Article

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Study on the Correlation between Hcy and Hs-CRP Levels and Cognitive Function in Patients with Bipolar Disorder and Borderline Personality Disorder

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Abstract

Objective: This study aims to explore the correlation and clinical significance of homocysteine and high-sensitivity C-reactive protein levels with cognitive function in patients with bipolar disorder (BD) and borderline personality disorder (BPD).

Methods: Patients with BD admitted to our hospital from January 2022 to December 2022 were chosen retrospectively. BPD patients were categorized into comorbidity groups, while those without BPD were assigned to non-comorbidity groups, each consisting of 60 cases. Enzyme-linked immunosorbent assay (ELISA) was utilized to assess serum levels of homocysteine (Hcy) and high-sensitivity C-reactive protein (hs-CRP) in both patient groups. Clinical symptoms were evaluated by the Hamilton Depression Rating Scale (HAMD) and the Young Mania Rating Scale (YMRS). Cognitive function was evaluated and compared using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Pearson correlation analysis was performed on the correlation between patients' serum Hcy and hs-CRP levels and HAMD, YMRS, and RBANS scores.

Results: In the comorbidity group, patients exhibited significantly elevated serum Hcy and hs-CRP levels compared to the non-comorbidity group ($p < 0.05$). Patients in the comorbidity group displayed higher HAMD and YMRS scores than those in the non-comorbidity group ($p < 0.05$). Additionally, attention, speech, visual span, immediate memory, and delayed memory in the comorbidity group were notably lower than in the non-comorbidity group ($p < 0.05$). The speech, visual span, and immediate memory of RBANS in bipolar depressive patients with comorbid BPD were lower than those in bipolar depressive patients without comorbid BPD ($p < 0.05$), the speech of RBANS in bipolar manic patients with comorbid BPD was lower than those in bipolar manic patients without comorbid BPD ($p < 0.05$). Pearson correlation analysis showed that the expression of Hcy and hs-CRP in the comorbid group was positively correlated with HAMD and YMRS scores, and negatively correlated with attention, speech, visual span, immediate memory, and delayed memory, and these differences were statistically significant ($p < 0.05$).

Conclusion: High serum Hcy and hs-CRP expression levels may regulate inflammatory responses, aggravating cognitive impairment in patients with BD and BPD. Serum Hcy and hs-CRP expression levels are significantly related to cognitive dysfunction. They are expected to guide the prevention and treatment of BD comorbid BPD patients.

Keywords

bipolar disorder; borderline personality disorder; homocysteine; high-sensitivity C-reactive protein; cognitive function

Introduction

Bipolar disorder (BD) is a chronic neuropsychiatric disorder characterized by altered mood and energy states [1,2]. BD is characterized by recurrent episodes of depression and mania or hypomania, associated with a significant burden of morbidity and premature mortality [3–5]. Patients with BD show significant social-cognitive deficits in both healthy and symptomatic states [6]. BD has the characteristics of high morbidity, high suicide rate, and high disability, which cause a considerable burden to society and patients' families [7,8]. BD also has a high comorbidity rate, often with anxiety, substance abuse, obsessive-compulsive disorder, and personality disorders [9]. Comor-

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bidity with other diseases has a significant adverse impact on the treatment and prognosis of BD and is also a major factor in recurrence [10]. Borderline personality disorder (BPD) usually develops before or together with internalizing disorders (depression and anxiety), externalizing disorders (behavioral problems, hyperactivity, and substance use), or both [11]. BPD is characterized by mood dysregulation, impulsivity, identity disorders, and a higher risk of suicide [12]. It often coexists with other psychological or psychiatric diseases such as BD. The incidence of comorbid BPD in BD patients is about 20%, which is significantly higher than other types of personality disorders [13]. Some foreign studies have shown that compared with bipolar patients without comorbidities, BD patients having comorbidities with BPD show more severe symptoms and worse outcomes in multiple aspects, such as more frequent mixed episodes and depressive episodes, more severe emotional symptoms, and more hospitalizations [14,15]. In addition, Lapomarda G *et al*. [16] found that compared with patients with BD who did not have comorbidity BPD, patients with comorbidity had impaired cognitive function, which was represented by slower perceptual speed and poorer performance in visual, auditory, and dual-channel working memory. However, it is not clear whether the comorbidity of BD and BPD will aggravate the cognitive impairment in patients. For this reason, identifying and treating BD comorbid BPD plays a crucial role in enhancing patients' quality of life.

Homocysteine (Hcy) is a normal product of methionine conversion and is a vascular risk factor [17]. The research investigation has indicated that elevated Hcy levels may be associated with a heightened risk of cognitive dysfunction [18]. The expression level of high-sensitivity C-reactive protein (hs-CRP) is one of the typical indicators reflecting neuroinflammation, and it can promote phagocytosis and activate complement [19]. Both contribute significantly to the onset and progression of cognitive dysfunction in BD and are anticipated to emerge as novel biomarkers [20]. Domestic and international research predominantly examines Hcy, hs-CRP, and cognitive function within dementia, cerebrovascular diseases, and similar conditions. However, the number of studies on bipolar disorder and BPD comorbidities is insufficient. Drawing from prior research findings, this study investigated the levels of Hcy and hs-CRP alongside cognitive function in patients with BD and BPD, explored the correlation between the two and cognitive function, and actively identified influential factors affecting cognitive function. Timely identification and intervention can enhance the outlook for patients and provide a reference for the clinical diagnosis and treatment of BD patients with BPD.

Materials and Methods

Research Subjects

Patients with BD admitted to the First Hospital of Hebei Medical University from January 2022 to December 2022 were chosen as the study subjects, and the Personality Diagnostic Questionnaire (PDQ-4+) test was conducted on the enrolled subjects. Those with borderline personality disorder scores of 6 points or above were diagnosed using the Standardized Clinical Examination for Personality Disorders (SCID-II). BPD patients were categorized into comorbidity groups, while those without BPD were assigned to non-comorbidity groups, each consisting of 60 cases. The entire experimental procedure adhered to the principles of informed consent, with patients or their family members being provided with information about the study. The study was carried out in compliance with the Declaration of Helsinki.

Inclusion criteria: ① Meet the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) clinical interview (SCID-I/P) diagnostic criteria for bipolar disorder. ② Antidepressants, atypical antipsychotics, or mood stabilizers were given for a duration of fewer than 14 days, with no utilization of benzodiazepines. ③ Age: 18–45 years old, with no restrictions based on gender. ④ The patients have had this illness for over 2 years, and there had been no instances of electroconvulsive therapy without seizures in the last six months. ⑤ Education level of at least junior high school or higher, possessing the capacity to read and grasp the content of the scale employed in the study. ⑥ The patients willingly participated in the research, secured informed consent from the patient and their family members, and affixed signatures to the informed consent document.

Exclusion criteria: ① Record of drug, alcohol, or other psychoactive substance abuse or dependence. ② History of past or current organic brain diseases or severe physical diseases that are not relieved. ③ Individuals who identify irregularities in brain structure following a standard MRI scan. ④ Physical diseases that affect cognitive function testing. ⑤ Expectant or breastfeeding females. ⑥ Patients with mental retardation and other mental illnesses. ⑦ Visual (including color blindness) and hearing diseases.

Research Tool

Self-Compiled General Situation Questionnaire

General Information Questionnaire: This study utilized a self-compiled general information questionnaire to

collect sociodemographic information about the research subjects. The main content of the questionnaire includes personal information such as gender, age, ethnicity, education level, marital status, and other general information, as well as bipolar disorder classification, age of first onset, disease duration, and other disease conditions.

Detection of Hcy and Hs-CRP Levels in Serum

Retrieve 5 mL of fasting peripheral venous blood from all study participants, subject it to centrifugation at 3000 r/min with a centrifugal radius of 10 cm for 15 minutes, and extract the upper serum for storage in preparation for testing. Before conducting measurements, the enzyme-linked immunosorbent assay (ELISA) kit and serum were equilibrated to room temperature. Subsequently, ELISA was utilized to evaluate the expression level of Hcy in the serum. The assessment of Hcy levels in the serum was performed following the guidelines outlined in the Hcy ELISA kit (QT13290, Shanghai Qitai Biotechnology Co., Ltd., Shanghai, China). The serum's hs-CRP level (ml092638, Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China) was determined using the immunoturbidimetric method, with strict adherence to the provided instructions throughout all procedures.

Hamilton Depression Rating Scale (HAMD)

The extent of depressive symptoms in both groups was evaluated utilizing the HAMD [21]. Developed by Hamilton in 1960 [21], this rating scale is widely employed in clinical evaluations of depressive symptoms. This scale has three versions: 17-item, 21-item, and 24-item. The version utilized in this study is the 17-item HAMD, designed to evaluate a patient's depression over the last week. According to the scoring system, the classification is as follows: a score of $\geq$17 points suggests the presence of depressive symptoms; scores ranging from 18 to 24 points suggest mild to moderate depression; scores of 24 points and above suggest severe depression; while a score of $\leq$7 points indicates the absence of depressive symptoms and clinical recovery.

Young's Mania Rating Scale (YMRS)

YMRS, compiled by Young RC *et al*. [22] in 1978, was conducted to assess the manic symptoms of the patients in both groups. This symptom rating scale is mainly used to evaluate manic symptoms and severity. The scale has 11 items in total, of which items 1, 2, 3, 4, 7, 10, and 11 are scored on a 0–4 scale, and items 5, 6, 8, and 9 are scored on a 0–8 scale. To assess the patient's manic condition during the previous week, it is important to meticulously adhere to the scoring criteria and instructions provided when utilizing the scale. The evaluation should be grounded in the patient's typical or usual state as a reference point; when making judgments about symptoms, the principle is to choose the high score for items with 0–4 points and the middle score for items with 0–8 points. Result judgment criteria: normal: 0–5 points; mild: 6–12 points; moderate: 13–19 points; severe: 20–29 points; extremely severe: more than 30 points.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS was employed to evaluate cognitive levels in both groups [23]. RBANS consists of 12 subtests categorized into five neuropsychological factors: attention, speech, visual span, immediate memory, and delayed memory. Immediate memory comprises vocabulary learning and story recall, while verbal test factors include graphic copying and line orientation tasks. The language factor includes tasks like picture naming and semantic fluency tests, while attention involves tasks like digit span and coding. Delayed memory includes assessments of vocabulary recall, story recall, and figure recall. Each factor's score is determined by referencing a table using the original scores of the included items. The overall scale score is computed by consulting a table with the sum of scores from the five factors. RBANS is a quick and efficient instrument for evaluating cognitive function, demonstrating strong reliability and validity. Additionally, it can serve as a screening tool for identifying cognitive impairment.

Statistical Analysis

The data was analyzed using SPSS 23.0 software (IBM, Armonk, NY, USA). The results were expressed as mean $\pm$ standard deviation ($\bar{x} \pm$ s) for measurement data displaying a normal distribution. An independent sample *t*-test was employed to compare data between groups. Count data were presented in the format [n (%)], and data comparisons were performed using the χ^2 test. Pearson correlation analysis was utilized to examine the correlation between patients' serum Hcy and hs-CRP levels, general information, and RBANS scores. $p < 0.05$ represents a statistically significant difference.

Table 1. Comparison of general information between the two groups of patients ($\bar{x} \pm s$).

Items	Comorbidity group (n = 60)	Non-Comorbidity group (n = 60)	χ^2/t value	*p* value
Gender (Male/Female)	26/34	29/31	0.302	0.583
Age (years)	34.93 ± 6.54	35.72 ± 5.68	0.706	0.481
Years of education (years)	13.96 ± 2.17	14.28 ± 2.19	0.804	0.423
Age at first onset (years)	25.05 ± 2.25	24.72 ± 2.51	0.758	0.450
Bipolar disorder classification (depression/mania)	25/35	23/37	0.139	0.709
Duration of disease (years)	11.50 ± 3.42	12.42 ± 3.68	1.418	0.159

Table 2. Comparison of serum Hcy and hs-CRP levels between the two groups of patients ($\bar{x} \pm s$).

Group	Number of cases (*n*)	Hcy (μmol/L)	Hs-CRP (mg/L)
Comorbidity group	60	18.32 ± 3.15	14.45 ± 3.24
Non-Comorbidity group	60	14.76 ± 3.02	9.31 ± 2.19
t value		6.319	10.181
p value		<0.001	<0.001

Note: Hcy, homocysteine; hs-CRP, high-sensitivity C-reactive protein.

Table 3. Comparison of HAMD and YMRS scores between the two groups of patients ($\bar{x} \pm s$, score).

Group	Number of cases (*n*)	HAMD	YMRS
Comorbidity group	60	28.56 ± 4.59	18.58 ± 1.76
Non-Comorbidity group	60	25.40 ± 4.27	12.82 ± 1.13
t value		3.904	21.332
p value		<0.001	<0.001

Note: HAMD, Hamilton Depression Rating Scale; YMRS, Young's Mania Rating Scale.

Results

Comparison of General Information between the Two Groups of Patients

General information, including gender, age, years of education, age of first onset, disease course, and bipolar disorder classification between the two groups of patients, showed no statistically significant difference ($p > 0.05$). See Table 1.

Comparison of Hcy and Hs-CRP Levels between the Two Groups of Patients

The results showed that the serum Hcy and hs-CRP levels of patients in the comorbidity group were higher than those in the non-comorbidity group ($p < 0.05$), see Table 2.

Comparison of HAMD and YMRS Scores between the Two Groups of Patients

The results showed that the HAMD and YMRS scores of patients in the comorbidity group were higher than those in the non-comorbidity group ($p < 0.05$), see Table 3.

Comparison of Cognitive Functions between the Two Groups of Patients

RBANS assessment of cognitive functions in both groups revealed that attention, speech, visual span, immediate memory, and delayed memory were significantly lower in the comorbidity group compared to the non-comorbidity group ($p < 0.05$), see Table 4.

Comparison of Cognitive Functions between Two Groups of Patients with Bipolar Depression

The speech, visual span, and immediate memory of RBANS in bipolar depressive patients with comorbid BPD were lower than those in bipolar depressive patients without comorbid BPD ($p < 0.05$); see Table 5.

Comparison of Cognitive Functions between Two Groups of Patients with Bipolar Mania

The speech of RBANS in bipolar manic patients with comorbid BPD was lower than those in bipolar manic patients without comorbid BPD ($p < 0.05$); see Table 6.

Table 4. Comparison of RBANS scores between the two groups of patients ($\bar{x} \pm s$, score).

Group	Number of cases (*n*)	Attention	Speech ability	Visual span	Immediate memory	Delayed memory
Comorbidity group	60	74.25 ± 4.29	29.64 ± 2.32	23.79 ± 2.28	42.08 ± 3.04	39.48 ± 3.51
Non-Comorbidity group	60	80.55 ± 5.17	34.17 ± 3.01	29.04 ± 2.40	48.42 ± 3.43	44.74 ± 3.72
t value		7.264	9.233	12.285	10.715	7.966
p value		<0.001	<0.001	<0.001	<0.001	<0.001

Note: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Table 5. Comparison of RBANS scores between two groups of patients with bipolar depression ($\bar{x} \pm s$, score).

Group	Number of cases (*n*)	Attention	Speech ability	Visual span	Immediate memory	Delayed memory
Comorbidity group	25	76.98 ± 5.87	30.71 ± 3.77	24.78 ± 3.08	40.93 ± 5.08	40.37 ± 4.96
Non-Comorbidity group	23	78.04 ± 6.76	34.83 ± 4.27	28.70 ± 2.75	49.63 ± 4.70	41.93 ± 5.08
t value		0.581	3.550	4.636	6.143	1.076
p value		0.564	<0.001	<0.001	<0.001	0.288

Table 6. Comparison of RBANS scores between two groups of patients with bipolar mania ($\bar{x} \pm s$, score).

Group	Number of cases (*n*)	Attention	Speech ability	Visual span	Immediate memory	Delayed memory
Comorbidity group	35	77.98 ± 6.81	28.73 ± 3.45	24.56 ± 3.47	45.78 ± 4.08	41.82 ± 4.37
Non-Comorbidity group	37	80.72 ± 6.24	36.07 ± 4.50	25.98 ± 3.31	46.07 ± 5.28	42.86 ± 4.86
t value		1.781	7.735	1.777	0.260	0.953
p value		0.079	<0.001	0.080	0.796	0.344

Correlation Study of Hcy and CRP Expression with HAMD, YMRS, and Cognitive Function Scores in Complication Group

The results indicated a statistically significant positive correlation between the expression of Hcy and hs-CRP in the comorbid group with HAMD and YMRS scores. Additionally, a negative correlation was observed with attention, speech, visual span, immediate memory, and delayed memory, see Table 7 ($p < 0.05$).

Table 7. Correlation study of Hcy and CRP expression with HAMD, YMRS, and cognitive function scores in patients with comorbidities (*r*).

	Hcy	Hs-CRP
HAMD	0.372*	0.333*
YMRS	0.416*	0.381*
Attention	–0.402*	–0.339*
Speech ability	–0.319*	–0.346*
Visual span	–0.354*	–0.328*
Immediate memory	–0.361*	–0.341*
Delayed memory	–0.316*	–0.352*

Note: *$p < 0.05$.

Discussion

BD is a common severe mental disorder in psychiatry. Although patients are in remission, chronic decline in cognitive function is typical, and it is difficult to return to normal cognitive status [24]. The patient alternates between different periods of mood attacks and mood instability, resulting in poorer overall functioning and quality of life [25]. The comorbid diagnosis of BPD is often easily overlooked in clinical practice, causing patients to miss potentially effective treatment and appropriate management strategies [26].

In this study, patients with BD comorbid BPD and BD non-comorbid BPD were chosen as the subjects for the study. The RBANS cognitive function measurement instrument was employed to perform a more thorough evaluation of cognitive function. The results of this study showed that bipolar depressive patients with comorbidities BPD had lower immediate memory, visual span, and speech function than bipolar depressive patients without comorbidities BPD. These results suggest that the cognitive function of bipolar depressive patients with comorbidity BPD is worse than that of bipolar depressive patients without comorbidity BPD. In the study, bipolar manic patients with comorbid BPD had lower speech function in RBANS than bipolar patients without comorbid BPD. By analyzing the causes, patients usually have neuroinflammatory responses to varying degrees, which can lead to abnormal changes in glial

cell density, neuronal damage, and inflammatory stress response, and further affect cognitive function [27]. Changes in inflammatory and metabolic markers are associated with the pathogenesis of the onset and progression of BD [20]. We explored their association with cognitive function by detecting Hcy and hs-CRP expression levels in the patient's serum. The results indicated that the serum levels of Hcy and hs-CRP in the comorbidity group were notably elevated compared to the non-comorbidity group. The elevated levels of Hcy and hs-CRP indicated that patients in the comorbid group have damage to nerve cells and are accompanied by severe neuroinflammatory reactions in the body. Elevated Hcy will activate the inflammatory response in the body and promote the formation of oxygen-free radicals [28]. Hcy damages vascular endothelial cells, causing neuronal damage and apoptosis [29]. Studies have shown that the higher the degree of cognitive function impairment, the higher the Hcy level in the body [30]. This is consistent with the results of this study. Hamdi G *et al*. [31] found a significant association between elevated hs-CRP and the mean value of the disease severity item in patients with BD.

Clinical research reports suggest a positive correlation between the peripheral inflammatory status in individuals with abnormal inflammatory responses and the decline in cognitive function among patients [32]. Observations revealed that individuals within the comorbidity group exhibited higher HAMD and YMRS scores compared to those in the non-comorbidity group, signifying heightened severity of depression and mania among the comorbid patients. The study findings revealed a positive correlation between the serum expression levels of Hcy and hs-CRP in the comorbidity group and HAMD and YMRS scores. Additionally, a negative correlation was observed with attention, speech, visual span, immediate memory, and delayed memory. This suggests that the compromised cognitive function in patients with BD comorbid BPD is related to increased expression levels of Hcy and hs-CRP. The possible mechanism is that Hcy, a metabolite of amino acids, can promote the production of free radicals and hydrogen peroxide [17]. This suggests Hcy may inhibit vasodilation and nerve conduction function, causing brain hypoxia and cognitive dysfunction in patients, respectively. Therefore, there is a significant correlation between high levels of Hcy and the intensity of cognitive dysfunction in patients with BD and BPD, and whether reducing Hcy levels can improve patients' cognitive function requires in-depth research to confirm. Wang Y *et al*. [33] have shown that high expression levels of hs-CRP can participate in the inflammatory response process in the body, stimulate the body's inflammatory response to intensify, lead to metabolic disorders in the body, promote the activation and proliferation of microglia in the central nervous system, stimulate neuron cytotoxic substances to increase and damage neurons, and exacerbate the risk of cognitive dysfunction. The serum Hcy and hs-CRP expression levels can be used as diagnostic indicators of molecular markers. As an auxiliary diagnosis method, it can help clinicians diagnose and treat BD and BPD comorbidities early to improve patients' quality of life and clinical prognosis with BD and comorbid BPD.

These results showed that serum hs-CRP and Hcy levels were significantly higher in the comorbidities group than in the non-comorbidities group, and serum hs-CRP and Hcy expression levels were positively correlated with HAMD and YMRS scores. These results also suggest that cognitive function impairment in BD patients with BPD was related to hs-CRP and Hcy inflammation levels. Therefore, regulating the Hcy level of patients in a reasonable range is of great significance for preventing and treating BD and BPD patients.

The study's sample size is constrained, and the evolving alterations in the serum of patients with BD and BPD comorbidity were not monitored throughout the treatment. Broadening the sample size is necessary for more comprehensive investigations.

Conclusion

In conclusion, serum Hcy and hs-CRP expression levels may participate in the occurrence and development of BD comorbid BPD by regulating the inflammatory response and metabolic levels. It aggravates the cognitive impairment of patients with BD and BPD, and serum Hcy and hs-CRP expression levels are significantly related to cognitive dysfunction, which is expected to guide the prevention and therapeutic interventions for individuals with BD and BPD.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

CMW and KZ designed the research study. LZL and BX performed the research. NL, CXA and JCW analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of the First Hospital of Hebei Medical University (20210696). The entire experimental procedure adhered to the principles of informed consent, with patients or their family members being provided with information about the study.

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Conflict of Interest

The authors declare no conflict of interest.

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