Clinical and Experimental Health Sciences

Corpus Callosum Volume in Patients with First-Episode Psychosis

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ABSTRACT

Objective: In first-episode psychosis, a relationship may exist between disruption communication between two brain hemispheres and psychosis symptomatology. We aimed to investigate the relationship between corpus callosum (CC) volume and psychosis symptomatology in patients with first-episode psychosis.

Methods: This is a retrospective case-control study wherein first-episode psychosis cases and healthy controls were included from inpatient unit archives of the Department of Psychiatry and Department of Radiology, Dokuz Eylül University School of Medicine. Psychosis symptoms were assessed using the positive and negative syndrome scale (PANSS). The CC, the chief connection between two brain hemispheres, was examined using magnetic resonance imaging (MRI); 27 patients with first-episode psychosis and 29 healthy volunteers were evaluated via 1.5-T MR. MRI findings of CC volumes of the two groups were compared. Correlations between PANSS scores and CC volume were also evaluated.

Results: The CC volume was lower in patients with first-episode psychosis than in healthy controls. Moreover, we observed a significant negative correlation between the CC volume and emotional withdrawal scores, and a significant positive correlation between the CC volume and hallucinations.

Conclusions: The CC is a vital structure that connects two frontal lobes of the brain. There may be CC abnormalities in first-episode psychosis. Emotional withdrawal is associated with decreased CC volume, whereas hallucinations are associated with increased CC volume. The development of these symptoms may be associated with changes in CC connections.

Keywords: First-episode psychosis, corpus callosum, emotional withdrawal, hallucinations

1. INTRODUCTION

The most frequently occurring signs associated with psychosis and detected in advanced MRI studies were, until recently, as follows: (a) temporolimbic changes caused by the enlargement of lateral and third ventricles, (b) cerebral volume loss (especially in the frontal lobe), and (c) the effacement of cortical sulci (1,2).

Abnormal constitutional connections between hemispheres in schizophrenia lead to variability in brain asymmetry. Numerous reports have revealed a lower CC volume or lower CC to brain ratio in patients with schizophrenia compared with subjects in control groups (3). Decreases in CC dimensions were noted more frequently in first-episode schizophrenia cases compared with psychotic patients and normal control groups. Smaller anterior genu of the CC and a decrease in the isthmus and anterior splenium are relevant in schizophrenia cases. This decrement is caused by cellular loss and a decrease in cell size. Together with this, a decrease in CC volume is observed in anterior genu, corpus (prefrontal cortex connections), isthmus (inferior parietal cortex connections), and anterior splenium (superior temporal cortex connections) (4,5,6,7).

Studies including treatment-naïve patients with first-episode psychosis are crucial with respect to differentiating between alterations due to the chronic nature of the disease and alterations induced by drug therapies. In cases of first-episode psychosis, corpus callosum changes were detected, which supports the disconnection hypothesis, which is thought to be due to the clinical pattern observed in the formation of psychotic attacks (8).

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Psychosis is associated with a significantly smaller CC area, as well as a smaller anterior splenic area (9). Neuroimaging studies describe that negative symptoms are linked with volume loss in the frontal cortex (10). Corpus callosum volume and the association of first-episode psychosis symptomatology have not yet been investigated. In this study, we aimed to investigate the association between CC volume and psychosis symptomatology in patients with first-episode psychosis.

2. METHODS

2.1. Study Design and Participants

This investigation was designed as a case-control study in which patients with first-episode psychosis admitted to the Inpatient Unit of the Psychiatry Department of Dokuz Eylül University School of Medicine between 2009 and 2013 were included. Archived case records were utilized in this retrospective study. This study was approved by the ethical board of Dokuz Eylul University Faculty of Medicine (No: 2015/02-36). The cases diagnosed as first-episode of acute psychosis according to DSM-IV criteria composed the case group of the study (n=27), while the control group was composed of records of healthy volunteer subjects who attended the radiology department and underwent MRI imaging (n=28).

Inclusion criteria for first attack acute psychosis patients; Satisfying DSM-IV diagnostic criteria for acute psychosis and being literate. The control group has identified healthy individuals with similar age, gender, and educational status. This group consisted of persons who had never had any psychiatric treatment and were not present with any psychiatric illnesses. Volumetric evaluation of 28 individuals aged 18-55 years who volunteered and met certain criteria (especially those with no neurological, psychiatric, and chronic illnesses, no problems with hearing and vision functions, and no continuous use of drugs) Exclusion criteria; The history of any psychiatric illness in the control group and the presence of neurological disease in the control and patient group.

Power of study calculated in G power software. According to minimum r=0,37 correlation, Type I error=0.05, 1-β=0,80 total sample size was 55. We have a total of 55 participants in the study.

2.2. Data Collection

Sociodemographic data and positive and negative syndrome scale (PANSS) scores of the patients were obtained from their medical records, PANNS scores are calculated routinely inpatient clinic. In patients with first-episode psychosis, the standard procedure was to undertake MRI scans to establish that the psychosis was not associated with other neurological disorders. Volumetric measurements of the CC were evaluated using patients' MRI scans taken in the first week of diagnosis.

Measurement of the Size of the Corpus Callosum

MRI images used in the study were obtained using standard head coil Achieva and Intera (Philips, Holland) 1.5 Tesla strength MRI units available in the Radiology Department of Dokuz Eylül University Medical Faculty.

Volumetric measurements were carried out on sagittal plane SE T1-weighted images (parameters; 25 consecutive sections, 5 mm section thickness, TR 600 msec, TE 15 msec; FOV 24 cm; matrix 256 × 256).

MRI images stored in Digital Imaging and Communications in Medicine format were analyzed using Easy Vision 4.4 workstation (Philips, Holland). Segmentation of the CC (volume of interest) and volumetry was carried out using a region-growing algorithm assisted by using a mouse-guided cursor. A midline section of the CC and sections on both sides of this section (three sections in total) were used for volumetry measurement.

For measurements, sections were selected from T1-weighted images in which CC was best shown in the midsagittal plane. The area contained within a closed line drawn around the circumference of CC was calculated. Area measurements were automatically calculated by the tool, which had a sensitivity of 1% per square millimeter. Measurements were conducted retrospectively using the TSE/T1 sequence, which is routinely used in brain MRI protocols. All the measurements were carried out by the same investigator.

2.3. Data Analysis

Categoric variables were defined as numbers and percentages. Chi-Square test was used for the comparison of categorical variables. Continuous variables were defined by mean, standard deviation, and quartile; continuous variables to the normal distribution were examined by Kolmogorov–Smirnov test. CC volume for patients with psychosis and control group subjects was measured, and t-test or Mann–Whitney U test were used to compare groups according to the distribution of data. The correlations between PANSS points and CC measurements were analyzed using Pearson's correlation coefficient; if the normal distribution was not determined, analysis was conducted using Spearman's rank correlation coefficient (Spearman Rho).

CC callosum values were compared between case and healthy control groups with age and gender adjustment in multiple linear regression. Significant subscales of PANSS associated with CC were analyzed with multiple linear regression, and age – and gender-adjusted subscales were analyzed using multiple linear regression analysis; B coefficients were expressed together with a 95% confidence interval (CI).

3. RESULTS

A total of 27 first-episode psychosis cases were examined with regard to sociodemographic characteristics, disease characteristics (PANSS score), and CC volume.

3.1. Descriptive Statistics

Mean age of first-episode psychosis cases was 30.2±12.6 (median=26.0 25p–75p=21.0–35.0 minimum–maximum=18.0–57.0); 63% of those included in the study were male (n=17), 70.4% (n=19) single, 25.9% (n=7) married, 3.7% (n=1) widowed. When looking at the educational status, 18.5% (n=5) of subjects had graduated from primary school, 25.9% (n=7) from high school, and 55.6% (n=15) from university. None of the participants had graduated from secondary school (Table 1).

Table 1. *In first episode psychosis cases and healthy controls, evaluation of the association between gender and volume of corpus callosum.*

	Control (n=28)	First Episode psychosis (n=27)	Test values	p
Gender				
Female	60,0% (15)	40,0% (10)	Chi-Square =1,5	0,218
Male	43,3% (13)	56,7% (17)		
Age	30,2±12,6	35,7±7,3	Mann-Whitney-U=224,0	0,009
Volume of corpus callosum	24,0±3,0	22,0±2,3	t=-2,8	0,008

The frequency of alcohol use was low in first-episode psychosis cases (user 3.7% n=1). The frequency of smoking was 22.2% (n=6). Only 11.1% (n=3) of first-episode psychosis cases were cannabis users. The frequency of first-episode psychosis cases in which there was a family history of the psychiatric disease was 40.7% (n=11) (Table 2).

Table 2. *Results of volume of corpus callosum in first attack psychosis and control group adjusted by age and gender.*

Model*	Coefficient		P	95% Confidence Interval for B coefficient	
	B	Std. Error		Minimum	Maximum
Age	0,019	0,036	0,598	-0,054	0,092
Gender	-0,479	0,742	0,521	-1,969	1,010
Healthy control (r)	-1,791	0,764	0,023	-3,324	-0,258

**Association between age, gender, first episode psychosis case or healthy control, and volume of corpus callosum was tested.*

When examining emotional characteristics of patients with first-episode psychosis, it was observed that 40.7% (n=11) of them were blunted, 15.5% (n=5) irritable, 14.8% (n=4) inappropriate, 11.1% (n=3) depressive, and 11.1% (n=3) anxious.

A total of 10 patients (37%) with first-episode psychosis cases had visual-auditory hallucinations. No hallucinations were observed in 33.3% (n=9) of cases. A total of 11% (n=3) cases were auditory, 7% (n=2) were separately existing visual hallucinations, and in 3% (n=1) olfactory–visual, olfactory–visual–auditory, and auditory–tactile–visual hallucinations were present.

In 70.4% (n=19) of first-episode psychosis cases, insight was not present; in 25.9% of cases (n=7) it was restricted; and in 3.7% of cases (n=1) insight was present.

The mean age of first-episode psychosis cases was 30.2±12.6, mean age in healthy controls was 35.7±7.3; there was a statistically significant difference between groups concerning mean age (p=0.009). In total, 40% (n=10) of females and 56.7% (n=17) of males were included in the study. There was no significant difference between the case and control groups regarding gender (p=0.218).

3.2. Corpus Callosum Volumes

The mean volume of CC in first-episode psychosis cases was 22.0cm3±2.3cm3; in healthy controls, it was 24.0cm3±3.0cm3 (Table 1).

The volume of CC in first-episode psychosis cases was significantly smaller than in healthy controls (p=0.008) (Table 1). When age and gender were adjusted, CC volume was 1.7 cm lower in first-episode psychosis cases than in healthy controls (R square=0,137, B=−1.7, p=0.023, 95% CI=from −3.3 to −0.3) (Table 2).

First episode psychosis symptomatology and CC volume

We observed a significant positive correlation between CC volume and hallucinations subitem of the positive symptoms subscale of PANSS. As CC volume increased, hallucination subitem scores increased (42.7%, p=0.026) (Table 3). No significant associations were determined between CC volume and other items of the positive symptom subscale of PANSS (Table 3). When adjusting by age and gender effect, the volume of CC increased by 0.781 units with each one-point increase in hallucination score (R square change=0,395, p=0.002, 95% CI=0.308–1.251) (Table 4).

We observed a significant negative correlation between the emotional withdrawal of negative symptom subscales of the PANSS scores and CC volume. Emotional withdrawal subscale scores increased with decreasing CC volume (−%46.8, p=0.014) (Table 3). There were no significant associations between CC volume and the scores of other components of the negative symptom subscale of PANSS. When age and gender effects were controlled, CC volume decreased by −0.752 units with each point increase in emotional withdrawal score (R square change=0,264, p=0.028, 95% CI= from −1.416 to −0.088) (Table 4).

Table 3. *Correlation coefficient (Rho) and significance levels of association between volume of Corpus Callosum (CC) and PANSS scores*

	Spearman rho	p		Spearman rho	p
P1. Delusions	-0,122	0,546	N1. Affective blunting	-0,342	0,081
P2. Thought dispersion	-0,233	0,242	N2. Emotional withdrawal	-0,468*	0,014
P3. Hallucinations	0,427*	0,026	N3. Difficulty in communicating	-0,214	0,284
P4. Expansiveness	0,009	0,965	N4. Social withdrawal	-0,225	0,258
P5. Grandiose sensations	0,051	0,799	N5. Difficulty in abstract thinking	-0,258	0,194
P6. Scepticism/ persecution	0,023	0,910	N6. Impairment of speech	-0,170	0,396
P7. Hostility	0,167	0,404	N7. Stereotypical thinking	-0,247	0,214

Table 4. *Age and Gender Adjusted Results of Corpus Callosum Volume and Hallucination and Emotional Withdrawal Scores.*

		Coefficient		p	95% Confidence Interval for B coefficient	
		B	Standard Deviation		Minimum	Maximum
Model I	Age	0,106	0,035	0,005	0,035	0,178
	Gender	0,804	0,832	0,344	-0,917	2,525
	Hallucinations	0,781	0,228	0,002	0,308	1,253
Model II	Age	0,033	0,036	0,366	-0,041	0,107
	Gender	-0,111	0,882	0,901	-1,934	1,713
	Emotional withdrawal	-0,752	0,321	0,028	-1,416	-0,088

4. DISCUSSION

Numerous studies have reported the decrease in the size of the CC in schizophrenia; however, in some studies, no differences in size or larger CC were determined (11,12). These inconsistencies could be based on the differences in case of characteristics (gender, experiencing different psychotic symptoms, use of dominant hand, age at disease onset), and the measurement method of CC volume could also be effective as the others (4). Thus, as antipsychotic therapy is another confounding factor, it has been reported that such therapy causes alterations in white matter volume (13). For example, olanzapine therapy in schizophrenia led to an increase in white matter (14). Similarly, treatment with risperidone increased myelinization in white matter (15). Antipsychotic therapy also probably results in a potentially increased size of the CC. In addition, few studies have investigated the CC of patients who did not use antipsychotic agents (11).

Age at disease onset is an important factor with respect to neurodevelopmental differentiations and to effects of CC measurements beside the others (16,17). The CC is the last part of the brain to mature, and its development continues until late adolescence/early adulthood (18).

In a large number of neuroimaging studies investigating schizophrenia, a substantial amount of evidence regarding morphological brain pathology was gathered (19). The major interhemispheric commissure, which is part of the CC, is one of the affected parts of the brain (20). The CC constitutes the transition of axons emanating from the neocortex and fibrils of white matter from both brain hemispheres. Abnormal interhemispheric connections have been identified on the basis of the variability of brain asymmetry in schizophrenia (21,22,23). A large number of studies have shown that in psychosis cases, a lesser volume of the CC or lower CC to brain ratio is present in comparison with control groups (24). Two groups of investigators examined first-episode psychosis cases, and one group determined gender differences in case and control groups (25), whereas the other group determined the deformation of shape (26).

Even though considerable data point to disturbed communication between the two hemispheres of the brain in schizophrenia, communication disorder cannot be anatomically shown. Diffusion tensor imaging studies can reveal that connection has been focally disturbed in commissural relations (27).

In patients with schizophrenia who had not yet been treated, smaller corpus callosa were identified compared with healthy controls; together with this, the existence of larger corpus callosa was greater in females compared with males. Evidence regarding gender was consistent with the findings for the brain of normal subjects (7). In our study, there were no statistically significant associations between CC volume, age, and gender. Consistent with previous studies, the volume of CC in first-episode psychosis cases was significantly smaller than in control cases in our study.

In the present study, a decrease in CC volume was found to be associated with emotional withdrawal, which is one of PANSS negative scores. It was shown that hallucinations that were part of the positive signs were positively associated with CC volume. Hence, it led us to think that variabilities of CC volume could be separated from symptomatology. Furthermore, it was thought that the calculation of the volume of subsections of the CC could elucidate this situation.

The association between negative symptoms and loss of gray matter in the schizophrenic brain has been investigated. Alterations were most prominently observed in prefrontal, temporal, limbic, and subcortical regions. In schizophrenia cases where negative symptomatology was dominant, decreases in the bilateral limbic and prefrontal gray matter had been determined. These results explained cases where social functioning deteriorated, a situation created

by beginning and ongoing negative symptoms. These insufficiency symptoms have shown consistency with PANSS titles such as "emotional withdrawal" or "blunted affect," which consisted of a high factor burden consistent with core negative symptom content of negative signs. These PANSS titles reflected disorders of social and emotional functioning (28).

In Walterfrang's study, no associations between positive symptoms determined by PANSS and CC measurements were detected in patients with first-episode psychosis diagnosed with schizophrenia and similar spectrum disorders.

On the contrary, negative symptoms were negatively correlated with the tangle of twist of CC ($r=-0.215$, $p=0.013$). While there were no associations between the variables of CC and relevant variables in the groups of the same study, a positive correlation was observed between negative symptoms, and callosal area ($r=0.307$, $p=0.018$), and thickness ($r=0.288$, $p=0.027$). These associations could not be shown in regression analysis. In addition to this, CC was found to be significantly different in patients with schizophrenia compared with healthy controls, and some changes were determined even in first-episode cases. A decrease in volume may be associated with a decrease in axon number of axon diameter or myelin sheath loss. It may be mentioned about the decrease in genu and isthmus as fibers of the connection cortex (29).

Correlation analysis carried out between symptom severity scores achieved from PANSS and CC measurements in schizophrenia cases revealed that increased superior genu volume was associated with increased severity of positive symptoms (30,31). Similarly, in the study by Whitford et al., a positive correlation was noted between the sum of hallucination and delusion severity scores of the positive signs' subscale and the existence of fractional anisotropy in the region of the CC that frontal fibrils passed through. In the same study, a negative correlation was noted between the severity of difficulty in abstract thinking (N5) and the existence of fractional anisotropy in the same region (32).

In studies including schizophrenia cases under therapy, healthy controls, and healthy relatives, a negative association was found between scores of the hallucination severity subscale of the PANSS scoring system and CC volume. A negative correlation was also determined between fractional anisotropy values of the hallucination severity subscale of PANSS and the volume of the posterior genu region of the CC. In our study, a statistically significant positive correlation was determined between CC volume and hallucination severity scores achieved from the PANSS subtitle. This finding could be specific to first-episode psychosis cases in which therapy has not yet been started and evaluated with imaging modalities during onset. Volume increase in white matter may be related to increased efficiency of pathways in connection with the CC. However, the relationship between emotional withdrawal and decreased CC volume may be interrelated with decreased efficiency of these pathways. For detailed information, CC requires investigation at a regional level.

There are some limitations, and generalizations should be made with caution. First, the study sample was small. In some details, we relied on the information given by our healthy controls and patients. Since we acquired retrospective data, our findings can only support the hypothesis of first-episode psychosis symptoms as hallucinations and emotional withdrawal. However, because first-episode psychosis cases were examined, the response of the CC with respect to chronic alterations could have been excluded. In addition, the dominant hand could not have been determined. Control group and first-episode psychosis cases could not have been matched case by case according to age and gender. The results have been analyzed by statistically adjusting to age and gender.

5. CONCLUSIONS

In this study, we found that hallucinations, one of the positive signs observed in first-episode psychosis, were associated with increased CC volume. Decreased CC volume may be associated with emotional withdrawal. Volumetric changes in the CC are associated with axonal structure, cellular changes, and the number of fibrils in this region. First-episode psychosis cases are those in which pathology has not yet been treated, and as such, it is known that the pathology has not been altered using drug therapy. In this group of patients, volumetric changes in the CC suggest that the neurodevelopmental hypothesis and the hypothesis of disrupted connection are in play. It was observed that different cognitive functions implicated by the fibers emanating from the frontal lobe were altered as suggested by correlation with CC volume in first-episode psychosis cases.

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