ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatry 2024 December 19; 14(12): 1783-1991

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

Contents

Monthly Volume 14 Number 12 December 19, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

World Journal of Psychiatry

Monthly Volume 14 Number 12 December 19, 2024

Contents

World Journal of Psychiatry

Monthly Volume 14 Number 12 December 19, 2024

Contents

World Journal of Psychiatry

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Contents

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

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https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
December 19, 2024

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World Journal of Psychiatry

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World J Psychiatry 2024 December 19; 14(12): 1804-1814

DOI: 10.5498/wjp.v14.i12.1804

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

Interaction between serum inflammatory cytokines and brain-derived neurotrophic factor in cognitive function among first-episode schizophrenia patients

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Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Xu ZL

Received: May 1, 2024
Revised: August 24, 2024
Accepted: September 14, 2024
Published online: December 19, 2024
Processing time: 209 Days and 20 Hours

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Abstract

BACKGROUND

The pathogenesis of cognitive impairment in schizophrenia (SCZ) remains unclear. Accumulating studies showed that inflammatory-immune dysregulation and altered brain derived neurotrophic factor (BDNF) levels play a crucial role in the psychopathology of SCZ. However, their association with cognitive dysfunction in first-episode SCZ patients has not been thoroughly investigated.

AIM

To explore the interaction effects between cognitive function and inflammatory cytokines and BDNF in first-episode SCZ.

METHODS

The current study is a cross-sectional case-control investigation that recruited 84 patients with first-episode SCZ (SCZ group) and 80 healthy controls (HCs group) at the Huzhou Third Municipal Hospital between August 2021 and September 2023. ELISA was employed to measure the serum levels of interleukin (IL)-1β, IL-4, IL-6, IL-10, and BDNF. The Chinese brief cognitive test (C-BCT) and the positive and negative syndrome scales were measured the severity of cognitive impairment and psychiatric symptoms.

RESULTS

Compared to the HC group, the SCZ group exhibited elevated IL-1β and IL-6 levels, decreased BDNF levels, and reduced C-BCT scores (all $P < 0.001$). In SCZ, BDNF was negatively correlated with IL-6 ($r = -0.324$, $P < 0.05$). Information processing speed was negatively correlated with IL-6 ($r = -0.315$, $P < 0.05$) and positively with BDNF ($r = 0.290$, $P < 0.05$); attention, working memory, comprehensive ability, and executive function were negatively correlated with IL-1β and IL-6 (all $P < 0.05$) and positively with BDNF (all $P < 0.05$). Multiple regression analysis showed IL-6 influenced C-BCT dimensions ($\beta = -0.218$ to -0.327, all $P < 0.05$); attention and executive ability were influenced by IL-1β ($\beta = -0.199$ to -0.261, all $P < 0.05$); comprehensive executive ability was influenced by BDNF ($\beta = 0.209$, $P < 0.05$).

CONCLUSION

Our findings suggested that interrelationships between immune dysfunction and neurotrophic deficiency might underlie the pathological mechanisms of cognitive impairments in first-episode SCZ patients.

Key Words: Brain-derived neurotrophic factor; Inflammatory cytokines; First-episode schizophrenia; Cognitive function; Pro-inflammatory cytokines; Neuroinflammation; Serum biomarkers

Core Tip: The previous literature has demonstrated that dysregulation of the inflammatory immune and alterations in brain derived neurotrophic factor (BDNF) levels play a pivotal role in the pathophysiology of schizophrenia (SCZ). In this study, 84 patients with first-episode SCZ and 80 healthy volunteers were recruited. We assessed the cognitive function and psychiatric symptoms of the subjects, measured their serum inflammatory cytokines and BDNF levels, and explored the interaction between cognitive impairment and serum inflammatory cytokines and BDNF in first-episode SCZ. The findings of this study suggest that cognitive impairment in first-episode SCZ was related to immune inflammation imbalance and neurotrophic deficiency.

Citation: Cui LJ, Cai LL, Na WQ, Jia RL, Zhu JL, Pan X. Interaction between serum inflammatory cytokines and brain-derived neurotrophic factor in cognitive function among first-episode schizophrenia patients. *World J Psychiatry* 2024; 14(12): 1804-1814
URL: https://www.wjgnet.com/2220-3206/full/v14/i12/1804.htm
DOI: https://dx.doi.org/10.5498/wjp.v14.i12.1804

INTRODUCTION

Schizophrenia (SCZ) is a prevalent severe mental disorder with an incidence rate of approximately 1%[1]. The exact etiology remains unclear, believed to arise from the complex interplay of biological, psychological, social, and other factors[2]. Cognitive impairment stands out as a fundamental symptom of SCZ, significantly impacting patients' quality of life, social function, and imposing a substantial burden on family and society[3]. In clinical practice, nearly 90% of first-episode schizophrenic patients have cognitive impairment, primarily characterized by executive dysfunction and working memory deficits which display a broad and continuous progression[4]. Moreover, the cognitive function of most patients was much different than predicted based on pre-onset intelligence and education level[5]. Despite recent research has made progress, the pathogenesis is still unclear for cognitive impairment in patients with first-episode SCZ.

Inflammation, or the inflammatory response, is a consequence of immune system activation. Substantial evidence suggests that immune inflammation plays a crucial role in the onset and progression of SCZ[6-8]. The central inflammatory reaction includes pro-inflammatory and anti-inflammatory responses[9]. Pro-inflammatory cytokines that are generated as part of the pro-inflammatory response have the ability to activate microglia and hinder the formation of nerve cells in the hippocampus[10]. This leads to the impairment of synaptic plasticity, which in turn hinders the repair of neurological dysfunction and ultimately results in cognitive decline. The anti-inflammatory reaction can produce anti-inflammatory cytokines, which have a certain protective effect on neural cells related to cognitive function[11]. Maes and Anderson[12] and Maes *et al*[13] found that patients with first-episode SCZ have increased levels of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-17, tumor necrosis factor (TNF-α), and eotaxin (CCL11). These cytokines trigger tryptophan catabolism through the TRYCAT pathway, increase IgA levels, and ultimately lead to the accumulation of neurotoxic substances such as pyridinic acid, xanthine aci, quinolinic acid, and 3-oh-kynurenin. This accumulation may disrupt functional connectivity in brain regions associated with cognitive functions[14]. Studies have also reported unaltered levels of IL-6 and IL-8 in the cerebrospinal fluid of newly diagnosed SCZ patients[15].

A study of multicenter longitudinal found that lower levels of anti-inflammatory cytokines (IL-2 and IL-10) in patients with SCZ were associated with higher suicide risk scores[16]. At the same time, other studies have reported unchanged in anti-inflammatory cytokines levels (IL-4 and IL-10) in patients with acute SCZ. The above studies have reflected that the abnormalities of immune regulation in SCZ are the result of the joint action of pro-inflammatory and anti-inflammatory

cytokines to antagonize each other. The current literature lacks research investigating the collaborative involvement of pro-inflammatory cytokines and anti-inflammatory cytokines in the cognitive impairment process among first-episode SCZ patients.

It is important to study the potential neurochemical basis associated with cognitive impairment in first-episode patients with SCZ. Abnormalities in neurotrophic molecules are one of the important candidate factors for explaining cognitive impairment in first-episode patients with SCZ[17,18]. The brain derived neurotrophic factor (BDNF) plays an important role in maintaining neuronal survival, differentiation migration, neurogenesis, and synaptic plasticity[19,20]. Most studies have found a decrease in serum BDNF levels in patients with SCZ, which is closely related to cognitive function[21,22]. The abnormal BDNF-mediated pathways, including the extracellular regulatory protein kinase (MEK-ERK), phosphatidylinositol kinase (PI3K), and phospholipase CPC-γ pathway, are considered to serve as mediators between neuroinflammation and neuronal dysfunction[23]. This suggests that the cognitive impairment observed in SCZ may involve a reciprocal regulation between various inflammatory cytokines and BDNF. However, there are currently few studies on the interaction between cognitive impairment in first-episode SCZ and inflammatory cytokines and neurotrophic factors[24]. Therefore, it is necessary to further understand the role of the regulatory mechanisms of inflammatory cytokines and neurotrophic factors in cognitive impairment in first-episode SCZ. It may have some enlightening effects on early clinical intervention and treatment. Therefore, this study aims to explore by analyzing 84 patients with first-episode SCZ and 80 healthy controls (HCs) to address two questions: (1) The disparity in serum levels of IL-1β, IL-4, IL-6, IL-10, and BDNF between first-episode SCZ patients and HCs; and (2) The correlation between serum inflammatory cytokines, BDNF, and the severity of cognitive impairment in first-episode SCZ patients.

MATERIALS AND METHODS

Research participants

SCZ group was admitted to the Third People's Hospital of Huzhou City from August 2021 to September 2023.

Inclusion criteria: (1) Meeting the diagnostic criteria for SCZ in The American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition; (2) Aged between from 18 to 65 years old; (3) Having a positive and negative symptom scale (PANSS) score of ≥ 60; (4) Experiencing the first onset of illness without prior use of any antipsychotic medication; (5) Possessing a junior high school or above education level and being able to cooperate in completing tests; and (6) Obtaining informed consent from the patient's parents or legal guardians.

Exclusion criteria: (1) Mental disorders caused by organic brain diseases, mental retardation, *etc.*; (2) Patients with severe physical illnesses, especially those with a history of immune system related diseases or recent use of nonsteroidal anti-inflammatory drugs or immune modulators; (3) Patients receiving physical intervention for mental symptoms, such as repeated transcranial magnetic stimulation or modified electroconvulsive therapy; and (4) Pregnant/lactating women. HCs group were recruited from healthy volunteers who came to the hospital for physical examination at the same time, as well as medical staff in our hospital. Exclusion criteria are the same as those for the SCZ group. Fully inform all participants and their guardians of the content of this study and sign an informed consent form before enrollment. This study was approved by the Ethics Committee of Huzhou Third Municipal Hospital (Ethical Approval No. 2021-018). According to the sample size calculation formula of correlation analysis, $\alpha = 0.05$, $\beta = 0.20$, 85 patients with SCZ need to be included, and HCs will be matched 1:1. Finally, 80 healthy volunteers will be recruited.

Method

Clinical data collection: The present study is a cross-sectional case-control investigation that recruited 84 patients with first-episode SCZ (SCZ group) and 80 HCs (HCs group) at the Huzhou Third Municipal Hospital between August 2021 and September 2023. To minimize potential confounding factors, control group participants were matched for age, sex, and educational level. Additionally, a family history of psychiatric disorders was considered during selection to further refine matching.

Clinical assessment: Two psychiatrists evaluated the psychiatric symptoms of the SCZ group using the PANSS scale and evaluated the cognitive function of all subjects using Chinese brief cognitive test (C-BCT)[25], and the consistency test kappa value ≥ 0.90.

The PANSS consists of positive symptoms, negative symptoms, and general pathology. Positive symptoms include delusions, hallucinations, excitement, confusion, arrogance, suspicion or persecution, and hostility. Negative symptoms include emotional passivation, affective disturbance, emotional withdrawal, passivity or apathy, lack of spontaneity in conversation, abstract thinking, and rigid thinking. General pathology includes 16 items, such as worry about physical health, anxiety, guilt, tension, affectation, depression, and slowness. The above three sub-items are scored on a scale of 1-7 points. Scores 1-7 represent no symptoms, very mild symptoms, mild symptoms, moderate symptoms, mild symptoms, severe symptoms, and very severe symptoms, respectively. The higher the PANSS score, the more severe the symptoms.

BCT operates electronically and has a duration of approximately 15 minutes. It includes four dimensions: Connectivity test, continuous operation, digital breadth, and symbol encoding. These dimensions include information processing speed, attention, working memory and comprehensive + executive ability, respectively. During the test, information such as age, gender, and education level of the subjects are entered, and scores for each dimension are generated. Each dimension is evaluated based on its T score, deficit score, level of impairment, and percentile ranking in the Chinese test population. The relationship between the T score, deficit score, and damage degree is defined as follows: A T score of 40

or above indicates no deficits and normal functioning; a T score of 35-39 indicates a deficit score of 1 and mild impairment; a T score of 30-34 corresponds to a deficit score of 2 and mild to moderate impairment; a T score of 25-29 corresponds to a deficit score of 3 and moderate impairment; a T score of 20-24 indicates a deficit score of 4 and moderate to severe impairment; finally, a T score below 19 indicates a deficit score of 5 and severe impairment.

Blood sample collection and indicator testing: The 5 mL of fasting venous blood was collected from all subjects on the day of enrollment or the next morning from 6: 30 to 7: 30 to avoid the influence of changes in the biological rhythm of the measured factors. After collection, the blood was centrifuged at 3000 r/min at 4 °C for 10 minutes after stewing for 30 minutes. The isolated serum was stored in a refrigerator at -80 °C before testing. The using reagent kits were provided by Jiangsu Jingmei Biotechnology Co., Ltd. The ELISA was used to detect IL-1β, IL-4, IL-6, IL-10, and BDNF in serum levels.

Statistical analysis

Statistical analysis was performed using SPSS 19.0. Quantitative data that conform to a normal distribution are represented by (mean ± SD, and independent sample *t*-tests are used for inter group comparisons. Count data is represented as [*n* (%)], and inter group comparison is used χ^2 inspection. Using Pearson correlation analysis test the correlation between serum biomarkers and cognitive function, and screen for independent variables with statistical differences. Multiple linear regression analysis was employed to assess the impact on cognitive function, with significance denoted by $P < 0.05$, indicating a statistically significant difference.

RESULTS

Comparison of clinical data and serum inflammatory cytokines and BDNF between two groups

The final study included 84 first-episode SCZ patients (40 males and 44 females), 1 patient who withdrew midway without completing C-BCT, and 80 HCs (51 males and 49 females). There was no statistically significant difference in general information such as sex, age, years of education, and smoking history between the two groups (all $P > 0.05$). The scores of all dimensions of C-BCT in the SCZ group were lower than those in the HCs group, and the differences were statistically significant (all $P < 0.001$). The serum BDNF levels in the SCZ group were significantly lower than those in the HCs group, and the difference was statistically significant (all $P < 0.001$). The levels of IL-1β and IL-6 of the SCZ group were higher than the HCs group, and the difference was statistically significant (all $P < 0.001$; Table 1).

Individuals with first-episode SCZ exhibit extensive cognitive impairments in cognitive function assessments, particularly evident in significant reductions in information processing speed, attention, working memory, and overall executive functions. Simultaneously, these patients show elevated levels of inflammatory cytokines IL-1β and IL-6 in their serum, while the levels of BDNF are decreased. The alterations in these biomarkers are closely associated with cognitive dysfunction.

Correlation analysis between serum BDNF and inflammatory cytokines in the SCZ group

The serum BDNF level in the SCZ group had a negative correlation with IL-6 ($r = -0.324$, $P < 0.05$), and there was no correlation between the levels of IL-1β, IL-4, and IL-10 (all $P > 0.05$; Table 2).

As a vital neurotrophic factor, the decrease in BDNF levels may be attributed to neuroinflammatory damage mediated by elevated inflammatory cytokines such as IL-6. This interaction suggests that inflammatory factors may further lead to cognitive impairment by influencing the expression of BDNF.

Correlation analysis between the scores of various dimensions of C-BCT in the SCZ group and serum BDNF and inflammatory cytokines

Correlation analysis was conducted between the scores of various dimensions of C-BCT in the SCZ group and serum inflammatory cytokines and BDNF. Wherein the information processing speed score was a negative correlation with IL-6 ($r = -0.315$, $P < 0.05$) and a positive correlation with BDNF ($r = 0.290$, $P < 0.05$); attention was a negative correlation with IL-1β and IL-6 ($r = -0.226$, -0.412, all $P < 0.05$); working memory was a negative correlation with IL-1β and IL-6 ($r = -0.324$, -0.236, all $P < 0.05$) and positive correlation with BDNF ($r = 0.296$, $P < 0.05$); comprehensive + execution ability was a negative correlation with IL-1β and IL-6 ($r = -0.284$, -0.386, all $P < 0.05$) and a positive correlation with BDNF ($r = 0.357$, $P < 0.05$; Table 3).

The above results indicate that the elevation of IL-6 levels, in conjunction with the reduction of BDNF levels, collectively impacts various dimensions of cognitive function, such as information processing speed, attention, working memory, and executive function. Elevated concentrations of IL-1β and IL-6 may potentially impair cognitive function by disrupting signaling between neurons, while the decrease in BDNF levels further exacerbates this impairment.

Multiple linear regression analysis of factors affecting the degree of cognitive impairment in first-episode SCZ patients

The T score of each dimension of C-BCT was used as the dependent variable. The biological markers, such as inflammatory cytokines with statistical differences obtained from Pearson correlation analysis, were included as independent variables in the multiple linear regression equation. The results showed that IL-6 had an impact on the scores of each dimension of C-BCT in the SCZ group ($\beta = -0.218$, -0.426, -0.321, -0.327, $t = -2.039$, -4.219, -3.039, -3.242, all $P < 0.05$); IL-1β has an impact on attention, comprehensive + execution ability ($\beta = 0.209$, $t = 2.041$, $P < 0.05$, all $P < 0.05$). BDNF only has an impact on comprehensive + execution ability ($\beta = 0.209$, $t = 2.041$, $P < 0.05$; Table 4).

Table 1 Comparison of clinical data and serum inflammatory cytokines and brain derived neurotrophic factor between the schizophrenia and healthy controls groups

Variable	SCZ group (84 cases)	HCs group (80 cases)	χ^2/t value	*P* value
Sex, *n* (%)			0.216	0.642
Male	40 (48)	41 (51)		
Female	44 (52)	49 (49)		
Age (years, mean ± SD)	39.09 ± 10.24	40.35 ± 11.11	0.224	0.815
Education years (years, mean ± SD)	13.41 ± 3.35	14.54 ± 4.02	1.121	0.262
Smoking history, *n* (%)			0.081	0.776
Yes	28 (30)	25 (31)		
No	56 (70)	55 (69)		
Duration of illness (months, mean ± SD)	9.75 ± 3.42	NA	NA	NA
PANSS score (points, mean ± SD)				
Positive symptom score	24.63 ± 1.71	NA	NA	NA
Negative symptom score	20.05 ± 2.09	NA	NA	NA
General pathology score	41.77 ± 2.06	NA	NA	NA
Total score	80.05 ± 4.28	NA	NA	NA
C-BCT cognitive function assessment scores for various dimensions (points, mean ± SD)				
Information processing speed	32.95 ± 5.12[a]	47.58 ± 5.69	17.313	< 0.001
Attention	31.17 ± 7.47[a]	41.55 ± 7.76	12.073	< 0.001
Working memory	35.01 ± 7.18[a]	47.071 ± 1.16	8.271	< 0.001
Comprehensive + execution ability	32.31 ± 9.89[a]	47.30 ± 7.48	12.395	< 0.001
Levels of serum inflammatory factors and BDNF (pg/mL, mean ± SD)				
IL-1β	37.08 ± 5.11[a]	26.95 ± 3.54	14.579	< 0.001
IL-4	30.85 ± 7.59	29.35 ± 4.13	1.558	0.121
IL-6	41.15 ± 5.92[a]	29.37 ± 7.58	11.104	< 0.001
IL-10	28.76 ± 9.51	26.43 ± 6.58	1.690	0.093
BDNF	1383.98 ± 315.33[a]	2692.42 ± 301.03	17.711	< 0.001

[a]$P < 0.001$.

SCZ: Schizophrenia; HC: Healthy control; C-BCT: Chinese brief cognitive test; PNASS: Positive and negative symptom scale; BDNF: Brain derived neurotrophic factor; IL: Interleukin; NA: Not available.

Through multiple linear regression analysis, it is evident that IL-1β and IL-6 serve as risk factors for cognitive impairment, while BDNF acts as a protective factor for cognitive function. This indicates the significant roles of inflammatory cytokines and neurotrophic factors in the cognitive impairment of first-episode SCZ patients.

DISCUSSION

This research focuses on cognitive impairment in first episode of SCZ and investigates the correlation between serum inflammatory cytokines, including IL-1β and IL-6, and BDNF. The findings revealed a notable presence of cognitive deficits in first-episode SCZ individuals accompanied by elevated levels of inflammatory cytokines, specifically IL-1β and IL-6, and a reduction in BDNF levels. Further analysis negative association between IL-6 levels and BDNF. The study also established a connection among IL-1β, IL-6, BDNF, and the severity of cognitive impairment in these patients, suggesting that abnormal neuroimmune activity and nutritional deficiencies may converge in contributing to cognitive impairment during the initial stages of SCZ.

This study employs C-BCT to assess the cognitive functions of all participants, focusing on information processing speed, working memory, attention, and executive function. The analysis revealed that the T scores of individuals with first-episode SCZ patients were notably lower than those of the HCs group. The result indicates that the SCZ patients had

Table 2 Correlation analysis between serum brain derived neurotrophic factor levels and inflammatory cytokines and brain derived neurotrophic factor in the schizophrenia group (*n* = 84)

Serum inflammatory factors	BDNF	
	r value	*P* value
IL-1β	-0.160	0.145
IL-4	0.196	0.073
IL-6	-0.324[a]	0.003
IL-10	0.080	0.470

[a]*P* < 0.05.
BDNF: Brain derived neurotrophic factor; IL: Interleukin.

Table 3 Correlation analysis between Chinese brief cognitive test scores of various dimensions in the schizophrenia group and serum brain derived neurotrophic factor and inflammatory cytokines (*n* = 84)

Variable	Information processing speed		Attention		Working memory		Comprehensive + execution ability	
	r value	*P* value	*r* value	*P* value	*r* value	*P* value	*r* value	*P* value
IL-1β	-0.198	0.071	-0.226[a]	0.039	-0.324[a]	0.003	-0.284[a]	0.009
IL-4	0.123	0.266	0.025	0.823	0.089	0.421	0.116	0.294
IL-6	-0.315[a]	0.004	-0.412[b]	< 0.001	-0.236[a]	0.030	-0.386[b]	< 0.001
IL-10	0.122	0.270	0.161	0.143	-0.025	0.822	0.105	0.343
BDNF	0.290[a]	0.008	0.189	0.085	0.296[a]	0.006	0.357[b]	< 0.001

[a]*P* < 0.05.
[b]*P* < 0.001.
BDNF: Brain derived neurotrophic factor; IL: Interleukin.

comprehensive cognitive impairment.

The findings align with previous research[26,27] supporting the assertion that cognitive impairment significantly contributes to the social deterioration observed in individuals with SCZ[28]. This impairment is believed to stem from a multifaceted pathological mechanism that may involve genetic predisposition, neuroimmunity, and environmental influences. Increasingly, research suggests that dysregulated neurobiochemical processes and immune-inflammatory responses may underlie the cognitive deficits seen in SCZ patients[29-31]. Our study found that the serum levels of IL-1β and IL-6 in first-episode SCZ patients were higher than those in HCs, while the concentration of BDNF was lower than that of the HCs group. The results are consistent with those of most previous groups[3,32]. Pro-inflammatory cytokines are secreted by persistently stimulated macrophages and T lymphocytes. Formerly recognized as indicative markers for SCZ, cytokines like IL-1β and IL-6 are known for their pro-inflammatory properties within the immune system[33]. That is, they increase during the exacerbation of mental illness and gradually recover after drug treatment[34]. The central nervous system's immune abnormalities further stimulate the active activity of microglia. Then, cytokine secretion disorders are promoted, which lead to abnormal brain neuron and synaptic function, cell apoptosis, decreased neuronal production, and secretion of BDNF levels[35]. The negative effects of reduced BDNF levels on cortical integrity (that is, inner temporal lobe and other temporal lobe regions) and white matter microstructure (that is, frontotemporal connectivity disorder) may eventually manifest the cognitive functional damage of patients with SCZ[31]. At the same time, studies have also found that there is no significant change in the levels of anti-inflammatory cytokines IL-4 and IL-10 in patients with first-episode SCZ, and our study also issued the same results[36]. Parksepp *et al*[37] have also reported a 5-year follow-up study on inflammation and metabolic indicators in first-time SCZ patients, and there was no significant change in IL-4 and IL-10 Levels before treatment with antipsychotic drugs. However, Borovcanin *et al*[38] found that the serum levels of IL-4 increased and IL-10 decreased in patients with first-episode SCZ and recurrent SCZ. After treatment with antipsychotic drugs, the expression levels were reversed of these two inflammatory cytokines[39]. The different results may be related to factors such as the race, age, and duration of illness of the patients in their study. This inconsistent manifestation precisely reflects the imbalance between anti-inflammatory and pro-inflammatory immune regulation in first-episode SCZ patients, which plays an important role in the pathological process of SCZ.

In this study, we found that serum IL-6 Level was negatively correlated with BDNF in patients with first-episode SCZ, suggesting that the expression of pro-inflammatory cytokines IL-6 mediated neuroinflammatory damage, resulting in decreased expression of synaptic plasticity related proteins, which was manifested as decreased level of neurogenic factor

Table 4 Multiple linear regression analysis of factors affecting the degree of cognitive impairment in first-episode schizophrenia patients

Dependent variable		Non standardized coefficient		Standard coefficient	*t* value	*P* value	95%CI of *B*	
		B	Standard error	*β*			Lower limit	Upper limit
Information processing speed	Constant	35.834	5.378		6.663	0.000	25.134	46.535
	BDNF	0.002	0.002	0.156	1.396	0.167	-0.001	0.005
	IL-6	-0.173	0.088	-0.218	-2.039	0.046	-0.349	0.003
Attention	Constant	61.450	7.025		8.747	0.000	47.473	75.428
	IL-6	-0.492	0.114	-0.426	-4.329	0.000	-0.718	-0.266
	IL-1β	-0.312	0.155	-0.199	-2.019	0.047	-0.619	-0.005
Working memory	Constant	48.866	9.263		5.276	0.000	30.433	67.300
	IL-1β	-0.230	0.150	-0.155	-1.532	0.129	-0.529	0.069
	BDNF	0.004	0.002	0.192	1.793	0.077	0.000	0.008
	IL-6	-0.350	0.115	-0.321	-3.039	0.003	-0.580	-0.121
Comprehensive + execution ability	Constant	52.628	8.983		5.858	0.000	34.751	70.505
	IL-1β	-0.394	0.146	-0.261	-2.699	0.008	-0.684	-0.103
	BDNF	0.004	0.002	0.209	2.041	0.045	0.000	0.008
	IL-6	-0.362	0.112	-0.327	-3.242	0.002	-0.585	-0.140

BDNF: Brain derived neurotrophic factor; IL: Interleukin.

BDNF. Williams *et al*[40], in their investigations on inflammation and brain structure in SCZ, also discovered that the elevation of serum IL-6 could potentially impact the volume of the hippocampus and the thickness of the cortex while concurrently reducing BDNF expression. Further analysis revealed significant correlations between cognitive function scores and levels of serum inflammatory cytokines as well as BDNF.

Elevated IL-6 levels are linked to lower BDNF levels, indicative of a more significant impairment in information processing speed[41]. Increased IL-1β and IL-6 Levels are associated with reduced attention. Elevated IL-1β and IL-6 levels, along with decreased BDNF levels, are connected to impairments in working memory and declining comprehensive executive function. Notably, there was no observed correlation between serum IL-4, IL-10 levels, and cognitive function. The study findings suggest that heightened levels of pro-inflammatory cytokines disrupt signal transmission among neuronal synapses in the brain, contributing to cognitive dysfunction. Previous research has also established a relationship between elevated IL-6 Levels, decreased BDNF levels, and impaired information processing in the cognitive function of individuals with SCZ[30,42]. Furthermore, the overexpression of IL-1β can trigger localized and persistent inflammation in the hippocampus, hindering hippocampal-mediated memory formation[43].

Şimşek *et al*[44] found that the severity of negative symptoms in patients with first-episode SCZ was positively correlated with serum IL-4 level and negatively correlated with IL-10, while the changes in cognitive function were not correlated with the two anti-inflammatory cytokines. Our study carefully selected relevant independent variables for conducting multiple linear regression analysis. The findings revealed that IL-1β and IL-6 are significant risk factors for cognitive impairment among patients with first-episode SCZ, while BDNF emerged as a protective factor for cognitive function in the same population. Hakeim *et al*. also found[45] that IL-6 levels increase during the acute phase of SCZ. After controlling for variables such as body mass inde, smoking history, and duration of illness using multiple regression analysis, elevated levels of IL-6 persist as a significant risk factor for cognitive impairment.

Immunoinflammation and neurotrophic deficiencies do not exist in isolation in SCZ, but were part of a tight neural network composed of protein-protein interactions[46]. Elevated IL-1β, IL-6 and other related pro-inflammatory cytokines had a variety of neuroimmunotoxic effects, including activation of autoimmune response, maintenance of persistent peripheral inflammation and neuroinflammation, reduction of hippocampal neurogenesis, activation of microglia, tissue damage in the central nervous system, and induction of MAPK pathway[47-49], these mechanisms are associated with neuroplasticity, synaptic assembly, axonogenesis, and abnormalities in presynaptic and postsynaptic neural connections, leading to impairment of neuronal function[13,46]. The impact of this phenomenon may be more pronounced in cases of neuronutrition deficiency, particularly when there is a reduction in BDNF levels[46]. The activation of immunoinflammatory pathways and the decrease in BDNF could potentially play a pivotal role in cognitive impairment observed in individuals with SCZ[50].

This study focuses on the first episode of SCZ and explores the correlation between cognitive impairment and serum inflammatory cytokines and BDNF. Our findings are consistent with previous research that shows elevated levels of IL-1β

and IL-6 and decreased BDNF levels in SCZ patients. However, we specifically highlight the interaction between these cytokines and BDNF in relation to cognitive impairment, which has been less explored in existing literature. Additionally, our study uses the C-BCT for a comprehensive evaluation of cognitive functions, including information processing speed, working memory, attention, and executive function, providing a multidimensional perspective. The study's innovation lies in its focus on the first-episode SCZ patients, which offers insights into early intervention and treatment strategies.

Longitudinal studies are needed to observe the dynamic changes in BDNF levels and cognitive function throughout the progression of SCZ. Such studies would enable a deeper understanding of how these factors interact over time and in response to treatment, potentially guiding more effective intervention strategies. Moreover, the current study utilized specific cognitive assessment tools, but future research should incorporate more comprehensive neuropsychological test batteries. This approach would provide a fuller picture of cognitive impairments, covering a wider range of cognitive domains and offering more detailed insights into the nature of these impairments in SCZ. Additionally, it is important to consider the impact of various confounding factors on the relationship between BDNF levels and cognitive function. Future research should include genetic predispositions, environmental influences, and medication use as covariates or through stratified analyses. This would help in isolating the specific contributions of inflammatory cytokines and neurotrophic factors to cognitive impairments, thereby refining our understanding of the underlying mechanisms.

This study has several limitations that warrant consideration. Firstly, inflammatory cytokines and BDNF levels were measured in peripheral blood, raising uncertainty about whether changes observed reflect similar alterations in the central nervous system. Furthermore, the origin of IL-1β, IL-6, and BDNF in serum from the brain is unclear, necessitating further investigation. Secondly, the cross-sectional design employed does not establish causality between biomarkers like inflammatory cytokines and cognitive impairment in first-episode SCZ patients. Thirdly, the study focused on patients with first-episode SCZ characterized by more severe clinical symptoms, particularly positive symptoms, potentially limiting the generalizability of these findings to outpatient populations.

CONCLUSION

In summary, our study revealed aberrant immune function and neurotrophic deficiency in patients with first-episode SCZ, while also establishing a correlation between elevated serum levels of IL-1β and IL-6 and reduced levels of BDNF as well as cognitive impairment. Further longitudinal studies with larger sample sizes were warranted to validate these findings. The underlying mechanisms or pathways linking peripheral immune cytokines to cognitive function in first-episode SCZ still require elucidation.

FOOTNOTES

Author contributions: Cui LJ, Cai LL and Na WQ contributed to the writing of the manuscript; Jia RL contributed to data analysis and statistical processing; Zhu JL contributed to conduct experimental operations; Cai LL and Pan X devised the study design; all authors have read and agreed to the published version of the manuscript.

Supported by Huzhou Public Welfare Research Project Social Development Category, No. 2021GYB09, No. 2021GY38, No. 2019GY26 and No. 2019GZB02.

Institutional review board statement: This study was approved by the Ethics Committee of Huzhou Third Municipal Hospital (Ethical Approval No. 2021-018).

Informed consent statement: Fully inform all participants and their guardians of the content of this study and sign an informed consent form before enrollment.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Data sharing statement: The data for this study can be obtained from the corresponding author upon request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country of origin: China

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S-Editor: Lin C
L-Editor: A

P-Editor: Yu HG

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