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Thalamus volume change and cognitive impairment in early relapsing–remitting multiple sclerosis patients

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Abstract

Aims: The objective of the study was to assess whether changes in the volume of the thalamus during the onset of multiple sclerosis predict cognitive impairment after accounting for the effects of brain volume loss.

Methods: A prospective study included patients with relapsing–remitting multiple sclerosis less than 3 years after disease onset (defined as the first demyelinating symptom), Expanded Disability Status Scale of 3 or less, no history of cognitive impairment and at least 2 years of follow-up. Patients were clinically followed up with annual brain magnetic resonance imaging and neuropsychological evaluations for 2 years. Measures of memory, information processing speed and executive function were evaluated at baseline and follow-up with a comprehensive neuropsychological test battery. After 2 years, the patients were classified into two groups, one with and the other without cognitive impairment. Brain dual-echo, high-resolution three-dimensional T1-weighted magnetic resonance imaging scans were acquired at baseline and every 12 months for 2 years. Between-group differences in thalamus volume, total and neocortical grey matter and white matter volumes were assessed using FIRST, SIENA, SIENAXr, FIRST software (logistic regression analysis $P < 0.05$ significant).

Results: Sixty-one patients, mean age 38.4 years, 35 (57%) women were included. At 2 years of follow-up, 17 (28%) had cognitive impairment. Cognitive impairment patients exhibited significantly slower information processing speed and attentional deficits compared with patients without cognitive impairment ($P < 0.001$ and $P = 0.02$, respectively). In the cognitive impairment group a significant reduction in the percentage of thalamus volume ($P < 0.001$) was observed compared with the group without cognitive impairment.

Conclusion: We observed a significant decrease in thalamus volume in multiple sclerosis-related cognitive impairment.

Keywords

Multiple sclerosis, thalamus, cognitive impairment, brain volume

Introduction

Cognitive impairment (CI) is frequently observed in multiple sclerosis (MS) patients even in the early stages of the disease.[1–3] CI may reflect damage to brain structures, pathophysiological impairment or both that are usually detected too late to implement an effective preventive therapy.[4]

It has been shown that the thalamus is particularly affected in patients with MS.[5] The thalamus is a relay and integration centre connecting subcortical and cortical regions, thereby playing a crucial role in awareness, sensory, motor and cognitive functions.[5] There is no clear evidence, however, as to whether there is a relationship between structural volume changes of the thalamus and CI in the early stages of the disease.[6] Anatomical neuroimaging is crucial in detecting subtle structural abnormalities, especially in neurologically intact patients.[3]

The objective of our study, therefore, was to determine whether changes in the volume of the thalamus in a cohort of MS patients during the onset of the disease are associated with CI.

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Methods

The study was a prospective cohort study in which patients with relapsing–remitting multiple sclerosis (RRMS), defined according to validated criteria, were enrolled.[7] Clinical assessment was conducted in all cases by neurologists with experience in the management of demyelinating diseases (JIR, LP, JM and EC), considering demographic, clinical features and supplementary studies. Eligible patients were over 18 years of age and in the early stages of the disease. They had to have a minimum disability (less than 3 years since disease onset and one disability assessment score Expanded Disability Score Scale (EDSS) ≤ 3), no CI (measured by neuropsychological evaluation at baseline) and at least 2 years of follow-up. At the time of inclusion, patients had to be relapse free and without steroid treatment for at least 2 months. All consecutive potentially eligible patients were invited to participate in the study, and once included patients were evaluated clinically during follow-up with annual brain magnetic resonance imaging (MRI) and neuropsychological evaluations for 2 years. Disease onset was defined as the detection of the first sign/symptom that suggested central nervous system demyelination in the optic nerves, brain stem, spinal cord or other regions and that was not attributable to other diseases. Patients were recruited from Buenos Aires Multiple Sclerosis Center from January 2011 to January 2014. The centre has provided comprehensive medical and health services since 1990 through two main hospitals and 24 medical office buildings to over 164,456 members primarily located in the urban areas around the autonomous city of Buenos Aires, Argentina.

The study was approved by the research protocol ethics committee of the Italian Hospital of Buenos Aires, and all cases granted their informed consent prior to study enrollment.

Neuropsychological evaluation

Subjects underwent a comprehensive set of neuropsychological tests at study entry and then with annual evaluations. Evaluations involved the brief repeatable battery of neuropsychological tests,[8] the Stroop colour-word test, and the memory comparison test (MCT). *Z* scores were calculated based on the mean and standard deviations (SDs) of healthy people for executive functioning (CST, word list generation), verbal memory (SRT), information processing speed (symbol digit modalities test; SDMT), visuospatial memory (spatial recall test), working memory (MCT), attention (Stroop) and psychomotor speed (CST, SDMT) domains. Tests were performed in each patient by an experienced group of neurologists (MCF and AG) and a neuropsychologist (GM), unaware of the MRI results, using validated translations of the neuropsychological tests.

MRI assessment

For their enrollment, patients had to have at least one brain MRI scan within the first 30 days of study entry. The MRI scan was performed with a Siemens 1.5 Tesla MRI device and included images obtained in the following sequences: T1-weighted conventional spin-echo; T2-weighted fast spin-echo; fluid-attenuated inversion recovery (FLAIR) spin-echo; and T1-weighted conventional spin-echo after a single dose of gadolinium (0.1 mg/kg). All images had a section thickness of 3 mm and an intersection gap of 0.3 mm. The scanner did not undergo hardware upgrade during the study period.

An analysis was made of each patient's MRI performed at study entry and then annually during 2 years of follow-up to measure total brain volume (TBV), total grey matter volume (GMV), neocortical grey matter volume (NGMV) and white matter volume (WMV), as well as lesion volume.

Brain volume measurement

Using the volume sagittal sequences in MRI T1, measurements of brain volumes (TBV, GMV, NGMV and WMV) were taken by applying the brain atrophy measurement method and automated software SIENAXr.[9] To carry out the measurement, SIENAXr uses the brain extraction tool, which is part of FSL-FMRIB's software library to extract the brain and skull from magnetic resonance images. Once extracted, a tissue segmentation program (FAST, another software program from the FSL software library)[10,11] then segments the image obtained into neocortical grey matter, white matter and estimated cerebrospinal fluid once the TBV, GMV, NGMV and WMV are segmented. Thus SIENAXr is able to obtain accurate brain volumes in an automated fashion. Once obtained, the brain volume is then multiplied by a pre-established standardisation factor already incorporated into the software that establishes standard final brain volumes for the patient. The total normalised thalamic volume was estimated using FIRST (part of FSL) and normalised using the V-scaling factor from SIENAX. The sum of the normalised left and right thalami was used as one thalamic volume measure.[6] For atrophy measurement, three-dimensional T1-weighted images sequence (MPRAGE, 176 partitions; flip angle 15°, 1.2 mm slices, matrix size 256×256, voxel size $1 \times 1 \times 1\,mm^3$, repetition time (TR) 1900 ms; echo time (TE) 4.0 ms; inversion time (TI) 300 ms) was used (Figure 1).

Labeling of T1 lesion volume was performed by employing a semi-automated segmentation technique based on user-supervised local thresholding (SepINRIA software).[12] The value of T1 total brain lesion volume was calculated by multiplying the lesion area by slice thickness.

Study design and data collection

At study entry all patients were without cognitive impairment (non-CI) after neuropsychological assessment. The cohort was followed for 2 years and

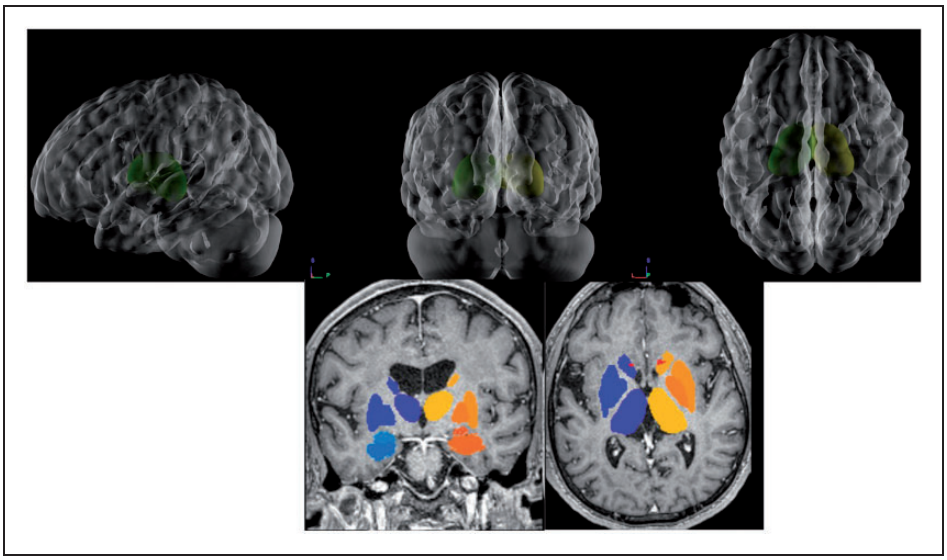

Figure 1. Normalised thalamic volume estimated using FIRST software. Colours are only for illustration of thalamic volume estimated using FIRST (part of FSL) and normalised using the V-scaling factor from SIENAX. The sum of the normalised left and right thalami was used as one thalamic volume measure.

subsequently re-assessed. After re-assessment, the cohort was subdivided into two groups, representing the CI and non-CI groups, using cognitive domain Z scores. All patients who scored at least 2 SDs below controls on at least two domains were designated as CI.[13] The remaining patients (scoring better than 2 SDs below controls) were designated as non-CI. The Z scores from all cognitive domains were also averaged to form one summary statistic of average cognition, which was used to explore relations between MRI metrics and cognition but was not used to form patient groups.

Statistical analysis

Means and percentages were used to describe variables at baseline. After 2 years of follow-up and the identification of CI and non-CI patient groups, comparisons were performed using the Mann–Whitney test, Kruskal–Wallis test and chi-square test, as appropriate. A stepwise logistic regression analysis was performed to assess the contributions of the main demographic (age, sex and years of education), clinical (disease duration, EDSS) and MRI (T1 lesion volume, WMV, NGMV, percentage of brain volume change and thalamus volume) variables in predicting the CI status. Forward and backward stepwise analyses were conducted using the Wald statistic as a criterion, with $P = 0.05$ for entry and $P = 0.10$ for removal. STATA 10.1 software was used for data collection and analysis.

Table 1. Patients demographic at baseline.

Included patients	$N = 61$
Mean age, years (SD)	38.4 ± 3 (5.7)
Female sex, *n* (%)	35 (57)
EDSS at study entry	1.5 ± 1
Disease-modifying treatment, *n* (%)	61 (100)
Mean follow-up time, years (SD)	3 ± 0.5
Years of education, SD	12 ± 3
Disease duration, months (SD)	10 ± 6
Cognitive impairment, *n* (%)	0

Table 2. Brain volumes at baseline of included patients.[a]

	All included patients ($n = 61$)
T1 lesion volume, mm^3	254 ± 54
TBV $\times 10^6 mm^3$	1.69 ± 0.3
WMV $\times 10^6 mm^3$	1.1 ± 0.13
NGMV $\times 10^6 mm^3$	0.59 ± 0.1
PBVC	NA
TV ml	17.7 ± 0.7

[a]At inclusion all patients were cognitive preserved after baseline neuropsychological assessment. TBV: total brain volume; WMV: white matter volume; NGMV: neocortical grey matter volume; PBVC: percentage brain volume change; TV: thalamus volume; NA: not applicable.

Results

Between January 2011 and January 2014, a total of 61 RRMS patients was enrolled, with a mean age of 38.4 years; 35 (57%) were women. The mean EDSS of the cohort was 1.5, and all patients were under disease-modifying treatment at study entry. The mean follow-up time of the entire cohort was 3 ± 0.5 years. The disease duration of included patients was 10 ± 6 months and the mean years of education was 12 ± 3 years (Table 1). Brain volumes at study entry are displayed in Tables 1 and 2. After 2 years of follow-up, 25 (41%)

patients showed abnormal performance on attention/information; 20 (33%) on executive function; nine (15%) on verbal fluency; seven (11%) on verbal memory and two (3%) showed abnormal performance on spatial memory. A total of 17 (28%) patients fulfilled criteria for CI while 44 (72 %) did not (Table 3). In the CI group a significant reduction in thalamus volume ($P < 0.01$, odds ratio (OR) 1.97, 95% confidence interval 1.73–2.24) was observed compared with the non-CI group after accounting for the influence of demographics and brain volume loss after multivariate analysis was performed (Table 4). The percentage of brain volume change per year also shows a significant difference ($P < 0.001$, OR 2.13, 95% confidence interval 1.63–2.31) between groups, while for WMV no statistical gap was shown (Tables 3 and 4, Figure 2).

Table 3. Demographic and brain volumes after 2 years' follow-up time between CI and non-CI groups.

	At 2 years		
	Non-CI	CI	*P* value
Mean age, years (SD)	40.1 ± 4	42 ± 3	0.45
Female sex, *n* (%)	19 (31)	16 (26)	0.19
EDSS	2 ± 1.1	2.5 ± 0.5	0.09
Years of education, SD	13 ± 2	11 ± 3	0.27
T1 lesion volume, mm^3	353 ± 67	401 ± 165	0.12
TBV $\times 10^6 mm^3$	1.56 ± 0.25	1.5 ± 0.9	0.01
WMV $\times 10^6 mm^3$	1.05 ± 0.14	1.0 ± 0.1	0.12
NGMV $\times 10^6 mm^3$	0.54 ± 0.02	0.5 ± 0.03	0.02
PBVC	-0.5%	-0.8%	<0.01
TV ml	17.1 ± 1	15 ± 0.09	<0.01

CI: cognitive impairment; non-CI: no cognitive impairment; TBV: total brain volume; WMV: white matter volume; NGMV: neocortical grey matter volume; PBVC: percentage brain volume change; TV: thalamus volume.

Table 4. Regression analysis assessing the contributions of the demographic, clinical and magnetic resonance imaging variables in predicting cognitive impairment.

Variable	OR	*P* value	95% CI
Age	1.12	0.24	0.92–1.19
Gender	0.97	0.56	0.78–1.15
EDSS	1.24	0.16	0.95–1.34
Education	0.76	0.09	0.56–1.26
T1 lesion volume	1.14	0.12	0.85–1.32
TBV	1.45	0.10	0.79–1.57
WMV	1.23	0.19	0.82–1.51
NGMV	1.72	0.05	0.99–2.1
PBVC	2.13	<0.01	1.63–2.31
TV	1.97	<0.01	1.73–2.24

TBV: total brain volume; WMV: white matter volume; NGMV: neocortical grey matter volume; PBVC: percentage brain volume change; TV: thalamus volume; CI: confidence interval.

Complementary to other measurements, the NGMV demonstrates significant differences when comparing the CI group with the non-CI group (Tables 3 and 4). The group of CI patients exhibited significantly slower information processing speed and attentional deficits compared to those with no CI symptoms ($P < 0.001$ and $P = 0.02$, respectively).

Discussion

In our study, we observed a significant decrease in thalamus volume in MS patients who developed CI after 2 years of follow-up time, after controlling for the influence of global and neocortex atrophy. We also observed a significant decrease in NGMV together with a decrease in the percentage of brain volume loss during the follow-up.

Thalamic atrophy was previously shown to be more severe in a progressive phenotype and was also related to increased disease duration and more severe disability.[14,15] Previous cognition studies have shown that thalamic atrophy is one of the most important predictors of cognitive performance in MS.[16–18] Schoonheim et al., in an inception cohort of 157 patients, found a significant decrease in thalamic volume in MS patients compared with healthy controls as well as a more severe reduction in thalamic volume in MS patients with CIt when compared with patients without CI and mild CI.[6] Thalamic volume was significantly lower in MS patients compared with healthy controls, with the lowest volumes in MS-affected patients with severe CI when compared with cognitive preserved and also with mild CI MS patients.[6] They additionally found that the thalamic skeleton of fraction of anisotropy was decreased in severe CI patients compared to healthy controls. In that study, the thalamic volume was shown to be an independent predictor in a linear regression model, together with male sex and a lower level of education of CI in MS patients, while lesion and whole-brain volumes were not significant predictors.[6] Bisecco et al., in a multicentre study performed in Europe, found that in MS cognitive impaired compared to cognitive preserved patients an increase in fractional anisotropy of frontal, motor, postcentral and occipital connected connectivity defined regions ($0.002 < P < 0.02$).[19] Affected patients also experienced more pronounced atrophy in anterior thalamic regions and abnormal diffusion tensor magnetic resonance indices of all cortico-thalamic tracts.[19] Damage of specific cortico-thalamic tracts explained global cognitive dysfunction and impairment of selected cognitive domains better than all other magnetic resonance variables in the study performed.[19] A possible explanation of previous findings could be that when thalamic neurodegeneration reaches a critical point, changes in diffusion and functional connectivity could appear, which would be the first step of strong cognitive dysfunction; however, more research is needed to elucidate these findings.[6] There may be several mechanisms by which the

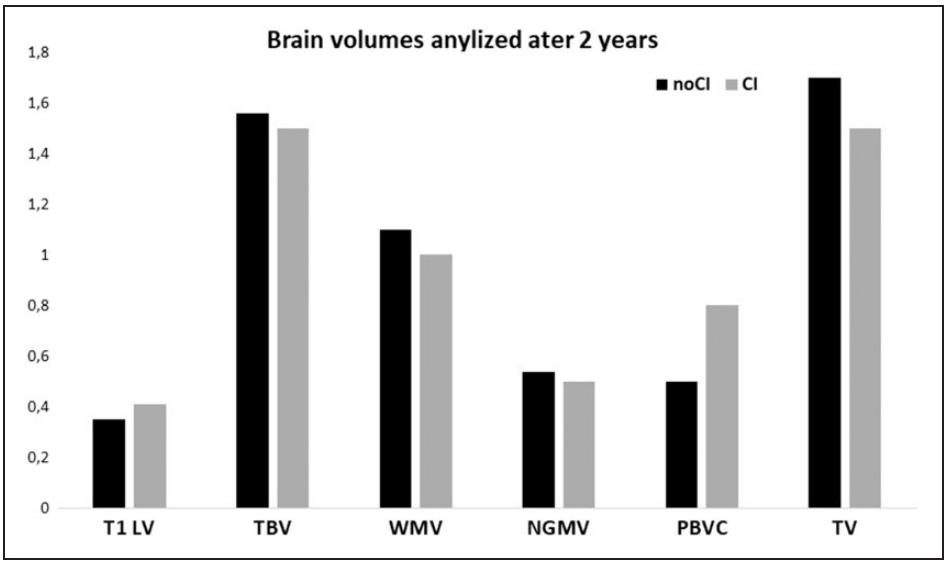

Figure 2. Brain volumes after 2 years' follow-up time between CI and non-CI groups. CI: cognitive impairment; non-CI: no cognitive impairment; TBV: total brain volume; WMV: white matter volume; NGMV: neocortical grey matter volume; PBVC: percentage brain volume change; TV: thalamus volume.

thalamus is vulnerable to volumetric loss. It is possible that Wallerian degeneration can follow the known white matter injury in MS, resulting in neuronal loss in both cortical and subcortical grey matter structures, as has previously been described in traumatic injury case.[18,20] Among the cognitive measures obtained in this study, slower processing speed was a finding in the CI group and was shown to be correlated with reduced volume in several cortical and subcortical structures, including the thalamus in previous reports.[21] However, processing speed is very non-specific, and while slowing may be related to thalamic involvement, it is difficult to rule out other factors in MS. The deficit in attentional tests found in our study may be explained by thalamic volume reduction, as well fronto-striatal circuits linking dorsolateral prefrontal, anterior cingulate and orbitofrontal cortex regions[22] by the striatum/globus pallidus to ventral anterior and medial dorsalnuclei of the thalamus.[23] We hypothesise that the attentional deficit in our patients could be associated with a dysfunction in pulvinar. Unfortunately, we do not have thalamus segmentation data as to whether there is an atrophy in certain nuclei.

While a greater number of patients enrolled may increase the strength of the analysis, the measurement of structures and the accuracy with which they are obtained permit an analysis powerful enough to detect differences among groups. It is important to note that a longitudinal design in which connectivity is studied together with brain volume structures would allow a better evaluation of damage progression and its correlation with CI in MS.

In conclusion, we observed a significant decrease in thalamus volume in MS-related CI after controlling for the influence of global and neocortex atrophy. Future studies will have to investigate the link between structural and functional connectivity of the thalamus in relation to CI to elaborate on the (longitudinal) interplay between structure and function in MS.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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