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Cognition in multiple sclerosis: Between cognitive reserve and brain volume

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ABSTRACT

Background: Several correlations between cognitive impairment (CI), radiologic markers and cognitive reserve (CR) have been documented in MS.
Obiective: To evaluate correlation between CI and brain volume (BV) considering CR as possibile mitigating factor.
Methods: 195 relapsing MS patients underwent a neuropsychological assessment using BICAMS. BV was estimated using SIENAX to obtain normalized volume of brain (NBV), white matter (NWV), gray matter (NGV) and cortical gray matter (CGV). CR was estimated using a previously validated tool.
Results: Pearson test showed a correlation between the symbol digit modality test (SDMT) score and NBV ($r = 0.38$; $p < 0.000$) NGV($r = 0.31$; $p < 0.000$), CGV ($r = 0.35$; $p < 0.000$) and CRI score($r = 0.42$; $p < 0.000$). Linear regression (dependent variable:SDMT) showed a relationship with CR scores ($p = 0.000$) and NGV($p < 0.000$). A difference was detected between cognitive impaired and preserved patients regarding mean of NBV($p = 0.002$), NGV($p = 0.007$), CGV($p = 0.002$) and CR Scores ($p = 0.007$). Anova showed a association between the presence of CI (dependent variable) and the interaction term CRIQ × CGV ($p = 0.004$) whit adjustment for age and disability evaluated by EDSS.
Conclusions: Our study shows a correlation between cognition and BV, in particular gray matter volume. Cognitive reserve is also confirmed as an important element playing a role in the complex interaction to determine the cognitive functions in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system caused by a complex interplay of genetic and environmental factors [1,2,3]. Heterogeneous clinical signs and symptoms characterise the disease from its early stages. Traditionally, symptoms are classified in visible (i.e., motor, gait, balance, optic) or invisible (i.e., mood disorder, bladder dysfunction, fatigue, pain, dysphagia) symptomatology [4,5,6]. Among invisible symptoms of the disease, growing attention has focused on cognitive functions. In fact, cognitive impairment is frequent in MS patients, with a variable prevalence regarding patient selection, neuropsychological diagnostic tools and definition of deficits [7,8].

In daily clinical practice, several issues limit the correct assessment of cognitive functions, replacing objective quantification with anamnestic evaluation. First, the majority of neuropsychological assessment methods are time consuming [7,8]. In addition, these diagnostic tools require the presence of qualified personnel. These conditions are not often met in the setting of daily clinical practice [7,8].

Recently, a new diagnostic tool was developed—the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)—to obtain a brief evaluation of the principal domains involved in cognitive impairment in MS as processing speed, verbal and visual memory. BICAMS can be performed even by healthcare staff without specific training [9]. Subsequent data also demonstrated significant correlation between BICAMS and more complex evaluations [10].

To better understand features of cognition in MS, several studies evaluated the principal neuroradiological markers [11]. Recent studies [12,13,14] have highlighted the role of gray matter, especially in the cortex, as a fundamental correlation of cognitive functions, considering the presence of focal lesions and volume change. However, the correlations between cognition with neuroradiological and clinical correlates

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are not sufficient to fully explain the presence of deficits [15]. For this reason, as in pathologies such as Alzheimer's disease and other inflammatory, degenerative and psychiatric disorders [16], some studies in MS have also explored the role of the cognitive reserve as a possible moderator of the relationship between structural damage and cognitive function [17,18]. Such studies have already recognized the protective role of the cognitive reserve against cognitive decline in MS [17,18].

Cognitive reserve can be defined as "the ability to optimize or maximize normal performance, and compensation, an attempt to maximize performance in the face of brain damage by using brain structures or networks not engaged" ([16], p. 448). The cognitive reserve cannot be measured directly but is generally evaluated by estimating some proxies that are directly related, such as education, occupational attainement and leisure activities, and participation in cognitive stimulating activities. These are considered protective agents against cognitive impairment.

In light of these considerations, the aims of our study were to evaluate the relationship between the presence of cognitive impairment, brain volume, and cognitive reserve in a cohort of MS patients.

2. Material and methods

2.1. Patient recruitment

Patients with diagnosis of relapsing remitting MS according to the 2010 McDonald Criteria [19] were recruited at Multiple Sclerosis Centre of University of Cagliari. Exclusion criteria were: corticosteroid administration or relapse in the previous 30 days, change in DMD therapy in the previuous six months, major comorbidity, intake of drugs with activity on the central nervous system, contraindications to MRI, physical disability that did not permit neuropsychological evaluation (i.e., blindness).

All included patients underwent MRI acquisition as well as clinical and neuropsychological assessment in the same week. The following clinical and demographic data were retrieved for all patients: gender, age, education, age at onset, Expanded Disability Status Scale (EDSS) and disease duration.

All included subjects signed informed consent form. The study received approval from the local ethics committee.

2.2. MRI acquisition

Brain MRIs were acquired in a single session using a Magnetom Avanto Scanner (Siemens, Enlargen) at 1.5 T. A sagittal survey image was used to identify the anterior commissure and posterior. The MRI protocol included the following sequence: 3D T1-Magnetization Prepared Rapid Acquisition Gradient-Echo (MPRAGE): echo time (TE): 2.37 ms; repetition time (TR): 1730 ms; inversion time (TI): 1050 ms; field of view (FOV): 244 mm; voxel size: 1 × 1 × 1 mm, (176 contiguous slices). Morevoer a dual-echo, turbo spin-echo sequence (repetition time/echo time 1/echo time 2 5 2075/30/90 milliseconds, 256 3256 matrix, 1 signal average, 250-mm field of view, 50 contiguous 3-mm slices) yielding proton density–weighted and T2-weighted images oriented to exactly match the MPRAGE image acquisition.

Brain parenchyma volumes were measured on T1W gradient echo images using the cross-sectional version of SIENA (structural image evaluation using normalization of atrophy) software, SIENAX (part of FSL 4.0: http://www.fmrib.ox.ac.uk/fsl/), and a previously described method to estimate the overall brain volume, normalized for head size. MRI analysis allowed us to obtain normalized brain volume (NBV), normalized gray matter volume (NGV), normalized white matter volume (NWV) and normalized cortical gray matter volume (CGV) [20].T1 hypo-intense lesion refilling was performed as previous described [21].

The radiologist was blinded to the results of the cognitive and neurological evaluation.

2.3. Neuropsychological assessment

All recruited patients underwent BICAMS, including a symbol digit modality test (SDMT) to evaluate information processing speed, California Verbal Learning Test-II (CVLT-II) to evaluate verbal learning and memory and brief visual memory test–revised (BVMT-R) to evaluate visual learning and memory. According to authors definition, each test was classified as altered if the T Score was below 35. Patients failed at least one BICAMS test were classified as cognitive impaired (CI) while patients without any BICAMS altered test were classified as not cognitive impaired (Not-CI). All evaluation was performed by an expert neuropsychologist in a quiet room. A correction for age, gender and education was performed using normative values for the Italian population [22].

Cognitive reserve was evaluated using the Cognitive Reserve Index Questionnaire (CRIQ), a previously described tool validated for Italian population [23]. This questionnaire obtains sub-items scores in four areas: Work, Education, Leisure Activities and Total.

The questionnaire evaluates how long and, if applicable, how often the various activities pertaining to each sub-item have been performed. The Italian and English versions of the questionnaire, with instructions for administration and correction, can be found at the following link: http://www.cirmanmec.unipd.it/index.php?page=criq.

Depression and anxiety were evaluated using the Beck Depression Inventory (BDI) [24].

The neuropsychologist was blinded to clinical and MRI features.

3. Statistical analysis

MRI measurements and some clinical variables between groups (cognitive impaired and not cognitive impaired) were compared using *t*-test for independent samples. Pearson test was used to evaluate correlation between continuous variable each other (MRI measures, BICAMS tests results, Cognitive Reserve Index Questionnaire Scores). Linear regression was used to evaluate relationship between BICAMS results as number of altered tests and T score of each BICAMS tests (dependent variable) and MRI measures and Cognitive Reserve Index Questionnaire Scores with adjustment for age and disability. ANOVA was used to evaluate as primary outcome the relationship between presence of cognitive impairment (dependent variable) and MRI measures and Cognitive Reserve Index Questionnaire Scores with adjustment for age and disability evaluated by EDSS.

Results were considered significant when $P \leq 0.05$. Analyses were performed using SPSS 20.0 for Mac.

4. Results

We recruited 195 MS patients. Their clinical and demographic features are the following: female gender: 122/195; mean age: 43 years (Standard deviation, S.D.: 11.2); mean of EDSS 2.48 (S.D.1.70); mean of year of education: 11.8 (S.D.:2.2); mean years of disease duration: 10.8 (S.D.: 8.0).

The ongoing DMD treatments during the study were: interferon for 64 patients (32.82%), glatiramer acetate for 42 (21.54%), fingolimod for 14 (7.18%), natalizumab for 30 (15.38%), dimethyl fumarate for 26 (13.3%), teriflunomide for 10 (5.13%) and azatioprine for 9 (4.62%). All patients were stable with ongoing treatment for at least six months.

Cognitive deficits (at least 1 test altered) were detected in 87/195 patients (44.6%) and classified as cognitive impaired (CI), while patients without the altered test were classified as not-cognitive impaired (not-CI).

The Pearson test showed a significant correlation between the T scores of each BICAMS test (and number of altered tests) and NBV, NGV and pNGV (Table 1a). In addition, the total CRI showed a statistically significant correlation with both the T score SMDT ($r = 0.421$; $p < 0.000$) and the T-score BVMT-R ($r = 0.367$; $p < 0.000$).