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Gray and white matter structural changes in corticobasal syndrome

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ABSTRACT

We investigated gray matter and white matter (WM) changes in corticobasal syndrome (CBS). T1-weighted and diffusion tensor images (3T-magnet) were obtained in 11 patients and 11 healthy subjects (HS). Magnetic resonance imaging data were analyzed using FreeSurfer and Tracts Constrained by Underlying Anatomy to evaluate cortical thickness (CTh), surface area, and subcortical volumes as well as diffusion tensor image parameters along the major WM tracts. Compared with HS, the whole patient group showed decreased CTh in the prefrontal cortex, precentral gyrus, supplementary motor area, insula, and temporal pole bilaterally. When we divided patients into 2 subgroups (left: L-CBS, right: R-CBS) on the basis of the clinically more affected upper limb, the most prominent decrease in CTh occurred in the hemisphere contralateral to the more affected side. The whole patient group also had volume loss in the putamen, hippocampus, and accumbens bilaterally, in the corpus callosum and right amygdala. Finally, we found diffusion changes in several WM tracts with axial diffusivity being altered more than radial diffusivity. The upper limb motor severity negatively correlated with the contralateral CTh in the precentral and/or postcentral gyri and contralateral volumes of putamen and accumbens. The CTh asymmetry in postcentral and/or paracentral gyri also negatively correlated with disease duration. Cortical thinning, volume loss, and fiber tract degeneration in specific brain regions are important pathophysiological abnormalities in CBS.

1. Introduction

Corticobasal syndrome (CBS) is a progressive movement disorder characterized by akinetic-rigid parkinsonism and a varying combination of motor and nonmotor symptoms that are typically asymmetric and affect a single body region, particularly the upper limbs. Motor and nonmotor symptoms include dystonia, myoclonus, apraxia, cortical sensory deficit, alien limb phenomena, and cognitive and behavioral impairment (Armstrong et al., 2013; Burrell et al., 2014). CBS is typically associated with corticobasal degeneration (CBD), a neuropathological condition characterized by abnormal tau protein accumulation in both neurons and glia (Dickson et al., 2002). CBS may also be the clinical presentation of neurodegenerative conditions other than CBD, including progressive supranuclear palsy (PSP), Alzheimer disease (AD), and frontotemporal lobar degeneration (FTLD). Separately, patients with a neuropathological diagnosis of CBD may present in life with the clinical syndrome of PSP, AD, or FTLD (Boeve et al., 2011 and Ouchi et al., 2014).

Although the pathophysiology of CBS is largely unknown, recent advances in neuroimaging have shed light on specific structural neuroanatomical changes that occur as a result of this disorder. Studies based on voxel-based morphometry (VBM) have revealed gray matter (GM) loss in frontoparietal regions and subcortical structures, including the basal ganglia (Boxer et al., 2006; Gröschel et al., 2004; Josephs KA et al., 2008; Whitwell et al., 2010; Yu et al., 2015). Surface-based morphometry, which is a more advanced technique than VBM, can be used to evaluate cortical thickness (CTh) and surface area, 2 orthogonal components of volume, thereby providing a more reliable direct quantitative index of GM changes (Hutton et al., 2009).

Research based on diffusion tensor imaging (DTI) in CBS has demonstrated white matter (WM) abnormalities in associative fiber bundles, in the corpus callosum and in the cortico-spinal tract (Boelmans et al., 2009; Borroni et al., 2008; Tovar-Moll et al., 2014; Whitwell et al., 2014). Previous DTI studies have, however, only

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reported changes in fractional anisotropy (FA) and mean diffusivity (MD) (Boelmans et al., 2009; Borroni et al., 2008; Tovar-Moll et al., 2014; Whitwell et al., 2014), which provide information on damage in both myelin content and axonal density. In CBS, no investigations have been conducted on axial diffusivity (AxD) and radial diffusivity (RD), 2 measurements that may shed light on the extent to which WM changes reflect axonal damage or demyelination processes. Neuropathological studies in which tau-positive inclusions were detected in oligodendroglia in CBD have raised the hypothesis that WM fiber tracts in CBS are affected not only by axonal loss but also by myelin damage (Dickson et al., 2002; Matsumoto et al., 1996).

No previous studies have evaluated structural GM changes as reflected by CTh in a cohort of patients with CBS. A previous study examined CTh in patients with posterior cortical atrophy (PCA), a neurodegenerative syndrome characterized by progressive impairment of higher visual processing skills. This study found that the subset of PCA patients who also had asymmetric motor features typically seen in CBS showed greater asymmetry of atrophy, particularly involving frontoparietal and perirolandic cortices contralateral to the affected limb (Ryan et al., 2014). Moreover, none have clarified with DTI whether axonal loss and myelin damage equally contribute to changes in WM fiber tracts in CBS. Finally, none have evaluated the association between asymmetry in patients' motor and nonmotor symptoms and asymmetry in the assessed neuroimaging measurements.

To this end, we decided to assess GM and WM changes in CBS by investigating CTh and subcortical volumes in patients with CBS and calculating all the DTI parameters in the major WM fiber tracts. Furthermore, to shed light on the pathological mechanisms underlying the asymmetry of motor and nonmotor symptoms, which is a typical clinical feature of CBS, we calculated the absolute percent asymmetry values in all the neuroimaging measurements and investigated any correlations between neuroimaging findings and the patients' clinical scores.

2. Methods

2.1. Subjects

We recruited 11 CBS patients (3 males and 8 females, mean age ± SD: 68 ± 6.9) and 11 age- and gender-matched healthy subjects (HS) (3 males and 8 females, mean age ± SD: 66 ± 6.4). All the participants were right handed. CBS was diagnosed by movement disorder experts using the 2013 criteria for the diagnosis of CBS (Armstrong et al., 2013). According to the Armstrong et al. (2013) criteria, the diagnosis of CBS is based on at least 2 asymmetric motor symptoms (bradykinesia, rigidity, dystonia, and myoclonus) and at least 2 nonmotor symptoms (apraxia, cortical sensory deficit, and alien limb phenomena). Patients and HS were all recruited from the Department of Neurology and Psychiatry, Sapienza University of Rome, Italy. None of the HS reported any history of neurological and psychiatric disorder and all of them had a normal magnetic resonance imaging (MRI) scan. Parkinsonian motor signs were scored using the Italian version of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (Antonini et al., 2013). The severity of dystonia was assessed by means of the Burke-Fahn-Marsden Movement and Disability Scale (Burke et al., 1985). Cortical signs (apraxia, cortical sensory deficit, and the alien limb phenomena) were evaluated in all patients through a conventional clinical examination. Cognitive functions were evaluated in both HS and CBS using the Mini–Mental State Evaluation (MMSE) (Folstein et al., 1975). CBS patients were also evaluated with the frontal assessment battery (FAB) (Dubois et al., 2000). Depression was assessed by means of the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1976). None of the patients received L-DOPA or any other drugs that act on the central nervous system while they were being studied. The demographic and clinical characteristics of 11 patients with CBS are shown in Table 1. Patients were divided into 2 groups, left (L-CBS) and right (R-CBS), on the basis of the more affected upper limb (Jütten et al., 2014).

Subjects gave their informed consent, and the study was approved by the institutional review board and conformed with the Declaration of Helsinki.

2.2. MRI acquisition

All the participants underwent a standardized protocol on a 3.0 T Siemens scanner (Verio, Siemens AG, Erlangen, Germany) using 12-channel head coil designed for parallel imaging (Generalized Autocalibrating Partially Parallel Acquisitions [GRAPPA]). We acquired and analyzed (1) high-resolution 3-dimensional T1-weighted (T1-3D) magnetization-prepared rapid acquisition with gradient echo sequence (repetition time [TR] = 1900 ms, echo time [TE] = 2.93 ms, flip angle = 9°, field of view [FOV] = 260 mm, matrix = 256 × 256, 176 sagittal 1-mm thick slices, without gap); (2) DTI single-shot echo-planar spin-echo sequence with 30 gradient directions (TR = 12,200 ms, TE = 94 ms, FOV = 192 mm, matrix = 96 × 96, b = 0 and 1000 s/mm-2, 72 axial 2-mm thick slices, no gap). Dual turbo spin-echo proton density and T2-weighted images (TR = 3320 ms, TE = 10/103 ms, FOV = 220 mm, matrix = 384 × 384, 25 axial 4-mm thick slices, 30% gap) were also acquired to exclude subjects with brain alterations due to concomitant diseases.

2.3. Data analysis

Data analysis was performed using automated streamlines in the FreeSurfer 5.3.0 software library (http://surfer.nmr.mgh.harvard.edu/) on a Dell workstation (OPTIPLEX 9020) with an Intel Core i7 processor. The processing streams were divided into 2 parts:

(1) T1-3D images were first processed with FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/). The image analysis steps include motion correction, Talairach transformation, removal of nonbrain tissues, and automated segmentation of data into GM/WM, according to Dale et al. (Dale et al., 1999) and Fischl et al. (Fischl et al., 1999). Deformable procedures, including cortical inflation, registration to a spherical atlas, and parcellation of the cerebral cortex into gyral and sulcal units, were applied (Desikan et al., 2006). Map labels were then created from the parcellated cerebral cortex in 34 cortical regions on the basis of the Desikan/Killiany atlas (Destrieux et al., 2010). Thickness was calculated as the closest distance from the pial to WM boundary at each vertex; surface area was computed at the interface between GM and WM (Fischl and Dale, 2000). CTh and surface area maps were spatially smoothed with a Gaussian kernel with a half-maximum width of 10 mm. All individual images were visually checked to ensure that GM and WM voxels had not been misclassified. The volumes of 7 subcortical GM structures (thalamus, caudate, nucleus accumbens, pallidum, putamen, hippocampus, and amygdala) in each hemisphere, of the brainstem and of the corpus callosum (divided in 5 segments), were extracted from volumetric measurements generated by automated volumetric processing based on a probabilistic atlas containing information of the location of structures in FreeSurfer (Fischl et al., 2002).

2) DTI data were then processed using the Tracts Constrained by Underlying Anatomy (TRACULA) toolbox, a component in the