

## ORIGINAL ARTICLE

# Anti-Streptolysin O (ASO) Antibodies are Elevated in Patients with First Episode Psychosis and Chronic Schizophrenia Compared to Controls

Musa Sahpolat 

Department of Psychiatry, Kilis State Hospital, Kilis, Turkey

## Abstract

**Objectives:** Increasing evidence demonstrates that infections and activated immune system may play a role in the pathogenesis of schizophrenia. In this study, we aimed to investigate the possible relationship between anti-streptolysin O (ASO) antibodies titer and schizophrenia.

**Methods:** This study included 33 patients with first episode psychosis, 42 patients with chronic schizophrenia, and 41 randomly selected age – and gender-matched healthy volunteers. The severity of schizophrenia symptoms in the patients were evaluated using the Positive and Negative Syndrome Scale (PANSS). The enzyme-linked immunosorbent assay (ELISA) method was used to measure ASO titer.

**Results:** Three groups had similar demographic characteristics. The mean ASO titer was  $200.23 \pm 173.14$  IU/ml in patients with first episode psychosis,  $151.66 \pm 128.74$  IU/ml in patients with chronic schizophrenia and  $108.56 \pm 93.67$  IU/ml in healthy controls. According to pairwise comparison; ASO titer of the first episode psychosis and chronic schizophrenia groups were significantly higher than the healthy controls ( $F=4.367$ ,  $p=0.015$ ). There was a statistically significant positive correlation between total PANSS score and ASO titer (the total PANSS score increases with ASO titer) ( $r=0.193$ ,  $p=0.037$ ).

**Conclusion:** To our knowledge, this study is the first study in the literature investigating ASO titer in patients with first episode psychosis and chronic schizophrenia. The findings of our study suggest that there is a relationship between psychosis severity and ASO titer in both patients with first episode psychosis and chronic schizophrenia. Based on these results, streptococcal infections may be related to some central nervous system pathologies such as schizophrenia.

**Keywords:** First Episode Psychosis, Chronic Schizophrenia, Anti-Streptolysin O (ASO) Antibodies

## INTRODUCTION

Schizophrenia is a devastating and complex mental disorder. Both genetic and environmental factors play a key role in the development of schizophrenia. It has been suggested that schizophrenia is caused by disturbances of brain development (1,2). These disturbances can originate from both environment and genetics. However, the etiology of schizophrenia remains unclear although a considerable number of research studies have been conducted. In general, schizophrenia affects about 1% of the total population. The idea that microbial agents

can cause psychotic disorders has a very interesting and lengthy history. Epidemiological, clinical and post-mortem studies report that immune/inflammatory reactions are involved in the mechanisms of affective and schizophrenic spectrum disorders (3-5).

It has been indicated that infections cause an apparent increase in the risk of psychiatric disorders at various time points (during pregnancy, around delivery or later during childhood) by different pathogenetic mechanisms (3,6-9). The immune system can produce autoantibodies that react against the body's own tissue. This can lead to a variety of autoimmune diseases. Some autoantibodies that can cross-react with brain tissue have been associated with psychiatric and neurological disorders (10). The brain is protected by the blood-brain barrier (11). A barrier-compromising insult may be needed in order to induce a syndrome in the central nervous system (CNS) by autoimmune diseases (12). There are various possible insults such as stress,

**Corresponding Author:** Musa Sahpolat

Department of Psychiatry, Kilis State Hospital, Kilis, Turkey.

**E-mail:** drmsahpolat@hotmail.com

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infections and inflammations. Insights that enhance the permeability of this barrier can allow the influx of brain-reactive antibodies or other immune components into the brain (10,12,13). There are several lines of evidence that associate adult-onset psychiatric disorders to autoantibodies (14,15). Some autoimmune diseases have a high prevalence of neuropsychiatric symptoms that are suspected to be caused by brain-reactive autoantibodies (12,16,17).

Increasing evidence demonstrates that infections and activated immune system may play a role in the pathogenesis of schizophrenia. In this study, we aimed to investigate the possible relationship between anti-streptolysin O (ASO) antibodies titer and schizophrenia.

## METHODS

### Participants

This study included 33 patients with first episode psychosis, 42 patients with chronic schizophrenia, and 41 randomly selected age – and gender-matched healthy volunteers. The participants were divided into three groups. The first group consisted of patients with first episode psychosis. The second group consisted of patients with chronic schizophrenia. The third group consisted of healthy controls. The diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition diagnostic criteria for schizophrenia.

For the patient groups, those with any chronic medical conditions (especially the diseases known to play a role in the etiopathogenesis of inflammation were investigated diligently), additional mental health disorders, mental retardation, and organic brain damage were also excluded from the study. For the control group, those with any psychiatric or medical conditions were excluded from the study. For the three groups, those who had any chronic diseases (such as autoimmune and neurological disorders), were under 18 years of age and over 65 years of age, and pregnancy were excluded from the study.

Research ethics approval was obtained from the Ethics Committee of the Medical School of Mustafa Kemal University (2013/169). Written informed consent was obtained from all subjects. Our study was conducted in accordance with the principles of the Declaration of Helsinki. Before enrolling, the relationships between ASO titer and sociodemographic characteristics were examined. ASO titer was compared between the patients and healthy controls. The severity of schizophrenia

symptoms in the patients were evaluated using the Positive and Negative Syndrome Scale (PANSS) (18). Physical and neurological examinations were performed in all participants.

### Blood Collection and Clinical Laboratory Measurements

Venous blood samples were taken from the forearm in the morning (8.00 am) after 12 hours of fasting. Routine psychiatric examination and PANSS assessments were performed on the day of blood collection. For serological assessment, a 2-3 ml venous blood sample was drawn from each subject. Then, serum was separated and measured for ASO titer by an ELISA technique (ASO-ELISA Kit, Norton, UK) as described previously (19). This method provides an inexact figure for low titers of ASO.

### Statistical Analysis

Statistical analysis was performed using NCSS 2007 software (Number Cruncher Statistical System, Kaysville, Utah, USA). Descriptive data were expressed as the mean, standard deviation, frequency, and rate. To compare two groups, the Student's t-test was used for normally distributed quantitative data. To compare three or more groups, the One-Way ANOVA and Bonferroni post-hoc test were used for normally distributed quantitative data. The Pearson's chi-square test was used for comparing qualitative data. The relationships between the variables were assessed by the Pearson and Spearman correlation analyses. P-values below 0.05 were considered statistically significant.

## RESULTS

The three groups had similar demographic characteristics. The demographic and biochemical characteristics are shown in Table 1. White blood cell (WBC) count was  $8.24 \times 10^3/\text{mm}^3$  in patients with first episode psychosis,  $8.07 \times 10^3/\text{mm}^3$  in patients with chronic schizophrenia and  $7.41 \times 10^3/\text{mm}^3$  in healthy controls, respectively. There was no statistically significant difference in WBC count between the three groups ( $F=1.689$ ,  $p=0.189$ ).

The mean ASO titer was  $200.23 \pm 173.14$  IU/ml in patients with first episode psychosis,  $151.66 \pm 128.74$  IU/ml in patients with chronic schizophrenia and  $108.56 \pm 93.67$  IU/ml in healthy controls. According to pairwise comparison; ASO titer of the first episode psychosis and chronic schizophrenia groups were significantly higher than the healthy controls ( $F=4.367$ ,  $p=0.015$ ). There was no statistically significant difference in ASO titer between patients with first episode psychosis and

chronic schizophrenia ( $p>0.05$ ).

There was a statistically significant positive correlation between PANSS total score and ASO titer (PANSS total score increased with ASO titer) ( $r=0.193$ ,  $p=0.037$ ). There was no statistically significant relationship between sociodemographic variables and ASO titer in the three groups ( $p>0.05$ ). ASO titer was not statistically significantly associated with WBC in the three groups ( $p>0.05$ ).

**Table 1.** Comparison of the mean values of study variables in the three groups

| Variables                               | First-episode psychosis group (n=33) | Chronic schizophrenia group (n=42) | Control group (n=41) | Significance                |
|---|--------------------------------------|------------------------------------|----------------------|-----------------------------|
| Age (X± SD)                             | 30.64 ± 11.54                        | 34.50 ± 10.75                      | 29.39 ± 7.46         | $p:0.057$<br>$F:2.939$      |
| WBC count ( $\times 10^3/\text{mm}^3$ ) | 8.24 ± 2.01                          | 8.07 ± 2.25                        | 7.41 ± 1.98          | $p:0.189$<br>$F:1.689$      |
| ASO (IU/ml)                             | 200.23 ± 173.14                      | 151.66 ± 128.74                    | 108.56 ± 93.67       | $p:0.015$<br>$F:4.367$      |
| Total PANSS Score                       | 102.42 ± 18.02                       | 96.02 ± 21.25                      | -                    | $p:0.171$<br>$t:1.382$      |
| Sex (female/male)                       | 13/20                                | 20/22                              | 24/17                | $p:0.254$<br>$\chi^2:2.742$ |

WBC:White blood cell; ASO:Anti-streptolysin O; PANSS:Positive and Negative Syndrome Scale; t:Student-t test;  $\chi^2$ :Pearson's chi-square test; F:One-way ANOVA test; Adjustment for Multiple Comparisons: Bonferroni; \* $p<0.05$

## DISCUSSION

There is limited information on the inflammatory process in psychiatric disorders such as schizophrenia. This study was planned to determine whether there was a significant change in ASO titers of schizophrenic patients without additional comorbid diseases.

Immune system dysregulation has a significant place in the etiopathogenesis of schizophrenia. It is considered that there is a close relation between schizophrenia and autoimmune/inflammatory processes. In particular, there is strong evidence on proinflammatory processes in schizophrenia (20,21). The findings of our study also support this hypothesis.

The most substantial finding in our study is that the mean ASO titer was significantly higher in the first episode psychosis and chronic schizophrenia groups than the control group. We also found that there was a statistically significant positive correlation between PANSS total score and ASO titer (PANSS total score increased with ASO titer).

Several studies revealed that ASO titer was elevated in some psychiatric disorders such as attention deficit hyperactivity disorder (22), pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (23), obsessive compulsive disorder (OCD) (24), tic disorder (25) and Tourette's syndrome (26). Peterson et al. reported that these results were caused by a simultaneous attention deficit hyperactivity syndrome and not by OCD or tic disorder (22). ASO titer has a close relationship with many psychiatric disorders. These studies support finding in our study.

It has also been shown that there is a relationship between no specified childhood meningitis (bacterial and viral) and adult-onset schizophrenia (27). A study from Sao Paulo involving 173 individuals, who had suffered from "epidemic meningitis" during childhood (mainly of bacterial origin), reported that there was a fivefold increase in the prevalence of psychotic disorders (28), but the study has a very high dropout rate. Another study has underlined that there is an association between schizophrenia and immune-inflammatory processes. Benros et al. (29) investigated whether autoimmune diseases combined with exposures to severe infections may increase the risk of schizophrenia. They analyzed data from nationwide population-based Danish registries during the period 1977–2006 and associated individuals with autoimmune diseases and infections with individuals with a diagnosis of schizophrenia spectrum disorder in the Danish Psychiatric Central. They found that the risk of schizophrenia might increase by 29% in case of autoimmune diseases and by 60% in case of infections.

Some studies have revealed that patients with schizophrenia have increased autoantibody reactivity and elevated autoantibody levels (11,30), as well as CNS inflammation and blood-brain barrier dysfunction (31). Sydenham's chorea is characterized by anti-basal ganglia antibodies that react with N-acetyl-beta-D-glucosamine of S.Pyogenes and with lysoganglioside and tubulin of the brain (32,33). This cross-reaction is made possible by a mimicry process (32). Moreover, Cox et al. have recently shown that these antibodies could react with the D2-receptor (D2R) complex (34). It was found that antibodies in children suffering from PANDAS bound more to cholinergic interneurons of mice than control antibodies when mice were infused with patient and control serum in their striatum (35). Considering together, these results appear to overlap the receptor theories involved in the etiology of schizophrenia.

Nevertheless, this study has some limitations. First, this

study is a cross-sectional study with a small sample size. Second, blood samples that were collected only once from patients with first episode psychosis complicated the interpretation and generalization of study results. Third, there were no data relating to the duration of first episode psychosis and chronic schizophrenia in psychotic patients.

In conclusion, to our knowledge, this study is the first study in the literature investigating ASO titer in patients with first episode psychosis and chronic schizophrenia. The findings of our study suggest that there is a relationship between psychosis severity and ASO titer in both patients with first episode psychosis and chronic schizophrenia. Based on these results, streptococcal infections may be related to some central nervous system pathologies such as schizophrenia. However, further large-scale studies are required to establish clear conclusion.

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