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Serum high-sensitivity C-reactive protein levels are positively associated with cognitive impairments in patients with first-episode schizophrenia

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ABSTRACT

Background: To clarify the controversy regarding the relationship between serum high-sensitivity C-reactive protein (hs-CRP) levels and cognitive impairments in first-episode schizophrenic patients and examine whether hs-CRP is a potential objective biological indicator for evaluating cognitive impairment in first-episode schizophrenic patients.
Methods: Serum hs-CRP levels were measured in 58 first-episode schizophrenic patients and 31 healthy controls using immunofluorescence. The Brief Psychiatric Rating Scale (BPRS) and the P300 event-related potential were assessed. The relationship between serum hs-CRP levels and both BPRS scores and P300 were analyzed.
Results: Serum hs-CRP levels and BPRS scores were significantly higher in the study group than in the control group. The incubation period of P3 was longer, and the amplitude of P3 was larger in the study group than in the control group. Correlation analysis showed that in the study group, serum hs-CRP levels were positively correlated with BPRS total scores. Serum hs-CRP levels were also positively correlated with the incubation period of P3 and negatively correlated with P3 amplitudes.
Conclusions: Serum hs-CRP levels were positively associated with cognitive impairment in first-episode schizophrenic patients and potentially represent an objective biological indicator for the rapid evaluation of cognitive impairment in first-episode schizophrenic patients.
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1. Introduction

Schizophrenia is a disabling psychiatric disease associated with deficits in cognition, emotion, psychosocial and occupational functioning [1]. With advances in symptom rating scales, such as the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI), the diagnosis of schizophrenia has been largely improved. However, the evaluation of cognitive impairments in patients with schizophrenia is still challenging because the pathogenesis has not been fully defined. In urban areas, the cognitive impairments observed in patients with schizophrenia can be properly diagnosed by professional psychologists. However, in less developed zones where there are few experienced psychologists, a reliable biological indicator for the quick and objective evaluation of cognitive impairments in schizophrenia is urgently needed. Previous reports have shown that some methods, such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [2,3], the MATRICS Consensus Cognitive Battery (MCCB) [4,5] and the P300 event-related potential [6,7], can be used as tools to evaluate cognitive function in patients with mental disorders. However, these methods have limitations. Some methods require experienced psychiatrists to spend a great deal of time evaluating patients with mental disorders; these include the RBANS and MCCB, which take 45–65 min to test [8]. Other methods require a large amount of money to buy equipment and train operators; these include the P300 event-related potential.

Previous studies have suggested that infection and inflammation play important roles in cognitive impairment in schizophrenia [9]. High-sensitivity C-reactive protein (hs-CRP) is a highly sensitive acute phase-response protein [10]. As an accurate and objective index for reflecting inflammatory activity in vivo, it is widely used to assess the severity of illness in patients with depressive disorders [11]. Previous studies have reported that there is a clear relationship between serum hs-CRP levels and cognitive functional impairments in schizophrenia patients [12–14]. However, the conclusions reached by different research groups are somewhat contradictory. In a clinical investigation by Bulzacka, a positive correlation was found between abnormal CRP levels and cognitive impairment in schizophrenia [15], whereas in another study, no significant relationship was found between serum hs-CRP levels and cognitive performance, such as verbal cognition and performance abilities, in patients with schizophrenia [16]. Similarly, another study also found no significant correlations between CRP levels

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and cognitive impairments in patients with schizophrenia or schizoaffective disorder [17]. Possible reasons for these differences include the following: 1) the research groups used a scale to assess the cognitive function of the subject, and the test results are susceptible to subjective factors related to the subject and examiner; 2) the subjects in these studies were consecutively treated schizophrenia patients, and the test results may therefore be affected by psychotropic drugs; 3) differences in subject populations, hs-CRP detection methods, and statistical methods are also factors that could lead to the opposite results reached by these studies.

In this paper, we examined the relationship between serum hs-CRP levels and cognitive impairments in 58 patients with schizophrenia. In contrast to previous studies, we used multiple objective approaches to quantify cognitive impairments in patients with first-episode schizophrenia. Both the BPRS and the P300 event-related potential were used. The results from both assessments showed that there was a strong positive correlation between serum hs-CRP levels and cognitive impairments in schizophrenia. Our results support the notion that hs-CRP could be a potential biological indicator for the fast and cost-effective evaluation of cognitive impairments in first-episode patients with schizophrenia.

2. Methods

2.1. Study overview and participants

Cases included the study group were inpatients at Xuzhou Oriental People's Hospital from January to June 2018. The following inclusion criteria were applied: (1) met the diagnostic criteria for schizophrenia in accordance with the international classification of diseases Tenth Edition (ICD-10); (2) first-episode patients; (3) age between 18 and 60 years old; (4) score on the BPRS >35 points [18]; and (5) right-handed. The following exclusion criteria were applied: (1) accompanied by serious heart, liver, kidney, endocrine, blood or other medical diseases or surgery, trauma, tumors, inflammation or infectious diseases; (2) alcohol or drug abuse reported within one year; (3) lactating and gestational women; and (4) patients taking antipsychotics and sedative hypnotics before entering the group.

The control group consisted of staff, interns and health volunteers in the same period excluding those who had a history of mental illness or a family history of definite physical and infectious diseases, drug use or other psychoactive substance dependence. The exclusion criteria were the same as those used in the study group.

2.2. Inspection method

2.2.1. The method of detecting serum hs-CRP

After admission, 5 ml of fasting venous blood was collected from 6:00 am to 7:00 am, and the serum was separated. The instrument used was a Flying Immunofluorescence Detector (Guangzhou Wanfu Biotechnology Co., Ltd.), and the reagents were provided by Guangzhou Wanfu Biotechnology Co., Ltd. Serum hs-CRP levels were measured by immunofluorescence. The normal range is 0–1 mg/l.

2.2.2. Detection of the P300 event-related potential

Event-related potentials (ERPs) are widely used as an objective method to reflect the brain's advanced thinking activities, and P300 waves are the most typical and commonly used component of ERP. They are closely related to cognitive processes and are regarded as a window for “peeping” at mental activities. Therefore, they are considered an important means of studying brain cognitive activities.

This study selected the P300 event-related potential as a measure of cognitive function in patients with schizophrenia. All subjects were tested in the brain-evoked potential room of Xuzhou Oriental People's Hospital according to the operation rules. The instrument is a brain evoked potential instrument produced by the British Oxford company (model: 040C004). According to the international standard 10/20 system, the electrode used is a disc silver chloride electrode and has a diameter of 8 mm. The recording electrode was placed in the top area (Pz), the reference electrode was placed in the left earlobe (A_1), and the frontal area (FPz) was grounded. The resistance between the electrode and the scalp was <5 kΩ, and the resistance between the electrode was <2 kΩ. An auditory oddball stimulation sequence was used to stimulate sound through an earphone, and the stimulation intensity was 80 dB. Two sets of trigger and stimulation systems and two independent time windows were used for P300 detection. The nontarget stimulus (NT) was a regular low-frequency tone of 1000 Hz, while the target stimulus (T) was a random high-frequency tone of 2000 Hz. Target stimuli were randomly inserted into nontarget stimuli at a frequency ratio of 0.2/0.8 and stacked 100 times. The analysis time was within 1000 ms after stimulation. The recorded indicators were the incubation period of the target stimulation P3 and the P3 amplitude.

2.2.3. Assessment of mental symptoms

The BPRS is an assessment scale used to assess the severity of psychotic symptoms. Because of its simple operation and short duration, it is often used as a descriptive indicator for the severity of illness and psychopathological manifestations in patients with schizophrenia. In this study, mental symptoms were assessed with the BPRS. Each item was scored on a 7-grade scale as not present, very mild, mild, moderate, moderately severe, severe or extremely severe. A double-blind evaluation was conducted by 2 attending physicians. The intraclass correlation coefficient (ICC) of 58 schizophrenic patients was 0.82.

2.3. Statistical analyses

SPSS 20 was used for statistical analyses. Spearman correlation analysis was performed between clinical features and both BPRS scores and P300 in the study group. Serum hs-CRP levels, BPRS scores, and P300 indexes were compared between the two groups by independent sample *t*-tests. Pearson correlation analysis was performed between the levels of hs-CRP and both BPRS scores and the incubation period and amplitudes of P300 waves. The test level was 0.05.

3. Results

3.1. Descriptive analysis and clinical features

There were 58 patients in the study group, including 25 males and 33 females aged 20–60 years old with an average age of 38.81 ± 11.64 years old. The years of education of the subjects ranged from 6 to 19, with an average of 9.60 ± 2.82 years. The course of disease ranged from 1 to 60 months, with an average of (21.78 ± 14.95) months. A total of 31 subjects were enrolled in the control group, including 12 males and 19 females aged 21–59 years old with an average age of 36.77 ± 11.56 years old. The average years of education were 6–19 (9.42 ± 2.98). There was no significant difference between the two groups in sex (χ^2=0.161, $P = 0.689$), age ($t = 0.800$, $P = 0.426$), or length of education ($t = 0.288$, $P = 0.774$).

Correlation analysis showed that the ages of the patients were negatively correlated with P3 amplitudes ($r = -0.370$, $P = 0.004$) and were not significantly correlated with BPRS total scores ($r = 0.103$, $P = 0.440$) or the P3 incubation period ($r = 0.117$, $P = 0.383$). The course of the disease was positively correlated with P3 amplitudes ($r = 0.128$, $P = 0.340$) but was not significantly correlated with BPRS total scores ($r = -0.186$, $P = 0.162$) or the incubation period of P3 ($r = -0.083$, $P = 0.537$). There was no significant correlation between the duration of education and BPRS total scores ($r = -0.155$, $P = 0.245$), the incubation period ($r = 0.143$, $P = 0.283$) or P3 amplitudes ($r = 0.010$, $P = 0.940$) (Table 1).

Table 1
Correlation analysis between the clinical features, BPRS scores and P300 in the study group (r).

	BPRS	P3	
		Incubation period (ms)	Amplitude (μV)
Age (year)	0.103	0.117	−0.370**
Years of education (year)	−0.155	0.143	0.010
Course of disease (month)	−0.186	−0.083	0.128

** P<0.01.

3.2. Comparison of serum hs-CRP levels, BPRS and P300 in the two groups

Serum hs-CRP levels were higher in the study group than in the control group ($t = 4.453$, $P = 0.000$), as were BPRS scores ($t = 24.805$, $P = 0.000$). The P3 incubation period was longer in the study group than in the control group ($t = 11.483$, $P = 0.000$), and P3 amplitudes were lower in the study group than in the control group ($t = -2.759$, $P = 0.007$). These differences were significant (Table 2).

3.3. Correlation analysis between serum hs-CRP levels and both BPRS scores and the P300 index

Correlation analysis showed that in the study group, serum hs-CRP levels were positively correlated with somatic concern ($r = 0.209$, $P = 0.050$), emotional withdrawal ($r = 0.274$, $P = 0.009$), conceptual disorganization ($r = 0.267$, $P = 0.012$), tension ($r = 0.310$, $P = 0.003$), mannerisms and posturing ($r = 0.298$, $P = 0.005$), hostility ($r = 0.283$, $P = 0.008$), suspiciousness ($r = 0.275$, $P = 0.009$), hallucinations ($r = 0.348$, $P = 0.001$), uncooperativeness ($r = 0.290$, $P = 0.006$), insight disorder ($r = 0.296$, $P = 0.005$), work disability ($r = 0.387$, $P = 0.000$) and total scores ($r = 0.380$, $P = 0.000$). The associations between serum hs-CRP levels and anxiety ($r = 0.165$, $P = 0.122$), Guilt feelings ($r = 0.103$, $P = 0.337$) or grandiosity ($r = 0.053$, $P = 0.624$), depressive mood ($r = 0.209$, $P = 0.050$), motor retardation ($r = 0.187$, $P = 0.079$), unusual thought content ($r = 0.102$, $P = 0.342$), blunted affect ($r = 0.180$, $P = 0.092$), excitement ($r = 0.159$, $P = 0.138$) and disorientation ($r = -0.005$, $P = 0.964$) were not significant (Table 3).

In the study group, serum hs-CRP levels were positively correlated with the incubation period of P3 ($r = 0.445$, $P = 0.000$) and negatively correlated with P3 amplitudes ($r = -0.313$, $P = 0.003$).

4. Discussion

Schizophrenia is a complex, chronic mental health disorder characterized by an array of symptoms, including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability [19]. Studies have shown that patients with schizophrenia exhibit specific low-grade inflammatory characteristics unrelated to sex and age [20]. Dorofeikova et al. also showed that among patients with schizophrenia, 21.4% had signs of a systemic inflammatory response, indicating a possible role for the inflammatory response in the development of schizophrenia [21]. Serum C-reactive protein (CRP) plays a role in the innate immune system by recognizing changes in its own and foreign molecules and binding to various ligands. Its concentration is often used as an alternative indicator of systemic inflammation [22]. Varun et al. found that CRP levels were higher in schizophrenic patients than that in healthy controls [23]. This study shows that serum hs-CRP levels were significantly higher in patients with first-episode schizophrenia than in the control group. These results are in line with those presented in previous studies, suggesting that this index may be related to schizophrenia. At the same time, this study found that serum hs-CRP levels, in patients with first-episode schizophrenia, were positively correlated with the BPRS scores for somatic concern, emotional withdrawal, conceptual disorganization, tension, mannerisms and posturing, hostility, suspiciousness, hallucinations, uncooperativeness, insight disorder, work disability, and total scores. The level of hs-CRP could therefore reflect the condition of first-episode schizophrenics, to a certain extent.

Schizophrenia patients have extensive cognitive impairment [24]. Cognitive symptoms comprise disorganized speech, attention, and thought and eventually impair the person's ability to communicate [25]. The P300 event-related potential, as a recognized and common “peep-in” means of examining the cognitive functions of the brain, can be used to record the brain's response to information rather than to stimuli themselves. Because of its “endogenous” characteristics, it can reflect the electrophysiological changes of the brain during the cognitive process, and it is the only objective index that reflects a psychological process and is not affected by response selection or response execution. Although P300 cannot be directly used for the diagnosis of any cognitive impairment, such as trouble remembering, learning new things, concentrating, or making decisions that affect everyday life, previous studies have shown that P300 is a reliable index for the evaluation of cognitive impairments [26–29]. This study shows that the P300 event-related potential, in the study group, had a longer P3 incubation period and lower P3 amplitudes than were found in the control group, suggesting that cognitive impairment has already occurred in first-episode schizophrenics.

At present, an increasing amount of evidence indicates that cognitive function is related to inflammatory markers. Peripheral pro-

Table 3
Correlation analysis between serum hs-CRP levels and BPRS scores in the study group.

BPRS		Score	r
Total		47.29 ± 22.47	0.380**
Factor	Somatic concern	1.87 ± 1.60	0.209*
	Anxiety	2.85 ± 1.59	0.165
	Emotional withdrawal	3.15 ± 2.48	0.274**
	Conceptual disorganization	3.35 ± 2.18	0.267*
	Guilt feelings	1.13 ± 1.30	0.103
	Tension	2.82 ± 1.38	0.310**
	Mannerisms and posturing	2.74 ± 2.16	0.298**
	Grandiosity	1.21 ± 1.38	0.053
	Depressive mood	2.04 ± 0.96	0.118
	Hostility	2.27 ± 2.27	0.283**
	Suspiciousness	3.21 ± 2.62	0.275**
	Hallucinations	2.45 ± 2.31	0.348**
	Motor retardation	2.16 ± 1.51	0.187
	Uncooperativeness	2.31 ± 2.26	0.290**
	Unusual thought content	2.67 ± 2.00	0.102
	Blunted affect	3.13 ± 2.21	0.180
	Excitement	1.57 ± 1.74	0.159
	Disorientation	0.62 ± 0.63	−0.005
	Insight disorder	3.38 ± 2.66	0.296**
	Work disability	2.42 ± 1.94	0.387**

* P<0.05.
** P<0.01.

Table 2
Comparison of serum hs-CRP levels, BPRS scores and P300 in the two groups ($\bar{x}\pm s$).

Group	n	hs-CRP (mg/l)	BPRS	P3	
				Incubation period (ms)	Amplitude (μV)
Study	58	1.85 ± 1.73**	62.12 ± 11.13**	463.98 ± 88.38**	4.95 ± 4.11**
Control	31	0.77 ± 0.48	19.55 ± 5.01	323.46 ± 21.63	7.35 ± 3.49

** Compared with the control group, by independent sample t-test, P < 0.01.

inflammatory cytokines and anti-inflammatory cytokines are thought to mediate complex interactions between the peripheral immune system and the central nervous system, thus leading to "normal" and pathological cognitive impairment [30]. Krogh et al. found that an increase in serum hs-CRP levels observed in depressive patients was associated with lower psychomotor speed and poor executive functions at baseline [31]. Bulzacka also found that abnormal CRP levels may be associated with cognitive dysfunction in schizophrenic patients [12]. However, the above tests for patient cognitive function are mainly based on the use of scales and are consequentially subject to subjective factors. Through correlation analysis, we found that serum hs-CRP levels were positively correlated with P3 incubation periods and negatively correlated with P3 amplitudes in first-episode schizophrenic patients, suggesting that serum hs-CRP levels also reflect the cognitive function of patients to a certain extent. Because all the data used in this study were objective examination data, and because the influence of psychotropic drugs on the examination results was excluded, the evaluation method used in this study is relatively more reliable and more suitable for the preliminary screening of schizophrenic patients, especially those with an early diagnosis.

In summary, this study shows that serum hs-CRP levels are significantly higher in first-episode schizophrenia patients than in controls and related to the condition and cognitive function of the patient. In basic hospitals with limited resources, hs-CRP can be used as a potential biological indicator to roughly evaluate cognitive function in patients with schizophrenia. However, hs-CRP is not a specifically reactive protein; hence, any condition that could cause its level to rise, especially infection, should be excluded. However, due to the small sample size, the role of serum hs-CRP in the occurrence and development of schizophrenia and whether serum hs-CRP levels are effective in predicting patient conditions and the recovery of cognitive functions needs further study.

Ethics approval and consent to participate

The Ethics Committee of Xuzhou Oriental People's Hospital approved the protocol of this study. All participants provided written informed consent.

Consent for publication

Not applicable.

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Authors' contributions

The authors' contributions are as follows: Jing Zhu and Wei Hu conceived and developed the idea for the paper and revised the manuscript; Xue Chang and Zhu Tong contributed to data collection and wrote numerous drafts; Juan Qiao contributed to data analysis and interpretation of the data. Yi Zhou provided advice and helped with writing. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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