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Atypical antipsychotic drug treatment for 6 months restores N-acetylaspartate in left prefrontal cortex and left thalamus of first-episode patients with early onset schizophrenia: A magnetic resonance spectroscopy study

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ABSTRACT

Early onset schizophrenia (EOS) is often associated with poorer outcomes, including lack of school education, higher risk of mental disability and resistance to treatment. But the knowledge of the neurobiological mechanism of EOS is limited. Here, using proton magnetic resonance spectroscopy, we investigated the possible neurochemical abnormalities in prefrontal cortex (PFC) and thalamus of first-episode drug-naïve patients with EOS, and followed up the effects of atypical antipsychotic treatment for 6 months on neurochemical metabolites and clinical symptoms. We measured the ratios of N-acetylaspartate (NAA), choline (Cho) to creatine (Cr) in 41 adolescents with first episode of EOS and in 28 healthy controls matched for age, gender, and years of education. The EOS patients presented with abnormally low NAA/Cr values in the left PFC and left thalamus with a reduced tendency in the right PFC compared with healthy controls. No significant differences were detected between groups for Cho/Cr in PFC and thalamus in any hemisphere. After atypical antipsychotic treatment for 6 months, the reduced NAA/Cr in the left PFC and left thalamus in EOS patients was elevated to the normal level in healthy controls, without any alteration in Cho/Cr. We also found that there was no significant correlation between the neurochemical metabolite ratios in the PFC and thalamus in patients with EOS, and clinical characteristics. Our results suggest that there was neurochemical metabolite abnormalities in PFC and thalamus in EOS patients, atypical antipsychotic treatment can effectively relieve the symptoms and restore the reduced NAA in PFC and thalamus.

1. Introduction

Early onset schizophrenia (EOS) is defined as schizophrenia with onset before 18 years of age, with more serious cognitive deficits, premorbid dysfunction, structural and functional changes in brain, as well as worse prognosis compared with the patients with onset at adult age (Cannon et al., 1999). Genetic predisposition and neurodevelopmental deviance play an important role in the pathogenesis of EOS (Kumra and Charles Schulz, 2008; Vourdas et al., 2003). A large number of studies using MRI have shown that patients with EOS presented neuroanatomical structural abnormalities in frontal cortex (Arango et al., 2012), cingulate cortex (Tang et al., 2010) and parietal lobe (Kumra et al., 2012). Moreover, several functional magnetic resonance imaging (fMRI) studies have reported decreased regional homogeneity of resting-state brain activities in EOS in bilateral medial prefrontal cortex (mPFC) as well as increased functional connectivity between the medial frontal gyrus and other areas of the default mode network (Tang et al., 2013). Diffusion tensor imaging (DTI) studies have demonstrated that regional fractional anisotropy of the white matter was decreased in anterior cingulum, corpus callosum, prefrontal lobe and temporal lobe of patients with EOS and that the connectivity among these brain regions was abnormal (Tang et al., 2010; Wei et al., 2011).

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive analytical technique that allows quantification of several neurochemical metabolites in the brain, such as N-acetylaspartate

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(NAA), choline (Cho) and creatine (Cr). NAA is synthesized in neuronal mitochondria from acetyl-coenzyme A and aspartate by the enzyme NAA transferase, which has been considered as a marker of neuronal integrity and an indicator for the number of viable neurons (Klar et al., 2010; Reynolds and Reynolds, 2011). Cho arises from cell membrane phospholipids, which marks cellular density and membrane turnover (Han and Gross, 1991). Usually, the quite constant neuronal constituent Cr, representing the energy metabolism of the cell, is also detected to serve as a standard for comparison (Kraguljac et al., 2012; Uhl et al., 2011). Converging evidence has demonstrated that adult schizophrenic patients exhibited neurochemical metabolic abnormalities in several brain regions revealed by in vivo MRS, which was modulated by antipsychotic treatment (Kraguljac et al., 2012; Natsubori et al., 2013). To our knowledge, however, few studies have reported about the properties of neurochemical metabolites in the brain of patients with EOS by in vivo MRS.

In order to analyze the effects of atypical antipsychotic treatment on neurochemical metabolites, in the present study, using multiple-voxel ^{1}H-MRS, we investigated the alterations of NAA/Cr and Cho/Cr in the PFC and thalamus in first-episode EOS patients compared with the healthy age- and gender-matched controls.

2. Methods

2.1. Participants

2.1.1. Schizophrenic patients

Patients were recruited from psychiatric wards at the Mental Diseases Prevention and Treatment Institute of Chinese PLA, PLA 91st Central Hospital, Henan province, China, from August 2007 to October 2012. Inclusion criteria were (a) met DSM-IV criteria for schizophrenia; (b) never taken any antipsychotic medications; (c) did not take any drugs affecting the neurotransmitter acetylcholine within 14 days before enrollment; (d) the total positive and negative syndrome scale (PANSS) score for psychopathology ≥ 60; (e) age between 12 and 18 years, first episode schizophrenia, and right-handed; (f) no history of traumatic brain injury; (g) re-evaluated 6 months after enrollment to finally confirm the diagnosis of schizophrenia. Exclusion criteria were (a) any contraindications to MRI scanning; (b) serious physical illness or mental retardation; (c) alcohol or substance abuse history.

2.1.2. Healthy controls

Healthy volunteers (12–18 years of age) were recruited from the general community and underwent comprehensive interviews including the Structured Clinical Interview for DSM-IV (SCID I and SCID II (Bustillo et al., 2010)). Healthy controls were matched for age, sex and educational level to the patients. Healthy volunteers have no history of traumatic brain injury, family history of psychiatric or neurological disorders or psychoactive substance abuse. All subjects were right-handed, and their healthy conditions were confirmed by psychiatrists.

All participants or their guardians gave written informed consent before experiments. All experimental procedures were approved by the Ethics Committee of PLA 91st Central Hospital.

2.2. ^{1}H-MRS

The multiple-voxel ^{1}H-MRS was performed on a 1.5 T MR scanner (Siemens Avanto l.5, German) equipped with a standard head coil by a radiologist and a professional technician (Szulc et al., 2011). The head coil was used for radio frequency (RF) transmission and reception of the nuclear magnetic resonance (NMR) signals.

MRI acquisition: Axial T1- weighted spin-echo (SE) imaging with repetition time (TR) of 500 ms and echo time (TE) of 7.8 ms; axial and sagittal T2-weighted fast spin-echo (FSE) imaging with TR of 4000 ms and TE of 95 ms; water-suppressed imaging with TR of 9000.0 ms, TE of 90.0 ms and inversion time (TI) of 2500.0 ms; the slice thickness of 8 mm. Both axial and sagittal imaging was performed to confirm there were no intracranial lesions in the participants. All the parameters of the MRI imaging were verified by radiologist.

^{1}H-MRS acquisition: Axial T1-weighted MR image shows the position of the voxel for spectroscopy. To confirm the consistency, the symmetric regions of the same volume in bilateral PFC and thalamus were selected as the regions of interest (ROI) (Fig. 1). The ROIs in PFC were located in the frontal white matter anterior to the bi-lateral ventricle anterior angles and avoided influences of the sulci and cerebrospinal fluid. The ROIs in thalamus were located in the front of bi-lateral ventricle posterior angles. Spectra were acquired using the multiple-voxel FSE sequence scanning (TR/TE=1500/135 msec, number of averages (NA)=4, scanning time=7 min 12 s, field of view=230 mm, voxel size $10 \times 10 \times 15$ mm^3).

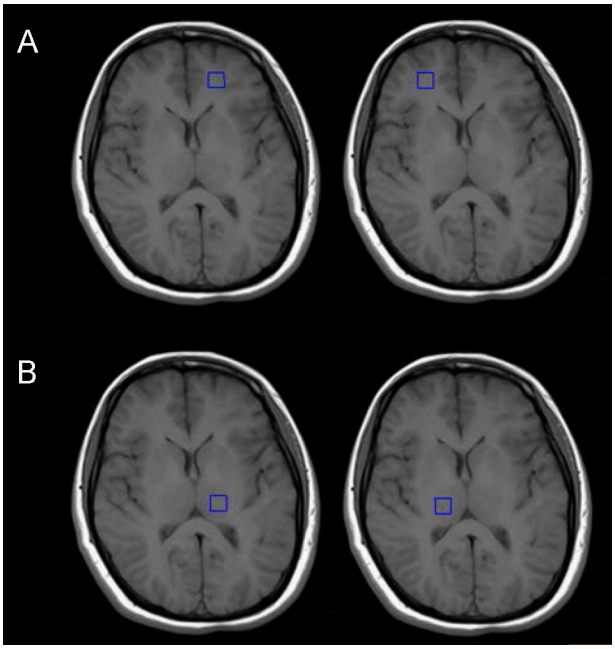

Fig. 1. Position of the ^{1}H-MRS voxels in the prefrontal cortex (A) and thalamus (B).

Manual shimming was performed, and the water peak full with half maximum (FWHM) linewidth was kept lower than 20 Hz. Water suppression was automatically processed by the scanner, and the ratio was larger than 97%. Signals were converted to data and spectrum figures by Siemens software (Syngo MR B15) to show the relative levels of NAA, Cho to Cr, and the data were expressed as 10-6. The area under the peak of NAA, Cho and Cr was measured, and the NAA and Cho were quantified with respect to Cr by the computer automatically. The assurance of spectrum quality was similar as previous report (Natsubori et al., 2013).

The ^{1}H-MRS scanning was performed within 24 h of hospital admission when the schizophrenic patients were free of antipsychotics (before treatment) and 6 months after atypical antipsychotic treatment (after treatment). Healthy controls underwent ^{1}H-MRS scanning after their enrollments. Scanning was applied daily from 4:30 to 6:00 p.m.

2.3. Psychopathological assessment and pharmacotherapy procedures

The clinical symptoms, severity of disease were evaluated with the PANSS (Kay et al., 1987) and clinical global impression (CGI) (Guy, 1976) by two psychiatrists, and the MRS scanning was performed on the same day. Values of the scales from the two psychiatrists were subjected to consistency test, the values of psychopathological assessment with interclass correlation coefficient above 0.80 were accepted.

All patients in the medication group received single atypical antipsychotic drugs for 6 months, including risperidone, quetiapine, and aripiprazole. Oral dosages of antipsychotics were adjusted according to the principle of producing maximum efficacy with minimum adverse reactions. Patients with untoward side effects were given single symptomatic treatment, but never received any other drugs within 24 h before MRS scanning.

2.4. Statistical analysis

All analyses were performed using the statistical package SPSS 16.0. Paired *t*-test (two-tailed) was applied to evaluate significant changes in clinical symptoms and index of ^{1}H-MRS in the same individual before and after atypical antipsychotic treatment. Differences between control and patient groups in demographical characteristics and index of ^{1}H-MRS were determined by independent *t*-test. The correlation between ^{1}H-MRS index was tested using Pearson correlation analysis. The level of significance was set at $\alpha=0.05$.

3. Results

3.1. Demographical and clinical characteristics

The demographical and clinical characteristics of schizophrenic patients and healthy controls were summarized in Table 1. 46 patients were recruited, of which five patients did not finish