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Research Article

Pro-Inflammatory and Diagnostic Roles of Serum Amyloid A and C-reactive protein in Schizophrenia

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ABSTRACT

Schizophrenia is a chronic and severe disorder of the mind which affects a person's way of thinking, acting, expressing emotions, perceiving reality, and being related to others. C-reactive protein (CRP) and Serum Amyloid A (SAA) are acute-phase proteins that play critical roles in inflammatory processes and the body's response to infection. SAA is an apolipoprotein in the body that is linked to high-density lipoprotein (HDL). This study looks at the pro-inflammatory role of CRP and SAA as acute-phase protein biomarkers in schizophrenia patients. A total of 70 subjects participated in this study, including 40 schizophrenic patients and 30 apparently healthy individuals with no symptoms of schizophrenia. Serum level of lipid profile was determined using standard spectrophotometric method while SAA and CRP were determined using enzyme-linked immune sorbent assay (ELISA). In schizophrenic subjects, mean total cholesterol (TCHOL), triglyceride (TRIG), HDL, SAA, and CRP levels were significantly higher ($p<0.05$) than in the control group. At the same time, LDL was significantly lower. Under the ROC curve, SAA diagnostic efficiency was shown to be better than CRP. It was observed that SAA and CRP are sensitive markers of inflammation and acute phase reactants in schizophrenia patients, with SAA being a better predictor of a schizophrenia diagnosis.

Keywords: *schizophrenia, depression, inflammation, acute phase reactants, dyslipidaemia*

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INTRODUCTION

Delusions, hallucinations, disordered thinking, social withdrawal, and apathy are all symptoms of schizophrenia. The diagnosis is made based on observed behavior, the person's reported experiences, and the opinions of others who know them (Gonzalez-Liencres *et al*., 2014; Atere *et al*., 2018). Anxiety, depression, and substance abuse are all common mental health issues in people with schizophrenia. Environmental and genetic factors play a role in developing schizophrenia (Opler *et al*., 2013). Growing up in town, adolescent cannabis use, some infections, age of a parent, and poor pregnancy nutrition are all possible environmental factors (Walton *et al*., 2018).

Schizophrenia affects about 0.3% to 0.7% of people at some point in their lives (Shetty and Bose, 2014). In 2017, an estimated 1.1 million new cases were reported, bringing the total number of cases to 19.8 million globally. It is more likely that men are affected, and on average, it starts at a younger age. About 20% of people recover completely, and a few others do well (Borgwardt *et al*., 2013; Ogbonna *et al*., 2019). Depression is commonly caused by social issues such as long-term unemployment, poverty, gender inequality, and homelessness (Patel *et al*., 1995; Ademola *et al*., 2019; Olaseni *et al*., 2020). People with the disorder have a life expectancy of 10–25 years less than the general population. This is due to an increase in physical health issues and a higher suicide rate (around 5%) (Buckley *et al*., 2009; Umar *et al*., 2018; Adeyemo *et al*., 2020).

C-reactive protein (CRP) is a ring-shaped pentameric protein found in blood plasma whose levels rise in response to inflammation. It is the acute hepatic protein released into the blood within a few hours of tissue damage, the start of an infection or another cause of inflammation after macrophages and the T cells secrete interleukin-6 (Laursen *et al*., 2012; Morgan *et al*. 2014; Contreras-Zentella *et al*., 2016). Another acute-phase protein (APP) that has recently been studied is serum amyloid A (SAA). It plays an important role in the inflammatory process and can cause neutrophils to secrete IL-8 (Sproston and Ashworth, 2018). SAA is an apolipoprotein found in plasma linked to high-density lipoproteins (HDL) (Overgaard *et al*., 2013; Wilson *et al*., 2018). SAA levels can increase by 1000-fold during acute inflammation, and SAA displaces apolipoprotein A-I from HDL, becoming the major

apolipoprotein of circulating HDL-3. The role of SAA in inflammatory defense is unknown, but it has been linked to cholesterol binding, leukocyte chemotaxis, immunomodulatory activity, and opsonization, among other things (Ko *et al*., 2016; Wilson *et al*., 2018).

Schizophrenia is a complex illness linked to genetic, environmental, and epigenetic factors (Fagiolini *et al*., 2013). On the other hand, psychiatric disorders appear to be linked to a chronic inflammatory state at the level of specific cerebral areas, which have been discovered to be impaired and responsible for schizophrenia symptomatology (Moelants *et al*., 2013; Upthegrove and Khandaker, 2020; Kilic *et al*., 2021). Inflammatory mediators and cytokines have well-defined roles in some medical conditions, but little is known about acute inflammatory phase proteins like CRP and SSA in the management of mentally challenged patients. The goal of this research is to close the knowledge gap in the medical and scientific communities.

MATERIALS AND METHODS

Study Design: This is a comparative cross sectional study. After an informed consent from each participant and an ethical approval with registration number ERC/2018/04/04/116B was obtained from the Federal Teaching Hospital, Ido-Ekiti (FTHI), Forty (40) schizophrenia patients and thirty (30) age and sex matched controls were recruited into this study. All the participants were aged 18-65years. The schizophrenic patients were recruited from the psychiatric clinic of FTHI, while the control groups were members of the staff of the hospital who have no symptoms of schizophrenia. The schizophrenia group was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-4TR) by clinically trained and experienced psychiatrists. A trained psychiatrist administered the Positive and Negative Syndrome Scale (PANSS) and recorded scores appropriately. PANSS is a medical scale used for measuring symptom severity of patients with schizophrenia (Stefanović *et al.*, 2015).

Inclusion Criteria (Cases and Control): Participants in the study had to give informed consent, meet PANSS criteria for schizophrenia diagnosis, have positive and negative scales were ≤ 7 x ≥ 49 (Schizophrenia), and be between the ages of 18 and 65. Control participants were 18 to 65 years old and had a PANSS scale score of less than 7 (non-schizophrenia).

Exclusion Criteria (Case and Control)
Geriatric subjects (> 65 years), subjects under the age of 18, subjects taking nonsteroidal anti-inflammatory agents, steroids, antidepressants, antipsychotic medications, and anti-convulsants 3 weeks prior to presentation, subjects with a previous history of mania or hypomania, or any concurrent psychotic symptoms, subjects with pregnancy, presence of serious and/or unstable medical disorders, and subjects with a history of mania or hypomania, Addison's disease, Cushing's disease or thyroid diseases or diabetic and hypertensive subjects were all excluded from the study.

Sampling Techniques and Storage of Samples: Five milliliters (5 ml) of venous blood was collected from each patient using an aseptic procedure. The sample was dispensed in the corresponding bottle for each of the parameters to be analyzed. Each sample was spun for 5 minutes at 4000 rpm to obtain serum, which was then stored at -20^0C until analysis.

Analytical Methods: Serum level of Total cholesterol (TCHOL), Triglyceride (TRIG), High density lipoprotein (HDL) and Low density lipoprotein (LDH) were determined by standard enzymatic methods as described by Atere *et al*. (2020) using reagents supplied by Randox Laboratories Ltd. (UK). Serum level of SAA and CRP were determined using sandwich enzyme linked-immuno-sorbent Assay (ELISA) obtained from Melsin Medical Comapany, USA as described by Johnson *et al*. (1999).

Statistical Analysis
For the analysis of data, a Social Science Statistical Package (SPSS) v.23.0 was used. The Student's t-test was used to compare the groups. The association between variables among schizophrenic subjects was tested using a correlation. For all quantitative values, mean±standard deviation (mean±SD) was used to present the data. A graphical plot of sensitivity (receiver operating curve, ROC) of SAA and CRP was compared using pair-wise comparison. 95% confidence interval was used to determine the significance level, and p values less than or equal to 0.05 were considered significant.

RESULTS

When the mean of all the parameters was compared between the case and control groups using an independent t-test, the mean TRIG, SAA, and CRP were significantly higher in schizophrenic subjects than in the control group, while LDL was lower but not statistically significantly lower (Table 1).

Table 1:
Comparison of Biochemical Parameters between Schizophrenic Subjects and Control Group Using Independent Student t-test

Parameters	Schizophrenic Subjects (n=40)	Control group (n=30)	P-value
TCHOL (mmol/L)	4.20±0.92	3.83±0.89	0.092
TRIG (mmol/L)	1.76±0.56	1.32±0.32	0.000*
HDL (mmol/L)	1.88±0.60	1.62±0.60	0.067
LDL (mmol/L)	1.52±0.53	1.61±0.34	0.405
SAA (µg/ml)	18.60±11.72	8.79±2.60	0.000*
CRP (µg/ml)	1.27±0.32	1.07±0.11	0.002*

**Significant at p≤0.05*
Keys: n= sample size, TCHOL= total cholesterol, TRIG= triglycerides, HDL= high density lipoprotein, LDL= Low density lipoprotein, SAA= serum amyloid A, CRP= C-reactive protein

Table 2:
Comparison of Mean of all Parameters among Schizophrenic Subjects based on gender using Independent student t-test

Gender	Male (n=24)	Female (n=16)	P-value

TCHOL (mmol/L)	4.33±0.89	4.01±0.92	0.298
HDL (mmol/L)	1.92±0.57	1.83±0.65	0.671
LDL (mmol/L)	1.56±0.57	1.45±0.49	0.510
SAA (µg/ml)	15.94±7.71	22.59±15.42	0.078
CRP (µg/ml)	1.28±0.33	1.27±0.32	0.925

**Significant at p≤0.05*

Keys: n= sample size, T.CHOL= total cholesterol, TRIG= triglycerides, HDL= high density lipoprotein, LDL= Low density lipoprotein, SAA= serum amyloid A, CRP= C-reactive protein

Furthermore, when the female and male groups of schizophrenic subjects were compared using an independent t-test, there was no significant difference in all of the parameters, as shown in table 2. CRP and SAA were correlated with other parameters in case subjects using correlation analysis. Even though the correlations were not statistically significant, CRP and SAA showed a positive correlation with HDL but a negative correlation with LDL (Figure 1). SAA and CRP were also tested for diagnostic performance. SAA had a better area under the ROC curve (AUROC) of 0.836 than CRP, which had an AUROC of 0.747 (Figure 2).

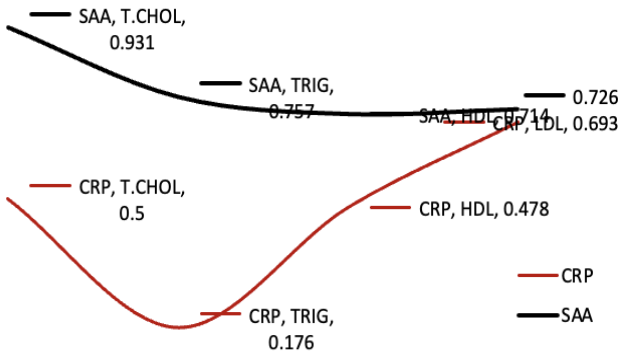

Figure 1:
Line graph showing correlation between CRP, SAA and atherogenic indices.

DISCUSSION

When the mean of all the indices was compared between the case and control groups using an independent t-test, the mean TRIG, SAA, and CRP were significantly higher in schizophrenic subjects than in the control group, while LDL was lower but not statistically significantly lower (Table 1). C-Reactive Proteins and Serum Amyloid A are acute phase proteins that play an important role in inflammatory processes and the body's response to infection (Stefanović *et al*., 2015; Ko *et al*., 2016). Previous research has found that schizophrenic subjects have higher pro-inflammatory biomarkers like TNFα and CRP (Boll *et al*., 2017; Atere *et al*., 2018; Fond *et al*., 2018). CRP is an acute-phase protein (APP) produced in large amounts by hepatocytes in response to interleukin-6 (IL-6) stimulation during an acute-phase response, which is scientifically reasonable (Vermeire *et al*., 2005; Overgaard *et al*., 2013).

In addition, high levels of lipids were discovered in this study. The pathophysiology of schizophrenia may be impacted by aberrant lipid biology caused by the use of antipsychotic drugs, either alone or in combination. Therefore, the result of antipsychotics and lifestyle factors could be attributed to this dyslipidaemia (Smith *et al*., 2005; Jombo *et al*., 2020). This is in line with Paton *et al*. (2004), who found that patients with schizophrenia have higher dyslipidaemia than the healthy population, despite the fact that the findings of this study show a concurrent increase in both pro-inflammatory markers and HDL.

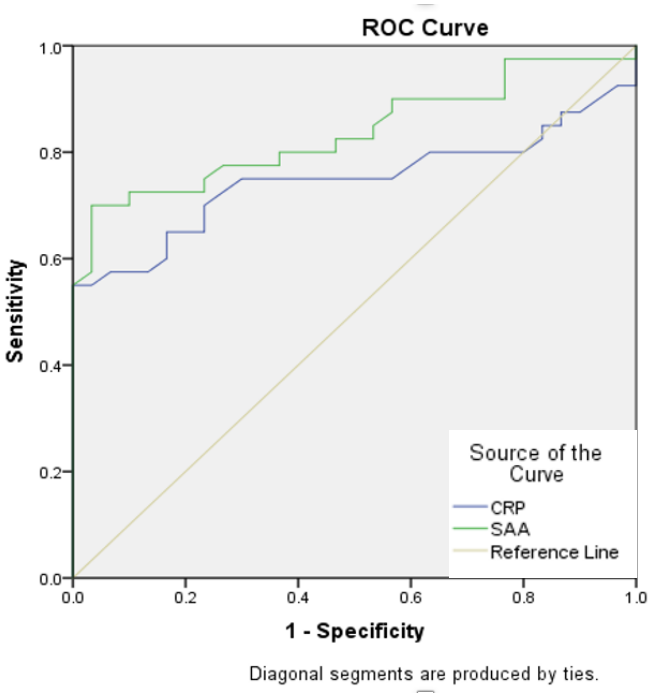

Figure 2:
The ROC Curve of SAA and SAA as diagnostic tool in Schizophrenic subjects

When the mean of all the components (TCHOL, TRIG, HDL, SAA, and CRP) was compared based on gender, no significant differences were found (table 2). Nonetheless, several studies reiterated that women are less likely than men to develop schizophrenia, but women appear to have a better prognosis, social functioning, and treatment response (Ochoa *et al*., 2012; Sommer *et al*., 2020). According to Ochoa *et al*. (2012), one possible explanation is that women have a higher age of onset than men, allowing them to better adapt to the needs of the community. The current study has shown positive and negative correlations between CRP and SAA serum levels, with HDL and LDL, respectively, in schizophrenic subjects (Fig. 1). Toffoli *et al*. (2016) found a positive correlation between APP and HDL, indicating that the inflammatory pathway may play a role. On the other hand, Lim *et al*. (2007) found that chronic inflammation lowers HDL levels in the blood.

The diagnostic performance of SAA and CRP was determined using the area under the ROC curve (AUROC). With an area of 0.836 and 0.747, SAA had a higher AUROC than CRP, respectively (Fig. 2). Although neither SAA nor CRP is specific to any illness, they are both sensitive markers of inflammation that correlate with the severity of inflammation (Calderon and Wener, 2012; Ko *et al*., 2016).

CRP is a non-specific plasma protein marker produced by the liver in both acute and chronic inflammatory conditions as part of the acute-phase response, and it appears to play a role in the immune response to schizophrenia (Roberts *et al.*, 2000; Atere *et al*., 2018).

According to Wang *et al*. (2017), sensitivity analysis revealed that plasma CRP levels were moderately elevated in studies using only high-sensitivity CRP assays. However, when we used AUROC to compare SAA and CRP's diagnostic performance, we discovered that SAA performed better than CRP. As a result, this study demonstrated the diagnostic value of SAA in the treatment of schizophrenia when used in conjunction with other conventional laboratory data, and the estimated technique and cost are both readily available and inexpensive. Incorporating these pro-inflammatory markers with symptoms and other laboratory tests could help predict or monitor schizophrenia treatment, significantly improving schizophrenia management.

In conclusion, SAA and CRP were higher in schizophrenic patients than non-schizophrenic groups as sensitive markers of inflammation and acute phase reactants, despite the fact that they had no significant correlation with atherogenic indices. Furthermore, SAA was found to be a better predictor of schizophrenia diagnosis than CRP. This would significantly improve the care of mentally challenged patients.

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