

Accepted Manuscript

Accepted Manuscript (Uncorrected Proof)

Title: Brain Atrophy and Physical and Cognitive Disability in Multiple Sclerosis

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To appear in: Basic and Clinical Neuroscience

Received date: 2019/06/4

Revised date: 2020/04/9

Accepted date: 2020/11/21

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Please cite this article as:

Casanova Peño, L. I., De Silanes De Miguel, C. L., de Torres, L., Emil Ortiz, M., Gil Moreno, M. J., Oyanguren Rodeño, B., & et al. (In Press). Brain Atrophy and Physical and Cognitive Disability in Multiple Sclerosis. *Basic and Clinical Neuroscience*. Just Accepted publication Aug. 15, 2021. Doi: <http://dx.doi.org/10.32598/bcn.2021.1893.1>

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Abstract

Introduction: brain atrophy is associated with physical disability in multiple sclerosis (MS), but there is a great variability between different studies and methodologies, and its use is still limited to research projects.

Objective: to analyze the relationship between several volumetric measurements and physical disability and cognitive functioning in MS patients in a clinical practice setting.

Material and methods: cross-sectional study. 41 patients (31 relapsing-remitting MS, 6 secondary-progressive MS and 4 primary-progressive MS). Whole brain volume (WBV), Gray Matter Volume (GMV) and T2 lesion load (T2L) were obtained using Icometrix[®] software. Physical disability was measured with the Expanded Disability Status Scale (EDSS), and cognitive status was evaluated with the Brief Repeatable Battery of neuropsychological tests (BRB-N). The relationship between brain volumes and EDSS was analyzed through lineal multivariate regression. The association between volumetry measurements and the number of affected cognitive domains was studied with negative binomial regression.

Results: GMV was associated with age ($b=-1.7$; $p=0.014$) and with EDSS ($b= -7.55$; $p=0.013$). T2L was associated with EDSS ($b= 2.29$; $p=0.032$). The number of affected cognitive domains was associated with clinical phenotype, worse in primary progressive MS (PPMS). There was not correlations between cognitive impairment and cerebral volumes.

Conclusions: Brain atrophy measurement is feasible in clinical practice setting, and it is helpful in monitoring the EDSS progression. Primary progressive phenotype is associated with greater risk of cognitive dysfunction.

Keywords: Brain atrophy, Cognitive dysfunction, Multiple sclerosis, Physical disability, MRI, Volumetry.

Introduction

Conventional MRI sequences continue to be the mainstay in the diagnosis and monitoring of multiple sclerosis (MS) patients. However, they mainly assess the inflammatory processes of MS and therefore its correlation with clinical outcomes is only partial [1-6]. Brain volumes analysis allow the evaluation of its neurodegenerative mechanisms. There is a robust evidence linking brain atrophy with disability in MS [7-16], and the incorporation of these techniques into the routine daily basis could be of great value to improve the follow-up of this disease. Nonetheless there are still many methodological and biological factors that generate an important variability in their results, and hold back its use to research projects [17]. The objective of this study is to analyze the relationship between advanced MRI sequences and physical disability and cognitive functioning in MS patients in a clinical practice setting in order to increase our knowledge of these techniques and move forward its implementation as another routine evaluation tool.

Material and methods

Cross-sectional study. We included MS patients according the McDonald 2010 criteria [18] attending the demyelinating diseases unit at Torreon University Hospital, Madrid, between December/2015 and December/2016. The patients gave their informed consent. The study complied with the Helsinki declaration and the results are completely confidential according to the personal data protection law (1999).

Clinical and epidemiological data were obtained retrospectively through review of the medical charts. Cognitive functioning was evaluated with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) [19], which consists of the Selective Reminding Test (verbal memory), the Paced Auditory Serial Addition Test (PASAT) (working memory), verbal fluency test and Symbol Digit Modalities Test (SDMT) (executive functions and speed processing) and Spatial Recall Test (SPART) (visual memory). The results were adjusted to age, sex and education level for the Spanish population [20]. We also obtained the Beck Depression Inventory-II (BDI-II) [21] and the Multiple Sclerosis Fatigue Scale [22, 23]. Advanced MRI evaluation was done by Icometrix[®] software through T1-3D and FLAIR-3D sequences. We analyzed whole brain volume (WBV), Gray Matter Volume (GMV) and T2 lesion load (T2). We defined cognitive dysfunction for a cognitive domain as a score lower than 1.5 standard deviations in its neuropsychological test. The association between brain volume measurements and clinical variables was studied with lineal multivariate regression, and between brain volumetry and number of affected cognitive domains with negative binomial regression. Statistical analysis was done with SPSS[®] software, version 19. Statistical significance was set at $p < 0.05$.

Results

41 patients were included. 31 relapsing-remitting MS (RRMS), 6 secondary progressive MS (SPMS) and 4 primary progressive MS (PPMS). 27 women. Mean age was 43.85 years (SD 11.1), and mean duration of MS was 8 years (SD 10.9). Mean EDSS was 2.6 (SD 1.9) and median EDSS 2 (Interquartile range (IQR): 1.0-4.0). Average education level was 11.5 (SD 3.3). Mean BDI-II score was 12.2 (SD 9), and mean MSFS 9.4 (SD 8.9). (Table I).

Average number of affected cognitive domains was 0.83 (SD 1.3). 25 patients (61%) obtained normal punctuations in all the tests. 7 patients had impairment in 1 cognitive domain, and 9 patients (22%) had two or more. (Table II). The most frequent affected cognitive domain was working memory (29.3%), followed by speed processing (17.1%) and verbal memory (12.2%). (Table III).

Multivariate regression analysis found a relationship between WBV and age ($b = -2.4$; $p = 0.037$), GMV with age ($b = -1.7$; $p = 0.014$) and EDSS ($b = -7.55$; $p = 0.013$), and finally T2L with EDSS ($b = 2.29$; $p = 0.032$).

Negative binomial regression analysis revealed an association between cognitive dysfunction and clinical phenotype (greater dysfunction in PPMS) (OR RRMS/PPMS 0.037, $p = 0.016$; OR SPMS/PPMS 0.02, $p = 0.028$), but not with MRI data (WBV $p = 0.383$; GMV $p = 0.495$ y T2L $p = 0.451$).

Discussion

In our study we obtained a proportion of cognitive dysfunction (impairment in 2 or more cognitive domains) of 22%, lower than other published series, normally ranging 40-60%. This difference could be explained to the composition of our sample with a predominance of RRMS, which is associated with a lesser cognitive damage [24-26], and low disability (global mean EDSS: 2.6, and mean EDSS in the RRMS group of 1.8). Nonetheless, cognitive impairment can be present even in early phases of the disease, and in patients with a good clinical situation [27-29], so the differences between different samples must be related to other factors not completely understood.

Regarding the affected cognitive domains we obtained similar results to other studies, with more repercussion in executive functions, speed processing and verbal memory [30, 31], although we also got a lower percentage of dysfunction of these domains compared to other studies.

When we analyzed the relationship between volumetry measurements and cognitive status we only obtained an association with the clinical phenotype. This result is in line with previous

works, in which cognitive dysfunction is more frequent and more intense among progressive forms of the disease [24-26]. In our study it is noteworthy the lack of association between cognitive impairment and advanced MRI sequences (WBV and GMV). In spite of the differences in the methodologies of different studies, most of them find correlations between brain volumes and physical and cognitive functioning [32, 33]. In our study is especially striking for the GMV which is one of the brain volume measurements with a greater impact in the disability in MS [34-37]. Again, these differences could be justified by methodological reasons, regarding the design of the study (cross-sectional instead of longitudinal), the characteristics of our sample (low frequency of cognitive impairment), as well as technical factors related to the acquisition and analysis of the images [38].

Multivariate regression showed a significant relationship between EDSS and GMV and T2L. In this regard there is also a great variability among different studies, but most of them find a positive association between these data, especially with the atrophy of the gray matter [38], and even with composite measurements of GMV-T2L [39-40]. At last, we also found a correlation between age and a loss of cerebral volume, both global and gray matter. This result could be expected as brain volume decrease physiologically with age and with a longer duration of the disease.

In conclusion, we can say that our study corroborates that brain atrophy measurements can be incorporated into the daily basis evaluation of MS patients. Specifically T2 load and Gray Matter volume are helpful in monitoring the EDSS progression. On the other hand, we also add evidence to the importance of the cognitive impairment and volumetric changes occurring in MS, as well as the differences between the different clinical forms of the disease (greater cognitive impairment in progressive MS). Finally some results, in particular the lack of association between volumetry data and cognitive dysfunction, show the importance of continuing the research of the neurodegenerative processes of MS.

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Table I. Clinical and demographic characteristics of our sample.

MS phenotype N RRMS/SPMS/PPMS	Sex M/F	Age (mean) (SD)	DD (mean) (SD)	EDSS Mean (SD) Median (IQR)	Ed. level Mean (SD)	BDI-II	MSFS
31 / 6 / 4	27:14	43,9 (11,1)	8 (10,9)	2,6 (1,9) 2 (1-4)	11,5 (3,3)	12,2 (9)	9,4 (8,9)
RRMS	22:9	41,9 (11)	11,2 (10,7)	1,8 (1,2) 2 (1-3)	11,9 (3,5)	12 (9,9)	6,6 (7,3)
SPMS	3:3	47,8 (9,6)	22,5 (7,9)	5,2 (1,7) 5 (3,5-7)	9,7 (2,3)	12,8 (5,3)	22 (4,7)
PPMS	2:2	53,3 (9,8)	3,5 (2,1)	4,5 (2,3) 4 (4-6,5)	11,3 (2,9)	13 (7)	10 (4)

N: Number of patients. RRMS: Relapsing-remitting multiple sclerosis; SP: secondary progressive multiple sclerosis; PPMS: primary-progressive multiple sclerosis. M/F: male/female. DD: Duration of the disease. EDSS: Expanded Disability Status Scale. Ed. Level: education level (years). BDI-II: Beck depression inventory-II; MSFS: Multiple Sclerosis Fatigue Scale.

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Table II. Number of affected cognitive domains

	0	1	2	3	4	5
N (%)	25 (61%)	7 (17%)	3 (7%)	3 (7%)	3 (7%)	0 (0%)

N: number of patients.

Table III. Results of Brief Repeatable Battery of Neuropsychological Tests

	Verbal memory SRT-S SRT-R SRT-D	Visual memory SPART-Total SPART-D	Working memory (PASAT)	Speed processing (SDMT)	Fluency
Normal	37 (90,2%) 36 (87,8%) 38 (92,7%)	41 (100%) 41 (100%)	29 (70,7%)	34 (82,9%)	38 (92,7%)
Impaired	4 (9,8%) 5 (12,2%) 3 (7,3%)	0 (0%) 0(0%)	12 (29,3%)	7 (17,1%)	3 (7,3%)

SRT-S: Selective reminding test-Storage; SRT-R: Selective reminding test-Retrieval; SRT-D: Selective reminding test-Delayed; SPART: Spatial recall test-Total; SPART-D: Spatial recall test-Delayed. PASAT: Paced auditory serial addition test. SDMT: Symbol digit modalities test.