Altered Metabolic Integrity of Corpus Callosum Among Individuals at Ultra High Risk of Schizophrenia and First-Episode Patients

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Background: The disconnectivity hypothesis as part of the neurodevelopmental model of schizophrenia states that an abnormality in brain development causing impaired corticocortical or interhemispheric connectivity leads to cognitive deficits and symptoms of the illness. Previous studies showed the altered morphology of corpus callosum in patients with schizophrenia. We investigated the metabolic integrity of corpus callosum of individuals at ultra high risk (UHR) of developing schizophrenia and first-episode patients.

Methods: We studied 17 individuals at UHR of developing schizophrenia, 14 first-episode schizophrenia patients, and 30 healthy control subjects. We measured the absolute concentrations of neurometabolites and T2 relaxation time of tissue water ($T2_B$) in the genu region of corpus callosum by using proton magnetic resonance spectroscopy.

Results: N-acetylaspartate (NAA) concentrations were decreased and $T2_B$ values were prolonged in the UHR cases as well as in the first-episode patients, compared with the control subjects. The difference between the NAA concentrations of the UHR cases and first-episode patients was also significant. The NAA concentrations of the UHR cases and first-episode patients were correlated with the severity of negative symptoms.

Conclusions: We demonstrated the disrupted metabolic integrity of corpus callosum among individuals at UHR of schizophrenia and the first-episode patients.

The neurodevelopmental model of schizophrenia postulates that genetically mediated biological factor(s) cause subtle abnormalities in brain development, which eventually lead to the cognitive deficits and psychotic symptoms of the illness (1,2). Recent studies have provided increasing evidence for the disruption of white matter integrity in schizophrenia, which might impair corticocortical connectivity (3–9). Corpus callosum (CC) is the major interhemispheric white matter commissure that contributes to the development of cerebral lateralization by enabling the functional integration of neuronal systems that are located in separate cerebral hemispheres. Previous studies have demonstrated the decreased functional and structural cerebral lateralization in patients with schizophrenia, which indicated the possibility of a disturbed interhemispheric connectivity in schizophrenia (10–12).

The size and shape differences of CC in schizophrenia have been extensively studied in previous research, hypothesizing that structural changes in CC might be a substrate for impaired interhemispheric connectivity. However, the results of these morphometric studies are inconsistent. Although the majority of these reported a reduced size of CC in patients with schizophrenia, several others found no difference (13–18). A meta-analysis by Woodruff *et al.* (19) on 313 cases demonstrated a small but significant decrease in midsagittal area of CC in patients with schizophrenia. Moreover, the correlation of decreased callosal

size with the severity of psychotic symptoms was demonstrated (20,21). Previous diffusion tensor imaging (DTI) studies in patients with schizophrenia are not conclusive about the macrostructural integrity of CC. Some of the DTI studies with a voxel-based design demonstrated the significant alteration of fractional anisotropy in CC of patients with schizophrenia (7,22–27). However, others revealed no significant change in CC (3,28,29). DTI studies with a region-of-interest design investigating CC confirmed the alteration in the callosal fractional anisotropy in schizophrenia (30,31). However, some contrary results have also been reported (32,33).

Although previous morphometric studies seem to support the callosal disconnectivity hypothesis, their results are not consistent enough to draw a conclusion. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive method to investigate neurochemical changes in various pathologic and physiologic conditions of brain. ^{1}H-MRS can demonstrate subtle neuro and axonal dysfunction, even in normal-appearing cerebral tissue on magnetic resonance imaging (MRI) and DTI images (34,35). Recent studies have demonstrated the strong correlation between ^{1}H-MRS measurements and functional integrity of white matter (36). Thus ^{1}H-MRS is an alternative imaging method that can be used to investigate white matter integrity in schizophrenia. Previous MRS studies are not conclusive about the integrity of white matter in schizophrenia, although a number of them revealed an altered metabolic integrity in frontotemporal white matter (9). In our previous study, we had assessed the metabolic integrity of CC in patients with schizophrenia by using ^{1}H-MRS (37). Its results revealed a decrease in callosal N-acetylaspartate (NAA) concentration. Because we had not found any correlation between NAA concentration and duration of illness, we had proposed that the pathophysiologic changes leading to the altered metabolic integrity in CC had a neurodevelopmental basis. In the current study, we aimed to test this proposal by investigating the metabolic integrity of CC in prodromal phase of the illness.

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The onset of frank psychotic symptoms of schizophrenia is generally preceded by a prodromal phase, which is clinically characterized by the presentation of nonspecific negative and attenuated positive symptoms (2,38,39). The detection of prodromal patients before the onset of formal psychosis has been investigated in recent studies (38,40,41), and the criteria to identify prospectively individuals at ultra high risk (UHR) of developing schizophrenia, who are supposed to be in prodromal phase, have been defined (41,42). We aimed to investigate the metabolic integrity of CC in individuals at UHR of schizophrenia. On the basis of the neurodevelopmental model of schizophrenia and the results of our previous study, we hypothesized that the pathology leading to callosal metabolic alterations exists in prodromal phase of the illness. We sought to measure the absolute concentrations of major neurometabolites and T2 relaxation times of tissue water ($T2_B$) in CC of individuals at UHR, first-episode schizophrenia patients, and healthy control subjects. We also investigated the relationship between neurometabolite concentrations, $T2_B$ values in CC, and severity of symptoms.

Methods and Materials

Subjects

We studied 17 individuals at UHR of developing schizophrenia and 14 first-episode schizophrenia (Structured Clinical Interview for DSM-IV [SCID]) patients. We used the previously defined criteria for identification of individuals at UHR of schizophrenia (41–43). The individuals at UHR met the criteria for at least one of three groups at intake, characterized by specific state or trait risk factors (or both) for psychosis. The three groups were 1) brief, limited intermittent psychotic symptoms (BLIPS; $n = 4$); 2) attenuated symptoms ($n = 9$); and 3) trait plus state risk factors (i.e., genetic risk plus decrease in functioning; $n = 4$). The first group was characterized by brief episodes of psychotic symptoms above the threshold but not sustained beyond a week. BLIPS was operationally defined using the Brief Psychiatric Research Scale (BPRS; 1–7 points) as follows: a score of 4 or more on the hallucination subscale, a score of 5 or more on the unusual thought content, or a score of 4 or more on the conceptual disorganization items of the BPRS. These levels had to be sustained for less than 1 week. Operational criteria for the group with attenuated symptoms defined as follows; to meet at least one of the criteria for DSM-IV schizotypal personality disorders plus a score of 2–3 on hallucination, or 3–4 on unusual thought content, or 3–4 for suspiciousness items of BPRS. The third group comprised patients with a family history of psychotic disorder in a first-degree relative plus nonspecific symptoms and impaired functioning resulting in a decrease of 30 points on the Global Assessment of Functioning scale within the previous 12 months. Details of our definition of first-episode schizophrenia and procedure were given in our previous publications (44,45). Briefly, the patients diagnosed as schizophrenia by means of the SCID were then reevaluated at a consensus meeting, incorporating clinical and SCID data (46). A patient was accepted in his or her first psychotic episode if the following conditions were fulfilled: no past diagnosis of nonaffective psychosis; no previous inpatient care and antipsychotic treatment. The date of onset of the first identifiable positive symptoms was timed in the research team on the basis of a best-estimate approach using data gathered from multiple sources including medical records and patient and family interview. For the first-episode patients, we defined duration of untreated psychosis (DUP) from the time of onset of the first positive symptoms to the first admission. All the UHR cases were drug-naïve during their ^{1}H-MRS examinations. Seven of the first-episode patients were taking risperidone, and three of them were taking olanzapine. The mean duration of antipsychotic treatment during the ^{1}H-MRS examinations was 5.1 ± 3.4 days. The mean antipsychotic dose of equivalent for risperidone was 3.9 ± .8 mg (47).

We evaluated the psychopathology by using BPRS (48), the Scale for the Assessment of Positive Symptoms (SAPS) (49), and the Scale for the Assessment of Negative Symptoms (SANS) (50).

Because the first-episode patients and UHR individuals differed in respect to age and sex distribution, two control groups for each patient group were created. Thirty control subjects (15 control subjects for each patient group) who were age-, sex-, and education-level-matched with the patients were recruited from the healthy volunteers (SCID, nonpatent edition). The exclusion criteria for patients and control subjects included any contraindication for MRI, organic psychosis, disorders known to cause cognitive deficits, alcohol or drug abuse, marijuana use, any history of previous psychotic or manic episode, or previous treatment with an antipsychotic or mood stabilizing agent, or a substance-induced psychotic disorder, neurodegenerative disease, seizure, central nervous system infection, cerebrovascular disease, diabetes mellitus, and head trauma causing loss of consciousness that lasted more than 30 min or that required hospitalization. All the patients and control subjects were right-handed (according to the Edinburgh handedness inventory). Written informed consent were obtained from patients and control subjects before ^{1}H-MRS examinations, and the study was approved by the local Human Subject Committee.

Cranial MRI

We performed all the conventional cranial MRI and ^{1}H-MRS examinations on a 1.5-T superconducting MRI and spectroscopic system (Symphony Maestro, Siemens Medical Systems, Erlanger, Germany). Conventional cranial Muris were acquired to position ^{1}H-MRS volume of interest (voxel) to identify any cerebral pathology defined in the exclusion criteria and to calculate the cerebral parenchymal volumes. Anatomic MRI sequences included 1) axial fast spin echo T2-weighted images (repetition time [TR] = 5790 msec, echo time [TE] = 103 msec, slice thickness = 5 mm); 2) coronal SE T1-weighted images (TR = 530 msec, TE = 30 msec, slice thickness = 3 mm); 3) sagittal T1-weighted magnetization-prepared rapid acquisition gradient echo images (MP-RAGE; TR = 11.08 msec, TE = 4 msec, inversion time = 300 msec, relaxation delay time = 500 msec, flip angle = 15°, field of view = 256 × 192 mm, matrix size = 256 × 192, voxel size = 1 × 1 × 1.3 mm).

^{1}H-MRS: Data Acquisition and Metabolite Quantification

On sagittal MR images, CC was divided into sub regions as described in previous studies by Highley (51) and Witelson (52). The ^{1}H-MRS voxels were placed into superior and posterior genu regions of CC by excluding cingulate gyrus and cerebrospinal fluid (CSF) around CC (Figure 1).

Quantification of metabolite concentrations was performed by using the internal water standard method (53). We obtained water-suppressed and nonsuppressed proton MR spectra. Localization of both water-suppressed and unsuppressed MR spectra was achieved with the use of a stimulated echo acquisition (STEAM; TR = 3.5 sec) sequence. Water suppression was performed with three chemical shift selective (CHESS) saturation pulses at the water resonance. For computation of T2 relaxation