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Original Article

Relationship between network connectivity of corpus callosum and cognitive impairment in leukoaraiosis

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Abstract: Objective: This study aimed to evaluate the network connectivity of the corpus callosum by diffusion tensor imaging (DTI) and explore its relationship with cognition impairment. Methods: This was a prospective, single-center study. A total of 30 leukoaraiosis (LA) patients with Fazekas score of 2-3 and 20 MRI proven healthy subjects as controls were recruited into present study. The LA group was further divided into normal cognition group and mild cognition impairment group. The risk factors of cerebrovascular diseases, findings from blood biochemistry, cognition status and findings from MRI and DTI were recorded. DTI data were processed with PANDA software, and the FA and MD values of the genu, truncus and splenium of the corpus callosum were extracted. Results: There were no significant differences in the age, gender, education level, risk factors of cerebrovascular diseases and blood biochemical findings (P>0.05). In LA group, mini-mental state examination (MMSE) score and Montreal Cognitive Assessment (MoCA) score were significantly lower than in control group (P<0.05). In LA group, the FA value of the genu, truncus and splenium reduced dramatically when compared with control group, but MD value in LA group was significantly higher than in control group (P<0.05). In LA group, the MMSE score and MoCA score were positively related to FA value of the genu, truncus and splenium, but had no relationship with their MD value (P<0.05). Conclusion: The network connectivity of the corpus callosum is altered in patients with leukoaraiosis, and FA decline of the corpus callosum is closely related to the cognition impairment.

Keywords: Leukoaraiosis, diffusion tensor imaging; corpus callosum, network connectivity, cognitive impairment

Introduction

Leukoaraiosis (LA) is also known as white matter lesion (WML) [1]. The occurrence of LA is age dependent, and it has a high incidence in the old population. The typical presentations of LA on imaging examination are the symmetrical patchy or blotchy change in the white matter of the periventricular and semi-oval areas without morphological changes in the corpus callosum. LA is closely related to cognition disorder and may be a warning signal of early cognition impairment [2-4]. However, not all the patients with severe LA develop cognition impairment, suggesting that the severity of LA is not the sole factor related to the cognition impairment. There is evidence showing that the corpus callosum atrophy is closely associated with the cognitive dysfunction in LA patients [5, 6]. The corpus callosum is the largest fiber bundle connecting the left and right cerebral hemispheres and a channel bridging the cognition between hemispheres. We hypothesize that LA related cognition impairment is related to the abnormal network connectivity of the corpus callosum. In this study, diffusion tensor imaging (DTI) was performed to evaluate the network connectivity of the corpus callosum and assess its relationship with cognition impairment.

Subjects and methods

Subjects

This was a prospective, single-center study. Thirty patients with moderate to severe LA were recruited from the Department of Neurology of Tongji Hospital. The major symptoms included dizziness, headache, memory impairment, insomnia and anxiety. According to the cognition status, patients were subdivided into 2 groups: normal cognition group and mild cogni-

Table 1. Patients' characteristics at baseline and cognition

	LA group (n=30)	Control group (n=20)	P
Gender (M)	14	9	0.569
Age (yr)	65.5±9.78	64.25±6.27	0.616
Hypertension	21	11	0.217
Diabetes	10	4	0.242
Coronary heart disease	11	6	0.430
Smoking	6	3	0.477
Education (yr)	11.77±3.55	11.05±2.98	0.460
MMSE score	26.33±3.35	29.05±0.76	0.001
MoCA score	25.03±4.09	27.65±1.27	0.008

Notes: LA: Leukoaraiosis; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment.

tion impairment (MCI) group. Inclusion criteria for LA: (1) patients were aged 50-80 years; (2) Fluid-attenuated inversion recovery (Flair) MRI indicated LA and Fazekas score was 2-3 (score 2: n=18; score 3: n=12). Exclusion criteria: (1) patients had a history of stroke; (2) patients had other diseases of the central nervous system (such as infection, demyelinating disease and Parkinson's disease), (3) patients had a history of mental illness (such as schizophrenia and severe depression; (4) patients had dementia; (5) patients had severe somatic disease; (6) patients had alcohol or drug addiction; (7) patients were unable to cooperate with examination or follow up; (8) patients had contradictions to MRI examination. In addition, 20 subjected without abnormalities on the cranial MRI and any severe somatic disease were recruited as controls. The risk factors of cerebrovascular diseases, findings from neuropsychological assessment and blood biochemistry were recorded for each patient, and cranial MRI (T1+T2+ Flair) and DTI were conducted in all the patients. Cognition status was evaluated with Montreal Cognitive Assessment (MoCA) scale and MMSE scale. The diagnostic criteria for MCI were as follows [7]: 1) a memory complaint, 2) evidence of impaired memory, 3) generally preserved activities of daily living, and 4) not demented. The severity of LA was determined with Fazekas scale: score 0, no or only one spotty hyperintensity in the white matter by FLAIR MRI; score 1, multiple spotty hyperintensity in the white matter; score 2, hyperintensity become to merge (bridge formation) in the white matter; score 3, hyperintensity in the white matter become patchy. Score 1-3 may be physiologically present, and thus patients with score 1-3 were not diagnosed with LA.

Methods

MRI examination: All the MRI examination was conducted with Siemens magneto Trio 3.0 T in the Tongji Hospital of Tongji University. The head was fixed with a pad, and the body movement should be minimized. During the scanning, patients lied in a supine position and were asked to smoothly breathe. First, routine MRI scanning was performed (T1WI and FLAIR at cross section with SE sequence) to exclude lesions outside of the white matter. The parameters used for MRI scanning were as follows: TIWI (TR: 1530 ms, TE: 9 ms, FOV: 220×220 mm, slice thickness: 5 mm, FLIP: 150°, slices: 22); FLAIR (TR: 8500 ms, TE: 90 ms, TI: 2438.9 ms, FOV: 235×235 mm, slice thickness: 3 mm. FLIP: 150°, slices: 40); DTI (TR: 3100 ms, TE: 92 ms, thickness/gap=2 mm/0 mm, Matrix: 128×128, slices: 70, Nex: 2, Directions: 30, b value=0, 1000 s/mm^2).

Processing of DTI data: DTI data were processed with PANDA software (http://www.nitrc.org/projects/panda) [8]. Procedures used for processing were as follows: format transformation (DICOM into NifTI), extraction of b0 value, removal of non-brain components, image cropping, adjustment for vortex and head movement, calculation of DTI parameter, spatial standardization, Gaussian smoothing and fractional anisotropy (FA) and mean diffusivity (MD) based on the Johns Hopkins University white matter tractography were calculated. Importantly, the FA and MD values of the genu, truncus and splenium of the corpus callosum were extracted.

Statistical analysis: Statistical analysis was performed with SPSS version 18.0. Qualitative data were compared with Chi square test. Quantitative data with normal distribution are expressed as mean ± standard deviation. t test was used for comparisons of FA and MD values of the corpus callosum if normal distribution was found in these data. Pearson correlation analysis was employed for the evaluation of correlation between DTI data and cognition status. A value of $P<0.05$ was considered statistically significant.

Table 2. Biochemical parameters of LA patients and controls

	LA (n=30)	Control group (n=20)	P
Alanine aminotransferase	17.10±5.48	18.45±8.70	0.503
Creatinine	75.50±11.60	72.05±13.67	0.342
Total cholesterol	3.97±0.81	4.84±0.98	0.001
Low density lipoprotein-cholesterol	2.63±0.68	3.34±0.85	0.002
Homocysteine	14.79±6.24	12.63±3.41	0.166
Fasting plasma glucose	6.01±1.41	5.99±2.03	0.966
HaemoglobinA1C	6.46±1.26	6.55±1.29	0.800

Table 3. FA and MD values of the corpus callosum determined by DTI in LA patients and controls

	LA (n=30)	Control group (n=20)	P
Genu of the corpus callosum			
FA	0.531±0.021	0.565±0.168	0.000
MD×10^{-3} mm^2/s	0.884±0.058	0.845±0.042	0.013
Truncus of the corpus callosum			
FA	0.524±0.031	0.554±0.020	0.000
MD×10^{-3} mm^2/s	0.978±0.092	0.914±0.041	0.006
Splenium of the corpus callosum			
FA	0.574±0.035	0.608±0.068	0.026
MD×10^{-3} mm^2/s	0.958±0.078	0.907±0.031	0.007

Notes: FA: Fractional anisotropy; MD: Mean diffusivity.

Results

There were no marked differences in the gender, age, education level and risk factors of cerebrovascular diseases between LA patients and controls (P>0.05) (**Table 1**). In addition, the blood biochemical parameters (such as fasting plasma glucose, glycated hemoglobin, liver and kidney function, and homocysteine) were also comparable between them (P>0.05). In LA patients, the total cholesterol and low-density lipoprotein cholesterol were significantly lower than in controls (P<0.05) (**Table 2**).

The results from cognition evaluation are shown in **Table 1**. Normal cognition was found in 17 patients and MCI in 13 patients of LA group. All the controls had normal cognition. In LA group, the MMSE score was 26.33±3.35, which was significantly lower than in control group (29.05±0.76; P=0.001). In LA group, the MoCA score was 25.03±4.09, which was markedly lower than in control group (27.65±1.27; P=0.008).

The DTI data (FA and MD values) of the genu, truncus and splenium of the corpus callosum are shown in **Table 3**. In LA group, the FA values of the genu, truncus and splenium of the corpus callosum were significantly lower than in control group, but MD values in LA group were markedly higher than in control group (P<0.05). As shown in **Figure 1**, the number of fiber bundles reduced in the corpus callosum of LA patients as compared to controls.

Correlation between cognition status and DTI data in LA patients: Pearson correlation analysis showed the MMSE score and MoCA score were positively related to the FA value of the genu, truncus and splenium of the corpus callosum (P<0.05), but negatively associated with MD value although statistical significance was not observed (P>0.05) (**Table 4**).

Discussion

The changes in the brain are usually symmetrical in LA patients. Corpus callosum is a structure in the brain crossing the white matter of both hemispheres. Thus, it is speculated that LA might be associated with abnormality of network connectivity or degeneration of the corpus callosum. This study demonstrated that the network connectivity of the corpus callosum was definitely abnormal in LA patients.

Some LA patients have risk factors of cerebrovascular diseases such as hypertension and diabetes. Thus, LA has been regarded one of cerebral small vessel diseases in clinical practice. In our study, the blood lipids in LA patients were significantly lower than in controls. However, this finding has no significant clinical importance because some of patients have multiple hospital visits and received lipid-lowering therapy. LA is closely related to the age, and patients with mild, simple LA usually have no clinical symptoms. Our results showed LA could cause damage to the cognition which was characterized by the reductions in the attention, memory and execution of actions. The fibers related to the cognition and emotion surround the cerebral ventricle and are functionally asso-

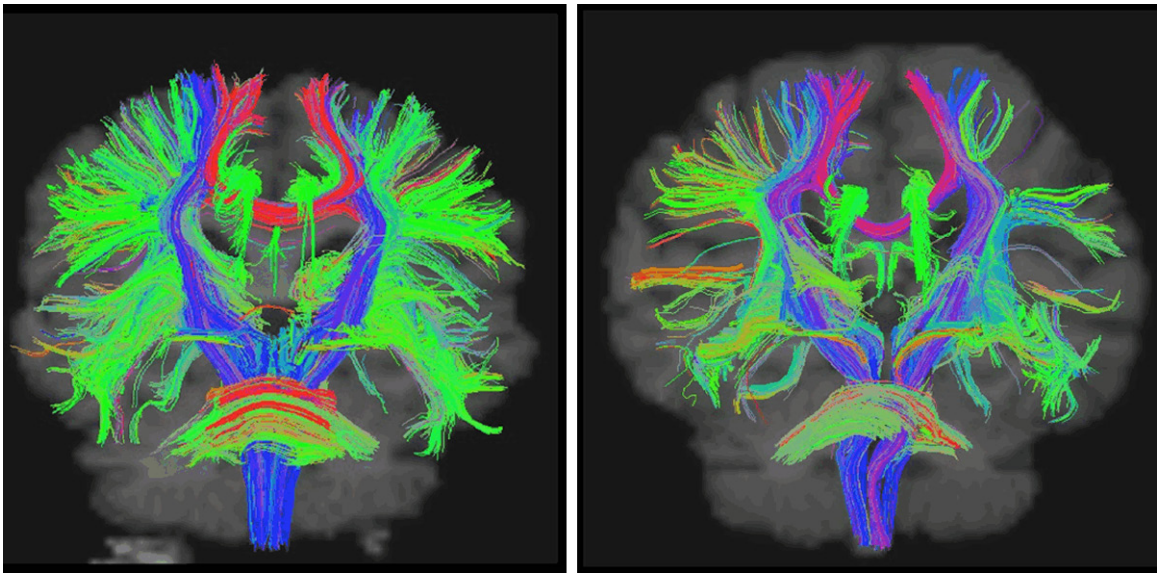

Figure 1. Fiber bundles in the white matter of LA patients (right) and healthy controls (left) displayed with TrackVis software. The number of fiber bundles reduced significantly in LA patients as compared to healthy controls, and some fiber bundles were discontinuous in LA patients.

Table 4. Correlation between cognition status and DTI parameters in LA patients (n=30)

	Genu				Truncus				Splenium			
	FA		MD		FA		MD		FA		MD	
	r	P	r	P	r	P	r	P	r	P	r	P
MMSE	0.78	0.000	-0.23	0.232	0.649	0.000	-0.076	0.690	0.413	0.023	-0.189	0.316
MoCA	0.771	0.000	-0.247	0.188	0.64	0.000	-0.062	0.744	0.435	0.016	-0.167	0.377

Notes: DTI: Diffusion tensor imaging; LA: Leukoaraiosis; FA: Fractional anisotropy; MD: Mean diffusivity; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment.

ciated with the cortex. Thus, severe LA may cause degeneration of these fibers, resulting in a series of disorders. Meta analysis shows WML is significantly related to different types of dementia [3]. Cross-sectional study in large communities and longitudinal cohort studies have revealed that LA volume has relationship with overall cognition status, LA progression is closely related to the deterioration of cognition impairment, especially in patients with lesions in the para-ventricular white matter, and the damages to the execution of actions, visual-spatial structure, processing rate and memory are the most obvious [2, 9]. LADIS study [2] showed LA was independently related to the cognition reduction, and severe LA was associated with systemic cognition dysfunction, especially the compromised execution of actions. Although LA is an important cause of cognition impairment, not all the patients with severe LA develop dementia. This implies that the severity of LA is not the sole cause of cognition impairment. The corpus callosum is composed of fiber bundles connecting the left and right hemispheres and an important structure bridging the signal transmission between two hemispheres. Whether cognition impairment is related to the change in the corpus callosum is still unclear. Previous study showed corpus callosum atrophy is closely associated with the cognition reduction in WML patients [5]. The LADIS study with 3-year follow up showed age-related white matter changes (ARWMC) may cause the progressive loss of tissues in the corpus callosum, resulting in corpus callosum atrophy. When LA causes the disruption of the network connectivity of the corpus callosum or the corpus callosum atrophy, the signal transmission and signal integration between hemispheres are affected, which may lead to a series of clinical symptoms (such as reductions in cognition and execution of actions as well as motor dys-

function) [10-12]. Thus, the abnormal network connectivity of the corpus callosum or the corpus callosum atrophy may be used to predict the cognition impairment.

In the presence of cerebral small vessel diseases, there is diffuse disruption of the network connectivity of neurons in the brain, which is characterized by reductions in the density and weight of the network connectivity, finally causing reduction in the signal transmission [13]. The change in the network connectivity of the corpus callosum occurs earlier than its morphological change. Thus, the detection of network connectivity of the corpus callosum is helpful for the early monitoring of cognition status in LA patients in clinical practice. MRI may provide the changes in the WML volume and DTI parameters and has been a major technique used to evaluate cerebral small vessel diseases and their progression [14]. In early LA, there is no structural change in the corpus callosum, and routine MRI usually fails to identify the abnormality of the corpus callosum. DTI overcomes the disadvantages of routine MRI and may reflect the amount of nerve fibers, the consistency of nerve fiber arrangement and the integrity of fiber bundles in the brain. Pathological evidence indicates FA value and MD value are associated with the amount of axons and myelin in the white matter of the brain, and the microstructural degeneration of the white matter in the brain is usually accompanied by the FA reduction and MD increase [15]. Thus, the FA reduction or MD increase reflects the disruption of white matter integrity in the brain.

In this study, DTI was employed to evaluate the network connectivity of the corpus callosum. Our results showed the FA values of the genu, truncus and splenium of the corpus callosum reduced, but their MD values increased significantly in LA patients, suggesting that the fiber integrity of the white matter is disrupted in the corpus callosum. In addition, the FA value was positively related to the cognition in LA patients, but MD negatively to the cognition, indicating that the microstructural change in the corpus callosum is accompanied by cognition impairment. However, the reason for this change is still poorly understood, and might be ascribed to low blood perfusion in the white matter of the deep brain because low perfusion may affect the fiber bundles crossing this area including the associative fibers, projecting fibers and joint fibers as well as to the degeneration of the corpus callosum itself. Microstructural degeneration is a precursor change of the corpus callosum atrophy. Otsuka et al found the reduction in diffusion anisotropy (DA) value of the corpus callosum was closely related to the corpus callosum atrophy, and the reductions in DA value and volume of the corpus callosum were independently associated with cognition impairment [16].

LA is an important warning factor of cognition impairment. It not only presents the signal change in the cerebral white matter, but the change in the network connectivity of the corpus callosum. Moreover, FA reduction of the corpus callosum is closely related to the cognition impairment.

Disclosure of conflict of interest

None.

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