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Association of levels of c-reactive protein with positive and negative syndrome scale among patients with schizophrenia

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Abstract

The research was done to explore the "association of levels of CRP with Positive and Negative Syndrome Scale Score (PANSS) among patients of schizophrenia. This Cross-Sectional study comprised of a sample of 310 pre-diagnosed patients with Schizophrenia (diagnosed by psychiatrist as per the DSM V Criteria) of both gender with age range between 18 and 60 years with more than 6 months duration of illness. Patients were taken from Inpatient and Outpatient Department of Sir Cowasjee Jehangir Institute of Psychiatry, Hyderabad, chosen via non-probability consecutive sampling. An anonymous self-structured proforma which contained questions related to basic personal details, and particulars of disease (duration of illness and family history) and PANSS. Range of age in total patients in sample (n= 310) was 18-60 years with mean range of 32.88±8.29 years. The mean PANSS Score was found to be 57.08 ± 11.88. The General Psychopathology Scale Score was found to be 15.16 ± 5.62. The Positive Scale Score was 12.50 ± 3.65 while Negative Scale Score was found to be 29.42 ± 9.62. Raised CRP levels were significantly associated with Negative Symptoms Scale Score. The results of our research study suggest that there is a positive association of raised CRP levels with negative symptoms scales scores of schizophrenia. Future research studies are the need of the time to explore the relationship of inflammation in schizophrenia patients.

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Introduction

Localized markers of immunopathology in peripheral and central nervous system, including expression of cytokines and microglial cell activation, have been linked to different psychiatric disorders like schizophrenia, bipolar affective disorder and major depressive disorders. Experiments on different animal have demonstrated that chronically raised levels of pro-inflammatory cytokines and other biological markers like SNPs (single nucleotide polymorphisms), CRP and Interleukin 6 in brain, which is thought to cause anomalous neural network of the developing brain might also have role in development of psychosis (Kim *et al.*, 2016).

C-Reactive protein (CRP) is an acute phase reactant and non-specific serum marker of inflammation. Raised levels of CRP in blood have been seen in different psychiatric illnesses like schizophrenia, major depressive disorder and drug abuse disorders (Fernandes *et al.*, 2016). Essentially, it has been reported that raised CRP levels in youth is as often as possibly related with consequent development of psychiatric disorders in later adulthood (Metcalf *et al.*, 2017). So also, individuals with history of suicide attempt have also been reported to have raised CRP levels (Courtet *et al.*, 2015).

When tried to study the low grade neuro-inflammation, it was hypothesized to be present in the different psychiatric disorders, which when treated adjunctively with anti-inflammatory agents like minocycline and celecoxib have been studied in several research projects albeit with mixed results (Andrade , 2016; Husain *et al.*, 2020). However, the relationship between inflammation and schizophrenia is still misunderstood but a causal link between schizophrenia and chronic systemic inflammation has been suggested (Inoshita *et al.*, 2016) but not confirmed yet. Furthermore, one study observed a negative correlation between several systemic inflammatory markers i.e., CRP, IL6, and TNF-β and cognitive functioning along with all facets of working memory (Fond *et al.*, 2019) in schizophrenia patients.

Three studies found that schizophrenia patients and higher serum CRP levels were scored higher on severity rating scales of psychotic symptom in comparison to those patients with lower serum CRP levels (Dimitrov *et al.*, 2016). The raised levels of CRP were estimated to be in up to 28% of the patients with schizophrenia (Miller *et al.*, 2014).

Rationale of the study is that although some studies till date have reported the association of raised CRP levels with negative symptoms in schizophrenia patients, but no one has attempted to find relationship of CRP with overall Positive and Negative Syndrome Scale Score (PANSS). This study is aimed to contribute to the literature deficient in evaluating the association between serum CRP levels and positive, negative, general psychopathology, and total psychotic symptoms of schizophrenia among patients with schizophrenia.

The objective of our research is to determine the association between levels of CRP and Positive and Negative Syndrome Scale Score (PANSS) among patients of schizophrenia.

Materials and methods

The design of study is cross-sectional and it was carried out at “Inpatient and Outpatient Department of Sir Cowasjee Jehangir Institute of Psychiatry, Hyderabad and Department of Community Medicine, Gomal Medical College, Dera Ismail Khan from Feb to Aug 2022. Non-probability, consecutive sampling technique was used. A total of 310 (Margin of error: 5%, Confidence level: 95%) cases were studied. This was calculated using Open-Epi sample size calculator, expected prevalence of raised CRP among patients with schizophrenia is taken as 28% (Miller *et al.*, 2014).

After ethical approval of the research (Research Ethics Committee approval letter No. LUMHS/REC/-226), the patients and relatives (if and when the patient is not in a state to answer reliably) were included in the study after evaluating against the eligibility criteria. Data was collected onto a self-

structured proforma which contained questions related to basic personal details, and particulars of disease (duration of illness and family history) and PANSS. After taking informed written consent from the patient or the attendant (if patient is not able to provide consent), 3 cc blood was drawn from each patient for assessing the levels of CRP. Privacy of the patients were kept secret by password protecting and coding the data set instead of using names.

SPSS v. 21.0 Microsoft Excel 2016 was used to analyze data. Qualitative data (gender, socioeconomic status, family history of psychiatric illness and suicide and No. of patients with normal or raised CRP levels) were expressed as number and percentage (No. & %). Quantitative data (CRP level, age, duration of illness, positive, negative and general psychopathology symptom scores) were expressed as mean & standard deviation (X ± SD). Pearson's coefficient was used to check for association between levels of CRP with PANNS score and its sub-scales. P value ≤ 0.05 was considered statistically significant.

Operational definitions

C-reactive protein

It is anti-inflammatory marker which is raised in response to inflammation/infection in the body. The levels of CRP are classified as:

Normal : < 5mg (less than 5 milligram per deciliter of blood)

Raised : > 5mg (more than 5 milligram per deciliter of blood)

Positive and negative syndrome scale score (PANSS)

It is medical scale to measure symptom severity of schizophrenia patients. It is comprised on 7-point Likert type 30 items which are divided into 3 sub-scales, 7 items each in Positive & Negative Symptoms Scale, each having score range from 7 to 49 and 16 items in General Psychopathology Scale, having score range of 16-112 (Santor *et al.*, 2007).

Schizophrenia

DSM-5 defines it as presence of at least two of symptoms in patient with time duration of six months and active one month of patient experience of symptoms in association with occupational and social disorientation. Major symptoms are delusions, hallucinations, disorganized speech and associated symptoms are disorganized behavior, negative symptoms (American Psychiatric Association, 2013).

Inclusion criteria of the sample was as follows.

1. Pre-diagnosed patients with Schizophrenia (diagnosed by psychiatrist as per the DSM V Criteria)
2. Patients with age range between 18 and 60 years with more than 6 months duration of illness
3. Both gender
4. Both drug naïve patients and patients on psychiatric medication will be taken
5. Living with at least one family member who can give reliable history

Similarly, exclusion criteria were as given below.

1. Non-Consenting Patient / Attendant
2. Patients reporting for having fever in last 7 days.
3. Patients with comorbid major chronic medical disorders like Diabetes, Hypertension, and Chronic Liver Disease etc.
4. Patients with comorbid psychiatric illness

Results

Range of age in total patients in sample (n= 310) was 18-60 years with mean range of 32.88±8.29 years. Majority of population was of male gender i.e., 82% (n=254) with mean age 44.78 ± 9.877 years while the mean age of females was found to be 27.24 ± 15.85 years (Fig. 1). The mean duration of illness was recorded 18.92 ± 7.16 years. Most of the patients were of healthy weight i.e., 64.84% while 27.1% of the patients were in overweight group. The mean BMI of the patients was found to be 21.0 ± 3.35 Kg/m^2 (Table 1).

Because of the Public Sector Hospital, most of the patients belonged to lower socioeconomic class i.e., 78.50% (n=243) while around 1/5th of the patients belonged to middle class i.e., 21.50% (n=67). 30% of the patients were non-formally educated while only 12.9% were educated up to primary level, 41% were up to secondary education and while 16.4% had higher education (Table 1).

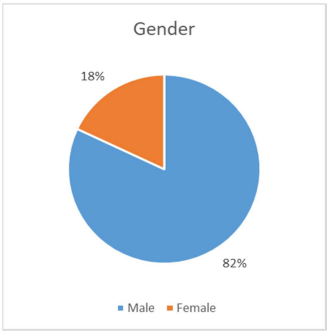

Fig. 1. Gender distribution

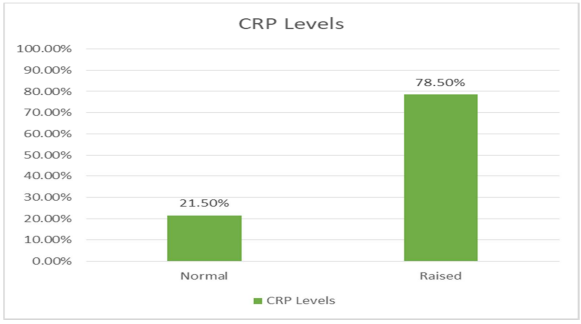

Fig. 2. Status of CRP levels

Table 1. Sociodemographic profile

Socioeconomic status	
Lower Class	243 (78.50%)
Middle Class	67 (21.50%)
Educational status	
Un-Educated	92 (29.7%)
Primary	40 (12.9%)
Secondary	127 (41%)
Higher Education	51 (16.4%)
BMI status	
Underweight	25(8.06 %)
Healthy Weight	201(64.84 %)
Overweight	84(27.1 %)
Total	310(100%)
Mean and S.D	21.0 ± 3.35 Kg/m²
Sample description	
Mean Age of Patients	32.88 ± 8.29 Years
Male	254 (82%)
Female	56 (18%)
Mean Age of Males	44.78 ± 9.877 Years
Mean Age of Females	27.24 ± 15.85 years

Table 2. PANSS score

Variable	Mean ± SD
PANSS Score	57.08 ± 11.88
General Psychopathology Scale Score	15.16 ± 5.62
Positive Scale Score	12.50 ± 3.65
Negative Scale Score	29.42 ± 9.62

When CRP levels were recorded, 243 (78.5%) patients had raised CRP levels while 67 (21.61%) patients had normal CRP levels (Table 3, Fig. 2).

Table 3. PANSS score vs CRP levels

Parameters	Normal CRP (N=67)	Raised CRP (N=243)	*P*- value
Positive scale score	09.76 ± 6.52	14.34 ± 8.37	> 0.05
Negative scale score	18.23 ± 7.54	37.21 ± 16.86	<0.05*

The mean PANSS Score was found to be 57.08 ± 11.88. The General Psychopathology Scale Score was found to be 15.16 ± 5.62. The Positive Scale Score was 12.50 ± 3.65 while Negative Scale Score was found to be 29.42 ± 9.62. Raised CRP levels were significantly associated with Negative Symptoms Scale Score (Table 2, 3).

Discussion

This study is the first attempt to examine the association of serum levels of CRP with the psychopathology profile of schizophrenia. Our research found association of raised serum CRP levels with severe clinical symptoms in patients of schizophrenia which could be assessed from total PANSS score, negative symptom subscale score and general psychopathology subscale score. Findings of this study are in agreement with other related studies according to which schizophrenia activates inflammatory response system (Rapaport *et al.*, 1994; Lin *et al.*, 1998; Maes *et al.*, 2000; Sirota *et al.*, 2005; Müller *et al.*, 2000).

Mechanisms responsible for inflammation in schizophrenia are yet to be understood fully. Some research studies have also linked schizophrenia patients to decreased blood flow in different regions of brain, particularly frontal and temporal lobes (Bachneff *et al.*, 1996; Shinba *et al.*, 2004). Deficient blood supply in frontal lobe of brain is associated with negative symptoms (Lahti *et al.*, 2001; Vaiva *et al.*, 2002). Hanson and Gottesman (2005) on the basis of their results proposed that micro-vascular system in the brain might be damaged due to chronic inflammation which results in disturbance of blood-brain barrier regulation and cerebral blood flow. Such changes in mechanisms of homeostasis of the brain might result in incidence of psychotic symptoms (Hanson and Gottesman, 2005).

Some of the limitations in this research includes small sample size. Apart from it, there are some other significant methodological shortcomings in this study also. First, patients included in this research study were mostly schizophrenia admitted patients which were stable. Admitted patients during their hospital stay were either prescribed antipsychotics or started again with already used antipsychotic drugs, or switched around multiple antipsychotic drugs. This posed difficulty in estimating the influence and duration of a specific antipsychotic medication for all patients. Yet, the inflammatory process and immune function may be affected by different antipsychotic medications (Maes *et al.*, 1995; Akiyama, 1999).

Second, because the design of the research is cross-sectional and sample size is also small in this project, a causal relationship associating levels of serum CRP with severity of psychopathology is still unclear. It is not understood yet whether inflammation is secondary to the pathophysiology of schizophrenia or directly causes schizophrenia (Pollmächer *et al.*, 2000; Song *et al.*, 2005).

More prospective research projects are required to know actual and certain association between inflammation, treatment response, as well as the modifying role of specific antipsychotic drugs in schizophrenia patients. Still, it is too early to propose whether inflammation could be a beneficial or valuable target for new treatment strategies.

Conclusion

The results of our research study suggest that there is a positive association of raised CRP levels with negative symptoms scale score of schizophrenia. Future research studies are the need of the time to explore the relationship of inflammation in schizophrenia patients.

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