Role of High-Sensitivity C-Reactive Protein as a Biomarker and Endophenotype in Mania

Mohamed Abshad, DPM[a]; Basudeb Das, MD[a]; Mahesh Kumar, MD[b]; Pranjal Dey, MD[c,*]; and Khisith Kumar Kshitiz, MD[d]

ABSTRACT

Objective: To assess the role of high-sensitivity C-reactive protein (hs-CRP) as a biomarker, trait marker, and endophenotype in mania.

Methods: Forty patients with mania, 40 of their first-degree relatives, and 30 healthy controls were recruited via a purposive sampling method from May 2020 to February 2021. hs-CRP levels were measured in all groups at baseline. The patient group was evaluated with the Young Mania Rating Scale, and hs-CRP levels were assessed in all participants at baseline, 2 weeks, and 6 weeks. Data were analyzed with SPSS version 25.

Results: hs-CRP levels were significantly higher in patients than in controls and first-degree relatives ($P = .001$). However, hs-CRP levels were not higher in first-degree relatives compared to healthy controls. There was a significant reduction in total YMRS and domain scores and hs-CRP levels in patients at weeks 2 and 6 compared to baseline ($P = .02$).

Conclusions: The blood hs-CRP level is a biomarker in mania, which may be a newer approach to detect disease progression and perhaps guide novel therapies. hs-CRP as an endophenotype requires further evaluation in future studies.

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[a]Department of Psychiatry, Central Institute of Psychiatry, Ranchi, India
[b]Dr Baba Sahib Ambedkar Medical College and Hospital, New Delhi, India
[c]All India Institute of Medical Sciences, Guwahati, India
[d]Department of Biochemistry, Central Institute of Psychiatry, Ranchi, India
**Corresponding author:* Pranjal Dey, MD, All India Institute of Medical Sciences, Silbharal Changsari, Guwahati, Assam 781101, India (pranjalde80@gmail.com).

Mood disorders are increasingly recognized as having a strong association with a proinflammatory state, providing the basis for investigating novel therapeutic targets.[1] The term *biomarker*, a portmanteau of *biological marker*, refers to "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease."[2] The cytokines and chemical factors produced during inflammatory responses serve as excellent biomarkers when investigating the potential relationship between inflammation and mood disorders.[3,4] Proinflammatory markers have shown substantial evidence for increased inflammation during manic and depressive episodes, with particularly increased levels of C-reactive protein (CRP), cytokines, and tumor necrosis factor α (TNF-α).[5] Despite a growing body of evidence regarding the involvement of cytokines in psychiatric and neurodegenerative disorders, findings are still limited in mood disorders.

CRP and hs-CRP as Inflammatory Markers in Mood Disorders

Inflammation is a condition characterized by cytokine cascades, cellular immune responses with increased levels of acute phase proteins, and complement factors. Interleukin-1 (IL-1) and TNF are the primary inflammatory mediators that induce the production of acute phase proteins, such as haptoglobin and CRP.[6] CRP is a pentameric protein that is generated in the liver and secreted in the blood, and its measurement provides a reliable marker of chronic inflammation caused by infectious and other inflammatory agents.[7] Traditional CRP measurement only detects CRP in the range of 10 to 1,000 mg/L, whereas high-sensitivity CRP (hs-CRP) detects levels in the range of 0.5 mg/L to 10 mg/L. In simpler terms, hs-CRP measures trace amounts of CRP in the blood.[8] A few studies have measured the prevalence of hs-CRP, a more sensitive assay, in bipolar disorder patients. Two studies[9,10] showed that patients with manic episodes had higher mean hs-CRP levels than healthy controls. Another study[11] found that the levels of hs-CRP were increased in manic patients compared to euthymic and depressed patients, suggesting that the episodes of mania are particularly sensitive to inflammatory changes.

Role of CRP and hs-CRP as Trait Markers in Mood Disorders

The concept of the endophenotype was introduced to psychiatry over 30 years ago but has gained popularity more

Clinical Points

- High-sensitivity C-reactive protein (hs-CRP) levels in the blood can be a useful biomarker in patients with mania.
- Treatment response in patients with mania can be assessed by measuring blood hs-CRP levels over time.
- The role of blood hs-CRP level as a trait marker in mania requires further research.

recently.[12] In psychiatry research, a biomarker may be called an endophenotype when it is heritable and segregate with illness in the population. It must co-segregate with illness within families and not be state dependent. Also, it must be amenable to reliable measurement, be specific to the illness of interest, and present at a higher rate within affected families than in the population.[13] Thus, endophenotypes may be useful for many reasons, such as indicating trait markers of susceptibility to psychiatric illness by providing biological markers of the disease. Studies[7,11,14] established that a higher level of hs-CRP as a biological marker in manic episodes of bipolar disorder was correlated with Young Mania Rating Scale (YMRS)[15] scores for evaluating treatment response. Thus, hs-CRP was interpreted as an episode-specific marker. The higher hs-CRP levels observed in patient groups compared to controls before and after response to treatment in those studies[7,11,14] suggest that hs-CRP may be a trait marker in bipolar disorder.

Thus, hs-CRP is a potential marker of bipolar disorder; however, the nature of the association is uncertain. The objective of this study was to investigate hs-CRP as a biomarker, trait marker, and endophenotype in mania.

METHODS

Sample

This was a hospital-based prospective study. The sample was recruited via a purposive sampling method from May 2020 to February 2021. The sample included inpatients from the department of psychiatry of a tertiary care hospital located in eastern India, their first-degree relatives, and healthy individuals as controls.

Patients

After informed consent was obtained, 40 patients aged 18–60 years diagnosed with first-episode mania or bipolar affective disorder, current episode mania as per *ICD-10* criteria with a YMRS score > 20 were included in the study.[16] We included only those aged ≥ 18 years because findings based on studies of childhood-onset bipolar disorder may not be applicable to adult-onset bipolar disorder and vice versa.[17] Patients with present or prior history of any major physical or psychiatric illness other than manic episode were excluded. Patients with any other comorbid substance dependence except nicotine and caffeine, those with any infectious disease during the study, and pregnant women and lactating mothers were excluded. These patients were excluded because all these conditions are known to alter the phenomenology and course of the disorder as well as levels of the biomarkers.[5] Patients with previous episodes of either unipolar or bipolar depression were excluded.[18,19]

First-Degree Relatives

This group comprised 40 first-degree relatives of the selected patients (ie, twin sibling > sibling [male > female] > parents [father > mother]) who were willing to provide informed consent. Individuals with present or prior history of any major physical or psychiatric illness and having any other substance dependence except nicotine and caffeine were excluded. Pregnant women, lactating mothers, and individuals with any infectious disease during the study were excluded.[5]

Controls

The control group comprised 30 individuals who worked at the hospital and had no psychiatric or major medical illness. They were required to have a 12-item General Health Questionnaire (GHQ-12)[20] score < 3 and to provide informed consent. Those with a family history of mood disorder, substance dependence except for nicotine or caffeine, or infectious disease during the study, as well as pregnant women and lactating mothers were excluded.[5] The controls were demographically matched with the patients.

Instruments

Sociodemographic and clinical data sheet. A semistructured proforma for recording demographic details such as age, sex, marital status, religion, education, occupation, income, and socioeconomic status was created. Also, clinical data were recorded by interviewing the patient and from the case record file. The form also included history of medical and psychiatric illness, treatment history, and details of the physical and mental status examination. Finally, diagnosis of the patient was made according to *ICD-10* diagnostic criteria for research.[16]

YMRS. The YMRS is a rating scale used to evaluate manic symptoms at baseline and over time in individuals with mania. It has 11 items and is based on the patient's subjective report of his/her clinical condition over the previous 48 hours. The YMRS score was > 20 for the patient group at baseline.[15]

GHQ-12. The GHQ-12 is a screening instrument used to identify minor psychiatric disorders in the general population and within community or nonpsychiatric clinical settings such as primary care or in general medical outpatients.[20]

hs-CRP by Immunoturbidimetric Assay

Blood was drawn from patients, first-degree relatives, and healthy controls and allowed to clot at room temperature in a plain vial. It was centrifuged at approximately 2,500 rpm for 5 minutes. The serum was analyzed for levels of hs-CRP using immunoturbidimetric assay, which is based on the principle of agglutination reaction. The test specimen was mixed with activation buffer and latex reagent and allowed to

Table 1. Comparison of Sociodemographic Variables Among the Groups (N = 110)

Variable	Patients (n = 40)	First-Degree Relatives (n = 40)	Controls (n = 30)	Fisher Exact Test/ Pearson χ^2	*df*	*P*[a]
Age, mean ± SD, y	35 ± 9.2	45 ± 7.9	37.3 ± 9.7	6.828	2	**.002**
Income, mean ± SD, rupees	7,725 ± 3,408	6,650 ± 1,694	6,833 ± 1,331	1.120	2	.334
Education, mean ± SD, y	7.8 ± 3.7	4.6 ± 2.7	4.2 ± 2.9	6.975	2	.132
Sex, n (%)				0.151	2	.927
Male	30 (75.0)	30 (75.0)	24 (80.0)			
Female	10 (25.0)	10 (25.0)	6 (20.0)			
Marital status, n (%)				0.301	2	.860
Married	30 (75.0)	28 (70.0)	20 (66.7)			
Unmarried	10 (25.0)	12 (30.0)	10 (33.3)			
Occupation, n (%)				2.618	2	.270
Employed	18 (45.0)	28 (70.0)	16 (53.3)			
Unemployed	22 (55.0)	12 (30.0)	14 (46.7)			

[a]Bolding indicates statistical significance.

react. The presence of CRP in the test specimen resulted in the formation of an insoluble complex producing turbidity, which was measured at a wavelength of 630 nm. The increase in turbidity corresponded to the concentration of CRP in test specimens measured at baseline, 2 weeks, and 6 weeks.

Operational Procedure

The study was initiated after obtaining approval from the hospital's institutional ethics committee. Clinically diagnosed patients with first-episode mania or bipolar affective disorder, current episode mania who fulfilled the inclusion and exclusion criteria were included in the study. The YMRS was administered to the patient group to measure the total score and different parameters of mania. Sociodemographic and clinical information was obtained from patients, their first-degree relatives, and controls. Infections were ruled out in all the 3 groups by detailed clinical examination and via blood examination in parameters of total leukocyte count, differential leukocyte count, and erythrocyte sedimentation rate, which had to be within normal range.[21] Patients were started on mood stabilizers, antipsychotics, or benzodiazepines as decided by the treatment team. Treatment along with dosage was clinically determined by the treatment team based on effectiveness of the drug and the patient's tolerance. Healthy controls were administered the GHQ-12.

Patients repeated the YMRS at weeks 2 and 6. Blood samples were collected from patients in the morning after admission, as well as from the first-degree relatives and healthy controls. Follow-up blood samples of the same patients were collected after 2 weeks and 6 weeks of treatment. Blood (10 mL) was drawn under standardized conditions (sitting patient from cubital vein). After the blood was collected, it was allowed to clot in a serum separator tube at room temperature. It was centrifuged for approximately 5 minutes. The serum was aliquoted and stored at −80°C for later analysis. The blood samples were tested for serum levels of hs-CRP using immunoturbidimetric assay. The measured level was reported by a biochemist and recorded.

Table 2. Comparison of Biochemical Parameters Among the Groups at Baseline (N = 110)[a]

Variable	Patients (n = 40) (A)	First-Degree Relatives (n = 40) (B)	Controls (n = 30) (C)	*F* (*df*)[b]	*P*[c]	Post Hoc
hs-CRP level	6.863 ± 7.907	1.215 ± 2.485	1.233 ± 2.275	2, 52	**.001**	A > C C > B

[a]Data are presented as mean ± SD.
[b]1-way analysis of variance.
[c]Bolding indicates statistical significance.
Abbreviation: hs-CRP = high-sensitivity C-reactive protein.

Data Analysis

Data were tabulated and analyzed using SPSS for Windows, version 25.0. Group differences of continuous variables were measured by independent Student *t* test. Group differences of categorical variables were computed by χ^2 test. Analysis of variance (ANOVA) was applied for comparison of biochemical markers at baseline among patients, first-degree relatives, and healthy controls. Paired *t* test was applied for comparison of biochemical markers of patients at baseline and remission. Correlation between the clinical and biochemical variables was done with Pearson correlation test. A *P* value < .05 was considered significant.

RESULTS

Sociodemographic Variables of the 3 Groups

Table 1 compares the sociodemographic variables among the patients, first-degree relatives, and controls. All 3 groups were comparable in terms of sex, education, occupation, family income, and marital status. Most patients in this study were male, as were controls and first-degree relatives. All 3 groups had comparable monthly income, and there were no significant differences in education. Regarding age, first-degree relatives were older than the other 2 groups, and this difference was significant given that most first-degree relatives were parents or siblings who were older than the patients.

Table 3. Comparison of Changes in the Biochemical Parameter and the YMRS Total Score and Domains in Patients (N = 40)[a]

Variable	Baseline	Week 2	Week 6	Statistic/ Type[b]	*P*[c]
hs-CRP level	6.863 ± 7.907	2.713 ± 4.862	1.606 ± 3.736	6.271/ Greenhouse-Geisser	.020
YMRS					
Total score	39.450 ± 5.978	16.900 ± 7.711	4.500 ± 4.489	163.301/*F*	**<.001**
Elevated mood	2.850 ± 0.988	1.500 ± 1.051	0.500 ± 0.688	32.658/*F*	**<.001**
Energy	2.850 ± 0.933	1.400 ± 0.940	0.400 ± 0.598	43.087/*F*	**<.001**
Sexual interest	0.800 ± 0.894	0.150 ± 0.366	0.050 ± 0.223	10.110/*F*	**<.001**
Sleep	3.100 ± 1.020	0.800 ± 0.767	0.050 ± 0.223	90.124/*F*	**<.001**
Irritability	5.900 ± 1.651	2.500 ± 1.820	0.600 ± 0.940	62.457/*F*	**<.001**
Speech	5.400 ± 1.465	1.900 ± 1.518	0.400 ± 0.820	77.053/*F*	**<.001**
Language	2.600 ± 0.940	1.100 ± 1.020	0.250 ± 0.550	38.112/*F*	**<.001**
Content	5.400 ± 1.465	2.200 ± 1.823	0.700 ± 0.978	53.766/*F*	**<.001**
Aggressive behavior	5.400 ± 1.602	2.100 ± 1.774	0.200 ± 0.615	68.157/*F*	**<.001**
Appearance	1.800 ± 1.196	0.650 ± 0.670	0.150 ± 0.366	21.307/*F*	**<.001**
Insight	3.850 ± 0.366	2.600 ± 1.095	1.200 ± 0.951	47.087/*F*	**<.001**

[a]Data are presented as mean ± SD.
[b]*F* = repeated measure analysis of variance.
[c]Bolding indicates statistical significance.
Abbreviations: hs-CRP = high-sensitivity C-reactive protein, YMRS = Young Mania Rating Scale.

Table 4. Correlation Between Sociodemographic and Clinical Variables (0, 2, and 6 weeks) With hs-CRP Level in the Patient Group (N = 40)

Variable	hs-CRP at Baseline r (*P*)[a]	hs-CRP at 2 Weeks r (*P*)[a]	hs-CRP at 6 Weeks r (*P*)[a]
Age	−0.063 (.792)	−0.014 (.955)	−0.044 (.854)
Education	0.121 (.611)	0.069 (.772)	0.094 (.694)
Income	0.279 (.233)	0.076 (.751)	0.120 (.614)
Elevated mood	−0.390 (.089)	0.223 (.344)	−0.062 (.794)
Energy	−0.098 (.680)	0.321 (.167)	0.274 (.242)
Sexual interest	0.318 (.172)	0.065 (.786)	0.113 (.635)
Sleep	0.113 (.634)	0.336 (.147)	0.113 (.635)
Irritability	0.018 (.939)	0.130 (.585)	0.397 (.083)
Speech	−0.214 (.366)	0.123 (.607)	0.011 (.963)
Language	0.107 (.654)	−0.083 (.728)	0.041 (.864)
Content	−0.259 (.271)	0.058 (.807)	−0.129 (.589)
Aggressive behavior	−0.026 (.912)	0.217 (.359)	0.043 (.857)
Appearance	0.141 (.553)	0.086 (.718)	−0.024 (.920)
Insight	−0.064 (.787)	0.039 (.872)	−0.041 (.864)
YMRS total	−0.048 (.840)	0.227 (.337)	0.096 (.688)

[a]r = Pearson correlation coefficient; *P* = significant value.
Abbreviations: FDR = first-degree relatives, hs-CRP = high-sensitivity C-reactive protein, YMRS = Young Mania Rating Scale.

Comparison of Biochemical Parameter (hs-CRP Level) Among the 3 Groups at Baseline

Table 2 shows a significant difference in the levels of hs-CRP between the patients and controls. The mean ± SD hs-CRP level was higher in patients (6.863 ± 7.907) than in controls (1.233 ± 2.275). There was a trend for hs-CRP levels to be higher in controls than in first-degree relatives. Measurement was conducted using 1-way ANOVA and post hoc Bonferroni correction.

Comparison of Changes in Biochemical and Clinical Parameters in Patients Over Time

Table 3 compares the changes for hs-CRP in blood, as well as YMRS scores and its different domains over time in patients using repeated measures ANOVA. Significant changes with declining value were seen in 3 clinical observations with a *P* value of .020 and observed power of 0.637 in hs-CRP level. Regarding clinical parameters, there was a statistically significant decline in the YMRS total score and its domains over time from baseline to 6 weeks.

Correlation

Table 4 shows the correlation between sociodemographic variables and hs-CRP levels taken at baseline, week 2, and week 6 in the patient group. No significant correlation was found between these 2 parameters. Regarding clinical parameters, the correlation was measured between YMRS total and domain scores at baseline, week 2, and week 6 with hs-CRP levels taken during the same period. No significant correlation was found between these parameters in the patient group.

DISCUSSION

Our study showed that hs-CRP levels were significantly higher in patients compared to controls and first-degree relatives. But levels were not higher in first-degree relatives compared to healthy controls. Although no significant correlation was found between sociodemographic variables, YMRS score, and hs-CRP levels in patients over time, the mean YMRS score and hs-CRP levels in patients were found to be significantly reduced at weeks 2 and 6 compared to baseline, indicating better treatment response over time. Thus, we found the hs-CRP level in blood to be a biomarker in mania, but whether it might be an early prodromal marker of developing disease or an early marker of disease response and an indicator for patient-specific treatment response was difficult to answer.

In our study, there was a significant difference in the levels of hs-CRP between the patients and controls. Thus, hs-CRP level was a marker of the disease state as compared to healthy controls. A previous study[22] found

that cytokines such as TNF-α, INF-γ, IL-6, and hs-CRP were significantly higher in patients with a manic episode of bipolar I disorder before treatment than in healthy controls. Another study[23] found mean levels of CRP were higher in patients with mania then in healthy individuals, but no significant difference was found with other disease conditions like acute schizophrenia, unipolar depression, and bipolar depression.

In our study, there was a trend for the levels of hs-CRP to be higher in controls than in first-degree relatives. So, it was difficult to establish hs-CRP as an endophenotype according to our study findings. Although research on endophenotypes in bipolar disorder is growing and first-degree relatives have been recruited to investigate trait markers, little is understood about the possible interactions of biomarkers and their role as a trait marker of bipolar disorder, especially in the manic phase.[24]

Regarding the evaluation of changes in mean YMRS total score and domains and hs-CRP levels in the patient group, statistically significant changes were seen in 3 clinical observations in both parameters. These results indicate that there was a significant effect of treatment on the levels of hs-CRP and the manic symptoms. hs-CRP does appear to be a marker of disease state and response to therapy. This finding was in concordance with previous study findings in which hs-CRP was observed to be the only parameter correlated with clinical response.[22]

No significant correlation was found between hs-CRP levels and sociodemographic variables or YMRS total and domain scores over time from baseline to weeks 2 and 6 in the patient group. To our knowledge, no study has found any such correlation in mania patients, which requires further evaluation in future research.

Our study had a few limitations. The sample size was small, and the intervals between blood sample collections from patients were relatively short. The effect of drugs and their dosage on the biomarkers could be varied. So, a larger sample size with patients with mania from the community would have provided better generalization of the result. Using an objective measure for assessment of symptoms, uniform usage of medication and longer intervals between blood sample collections could have yielded a better result.

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