Journal of the Neurological Sciences 380 (2017) 215–222

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

High angular resolution diffusion imaging abnormalities in the early stages of amyotrophic lateral sclerosis

Francesca Trojsi [a,*,1], Giuseppina Caiazzo [a,1], Federica Di Nardo [a], Michele Fratello [a], Gabriella Santangelo [b], Mattia Siciliano [a,b], Cinzia Femiano [a], Antonio Russo [a], Maria Rosaria Monsurrò [a], Mario Cirillo [a], Gioacchino Tedeschi [a], Fabrizio Esposito [c]

[a] Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, MRI Research Centre SUN FISM, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
[b] Department of Psychology, University of Campania "Luigi Vanvitelli", Caserta, Italy
[c] Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, University of Salerno, Baronissi, Salerno, Italy

ARTICLE INFO

Article history:
Received 24 March 2017
Received in revised form 7 July 2017
Accepted 26 July 2017
Available online 27 July 2017

Keywords:
Amyotrophic lateral sclerosis
High angular resolution diffusion weighted imaging
Phenotype
Structural neuroimaging

ABSTRACT

Objective: Using magnetic resonance (MR) high angular resolution diffusion imaging (HARDI), we aimed at revealing possible microstructural alterations in the early stage of amyotrophic lateral sclerosis (ALS), still not completely elucidated.
Methods: We studied 22 patients with ALS, in stages 1 or 2 according to the King's staging system, compared to 18 healthy controls (HCs). Statistical mapping of HARDI-derived parameters and tractography measures were performed using the Q-ball imaging diffusion data model.
Results: When compared to HCs, the ALS group showed a highly significant decrease of generalized fractional anisotropy (GFA) and fiber length and density in the corticospinal tracts (CSTs) and in the corpus callosum (CC) ($p < 0.05$, corrected level of significance). Moreover, stratifying the ALS population considering the disease phenotype, larger areas of decreased GFA were found in patients with bulbar phenotype compared to those with classic phenotype in several bilateral associative fiber tracts, such as superior and inferior longitudinal, inferior fronto-occipital and uncinate fasciculi.
Conclusions: Our whole-brain HARDI results provided preliminary evidence of an early pattern of microstructural degeneration in ALS, mainly involving the CSTs and the CC, although divergent patterns of microstructural abnormalites could be related to different disease phenotypes.

1. Introduction

Microstructural brain correlates of clinical features and phenotypic variability in amyotrophic lateral sclerosis (ALS), although widely investigated in vivo by advanced neuroimaging approaches [1–4], have not been still completely elucidated. In particular, the more commonly used diffusion tensor imaging (DTI) model, although recognized as very suitable for large-scale whole-brain structural investigations [4], may exhibit some limitations in exploring white matter (WM) regions with multiple fiber orientations, including corticospinal tracts (CSTs) and several associative fiber tracts [5,6]. This limitation has stimulated the adoption of higher order diffusion models in the context of high angular resolution diffusion imaging (HARDI), more sensitive to intravoxel orientation heterogeneity [6]. Moreover, for both anisotropy and tractographic analyses, the application of the Q-ball imaging (QBI) model [7] to both HARDI and non-HARDI acquisition schemes has been recently shown to increase the accuracy of both anisotropy mapping and tract depiction in WM regions with expected prevalence of crossing fibers [8,9].

The objective of the present cross-sectional analysis was to test the distribution of possible HARDI-derived structural connectivity abnormalities in a group of ALS patients, evaluated in the early stages of disease according to the King's clinical staging system [10], using both whole-brain tract-based spatial statistics (TBSS) [11] and volume of interest (VOI)-based tractography of QBI-derived parameters. We hypothesized that a specific pattern of microstructural degeneration would emerge from the early stages of disease when comparing the ALS patients with healthy controls, also revealing possible divergent microstructural pathways of WM abnormalities by stratifying the ALS population for disease phenotype.

* Corresponding author.
E-mail address: francesca.trojsi@unicampania.it (F. Trojsi).
[1] These authors equally contributed.

http://dx.doi.org/10.1016/j.jns.2017.07.039
0022-510X/

2. Methods

2.1. Subjects

Twenty-two right-handed patients (11 M; mean age 60.3 ± 11.2), 14 with definite and 8 probable with laboratory-supported ALS, according to the revised El-Escorial criteria [12], were recruited at the First Division of Neurology of the University of Campania "Luigi Vanvitelli" (Naples, Italy). Inclusion criteria were: 1) to be in stages 1 and 2 of ALS according to the King's clinical staging system [10], that is based on the appearance of sequential clinical milestones during the ALS course and does not include cognitive information (i.e., stage 1 = impairment of one body site; stage 2 = impairment of two body sites; stage 3 = impairment of three body sites; stage 4 = non-invasive ventilation or percutaneous endoscopic gastrostomy); 2) to exhibit forced vital capacity above 70%, with no evidence of nocturnal hypoventilation. We excluded from the analysis patients with dominant lower motor neuron impairment (i.e., pure lower motor neuron syndrome, flail leg/arm syndrome), primary lateral sclerosis, post-poliomyelitis ALS and motor neuron disease with comorbid dementia and other causes of focal or diffuse brain damage, previously documented by magnetic resonance imaging (MRI). According to ALS phenotypes classification of Chiò et al. [13], 11 patients exhibited a classic phenotype with spinal onset and 11 a bulbar phenotype, and, according to the King's clinical staging system for ALS [10], 8 patients were in stage 1 (i.e., with involvement of one region) and 14 patients in stage 2 (i.e., with involvement of two regions).

As index of general disability status, we measured the ALS functional rating scale-revised (ALSFRS-R) score [14], and, as measure of pyramidal dysfunction, the UMN score, through the evaluation of the number of pathologic reflexes elicited from 15 body sites [15]. Respiratory function, measured by forced vital capacity, was above 70% in all ALS patients and there was no evidence of nocturnal hypoventilation. All patients included underwent a 60-min neuropsychological battery, aiming to assess a broad range of cognitive skills. We evaluated: global cognitive impairment by Addenbrooke's Cognitive Examination Revised (ACE-R); executive performances by Stroop Colour-Word Interference test, calculating the Stroop Executive Factor, used to determine performance while accounting for motor disabilities, and working memory and sustained attention by digit span and backward digit span from Wechsler Adult Intelligence Scale-Third Edition; verbal comprehension abilities by Token Test; visuo-spatial abilities by Scrawls' discrimination test; behavioural dysfunctions by Frontal Systems Behaviour Scale (referring to the total scores at the time of examination, derived from the caregivers' forms) and apathy evaluation scale (AES) (referring to the total scores derived from both patients' and caregivers' forms); depressive symptoms by Beck Depression Inventory-II. The tests were scored according to Italian normative values, correcting for age and level of education (details about the Italian versions of the adopted tests are provided in Supplemental materials S1).

All patients did not show any mutation of most genes involved in familial ALS, such as SOD1, TARDBP, FUS/TLS and C9ORF72.

Right-handed HCs were enrolled by word of mouth. They underwent neurological examination and the same multidimensional assessment of ALS patients, except for behavioural scales. Eighteen neurologically and cognitively normal subjects (9 M, 9 F; mean age 61 ± 8.1) were included in the study.

This work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Ethics approval was obtained from the Ethics Committee of the University of Campania "Luigi Vanvitelli". Patient or family written consent was obtained from each participant.

2.2. Imaging acquisition

Magnetic-resonance images were acquired on a 3T scanner equipped with an 8-channel parallel head coil (General Electric Healthcare, Milwaukee, Wisconsin). Whole brain HARDI was performed using a Spin-Echo (SE) EPI sequence with high b-value and high number of directions (repetition time = 16,000 ms, echo time = 104 ms, field of view = 320 mm, isotropic resolution = 2.5 mm, b value = 3000 s/mm, 54 isotropically distributed gradients frequency encoding LR). A T2-weighted FLASH sequence was also acquired during the same session (24 slices, slice thickness = 5 mm, distance factor = 20%, 256 × 256 matrix size, 0.9 × 0.9 mm^2) to exclude vascular pathology.

2.3. Data analysis

Image data post-processing and analyses were performed with the software packages Functional MRI of the Brain (FMRIB) Software Library (FSL) (www.fmrib.ox.ac.uk/fsl) and Trackvis (www.trackvis.org), and with custom scripts in Matlab (Mathworks, USA, www.mathworks.com). HARDI data preprocessing included eddy current and motion correction, using the "eddy_correct" tool in FSL, and brain-tissue extraction, using the Brain Extraction Tool in FSL. The QBI model was fitted at each voxel with "q-boot", a command line tool of FSL. This command allows estimation of diffusion orientation distribution functions using the q-ball constant solid angle model [8]. As an extension of the FA metric commonly used in DTI [i.e., FA = std(λ)/rms(λ)] where λ are the eigenvalues of the diffusion tensor, here we defined the generalized fractional anisotropy (GFA) ratio as GFA = std(ψ)/rms(ψ) where ψ are the orientation distribution function values [7].

We planned to use both whole-brain TBSS and VOI-based tractography of QBI-derived parameters, according to previous QBI studies [9,16,17], both to describe specific characteristics of some WM tracts of interest and to evaluate GFA alterations across the whole brain of the studied cohort of patients. Deterministic fiber tracking was performed with the QBI model using the diffusion toolkit of the Trackvis software package (Version 0.5.1). This tool implements a deterministic streamline approach over the whole brain [18].

2.3.1. HARDI VOI-based analysis

A VOI analysis was carried out using the FMRIB FSL software package. Here we defined as VOIs all main WM fiber bundles derived from the Johns Hopkins University (Baltimore, Maryland) WM tractography Atlas of FSL [19,20], selected on the base of a priori hypotheses derived from previous evidence described in several cohorts of ALS patients [1–4,21–35]: corpus callosum (CC), CST, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UF) and cingulate bundle. These VOIs were non-linearly registered onto the single GFA subject map using first linear followed by non-linear registration and exported to Trackvis for tractography. All VOIs were overlaid on the whole brain tractography map to calculate the mean fiber length, the tract volume, the track count and mean GFA for each VOI and each data set. Fiber density values were also computed as the ratio between track count and volume [36].

2.3.2. Whole-brain TBSS analysis

A TBSS analysis was performed using GFA maps to create the "skeleton", which represents the center of all fiber bundles in common to all subjects. To this purpose, GFA images of all subjects were first aligned to a common target (FMRIB58_FA standard space) using nonlinear registration, and then registered to a 1 × 1 × 1 mm Montreal Neurological Institute 152 standard space. A mean GFA skeleton was created with threshold of GFA > 0.1. Individual skeleton images were submitted to a general linear model analysis with appropriate design matrices and linear contrasts defined for the group comparisons and the correlations between GFA and clinical measures of disease disability (i.e., ALSFRS-R