Multiple Sclerosis and Related Disorders 5 (2016) 29–33

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Longitudinal associations between brain structural changes and fatigue in early MS

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ARTICLE INFO

Article history:
Received 7 August 2015
Received in revised form
15 October 2015
Accepted 20 October 2015

Keywords:
Multiple sclerosis
MRI scans
Grey matter
Atrophy
Fatigue

ABSTRACT

Background: Fatigue is a common and disabling symptom of multiple sclerosis (MS) patients. Structural changes in several brain areas have been reported to correlate with fatigue in MS patients but none consistently.
Objective: To study the association between global and regional measures of brain atrophy and fatigue in patients with early relapsing MS.
Methods: Clinically isolated syndrome and 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. MRI metrics included brain volumes measured by SIENAX normalized measurements [normalized brain parenchymal volume (nBPV), normalized normal-appearing white and gray matter volume (nNAWMV and nGMV)] and T2 lesion volume (T2LV). Cortical thickness, thalamic volume and cerebellar cortical volume were measured using Freesurfer's longitudinal pipeline (v5.3) and a lesion inpainting approach. Fatigue was evaluated using the Modified Fatigue Impact Scale (MFIS). Mixed model regression measured time trends and associations between imaging and fatigue severity, adjusting for age and sex.
Results: Forty-three patients (mean age 36 years; 31 females) were enrolled within 7.5 ± 4.9 months of symptom onset. Baseline and change over baseline in lesion volumes, grey matter, white matter, basal ganglia and total parenchymal volumes were not associated with change in MFIS score over time. Lower thalamic volume at baseline predicted increasing physical subscale of MFIS score during the study ($p=0.017$). There was a trend toward baseline thalamic volume and cerebellar cortical volume predicting subsequent change in total MFIS score ($p=0.055$ and 0.082 respectively). On-study change in thalamic or cerebellar cortical volume was not associated with on-study change in MFIS score.
Conclusion: Global measures of tissue loss are not strongly associated with fatigue in patients with early MS. However, thalamic and cerebellar cortical atrophy may be predictive of subsequent changes in fatigue in these patients.

1. Introduction

Fatigue is a common and disabling symptom in MS patients (Krupp et al., 1988). Although comorbidities (such as pain, sleep dysfunction and depression) contribute to the development and severity of this symptom, primary fatigue in MS is thought to arise from structural and functional changes in the brain resulting from an inflammatory demyelinating and neurodegenerative process (Schwid et al., 2002). Despite the characteristic white matter inflammation in MS, global white matter damage measured by total T2 lesion load does not appear to correlate with severity of fatigue in MS patients (Bakshi et al., 1999; van der Werf et al., 1998) while changes in cortical, thalamic and basal ganglia structure and function have been proposed to play important roles in MS fatigue (DeLuca et al., 2008; Téllez et al., 2008). These studies have been performed in patients with long standing MS. It is not clear if these findings hold up in patients with early disease. Our aim was to study cross-sectional and longitudinal associations of MRI measures and fatigue in early MS.

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http://dx.doi.org/10.1016/j.msard.2015.10.006
2211-0348/

2. Methods

This is an exploratory analysis of a 2-year randomized, double-blind, placebo-controlled trial of riluzole versus placebo in patients with clinically isolated syndrome or MS. Subjects had symptom onset within the previous 12 months and concomitantly received intramuscular interferon beta-1a. Details of trial design, inclusion and exclusion criteria and the report of riluzole effect on primary and secondary end points of the trial have been published elsewhere (Waubant et al., 2014). The study protocol was approved by the University of California, San Francisco (UCSF) and Oregon Health and Sciences University (OHSU) Committees on Human Research. All patients provided written informed consent prior to enrollment.

2.1. Fatigue assessment

Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS) (Fischer et al., 1999), a 21-item self-reported measure of fatigue that assesses impact on psychosocial, physical and cognitive function. The total score ranges from 0 to 84 (the higher the score, the worse the fatigue). MFIS items can be aggregated into 3 subscales: physical (score range 0–36); cognitive (score range 0–40) and psychosocial (score range 0–8). The MFIS is a valid and reliable tool for assessing fatigue, has a low floor and ceiling effect and captures both physical and cognitive aspects of fatigue better than another commonly used tool, the Fatigue Severity Scale (FSS) (Amtmann et al., 2012). It is the recommended tool for assessing fatigue in clinical practice and research in MS patients.(Braley and Chervin, 2010) The MFIS was administered at baseline, months 3, 6, 12, 18, 24 and for the first half of patients enrolled in the study, months 30 and 36.

2.2. MRI acquisition and post-processing

Details of the MRI protocol have been described previously (Waubant et al., 2014). Brain MRIs were performed on 3.0 T 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- and T2-visible white matter lesions were manually segmented at the baseline time point by an experienced MRI reader using commercially available Osirix software. These regions of interest were converted to binary lesion masks. After co-registration of follow up images, lesion masks at subsequent time points were generated using an in-house, automated lesion segmentation pipeline, and T2 lesion volume was calculated at each time point.

T1 lesion masks were used to inpaint 3D-IRSPGR images prior to submission to SIENAX (Smith et al., 2002) and FreeSurfer (Reuter et al., 2012) to avoid voxel misclassification errors. Normalized normal-appearing white matter volume (nNAWMV), normalized grey matter volume (nGMV) and normalized brain parenchymal volume (nBPV) were derived from SIENAX output. Anatomic segmentation and cortical thickness measurements were performed using FreeSurfer's longitudinal processing stream (v5.3; Desikan-Killiany atlas for surface parcellation and probabilistic atlas for subcortical segmentation) (Reuter et al., 2012). In order to ensure accuracy, FreeSurfer's output was reviewed, manually corrected and rerun 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.

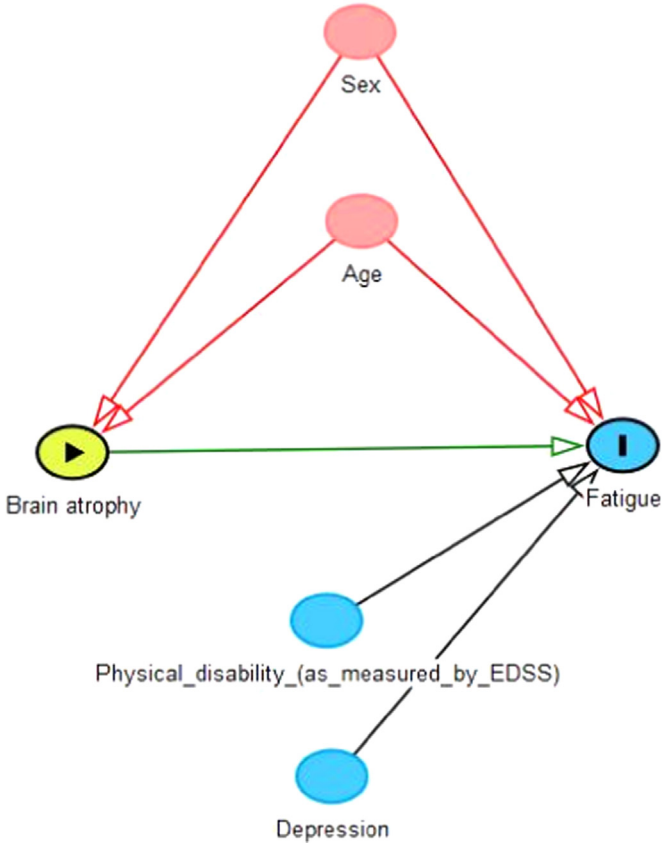

Fig. 1. A directed acyclic graph; depicting the relationship between potentially important variables in the association of atrophy of different brain structures and fatigue.

2.3. Statistical analysis

Spearman correlation was used to assess the cross-sectional association of clinical and imaging outcomes at baseline. To account for the longitudinal nature of the data, a mixed effects regression model was used with the changes over baseline in the imaging variables as the predictor and fatigue severity as the outcome. The mixed effects model allowed subject-specific intercepts and slopes to accommodate the repeated measures nature of the data and possible time trends during the course of the study (Vittinghoff et al., 2012). This model can isolate the between-individual changes (using the baseline value of the predictor) from the within-individual changes (using the difference between each value of the predictor and its baseline value). We used a directed acyclic graph (DAG) to decide about the confounding factors that had to be adjusted for in the models (Fig. 1) (Textor et al., 2011). As it is clear on the DAG; age and sex seems to be important confounder on the association between brain atrophy measures and fatigue. While physical disability and depression might be causally related to the severity of fatigue; but they are not likely to affect the volume of different brain structure. As riluzole showed no effect on primary and secondary outcomes of the study, we combined both treatment groups for the analysis of the associations (Waubant et al., 2014). We considered a nominal p value of ≤ 0.05 as statistically significant and because of the exploratory nature of the study, did not make adjustments for multiple comparisons. All analyses were conducted in Stata Version 13.1 (Stata Corp, College Station TX).