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The association of cognitive impairment with gray matter atrophy and cortical lesion load in clinically isolated syndrome

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ABSTRACT

Background: Multiple sclerosis can impair cognition from the early stages and has been shown to be associated with gray matter damage in addition to white matter pathology.
Objectives: To investigate the profile of cognitive impairment in clinically isolated syndrome (CIS), and the contribution of cortical inflammation, cortical and deep gray matter atrophy, and white matter lesions to cognitive decline.
Methods: Thirty patients with clinically isolated syndrome and twenty demographically- matched healthy controls underwent neuropsychologic assessment through the Rao Brief Repeatable Battery, and brain magnetic resonance imaging with double inversion recovery using a 3T scanner.
Results: Patients with clinically isolated syndrome performed significantly worse than healthy controls on tests that evaluated verbal memory, visuospatial learning and memory, and verbal fluency. Significant deep gray matter atrophy was found in the patients but cortical volume was not lower than the controls. Visual memory tests correlated with the volume of the hippocampus, cerebral white matter and deep gray matter structures and with cerebellar cortical atrophy. Cortical or white matter lesion load did not affect cognitive test results.
Conclusion: In our patients with CIS, it was shown that cognitive impairment was mainly related to cerebral white matter, cerebellar cortical and deep gray matter atrophy, but not with cortical inflammation, at least in the early stage of disease.

1. Introduction

Cognitive impairment may be present during the early stages of multiple sclerosis (MS) (Achiron and Barak, 2003) with a prevalence ranging from 40% to 70% (Amato et al., 2006). It has a dramatic impact on personal, social and occupational function (Amato et al., 2006). MS-related cognitive deterioration is characterized by involvement of recent memory, sustained attention, information processing speed, and executive function (Rao et al., 1991). The Brief Repatable Battery of Neuropsychological Tests (BRBN) assesses cognitive domains that are most frequently impaired in MS and incorporates tests of verbal memory, visual memory, attention, concentration, speed of information processing, and verbal fluency (Rao et al., 1991). Although cognitive profile has interpatient heterogenicity, information processing speed is generally accepted as the mostly affected cognitive domain in MS (DeLuca et al., 2004; Tekok-Kilic et al., 2007).

Recent studies showed that brain atrophy assesment was a better predictor of cognitive impairment in MS than lesion burden (Benedict et al., 2004; Bermel and Bakshi, 2006). Although the relationship between cognitive deterioration and subcortical white matter (WM) pathology remains controversial (Benedict et al., 2004; Rovaris et al., 2000; Rao et al., 1989), there is increasing evidence of a primary role of cortical pathology in determining cognitive disability (Tekok-Kilic et al., 2007; Portaccio et al., 2006; Benedict et al., 2006a,b). Gray matter (GM) atrophy appears to have unique, (Sanfilipo et al., 2006) if not greater (Dalton et al., 2004; Bakshi et al., 2005) clinical significance than WM lesions and/or volume. GM atrophy is more strongly related to cognitive decline, especially when the cerebral cortex is assessed (Benedict et al., 2006a,b; Amato et al., 2004). Besides cortical atrophy, cortical lesion load was recently shown to be

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associated with progression of cognitive disability in MS (Calabrese et al. (2012). Increased ability of detection of cortical lesions in MS by double inversion recovery (DIR) sequences has been shown previously (Wattjes et al., 2007).

In this study, we assessed the extent and the most affected domains of cognitive impairment and its probable correlations with GM pathology in a clinical cohort of patients with clinically isolated syndrome (CIS) who presented with a first episode suggestive of MS.

2. Materials and methods

2.1. Participants

Thirty patients with CIS were studied [20 women and 10 men, mean age ± standard deviation (SD) 31.4 ± 8.5 years]. The recruited patients had been followed up at the neuroimmunology clinic of Hacettepe University Hospital between 2012 and 2014. McDonald's criteria were used for the diagnosis of CIS. Patients with visual or upper limb involvement that would interfere with neuropsychologic testing, other neurologic disease, major systemic disease, major psychiatric illness, drug or alcohol addiction, any drug use that could interfere with cognitive function were excluded from the study. All patients were relapse free and had not taken any steroids for at least 1 month before the assessment (mean disease duration ± SD 11.8 ± 15.5 months; range, 1–76 months). Eight (26.7%) of the 30 patients were under treatment with beta-interferons or glatiramer acetate at the time of study entry. For each patient, a neurologic evaluation including disability rating on the Expanded Disability Status Scale (EDSS) and cognitive assessment using the BRBN were performed within a week of magnetic resonance imaging (MRI) acquisition. None of the patients had any treatment procedure changes during this interval. The test performances and MRI results of the patients were compared with those of 20 demographically-matched healthy controls (7 men and 13 women, mean age ± SD 32.25 ± 8.58 years) who were recruited among healthy volunteers with a normal neurologic examination and with no history of neurologic disorders. The study was approved by the Ethics Committee of the Faculty of Medicine of Hacettepe University, and written informed consent was obtained from all participating subjects.

2.2. Clinical and neuropsychologic assessment

Depression was evaluated and excluded with the Beck's Depression Scale (Beck et al., 1961). The performance on each test of the BRBN was assessed by applying the available Turkish normative values, which for each test provided a mean test score (± SD) obtained from 106 healthy individuals who were grouped by sex, age (15-30, 31-45, 46-60) and education level (< 7 years, 7-12 years, > 12 years) (Bingol and Tütüncü, 2010). In particular, we defined the failure of a test when the score was at least 2 SDs below the corresponding mean normative value. Patients who failed at least two tests were considered cognitively impaired, and those who failed fewer than two tests were considered cognitively preserved. In brief, the BRBN consists of the following subtests:

1. The Selective Reminding Test (SRT), (Ehrenreich, 1995) which tests for verbal learning and memory using a list of 12 words. From up to six test trials, a total learning score (SRT-TL) is achieved, plus after 25 min, a score for delayed recall (SRT-DR) is generated.

2. The 10/36-Spatial Recall Test (SPART) (Boringa et al., 2001) measures visuospatial learning and memory. Participants try to recall the location of 10 checkers that are randomly placed on a 6 × 6 checkerboard. The sum of the correct responses in the three immediate recall trials (total learning, SPART-TL), and the delayed recall after 15 min (SPART-DR) are recorded.

3. The Symbol Digit Modalities Test (SDMT) (Smith, 1991) measures information processing speed, sustained attention, and concentration. Subjects are given 90 s to substitute symbols for numbers as part of a set code.

4. The Paced Auditory Serial Addition Test (3 s version; PASAT3) (Gronwall, 1977) examines sustained attention, working memory, and information processing speed by evaluating an addition task regarding acoustically presented digits at a rate of 3 s per digit.

5. Word List Generation (WLG), (Rao et al., 1991) which measures verbal fluency on semantic stimulus by evaluating the spontaneous production of words in a given category within 90 s.

The BRBN, which has been translated and validated in Turkish, (Bingol and Tütüncü, 2010) was applied in a standardized, single-test session in the following order: SRT-TL, SPART-TL, SDMT, PASAT3, SRT-DR, SPART-DR, and WLG, and lasted for approximately 30–45 min.

2.3. MR examination and analysis

A cranial MRI examination of each participant was performed in the same week as the neuropsychologic examination using a 3T scanner (Magnetom, Trio Tim, Siemens) in the National MR Research Center (UMRAM, Bilkent University, Ankara). The MRI protocol included axial T1-weighted (W) (TR/TE; 500/10 msec), FLAIR (TR/TE/TI; 9000/97/2499.5 msec , slice thickness (ST)/inter-slice gap (IG): 4.0/0.8 mm), T2W (TR/TE; 4800/92 msec, ST/IG; 4.0/0.8 mm) imaging. To better delineate the lesions, a sagittal double-inversion recovery sampling perfection with application optimized contrasts using different flip angle evolution (DIR SPACE) sequence (TR/TE/TI: 7500/325/3000 msec, ST/IG; 1.12/0 mm, FOV: 215 × 215, matrix: 192 × 192) was also applied. The total MRI took about 30 min. No medication or contrast agent was used.

We used Freesurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/) volumetric segmentation to obtain regional measures of cortical volumes (mm^3), including the removal of non-brain tissue (skull, eyeballs, and skin), with an automated algorithm with the ability to segment the whole brain without any user intervention, and cortical surface reconstruction methods. Fischl et al. (2002) previously described the automated procedures for volumetric measures of the different brain structures. The reconstructed cortical surface models for each participant were checked to confirm segmentation accuracy and regions with poor segmentation accuracy resulting from poor image quality or misregistration were excluded. Cortical surfaces were automatically parcellated and combined to constitute the average cortical volume for total GM and for frontal, temporal, parietal, and occipital lobes. Each patient's intracranial volume was used to normalize the constituted regions. The volume of T1 hypointense lesions was also calculated using Freesurfer. Each volume of region was normalized to each patient's intracranial total brain volume.

We used BrainVoyager QX 2.6 for Linux (http://www.brainvoyager.com) to record the coordinations of each hyperintense WM and GM lesion on DIR SPACE imaging. The lesions were ranged using a bounding box in which all the intensities of voxels were fixed to a threshold for a clear visual distinction of lesions and parenchyma (http://support.brainvoyager.com/volumespace/107-volume-rendering/314-users-guide-masking-and-cutting.html). The number and total volume of the voxel-of-interest (VOI)s, thus lesions visible on DIR SPACE imaging were calculated. In this way, it was aimed to determine the demyelinating hyperintense lesion load in respect to the number and volume of lesions in patients with CIS.