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Short Communication

Psychiatry/Mental Health Section

C-Reactive Protein in Bipolar Disorder in an Indian Clinical Setting

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ABSTRACT

Introduction: Serious psychiatric illnesses like bipolar disorder lack specific biomarkers of diagnosis or prognosis. However, association between Bipolar Disorder (BD) and various inflammatory markers has been consistently demonstrated by earlier studies pointing to underlying inflammation/dysimmunity. Often implicated in particular is the acute phase C-Reactive Protein (CRP) of hepatic origin, a generic marker of inflammation which is robust and very easy to test even in field settings without the need for a laboratory.

Aim: To study the status of CRP, a generic marker of inflammation, in a well-characterised south Indian Tamil BD cohort, and investigate whether it can be a specifier of disease state.

Materials and Methods: CRP was qualitatively estimated by latex agglutination method in the serum of 145 BD patients and 151 healthy controls. Statistical analyses were performed to test the association of CRP with the disease state.

Results: It was found that, after controlling for age, gender, BMI and smoking status, CRP positivity (>0.6 mg/dL) was: (i) significantly higher among BD patients compared to healthy controls; (ii) significantly higher among patients having an acute mood episode (both mania (n=85), and depression (n=9) combined) compared to patients with residual symptoms or in remission, as well as compared to healthy subjects; (iii) not significantly different between patients in acute mania versus acute depression, but significantly higher in both acute mania and in acute depression compared to patients with residual symptoms or in remission.

Conclusion: CRP, a robust generic inflammatory marker is significantly higher among BD patients as compared to normal controls, pointing to underlying inflammation operating in the disease. Also, it can differentiate between patients in acute phase and those in remission or having residual symptoms. If validated in longitudinal follow-up studies, these results could be helpful in Point Of Care (POC), as well as field settings especially in low income countries to identify patients whose symptoms are progressing towards relapse, at low costs, and without the need for a sophisticated laboratory.

Keywords: Inflammation, Latex agglutination, Psychoneuroimmunology

INTRODUCTION

BD is frequently associated with immune dysfunctions and its association with various markers of inflammation has been consistently demonstrated. CRP which is of hepatic origin is a prominent marker of inflammation quite often used in clinical settings. It is produced as an acute phase reactant and secreted into the blood triggered by pro-inflammatory cytokines especially Interleukin-6 (IL-6).

In psychiatric settings, many studies have demonstrated an association between CRP levels and BD, accounting also for subgroup differences like acute mood episodes and stable phases [1-5]. While cross-sectional studies report increased hsCRP levels in manic BD patients, as compared to euthymic patients, depressed patients and healthy controls [1] and a correlation between CRP and scores of mania (YMRS), and not depression scores (Ham-D) [2], longitudinal studies have shown the relapse to bipolar mania to be accompanied by concomitant increase in hsCRP levels [4]. Given that chronically and moderately elevated level of CRP is a marker of low-grade inflammation as well as a risk factor for cardiovascular and malignant diseases, it has been proposed that measurement of CRP level might be relevant to the clinical care of bipolar patients [6].

The present study was part of a PhD thesis exploring the nature and extent of dysimmunity operative in major psychoses. The study assessed cost-effectively and qualitatively, the status of CRP in mood episodes of bipolar disorder in a well characterised south Indian Tamil BD cohort, in order to investigate whether it can be a specifier of disease status used in clinical settings.

MATERIALS AND METHODS

Study Subjects

One hundred and forty five (145) South Indian Tamil patients who had a diagnosis of Bipolar Disorder according to DSM-IV criteria (American Psychiatric Association) were enrolled for the present study [7]. The patients were recruited from both out-patient and in-patient services of the Department of Psychiatry at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, a major tertiary referral centre in South India between September 2012 and April 2016. Clinical history was obtained for each patient through structured interviews conducted by trained psychiatrists. All subjects were screened before inclusion for any recent infections and existing inflammatory conditions or ongoing treatment with immunomodulatory drugs. Psychiatric evaluations were performed to assess the severity of symptoms and level of functioning of the subjects. Severity of manic symptoms was rated with the Young's Mania Rating Scale (YMRS) [8] and depressive symptoms with the Montgomery-Asberg Depression Rating Scale (MADRS) [9]. Remission was defined as a score of <7 on YMRS, and <10 on MADRS. One hundred and fifty one (151) Healthy Control (HC) subjects (age, sex, and ethnicity matched) without a personal or family history (first degree) of psychiatric, neurological or autoimmune disorders were also enrolled from volunteers among hospital staff and the general public. All participants provided written informed consent for participation in the study which had previously been reviewed and approved by the institutional ethics committee.

Determination of CRP Status

CRP status was profiled in these subjects by qualitative latex agglutination method using "CRP Latex" kits (Reckon Diagnostics, Vadodara, India) according to the manufacturer's protocol. The commercial kit had a sensitivity of 0.6 mg/dL.

STATISTICAL ANALYSIS

The sample size for the study which had 80% power and 95% confidence interval was determined using the Sample Size for Unmatched Case-Control Studies (SSCC) module of the OpenEpi V3 open source calculator. The frequency of CRP positivity, defined as >0.6 mg/dL serum, was compared between BD and HC control groups using the chi-square test. The Odds Ratio (OR) with 95% confidence interval was determined. A (two tailed) p-value <0.05 after correction was regarded as statistically significant. Sensitivity, specificity, positive and negative predictive values were determined. GraphPad prism V7 was used to perform the statistical tests. Logistic regression analysis to control for potential confounders including age, gender, BMI, and smoking status was carried out using Statistical Package of Social Sciences (SPSS) Version 20.0.

RESULTS

The demographic details of the subjects are presented in [Table/Fig-1]. Overall, the mean age of patients and controls were 32.95 (±10.57) and 33.12 (±11.45) years respectively. Gender distribution was not significantly different between the patient and control groups [Table/Fig-1]. The mean BMI of the patient group was 24.17 (±4.34) and 16% of the patients were active smokers.

Demographic details	BD (n=145)	HC (n=151)	p-value
Age at inclusion (years)			
Mean±SD	32.95±10.57	33.12±11.45	0.89
Range	18-60	18-64	
Age at onset (years)			
Mean±SD	23.64±6.54		
Range	13-46		
Gender, n (%)			
Male	67 (46.2)	85 (56.3)	0.08
Female	78 (53.8)	66 (43.7)	

[Table/Fig-1]: Demographic details.
BD: Bipolar disorder; HC: Healthy controls; SD: Standard deviation

CRP status	BD (n=145)	HC (n=151)	Total	p value	OR (95% CI)
CRP Positive	31	9	40	0.0001	4.3 (2.0-9.4)
CRP Negative	114	142	256		

[Table/Fig-2]: Comparison of CRP status between BD cases and Healthy Controls (HC).
BD: Bipolar disorder; HC: Healthy controls; CRP: C-reactive protein; OR: Odds ratio; CI: Confidence interval

CRP positivity was significantly higher in BD patients (p=0.0001, OR=4.3, 95% CI=2.0-9.4) compared to controls [Table/Fig-2].

For the purpose of analysis, the patients who had residual symptoms were grouped with the patients in remission at the time of enrolment. Upon comparing subgroups of cases who were in acute mood episode at enrolment with those who were in remission/residual phase, it was found that CRP positive status was significantly higher in the acute disease group (p=0.003, RR=1.48, 95% CI=1.2-1.8) when compared to subjects in remission or residual disease [Table/Fig-3], and remained significant after controlling for confounders namely age, gender, BMI and smoking status of the subjects.

Further, upon comparing among patients in acute phase, It was found that CRP status did not differ significantly between patients in an acute manic episode (n=85) and in acute depression (n=9). However, CRP positive status was significantly higher in both

CRP status	Acute Phase BD (n=94)	Remission/Residual BD (n=51)	Total	p-value	RR (95% CI)
CRP Positive	27	4	31	0.0030	1.48 (1.2-1.8)
CRP Negative	67	47	114		

[Table/Fig-3]: Comparison of CRP status between BD cases in acute phase and cases in remission or residual phase.
BD: Bipolar disorder; HC: Healthy controls; CRP: C-reactive protein; OR: Odds ratio; CI: Confidence interval

CRP status	Acute Phase BD (n=94)	Remission/Residual BD (n=51)	p-value	RR (95% CI)
Mania (n=85)				
CRP Positive	27	4	0.0123	4.10 (1.33-12.71)
CRP Negative	67	47		
Depression (n=9)				
CRP Positive	4	4	0.0134	9.40 (1.78-49.68)
CRP Negative	5	47		

[Table/Fig-4]: Comparison of CRP status between patients in acute phase mania or acute depression and patients in remission or residual phase.
BD: Bipolar disorder; HC: Healthy controls; CRP: C-reactive protein; OR: Odds ratio; CI: Confidence interval

acute mania (p=0.01, OR=4.10, 95% CI=1.33-12.71) and acute depression (p=0.01, OR=9.4, 95% CI=1.8-49.7) when compared to subjects in remission or residual disease [Table/Fig-4].

The sensitivity of the test for distinguishing BD cases and healthy controls was 21.4% (95% CI=0.15-0.29) and specificity was 94.04% (95% CI=0.89-0.97); the positive and negative predictive values were 77.5% (95% CI=0.63-0.88) and 55.5% (95% CI=0.49-0.61) respectively. As for distinguishing acute mood episodes from remission/residual phase the sensitivity and specificity were 29.7% (95% CI=0.21-0.39) and 92.2 (95% CI=0.81-0.96) and the positive and negative predictive values were 87.1% (95% CI=0.71-0.95) and 41.2% (95% CI=0.33-0.50) respectively.

DISCUSSION

Immune related mechanisms are associated with the core psychopathology of BD [3] and a chronic low-grade inflammation is well admitted to be operative at least in a subset of BD patients, especially in those with more severe symptoms [2]. CRP, an acute phase reactant produced by the liver and secreted into the blood, is a marker of inflammation used quite often in the clinical settings. It has been shown that CRP association is not affected by psychotropic medication [2], increasing the utility of CRP as a marker if validated.

While in some studies high CRP levels has been shown to be significantly associated with acute mood states, especially mania [1,2,4], other studies did not demonstrate significant differences in CRP levels based on the mood states [3,5] although levels were higher compared to healthy controls. The differences in the findings could be attributed to variation in study design, relatively small sample sizes and not controlling for cofounders that could potentially influence CRP levels like BMI, smoking status etc. Also, medication, lifestyle and genetic factors could likely contribute to the confounding effect on the observations. In addition, in one study, the authors suggest that some of the patients could have had a shift in affective status between the time of clinical assessment and blood sampling as both were not carried out on the same day as done in the present study. Such confounders, it is suggested, could introduce random noise thereby reducing the likelihood of finding associations [3]. CRP alterations across mood states have also been demonstrated by prospective longitudinal studies [10]. The present study also did not distinguish acute phase mania from acute depression with respect to CRP status, although CRP status among patients with both acute mania and acute depression were

significantly different from patients in remission/ having residual symptoms. Yet, the lack of association in the present study should be addressed with caution, owing to the small sample sizes compared after subgrouping.

An earlier meta-analysis showed that apart from the acute mood states, elevated CRP was also observed in euthymic BD patients compared to healthy controls [6]. However, in the present study, no significant differences in CRP status were observed between euthymic BD and healthy controls.

As bipolar disorder is clearly associated with higher risk of metabolic syndrome [11] and conceived as a multi-system inflammatory disease [12], CRP has been demonstrated to be useful as a marker of metabolic syndrome in bipolar disorder patients [13] and thus of higher load of cardiovascular comorbidities.

A previous longitudinal study with a small sample of BD patients on treatment could not distinguish CRP level-based BD subgroups, and reported no statistically significant association between higher CRP values and a more unfavourable outcome in either euthymic or non-euthymic patients [14]. In the present study, upon cross-sectional examination, it was found that, significant difference in the CRP status between patients in an acute episode and those in remission/ residual status, after controlling for potential confounders.

The major aim of present study was to develop and validate CRP status as marker for impending acute episodes in BD patients, especially dedicated to our underserved poor socio-economic patient populations. The method of CRP testing used herein was simple and does not require much expertise, equipment, or sophisticated laboratory settings to carry out. It is also cost effective as the costs per test are as low as 0.2 USD (approx.).

CONCLUSION

The approach herein validated in a cross sectional design, although warranting further longitudinal validation, was simple, relatively sensitive, specific and cost-effective and easy to implement in point-of care-out-patient, bed side, or field psychiatric consultation settings without the requirement of a laboratory.

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