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ORIGINAL ARTICLE

Retrospective Study

Changes in neurotransmitter levels, brain structural characteristics, and their correlation with PANSS scores in patients with first-episode schizophrenia

Xian-Jia Xu, Tang-Long Liu, Liang He, Ben Pu

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Abstract

BACKGROUND

In patients with schizophrenia, the brain structure and neurotransmitter levels change, which may be related to the occurrence and progression of this disease.

AIM

To explore the relationships between changes in neurotransmitters, brain structural characteristics, and the scores of the Positive and Negative Symptom Scale (PANSS) in patients with first-episode schizophrenia.

METHODS

The case group comprised 97 patients with schizophrenia, who were evaluated using the Canadian Neurological Scale and confirmed by laboratory tests at Ningbo Mental Hospital from January 2020 to July 2022. The control group comprised 100 healthy participants. For all participants, brain structural characteristics were explored by measuring brain dopamine (DA), glutamic acid (Glu), and gamma-aminobutyric acid (GABA) levels, with magnetic resonance imaging. The case group was divided into negative and positive symptom subgroups using PANSS scores for hierarchical analysis. Linear correlation analysis was used to analyze the correlations between neurotransmitters, brain structural character-

istics, and PANSS scores.

RESULTS

Patients in the case group had higher levels of DA and lower levels of Glu and GABA, greater vertical and horizontal distances between the corpus callosum and the inferior part of the fornix and larger ventricle area than patients in the control group ($P < 0.05$). Patients with positive schizophrenia symptoms had significantly higher levels of DA, Glu, and GABA than those with negative symptoms ($P < 0.05$). In patients with positive schizophrenia symptoms, PANSS score was significantly positively correlated with DA, vertical and horizontal distances between the corpus callosum and the infrafornix, and ventricular area, and was significantly negatively correlated with Glu and GABA ($P < 0.05$). In patients with negative schizophrenia symptoms, PANSS score was significantly positively correlated with DA, vertical distance between the corpus callosum and the infrafornix, horizontal distance between the corpus callosum and the infrafornix, and ventricular area, and was significantly negatively correlated with Glu and GABA ($P < 0.05$).

CONCLUSION

In patients with first-episode schizophrenia, DA levels increased, Glu and GABA levels decreased, the thickness of the corpus callosum increased, and these variables were correlated with PANSS scores.

Key Words: Brain structural characteristics; Negative symptoms; Neurotransmitters positive symptoms; Schizophrenia

Core Tip: In this study, the relationship between the changes of neurotransmitter and brain structure characteristics and Positive and Negative Symptom Scale (PANSS) score in patients with first episodes of schizophrenia was investigated. It was found that there were differences in the levels of dopamine, glutamic acid and gamma-aminobutyric acid in the brain of the study subjects, as well as the brain structure characteristics detected by magnetic resonance imaging between the two groups, and there is a certain correlation with PANSS score.

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INTRODUCTION

Schizophrenia is a common, disabling clinical psychiatric disorder, and patients can have clinical manifestations such as positive and negative symptoms, decreased cognitive function, and abnormal mood. Research suggests that patients with schizophrenia have abnormal brain glial cell activity, abnormal prefrontal, anterior cingulate, and striatal functions, and disrupted neurotransmitter secretion, and the degree of their lesions is related to the severity of their symptoms[1,2]. The neurotransmitters, brain dopamine (DA), glutamic acid (Glu), and gamma-aminobutyric acid (GABA), are associated with mental activity, and their relationship with schizophrenia has been a popular topic in clinical research[3-5].

Magnetic resonance imaging (MRI) is a non-invasive imaging modality that clearly shows brain structures, reflects brain function, and is of great value in the diagnosis of psychiatric disorders[6]. The Positive and Negative Syndrome Scale (PANSS) is a common tool for clinically diagnosing and assessing schizophrenia, and is divided into five parts: Positive and negative symptoms, cognitive functioning, arousal symptoms, and depressive mood[7]. This study investigated the relationship between changes in neurotransmitters and structural brain features with PANSS scores in patients with first-episode schizophrenia.

MATERIALS AND METHODS

General information

Ninety-seven patients with schizophrenia, who were evaluated using the Canadian Neurological Scale and confirmed by laboratory tests at Ningbo Mental Hospital from January 2020 to July 2022, were selected as the case group. A further 100 healthy participants were selected as the control group. Participants in the case and control groups were statistically similar in terms of education level, marital status, sex composition, body mass index, or age-based factors, as detailed in Table 1.

Inclusion criteria: (1) Patients with a clinical diagnosis of schizophrenia mainly based on criteria in the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[8]; (2) patients aged 18 to 55 years; (3) schizo-

Table 1 Basic data of patients in the two groups

Group	*n*	Age (yr)	BMI (kg/m^2)	Gender (%)		Degree of education		Marital status	
				Male	Female	Junior high school and below	Senior high school or above	Married	Unmarried or widowed
Case group	97	39.60 ± 8.20	23.76 ± 2.21	41 (42.27)	56 (57.73)	62 (63.92)	35 (36.08)	81 (83.51)	16 (16.49)
Control group	100	37.40 ± 9.40	23.41 ± 2.40	50 (50.00)	50 (50.00)	55 (55.00)	45 (45.00)	77 (77.00)	23 (23.00)
t/χ^2		1.748	1.064	1.184		1.623		1.312	
P		0.082	0.289	0.276		0.203		0.252	

BMI: Body mass index.

phrenia patients with a total PANSS score[9] ≥ 60; (4) volunteers from our health screening who did not suffer from schizophrenia as control patients; and (5) schizophrenia patients who were all first-time patients and had not received relevant medication. This study met the basic requirements of medical ethics, and informed consent was signed with the patients before the examination.

The exclusion criteria were as follows: (1) Dementia; (2) malignancy; (3) use of glucocorticoids or immune-related drugs; (4) combined leukemia, lymphoma, or severe anemia; (5) illiteracy; (6) history of epilepsy or electroconvulsive therapy; (7) history of cranial trauma or cranial surgery; and (8) intracranial infections or other organic lesions.

Sampling of brain neurotransmitters

Three milliliters of fasting elbow venous blood were collected on the same day or the day after enrollment. Blood samples were centrifuged at room temperature for 1 h, the speed was set to 3200 r/min, the duration was set to 10 min, and the upper layer of serum was used to detect DA, Glu, and GABA using the Shenzhen Myriad RT-96A enzyme marker and the enzyme-linked immunosorbent assay kit (Shanghai Enzyme Link Biotechnology Co).

MRI craniocerebral examination

All participants underwent cranial MRI conducted by the same group of imaging physicians using an Alltech Comfort 1.5 T MRI scanner (AllTech Medical Systems, Cleveland, Ohio, United States) in the supine position with sponge pads on both sides of the head for immobilization. The sagittal T1 fluid attenuation recovery imaging sequence was performed using the following parameters: Recovery time, 24 ms; repetition time, 1800 ms; field of view, 23-26 cm, acquisition matrix, 256 × 256; layer thickness, 6 mm; layer spacing, 2 mm; and flip angle, 180°. A 3D gradient echo imaging sequence was used to localize the corpus callosum with T1 imaging in the sagittal position, and a whole brain scan was performed with a 3D brain volume scanning sequence with the following setup parameters: Recovery time, 3.9 ms; repetition time, 9.6 ms; field of view, 23-26 cm, flip angle, 14°; excitation number, 0.5; acquisition matrix, 256 × 288; layer thickness, 1.4 mm, and layer spacing, 0 mm.

PANSS scale scores

All patients were assessed using the PANSS upon admission, and all assessments were completed by the same team of physicians. The PANSS comprises seven items on seven positive symptom scales, seven items on seven negative symptom scales, and 16 items on the general psychiatric symptom scales, with a total of 30 items and three supplemental items. The scale ranges from 30 to 210 points, with higher scores indicating more severe conditions. Patients in the case group were divided into two groups comprising patients with mostly positive and those with mostly negative symptoms. Patients with predominantly positive symptoms had a PANSS score of ≥ 70, and at least two of the four items in the scale, P1 (delusions), P3 (hallucinatory behavior), P6 (patients with suspicion or delusions of victimization), and G9 (patients with other unusual thinking), had scores of more than 4. The criteria for patients with negative schizophrenia were as follows: The presence of negative symptom survey items and 14 items related to disintegrative thinking/cognition (P2, N1 to N6, G5, G7, G10, G11, G13, G15, and G16) on a scale with a total score > 40; total score of the eight survey items related to positive symptoms in patients with schizophrenia < 22, all of survey items (P1, P3, P6, G9) with scores > 4 were less than 2, and all 4 entries with scores ≤ 5.

Statistical analysis

The data were analyzed using SPSS 21.0 software (IBM Corp., Armonk, NY, United States). Descriptive statistics (mean ± SD) were used to express the count data of indicators such as DA, Glu, and GABA), which followed a normal distribution. The independent sample *t*-test was selected for hypothesis testing. Count data (sex, comorbidity rate) were described using frequencies and percentages, and the χ^2 test was used for between-group comparisons. The correlation between PANSS scores and variables was explored using linear correlation analysis. $P < 0.05$ was deemed significant.

Table 2 Comparison of brain neurotransmitter levels between case group and control group (mean ± SD)

Group	*n*	DA	Glu	GABA
Case group	97	5.74 ± 1.30	5.62 ± 0.87	6.34 ± 1.12
Control group	100	3.82 ± 0.96	6.48 ± 0.63	7.56 ± 1.43
t		11.817	-7.964	-6.653
P		0.000	0.000	0.000

DA: Dopamine; Glu: Glutamic acid; GABA: Gamma-aminobutyric acid.

Table 3 Changes of craniocerebral structure in case group and control group (mean ± SD)

Group	*n*	The distance between the midline of the brain and the inferior fornix (mm)	The vertical distance between the corpus callosum and the inferior part of the fornix (mm)	The horizontal distance between the corpus callosum and the inferior part of the fornix (mm)	The distance between the middle fornix (mm)	The area of the ventricles (mm^2)
Case group	97	5.15 ± 0.96	7.26 ± 1.49	6.64 ± 1.10	2.41 ± 0.45	115.2 ± 14.7
Control group	100	4.94 ± 0.80	5.80 ± 0.85	5.48 ± 0.95	2.50 ± 0.41	94.2 ± 10.0
t		1.670	8.479	7.929	-1.468	11.755
P		0.097	0.000	0.000	0.144	0.000

Table 4 Comparison of brain neurotransmitters in schizophrenia patients with different disease characteristics (mean ± SD)

Disease characteristics	*n*	DA	Glu	GABA
Positive symptom	57	6.52 ± 1.14	5.81 ± 0.75	6.56 ± 0.94
Negative symptom	40	4.63 ± 0.98	5.35 ± 0.71	6.03 ± 0.88
t		8.506	3.039	2.806
P		0.000	0.003	0.006

DA: Dopamine; Glu: Glutamic acid; GABA: Gamma-aminobutyric acid.

RESULTS

Brain neurotransmitter levels: Case vs control

Patients in the case group had significantly higher DA levels and significantly lower Glu and GABA levels than patients in the control group ($P < 0.05$) (Table 2).

Comparison of changes in brain structural characteristics between case group and control group

Patients in the case group had greater vertical and horizontal distances between the corpus callosum and the inferior part of the fornix and larger ventricle area than patients in the control group ($P < 0.05$). The distance from the midline of the brain to the lower part of the fornix and the distance from the middle part of the fornix did not differ significantly between the two groups ($P < 0.05$) (Table 3).

Comparison of brain neurotransmitter levels in patients with schizophrenia with different disease characteristics

Patients with positive schizophrenia symptoms had significantly higher levels of DA, Glu, and GABA than those with negative symptoms ($P < 0.05$) (Table 4).

Comparison of cranial structural characteristics in patients with schizophrenia with different disease characteristics

The vertical distance between the corpus callosum and the inferior fornix, the horizontal distance between the corpus callosum and the inferior fornix, the area of the ventricles, the distance between the midline of the brain and the inferior fornix, and the distance between the middle fornix in schizophrenic patients with positive symptoms were not statistically significant compared with those with negative symptoms ($P > 0.05$) (Table 5).

Table 5 Comparison of brain neurotransmitters in schizophrenia patients with different disease characteristics (mean ± SD)

Disease characteristics	*n*	The distance between the midline of the brain and the inferior fornix (mm)	The vertical distance between the corpus callosum and the inferior part of the fornix (mm)	The horizontal distance between the corpus callosum and the inferior part of the fornix (mm)	The distance between the middle fornix (mm)	The area of the ventricles (mm^2)
Positive symptom	57	5.20 ± 0.92	7.31 ± 1.33	6.71 ± 1.04	2.38 ± 0.41	116.80 ± 13.20
Negative symptom	40	5.08 ± 0.85	7.19 ± 1.18	6.54 ± 0.98	2.45 ± 0.38	113.50 ± 11.60
t		0.652	0.458	0.811	-0.853	1.273
P		0.516	0.648	0.419	0.396	0.206

Correlation between PANSS scores and brain characteristics

In patients with positive schizophrenia symptoms, PANSS scores were positively correlated with DA, horizontal distance between the corpus callosum and the inferior part of the fornix, vertical distance between the corpus callosum and the inferior part of the fornix, and ventricular area ($P < 0.05$). In patients with positive schizophrenia symptoms, PANSS scores were negatively correlated with Glu and GABA ($P < 0.05$). For patients with negative symptoms, PANSS scores were positively correlated with DA, horizontal distance between the corpus callosum and the inferior part of the fornix, vertical distance between the corpus callosum and the inferior part of the fornix, and ventricular area ($P < 0.05$). For patients with negative symptoms, PANSS scores were negatively correlated with Glu and GABA ($P < 0.05$) (Table 6).

DISCUSSION

In this study, the changes in neurotransmitters and brain structural characteristics in patients with first-episode schizophrenia, and their relationship with PANSS scores were analyzed. It was found that the in patients with first-episode schizophrenia, DA levels increased, Glu and GABA levels decreased, and the thickness of the corpus callosum increased, and there was a certain correlation with PANSS scores. The results can provide reference for a deeper understanding of schizophrenia and exploring new and effective treatment methods.

Schizophrenia is a heterogeneous disorder with multiple symptom clusters caused by a combination of genetic, developmental, and environmental factors. Most patients develop schizophrenia in young adulthood. Approximately 40% of patients have a good prognosis after pharmacological and psychosocial support treatment[10]. Antipsychotic drugs are the cornerstone of treatment for patients with first-episode schizophrenia and provide good relief for positive symptoms, but have limited efficacy for negative symptoms and cognitive impairment, and a significant proportion of patients relapse after discontinuing medication with a poor prognosis[8]. Therefore, clinical efforts have been devoted to the study of laboratory indicators related to schizophrenia to find new therapeutic targets and provide a basis for the clinical treatment of schizophrenia.

Neurotransmitters are important substances involved in neural signaling, and neurotransmitter disorders can induce brain and neurological dysfunctions[9]. Glu is the most abundant neurotransmitter in the brain and is a precursor of GABA, an inhibitory neurotransmitter[10,11]. DA regulates nervous system function and is involved in extrapyramidal activity[12]. Basic studies have found that Glu and GABA levels are reduced, and DA levels are increased in the brains of patients with schizophrenia[13]. In the present study, the changes of DA, Glu and GABA levels are consistent with the findings of previous studies[14].

It has been suggested that patients with schizophrenia have structural abnormalities in the middle temporal lobe, superior temporal gyrus, corpus callosum, hippocampal sulcus, and cingulate gyrus, and that there are some differences in the volumes of the lateral ventricle, third ventricle, cerebral gray matter, and cerebellar structures[15]. In this study, we found that the vertical and horizontal distances between the corpus callosum and the inferior part of the fornix and the area of the ventricles were greater in patients with first-episode schizophrenia than in healthy participants with unremarkable physical examinations. There were no significant differences between patients with first-episode schizophrenia and healthy participants in terms of the distance between the midline of the brain and the inferior fornix and the distance between the middle fornix. This suggests that the thickness of the corpus callosum is increased in patients with first-episode schizophrenia[16-18]. The corpus callosum produces connections with the nerve fibers in the cerebral hemisphere and is closely related to human emotions and thinking[19-22]. In patients with first-episode schizophrenia, the spatial structure of the lateral ventricles is altered, and the corpus callosum is enlarged under the stretching effect[13-27]. When the corpus callosum is abnormally connected to the nerve fibers of both cerebral hemispheres, abstract and figurative thinking functions are impaired, leading to abnormal thinking[28-30].

In this study, we found that DA, Glu, and GABA levels were higher in patients with mostly positive schizophrenia symptoms than in patients with mostly negative schizophrenia symptoms. Patients with mostly positive or mostly negative schizophrenia symptoms did not differ in terms of the vertical and horizontal distances between the corpus callosum and the inferior part of the fornix, area of the ventricles, the distance between the midline of the brain and the inferior fornix, and the distance between the middle fornix. These results suggest that DA, Glu, and GABA levels are

Table 6 Correlation between each index and Positive and Negative Symptom Scale score

Index	Patient with positive symptoms		Patient with negative symptoms	
	r	*P*	*R*	*P*
DA	0.628	0.000	0.533	0.000
Glu	-0.417	0.011	-0.631	0.000
GABA	-0.489	0.001	-0.567	0.000
The distance between the midline of the brain and the inferior fornix	0.182	0.284	0.154	0.354
The vertical distance between the corpus callosum and the inferior part of the fornix	0.577	0.000	0.475	0.003
The horizontal distance between the corpus callosum and the inferior part of the fornix	0.614	0.000	0.528	0.000
The distance between the middle fornix	0.208	0.256	0.117	0.461
The area of the ventricles	0.625	0.000	0.642	0.000

DA: Dopamine; Glu: Glutamic acid; GABA: Gamma-aminobutyric acid.

relatively higher in patients with schizophrenia with predominantly positive symptoms, which is consistent with the fact that patients with positive symptoms are more neuroexcitable and exhibit symptoms such as mania, euphoria, delusions, and hallucinations[31-33].

Correlation analysis revealed that for patients with predominantly positive schizophrenia symptoms, PANSS scores were significantly and positively correlated with DA, vertical and horizontal distances between the corpus callosum and the inferior fornix, and ventricular area, but negatively correlated with Glu and GABA. A similar pattern was noted for patients with predominantly negative schizophrenia symptoms. This suggests that the levels of DA, Glu, GABA, and other neurotransmitters and corpus callosum thickness in patients with first-episode schizophrenia are correlated with PANSS scores. In future clinical studies, neurotransmitter levels, such as those of DA, Glu, and GABA, and corpus callosum thickness can be used as important auxiliary assessment indices for evaluating the condition of patients with first-episode schizophrenia. However, the number of cases included in this study is limited, and the types of neurotransmitters and brain structure measurement indicators included in the study are limited. Further research is needed on the changes in neurotransmitter levels and brain structure in patients with schizophrenia[34,35].

CONCLUSION

In conclusion, DA levels increased, Glu and GABA levels decreased, and corpus callosum thickness increased in patients with first-episode schizophrenia, and these variables were correlated with PANSS scores.

ARTICLE HIGHLIGHTS

Research background

Patients with schizophrenia have abnormal brain glial cell activity, abnormal prefrontal, anterior cingulate, and striatal functions, and disrupted neurotransmitter secretion, and the degree of their lesions is related to the severity of their symptoms. The neurotransmitters, dopamine (DA), glutamic acid (Glu), and gamma-aminobutyric acid (GABA), are associated with mental activity, and their relationship with schizophrenia has been a popular topic in clinical research. The Positive and Negative Syndrome Scale (PANSS) is a common tool for clinically diagnosing and assessing schizophrenia.

Research motivation

The relationship between changes in neurotransmitters and structural brain features with the occurrence and development of schizophrenia remains unclear.

Research objectives

To explore the relationships between changes in neurotransmitters, brain structural characteristics, and the scores of the PANSS in patients with first-episode schizophrenia.

Research methods

A total of 97 patients with schizophrenia and 100 healthy participants were included into this study. For all participants, brain structural characteristics were explored by measuring brain DA, Glu, and GABA levels, with magnetic resonance imaging (MRI). The case group was divided into negative and positive symptom subgroups using PANSS scores for hierarchical analysis. Linear correlation analysis was used to analyze the correlations between neurotransmitters, brain structural characteristics, and PANSS scores.

Research results

Patients in the case group had higher levels of DA and lower levels of Glu and GABA, greater vertical and horizontal distances between the corpus callosum and the inferior part of the fornix and larger ventricle area than patients in the control group. In patients with positive schizophrenia symptoms, PANSS score was significantly positively correlated with DA, vertical and horizontal distances between the corpus callosum and the infrafornix, and ventricular area, and was significantly negatively correlated with Glu and GABA. In patients with negative schizophrenia symptoms, PANSS score was significantly positively correlated with DA, vertical distance between the corpus callosum and the infrafornix, horizontal distance between the corpus callosum and the infrafornix, and ventricular area, and was significantly negatively correlated with Glu and GABA.

Research conclusions

In patients with first-episode schizophrenia, DA levels increased, Glu and GABA levels decreased, the thickness of the corpus callosum increased, and these variables were correlated with PANSS scores.

Research perspectives

Further research with large cohort and more types of neurotransmitters and brain structure measurement indicators is needed.

FOOTNOTES

Author contributions: Xu XJ and Pu B designed the research study; Liu TL and He L performed the research; Xu XJ and Pu B analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Ningbo Mental Hospital.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

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