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ORIGINAL ARTICLE

Gray Matter Volume Changes over the Whole Brain in the Bulbar- and Spinal-onset Amyotrophic Lateral Sclerosis: a Voxel-based Morphometry Study

Zhiye Chen[1, 2], Mengqi Liu[1, 2], Lin Ma[1*]

[1]Department of Radiology, Chinese PLA General Hospital, Beijing 100853, China
[2]Department of Radiology, Hainan Branch of Chinese PLA General Hospital, Sanya, Hainan 572013, China

Key words: amyotrophic lateral sclerosis; gray matter; magnetic resonance imaging; precentral gyrus; voxel-based morphometry

Objective To investigate cerebral structural signatures of the bulbar- and spinal-onset amyotrophic lateral sclerosis (ALS) using voxel-based morphometry on magnetic resonance imaging.

Methods The MR structural images of the brain were obtained from 65 ALS patients (15 bulbar-onset, 50 spinal-onset) and 65 normal controls (NC) on a 3.0T MRI system. Gray matter (GM) volume changes were investigated by voxel-based morphometry, and the distribution of the brain regions with volume changes was compared between ALS and normal controls, as well as between bulbar-onset and spinal-onset ALS based on Neuromorphometrics atlas.

Results On voxel-level the decreased volume of brain regions in ALS patients was located in the right precentral gyrus (rPrcGy) and right middle frontal gyrus compared with that in NC. The bulbar-onset ALS presented extra-motor cortex atrophy (fronto-temporal pattern), including left medial orbital gyrus, left inferior temporal gyrus and right middle temporal gyrus; the spinal-onset ALS suffered from motor cortex atrophy (rPrcGy dominance) and extra-motor cortex atrophy (fronto-temporal and extra-fronto-temporal pattern) compared with NC. The spinal-onset ALS featured by GM volume loss of left postcentral gyrus and bulbar-onset ALS featured by GM volume loss of left middle temporal gyrus compared with each other.

Conclusions The asymmetric GM atrophy of the motor cortex and extra-motor cortex represents the common MRI structural signatures of spinal-onset ALS, and sole extra-motor cortex atrophy represents the structural signatures of bulbar-onset ALS. The present study also demonstrated that the pattern of GM damage is likely to distribute wider in spinal-onset ALS than in bulbar-onset ALS.

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*Corresponding author E-mail: cjr.malin@vip.163.com

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AMYOTROPHIC lateral sclerosis (ALS) is a progressive neurodegenerative disease with selected both upper and lower motor neuron lesions.[1-2] In ALS, many voxel-based morphometry (VBM) studies found that gray matter (GM) volume decreased widely, especially in motor cortex,[3-4] frontal and temporal regions,[4-6] corpus callosum,[7] amygdala,[8] caudate nucleus head.[9] However, Mezzapesa *et al*'s study showed that no volume reduction of primary motor cortices in ALS patients.[10] Voxel-wise meta-analysis[11-12] has revealed that ALS is a complex degenerative disease involving multi-systems besides motor system, and right precentral GM atrophy is a common finding and prominent feature of brain structural changes in ALS.[13] However, GM changes over the whole brain were not comprehensively studied in bulbar-onset and spinal-onset ALS patients.

The aim of this study is to investigate brain structural imaging signatures in clinical subtypes of ALS. We hypothesized that some brain regions may intrinsically suffered from volume loss in the patients with ALS. To address this hypothesis, we obtained brain structure images of 65 patients with ALS (ALS group) and 65 normal controls (NC) from 3.0T MRI system. All the ALS patients were classified into bulbar-onset group (ALS-bulbar, n=15) and spinal-onset group (ALS-spinal, n=50) according to the initial onset location. We firstly identified the alteration of GM changes over the whole brain between the ALS group and the NCs, and then the GM volume analysis was performed among the ALS-bulbar group, ALS-spinal group and the control group to identify the pattern of different GM volume loss.

PATIENTS AND METHODS

Participants

This study was approved by the institutional ethic review board and written informed consents were obtained from all participants. Sixty-five patients, including 34 cases with definite diagnosis of ALS and 31 cases with suspicious diagnosis of ALS according to the revised El Escorial,[14] were consecutively recruited from the Chinese PLA General Hospital from 2007 to 2010. The subjects were excluded for the following conditions: 1. history of cerebrovascular disease, long-standing hypertension, diabetes mellitus, inflammatory disease of the central nervous system and cranium trauma; 2. taking psychoactive drugs or hormone; 3. structural damage observed on the conventional MR images. All the subjects were right handed. ALS functional rating score (ALSFRS)[15] and Norris Scale[16] were administered to all the patients for clinical rating their ALS symptoms, and mini-mental state examination (MMSE)[17] was applied to evaluate the cognitive function of all subjects.

MRI examination and acquisition

MR structural images were obtained from a 3.0T MR imaging system (SIGNA EXCITE, GE Healthcare, Milwaukee, WI, USA) and a conventional eight-channel quadrature head coil. Three-dimensional T1-weighted fast spoiled gradient recalled echo (3D T1-FSPGR) sequence was used, and the parameters were as follows: TR (repetition time) = 6.3 ms, TE (echo time) = 2.8 ms, flip angle = 15°, FOV (field of view) = 24 cm× 24 cm, Matrix = 256×256, in-plane resolution of 0.9375×0.9375 mm^2, NEX (number of acquisition) = 1. Conventional T2-weighted images, T1-weighted images and diffusion weighted images were also obtained to exclude the patients with diseases other than ALS that inflecting brain morphometry. The imaging protocol was identical to each subject.

Data processing

All MR structural image data were processed using Statistical Parametric Mapping 12 (SPM 12) (http://www.fil.ion.ucl.ac.uk/spm/) running under MATLAB 7.6 (The Mathworks, Natick, MA, USA) to perform VBM.[18] The preprocess of VBM was as follows: (1) setting the image origin at the anterior commissure (AC); (2) normalizing the individual structural images to the DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) templates space; (3) segmenting the normalized images into GM, white matter and cerebrospinal fluid (CSF); (4) calculating the volume of 142 brain regions based on SPM Neuromorphometrics atlas; total GM volume (TGMV), total white matter volume (TWMV), and total CSF volume (TCSFV) were recorded. Total intracranial volume (TIV) was the sum of the volume of segmented brain tissue (TIV = TGMV + TWMV + TCSFV), and fraction of GMV (fGMV) was the ratio of TGMV to TIV (fGMV = TGMV/TIV); (5) smoothing the segmented GM images with a kernel of 8 mm FWHM (full width at half maxima) before statistical analysis.

Statistical analysis

VBM was performed using two-sample t test with TIV, age and sex as covariates by the factorial design specification tools of SPM. Significance was set if a *Puncorr*