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White matter abnormalities correlate with neurocognitive performance in patients with HBV-related cirrhosis

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ABSTRACT

Background: White matter (WM) abnormalities are common in cirrhotic patients and possibly contribute to hepatic encephalopathy (HE), a frequent neuropsychiatric complication of cirrhosis. However, little is known about these WM abnormalities and their relationship to neurocognitive deficits in patients with HBV-related cirrhosis.

Methods: Three-dimensional T1-weighted magnetic resonance imaging and diffusion tensor imaging (DTI) scans were obtained from 67 patients with HBV-related cirrhosis and 40 controls. Voxel-based morphometry and voxel-based DTI were performed to detect macroscopic atrophy and damage to the microstructural integrity of the WM, respectively. Correlation analyses were performed to investigate the relationships between WM abnormalities and neurocognitive performances.

Results: Patients with cirrhosis exhibited significantly decreased WM volume and fractional anisotropy (FA) values, especially in the corpus callosum, thalamus, extra-nuclear area, sensorimotor area, fusiform gyrus, lingual gyrus, and frontal lobes. These abnormalities were more severe with increasing Child–Pugh stage, minimal HE, and previous overt HE. Changes in the corpus callosum, frontal lobe, sensorimotor area, internal capsule, and temporal–occipital lobes were correlated with poor neurocognitive performance. Also, the significantly decreased global WM volume and mean FA value were correlated with poor neurocognitive performances.

Conclusions: Diffuse WM abnormalities are common in patients with HBV-related cirrhosis. Advanced liver disease and episodes of HE are two factors associated with WM abnormalities. The correlation between poor neurocognitive performance and WM abnormalities suggests that WM abnormalities may be one of mechanisms underlying neurocognitive deficits in patients with HBV-related cirrhosis.

1. Introduction

Liver cirrhosis is a global health problem with a high morbidity and mortality [1–3]. The distribution of cirrhosis varies according to the underlying liver disease: alcoholic liver disease and hepatitis C are the most common causes in the Western world, and hepatitis B virus (HBV) is the most common cause in most parts of Asia and sub-Saharan Africa [1]. Even though the prevalence of alcohol-related cirrhosis is increasing, HBV is still the most common cause of liver cirrhosis in Asia due to a high HBV-infection rate [4]. It was reported that approximately 34% of patients with chronic HBV develop severe fibrosis or cirrhosis [5].

Frequently, liver cirrhosis induces neuropsychiatric complications, namely hepatic encephalopathy (HE), which lead to impairment in daily functions [6] and increased mortality [7,8]. HE is characterized by varying degrees of neurocognitive impairment and disturbances in consciousness, which are observed in overt HE [9]. Neurocognitive dysfunction is common in Asian populations with HBV-related cirrhosis [10]. However, the relationships between these neurocognitive impairments and structural abnormalities of the brain in patients with HBV-related cirrhosis are not well-understood.

It has been demonstrated that patients with cirrhosis develop white matter (WM) abnormalities during the progression of the disease. These abnormalities include macroscopic WM atrophy [11], damage to the microstructural integrity [12], and focal WM lesions that may be compatible with WM edema [13]. Of note, these WM abnormalities may be associated with the neurocognitive deficits observed in HE. For example, diffuse WM atrophy was found in cirrhotic patients with minimal HE [11]. Among patients with low-grade HE diffusion tensor imaging (DTI) revealed that increased mean diffusivity and decreased

Abbreviations: HBV, hepatitis B virus; HE, hepatic encephalopathy; WM, white matter; DTI, diffusion tensor imaging; FA, fractional anisotropy; VBM, voxel-based morphometry; TMT-A, trail-making test A; TMT-B, trail-making test B; DST, digit–symbol test; BDT, block-design test.

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fractional anisotropy (FA) values were correlated with poor neurocognitive performances [12]. Additionally, cirrhotic patients who underwent liver transplantation showed decreased volumes of focal WM lesions and improvements in neurocognitive functioning [13] and HE [14]. However, the WM abnormalities of patients with HBV-related cirrhosis have not been studied as intensively as those of alcohol- and HCV-related cirrhosis. In this study, we aim to identify the WM abnormalities associated with HBV-related cirrhosis and their relationships with neurocognitive deficits using voxel-based morphometry (VBM) and voxel-based DTI.

VBM is an unbiased and automatic method of structural analysis that accurately detects anatomical abnormalities of the entire brain. It has been extensively employed to investigate morphological changes in aging and various neurological diseases, such as schizophrenia and Alzheimer's disease [15]. In addition, VBM has also been applied to investigate abnormal FA values that are computed from DTI data. Currently, voxel-based DTI analysis is a popular method for comparing DTI data across subjects [12,16–18]; however, it has been proposed that voxel-based DTI has a low replication rate [19]. Thus, more relevant studies may be needed to accurately ascertain the WM abnormalities detected by voxel-based DTI due to the low number of voxel-based DTI analyses conducted in cirrhotic patients.

In this context, we simultaneously performed DTI-FA and MRI volumetric analyses, which are both based on the VBM model, to confirm the WM abnormalities of patients with HBV-related cirrhosis and detect the relationships between WM abnormalities and neurocognitive deficits. The VBM analyses showed macroscopic atrophy of the WM and damage to the microscopic structure in cirrhotic patients. These abnormalities were aggravated by advanced hepatic decompensation with minimal HE and after a previous episode of overt HE. Furthermore, correlations between WM abnormalities and poor neurocognitive performance were found in patients with HBV-related cirrhosis.

2. Patients and methods

2.1. Subjects

Sixty-seven patients with chronic liver cirrhosis caused by HBV infection and forty healthy controls were recruited for this study. The clinical characteristics of the subjects are summarized in Table 1. The diagnosis of cirrhosis was made using liver biopsy and/or other clinical criteria (e.g., ultrasound, computerized tomography or biochemistry examination). Child–Pugh scores were used to assess the severity of liver disease. The medical history of each study participant was recorded. A battery of neurocognitive tests, including the trail-making test A (TMT-A), trail-making test B (TMT-B), digit–symbol test (DST), and block-design test (BDT), were administered. Using the criteria of previous studies [20,21], we defined minimal HE as the presence of abnormalities in at least two neurocognitive tests (i.e., two standard deviations beyond control values). Control values for the local population had been previously determined from a sample of 160 healthy volunteers who were matched by age and education to the patients.

The patients enrolled in this study did not have hepatic encephalopathy at the time of the exam. Participants were excluded from the study if they had neurological or psychiatric diseases, took psychotropic medications, suffered from uncontrolled endocrine or metabolic diseases, or abused alcohol in the 6 months prior to the study. This study was approved by the Institutional Ethics Committee of Southeast University, Nanjing, China. Written informed consent was obtained from each participant.

Table 1
Clinical characteristics of patients with cirrhosis and healthy controls.

	Healthy controls ($n=40$)	Patients with cirrhosis ($n=67$)	p-value
Age (years)	52.6 ± 7.8	51.0 ± 9.1	0.359
Education (years)	7.6 ± 2.8	8.3 ± 2.8	0.205
Sex (male/female)	36/4	61/6	1.000 (χ^2-test)
Ascites at inclusion (no/yes)	–	59/8	–
Child–Pugh stage (A/B/C)	–	25/21/21	–
Minimal hepatic encephalopathy (no/yes)	–	46/21	–
Previous overt hepatic encephalopathy (no/yes)	–	48/19	–
Trail making test A (second)	46.9 ± 14.6[a]	59.3 ± 21.5	0.020
Trail making test B (second)	112.9 ± 28.9[a]	148.7 ± 56.7	0.001
Digit symbol test (raw score)	42.8 ± 9.9[a]	33.7 ± 12.1	0.004
Block design test (raw score)	30.6 ± 8.5[a]	24.4 ± 9.5	0.013

[a] Results of neurocognitive tests were obtained from 19 of 40 healthy controls.

2.2. Imaging acquisition

Each participant was scanned with a 1.5 T MRI scanner (Vantage Atlas, Toshiba) using a standard quadrature head coil. Three-dimensional T1-weighted imaging was acquired using a gradient echo sequence in the sagittal orientation with the following parameters: repetition time = 12 ms, echo time = 5 ms, interval time = 300 ms, field of view = 256 × 256 mm, matrix = 256 × 256, flip angle = 20°, and slice thickness/gap = 1.5 mm/0 mm. The DTI data were obtained using an echo planar imaging sequence with diffusion gradients applied along 6 non-collinear directions and b = 1000 s/mm^2. For each subject, a total of 45 axial sections were obtained with following parameters: repetition time = 9450 ms, echo time = 100 ms, field of view = 260 × 260 mm, matrix = 128 × 128, flip angle = 90°, slice thickness/gap = 3.0 mm/0 mm, and NEX = 3. One volume was acquired without diffusion weighting (b = 0 s/mm^2) during each run. Additionally, the routine T1-weighted and T2-weighted fast-spin echo images were acquired to rule out any incidental pathological abnormalities. An experienced radiologist was responsible for providing an interview to ensure high-quality MR imaging.

2.3. Voxel-based morphometry

VBM was performed using Statistical Parametrical Mapping software 5 (SPM 5, http://www.fil.ion.ucl.ac.uk/spm) on MATLAB 7.10.0. The structural images were segmented into gray matter, WM and cerebrospinal fluid using a unified segmentation algorithm [22]. A non-linear registration tool was used to improve inter-subject registration. After "modulation", the images were affine-transformed to MNI space and smoothed with an 8 mm FWHM isotropic Gaussian kernel. Additionally, a WM mask was created using the Masking Toolbox (http://www.cs.ucl.ac.uk/staff/g.ridgway/masking/), based on the WM maps of all subjects.

2.4. Voxel-based analysis of FA images

After linear registration using automatic image registration, FA maps of each subject were computed using the DtiStudio software (https://www.mristudio.org/). Then, the b0 images of each subject were normalized to a mean T2-template in the SPM5 package, which generated the deformation parameters that were applied to the normalization for FA images. Finally, the normalized images were smoothed with a 10 mm FWHM isotropic Gaussian kernel.

2.5. Statistical analyses for VBM and voxel-based analysis of FA images

Random effect two-sample t-tests were conducted to detect regions with decreased WM volume and FA values. To compare WM volume between the cirrhotic patients and the healthy controls, the statistical thresholds were set at $p<0.05$ (false discovery rate (FDR) corrected) with a spatial extent threshold of cluster size = 500 mm^3. To compare