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Neocortical volume decrease in relapsing–remitting multiple sclerosis with mild cognitive impairment

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Abstract

The aim of the study was to assess neocortical changes and their relevance to cognitive impairment in early relapsing–remitting multiple sclerosis (RRMS). Conventional magnetic resonance was acquired in 41 RRMS patients and 16 demographically matched normal controls (NC). An automated analysis tool was used to obtain measures of cortical brain volumes normalized for head size. Neuropsychological performance of MS patients was assessed through the Rao's Brief Repeatable Battery. We identified 18 cognitively preserved (MS-cp) and 23 cognitively impaired (MS-ci) MS patients. Values of normalized cortical volumes (NCV) in the whole MS sample were lower than those in the NC group ($p=0.01$). MS-ci patients showed NCV values lower ($p=0.02$) than did both MS-cp patients and NC. Moreover, we found a positive correlation between NCV values and measures of verbal memory ($r=0.51$, $p=0.02$), verbal fluency ($r=0.51$, $p=0.01$) and attention/concentration ($r=0.65$, $p<0.001$) in MS-ci patients. Furthermore, NCV values were significantly decreased in patients who scored lower on a greater number of tests ($r=-0.58$, $p<0.01$) in the MS-ci group. Only MS-ci patients had cortical atrophy significantly correlated with a poorer neuropsychological performance. Grey matter pathology may contribute to the development of cognitive impairment in MS from the earliest stages of the disease.

Keywords: Multiple sclerosis; Cognitive impairment; Gray matter atrophy

1. Introduction

With the use of magnetic resonance (MR) imaging computerized methods to calculate total and regional brain volumes [1], progressive reduction of total brain volumes has been consistently reported in multiple sclerosis (MS) patients [2–7]. Moreover, a selective involvement of the cerebral neocortex in MS has been identified in recent post-mortem [8,9] and in vivo [10–13] studies.

Cognitive impairment can be demonstrated in 40–65% of MS patients [14], even in the early stages of the disease [15,16]. Although the decrease in cognitive performance has been generally ascribed to white matter and, eventually, subcortical pathology [17–19], the correlation between increasing cognitive impairment and T_2-weighted (T_2-W) MR lesion load is generally modest [20–23]. Many MR studies have focused on the association between cognitive impairment and cerebral atrophy [20,24,25], even in the early phases of the disease [26,27]. The objective of this study, whose main results have been previously published [28], was to assess the relevance of selective neocortical involvement to cognitive impairment in a cohort of relapsing remitting (RR) MS patients with prevalently short disease duration and low levels of physical disability.

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2. Materials and methods

2.1. Patients

Study population consisted of 41 patients (30 women, 11 men) with clinically definite MS [29]. Patients' inclusion criteria were: age ≤55 years (mean=35.1±8.6, range=20–55, median=34), RR disease course, disease duration ≤10 years (mean=4.0±2.8, range=0.5–10 years, median=3.5), Expanded Disability Status Scale (EDSS) [30] ≤4.0 (mean 1.5±0.6, range=1.0–4.0, median=1.5). Mean educational level was 10.9±3.1 years (range=5–18, median=13). At the entry in the study, all RRMS patients were relapse-free and were not taking steroids for at least 1 month before MR and neuropsychological assessment. No patient was taking psychoactive drugs or substances that might interfere with neuropsychological performance. Two patients were being treated with beta-interferon-1a at the time of the study. All patients underwent identical neuropsychological and MR protocols (see below). An informed consent was obtained from all participants.

2.2. Clinical and neuropsychological assessment

A neurological evaluation, including disability assessment on the EDSS and neuropsychological testing, was performed within 1 week of MR examination by a neurologist and a neuropsychologist who were both blinded to the MR results. The neuropsychological performance of MS patients was tested using the Rao's Brief Repeatable Battery (BRB) [31], which incorporates tests of verbal memory acquisition and delayed recall (Selective Reminding Test, SRT and SRT-D), spatial memory acquisition and delayed recall (10/36 Spatial Recall Test, SPART and SPART-D), sustained attention, concentration, and speed of information processing (Paced Auditory Serial Addition Test, PASAT at 3 and 2 s; Symbol Digit Modalities Test, SDMT) and verbal fluency on semantic stimulus (Word List Generation, WLG). Moreover, depression was assessed through the Montgomery and Asberg Depression Rating Scale (MADRS) [32]. Since this study aims at comparing neocortical brain volumes in RR MS patients with mild cognitive impairment and without even mild signs of cognitive dysfunction, the failure of at least one test on the BRB was considered as a predetermined primary measure of cognitive impairment. Therefore, we considered those patients who scored two standard deviations below the mean normative values [33] on at least one test of the BRB, *cognitively impaired* (MS-ci) and those patients who had all tests of the BRB within normal limits, *cognitively preserved* (MS-cp).

2.3. MR examinations

The MR protocol included a transverse dual-echo, turbo spin-echo sequence (TR/TE1/TE2=2075/30/90 ms, 256×256 matrix, 1 signal average, 250×250 mm field of view) yielding proton density (PD) and T_2-W images with 50 contiguous 3-mm-thick slices, acquired parallel to the line connecting the anterior and posterior commissures. Subsequently, transverse T_1-W, gradient echo images (TR/TE=35 ms/10, 256×256 matrix, 1 signal average, 250×250 mm field of view) were acquired. This sequence yielded image volumes of 50 slices, 3 mm thick, oriented to match exactly the PD/T_2 acquisition.

2.4. MR data analysis

2.4.1. Lesion volumes

Classification of T_2-W lesion volume (LV) was performed for each patient by a single observer employing a user-supervised thresholding technique while being unaware of the subjects' identity. Lesion borders were determined primarily on PD weighted images. Information from T_2-W and T_1-W images were also considered, as the software used (MEDx) offered the ability to toggle between the three sets of images providing the operator with convenient access to the information in both data sets while defining lesions and facilitating the discrimination of CSF from periventricular plaques. Total LV was calculated by multiplying the lesion area by slice thickness. The coefficient of variation was about 5% in serial measurements.

2.4.2. Brain volumes

On T_1-W MR images, normalized volumes of the whole of the brain parenchyma and neocortical grey matter were measured using a method for total and regional brain volume measurements (the cross-sectional version of the SIENA software [34] [SIENAX]). SIENAX uses BET (Brain Extraction Tool, part of FSL–FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl) to extract the brain and skull from the MR images, as previously described [5]. A tissue segmentation program (FAST another part of FSL) [35] is then used to segment the extracted brain image into grey and white matter, CSF and background, yielding an estimate of total brain tissue volume. The brain-extracted MR images are registered on a canonical image in a standardized space (using the skull image to provide the scaling cue), a procedure that also provides a spatial normalization (scaling) factor for each subject. For selective measurements of neocortical volumes, a standard space mask (which includes ventricles, deep grey matter, cerebellum and brain stem) is used to separate segmented grey matter into neocortical and non-neocortical. The estimated volumes for a subject are then multiplied by the normalization factor to yield either the volume of the total brain tissue (NBV) or the normalized cortical volumes (NCV). This fully automated method provides results with an accuracy of 0.5–1% for single-time point (cross-sectional) measurements [5,34].