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ELEVATED LEVEL OF C-REACTIVE PROTEIN IN DRUG NAÏVE PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

The well known inflammatory marker C-reactive protein (CRP), was investigated in the drug naïve and antipsychotic medicating patients to understand the role of inflammation in the etiopathology of schizophrenia.

The level of serum CRP was investigated among 64 schizophrenic patients, diagnosed with DSM IV criteria and categorized into different subgroup of schizophrenia. Latex agglutination test was performed to measure the level of CRP. The limitation of detection of serum CRP was less than 6 mg/L. CRP was treated as categorical variable: normal (6 mg/L) and elevated (≥ 6mg/L). Further, patients were made to answer a questionnaire, which included self-reported age, sex, medical history, age of onset, substance abuse etc. All subjects came from an India-born Bengali population.

3 Paranoid patients showed the elevated level of CRP (≥ 6mg/L) whereas rest of the patients had normal CRP (< 6mg/L). When the findings were compared to the demographic variables, the results showed a significant value for the elevated level of CRP and drug naïve status.

The study suggests that some kind of inflammatory process may be one of the etiological factors for schizophrenia and the antipsychotic drug might play an important role in down regulating this inflammatory process and thereby bringing the level of CRP to the normal state.

Key words: Schizophrenia, C-Reactive protein, Inflammation, Drug naïve

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INTRODUCTION

Schizophrenia is the paradigmatic illness of psychiatry. Although the worldwide prevalence of schizophrenia is about 1%, but it has become a leading public health problem now-a-days and exerts enormous personal and economic costs worldwide. Inspite of tireless research efforts, the etiological process or processes by which a causal agent creates the pathophysiology of schizophrenia is not yet clearly understood. However, a good deal is known about risk factors for developing schizophrenia, which leads to direct inferences regarding possible etiopathophysiologies[1]**.** A large number of studies have also shown the association between the HLA genes and schizophrenia. In such a study, we have reported the association of HLA A*03 allele with paranoid schizophrenia in Indian Bangalee population[2,3].

The roles of immune dysfunction and inflammation have been described in schizophrenia[4,5]. In the past a number of attempts have been made to identify the inflammatory markers for schizophrenia but with conflicting findings. The inconsistent results in the literature might be explained by the heterogeneity of schizophrenia, difference in illness state (acute versus chronic) and effects of antipsychotic medication[6].

One of the well known inflammatory markers is C-reactive protein (CRP). CRP is a normal alpha globulin, which increases in inflammatory processes. The name CRP is derived from the fact that this protein has the capacity to precipitate the somatic C-carbohydrate of Pneumococcus. Elevated CRP levels are usually observed in a variety of infections and inflammatory conditions where there is tissue destruction. Elevated CRP is known to be the risk factor for the cardiovascular diseases, diabetes and other metabolic dysfunction[7,8]. In addition, it is also known to be associated with the depression[9] and cognitive impairment[10].

However, very few studies have been carried out to investigate the association of CRP and schizophrenia. In one study, elevated serum levels of CRP was found in patients who showed more severe clinical symptoms of schizophrenia as reflected by the PANSS total score[11]. In another study, the elevated serum levels of C-reactive protein in schizophrenia are found to be associated with the severity of cognitive impairment but not of psychiatric symptoms[12].

In the present preliminary first hand study, we have investigated the level of CRP in serum of the patients with schizophrenia and its relation with other demographic variables.

EXPERIMENTAL

Materials and methods

India-born Bengali population referred to the psychiatric outpatient Department (OPD) of Psychiatry, North Bengal Medical College and Hospital were considered for the present study. Patients were diagnosed independently by two psychiatrists according to the standard diagnostic criteria of DSM IV and assessed by the Brief Psychiatric Rating Scale (BPRS). After diagnosis, 64 schizophrenic patients were included for the study.

Further, the schizophrenic patients and the family members were made to answer a questionnaire. The questionnaire included self-reported age, cast, sex, medical history, age of onset, month of birth, marital status, education, substance abuse, incidence of any autoimmune disease among patients or in family members etc. All the participants provided their written consent for giving the blood sample after the study procedures were explained.

Procedure

About 5 mL. of blood samples were collected from the each patient. The samples were allowed to coagulate at the room temperature for 2-3 hrs. Blood clot was cut and centrifuged for separating the serum. The CRP level in the serum was measured by latex agglutination slide test (Ranbaxy Fine Chemicals Ltd., HP, India). The limitation of detection of serum CRP level was less than 6 mg/L. CRP was treated as categorical variable: undetectable or normal(< 6 mg/L) and detectable or elevated (≥ 6 mg/L).

Statistical analysis

Statistical analysis was performed for the bivariate associations between elevated CRP groups versus normal group by employing one-way analysis of variance. The association between CRP groups and deficit was examined by Chi-square analysis. The association between CRP group and other clinical/demographic variables were also examined by utilizing one way analysis for continuous variables and Chi-square tests for dichotomous variables.

RESULTS AND DISCUSSION

Sera levels of CRP were measured for 64 schizophrenic patients. Out of them, 57 were paranoid, 2 residual, 3 undifferentiated and 2 were disorganised type. The elevated level of CRP (≥ 6 mg/L) was observed in 3 patients and 61 patients were found to have

normal CRP (< 6 mg/L). All the three elevated cases were found to be of paranoid type. No differences were found in CRP level among different subgroups of schizophrenia.

Further, when the level of CRP was compared to the other demographic variables as shown in the Table 1, only the drug naïve status of the patients showed statistically significant value ($\chi^2 = 16.997$, *P* value < 3.75×10^5).

Table 1. Comparison of demographic and clinical characteristics between the normal/elevated CRP groups

	Elevated CRP N = 3		**Normal CRP N = 61**		**Statistic (Z)**	**P value**
	Mean or N%	**S. D.**	**Mean or N%**	**S. D**		
Age	37.67	21.13	34.69	9.64	F[2,60] = 0.24	>0.62
Gender Men v/s Women	33.33%		70.49%		χ^2 [1] = 1.84	>0.17
Drug naïve patients v/s Patients under antipsychotic medication	100%		11.48%		χ^2 [1] = 17.00	<0.001 Significant
Substance abuse Yes v/s No	33.33%		55.74%		χ^2 [1] = 0.58	>0.44
First child Yes v/s No	33%		18.03%		X2[1] = 0.44	>0.50
Autoimmune disease in patients or in family Yes v/s No	0%		24.59%		χ^2 [1] = 0.97	>0.32

This preliminary first hand study provides further evidence of the involvement of inflammatory processes behind the etiopathology of schizophrenia. The elevated level of CRP in our study is in accordance to the findings of Fan et al.[11] and Dikerson et al.[12]. But unlike previously reported findings, we have considered the CRP level of patients with

their medication status, which showed significantly higher value. In one study, the level of CRP was found to be higher in the patient, who was experiencing psychotic symptoms, in the follow up study in the non-psychotic state, the level of CRP was found to be normal[13]. In this respect, the present study suggests that the antipsychotic drug may perhaps down regulate the inflammatory process, which in turn brings the CRP level to the normal state.

Thus, these findings further suggest that the inflammation may be another possible mechanism in the etiopathology of schizophrenia. It is, however, not clearly understood whether the elevation of the level of CRP is the by-product of the pathophysiology of schizophrenia or directly contributes to the clinical manifestations of the disorder[11].

Until now, it is not clearly understood regarding the mechanism of inflammation in schizophrenia. It is suggested that the vascular-structural brain abnormalities may be one of the factors in the etiology of schizophrenia, like psychoses[14-16]. It is proposed that chronic inflammation might damage the micro-vascular system in the brain and cerebral blood flow[17]. Further, scientific evidence suggests that an increase in the stress hormone like norepinephrine may activate the inflammatory arm of the immune system and triggers the expression of genes that cause chronic, low-grade inflammation. This inflammation is characterized by the degree of the levels of CRP[18]**.**

This is possibly the first reported study of association between CRP and schizophrenia in the Indian scenario. The limitations of the present preliminary study are that the psychopathology measures were not considered for the patients, unlike the previous studies. In contrary to the studies conducted by (Fan et al.[11] Dickerson et al.[12](5 mg/μL), the higher cut off value (6 mg/L) was used for the CRP levels. The sample size of the study is small and the patients were attended in the OPD, which has limited the follow up study.

The study provides further evidence that some kind of inflammation may play a role in the etiopathology of schizophrenia. The study further reveals the immunomodulatory effect of the antipsychotic drugs in the patients.

Additional studies with the highly sensitive techniques like ELISA with longitudinal follow up studies in the large sample size would be required to further strengthen the present study.

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Contributors -

Bisu Singh designed the study and wrote protocol and final manuscript; Sikta Banerjee contributed to the design of the study and recruitment of participants; Nirmal K. Bera is a psychiatrist and contributed to the diagnosis of patients; Chitta R Nayak provided the laboratory evaluations and the statistical analysis; Tapas K Chaudhuri contributed substantially in the design of the study and writing the final manuscript.

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