Brain atrophy at onset and physical disability in multiple sclerosis

Atrofia cerebral al inicio de la enfermedad y discapacidad fisica en esclerosis multiple

Juan Ignacio Rojas[1], Liliana Patrucco[1], Cristina Besada[2], Laura Bengolea[2], Edgardo Cristiano[1]

ABSTRACT

The aim of this study was to investigate if brain atrophy in multiple sclerosis (MS) patients during the disease onset predicts long term disability. **Methods**: MS patients with follow-up time of at least 7 years from disease onset and with baseline and second magnetic resonance 12 months later were included to measure brain atrophy. Expanded Disability Status Scale (EDSS) was categorized in three groups, EDSS=0, EDSS=1 and 2.5 and EDSS>2.5, and used as disability measure. **Results**: Twenty-six patients were included. Mean atrophy during the first year in patients that reached an EDSS≥3 was -0.76±0.45 %, in patients with an EDSS between 1 and 2.5 was -0.59±0.56, while in patients with an EDSS of 0 it was -0.38±0.42 (p=0.003). **Discussion**: Brain atrophy rates during the first year of disease were predictive of disease progression in our population.

Key words: multiple sclerosis, brain atrophy, Expanded Disability Status Scale.

RESUMEN

El objetivo fue evaluar en pacientes con esclerosis múltiple (EM) si la atrofia durante el primer año de iniciada la enfermedad predecía la discapacidad física a largo plazo. **Métodos**: Pacientes con EM seguidos al menos durante 7 años del inicio de la enfermedad y con una resonancia magnetica al inicio y una segunda a los 12 meses de la inicial fueron incluidos para evaluar la atrofia cerebral. El Expanded Disability Status Scale (EDSS) fue categorizado en tres grupos, EDSS=0, EDSS=1 y 2.5 y EDSS>2.5, y usado como medida de la discapacidad. **Resultados**: Veintiséis pacientes fueran incluidos. El porcentaje de atrofia durante el primer año de iniciada la enfermedad en los pacientes que alcanzaron un EDSS≥3 fue de -0.76±0.45%, de -0.59 ±0.56 en pacientes con EDSS entre 1 y 2.5; de -0.38±0.42 en pacientes con EDSS de 0 (p=0,003). **Discusión**: La tasa de atrofia cerebral durante el primer año de la esclerosis múltiple fue predictora de progresión de la discapacidad.

Palabras-Clave: esclerosis múltiple, atrofia cerebral, Expanded Disability Status Scale.

Multiple sclerosis (MS) is a chronic, inflammatory and neurodegenerative disorder of the central nervous system (CNS) that evolves over time clinically by a variable course[1], characterized by the appearance of multiple areas of myelin destruction, axonal loss and reactive gliosis[2]. Research during the last decade demonstrated not only focal but also diffuse damage affecting white, as well as grey, matter and neurodegeneration occurring in early stages of the disease[2-6]. This damage and consequent tissue loss lead to spinal and brain atrophy, reflecting the underlying and permanent neuroaxonal destruction produced[2,5].

Most patients develop significant disability 15–30 years after the onset of the disease as an expression of the aforementioned[1,7]. However, long term prognosis is difficult to predict at the beginning, since clinical and paraclinical parameters currently used in the clinical setting are not reliable prognostic factors[8,9].

Few recent studies suggest that early brain atrophy changes would predict long term disability[3,5,6,10,11]. These studies have been carried out in MS and in clinically isolated syndrome (CIS) patients, reporting valuable, but inconclusive data, determining whether brain atrophy in early stages is a valuable predictor of disease progression[3,5,10,12].

A sensible and specific disease progression biomarker at the beginning of the disease might optimize treatment decisions[11].

The aim of the present study was to investigate in a South American cohort of relapsing-remitting MS (RRMS) patients whether brain atrophy changes during the first year following disease onset independently predicted long term physical disability.

[1]MD. Neurology Department, MS Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina;
[2]Neuroradiology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.
Correspondence: Juan Ignacio Rojas; MS Section, Hospital Italiano de Buenos Aires, Gascón 450; C1181ACH Buenos Aires - Argentina; E-mail: juan.rojas@hospitalitaliano.org.ar
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METHODS

Patients

This study was designed as a cohort study. Patients were identified from a longitudinal cohort of MS patients from the MS Center of the Hospital Italiano de Buenos Aires, Argentina. Patients with MS (Poser or McDonald criteria[13,14]), with a follow-up time of at least seven years from disease onset (defined as a single event of acute onset in the CNS suggestive of demyelination: for example, unilateral optic neuritis, brainstem and partial spinal cord syndromes[8]). Patients must also have a baseline and second magnetic resonance (MR) 12 months later.

Clinical and paraclinical data analyzed

Age, gender, clinical onset, Expanded Disability Status Scale (EDSS) at onset and during follow-up (every three months) and number of relapses were recorded. All patients were followed for at least seven years. Paraclinical data obtained at onset were: serological tests for differential diagnosis, including antinuclear antibodies, B12 vitamin and folate levels, VDRL and HIV tests, and oligoclonal bands (OB) detection in cerebrospinal fluid (CSF) and serum samples performed by agarose isoelectric focusing combined with immunoblotting and avidin-biotin amplified double-antibody peroxidase staining. Brain MR was performed on a 1.5 Tesla machine with a standard head coil (Siemens Avanto) within two months of the first demyelinating event. MR study included images obtained in the following sequences: T1-weighted conventional spin-echo; T2-weighted fast spin-echo; FLAIR spin-echo and T1-weighted conventional spin-echo after single doses of gadolinium (0.1 mg/kg). All images had a section thickness of 3 mm and an intersection gap of 0.5 mm. A second MR was performed between 11 and 14 months after the first one, with the same machine, with the same acquisition sequences and patient alignment.

Brain atrophy measurement

Images were processed and analyzed in the neurological lab of the Hospital Italiano MS Center by a blinded physician. For brain atrophy analysis, percentage of brain volume change (PBVC) between baseline and one year was estimated from T1 weighted images with SIENA software (Structural Image Evaluation using Normalization of Atrophy), a part of the FSL library[15]. SIENA extracts brain and skull images from two-timepoint whole-head input data. The two images are then aligned to each other. Both brain images are resampled into the space halfway between the two. Next, tissue segmentation is carried out in order to find brain/no brain edge points, and then perpendicular edge displacement (between the two time points) is estimated at these edge points. Finally, the mean edge displacement is converted into a global estimate of PBVC between the two timepoints[15].

In addition to brain atrophy rate, T2 weighted lesion volumes at baseline were calculated. Follow-up brain scans were also used to determine T2 weighted lesion volume at one year and thus calculate the one year change on T2 lesion volume. The software used to segment and calculate T2 lesion load was SepINRIA by lesion segmentation edition[16].

Ethics approval was obtained from the Medical Ethics Committee of the Hospital Italiano de Buenos Aires, as well as written informed consent from all participants included in the study.

Statistical analysis

Data were stored and analyzed in STATA 9.1 software. All PBVC were annualized prior to statistical analysis. Ordinal logistic regression was used to determine which clinical and paraclinical variable, including MR, were related to disability assessed by EDSS during follow-up. EDSS was categorized in three groups, EDSS=0, EDSS between 1 and 2.5, and EDSS≥3. These groups were chosen because they were previously considered to represent different levels of disability[5]. Clinical and paraclinical variables were evaluated for independent prediction of progression in a logistic regression model. Regarding MR variables, PBVC, baseline T2 lesion volume and T2 lesion volume changes between baseline and one year after onset MR were considered as potential predictors in the analysis, $p<0.05$ was considered statistically significant.

RESULTS

Twenty-six patients fulfilled criteria and consequently were included in the study. Fifteen patients were female, and mean age at onset was 32.8±9 years. Mean follow-up time of the cohort was 9.3±2.5 years. Patient's demographic, clinical and paraclinical data are displayed in Table 1. All patients were under immunomodulatory treatments. PBVC between baseline and year 1 MR was -0.57±0.63%/year. Mean T2 lesion volume at baseline was 1.756±3.650 mm^3, and mean increase in T2 lesion volume at 1 year was 756±2.768 mm^3 for the whole cohort. Eleven (42.3%) patients reached an EDSS≥3, 12 (46.2%) had an EDSS between 1 and 2.5, and 3 (11.5%) had an EDSS of 0 when analysis were undertaken. Mean PBVC during the first year in patients that reached and EDSS≥3 was -0.76±0.45 %/year, in patients that had an EDSS between 1 and 2.5 were -0.59±0.56, while in patients with an EDSS of 0 the PBVC during the first year was -0.38±0.42 ($p=0.003$) (Figure). PBVC at year 1 was the only variable associated with physical disability measured by EDSS. Other clinical and radiological variables did not show association with disability (Table 2, Figure).

Table 1. Demographics at baseline.

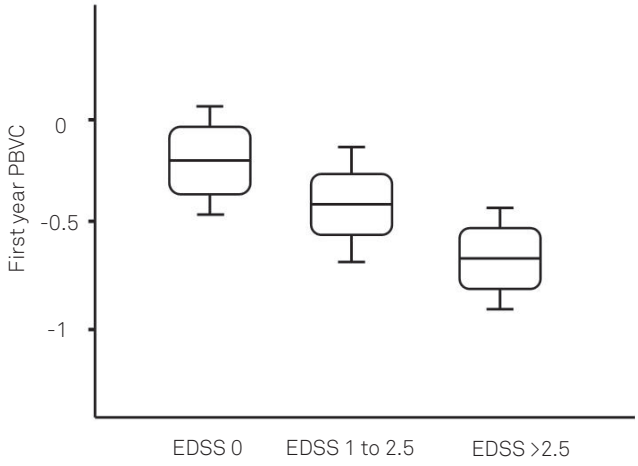
Variable	n=26
Mean age at onset (years)	32.8±9
Women (%)	15 (57.7)
Mean time follow-up (years)	9.3±2.5
EDSS at onset	1.1±0.3
Clinical syndrome at onset	
Optic neuritis (%)	9 (35)
Brainstem (%)	3 (11.5)
Polyregional (%)	11 (42)
Spinal cord (%)	3 (11.5)
Conversion to MS (%)	26 (100)
OB in CSF (%)	23 (88.5)
EDSS 0 during follow-up, n (%)	3 (11.5)
EDSS>0<3 during follow-up, n (%)	12 (46.2)
EDSS≥3 during follow-up, n (%)	11 (42.3)
Mean T2 lesion volume at baseline	1.756±3.650 mm^3
Mean PBVC at one year	-0.57±0.63 %/year
Mean increase in T2 lesion volume at one year	756±2.768 mm^3

EDSS: Expanded Disability Status Scale; OB: oligloconal bands; PBVC: percentage of brain volume change; CSF: cerebrospinal fluid.

Table 2. Ordinal logistic regression analysis.

Variable	p-value
Mean age at onset (years)	0.32
Female sex	0.44
EDSS at onset	0.18
OB in CSF (%)	0.22
Mean T2 lesion volume at baseline	0.12
Mean PBVC at year	<0.001
Mean increase in T2 lesion volume at one year	0.07

OB: oligloconal bands; CSF: cerebrospinal fluid; PBVC: percentage of brain volume change.



EDSS: Expanded Disability Status Scale; PBVC: percentage of brain volume change.

Figure. Box plot showing the median, interquartile, range for baseline to one year percentage of brain volume change in multiple sclerosis patients included in the study according to Expanded Disability Status Scale groups.

DISCUSSION

This study showed that brain atrophy changes during the first year after disease onset estimated by PBVC were associated with a worse outcome in terms of disability. It should be noted that the prediction of disability in patients with higher brain atrophy during the first year of disease onset was independent from other clinical and MR parameters, such as the presence of OB in CSF, EDSS at onset, T2 lesion load at baseline and increase of T2 lesion load at first year from disease onset (Table 2).

Currently, no studies have investigated the predictive value of lesion load and brain atrophy measures for disability at the beginning of MS with long clinical follow-up and none have been focused on MS patients in South America. One study, performed by Di Filippo et al.[5] in CIS patients with a prospective view considers clinical and MR aspects at the beginning of the disease to predict disability measured by EDSS, as well as by multiple sclerosis functional composite (MSFC). The study, that included nearly 100 patients, showed that in the univariate analysis the PBVC during the first year of disease onset was associated with disability, but, when logistic regression and multivariable adjustment were applied, increase in T2 lesion load over the first year and baseline Gd enhancing lesion number were found to be the only independent predictors of disability measured by the EDSS after six years. We found higher PBVC than Di Filippo et al. (-0.57±0.63 %/year versus -0.38±0.55 %/year), that might be explained by differences in the inclusion criteria: only half of their CIS cohort converted to MS while all of our patients had MS.

Another study[3] performed in patients with RRMS reported that brain atrophy rate measured by PBVC over two years was a predictor of disability after eight years.

Unlike Di Filippo et al.[5], we found no association between the increase of T2 lesion load during the first year and the increase of disability; however, a tendency did exist, though there was no association (p=0.07) due to the low number of patients included in our cohort.

Several limitations of this study must be noted. The design of the study, a retrospective cohort, means that some records might be missing. Notwithstanding, in the MS Center of the Hospital Italiano, patients are strictly followed every three months and records are standardized so that every patient included in this study, as well as those not included in the study, have their records fully registered. At the same time, physicians who follow patients have vast experience in the disease, with certified qualifications to perform the EDSS scale carried out on each patient visit (every three months). Another bias to consider is the impact that disease modifying drugs could have in disability progression during the follow-up[3]. However, as all patients converted to MS and, consequently, all patients received disease modifying drugs (DMD) during the follow-up, this bias could be partially controlled. A final limitation

that should be addressed is the modest number of patients included as a result of strict inclusion criteria designed to avoid bias in the population included, as well as in those patients followed, in determining disability during the course of their disease. Further analysis including more patients to confirm our initial findings in this MS population will be needed.

In summary, our study demonstrated that the higher PBVC during the first year of disease onset was associated with worse disability after seven years of follow-up in RRMS patients, independently from other clinical and MR parameters currently under evaluation. Further studies will elucidate whether this biomarker could be both sensible and specific in determining patients who will have an aggressive course of MS disease at onset, with the aim of tailoring care and specific treatment in this population.

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