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Table of Contents

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Original Article

Estimation of C-reactive protein level in schizophrenia

Mortoza Hassan, Jasmin Akhtar, Nazia Afrin Siddiqui

Background: The possible influence of pathogenesis of schizophrenia of an immunological process resulting in inflammation has long been neglected, although inflammatory processes have been implicated in etiology of schizophrenia. If inflammation is a factor in schizophrenia, then it presents a target for potential treatment.

Objectives: To estimate the C-reactive protein (CRP) levels in patients with schizophrenia attending the hospital and evaluate its association with different demographic and clinical factors.

Methods: It was a cross-sectional observational study conducted at National Institute of Mental Health (NIMH), Dhaka in 2019. A total 48 patients of schizophrenia were enrolled for the study and following enrollment data on sociodemographic and other relevant variables were collected by a semi-structured questionnaire. CRP levels were estimated in NIMH laboratory. Then CRP levels were interpreted and compared with different variables.

Results: Most of the respondents (66.7%) had normal level (<6.00mg/L) of C reactive protein. However, in 16 patients CRP level was more than 6.00 mg/L. Percent wise it was 33.3%. The mean CRP levels of 48 participants was 7.70 mg/L, 95% CI [5.42, 9.99]. The association of gender of the respondents and CRP level (p=0.414), family history of psychiatric illness and CRP level (p=0.001), previous treatment history and CRP level (p=0.117), drug non-compliance and CRP levels (p=0.036) and duration of illness difference between elevated and non-elevated CRP (t= 4.44, p=0.001) were assessed in the study.

Conclusions: CRP and its blood levels have been found higher amongst schizophrenic patients, which suggested a role of inflammation in the pathogenesis of schizophrenia. Further studies are needed to better understand if CRP may be considered a biomarker in schizophrenia.

Declaration of interest: None

Keywords: C-reactive protein; schizophrenia patients; tertiary care hospital.

Introduction

Schizophrenia is a highly heritable, chronic, severe, disabling neurodevelopmental brain disorder with a heterogeneous genetic and neurobiological background, which is still poorly understood.[1] It is characterized by positive and negative symptoms, cognitive dysfunction and functional decline, with a lifetime prevalence close to 1%.[2] The role of inflammation and immunity is suggested in the pathogenesis of schizophrenia in epidemiology and genetic study.[3] The investigation of immune system abnormalities in schizophrenia has more recently become a popular area of research. This interest has been at least partially stimulated by increased understanding of interactions between the immune system and the brain.[4] Evidence have pointed to the importance of immune system involvement in not only premorbid neurodevelopmental but also subsequent symptom generation and aging processes of brain change in schizophrenia.[5] We humans are constantly being assaulted by infectious agents, noxious chemicals, and physical traumata. Fortunately, we have evolved a complex process, the inflammatory response, to help fight and clear infection, remove damaging chemicals, and repair damaged tissue.[6] Kraepelin postulated dementia praecox (conceptual predecessor of current schizophrenia) was caused by 'autointoxication' from a focal somatic infection.[7] Following the 1918 influenza epidemic, Menninger described a series of 200 cases of post-influenzal psychosis; a third of whom were reported to resemble dementia praecox.[8]

The vulnerability-stress-inflammation model of schizophrenia includes the contribution of stress on the basis of increased genetic vulnerability for the pathogenesis of schizophrenia, because stress may increase pro-inflammatory cytokines and even contribute to a lasting pro-inflammatory state. Immune alterations influence the dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission.[9] C-reactive protein (CRP) is a homopentameric acute-phase inflammatory protein, a highly conserved plasma protein that was initially discovered in 1930 by Tillet and Francis.[10] CRP levels are known to increase dramatically in response to injury, infection, and inflammation. CRP is mainly classed as a marker of inflammation, but research is starting to indicate important roles that CRP plays in inflammation. CRP is the principal downstream mediator of the acute-phase response following an inflammatory event and is primarily synthesized by IL-6-dependent hepatic biosynthesis.[11] A systemic inflammatory challenge triggers microglia activation, resulting in the release of proinflammatory cytokines in the CNS. Microglia comprise ~15% of the total CNS cells and play role in the synthesis of these central cytokines.[9] Microglia can also extensively regulate the glutamatergic signaling pathway. They express and respond to glutamate, have dynamic interactions with NMDA receptors and glutamate signaling.[12] IL-6 and other proinflammatory cytokines activate indoleamine 2,3 dioxygenase (IDO), an enzyme that breaks down tryptophan along the kynurenine pathway, leading to increased levels of kynurenic acid and quinolinic acid, both involved in glutamatergic neurotransmission. Quinolinic acid is a NMDAR agonist and is neurotoxic, while kynurenic acid is the only naturally occurring NMDAR antagonist in the human CNS. NMDAR antagonism and glutamatergic hypofunction have long been proposed to underlie psychotic symptoms and cognitive dysfunction in schizophrenia.[13]

Methods

It was a cross-sectional observational study conducted at National Institute of Mental Health (NIMH), Dhaka in 2019. Research proposal was approved by the Institutional Review Board (IRB), NIMH, Dhaka and by convenient sampling technique 48 patients of schizophrenia were enrolled in this study where age limit of the participant was between 18 years to 45 years. The diagnosis of schizophrenia was confirmed by attending consultant psychiatrist according to DSM-5 criteria. Following enrollment sociodemographic and relevant data like age, sex, education, income, marital status, residence, duration of illness, previous treatment for schizophrenia, etc. were collected by a pretested semi-structured questionnaire. Then blood was drawn according to WHO blood draw guideline from the patients with all aseptic precaution in sterile tube with disposable syringe. The CRP test was based on the principle of the latex agglutination in NIMH laboratory. The collected data were entered into the computer with help of software SPSS (Statistical Package for Social Science) for windows version 24.0.

Results

A total of 48 patients were recruited whose mean (SD) age was 30.5 (±7.7) years with the age range between 18 and 45 years. Most frequent age group was between 31 to 40 years. Most of the respondents (66%) came from lower middle to low economic class background. Family history of respondents revealed 25% respondents had schizophrenia, 22.9% had major psychiatric illness, 14.5% had minor psychiatric illness and 37.5% had no family history of psychiatric illness. Most of the respondents (66.7%) had

normal level (<6.00mg/L) of CRP. However, in 16 patients CRP levels were more than 6.00 mg/L. Percent wise it was 33.3% (Table 1). Mean CRP level of all 48 participants was 7.70, 95% CI [5.42, 9.99].

Table 1: Distribution of respondents according to their sociodemographic and clinical characteristics (N=48)

Characteristic	Frequency (n)	Percentage (%)
Age (years)		
18-23	9	18.8
24-29	13	27.1
30-35	13	27.1
36-41	9	18.8
≥42	4	8.3
Economic Status		
Low	16	33.3
Lower-middle	18	37.5
Middle	11	22.9
Upper-middle	2	4.2
Upper	1	2.1
Family history of psychiatric illness		
Schizophrenia	12	25
Major psychiatric illness	11	22.9
Minor psychiatric illness	7	14.6
No psychiatric illness	18	37.5
CRP level		
Elevated (>6mg/L)	16	33.3
Not elevated (<6mg/L)	32	66.7

Chi-square tests were conducted to see the association between various sociodemographic and clinical factors. Table 2 shows that there were no association between gender of the schizophrenia patients (p=0.414) and previous treatment history (p=0.117) with elevation of CRP level. Those with family history of psychiatric illness (p=0.001) and drug non-compliance had significantly higher CRP levels than their counterparts. A one-way ANOVA test was done to see the relation between duration of illness and CRP level. P value of less than 0.001 signified that association is statistically highly significant.

Table 2: Association between CRP levels with schizophrenia patients' gender, family history of psychiatric illness, previous treatment history and drug compliance (N=48)

Variable	CRP Level		P Value
	Elevated	Not Elevated	
Gender			
Male	7 (28%)*	18 (72%)	0.414
Female	9 (39.1%)	14 (60.9%)	
Family history of psychiatric illness			
Schizophrenia	8 (66.7%)	4 (33.3%)	0.001
Major Psych. Illness	6 (54.5%)	5 (45.4%)	
Minor Psych. Illness	1 (14.2%)	6 (85.7%)	
No Family History	1 (5.5%)	17 (94.5%)	
Previous treatment history			
Yes	15 (38.4%)	24 (61.5%)	0.117
No	1 (11.1%)	8 (88.9%)	
Drug compliance			
Regular	3 (15.8%)	16 (84.2%)	0.036
Irregular	13 (44.8%)	16 (55.2%)	

*Row percentages, p values obtained from chi-square tests

Discussion

According to the analysis, mean age of respondents was 30.5 years and most frequent age group was between 31 and 40 years. The psychotic features of schizophrenia typically emerge between the late teens and the mid-30s; onset prior to adolescence is rare.[13] The peak age at onset for the first psychotic episode is in the early- to mid-20s for males and in the late-20s for females.[13]

People with schizophrenia are more likely to reside in areas characterized by higher social deprivation and occupy lower socioeconomic positions.[14] The economically disadvantaged social groups contribute disproportionately to the first-admission rate for schizophrenia. In this study most of the respondents (66%) came from lower middle to low economic class background.

Family history of respondents revealed 25% respondents had family history of schizophrenia, 22.9% major psychiatric illness, 14.5% minor psychiatric illness and

37.5% had no family history of psychiatric illness. Major psychiatric illnesses include disorders that produce psychotic symptoms, such as schizophrenia and schizoaffective disorder, and severe forms of other disorders, such as major depression and bipolar disorder. Minor psychiatric illnesses include those disorders which are neurotic in nature. Family history is the greatest predictor of schizophrenia.[15] But schizophrenia does not develop exclusively through the actions of damaged or mutated genes.[16] Instead, environmental factors interact with genetic determinants to produce conditions in the brain that allow the symptoms of schizophrenia to manifest.[17]

Elevated CRP levels were found in about 16.7% of respondents who had family history of schizophrenia. Whereas elevated levels of CRP levels were found in only 2.1% of the respondents those who had no family history of psychiatric illness. P value of .001 indicated that there was significant association between family history of psychiatric illness and CRP levels. Likelihood ratio of 17.2 indicated that those with a family history of schizophrenia or major psychiatric illnesses are 17 times more likely to have elevated CRP levels than those with no family history of psychiatric illness.

Both treated and untreated patient with schizophrenia were included in this study. Most of the respondents got treatment before and it was 81.3%. CRP levels were normal in 50% of the respondents who got treatment before. Drug compliance history was taken from both respondents and their informants. Most of the respondents had irregular drug intake history. About 60.4% of the respondents had history of irregular intake of medication, among them 27.1% had increased levels of CRP. Around 33.3% of patients who had normal levels of CRP had history of regular intake of antipsychotics. A likelihood ratio of 4.64 showed drug non-compliant patients were 4.64 times more likely to have elevated CRP levels than those who were taking drugs regularly.

Inflammatory responses and immune reactions may play a crucial role in the pathogenesis of schizophrenia. Various studies have reported abnormalities of the immune reactions with the implication of blood lymphocyte abnormalities, cytokine alterations, oxidative stress anomalies and CRP elevations in schizophrenia.[16] From a clinical perspective, elevated CRP levels are associated in schizophrenia with some pejorative psychiatric features, high psychotic symptoms and high cognitive impairment though these features were not included in this study but chronic inflammation assessed using CRP in patients with schizophrenia and linked it with the duration of illness.[17]
In a meta-analysis of eight studies, there was a 28% prevalence of an elevated blood CRP level in patients with schizophrenia and related disorders.[14] In 2016 Fernandes et al performed a meta-analysis of 26 cross-sectional or longitudinal studies of CRP. They found a medium-to-large effect size (ES =0.60) for significantly higher blood CRP in patients with schizophrenia vs controls.[15] Three studies have reported on CRP levels in patients with treatment-resistant schizophrenia, and findings suggesting that there is a transient increase in CRP with initiation of clozapine.[16] The meta-analysis included a total of 767 patients with schizophrenia and related disorders and 745 controls. CRP levels were significantly increased in patients compared to controls, with an effect size (ES) of 0.45, 95% confidence interval 0.34-0.55, $p<0.001$.[17]

Conclusions

Accessible biological markers are desperately needed to improve the timing and accuracy of a diagnosis of schizophrenia. These findings provide important support for a pathophysiological role for inflammation in patients with schizophrenia while not strong enough to stand as a predictor of schizophrenia on its own.

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References

1 Perkovic MN, Erjavec GN, Strac DS, Uzun S, Kozumplik O, Pivac N. Theranostic Biomarkers for Schizophrenia. Int J Mol Sci. 2017; 18(4): 733.

2 Johnsen E, Fathian F, Kroken RA, Steen VM6, Jørgensen HA, Gjestad R, et al. The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis. BMC Psychiatry, 2016; 16: 60.

3 Khandaker GM, Dantzer R. Is there a role for immune-to-brain communication in schizophrenia? Psychopharmacology. 2016; 233(9): 1559-1573.

4 Miller BJ, Goldsmith DR. Towards an immunophenotype of schizophrenia: progress, potential mechanisms, and future directions. Neuropsychopharmacology. 2017; 42(1): 299-317.

5 De Picker LJ, Morrens M, Chance SA, Boche D. Microglia and brain plasticity in acute psychosis and schizophrenia illness course: A meta-review. Front Psychiatry. 2017; 8: 238.

6 O'Neill LA. Immunology. How frustration leads to inflammation. Science. 2008; 320(5876): 619-620.

7 Noll R. Historical review: Autointoxication and focal infection theories of dementia praecox. World J Biol Psychiatry. 2004; 5(2): 66-72.

8 Yudofsky SC. Contracting schizophrenia: lessons from the influenza epidemic of 1918-1919. JAMA. 2009; 301(3): 324-326.

9 Müller N, Weidinger E, Leitner B1, Schwarz MJ. The role of inflammation in schizophrenia. Front Neurosci. 2015; 9: 372.

10 Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol. 2018; 9: 754.

11 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001; 286(3): 327-334.

12 Domercq M, Vazquez-Villoldo N, Matute C. Neurotransmitter signaling in the pathophysiology of microglia. Front Cell Neurosci. 2013; 7: 49.

13 Carlsson M, Carlsson A. Schizophrenia: a subcortical neurotransmitter imbalance syndrome? Schizophr Bull. 1990; 16(3): 425-432.

14 Miller BJ, Timonen M, Isohanni M. Cytokine abnormalities, inflammation and psychosis in the northern finland 1966 birth cohort. Eur Psychiatry. 2014. 29: S519.

15 Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry, 2016; 21: 554–564.

16 Carrizo E, Fernández V, Quintero J, Connell L, Rodríguez Z, Mosquera M. Coagulation and inflammation markers during atypical or typical antipsychotic treatment in schizophrenia patients and drug-free first-degree relatives. Schizophr Res. 2008; 103: 83–93.

17 Miller BJ, Culpepper N, Rapaport MH. C-reactive protein levels in schizophrenia: a review and meta-analysis. Clin Schizophr Relat Psychoses. 2014; 7(4): 223-230.

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