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The Development of Psychosis in Patients with Substance Use Disorder and Its Association with Cavum Septum Pellucidum and Adhesio Interthalamica

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ABSTRACT

Background: It is known that there is a relationship between psychotic disorders and the presence of cerebral midline defects, such as the cavum septum pellucidum and the absence of adhesio interthalamica. This study aims to investigate whether these defects in people with alcohol/substance use disorders are associated with the occurrence and persistence of psychotic symptoms.

Methods: The files of the patients who were hospitalized in an addiction inpatient unit were retrospectively scanned. The presence of cavum septum pellucidum and the absence of adhesio interthalamica were determined by evaluation of the magnetic resonance imaging findings. The presence of psychotic symptoms at admission and the persistence of psychotic symptoms after 2 weeks of detoxification treatment were used as dependent variables in different logistic regression models. The presence of cavum septum pellucidum and the absence of adhesio interthalamica were included in 2 separate models as independent variables.

Results: The results of the regression analyses showed no significant relationship with respect to cavum septum pellucidum. However, the analyses revealed that the absence of adhesio interthalamica increases the risk of the persistence of psychotic symptoms.

Conclusion: Our findings suggest that the absence of adhesio interthalamica can be considered a structural risk factor for the development of psychosis in people receiving treatment for substance use.

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INTRODUCTION

One of the leading models among the hypotheses regarding the etiology of psychosis is the neurodevelopmental model. According to this model, psychotic disorders occur due to disruptions in neurodevelopmental processes that start long before clinical symptoms appear as a result of the combination of genetic and environmental factors.[1] This neurodevelopmental model is helpful in understanding the neurophysiological abnormalities seen in psychosis. The presence of cavum septum pellucidum (CSP) and the absence of adhesio interthalamica (AIT) are thought to be a marker for cerebral midline defects or limbic system dysgenesis. Their relationship with psychosis has been of interest to researchers.

Septum pellucidum is a structure consisting of 2 laminar membranes. These laminae form the medial walls of the anterior horns of the lateral ventricles. In the early stages of the embryological development of the fetus, these layers are not united, and a physiological CSP emerges. At the sixth week of pregnancy, these layers are expected to start to merge and form the septum pellucidum. Even though the fusion is not complete in 80% of babies at birth, the gap is completely closed long before most people reach adulthood. However, this fusion never takes place entirely in some people, and a permanent gap is formed.[2] The prevalence of CSP variants in the general population is uncertain. In a study by Born et al in 2004, the overall incidence was 72%, and CSP larger than 6 mm was seen in 9% of healthy volunteers. No difference was found with regard to age or gender.[3]

In a meta-analysis, a relationship was found between schizophrenia spectrum disorders and only large CSPs, and it was interpreted that small CSPs could be considered a normal neuroanatomical variation.[4] A large CSP has been associated with some psychiatric disorders. It has

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been found that it is more common in people diagnosed with schizophrenia, obsessive-compulsive disorder, and antisocial personality disorder compared to healthy individuals. Since the length of CSP was observed to increase more in patients compared to healthy controls within 1 year, it was interpreted that it might be associated with the progression of the disease.[5] In a study comparing a large sample of mood disorders and psychotic disorders with healthy controls, the presence of CSP and absence of AIT were found to be associated with all diagnoses, and the authors interpreted that these diseases share a common neurodevelopmental etiology.[6]

Adhesio interthalamica (also called massa intermedia) is a midline structure connecting the medial borders of the thalamus through the third ventricle, and it contains neurons. Thalamic nuclei enlarge and connect during the 13th-14th weeks of gestation to form the AIT. Although it is a more prominent structure in most mammals, it is relatively small in humans and is absent in approximately 20% of humans, according to postmortem examinations. In addition, the absence of AIT is more common in men than women.[7]

Congenital absence of AIT was associated with schizophrenia,[8] especially in male patients.[9] The absence of AIT is significantly more common in first-episode schizophrenia patients than healthy controls.[10] It has been shown that negative symptoms are more severe in patients with schizophrenia who do not have AIT.[11] Adhesio interthalamica is shorter in patients with schizophrenia and schizotypal disorder than in healthy controls.[12] A meta-analysis study conducted in 2010 showed that the absence of AIT is more common in schizophrenia spectrum disorders.[13] In a longitudinal follow-up study comparing cranial magnetic resonance imaging (MRI) of patients diagnosed with first-episode psychosis at the beginning and approximately 1 year later, the length of AIT was found to be short from the beginning of the disease. This finding implies that it might be a neurobiological risk factor for the development of psychosis.[5]

There are few publications on the relationship between cerebral midline defects and alcohol/substance use disorders. One study showed that the prevalence of a large CSP is higher in people with alcohol dependence.[14] In another study, it was revealed that there is a relationship between broad CSP and opioid addiction, especially starting in adolescence.[15] To our knowledge, no publication has investigated the relationship between AIT and alcohol/substance use disorders.

Our study aims to determine whether the presence of CSP and the absence of AIT are associated with the incidence or the persistence of psychotic symptoms in patients with alcohol/substance use disorder admitted to an addiction inpatient unit. Investigating the effects of these 2 neurobiological variables may produce clinically significant outcomes as they might contribute to predicting the development of psychosis in alcohol/substance use disorders.

MAIN POINTS

- The absence of adhesio interthalamica increases the risk of developing persistent psychotic symptoms in patients admitted with substance use disorder.
- No significant relationship was found between cavum septum pellucidum and psychotic symptoms.
- Adhesio interthalamica was absent in 66.07% of the participants.
- Cavum septum pellucidum was present in 53.57% of the patients.

MATERIALS AND METHODS

This retrospective study was approved by the ethics committee of Üsküdar University (No:61351342; Date:30/06/2022). This is a retrospective study. It was not possible to take informed consent.

Participants

The present research was designed as a retrospective study conducted at a private psychiatric hospital in Turkey. The files of patients hospitalized in the addiction inpatient unit of the hospital between February and June 2022 were scanned, and 129 files were found. Patients with gambling disorders who did not use alcohol/drugs (n=4) were not included in the study. Patients who were under 18 (n=4), who had neurological/systemic diseases (n=2), and those with psychotic symptoms before alcohol/substance use (n=7) were excluded from the study. The diagnoses of the 2 patients excluded due to neurological/systemic disorders were as follows: one patient with alcohol use disorder was excluded because he had psychotic symptoms due to delirium; the other patient with substance use disorder was excluded because he had psychotic symptoms related to the treatment of Parkinson's disease. The histories of the 7 patients who were excluded because they had been diagnosed with psychotic disorders before they started using alcohol/drugs were obtained from the patients, their families, and previous medical records. Data were extracted from the files of the remaining 112 patients.

Clinical Evaluation

The following information was collected retrospectively and recorded in the data collection form by the clinician: age, gender, educational status, marital status, alcohol/substance used, family history of mental illness, whether the patient had psychotic symptoms or not at the time of admission, and whether the patient had psychotic symptoms persisting at the end of the second week of detoxification treatment. If the patient had former inpatient treatments, those files were also screened.

Magnetic Resonance Imaging

All patients had cranial MRI scans at admission as a routine procedure. All participants underwent a 1.5 Tesla MRI manufactured by Philips. Images were taken in complete 3-dimensional planes with 5-mm slices without inter-slice gaps, Time to repetition (TR) = 11 000 ms, Time to echo (TE) = 140 ms, Time to inversion (TI) = 2800 ms, matrix size 256 × 159 Field of view (FOV) Anterior-to-posterior (AP) × Right-to-left (RL) × Feet-to-head (FH) (mm) 230 × 188 × 142 mm, and scanning time 2 minutes and 56 seconds.

The presence (on at least one 1 mm coronal slice), length (total number of contiguous slices on which it was present)[16] and the grade of the CSP,[17] and also the presence or absence of the AIT structure in MRI were assessed by a neurologist and a neuroradiologist, who were unaware of the participant's clinical data. The grading of CSP was based on consideration of the length, width, and overall size, and it was coded as the following: 0 if absent, 1 if unclear, 2 if the cavum was not as wide as the width of the septum, 3 if the cavum was wider than the septum but smaller than half of the lateral ventricular volume, 4 if bigger than the lateral ventricular volume. The AIT was considered present if the grey matter band connecting the thalami could be identified at least on 2 adjacent coronal slices.[18] Otherwise, it was considered absent. The intraclass correlation for interrater reliability was calculated to be 0.91 for the number of slices, 0.88 for CSP grade, and 0.92 for AIT.

Statistical Analyses

All analyses were performed using STATA version 13.1 (StataCorp, 2013),[19] and statistical significance was defined as $P < .05$.

Age was treated as a continuous variable for the descriptive statistics, whereas it was dichotomized as ≤35 and >35 for the inferential statistics. The level of education was dichotomized as "high school or lower" and "university or higher.". Marital status was recorded as married, divorced, or never married. Family history of mental illness was categorized as follows: none, family history of non-psychotic disorder, and family history of psychotic disorder.

The distribution of sociodemographic variables such as gender, level of education, marital status, and family history of non-psychotic and psychotic mental illness was reported. Age was not normally distributed; therefore, the median, minimum, and maximum values were reported. The frequency of alcohol/substance use, presence of CSP, absence of AIT, and presence of psychotic symptoms at admission and also at the end of 2 weeks of detoxification treatment in the sample were calculated. The chi-square test was used for comparing gender and absence of AIT.

Logistic regression analysis was performed to investigate the association of CSP and AIT with psychotic symptoms. Two different logistic regression models were formed using the presence of psychotic symptoms versus no psychotic symptoms and persistent psychotic symptoms versus others as dependent variables. The independent variables, CSP and AIT, were added to the analyses in 2 different regression models. The absence of CSP and the presence of AIT were used as reference categories. Grade 3 CSP and grade 4 CSP groups were combined due to the low number of participants. The analysis included age, gender, marital status, and family history of psychiatric illness as confounding factors.

RESULTS

The data from 112 participants were included in the study. The median age of the participants was 31.5 (18-64). One hundred (89.29%) of them were male. Education level was high school or below for 70 (62.50%) of the participants and university or higher for 42 (37.50%). The marital status of the participants was as the following: 50 (44.64%) were married, 46 (41.07%) had never been married, and 16 (14.29%) were divorced. The distribution of alcohol/substance use in the sample is summarized in Table 1.

Of the 112 patients whose data were collected, 47 (41.96%) had psychotic symptoms at admission. Psychotic symptoms resolved within the 2-week detoxification treatment in 21 (18.75%) participants, whereas 26 (23.22%) participants had persistent psychotic symptoms at the end of the second week. A family history of non-psychotic mental illness was found in 31 (27.68%) of the participants, whereas 11 (9.82%) had a family history of psychotic illness.

Regarding MRI findings, a CSP was seen in 60 (53.57%) of the patients. The distribution of the CSP grades was as the following: grade 1 in 23 (20.54%), grade 2 in 27 (24.11%), grade 3 in 8 (7.14%), and grade 4 in 2 (1.79%). Adhesio interthalamica was absent in 74 (66.07%) of the participants. The rate of absent AIT was higher in men than in women (67.00% vs. 58.33%); however, the difference was not significant ($\chi^2 = 0.36$; $df = 73$; $P = .549$).

The results of the regression analyses showed no significant relationship between CSP and either psychotic symptoms at admission or persistent psychotic symptoms at the end of the detoxification treatment. However, the analyses revealed that the absence of AIT increases the risk of

Table 1. The Distribution of Alcohol/Substance Use Among Participants (n = 112)

Alcohol/Substance Used	n (%)
Multiple drugs/alcohol	52 (46.43)
Alcohol or benzodiazepines	29 (25.89)
Methamphetamine	11 (9.82)
Cocaine	10 (8.9)
Cannabis	6 (5.36)
Heroine or opioid analgesics	4 (3.57)

Table 2. Results of the Logistic Regression Analyses Regarding the Association Between the Presence of Cavum Septum Pellucidum and the Absence of Adhesio Interthalamica with Psychotic Symptoms at the Time of Admission and Also Persistent Psychotic Symptoms at the End of the 2-week Detoxification Treatment

	Persistent Psychotic Symptoms					
	RRR[1]*	95% CI[2]**	*P*	RRR	95% CI	*P*
MODEL 1			.020			.068
Age						
18-35	ref			ref		
36-65	0.17	0.06-0.49	**.001**	0.27	0.72-0.98	**.046**
Gender						
Female	ref			ref		
Male	3.09	0.74-12.91	.123	2.14	0.40-11.48	.373
Education level						
≤High school graduate	ref			ref		
≥University graduate	1.19	0.49-2.89	.695	1.48	0.56-3.94	.434
Marital status						
Married	ref			ref		
Never married	0.63	0.24-1.61	.331	1.28	0.43-3.82	.660
Divorced	2.04	0.56-7.40	.280	2.61	0.64-10.67	.182
Family history of mental illness						
None	ref			ref		
Non-psychotic illness	1.66	0.65-4.29	.293	0.47	0.14-1.64	.237
Psychotic illness	2.25	0.49-10.34	.296	3.78	0.77-18.53	.101
MODEL 2			.031			.023
CSP						
Absent	ref			ref		
Grade 1	0.45	0.14-1.43	.176	0.53	0.14-1.98	.344
Grade 2	0.57	0.20-1.66	.303	0.22	0.05-0.96	.054
Grades 3-4	1.53	0.32-7.21	.593	1.93	0.36-10.46	.445
MODEL 3			.015			.013
AIT						
Present	ref			ref		
Absent	2.03	0.81-5.04	.129	4.28	1.25-14.74	**.021**

AIT, adhesio interthalamica; CSP, cavum septum pellucidum.
*Relative risk ratio.
**Confidence interval.

developing persistent psychotic symptoms (Relative Risk Ratio [RRR]: 4.28, CI:1.25-14.74, *P*=.021). Age, gender, education level, marital status, and family history of mental illness have been controlled for in the analyses. The results of the regression analyses are shown in Table 2.

DISCUSSION

The main finding of our study is that the absence of AIT is associated with the risk of developing psychotic symptoms that persist after 2 weeks of detoxification treatment. Our finding supports the results of previous studies reporting that the absence of AIT is associated with schizophrenia spectrum disorders.[8-11,13] The finding of another study which showed that the length of AIT was short from the beginning of psychosis, was interpreted as an implication of AIT being a neurobiological risk factor for psychosis.[5] Our finding is in accordance with this implication. However, we could not track changes in AIT length over time since this is a cross-sectional study.

In this study, the absence of AIT was seen in 66.1% of the participants. This rate is markedly higher than the rate reported in other studies (20%).[7] There might be 2 reasons for this difference. First, this study was done in an inpatient service. Therefore, the rate of psychosis was high in the sample, as psychosis is a common reason for hospital admission. Since there is an association between psychosis and the absence of AIT, having a high rate of psychosis in the sample may have caused a high rate of absent AIT. Second, most of the participants were male,

and it is known that the absence of AIT is more common in men.[7] Although the rate of absent AIT did not significantly differ according to gender in our sample, it was found to be higher in men. The low number of women in the study may have prevented the difference from reaching statistical significance.

The results of the regression analyses showed no significant relationship with respect to CSP. However, the RRR was <1 for grades 1 and 2 CSP, whereas it was >1 for grades 3 and 4 CSP combined. The reason the results were not statistically significant might be that the number of participants who had a large CSP was small. The difference in the direction of the relationship for small and large CSP is in accordance with findings from previous studies claiming that a small CSP might be a neuroanatomic variation and only a large CSP should be considered pathological.[4]

The limitation of our study is that the percentage of men is high; therefore, our results should not be generalized to all genders. The advantageous side of the study is that we included all suitable patients who were admitted consecutively for 3 months. As a result, our findings also provide a descriptive summary of the psychosis spectrum in a drug addiction inpatient service. Another advantage is that all patients undergo cranial MRI scans at admission. The number of participants is adequate for an MRI study. However, repeating the study with a larger sample might help detect a possible significant association with a large CSP and perform the analyses with subcategories according to the alcohol/substance used.

Our findings show that the absence of AIT increases the risk of developing chronic psychotic disorders that persist after the effect of alcohol/substance has passed. This finding may suggest that the absence of AIT can be considered a structural risk factor for the development of psychosis in people receiving treatment for alcohol/substance use. Our results have a clinical implication because it is possible to say that patients who are being treated for alcohol/substance abuse and whose AIT is absent are more susceptible to having persistent psychotic symptoms than other patients. This information might be helpful for patients and families as a warning against a possible future psychotic disorder and also for clinicians as an indication for a more aggressive and prolonged antipsychotic treatment to prevent a possibly worse prognosis.

Ethics Committee Approval: This study was approved by Ethics Committee of Üsküdar University (Approval No: 61351342; Date: June 30, 2022).

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