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Occult white matter damage contributes to intellectual disability in tuberous sclerosis complex

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ABSTRACT

Whether patients with tuberous sclerosis complex (TSC) have brain normal-appearing white matter (NAWM) damage and whether such damage contributes to their intellectual disability were examined in 15 TSC patients and 15 gender- and age-matched healthy controls using diffusion tensor imaging (DTI). Histogram and region of interest (ROI) analyses of the mean diffusivity (MD) and fractional anisotropy (FA) were performed in the NAWM. Correlations between diffusion indices and the full-scale intelligence quotient (FSIQ) and normalized lesion volume were also investigated. Compared with controls, both histogram and ROI analyses showed significant ($P<.05$) increased MD and decreased FA in the NAWM of TSC patients. In TSC patients, some of the histogram- and ROI-derived diffusion indices of the NAWM were correlated with FSIQ ($P<.01$), but none of them were correlated with the normalized lesion volume. These findings indicate that TSC patients have occult damage in the NAWM, which might be an important neural basis for intellectual disability in these patients.

1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disease characterized by the involvement of multiple organs including the brain. More than 40% of patients with TSC have intellectual disability (Joinson et al., 2003; Seidenwurm & Barkovich, 1992; Shepherd & Stephenson, 1992). The neural basis of intellectual disability in TSC has been attributed to the cortical tubers and epilepsy (Goh, Kwiatkowski, Dorer, & Thiele, 2005; Jambaqué et al., 1991; Jambaqué, Chiron, Dumas, Mumford, & Dulac, 2000; O'Callaghan et al., 2004; Raznahan et al., 2007; Shepherd & Stephenson, 1992; Takanashi, Sugita, Fujii, & Niimi, 1995; Zaroff et al., 2006). Conventional MRI has been widely used to detect the four major cerebral lesions: cortical tubers, white matter abnormalities, subependymal nodules and subependymal giant-cell astrocytomas (Braffman et al., 1992). However, subtle pathological changes in the structure of the brain have not been studied extensively. A previous study has shown that neuropathological changes associated with TSC may be more extensive than previously suspected, involving the normal-appearing white matter (NAWM) (Ridler et al., 2001).

Diffusion weighted and diffusion tensor imaging (DTI) techniques have the potential to detect the occult damage in the brain tissue (especially brain white matter) which appears normal on conventional MRI (Ceccarelli et al., 2007; Yu et al., 2007). With the use of these techniques, several studies have attempted to investigate whether the NAWM is damaged in patients with TSC using region of interest (ROI) analysis (Firat, Karakas, Erdem, Yakinci, & Bicak, 2006; Garaci et al., 2004; Karadag et al., 2005; Peng, Lee, Wang, & Huang, 2004). However, conflicting results are obtained. Moreover, most of the previous studies have focused on the correlations of the cortical lesions and epilepsy with intellectual disability in TSC patients (Goh et al., 2005; Jambaqué et al., 1991; Jambaqué et al., 2000; O'Callaghan et al., 2004; Raznahan et al., 2007; Shepherd & Stephenson, 1992; Takanashi et al., 1995; Zaroff et al., 2006), but none of them have investigated the contribution of the

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NAWM damage to intelletual disability in these patients. The purposes of this study are to determine whether patients with TSC have brain NAWM damage using both DTI histogram and ROI analyses, and to investigate whether such damage contributes to the intellectual disability of these patients.

2. Materials and methods

2.1. Subjects

From November 2005 to October 2006, we prospectively examined 15 patients (6 men and 9 women; mean age, 25.8 ± 13.0 years; range, 8–49 years) with definite TSC according to the clinical diagnostic criteria (Gomez & Northrup, 1998). The inclusion criterion for the patient group was a definitive diagnosis of TSC based on clinical and radiologic findings. One neuroradiologist and two neurologists assigned final clinical diagnoses to all patients with consensus by reviewing all case histories, physical examinations, conventional MR images and laboratory data. Full-scale intelligence quotient (FSIQ) scores were measured by means of the Chinese Revised Wechsler Adult Intelligence Scale (WAIS-RC) (Gong, 1982) for subjects above the age of 16 years and the Wechsler intelligence scale for children Chinese revision (WISC-CR) (Gong & Cai, 1994) for subjects between the ages of 7 and 16 years. Their mean FSIQ is 77.2 ± 24.8 (range, 20–114), mean performance IQ (PIQ) is77.3 ± 25.7 (range, 20–112) and mean verbal IQ (VIQ) is78.7 ± 25.1 (range, 20–122). Their mean disease duration is 17.3 ± 11.9 years (range, 5–48 years). Their mean duration of epilepsy is 14.3 ± 13.9 years (range, 0–48 years). The mean total number of seizures is 924.9 ± 1598.2 (range, 0–5475). Ten of the 15 patients had a family history of TSC and 14 of them experienced seizures. Fifteen gender- and age-matched healthy volunteers (6 men and 9 women; mean age, 25.6 years; range, 9–49 years) with no history of neurological disorders and with normal neurological examinations were recruited to serve as controls. Their mean FSIQ is 117.4 ± 16.5 (range, 75–133), mean PIQ is119.2 ± 14.6 (range, 86–137) and mean VIQ is 111.8 ± 17.7 (range, 64–131). Written informed consent from each subject and approval by the Local Ethical Committee of the Xuanwu Hospital were obtained before the MR examinations.

2.2. Image acquisition

All subjects were examined with a 3.0 Tesla MR scanner (Trio system; Siemens Magnetom scanner, Erlangen, Germany). All sequences were performed in transverse plane with identical number of slices (n=45), slice thickness (3 mm) and interslice gap (0 mm). All slices of each sequence were consistently positioned to parallel to a line that joins the most infero-anterior and infero-posterior parts of the corpus callosum. Detailed scan parameters were as follows: 1) DTI scheme included the collection of 12 images with non-collinear diffusion gradients (b=1000 s/mm^2) and one non-diffusion-weighted image (b=0 s/mm^2), employing a single shot echo planar imaging sequence. Integrated parallel acquisition technique (iPAT) was used with an acceleration factor of 2. Acquisition time can be reduced by the iPAT method with less image distortion from susceptibility artifacts. The field of view (FOV) was 256×256 mm, the acquisition matrix was 128×128 and zero filled into 256×256, the number of averages was 3, and the echo time and repetition time were 87 ms and 6000 ms, respectively; 2) Turbo spin-echo (TSE) T2-weighted imaging with TR=7650 ms, TE=84 ms, signal averages=3, matrix=256×208, FOV=230×187 mm; 3) spin-echo T1-weighted imaging with TR=321 ms, TE=2.9 ms, signal averages=3, matrix=256×208, FOV=230×187 mm, echo-train length=15; 4) Fluid-attenuated inversion-recovery (FLAIR) sequence with TR=9000 ms, TE=99 ms, inversion time=2500 ms, signal average=1, matrix=256×208, FOV=230×187 mm, echo-train length=21.

2.3. Image processing

The diffusion tensor of each voxel was calculated by a linear least-square fitting algorithm (Basser, Mattiello, & LeBihan, 1994). After diagonalization of the diffusion tensor, diffusion tensor eigenvalues were obtained. The mean diffusivity (MD) and fractional anisotropy (FA) are derived for each pixel according to the following equations:

$$\mathrm{MD} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

$$\mathrm{FA} = \sqrt{\frac{(\lambda_1-\lambda_2)^2+(\lambda_1-\lambda_3)^2+(\lambda_2-\lambda_3)^2}{2(\lambda_1+\lambda_2+\lambda_3)^2}}$$

Here λ_1, λ_2, λ_3 are eigenvalues measuring the magnitude of diffusivity in the directions of maximum, median and minimum diffusion, respectively.

The T2-weighted images of the DTI scans (b=0) were coregistered with the TSE T2-weighted images based on normalized mutual information method using SPM2 (Wellcome Department of Imaging Neuroscience, London). The same transformation parameters were then used to coregister the MD and FA images.

Voxels containing extra-cerebral tissue were removed from T1-weighted images, using a semi-automated technique provided by MRIcro (http: //www. mricro.com). Gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) were automatically segmented using SPM2 software. Each voxel was classified as GM, WM, or CSF. The visible lesions were identified on the TSE T2-weighted and FLAIR images and were manually extracted. Then the lesion volume of each patient was calculated and these voxels were removed from the GM and WM images to generate normal-appearing gray matter (NAGM) and NAWM, respectively. As a consequence, the masks of the NAWM and NAGM of all subjects were created. The normalized brain tissue volume (NBTV) and the normalized lesion volume (NLV) for each subject were calculated: NBTV=volume (WM+GM)/volume (WM+GM+CSF) and NLV=volume (lesion)/volume (WM+GM+CSF).

The resulting NAWM and NAGM masks were superimposed onto the MD and FA images. Then the corresponding MD and FA images of the NAWM and NAGM were created. Histograms, which contain 100 bins, were created from these images. To compensate for variability of brain size, each bin was normalized by the total number of voxels contributing to the histogram. From each of the histogram, the following measures were extracted: the average value, the histogram peak height, and the histogram peak location.