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Callosal size in first-episode schizophrenia patients with illness duration of less than one year: A cross-sectional MRI study

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ABSTRACT

Previous studies have reported a reduction in the size of the corpus callosum (CC) on the mid-sagittal plane in patients with schizophrenia. However, findings for the size of the callosal area in patients with first-episode schizophrenia (FESz) are inconsistent. A possibility for these conflicting results is that the duration of illness in patients with FESz affects the CC size. The present study investigated the CC size abnormalities in patients with FESz. Forty-six patients with FESz whose duration of illness was less than 1 year and 46 age-, sex-, and handedness-matched healthy controls were recruited to examine the CC size using magnetic resonance imaging. We measured the area of the CC using the Witelson's scheme, which divided the whole area into seven subdivisions. Analysis of covariance indicated there was no difference in the whole or regional areas of the CC between patients with FESz and healthy controls. The rostrum of the CC was significantly correlated with the total score for negative symptoms and some of the subtotal scores. Our findings indicate that there was no reduction in the whole or regional area of the CC among patients with FESz. When comparing the callosal morphology and symptoms, negative symptoms increased in severity as the rostrum area of the CC decreased in size. Further studies are needed to investigate whether the size of the anterior CC is associated with the pathology observed in the early stages of FESz.

1. Introduction

The corpus callosum (CC) is a major commissural fiber connecting each hemisphere of the brain. It was presumed that the pathology observed in patients with schizophrenia involved dysfunctions in neural connectivity; thus, the CC has been the primary focus for schizophrenia research (David, 1994). Previous studies using magnetic resonance imaging (MRI) have shown morphological abnormalities associated with schizophrenia (Woodruff et al., 1995; Arnone et al., 2008). Results from studies indicated that a delay or reduction in myelination occurs in the CC of individuals with schizophrenia (Innocenti et al., 2003; Crow et al., 2007).

In studies on first-episode schizophrenia (FESz), patients with FESz also exhibited smaller whole and regional areas of the CC than healthy individuals (Hendren et al., 1995; Keshavan et al., 2002; Bachmann et al., 2003; Collinson et al., 2014). However, two studies reported inconsistent results and did not find reductions in the whole and regional areas of the CC in patients with FESz (Hoff et al., 1994; Walterfang et al., 2008a). One of the reasons for these inconsistent findings may be due to the confounding effect of illness duration. The studies that reported a reduction of the CC area included patients whose average illness duration was comparatively long (ranging from approximately 2 to 4 years) (Keshavan et al., 2002; Collinson et al., 2014). In contrast, the other studies that demonstrated no reduction included patients whose average illness duration was less than 1 year (Hoff et al., 1994; Walterfang et al., 2008a). Another morphological study showed similar results with regard to the relationship between illness duration and brain morphology. Molina et al. (2004) found that the prefrontal gray matter volume in patients with FESz whose illness duration was less than 1 year was not significantly reduced compared to healthy controls, while in short-term chronic patients

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with illness duration ranged from 1.5 to 6 years, the volume significantly decreased. Accordingly, significant morphological changes in the CC of patients with FESz having illness duration of less than 1 year may not have occurred. However, there have been no studies to investigate the morphological changes in the CC, including only the patients with FESz whose illness duration was less than 1 year.

Another challenge for studying the CC is to establish the subregions of the CC whose volumes are possibly reduced in patients with FESz. Various methods for dividing the CC into subregions have been proposed. Among them, the most popular method was proposed by Witelson (1989), which defined subdivisions of CC based on anatomical connectivity. In a study on FESz, Keshavan et al. (2002) used a method based on the Witelson's scheme to examine morphological abnormalities and reported regional reduction in the CC. However, this method has not been used to investigate abnormalities of the CC in patients with FESz having illness duration of less than 1 year.

The aims of this study were to examine the whole and regional areas of the CC using the Witelson's scheme and to investigate the morphological abnormalities of the CC within patients with FESz whose duration of illness is comparatively short (less than 1 year). These changes were compared to age-, sex-, and handedness-matched controls to avoid the influence of confounding factors known to affect callosal size (Witelson, 1989). Furthermore, we explored the relationships between the CC area and illness characteristics and symptoms.

2. Methods

2.1. Participants

The present study included 46 patients with FESz who met the ICD-10 research criteria for schizophrenia (World Health Organization, 1993). All patients were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. All patients were followed up regularly also after MRI scanning by experienced psychiatrists, and the diagnosis of schizophrenia was confirmed for all cases at least 6 months after the onset of illness based on the information acquired from a detailed chart review. Patients with FESz were defined as those experiencing their first episode of schizophrenia and whose illness onset was within 1 year at the time of scanning. Clinical symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984).

A total of 46 age- and sex-matched healthy individuals were also recruited from among the community, hospital staff, and university students. They were administered a questionnaire consisting of 13 items concerning their personal history of illness (e.g., history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, and substance use) and two items concerning their family history of illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives.

All participants were right-handed on the basis of a handedness rating scale (Okada et al., 2014) and were physically healthy. None of the participants had a serious head trauma, neurological illness, substance abuse disorder, or serious medical disease, but we did not assess their cigarette smoking behavior. All participants were screened for gross brain abnormalities by neuroradiologists. Demographic and clinical information of the participants are shown in Table 1. There was no significant difference in the demographic data except for the education level between patients with FESz and controls. There was no difference in all demographic data between males and females. For clinical information of illness, the age at onset for females was earlier than that for males ($t = 2.053$, $p = 0.046$), whereas other clinical information was not significantly different (all $p > 0.05$). A possible explanation for females exhibiting an earlier age at onset in contrast to previous studies (e.g., Castle et al., 1998; Häfner et al., 1998) was that our study included only adolescent and young adults because the age range of patients with schizophrenia influences results regarding the sex difference in age at onset (Thorup et al., 2007; Venkatesh et al., 2008). In this study, the age range of patients with FESz was relatively narrow (males: 16.9–37.6 years, females: 16.7–27.7 years).

This study was approved by the Committee on Medical Ethics of Toyama University. Written informed consent was obtained from all participants after the procedures had been fully explained.

2.2. Image acquisition

T1-weighted images were scanned using a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding contiguous slices of 1.0 mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time = 24 ms, echo time = 5 ms, flip angle = 40°, field of view = 256 mm, and matrix size = 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm.

2.3. Image analysis

Each T1-weighted image was realigned to standardize for difference in head till during the scanning and were then

Table 1
Demographic and clinical data of participants.

	Patients with FESz		Control		Diagnosis group comparison	
	male (n = 26)	female (n = 20)	male (n = 26)	female (n = 20)		
Age (years)	25.1 ± 5.2	22.6 ± 3.2	25.9 ± 3.3	25.1 ± 5.5	t = 1.630	$p = 0.107$
Education (years)	13.4 ± 2.1	13.5 ± 2.1	17.8 ± 2.0	15.3 ± 1.6	t = 7.422	$p < 0.001$
Parental education (years)	13.1 ± 2.3	13.1 ± 1.9	13.7 ± 2.1	13.6 ± 2.5	t = 0.281	$p = 0.779$
Age at onset (years)	24.7 ± 5.1	22.2 ± 3.3	–	–	–	–
Duration of illness (months)	4.3 ± 2.6	6.0 ± 3.8	–	–	–	–
Duration of medication (months)	2.8 ± 2.7	4.1 ± 8.1	–	–	–	–
HPD equivalent (mg/day)	10.6 ± 9.4	7.1 ± 8.3	–	–	–	–
SAPS total score	24.8 ± 24.5	29.9 ± 20.5	–	–	–	–
SANS total score	47.3 ± 25.2	57.5 ± 23.2	–	–	–	–
Intracranial volume (cm^3)	1522.4 ± 118.9	1 344.9 ± 86.3	1542.2 ± 108.6	1301.0 ± 78.0	t = 0.247	$p = 0.805$
Total brain volume (cm^3)	1233.9 ± 130.1	1117.2 ± 71.7	1252.7 ± 89.6	1087.1 ± 70.7	t = 0.101	$p = 0.920$

Data are shown as mean ± S.D. FESz, First-episode schizophrenia; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.