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COMPARISON OF INCIDENTAL FINDINGS OF BRAIN MAGNETIC RESONANCE IMAGING OF SCHIZOPHRENIA PATIENTS, FIRST-EPISODE PSYCHOSIS PATIENTS AND HEALTHY CONTROLS

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SUMMARY

Background: *It has been emphasized for a long time that neurodevelopmental and neurodegenerative processes play an important role in the etiology of schizophrenia.*

Subjects and methods: *In this study, brain magnetic resonance imaging (MRI) of 97 patients with schizophrenia (SCH), 42 first-episode psychosis (FEP) patients, and 70 healthy controls (HC) were analyzed, and abnormal findings on brain MRI were recorded. Participant's age, gender, and brain MRI findings were recorded retrospectively. Fazekas grades evaluated the distribution of white matter hyperintensities in the brain.*

Results: *The mean ages of FEP, SCH, and HC were 24.8±6.3, 36.9±11.5, and 36±10.5, respectively. Generalized cerebral atrophy was higher in SCH and HC than in FEP groups, and frontoparietal atrophy was higher in the SCH group than in HC and FEP groups ($p<0.001$). The percentage of Fazekas Grade-1 was higher in the SCH group than HC and FEP groups ($p=0.006$). Additionally, the cavum veli interpositi (CVI) rate was higher in FEP and SCH groups than in the HC group ($p=0.042$).*

Conclusion: *Although there was no significant age difference between the SCH and HC groups, the higher prevalence of generalized cerebral atrophy in the SCH group may indicate the neurodegenerative process of schizophrenia. The fact that CVI, a congenital brain anomaly, was detected more frequently in the FEP and SCH groups may suggest that schizophrenia may be associated with neurodevelopmental process.*

Key words: *schizophrenia - first-episode psychosis - brain magnetic resonance imaging*

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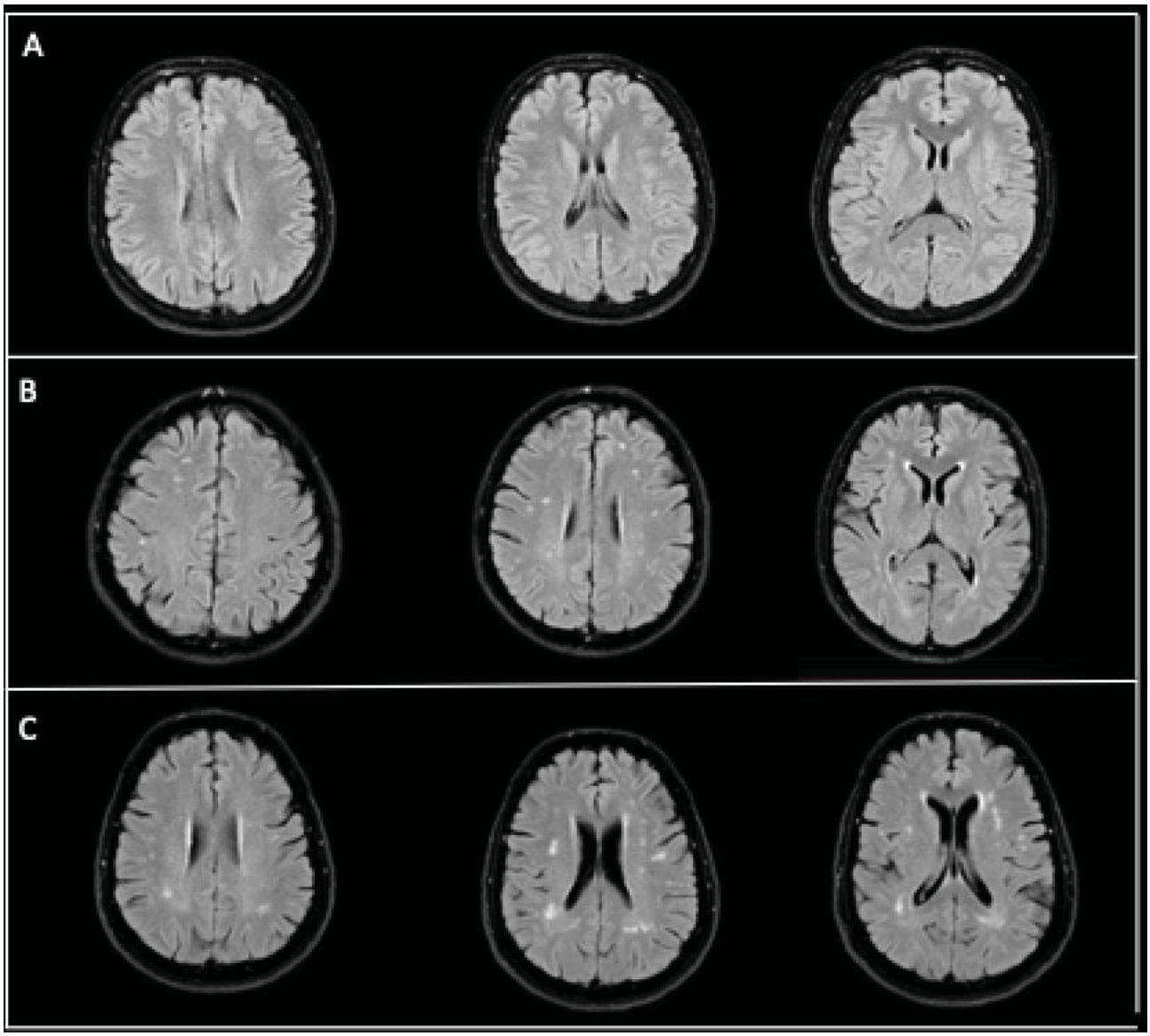
INTRODUCTION

Schizophrenia is a chronic mental illness that affects 1% of the population. Schizophrenia is often characterized by a prodromal period (social withdrawal, depressive symptoms, obsessive and compulsive symptoms) and subsequent psychotic exacerbations (delusions-halucinations and disorganized behavior or speech). Although the etiology of schizophrenia is not yet known, it is thought that brain abnormalities ultimately play a role in the development of schizophrenia (McCutcheon et al. 2020).

The neurodevelopmental theory proposes that schizophrenia results from a structural deficiency in the early life stages of development. These developmental stages are; neuronal precursors, glial proliferation and migration, axonal and dendritic proliferation, myelination of axons, programmed cell death, and synaptic pruning. A widely accepted model proposes that a neurodevelopmental defect leads to changes in morphology and cell architecture, resulting in a deficit in the modulatory capacity of neurons. However, it is thought that this neurodevelopmental defect leads to significant symptoms in adolescence and early adulthood when triggered by environmental factors such as stress. It is thought that the disappearance of synaptic connections compensating for the disorder as a result of pruning is responsible for the symptoms (Fatani et al. 2017).

Although schizophrenia is thought to result from an impairment in early development, neuronal maturation processes that occur during adolescence reveal psychosis. It is known that the human brain reaches approximately the adult brain size in primary school years, and this growth occurs from gray matter, not white matter. In addition, specific regulation of neural connections and remarkable shrinkage of cerebral structures also occur in early cerebral maturation. The delay between an early lesion and the onset of the disease is explained by genetic changes in some maturation mechanisms, such as cortical pruning that occurs at puberty (Walker et al. 2004).

Postmortem studies have reported limbic and temporal lobe abnormalities, including the amygdala-hippocampal complex and parahippocampal gyrus, and an enlargement of the temporal horn of the lateral ventricles. Most of these findings were lateralized to the left side of the brain, leading to speculation that schizophrenia might be an anomaly of brain development (Shenton et al. 2001).



On FLAIR axial images of Brain MRG: A: Fazekas Grade 0 B: Fazekas Grade I C: Fazekas Grade II

Figure 1. Illustration of Normal Brain MRI and Fazekas Grade I and Grade II

The magnetic resonance imaging (MRI) study conducted in 1984 illuminated the understanding of brain abnormalities in patients with schizophrenia. Subsequent brain MRI studies have shown enlarged lateral ventricles and specific gray matter volume reductions, particularly in the superior temporal gyrus and medial temporal lobe brain regions (amygdala, hippocampus, and parahippocampal gyrus). Decreases in the size of the cortical sulcus and the volume of the frontal and parietal lobes have also been reported (McCarley et al. 1999).

Brain MRI should be performed to exclude neurological diseases in patients with schizophrenia or patients with psychotic symptoms. In this study, we aim to compare the findings detected incidentally on brain MRI in patients with schizophrenia (SCH) and patients with first-episode psychosis (FEP) with the healthy control (HC) group.

SUBJECTS AND METHODS

Study Design

Brain MRIs of patients followed up with the diagnosis of schizophrenia and first-episode psychosis in the Psychiatry Clinic of Hospital between 01/01/2018 and 01/01/2022 were retrospectively analyzed. The Local Ethics Committee approved this research (Date of Decision: 18/01/2022, Number of Meetings:1, Number of Decisions: 2022/1-21).

Study Group

Ninety-seven patients with schizophrenia, 42 patients with first-episode psychosis without treatment, and 70 healthy controls were included. Among the patients with a diagnosis of schizophrenia, those with migraine (n=4), vitamin B12 deficiency (n=11), hypo-

thyroidism (n=2), diabetes mellitus (n=4), hypertension (n=3), operated brain tumor (n=1), mental retardation (n=3), iron deficiency anemia (n=2), alcohol or substance abuse (n=4) were excluded from the study. People without psychiatric diagnoses were selected as healthy controls based on their statements and medical records.

Brain MRI Examination

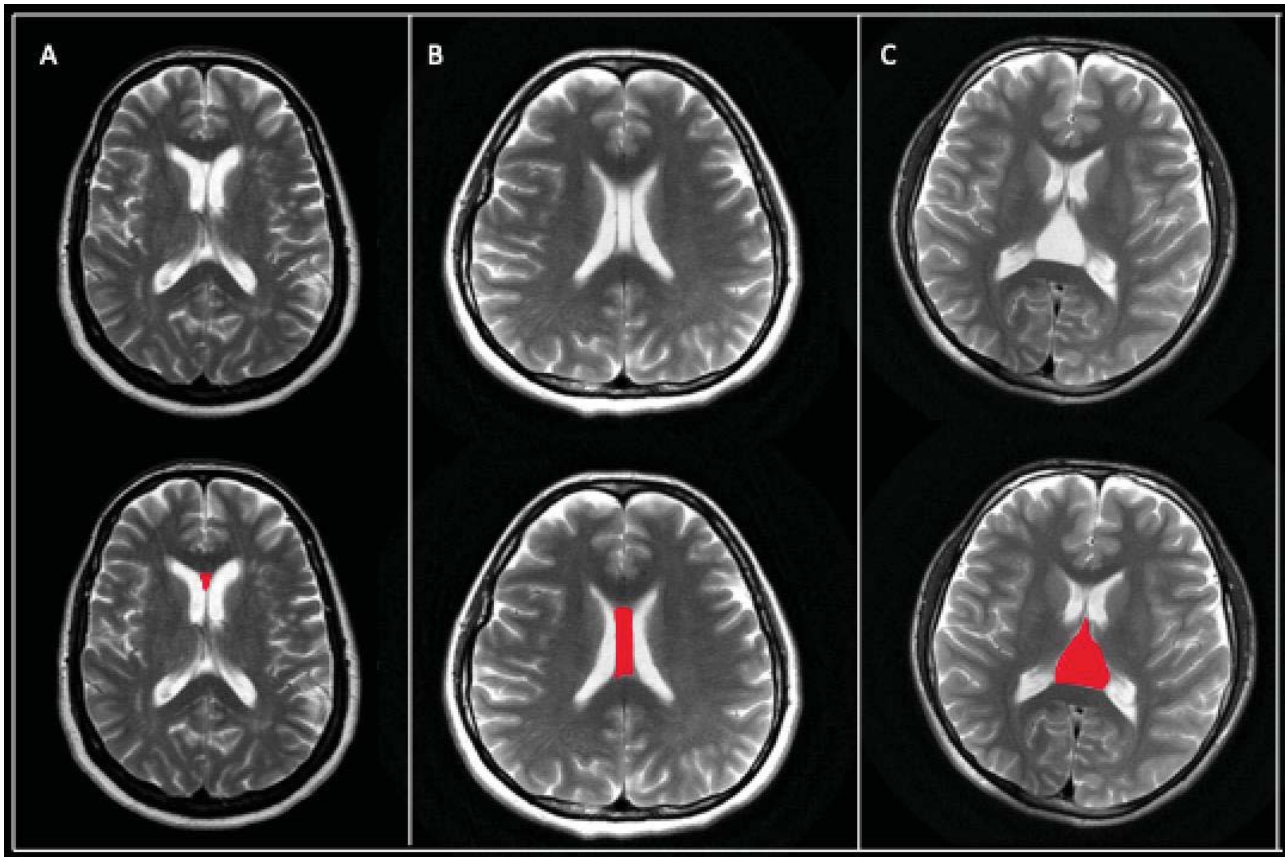
The MRI examination was obtained from the Philips Achieva MR device (Philips Medical Systems, Best, Netherlands) with a 1.5 Tesla magnetic field strength using a head coil. The evaluation was performed on brain MRI T1-weighted axial, T2-weighted axial, FLAIR axial, and T2-weighted coronal and T1-weighted sagittal images. Brain MRI findings, age, and gender information were recorded retrospectively. According to the region of atrophy on brain MRI, atrophy was divided into four classes: generalized cerebral, frontal, frontoparietal, and cerebrocerebellar. Fazekas scale was used to assess the level of brain aging. Fazekas scale was made according to WMH. Fazekas grade 0 (absence), 1 (punctate foci), 2 (beginning confluence of loci), or 3 (large confluent areas) (Scheltens et al. 1993). The appearance of Fazekas grade 0, grade1, and grade 2 on brain MRI is shown in figure 1. The appearance of the cavum septum pellucidum, cavum vergae, and cavum veli interpositi on brain MRI are given in figure 2.

Statistical Analysis

Continuous variables were given as mean ± standard deviation. Categorical variables were given as percentages (%). Kurtosis and skewness values and the Kolmogorov-Smirnov test were used to determine whether continuous variables were normally distributed. One-way Anova test and Tamhane test were used to compare the mean ages of SCH, FEP, and HC groups. The Chi-square test and Fischer's Exact test were used to compare categorical variables. IBM SPSS Statistics v.26 (IBM SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis, p values < 0.05 being considered significant.

RESULTS

The mean ages of FEP, SCH, and HC were 24.8±6.3, 36.9±11.5, and 36±10.5, respectively. There was a significant difference in age between the groups ($p<0.001$). According to the Post-hoc Tamhane test, the mean ages of SCH and HC groups were higher than the mean age of the FEP group ($p<0.001$ and $p<0.001$, respectively). There was no difference in age between the SCH and HC groups ($p=0.944$). 48.6% of HC, 66.7% of FEP, and 70.1% of SCH were male, and there was a significant difference between the groups in terms of gender distribution ($p=0.015$). Post-hoc analysis showed that the percentage of males was higher in FEP and SCH groups than HC group.



On T2- weighted axial images of Brain MRG: A: Cavum Septum Pellucidum B: Cavum Vergae C: Cavum Veli Interpositi

Figure 2. Cavum Septum Pellucidum, Cavum Vergae and Cavum Veli Interpositi

Table-1. Comparison of incidental MRI findings between first episode psychotic patients and chronic schizophrenic patients and healthy controls

	HC (n=70) N/%	FEP (n=42) N/%	SCH (n=97) N/%	χ^2	p
Atrophy				33.686	<0.001
Generalized Cerebral	5 / 7.1[a,b]	0 / 0[b]	15 / 15.5[a]		
Frontal	0 / 0	1 / 2.4	5 / 5.2		
Frontoparietal	0 / 0[a]	0 / 0[a]	12 / 12.4[b]		
Cerebrocerebellar	0 / 0	0 / 0	2 / 2.1		
Fazekas					0.006
Grade 1	1 / 1.4[a]	1 / 2.4[a]	13 / 13.4[b]		
Grade 2	0 / 0	0 / 0	2 / 2.1		
Cavum septum pellucidum	2 / 2.9	4 / 9.5	8 / 8.2		0.236
Cavum vergae	1 / 1.4	1 / 2.4	5 / 5.2		0.483
Cavum veli interpositi	1 / 1.4 [a]	5 / 11.9 [b]	8 / 8.2 [a,b]		0.042
Ethmoidal thickening	27 / 38.6	20 / 47.6	46 / 47.4	1.497	0.473
Maxillary thickening	9 / 12.9	10 / 23.8	22 / 22.7	3.074	0.215
Sphenoid thickening	5 / 7.1	2 / 4.8	7 / 7.2		0.878
Frontal thickening	5 / 7.1	2 / 4.8	6 / 6.2		0.935
Retention cyst	12 / 17.1	7 / 16.7	20 / 20.6	0.461	0.794
Septal Deviation	20 / 28.6	11 / 26.2	37 / 38.1	2.662	0.264
Sinus Polyp	0 / 0	1 / 2.4	0 / 0		0.201
Adenoid Hypertrophy	2 / 2.9	4 / 9.5	3 / 3.1		0.192
Concha Bullosa	0 / 0	0 / 0	1 / 1		N/A
Ranula Cyst	0 / 0	0 / 0	1 / 1		N/A
Tornwalt's Cyst	2 / 2.9	0 / 0	1 / 1		0.593
Nonspesific Gliotic foci	10 / 14.3	6 / 14.3	22 / 22.7		0.425
Gliosis	0 / 0	0 / 0	5 / 5.2		0.083
Encephalomalacia	0 / 0	0 / 0	3 / 3.1		0.306
Mastoiditis	1 / 1.4	1 / 2.4	1 / 1		0.783
Mega cisterna Magna	4 / 5.7	2 / 4.8	7 / 7.2		0.870
Scalp Lesion	0 / 0	1 / 2.4	0 / 0		0.201
Vertebral artery dolichoectasia	1 / 1.4	0 / 0	7 / 7.2		0.083
Venticular Asymmetry	2 / 2.9	1 / 2.4	1 / 1		0.544
Partial empty sella	0 / 0	1 / 2.4	2 / 2.1		0.436
Vertebral artery hypoplasia	0 / 0	0 / 0	1 / 1		N/A
Ferromagnetic Artifact	0 / 0	0 / 0	1 / 1		N/A
Mesial temporal sclerosis	0 / 0	0 / 0	2 / 2.1		0.688
Hydrocephalus	0 / 0	0 / 0	1 / 1		N/A
Dyke Davidoff Masson	0 / 0	0 / 0	1 / 1		N/A
Arachnoid Cyst	2 /2.9	0 / 0	0 / 0		0.473

Chi-square test was used; p values < 0.05 being considered significant

The frequency of incidental MRI findings of the groups was compared in Table 1. Accordingly, generalized cerebral atrophy was higher in SCH and HC than in FEP groups, and frontoparietal atrophy was higher in the SCH group than in HC and FEP groups (p<0.001). The percentage of Grade-1 Fazekas was higher in the SCH group than HC and FEP groups (p=0.006). Additionally, the percentage of cavum veli interpositi was higher in FEP and SCH groups than HC group (p=0.042).

DISCUSSION

The striking results we obtained in this study are as follows: i.) Generalized cerebral, frontal, and frontoparietal atrophies were significantly higher in the SCH group than in FEP and HC, ii.) Fazekas grade 1 was significantly higher in the SCH group than in FEP and HC, iii.) Cavum veli interpositi was significantly higher in FEP and SCH groups than HC iv.) Encephalomalacia and gliosis were found only in the SCH group.

Although it is known that Emil Kraepelin, who first described schizophrenia, talked about cellular damage in the cortical brain in patients with schizophrenia, the first findings of ventricular enlargement in patients with schizophrenia were obtained from pneumoencephalographic studies in the 1920s (DeLisi et al. 2022). When Smith et al. performed brain MRI for the first time on patients with schizophrenia in 1984, it became possible to understand the brain abnormalities of people with schizophrenia (Smith et al. 1984). White and gray matter changes, superior temporal gyrus, temporal and frontal lobe axonal connections, and uncinate and fornix abnormalities have been reported in schizophrenia (Shenton et al. 2001). While some studies on schizophrenia reported a reduction in brain volume, some studies did not find a difference with healthy controls. The difficulties of taking the head/brain size data, which is affected by many reasons such as age, gender, and nutrition, as an objective criterion, has reduced the importance of total brain volume (Ward et al. 1996). However, brain atrophy, characterized by enlargement of the cerebral sulci and ventricles, is a commonly acceptable finding in schizophrenia.

In this study, the mean age of the FEP group was lower than that of HC and SCH, and the FEP group included a diagnostically heterogeneous disease group (short psychotic episode, schizophreniform disorder, psychotic depression, schizophrenia, schizoaffective disorder, bipolar disorder, psychosis not otherwise specified). This may explain the differences in the distribution of brain abnormalities.

White matter hyperintensities (WMH), also known as leukoaraiosis, are characterized by a bright appearance on T2-weighted and FLAIR images of brain MRI. Although WMH is considered an incidental finding mainly in the elderly, it is thought to be associated with impairment in attention, processing, and executive functions. It is thought that WMH develops due to hypoxic damage, hypoperfusion and atherosclerosis. While Zanetti et al. found no difference in WMH between first-episode psychosis and healthy controls (Zanetti et al. 2008), Persaud et al. found focal signal intensities higher in SCH patients than in bipolar disorder patients and healthy controls (Persaud et al. 1997). Lubman et al. found more frequent WMH in schizophrenia patients than healthy subjects (Lubman et al. 2002). Our study found that the Fazekas grades determined by the WMH shape were higher in the SCH group than the FEP and HC group. Atherosclerosis is thought to be in the pathophysiology of WMH. According to the literature, atherosclerosis is also more common in schizophrenia than healthy population (Davidson 2002). In future studies, comparison of Fazekas scale with lipid parameters and carotis intima media thickness can be performed to evaluate atherosclerosis.

Anterior midline intracranial cysts such as cavum veli interpositi (CVI), cavum septum pellucidum (CSP), and cavum vergae (CV) are diagnosed with brain MRI (Tubbs et al. 2011). The velum interpositum is formed by the superposition of two layers of the tela choroidea of the third ventricle between the internal cerebral veins and the posterior medial choroidal artery. The velum interpositum is a space containing cerebrospinal fluid, and the expansion of this space is called CVI. It is an incidental finding on brain MRI and does not cause any complications. However, studies have associated CVI with psychosis, mental retardation, hydrocephalus, and epilepsy (De Leucio & Dossani 2022). CVI was found more frequently than HC in both FEP and SCH groups in this study.

CSP is a space located between the leaflets of the septum pellucidum located below the anterior part of the corpus callosum and above the fornix, and it regresses after birth. However, it can be seen in 10% of adults (Galarza et al. 2004). CSP has been reported more frequently in schizophrenia in many studies (DeLisi et al. 1993, Degreef et al. 1992, Nopoulos et al. 1997). We did not find a significant difference between the groups in terms of CSP frequency. Although the frequency of CSP was higher in the SCH and FEP groups. We think that increasing the sample size may make this difference statistically significant. If the CSP continues posteriorly, crosses the fornix and extends into the foramen of Monro, it is called CV. CV is seen in less than 1% of adults. It is emphasized that CV is more common in patients with schizophrenia (Degreef et al. 1992).

Encephalomalacia is defined as the loss of brain tissue due to cerebral injury, ischemia, or trauma. Encephalomalacia has been associated with neurological and neuropsychiatric diseases. Encephalomalacia is often accompanied by gliosis resulting from injury-induced glial cell proliferation (Das et al. 2018).

Limitations

This study has some limitations. The absence of information for disease severity and disease duration resulted in the inability to perform correlation analysis. Another limitation of the study is the follow-up of FEP patients after the first-episode. The fact that the mean age of the FEP group is smaller than the other two groups can be considered as a limitation.

CONCLUSION

Although schizophrenia is accepted as a psychiatric disorder, it should be evaluated as a neuropsychiatric disorder because of the frequent neurodevelopmental or neuroanatomical pathologies in schizophrenia. Although brain MRI has no place in the diagnosis of schizophrenia, brain MRI is often used in the differential diagnosis and exclusion of additional pathologies. This study is valuable because it shows that both neurodevelopmental abnormalities and acquired pathologies are more common in schizophrenia.

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Contribution of individual authors:

Olga Bayar Kapici & Atilla Tekin study design, data collection, first draft.

Aşar Kapici study design, first draft, statistical analysis.

All authors approved the final version of the manuscript.

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