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Subcortical grey matter volumes predict subsequent walking function in early multiple sclerosis

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ABSTRACT

Background: Atrophy of subcortical grey matter structures has been reported to be associated with clinical measures of disability in multiple sclerosis (MS) patients. It is not clear if the degree of tissue loss in patients with very early MS is associated with changes in disability measures.
Objective: To study the association between subcortical grey matter structure volumes and clinical disability outcomes.
Methods: Relapsing MS patients within 12 months of clinical onset were enrolled in a neuroprotection trial of riluzole versus placebo with up to 36 months of follow-up and serial brain MRI and clinical assessments. MRI metrics, including thalamic, putamen, caudate, pallidum and cerebellar cortical volume, were measured by an automated, custom-made FreeSurfer pipeline. Volumes were normalized for head size. Clinical measures included EDSS, MSFC scores and its components. Mixed model regression measured time trends and associations between imaging and clinical outcomes.
Results: 42 patients with a mean follow-up of 30.6 months were analyzed in this study. There was a statistically significant decrease in thalamus, caudate and putamen volumes, but not cerebellar cortical and pallidum volumes during the follow-up period. Baseline thalamus, caudate and putamen volumes predicted subsequent changes in the timed 25-ft walk test ($p = 0.036$) and MSFC ($p = 0.024$). There was a trend for an association between baseline caudate volume and subsequent change in the timed 25-ft walk test ($p = 0.084$). No association between baseline imaging and subsequent EDSS changes were seen.
Conclusion: Subcortical grey matter volumes at early stages of MS are associated with subsequent changes in disability measures.

1. Introduction

MS has been traditionally defined as an inflammatory, demyelinating disease affecting the white matter in the central nervous system (CNS); however, grey matter pathology is increasingly recognized to occur early and throughout the disease course, and is associated of irreversible disability [1].

Grey matter pathology can be evaluated by different methods, including studying grey matter lesions, volumetric changes or assessment of diffusion, magnetization transfer or spectroscopic changes [2]. Atrophy of the grey matter structures in the brain and spinal cord is a surrogate for neuronal loss. It better correlates with or predicts reaching disability milestones as compared to the markers of white matter injury [3]. Grey matter atrophy has been reported in patients within earliest stages of MS. [4–7] It has also been shown to correlate with physical disability [6,8,9]. However; this association has been shown in cross-sectional studies and in patients with long-standing disease. Studying neuronal loss and its relevance to clinical measures of performance and disability will help design future neuroprotection trials in early MS which might be an ideal time for intervention. Our aim was to study the cross-sectional and longitudinal associations of brain deep grey matter structures and disability outcomes as measured by Expanded Disability Status Scale (EDSS), timed 25-ft walk (T25FW), 9-hole peg

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test (9HPT) and paced auditory serial addition test (PASAT) in very early MS.

2. Methods

We analyzed data from a 2-year randomized double blind, placebo controlled trial of riluzole vs placebo. Details of the study, inclusion and exclusion criteria and the report of primary and secondary endpoints have been previously reported [10]. Relapsing-remitting and clinically isolated syndrome (CIS) patients within 12 months of symptom onset were offered participation in the trial. The first half of patients who completed the 24-month core study were offered continuation for another 12 months (mean follow-up of 30.6 months). Three months after randomizations, all patients started weekly interferon beta-1a. The study was approved by the institutional review boards of the participating centers (UCSF, OHSU). Informed consent was obtained from all participants before enrollment. Because riluzole, as compared to placebo did not show any significant effect on the primary and secondary outcomes of the study (including no effect on the clinical measures or grey matter structures), we combined both treatment groups for the analyses of the associations.

2.1. Clinical measurements

EDSS and MSFC [including PASAT3′] were used to monitor neurological changes [11,12]. Patients had screening and baseline MSFC to allow for practice effects. The screening MSFC was not used in the analyses.

2.2. MRI acquisition and post-processing

Details of the MRI protocol have been described previously [10]. Brain MRIs were performed on 3.0 Tesla MRI scanners equipped with an 8-channel phased array coil (General Electric, Milwaukee, WI) at baseline and months 6, 12, 18, 24 and for half of patients, at month 36. The standardized study protocol included a 3D, T1-weighted, volumetric, 1 mm-isotropic inversion recovery spoiled gradient-echo sequence (3D-IRSPGR, $1 \times 1 \times 1$ mm^3, 180 slices), which was used for all brain volume measurements, as well as a 2D multislice dual spin echo sequence (proton density and T2-weighted, 1 mm × 1 mm × 3 mm, no gaps).

T1 lesion masks were used to inpaint 3D-IRSPGR images prior to submission to FreeSurfer [13] to avoid voxel misclassification errors. Anatomic segmentation was performed using FreeSurfer's longitudinal processing stream (v5.3; probabilistic atlas for subcortical segmentation) [13]. FreeSurfer's output was reviewed, manually corrected and reran as needed by an experienced MRI postprocessor. Deep grey and cerebellar cortical volumes were extracted directly from FreeSurfer's output and normalized for head size using the estimated total intracranial volume, also taken from FreeSurfer. The resulting values are unitless.

2.3. Statistical analysis

Descriptive statistics for patient characteristics were presented either as percentages (%) or using mean ± standard deviation (SD). Spearman correlation was used to assess the cross-sectional association of clinical and imaging outcomes at baseline. Mixed effects regression models were used to account for the longitudinal nature of the data. To separate the between-participant from the within-participant effects, the baseline values and change from the baseline values of imaging markers were entered in the model as predictors [14]. We performed adequate model checking, including evaluation for non-linearity in the association between predictors and outcomes. We considered a nominal p value of ≤0.05 as statistically significant and employed Bonferroni method for adjusting the p-values for multiple hypothesis testing. All analyses were conducted in Stata Version 13.1 (Stata Corp, College Station TX).

3. Results

3.1. Patient's characteristics

Baseline demographic, clinical and radiographic characteristics of patients who were recruited in the study are shown in Table 1. Forty two of 43 patients enrolled in the clinical trial contributed to the longitudinal assessment of the association between MRI and clinical measures. MRI images of one patient could not be processed by the FreeSurfer. Only 5 patients (2 in the riluzole group and 3 in the placebo group) switched to another disease-modifying medication during the study, as treating physicians determined there was clinical or radiological disease activity on intramuscular weekly IFN-beta 1a. Relapse rate was 0.22 per year in the placebo and 0.15 in the riluzole group ($p = 0.27$).

3.2. Longitudinal changes in grey matter structures

During the study, there was a statistically significant decrease in the volume of thalamus (1.4% per year, 95%CI: 0.6%–2.3%, $p = 0.001$), caudate (2.8% per year, 95%CI: 2.1%–3.5%, $p < 0.001$) and putamen (2.5% per year, 95CI: 1.5%–3.4%, $p < 0.001$), but not cerebellar cortical and pallidum volumes (Fig. 1 and Table 2).

3.3. Longitudinal changes in the clinical measures

During the study, there was a statistically significant worsening in EDSS (0.18 point/year, 95%CI: 0.07–0.28, $p = 0.005$). There was no statistically significant longitudinal change in other clinical measures over time.

Table 1
Baseline demographic, clinical and MRI.

Demographics and clinical characteristics ($N = 42$)	
% Female	71%
Mean age in years ± SD	35.5 ± 9.6
Mean disease duration in months ± SD	7.5 ± 4.9
% White	98%
Mean education in years ± SD	15.5 ± 3.2
Median EDSS (range)	2.0 (0.0–5.5)
Mean PASAT 3′ ± SD	49.8 ± 10.6
Mean T25FW (seconds) ± SD	5.1 ± 2.8
Mean 9-HPT (dominant hand; seconds) ± SD	19.8 ± 4.3
Mean MSFC score ± SD	0.010 ± 0.794
Brain Imaging	
Mean nBPV (cm3) ± SD	1640 ± 118
Mean nGMV (cm3) ± SD	908 ± 70.7
Mean T2 lesion volume (cm^3) ± SD	4.3 ± 5.6
Mean thalamic volume (cm^3) ± SD	7.5 ± 1.0
Mean thalamic fraction ± SD[a]	9.8 ± 0.8
Mean cerebellar cortical volume (cm^3) ± SD	110.5 ± 13.8
Mean cerebellar cortical fraction ± SD[a]	72.5 ± 6.6
Mean caudate volume (cm^3) ± SD	3.7 ± 0.5
Mean caudate fraction ± SD[a]	4.9 ± 0.5
Mean putamen volume (cm^3) ± SD	5.4 ± 0.7
Mean putamen fraction ± SD[a]	7.1 ± 0.9
Mean globus pallidus volume (cm^3) ± SD	1.2 ± 0.2
Mean globus pallidus fraction ± SD[a]	1.6 ± 0.2

EDSS: Expanded disability status scale; PASAT: Paced auditory serial addition test; T25FW: Timed 25-ft walk test; 9-HPT: 9-hole peg test; MSFC: Multiple sclerosis functional composite; nBPV: Normalized brain parenchymal volume; nGMV: Normalized grey matter volume.

[a] Derived by dividing the structure volume by total intracranial volume; multiplied by 1000. The resulting numbers are unitless.