-related potentials in patients with clinically isolated syndrome

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ABSTRACT

Objectives: Cognitive impairment and fatigue are regarded as important aspects of multiple sclerosis. The aim of this study was to evaluate cognitive performance, the level of fatigue and parameters of event-related potentials (ERP) in patients diagnosed with clinically isolated syndrome (CIS).
Patients and methods: The study comprised 44 patients with CIS and 45 healthy controls. Cognitive performance was assessed using the Brief Repeatable Battery of Neuropsychological Tests (BRBNT), fatigue - using the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS). Auditory ERP were performed and the parameters of N200 and P300 components were analyzed. Neuropsychological and electrophysiological measures were referred to clinical and radiological features of the disease activity.
Results: Forty five% of patients failed in at least one test from BRBNT, mainly within the domains of memory and attention. In 18% of patients FSS corresponded with moderate or severe fatigue. The mean latency of N200 and P300 was significantly longer and amplitude of P300 was lower in those patients with CIS than in the controls. Significant correlations were found between the results of MFIS and tests evaluating verbal memory and attention, as well as between N200 latency and results of tests for verbal memory.
Conclusions: Cognitive performance and fatigue deserve attention from the earliest clinical stage of MS. Abnormalities of event-related potentials in CIS suggest early impact of the disease on functional neural networks.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system with a background associated with immune-mediated demyelinating processes accompanied by axonal loss. Multifocal and diffuse damage to the brain results in a diversity of symptoms and signs of neurological deficit. Among these, cognitive impairment and fatigue have already been recognized and investigated because they substantially affect patients' social and vocational functioning [1–4]. Impaired cognitive performance is reported in 30–70% of MS patients and is still supposed to be underestimated [1,2]. More than half of MS population (up to 90%) complains of fatigue [3,4]. Both these aspects deserve special attention at the earliest stage of MS, when physical disability is only minor [1–3,5–7].

Fatigue associated with CIS has been infrequently addressed [8–10]. Cognitive performance in patients with early stage MS, including clinically isolated syndrome (CIS), has already been analyzed in some studies [11–16], although these studies differed both in the characteristics of the patients and the methods used for neuropsychological assessment. Parallel to neuropsychological testing, event-related potentials (ERP) have been used as the electrophysiological measure of cognitive abilities in MS patients. [17–24] Abnormalities of evoked potentials in MS patients often allow to reveal subclinical dysfunction of neuronal pathways [19,21]. Therefore it seems feasible to use ERP as biomarkers of cognitive abilities at the earliest stage of MS [20,25], when the bioelectrical activity of the brain, including the function of neuronal networks responsible for mental processes, may have been already affected. Neuroimaging studies revealed that immune-mediated demyelinating damage to cerebral white and gray matter as well as axonal loss have already been developing in the preclinical stage of the disease [26,27]. However, apart from the single study by Kocer et al. [28], ERP has not been applied so far in evaluating cognitive dysfunction in the patients with CIS.

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The purpose of our study was therefore to evaluate cognitive performance, level of fatigue and parameters of event-related potentials in patients diagnosed with clinically isolated syndrome (CIS). We also investigated the relationships between neuropsychological and electrophysiological measures, as well as their connections with the clinical symptoms and radiological features of the disease activity.

2. Material and methods

The study group comprised 44 patients (17 men, 27 women, aged 21–48 years, mean 31.4) diagnosed with CIS during their hospitalization in the Department of Neurology between June 2012 and May 2014. All the patients diagnosed with CIS within this time period were included in the study.

The control group consisted of 45 healthy volunteers (13 men, 32 women, aged 23–47, mean 30.7 years), matched for educational level to the patients. None of the controls had any history of the nervous system disease or complaints/symptoms of central nervous system involvement, with a special regard to cognitive performance. They also underwent neurological examination to exclude any signs of neurological deficit.

In the patients with CIS, neurological examination and evaluation of disability on the Expanded Disability Status Scale (EDSS) [29] was performed during the initial hospitalization when CIS was recognized. The time since the onset of symptoms ranged between 3 and 20 days (mean 7.3). Symptoms and signs of CIS included: motor deficit in 36 patients (25 with pyramidal functional system/FS score 1 - abnormal signs without disability- and 11 with pyramidal FS score 2 - minimal disability; in 7 cases distribution of signs indicated involvement of spinal cord, in 9- brainstem, in 20 - hemispheric lesions), double vision with disturbed eye movements in 17, cerebellar syndrome (ataxia, disturbed balance) in 13, optic neuritis in 6, and sensory disturbances in 4; while multisystem involvement was found in 23 subjects. The degree of disability assessed on EDSS ranged between 1 and 2 (mean 1.39, median 1.5).

All the subjects with CIS performed magnetic resonance imaging (MRI) of the brain during hospitalization. In all of them McDonald criteria [30] for dissemination in space were fulfilled, and in 23 dissemination in time was confirmed as well (active, gadolinium contrast-enhanced lesions co-occurring with non-active ones). In 37 patients cerebrospinal fluid (CSF) was examined for the presence of immunoglobulin oligoclonal bands: the result was positive in 34 cases and negative in 3.

Coexisting conditions and other diseases were excluded as the potential background for clinical symptoms and brain lesions shown in MRI.

2.1. Assessment of cognitive functions and fatigue

To assess cognitive performance in those patients with CIS, the Brief Repeatable Battery of Neuropsychological Tests (BRBNT) [31] was administered, which consists of: Selective Verbal Reminding Test (SVRT), Spatial Recall Test (SpaRT), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Additive Test (PASAT) and Word List Generation (WLG).

The SVRT evaluates verbal learning and memory. Having listened to the list of 12 words read by examiner (one word per 2 s), the subject is asked to recall the words in 6 consecutive trials. After each trial the examiner reminds the missing words. After 15 min (other tests are performed in this time), the subject is asked to recall the words again. The results include: long term storage (LTS – count of words remembered in at least two consecutive trials), consistent long-term retrieval (CLTR – count of words remembered in all the trials until the end of the test), total count of remembered words and count of words recalled in a delayed part [31,32].

The 10/36 SpaRT evaluates visuospatial learning and memory. The subject is shown the pattern of 10 checkers on the board for 10 s and then he/she is asked to reproduce it. The main part of the test involves 3 trials and after 15 min, the subject is asked to recall the pattern again. The results include number of correctly placed checkers in the main and delayed part of the test [31,32].

The SDMT assesses concentration and sustained attention based on visual non-verbal scanning. The task involves substituting numbers 1–9 to corresponding geometrical symbols, according to the provided key. The result is the number of correct responses within 90 s [31,32].

The PASAT measures speed of auditory information processing as well as sustained and divided attention. The series of digits is presented and the subject is asked to add 60 pairs of them (each digit is added to the preceding one). The result is the number of correct responses. BRBNT contains 2 versions of PASAT, with the digits presented in 3 or 2 s intervals. Because of our previous experiences with PASAT (commonly disapproved by the patients who found it frustrating), we decided to conduct only one version with 3 s intervals [31,32].

The WLG evaluated verbal fluency and semantic executive functions. The subject is asked to list possibly many nouns of a given category ("fruits and vegetables") within 90 s. The result is the number of correct names [31,32].

The results of individual tests in the patients with CIS were referred to normative values, elaborated by Boringa et al. [32] in the group of 140 healthy controls. The results were regarded as abnormal if the score was 1.5 SD below the age-adjusted norm.

Fatigue in those patients with CIS as well as in the control group was evaluated using self-assessment questionnaires: Fatigue Severity Scale (FSS) [33], re-evaluated according to the version of Mills et al. (FSS-5) [34], and in addition (in the patients only) Modified Fatigue Impact Scale (MFIS) [35].

2.2. Event-related potentials

Auditory ERP were performed in those patients with CIS and in the healthy controls, according to the standards of the International Federation of Clinical Neurophysiology, using a Nicolet 1000 Viking device (a method already described in our previous studies) [36,37]. The auditory stimuli (tones of 70 dB intensity and 200 ms duration) were applied binaurally via earphones. In accordance with the "oddball paradigm", occasional target tones (frequency 2 kHz, 20% of each series) were randomly scattered among the frequent non-target ones (frequency 1 kHz, 80% of each series). The subjects were asked to lie with their eyes closed, stay awake and silently count the target tones. The averaged responses were recorded in Fz, Cz and Pz (the 10–20 system), with the use of Ag/AgCl surface electrodes; linked earlobes served as the reference electrode, while a ground electrode was attached to the forearm. The following parameters were used in the ERP recording and analysis: impedance of electrodes below 5 kOhm, bandpass filter 0.30/s, 70 Hz, a sweep time of 1000 ms and a pre-stimulus baseline of 250 ms. At least 30 target trials were averaged in each of the two runs performed on every subject. Artifacts were rejected automatically and additional correction was made during visual inspection. Within the averaged response to target stimuli, P300 was identified as the positive component with a latency of 300–500 ms after the start of the stimulus and N200 - as the negative component with a latency of 180–300 ms. The identified components were referred to the averaged responses to non-target stimuli and verified between two runs of stimulation series. Latencies and amplitudes ("peak to baseline") were measured for N200 and P300, and for each subject