Specific White Matter Impairments in Patients with Treatment-Refractory First-Episode Schizophrenia: A 1-Year Follow-up Pilot Study

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To the Editor: In the last 10 years, mounting evidence has confirmed that schizophrenia is associated with white matter (WM) impairment; this impairment exists even before the occurrence of an episode of schizophrenic symptoms. Widespread WM fiber tracts were affected in patients, especially in certain key brain regions, such as the arcuate fasciculus, fasciculi longitudinalis superior, and corpus callosum. A previous study reported that although there was no more than 1% WM impairments in schizophrenic patients, it is nonetheless a stable and specific aberrant pathological feature of schizophrenia.[1]

There are several methods based on the voxel-based morphometry or voxel-based analysis that can be used to investigate WM impairments in schizophrenic patients. However, the tract-based spatial statistics (TBSS) method is favored for investigations of schizophrenia because it minimizes the problem induced by smooth processing and avoids the problem of image registration inaccuracy. TBSS can also determine if the aberrant fractional anisotropy (FA) and mean diffusivity (MD) are induced by WM or adjacent tissue.[2] Hence, the present pilot study adopted the TBSS method to explore WM differences between first-episode schizophrenic patients with clinical remission (CR) and treatment-refractory (TR).

Twenty patients with first-episode schizophrenia who exhibited CR group and 20 well-matched first-episode schizophrenic patients who became TR group after a 1-year follow-up observation were analyzed. The patients were diagnosed using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) by two senior psychiatrists. Patients had not received systematic treatment (according to China's treatment guidelines for schizophrenia) in the 2 months before participating in the study. The positive and negative symptoms scale (PANSS) was used to assess the severity of the schizophrenic symptoms. According to the assessment at the time of 1 year of systematic treatment, the patients who were in remission or TR were determined according to the criteria listed in China's schizophrenia treatment guidelines.

The TR group's demographic and clinical information were as follows: mean age was 34.7 ± 7.2 years; 7 females, 13 males; mean educational level was 10.9 ± 2.1 years; mean illness duration was 6.1 ± 2.1 months; and mean score of PANSS was 122.2 ± 34.7. The CR group's demographic and clinical information were as follows: mean age was 32.5 ± 6.3 years; 7 females, 13 males; mean educational level was 11.7 ± 3.7 years; mean illness duration was 5.7 ± 1.4 months; and mean score of PANSS was 126.5 ± 32.9. The mean antipsychotic dosage (chlorpromazine equivalents) was 603.0 ± 40.6 mg/d in the TR group and 420.5 ± 74.0 mg/d in the CR group ($P < 0.05$).

Magnetic resonance imaging (MRI) data were acquired using a 3.0-Tesla MR system (Discovery MR750, General Electric, Milwaukee, WI, USA). Diffusion tensor images (DTIs) were acquired by an echo-planar imaging sequence with parameters as follows TR = 5800 ms; TE = 77 ms; matrix = 128×128; FOV = 256×256 mm; in-plane resolution = 2 mm $\times$ 2 mm, slice thickness = 3 mm, no gap; totally 48 axial slices; 25 encoding diffusion directions with two values of b (b = 1000 and 2000 s/mm²) for each direction and 10 nondiffusion-weighted images (b = 0 s/mm²). Analysis for DTI was performed by the FMRIB Diffusion Toolbox from the FSL processing software package (http://www.fmrib.ox.ac.uk/fsl). FSL's eddy correct tool was adopted to correct the motion and eddy current distortion in

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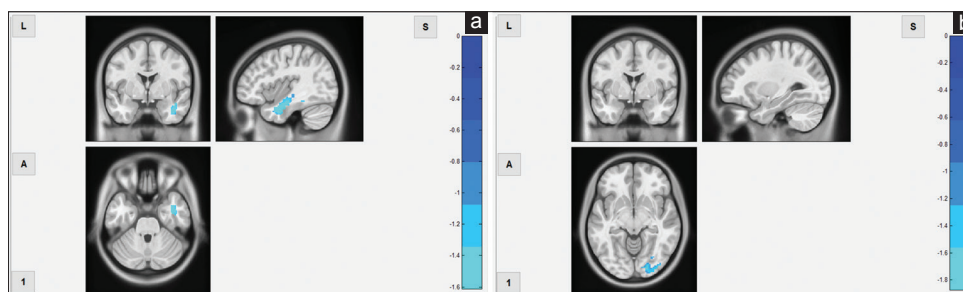E-Mail: kexynj@hotmail.com

Figure 1: In patients with treatment-refractory schizophrenia, white matter impairment located mainly in the right temporal lobe (a) and the right occipital lobe (b).

the first step which was run with its default options. FSL's Brain Extraction Tool was used to complete the step of skull-stripping from the raw data. FSL's dtifit tool was used to generate a diffusion tensor model that was fit at each voxel and thereafter used to generate maps for each of the diffusivity measures (MDs, axial diffusivity, radial diffusivity [RD], and FA). TBSS method was adopted to conduct voxel-wise processing of MDs. Group statistical analysis was then calculated on voxels within the WM skeleton mask only. This method restricted the voxel-wise level analysis to only those voxels with high confidence of lying within the equivalent WM manner in each individual. The nonlinear warps and skeleton projections were applied to MD and RD by TBSS non-FA. Differences in FA, MD, and RD between the two groups were calculated using voxel-wise independent two-sample t-tests by randomization, and the nonparametric analysis tool in FSL. The threshold-free cluster enhancement option was used to complete the family-wise error (FWE) corrected,[3] $P < 0.05$ to obtain cluster inferences.

Compared to CR group, the WM impairment of TR group was located mainly in the right temporal lobe [Figure 1a] and in the right occipital lobe [Figure 1b] after FWE correction. However, a deceased FA correlating to the severity of the TR schizophrenia (TRS) symptoms was not found in TR group. The brain regions in which WM impairment existed in the TR group indicated that information communication abilities were impaired in these and other brain regions, causing deterioration of schizophrenic symptoms, and the patient might become TR. Previous studies reported that WM impairment was associated with TRS, and those results combining with our findings supported the hypothesis that the impairment of information communication capability among brain regions is one of the pathological bases of TRS.[4,5]

There were several limitations in this study: the patients were only followed up for 1 year, and there was not enough follow-up to assess the possibility that some TRS patients might have acquired CR in the next year or months. Health controls were not set in this study. A long-term follow-up of a large sample study, including well-matched healthy controls, will be conducted in future studies to dynamically explore the neural basis of TRS.

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