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Higher Serum C-Reactive Protein Levels in Catatonic Patients: A Comparison to Non-catatonic Patients and Healthy Controls

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Catatonia is a psychomotor syndrome defined by a constellation of predominantly motor symptoms. The aim of the present study was to determine whether recently admitted psychiatric patients with catatonia exhibited higher serum C-reactive protein (hs-CRP) levels compared to non-catatonic psychiatric patients and healthy controls (HCs). Recently admitted psychiatric patients were screened and evaluated for the catatonia syndrome using the Bush-Francis Catatonia Rating Scale and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The study sample was formed by 150 individuals (39 male and 111 female), including 51 catatonic patients, 55 non-catatonic patients, and 44 HCs. Serum hs-CRP levels were processed with the enzyme-linked immunosorbent assay. Serum levels of creatine kinase (CK), adrenocorticotropic hormone (ACTH), immunoglobulin G (IgG), complement component 3 (C3), and complement component 4 (C4) were also determined. There was a significantly higher percentage of patients with high inflammatory levels (hs-CRP > 3000ng/ml) in the catatonic (43.1%) than in the non-catatonic (14.5%) or HCs group (9.1%) (χ^2 =18.9, P < .001). Logistic regression showed that catatonic patients had significantly higher hs-CRP levels compared to non-catatonic patients even after controlling for other clinical and laboratory variables (OR = 3.52, P = .015, 95% CI 1.28–9.79). Multiple linear regression analysis revealed that log-transformed hs-CRP was independently predicted by body mass index and log-transformed C4, ACTH, and Cortisol in catatonic patients. Findings of the present study suggest that catatonia is specifically linked to a higher level of systemic inflammation, not merely attributable to the overall psychopathology, or alterations in the stress level and complement system.

Key words: psychomotor syndrome/inflammation/serum concentration/psychotic disorders/mood disorders

Introduction

Catatonia is a psychomotor syndrome characterized by motor, affective, and behavioral symptoms, associated with a wide range of physical and mental disorders.[1] It has been reported in 4%–67% of patients with schizophrenia and 14%–71% of patients with mood disorders.[2] Although catatonia is common, the underlying mechanisms remain largely unclear. Earlier work by Gjessing and colleagues found a periodic nitrogen imbalance corresponding to the periodic rhythm of catatonic relapses.[3] They also demonstrated dysregulated norepinephrine and dopamine metabolism in the catatonic state.[4] Northoff and colleagues found that plasma homovanillic acid (HVA), a major metabolite of dopamine,[5] was higher in acute catatonia and higher levels were associated with positive responses to lorazepam.[6] A neuroimaging study showed diffuse cortical sulcal enlargement particularly in the left frontotemporal areas in catatonic schizophrenia patients.[7] It has also been shown that catatonic patients exhibited decreased rCBF in the right posterior parietal cortex, and functional connectivity between the medial orbitofrontal and premotor/motor cortex was also altered.[8,9] Recently, Walther and colleagues reviewed the cerebral motor network dysfunction, outlined convergent evidence on abnormal hyperactivity in the supplementary and pre-supplementary motor areas, and provided a model of catatonia as a psychomotor syndrome.[10] Another important review highlighted the aberrant higher-order frontoparietal networks and emphasized

the critical role of γ-aminobutyric-acid (GABA)-ergic dysregulation in the affective domain of catatonia.[11]

Catatonia was noted in various inflammatory brain diseases[12,13] and highly prevalent in psychiatric patients who were positive for *N*-methyl-D-aspartate (NMDA) receptor antibodies.[14,15] A recent review by Rogers and colleagues considered immune activation and downstream glutamatergic or GABA-ergic dysregulation played key roles in the pathogenesis of catatonia, as it occurs in various autoimmune conditions.[16] Myelin-producing oligodendrocytes and low-grade neuroinflammation have been implicated in the pathogenesis of catatonia.[17] The study by Janova and colleagues demonstrated reduced expression of the structural myelin protein 2′-3′-cyclic nucleotide 3′-phosphodiesterase (CNP) was associated with catatonic signs, both in humans and mice.[18] Furthermore, microglial ablation through inhibitor of CSF1 receptor kinase signaling PLX5622 alleviated the catatonia of $CNP^{-/-}$ mice.[18]

A variant of catatonia known as malignant or lethal catatonia with fever, delirium, and autonomic disturbances clinically resembles neuroleptic malignant syndrome (NMS).[19] Low levels of serum iron, a negative acute phase reactant, have been noted in NMS[20] and a neuroimmunological hypothesis has been proposed to explain the pathophysiology of NMS.[21] Low serum iron has also been found not only in malignant catatonia but also in nonmalignant acute catatonia episodes.[22,23] One would hence speculate that the positive acute phase reactant, C-reactive protein (CRP), is likely to be elevated in catatonia.

Accumulating evidence, as reflected by alterations in circulating inflammatory markers,[24–28] suggests a transdiagnostic association with low-grade systemic inflammation in schizophrenia, bipolar disorders, depressive, anxiety, and other psychiatric disorders. CRP is directly modulated by IL-6 and IL-1β[29–31] and is commonly used in clinical practice as a reliable biomarker of subclinical and systemic inflammation.[32,33] A number of studies have investigated CRP in schizophrenia and mood disorders with inconsistent results. While more than half of the studies reported an elevated blood CRP level,[29–31] others reported no difference between patients and healthy controls (HCs).[34–36] It remains controversial whether increased CRP in schizophrenia is merely a result of an increased prevalence of risk factors of systemic inflammation, such as stress,[37] smoking,[38] obesity,[39] and physical comorbidities.[40,41] Moreover, increased CRP levels may be associated with certain symptom dimensions in schizophrenia, such as negative symptoms,[42] aggressive behavior,[43] and cognitive symptoms.[44,45]

To our knowledge, there has been only one study in examining the association of CRP with clinical phenotypes in Arab schizophrenic patients, which found a higher CRP level in those with catatonia.[46] However, only chronic schizophrenia patients were included, and only 12 patients had catatonia. Catatonia was not evaluated using a standardized rating scale. Moreover, patients with catatonia (n = 12) were not matched with those without catatonia (n = 87) in terms of body mass index (BMI), smoking, physical comorbidities, and stress level. Catatonic patients often develop various physical complications (eg, pneumonia or deep vein thrombosis) due to symptoms, such as akinesia, stupor, rigidity, swallowing difficulties, or dehydration.[47–50] All these variables could contribute to a high systemic inflammatory level, possibly confounding the results.

In the present study, we systematically screened and evaluated patients admitted to the psychiatric inpatient units in a large teaching hospital in Beijing using a standardized catatonia rating scale. The aims of the present study were (1) to determine whether recently admitted patients with catatonia exhibited higher serum C-reactive protein (hs-CRP) levels compared to non-catatonic patients as well as HCs; (2) to clarify whether the increased serum hs-CRP level in catatonic patients was a primary or just secondary to more severe symptomatology or comorbidities; and (3) to identify the independent predictors of high inflammatory levels in catatonic and non-catatonic patients. The first hypothesis was that serum CRP levels would be higher in catatonic patients than in non-catatonic patients and HCs. The second hypothesis was that a higher serum CRP level would be a distinctive feature of catatonia regardless of the diagnosis, psychopathology, and stress level. The third hypothesis was that higher CRP levels can be independently predicted by a host of clinical and laboratory variables, including the psychopathology, stress hormones, and innate immune variables (complement C3 and/or C4).

Methods and Materials

Participants

Participants were consecutively recruited from in-patient departments at Beijing Anding Hospital between January 2018 and October 2018.

Inclusion criteria for the catatonic patients were as follows: (1) first episode or acute exacerbations of any type of psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[51]; (2) recently admitted patients with acute catatonia, according to DSM-5 and confirmed in a clinical interview by two attending psychiatrists.

Inclusion criteria for the non-catatonic psychotic patients were: (1) first episode or acute exacerbations of any type of psychiatric disorders according to DSM-5; (2) recently admitted patients without catatonia (fulfilling neither DSM-5 nor Bush-Francis Catatonia Screening Instrument criteria for catatonia),[52] which was confirmed by two attending psychiatrists in a clinical interview; (3) matched with catatonic patients in age and gender.

HCs were recruited from the community through advertisements and matched with catatonic patients in age and gender. They also had to go through a structured clinical interview for DSM-IV (The Structured Clinical Interview for DSM-5 is not available in Chinese version) to ensure they were not suffering from any psychiatric disorders or mood disorders.

Exclusion criteria for the three group were as follows: (1) history of or current substance abuse; (2) history of or current major physical conditions, including any symptoms or signs of infections; or any positive laboratory or imaging examinations indicating infections, determined by a thorough chart review, physical examination, routine blood tests, computed tomography (CT), or magnetic resonance imaging (MRI) scan; and (3) pregnancy or breastfeeding.

The study protocol was approved by the Clinical Research Ethics Committee of Beijing Anding Hospital. Written informed consent was obtained from all participants or their guardians (for those who were in catatonic state and not capable of giving a consent).

Clinical Assessments

Catatonia was screened and evaluated with Bush-Francis Catatonia Rating Scale (BFCRS).[52] BFCRS was a 23-item scale involving three factors: negative/withdrawn, automatic, repetitive/echo, and agitated/resistive phenomena.[53]The scale was developed based on the classical description of catatonia from previous literatures.[52,54,55] Item 1–14 were selected to form a standardized screening tool for catatonia (BFCSI). If 2 or more of the 14 symptoms were present for more than 24 hours, catatonia features should be considered. Each item was scored from 0 to 3, and the total score ranges from 0 to 69. The treating psychiatrists performed the BFCRS on the day of admission. The inter-rater reliability reached a high level among the treating psychiatrists (Cronbach's alpha value of 0.89).

Patients' psychopathology was assessed with the Chinese version of the Positive and Negative Symptom Scale (PANSS).[56,57] PANSS was performed on the day of admission or when the patients were able to cooperate with a clinical interview.

Blood Sample Collection and Assessment

Blood samples were drawn from the antecubital vein at 8 AM in the morning after an overnight fast of at least 8 hours, and then collected into pre-chilled 5-ml vacutainer tubes with clot activator (serum tube). Serum was isolated from the whole blood by centrifugation (3000*g* for 10 min), and transferred and aliquoted into Eppendorf tubes and stored in a −70°C freezer. Hs-CRP levels were processed with a commercially available (R&D) enzyme-linked immunosorbent assay (ELISA) at Beijing Key Laboratory of Mental Disorders. Samples were assayed in duplicate; the average concentration of the samples was taken as the final value. Other serum analytes were tested in Clinical Laboratory of Beijing Anding Hospital. Serum IgG and complement C3 and C4 were determined using nephelometry; serum creatine kinase (CK) was determined using enzyme-coupled assay; serum adrenocorticotropic hormone (ACTH) and cortisol were detected by immunoassay.

Data Analysis

All the data analyses were conducted by using SPSS 23.0 for Windows. Comparisons between catatonic patients, non-catatonic patients, and HCs with regard to sociodemographic, clinical, and laboratory variables were performed using independent sample *t*-tests, Mann-Whitney *U* tests, Kruskal-Wallis *H* tests, Fisher's exact test, and chi-square tests, where appropriate. One-sample Kolmogorov-Smirnov tests were used to check the normality of distributions for the continuous variables. Associations of hs-CRP with sociodemographic, clinical, and laboratory variables in catatonic and non-catatonic patients were analyzed using Pearson correlation analysis if the data followed a normal distribution; otherwise, log transformation was performed to the skewed variables before conduction analyses. Receiver operating characteristic (ROC) curves with the area under the curve (AUC) values were calculated for high inflammatory status (hs-CRP > 3000 ng/ml), showing the predicted probabilities from the final model of logistic regression analysis. Multivariate stepwise linear regression analyses were used to identify predictors of serum hs-CRP level in catatonic patients.

Two-tailed tests were used. With regard to hs-CRP levels and the percentage of high inflammatory individuals, the significance level was set at .05 for the comparisons between three groups, and Bonferroni adjustment was applied to the post hoc comparisons (critical α of $P < .017$). The Bonferroni adjustment was also applied to the exploratory comparisons between groups and correlation analyses, resulting in a critical α of $P < .0024$ for 21 comparisons (table 1) and a critical α of $P < .0038$ for correlation analyses between hs-CRP level and 13 variables (table 2).

Results

Comparison of Mean Serum hs-CRP Levels Between Groups

One hundred and fifty subjects were recruited in this study, including 51 catatonic patients, 55 non-catatonic patients, and 44 HCs. The mean age of the HCs was 31.4 ± 8.0 years old and 11 HCs were male (25.0%). There were no significant differences between the three groups in terms of age ($F_{(147, 2)} = 0.94$, $P = .40$) and sex composition ($\chi^2 = 0.08$, $P = .96$). All the catatonic patients had

Table 1. Comparison of Catatonic Patients, Non-Catatonic Patients (HCs) With Respect to Demographic and Clinical Characteristics

	Catatonic (n= 51)		Non-catatonic (n = 55)		Statistics*	
	N	Percent	*N*	Percent	χ^2	*P*-value
Men	13	25.5	15	27.3	0.04	.835
Diagnosis of schizophrenia	16	31.4	19	33.9	0.79	.778
Currently smoking	2	3.9	5	8.9	1.14	.287
On medication	48	94.1	53	96.4	0.30	.586
On antipsychotic	34	66.7	47	85.5	5.18	.023
FGAs	11	21.6	19	34.5	2.20	.138
SGAs	23	46.0	28	50.9	0.25	.615
	Mean	SD	Mean	SD	*t*	*P*-value
Age	32.8	8.7	33.9	10.2	−0.60	.553
Body Mass Index	22.4	3.1	23.1	3.4	−1.00	.321
PANSStot	81.4	2.4	57.0	18.6	7.02	<.001
PANSSpos	18.6	6.0	15.8	7.4	2.19	.031
	25th percentile	75th percentile	25th percentile	75th percentile	*Z*	*P*-value
Duration of illness	3.0	146.0	27.0	157.0	−1.51	.132
OLZeq	0	6.3	2.0	10.0	−2.55	.011
CK(U/l)	43.0	686.0	39.0	118.0	−3.09	.002
Cortisol (pg/ml)	14.6	20.6	13.7	20.8	−0.10	.922
ACTH (pg/ml)	20.4	41.4	24.7	64.0	−2.58	.010
IgG (g/l)	9.0	12.7	9.2	12.3	−0.79	.427
C3 (g/l)	0.7	0.9	0.7	1.0	−1.50	.133
C4 (g/l)	0.2	0.3	0.2	0.2	−0.61	.539
BFCRS	14.0	22.0	0	1.0	−9.05	<.001
PANSSneg	14.0	26.0	7.0	15.0	−6.11	<.001

Note: FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; PANSSpos, Positive subscale score of the Positive and Negative Syndrome Scale; PANSSneg, Negative subscale score of the Positive and Negative Syndrome Scale; PANSStot, total score of the Positive and Negative Syndrome Scale; BFCRS, Bush-Francis catatonia rating scale; CK, creatine kinase; ACTH, adrenocorticotropic hormone; IgG, immunoglobulin G; C3, complement component 3; C4, complement component 4; OLZeq, olanzapine equivalent dose.
*Bonferroni adjustment for the 21 comparisons to a critical α of $P < .0024$.

been in an acute catatonic state for less than a week. In the non-catatonic group, only one patient took benzodiazepine (lorazepam, 1.5 mg daily) before the day of blood test. In the catatonic group, 11 patients took lorazepam (ranging from 1.5 mg to 3 mg daily), and 10 patients took oxazepam (ranging from 15 mg to 90 mg daily) before the day of blood test.

Data of hs-CRP concentration were highly skewed as indicated in one-sample Kolmogorov-Smirnov tests ($P < .001$). Using hs-CRP > 3000 ng/ml as cutoff value for high inflammation, there was a significantly higher percentage of high inflammatory individuals in the catatonic group (43.1%) than in non-catatonic group (14.5%) or in HC group (9.1%) ($\chi^2 = 18.9$, $P < .001$; post hoc comparison between catatonic and non-catatonic groups: $\chi^2 = 10.7$, $P = .001$) (figure 1). Serum hs-CRP levels were compared between catatonic patients, non-catatonic patients, and HCs. Kruskal-Wallis test showed that hs-CRP level was significantly higher in catatonic patients (median = 1797.6 ng/ml) compared with non-catatonic (median = 891.7 ng/ml) and HCs (median = 1144.9 ng/ml) ($P = .023$; post hoc comparison between catatonic and non-catatonic groups: $P = .016$). The psychiatric diagnoses of individuals in catatonic as well as non-catatonic groups were shown in the supplementary table S4. Ten patients had extremely high hs-CRP levels (>10 mg/l), but none of them presented any signs or symptoms of infectious diseases (supplementary table S5).

The comparisons between catatonic and non-catatonic patients regarding sociodemographic, clinical, and laboratory variables are shown in table 1. With Bonferroni adjustment, catatonic patients exhibited a higher PANSS total score, PANSS positive score, and PANSS negative score compared with non-catatonic patients. However, after controlling for BFCRS total scores and the diagnosis of schizophrenia, Analysis of Covariance revealed no significant difference in PANSS total scores ($F_{(102, 3)} = 0.320$, $P = .573$), PANSS positive scores ($F_{(102, 3)} = 0.467$, $P = .496$), or PANSS negative scores ($F_{(102, 3)} = 1.713$, $P = 0.194$). In the whole patients' sample, PANSS negative scores were significantly correlated with BFCRS scores ($r = .61$, $P < .001$). However, no significant association was found between BFCRS scores and PANSS negative scores in

Table 2. Correlations Between Log_{10}-Transformed Serum Hs-CRP and Demographic, Clinical, and Laboratory Variables in Catatonic and Non-Catatonic Patients.

	Catatonic (n = 51)		Non-catatonic (n = 55)	
Lg (hs-CRP)	r	P-value*	r	P-value*
Men	.181	.203	.057	.680
Diagnosis of schizophrenia	.039	.783	−.086	.534
Currently smoking	.024	.867	−.019	.892
Age	−.008	.954	−.152	.269
Body mass index	.350	.012	−.044	.752
BFCRS[a]	.276	.0497	−.251	.065
Lg (DOI)	.197	.283	−.157	.254
Lg (CK)	.414	.003	.028	.837
Lg (Cortisol)	.326	.020	.045	.743
Lg (ACTH)	−.308	.028	.006	.965
Lg (IgG)	−.115	.423	.002	.989
Lg (C3)	.077	.591	.109	.429
Lg (C4)	.341	.014	.040	.769

Note: Lg, log_{10} transformed; DOI, duration of illness; BFCRS, Bush-Francis catatonia rating scale; CK, creatine kinase; ACTH, adrenocorticotropic hormone; IgG, immunoglobulin G; C3, complement component 3; C4, complement component 4; OLZeq, olanzapine equivalent dose; hs-CRP, high sensitivity C-reactive protein.
[a]All skewed data were log-transformed except for BFCRS in non-catatonic group. In non-catatonic group, 39 individuals were scored 0 on BFCRS, which made log-transformation impossible. In such case, Spearman's rank correlation was used.
*Bonferroni adjustment to a critical α of $P < .0038$ for the correlation analyses between lg (hs-CRP) and the 13 variables.

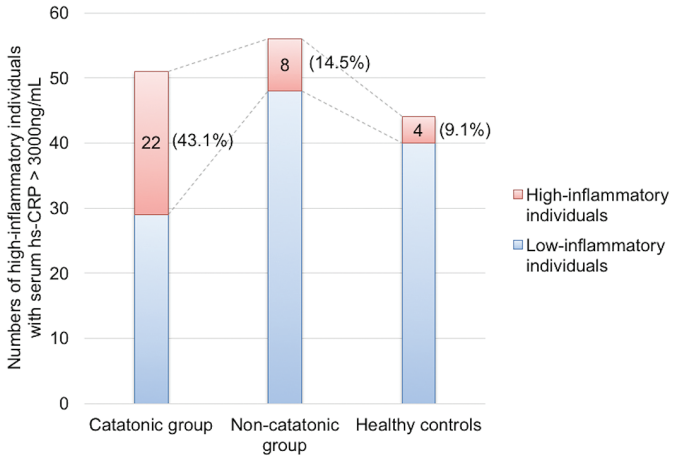

Fig. 1. Numbers and percentages of high inflammatory individuals (with a serum hs-CRP > 3000 ng/ml) differ by group. There was a significantly higher percentage of patients with high inflammatory levels in the catatonic (n = 22, 43.1%) than in the non-catatonic (n = 8, 14.5%) or healthy controls group (n = 4, 9.1%) ($\chi^2 = 18.9$, $P < .001$).

catatonic patients (r = .18, P = .198) or in non-catatonic patients (r = .257, P = 0059). Although not significant with Bonferroni adjustment, catatonic patients were more likely to have a higher serum level of hs-CRP, CK, and ACTH, and to be more unlikely to receive antipsychotics and to be on a lower OLZeq dose (nominal significance, $P < .05$).

To determine whether catatonia is independently associated with high inflammatory status, we conducted a multivariate logistic regression with backward Wald method. In the regression analyses, high inflammation was entered as the dependent variable and catatonia diagnosis and all the variables indicating stress level and symptomatology were entered as independent variables (ACTH, Cortisol, CK, Diagnosis of schizophrenia, OLZeq, PANSS total score, PANSS negative score, and PANSS positive score). Log-transformation was performed for all skewed variables before conducting regression analyses. The results suggested the independent predictors of high inflammation included catatonia diagnosis (OR = 3.52, P = .015, 95% CI 1.28–9.79), lg (CK) (OR = 2.29, P = .024, 95% CI 1.11–4.71), and lg (Cortisol) (OR = 21.47, P = .071, 95% CI 0.77–601.21). ROC curve for the predictive model showed the AUC was estimated to be 0.766 ($P < .001$, 95% CI 0.663–0.870), indicating that the overall accuracy of the final model to predict patients' remission (with a predicted probability of 0.5 or greater) was acceptable.

Exploring the Independent Predictors of High Inflammatory Level

Table 2 presents the relationships between hs-CRP and sociodemographic variables, clinical and laboratory variables. Log-transformation was performed for all skewed variables before conducting correlation analyses. With Bonferroni adjustment, lg (CK) was the only variable significantly associated with lg (hs-CRP) in the catatonic group. Although not significant with Bonferroni adjustment, higher lg (hs-CRP) was likely to be associated with

higher BFCRS total scores (figure 2), BMI, lg (Cortisol), lg (C4), and lower lg (ACTH) in the catatonic group ($P < .05$). No demographic, clinical, or laboratory variable was associated with hs-CRP level in non-catatonic psychotic patients (table 2).

In the stepwise linear regression analyses in catatonic patients, hs-CRP level was entered as the dependent variable, BMI, lg (CK), lg (Cortisol), lg (C4), and lg (ACTH) were entered as independent variables. The results suggested that higher serum level was significantly predicted by lg (C4) (Beta = .26, $P = .020$, 95% CI 0.20–2.23), lg (ACTH) (Beta = −.31, $P = .008$, 95% CI −1.28 to −0.21), lg (Cortisol) (Beta = .31, $P = .009$, 95% CI 0.35–2.34), and BMI (Beta = .33, $P = .006$, 95% CI 0.02–0.13) in catatonic patients (table 3).

Discussion

To the best of our knowledge, this is the first study to examine serum hs-CRP levels in catatonia using a standardized rating scale for catatonia. Results of the study partly confirmed the three hypotheses proposed. The hs-CRP level was significantly higher in catatonic patients compared with non-catatonic and HCs. A significantly higher percentage of individuals in the catatonic group (43.1%) had a clinically high hs-CRP level (>3000 ng/ml) than in the non-catatonic group (14.5%) or in HCs group (9.1%). For the second hypothesis, logistic regression analysis suggested that catatonia was significantly associated with a high inflammatory level even after controlling for stress, psychopathology, and other confounding variables. The third hypothesis, however, was proved to be true only in catatonic patients. Only in catatonic patients were hs-CRP levels independently predicted by C4, ACTH, Cortisol, and BMI, as revealed in the multiple linear regression analyses (adjusted $R^2 = 0.43$).

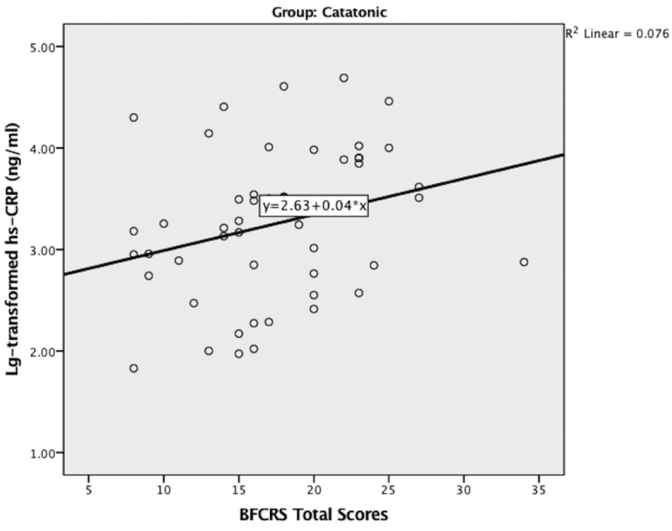

Fig. 2. Scatterplot for log-transformed hs-CRP vs BFCRS total scores in catatonic group ($n = 55$). Pearson's correlation revealed a nominally significant association between lg (hs-CRP) and BFCRS total scores ($r = .276$, $P = .0497$).

Inflammatory processes have been implicated as a key pathophysiological mechanism in schizophrenia,[58–60] and CRP, along with cytokines, has been considered as a potential inflammatory biomarker in schizophrenia.[61] Elevated hs-CRP levels have been observed in patients with schizophrenia, although the actual plasma concentration varied among different studies.[33,59] Elevated CRP levels suggesting low-grade systemic inflammation have also been shown in other psychiatric disorders, including psychotic disorders (32%), mood disorders (21%), neurotic disorders (22%), and personality disorders (42%),[62] indicating that CRP may be a transdiagnostic inflammatory biomarker across major psychiatric disorders.

Previous studies found that systemic inflammation can alter the CNS dopaminergic and glutamatergic neurotransmission and increase the generation of kynurenic acid, an NMDA receptor antagonist.[60,63,64] Notably, catatonia is often a prominent manifestation of anti-NMDA encephalitis,[12,13] and NMDAR antibodies have been found in patients with psychiatric disorders about three times as high as in HCs.[65] The GABA/glutamate functional balance plays a key role in maintaining normal brain functioning, including the modulation of motor functions.[66] Based on more recent neuroimaging studies in catatonia,[67,68] Hirjak and colleagues proposed catatonia as a paradigmatic model for Research Domain Criteria (RDoC)-based investigation of GABAergic system.[69] Benzodiazepines act as positive allosteric modulators of the GABA-A receptor.[70] Some benzodiazepines that are effective in resolving catatonia (eg, diazepam) also

Table 3. Results of the Stepwise Multiple Regression Analysis (Catatonic Patients; $n = 51$)

	Predictor	Beta	*P*-value	95% CI
Lg (hs-CRP) Adjusted $R^2 = 0.43$; $F_{(5, 45)} = 8.5$; $P < .001$	Lg (C4)	.26	.02	0.20–2.23
	Lg (ACTH)	−.31	.008	−1.28 to −0.21
	Lg (Cotisol)	.31	.009	0.35–2.34
	BMI	.33	.006	0.02–0.13

Note: Lg, $\log_{10}$ transformed; BMI, body mass index; hs-CRP, high sensitivity C-reactive protein; C4, complement component 4; ACTH, adrenocorticotropic hormone.

modulate immune function by binding to translocator protein (TSPO).[71,72] By activating GABA-A receptors, benzodiazepines might eventually lead to a reduced level of pro-inflammatory cytokines.[71,73]

It should be noted that a high inflammatory status also existed in 14.3% non-catatonic patients and 9.1% HCs in the present study. Logistic regression analysis also identified high levels of CK and cortisol (although marginally insignificant, $P = .071$) as independent predictors of high hs-CRP level in the whole patients' sample, which could partly explain the high inflammatory individuals in the non-catatonic group. In healthy people, Delongui and colleagues found a serum hs-CRP of >3.0 and ≤10.0 mg/l in 17.6% of adults in Brazil. Authors suggested smoking, lack of physical activity, female, and BMI could be potential contributors to the high hs-CRP level.[74] In a Chinese population, Tang and colleagues found that higher serum hs-CRP concentration was associated with older age, male gender, and higher level of serum uric acid but lower level of high-density lipoprotein cholesterol and superoxide dismutase in healthy adults.[75]

In stepwise linear regression, cortisol and ACTH were both identified as independent predictors of lg (hs-CRP) in catatonic patients, which indicates that stress plays an important role in systemic inflammation. Previous studies suggested that an increased level of stress hormone was linked to a chronic and low-grade inflammation state by alteration of the gene expression of the inflammatory arm of the immune system.[37] Elevated cortisol and its metabolites were noted in the first episode and recent onset psychoses and mood disorders.[76–79] However, our current study did not find an association between serum cortisol level and PANSS positive or PANSS negative scores, in either catatonic or non-catatonic groups (supplementary table S2). Furthermore, the hs-CRP level was not associated with PANSS positive or PANSS negative scores (supplementary table S1). These results were in line with most of the previous studies[76,80,81] but not with that of Murri and colleagues.[82] The discrepancies not only reflect the potential methodological heterogeneity among these studies,[83] but could also suggest that the abnormal stress response may be a preexisting condition of the illnesses, rather than merely a reaction to psychopathology.[84]

Stepwise linear regression also revealed that complement C4 was an independent predictor of hs-CRP levels in catatonic patients. Growing evidence indicates that complement is involved in brain development.[85,86] A recent genetic study implicated C4 as a susceptibility locus for schizophrenia.[87] Dysregulation of the complement system in schizophrenia has been noted in a few small studies.[88,89] It has been shown that high CRP levels were associated with high serum levels of complement components in a nonpsychiatric clinical population.[90]

The strength of the present study includes the stringent diagnostic criteria and standardized rating scale used to assess catatonia, the focus specifically on the inflammatory profile in catatonic patients, the control of confounding variables, such as physical comorbidities, infections, and BMI, and the taking into consideration of stress hormones and innate immune system (complement C3 and C4). The results of the study, however, should be interpreted with caution due to the following methodological limitations: (1) The cross-sectional design of the study does not reveal a causal relationship. We do not know whether the catatonia features are due to a premorbid high inflammatory level, or it is the catatonia syndrome that leads to a high level of inflammatory markers. (2) There has been evidence suggesting overlapping motor symptoms between different motor domains in psychotic disorders, and it is important to assess other motor symptoms, such as extrapyramidal symptoms. However, in the present study, OLZeq was relatively low in both patients' groups, particularly in the catatonic group (median: 3.34 mg in catatonic group vs 6.25 mg in non-catatonic group, $P = .011$), suggesting antipsychotics induced extrapyramidal symptoms unlikely to happen. (3) Correlation analysis revealed a significant correlation between BFCRS total score and PANSS negative scores in the whole patients' sample, but neither in catatonic nor in the non-catatonic group. This may suggest that the evaluation of negative symptoms could be potentially confounded by catatonic symptoms when assessing a mixed sample with both catatonic and non-catatonic patients. (4) In multivariate analyses, the significant variables only accounted for 43% of the variance in hs-CRP. Although we controlled potential confounding factors, such as BMI, comorbid physical condition, and also took into consideration the stress hormone and innate immune function, there may still be other factors that have a profound effect on systemic inflammation profile; (5) Serum concentration of hs-CRP may not be able to reflect the inflammatory status in the central nervous system (eg, cerebrospinal fluid).In conclusion, the present study shows that the catatonia could be specifically linked to a high level of systemic inflammation, independent of the primary psychiatric diagnoses. The high level of serum hs-CRP in catatonic patients could not be explained by more severe symptomatology, activation of stress system, or dysregulation of innate immune (complement) system, although the latter two variables are both independent predictors of inflammation. The findings of the present study suggest that catatonia could be a transdiagnostic clinical feature associated with inflammation dysregulation. These findings could have clinical implications when considering potential anti-inflammatory therapeutic interventions. Longitudinal studies with a larger sample size and measurement of inflammatory alteration in the central nervous system are warranted in the future.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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