CRP and its relation to cognitive performance in schizophrenia patients: a cross-sectional study

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Received: 24 October 2021
Revised: 29 November 2021
Accepted: 20 December 2021
Published: 24 June 2022

Egyptian Journal of Psychiatry 2022, 43:87–93

Background
Schizophrenia (SZ) is one of the most severe and chronic forms of mental illness. It involves cognition, emotion, perception, and behavior. There is an obvious role of neuroinflammation and immunogenetics in SZ. There is a relation between the severity of cognitive deficits and enhanced levels of inflammatory markers in schizophrenic patients, including C-reactive protein (CRP). Also, a relation between CRP and the negative-symptom subscale of Positive and Negative Syndrome Scale (PANSS) was observed.

Aims
To study the relation between CRP level with different cognitive domains in patients with SZ and its relation to the psychopathology of SZ.

Methods
A cross-sectional study was applied on 40 SZ patients and 40 healthy controls, serum CRP was measured, and they were cognitively assessed using Arabic version of Montreal Cognitive Assessment Basic (MoCA-B).

Results
SZ patients showed worse cognitive performance on all subtests (except orientation), MOCA-B, and the total score when compared with normal controls. A negative correlation between executive functions, calculation, abstraction, memory, naming, and attention subtests of MoCA-B and its total score with the serum CRP was found. A positive correlation between CRP and the negative subscale and total score of PANSS was found.

Conclusions
Serum CRP level was elevated in patients with SZ when compared with healthy controls and significantly negatively correlated with cognitive functions, and positively correlated with negative symptoms in SZ patients, which seconds the neuroinflammatory etiology of SZ.

Keywords:
cognition, cognitive disorders, CRP, MoCA-B, psychopathology PANSS, schizophrenia

Egypt J Psychiatr 43:87–93

1110-1105

Introduction

Schizophrenia (SZ) is one of the most severe and chronic forms of mental illness. It involves cognition, emotion, perception, and behavior (Minzenberg *et al.*, 2008). SZ affects nearly 1% of the world's population (Oertel-Knöchel *et al.*, 2011). It is estimated that the number of persons in Egypt with SZ would be within 0.5–1.5 million, with the current population-growth rate, these figures will double in about 40 years and be tenfold in 140 years (Zahran *et al.*, 2006).

Many etiological hypotheses for SZ have been suggested such as the neurodevelopmental, neurodegenerative, immunological, inflammatory, and the infectious hypothesis (Lakhan *et al.*, 2010). There is evidence for the role of neuroinflammation and immunogenetics in SZ, as there is an increase of serum concentration of several proinflammatory cytokines (Potvin *et al.*, 2008; Monji *et al.*, 2009). Also, inflammation has been suggested to play a role in the regulation of cognition in physiological conditions, especially the effect of peripheral and central inflammatory mediators (i.e., cytokines) on learning and memory abilities (Fourrier *et al.*, 2019).

A recent systemic review conducted on SZ patients reported an association between plasma C-reactive protein (CRP) levels and worse cognitive performance, including the domains of attention, memory, and learning abilities (Fourrier *et al.*, 2019). CRP is a pentameric protein that is generated in the liver and secreted in the blood. The

 DOI: 10.4103/ejpsy.ejpsy_44_21

measurement of CRP in the blood provides a reliable marker of chronic inflammation caused by infectious and other inflammatory agents (Dickerson *et al.*, 2013). It is considered to be a risk factor for the cardiovascular diseases, diabetes, and other metabolic dysfunction when elevated in the blood. It is also known to be associated with depression and cognitive impairment (Singh and Chaudhuri, 2014).

There is evident positive correlation between the severity of cognitive deficits and enhanced levels of inflammatory markers in schizophrenic patients, including CRP (Meyer *et al.*, 2011). Several studies were done to investigate the association between the level of CRP and cognitive impairment in patients with SZ.

In a study carried out in Texas involving 39 patients with SZ, a positive correlation was observed between CRP and the Positive and Negative Syndrome Scale (PANSS) negative-symptom subscale, PANSS general psychopathology subscale, and total PANSS score, but there was no correlation between CRP and positive symptoms (Boozalis *et al.*, 2018).

So, from the above-mentioned data, we hypothesized that (a) elevated levels of CRP in SZ patients are associated with worse cognitive performance than in normal controls. (b) High CRP is associated with more severe psychopathology, and accordingly, the aim of our study is to study the relation between CRP level with different cognitive domains in patients with SZ and its relation to the psychopathology of SZ.

Materials and methods

This study is a case–control cross-sectional study and the sample included was a convenient one. It was conducted from October 2019 to March 2020. It consisted of 80 participants divided into two equal groups: patients' group (no.=40 patients) and healthy-control group (no.=40 patients). They were recruited from both the inpatient unit and outpatient clinic of Psychiatry and Addiction Prevention Hospital, Kasr Al-Ainy Hospitals, Faculty of Medicine, Cairo University.

Inclusion criteria included the following: participants were consenting to participate in the research (informed written consent) and their consented data would be used in research purposes, male and female patients aged between 20 and 30 years, diagnosis of SZ meeting the criteria in Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), and can read and write. All were being treated with atypical antipsychotic medications at the time of data collection.

Any patients having acute infections or a primary inflammatory condition such as tuberculosis, current use of corticosteroids or immunosuppressive drugs, having autoimmune disorders such as rheumatoid disorder, any substance abuse or dependence, prior diagnosis of cognitive disorders, clinically significant neurological disorder that would affect cognitive performance such as epilepsy or encephalitis, significant head trauma, clinically below-average intelligence, history of electroconvulsive therapy for the past 3 months, or pregnancy were excluded from the study.

Forty healthy controls were recruited from volunteers working in Kasr Al-Ainy hospitals and matched for age, education, and sociodemographics. The same inclusion and exclusion criteria as the patient group were ensured while recruiting them.

Sample collection and CRP measurement: fresh peripheral blood was collected from all participants by a sterile venipuncture and added to serum-separator vacutainer tubes. Serum samples were freshly separated by centrifugation at 2000 rpm for 10–20 min and kept frozen at −20°C, until the time of the assay. Serum CRP was measured using the quantitative enzyme-linked immunosorbent assay (ELISA) technique by "Human C-Reactive Protein, CRP ELISA Kit; From Chongqing Biopsies Co., Ltd; China" catalog number BYEK1124, according to the manufacturer's instructions.

Patients were clinically interviewed using the clinical sheet of the psychiatry department of Kasr Al-Ainy Hospital, Faculty of Medicine, Cairo University. It was used for collection of sociodemographic variables and detailed clinical history. Also, we used the SZ section of the Structured Clinical Interview for DSM-IV Disorders (First *et al.*, 1997) in its Arabic version (El Missiry *et al.*, 2004) to confirm the diagnosis. Patients' group was subjected to PANSS (Kay *et al.*, 1987), which consists of positive, negative, and general psychopathlogy subscales.

In addition, the Arabic version of Montreal Cognitive Assessment Basic (MoCA-B) was used to assess six cognitive domains: visual perception (superimposed objects), executive functioning (simplified alternating trail making, word similarity, and problem solving),

language (fruit fluency and animal naming), attention (modified digit Stroop), memory (five-word delayed recall), and orientation (time and place) (Saleh *et al.*, 2019). It was published in the official website of Montreal Cognitive Examinations in May 2016 (http://www.mocatest.org) and the use of this test in patients with SZ was tested before (Fisekovic *et al.*, 2012; Yang *et al.*, 2018).

The Arabic version of the General Health Questionnaire-12 (Daradkeh *et al.*, 2001) was applied to the control group to exclude the presence of any psychiatric illness. It is a self-report instrument for the detection of mental disorders in the community.

Statistical analysis: data were summarized using mean and SD in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using parametric *t*-tests for continuous variables and were expressed as mean ±SD and the nonparametric test Mann–Whitney test. For comparing categorical data, χ^2 test was performed. Correlations were done using Spearman correlation coefficient. *P* values less than 0.05 were considered as statistically significant.

Ethical approval: the research ethics committee (REC) of Faculty of Medicine, Cairo University, has approved the study protocol in August 2019 with code no.: MS-146-2019.

Results

Demographic data and clinical characteristics of patients and controls groups are summarized in Table 1. There was a significant difference between the two groups as regards working, marital status, smoking, and serum CRP level. The duration of illness ranged from 1 year to 11 years with a mean of 5.01 years (±2.79).

Table 2 shows the patient scores (expressed as mean and ±S.D.) on general psychopathology subscale, positive subscale, negative subscale, and total score of PANSS.

When we compared the patients' group with controls, the former showed worse cognitive performance on all subtests (except orientation) of MOCA-B and the total score as shown in Table 3.

Then, we correlated serum CRP level with PANSS scores and there was a positive statistically significant correlation with the negative subscale of PANSS and the total PANSS score as shown in Table 4.

In addition, there were statistically significant negative correlations between executive functions, calculation,

Table 1 Characteristics of the participants

Demographic and clinical variables	Patient group	Control group	*P* value
Mean age±SD	26.50 ±3.23	27.40±2.18	0.393
Sex			
Male, *n* (%)	29 (72.5%)	24 (60%)	0.237
Female, *n* (%)	11 (27.5%)	16 (40%)	
Education			
Primary school	4 (10%)	0 (0.0%)	0.144
Preparatory school	4 (10%)	2 (5%)	
High school	14 (35%)	19 (47.5%)	
University graduate	18 (45%)	19 (47.5%)	
Occupation			
Working	6 (15%)	40 (100%)	<0.001
Not working	34 (85.0%)	0 (0.0%)	
Marital status			
Married	3 (7.5%)	20 (50.0%)	<0.001
Single	33 (82.5%)	20 (50.0)	
Divorced	4 (10.0%)	0 (0.0%)	
Smoking			
Yes	22 (55%)	7 (17.5%)	<0.001
No	18 (45%)	33 (82.5%)	
CRP	8.26±5.22	3.82±1.93	<0.001

CRP, C-reactive protein.

Table 2 Scores of patients' group on PANSS

	Patients' group	
PANSS	Mean	SD
General psychopathology	39.60	6.12
Positive subscale	25.98	5.96
Negative subscale	20.93	6.55
Total PANSS	86.38	14.97

PANSS, Positive and Negative Syndrome Scale.

Table 3 Comparison between both groups as regards MOCA-B subtests and total score

	Patients		Controls		
	Mean	SD	Mean	SD	*P* value
Executive functions	0.48	0.51	0.88	0.33	<0.001
Verbal fluency	1.18	0.59	1.75	0.44	<0.001
Orientation	5.70	0.46	5.82	0.38	0.194
Calculation	2.40	0.90	2.98	0.16	<0.001
Abstraction	2.05	1.04	2.83	0.45	<0.001
Memory	2.88	1.44	3.98	0.86	<0.001
Visuospatial	2.50	0.75	2.95	0.22	<0.001
Naming	3.60	0.74	3.95	0.22	0.006
Attention	1.98	1.07	2.75	0.54	<0.001
Total MoCA-B	22.75	4.58	28.08	1.40	<0.001

MoCA-B, Arabic version of Montreal Cognitive Assessment Basic.

abstraction, memory, naming, and attention subtests of MoCA-B and its total score with the serum CRP level as shown in Table 4. This means that patients who have high serum CRP levels showed poorer performance on assessment of these cognitive domains.

Finally, by multivariate linear regression with total MOCA as the dependent variable and duration of illness, age, sex, smoking, and CRP as independent predictors, we found that there was a significant inverse relation between MoCA-B and CRP after adjustment for the duration of illness, age, sex, and smoking as possible confounders.

Discussion

To our knowledge, this is considered to be the first study in Egypt that investigated the relation between serum CRP with different cognitive domains using MoCA-B, all with the severity of symptoms in a sample of patients suffering from SZ.

The mean duration of illness was 5.01 years as we aimed to limit the age of patients between 20 and 30 years to reduce the confounding effects of aging and duration of illness on the cognitive functions. It was taken into consideration that tests of memory performance and executive functioning have been found to show decline beyond the age of 50 (Horning and Davis, 2012). Also, longer duration of illness was associated with memory deficits (visual, auditory, and verbal), executive function, motor, and processing-speed deficits (Sponheim *et al*., 2010).

A higher serum CRP was among the patients' group when compared with the controls, these results were consistent with multiple previous studies. One study stated that patients with SZ, when compared with healthy controls, showed higher serum CRP levels together with higher CD4+/CD8+ ratio and lymphocytes with morphological abnormalities (Mazzarello *et al*., 2004). Solanki *et al*. (2009) and Mazzarello *et al*., (2004) concluded that patients with SZ had significantly higher serum CRP level when compared with healthy controls. Similar results (Solanki *et al*., 2009) also suggested that the elevated CRP may act as a causal risk for SZ. Two meta-analysis studies were previously done to verify whether serum CRP levels are indeed increased in SZ and they stated that patients with SZ showed higher serum CRP levels than healthy controls (Miller *et al*., 2013; Fernandes *et al*., 2016).

So, the presence of CRP is probably state-dependent expression of nonspecific humoral immune alteration in schizophrenic patients (Ohaer *et al*., 1993) and these findings support the notion that there is a possible neuroinflammatory etiology in SZ (Fourrier *et al*., 2019).

Cognitive functions were assessed using MoCA-B, its use to assess cognitive functions in SZ was validated in previous studies (Yang *et al*., 2018; Gil-Berrozpe *et al*., 2020). Patients' group showed poorer cognitive performance than controls as regards executive functions, verbal fluency, calculation, abstraction, memory, visuospatial abilities, naming, and attention subtests of MoCA-B. These results are concordant to the results of the meta-analysis conducted by Fioravanti *et al*. (2012), which assessed cognitive functioning in SZ and showed a statistically significant poorer performance than controls on tests applied to assess attention and executive functions.

The calculation and naming subtests of MoCA-B were considered as parts of the executive functions as evidenced by the Modified Six Elements Test used to assess executive functions and contain subtests for simple arithmetic and simple naming functions (Liu *et al*., 2011)

Abstraction is also considered as a dimension of executive functions and is assessed with a proverb test as a part of Delis–Kaplan Executive Function System in a previous study (Savla *et al*., 2012) and also assessed with word similarities (Akbar *et al*., 2019) as in MoCA-B. So, in the present study, executive functions were found to be the most commonly observed cognitive deficits in SZ patients as in Orellana and Slachevsky (2013).

Verbal fluency was less in the SZ group than in the control group. This is consistent with a Brazilian study that enrolled 141 patients with SZ and 119 healthy controls, the results showed deficits in verbal fluency in the SZ group where they generated fewer total words than the controls (Berberian *et al*., 2016), and this could be explained by the poverty of speech as one of the negative symptoms in SZ. Brébion *et al*. (2013) stated that verbal-fluency deficit in patients with SZ was found to be associated with more negative symptoms and attention disorders.

Memory when assessed by the memory subtest of MoCA-B was worse in the SZ group than in the control one. This was consistent with a meta-analysis study (Aleman *et al*., 1999), which showed a

Table 4 Correlation between serum CRP level with PANSS scores, MoCA-B subtests, and total score

	Correlation coefficient	*P* value
General psychopathology	0.062	0.702
Positive subscale	0.166	0.307
Negative subscale	0.467	0.002*
Total PANSS	0.354	0.025*
Executive functions	−0.349	0.020*
Verbal fluency	−0.155	0.341
Orientation	−0.232	0.148
Calculation	−0.367	0.020
Abstraction	−0.586	<0.001*
Memory	−0.448	0.004*
Visuospatial	−0.261	0.104
Naming	−0.458	0.003*
Attention	−0.468	0.002*
Total score	−0.693	<0.001*

CRP, C-reactive protein; MoCA-B, Arabic version of Montreal Cognitive Assessment Basic; PANSS, Positive and Negative Syndrome Scale.

significant memory impairment in SZ and it was not affected by age, medication, duration of illness, patient status, and severity of psychopathology.

Visuospatial abilities were also statistically significantly lower in patients with SZ than in controls, which was consistent with a Greece study conducted on 70 patients with SZ and 42 healthy controls and underwent a battery of neuropsychological tests, including a test for visuospatial abilities. Increased difficulties in visuospatial abilities were detected (Bozikas *et al.*, 2006).

Attention subtest of MoCA-B was statistically significant lower in patients' group when compared with the controls. This is consistent with a study in which 48 patients with SZ and 48 healthy controls were enrolled and underwent the Stroop Coloured Word Test (SCWT), the Digit Vigilance Test (DVT), the Symbol Digit Modalities Test (SDMT), the Backward Digit Span Test, and the Colour Trails Test to assess selective attention, sustained attention, switching attention, and attentional-control processing. The results of the mentioned study showed that patients with SZ performed poorer on SCWT, DVT, and SDMT relative to healthy controls (Chan *et al.*, 2004).

As regards the statistically negative correlation between the serum CRP level and the MoCA-B total score and its subtest scores for executive functions, calculation, abstraction, memory, naming, and attention could be understood by the higher levels of serum CRP that was associated with dysexecutive syndrome and a cerebral microstructure disintegration in frontal pathways (Wersching *et al.*, 2010; Fraguas *et al.*, 2014).

These findings were consistent with Misiak *et al.* (2018), who conducted a systematic review to investigate the association between peripheral levels of cytokines and CRP and cognition in patients with SZ and bipolar disorder, the study showed that most consistent results indicate worse cognitive performance in SZ patients with higher CRP levels. Our findings were also in line with multiple earlier studies (Diyanoosh *et al.*, 2012; Bulzacka *et al.*, 2016). In contrast, these results were inconsistent with Joseph *et al.* (2015), who concluded that there was no correlation between serum CRP level and cognitive impairment. This might be due to the inclusion of executive functions only in the cognitive assessment in the later study.

There was a statistically significant negative correlation between the serum CRP levels and the negative subscale of PANSS and the total PANSS score. However, no significant correlation was found between the serum CRP levels and the positive and general psychopathology subscales of PANSS. These findings were partially consistent with Fan *et al.* (2007) and Boozalis *et al.* (2018), who showed that there was a significant correlation between serum CRP levels and negative and general psychopathology subscales. Another study showed that serum CRP levels were associated with more severe psychopathology represented by higher PANSS scores (Fawzi *et al.*, 2011).

Our findings were inconsistent with other studies that found no correlation between serum CRP levels and PANSS scores (Faugere *et al.*, 2015; Fernandes *et al.*, 2016). One of these studies showed that the extent of the increase in peripheral CRP levels paralleled the increase in the severity of positive symptoms, but was unrelated to the severity of negative symptoms, these inconsistencies might be due to the huge differences regarding the sample size between the studies. It might also be due to differences in the sex distribution, duration of untreated illness, and the use of medications and inclusion of untreated patients such as the study conducted by Fernandes *et al.* (2016).

By using multivariate linear regression, we found that there was a significant inverse relation between MoCA-B and CRP after adjustment for the duration of illness, age, sex, and smoking as possible confounders, which seconds the effect of inflammation

that might be related to cognitive deficits in SZ (Misiak *et al.*, 2018).

Conclusions

To sum up, our research is the first study in Egypt that investigated the relation between serum CRP with different cognitive domains using MoCA-B and with the severity of symptoms in a sample of patients suffering from SZ.

Serum CRP level was elevated in patients with SZ when compared with healthy controls and significantly negatively correlated to cognitive functions and positively correlated with negative symptoms in SZ patients, which seconds the neuroinflammatory etiology of SZ. Altogether, with the literature, we suggest that abnormal CRP may be considered as a peripheral biomarker of cognitive impairment in SZ.

Being a cross-sectional study makes it one of the limitations that hindered us to determine the cause-and-effect relationship. Also, multicenter studies with larger sample sizes are also recommended to demonstrate generalizability of our current findings.

Finally, longitudinal studies are necessarily needed to assess the change in cognitive functions in patients with SZ across the course of their illness and studying their correlation with serum CRP levels at various intervals and to assess the role of anti-inflammatory treatment in amelioration of the various symptoms of SZ.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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