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# A Study of Autoantibodies against Some Central Nervous System Antigens and the IL-35 Serum Level in Schizophrenia

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## ABSTRACT

Schizophrenia (SCZ) is a debilitating mental disorder with various causes involving complex interactions between genetic factors and environmental agents. The immune system plays a vital role in the pathology and function of the nervous system. Interleukin 35 (IL-35) is a regulatory and anti-inflammatory cytokine that can prevent autoimmune and inflammatory diseases. This study aimed to investigate the role of autoantibodies against some central nervous system (CNS) antigens and IL-35 serum levels in patients with Schizophrenia.

This case-control study involved 80 participants. The serum levels of IL-35 were measured by enzyme-linked immunosorbent assay and the autoantibodies in the CNS by indirect immunofluorescence assay (IFA).

The serum levels of IL-35 were decreased in patient groups compared to healthy subjects. Autoantibodies against N-methyl-D-aspartate receptor (NMDAR) and myelin-associated glycoprotein (MAG) were positive in 15% (6/40) and 7.5% (3/40), respectively; however, no antibodies against myelin, aquaporin-4 (AQP4), myelin oligodendrocyte glycoprotein (MOG),

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voltage-gated potassium channel (VGKC), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), γ-butyric acid receptor type B1 γ-butyric acid receptor type B1 (GABABR), antidipeptidyl peptidase-like protein-6 (DPPX), immunoglobulin-like cell adhesion molecule 5 (IgLON5), Glycine receptor (R) and acetylcholine receptor (Ach R) were detected (No statistics were computed).

We found that decreased serum IL-35 levels and the existence autoantibodies against NMDAR antigen may contribute to the pathogenesis of SCZ.

**Keywords:** Autoantibodies; Interleukin 35 microglia; Neurogenic inflammation; Schizophrenia

## INTRODUCTION

Schizophrenia (SCZ) is a debilitating mental disorder.[1-3] It's known as one of the leading causes of disability in men and women.[4] The global prevalence of SCZ is between 0.3–0.7% and usually happens in late adolescence and early adulthood.[1-3] Cognitive impairments, thinking problems, behavior disorders, and hallucination are some of the clinical manifestations of SCZ.[5] A definite etiology for SCZ is uncertain still, but genetic, dysfunction of the immune system, and environmental factors (such as infectious agents, season, birthplace, exposure to viruses, low birth weight, high paternal age, tobacco) can affect SCZ progression.[6-8]

Microglia are the most ingredient immune system cell in the central nervous system (CNS) and are known as resident macrophages. About 10 to 20% of CNS immune cells are microglia.[9,10] Disruption of the blood-brain barrier (BBB) is due to microglial activation and cytokine generation. This increases barrier permeability, resulting in some inflammatory molecules, immune cells, and antineuronal autoantibodies in the brain.[11,12] Therefore, microglia activation leads to the formation of autoimmunity and severe synaptic pruning.[13] Lymphocytes are not in the normal cerebral tissue, but in SCZ, their count is increased.[14] Interaction between B lymphocytes and the brain cells can stimulate them and may lead to an inflammation that damages the brain cells.[15,16] Activation of microglia and lymphocytes that result in pro-inflammatory cytokine production (such as IL-1β, IL-6, and TNF-α) play the leading role in the pathophysiology of SCZ.[17-20]

Interleukin-35 (IL-35) is one of the new cytokines that have a regulatory and anti-inflammatory role.[21] In recent years, several studies have reported decreased levels of IL-35 and its autoantibody in autoimmune diseases.[21,22] However, the role of IL-35, as well as autoantibodies in the nervous system in schizophrenia, is not clear. So, this study aimed to evaluate the serum IL-35 level and the frequency of autoantibodies against some CNS antigens such as N-methyl-D-aspartate (NMDA) receptor, myelin oligodendrocyte glycoprotein (MOG), myelin-associated glycoprotein (MAG), myelin, aquaporin-4 (AQP4), voltage-gated potassium channel (VGKC), γ-butyric acid receptor type B1 (GABARB1), antidipeptidyl peptidase-like protein-6 (DPPX), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, immunoglobulin-like cell adhesion molecule 5 (IgLON5), acetylcholine (Ach) receptor and glycine receptor (Gly R) in schizophrenic patients and healthy controls in the nervous system to better understand the pathogenesis of the disease.

## MATERIALS AND METHODS

### Subjects

This was a case-control study conducted in 2021 in Shahrekord, Iran. In this study, a total of 40 patients with schizophrenia (20 female, 20 male) whose illness was confirmed by a psychiatrist based on ICD-10 criteria (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) were recruited. For patients with schizophrenia, symptom severity was assessed on the day of scanning; using the Positive and Negative Syndrome Scale (PANSS).[23] All patients were in the chronic phase of the disease. Healthy subjects did not have any history of neurological problems. Participants with a history of alcohol use, immunosuppressive therapies, infections, and inflammatory diseases, HIV-1/HIV-2, hepatitis A, B, or C, autoimmune diseases such as diabetes type 1, multiple sclerosis, Parkinson's, brain injury, cerebrovascular injury, Alzheimer, and COPD were excluded. After obtaining a written consent form, 5 mL of blood was taken and centrifuged (2500 rpm for 10

minutes). Serums were stored at -80°C. The ethical board of Shahrekord University of Medical Sciences approved this study (IR.SKUMS.REC.1399.205).

**Indirect Immunofluorescence Assay (IFA)**

The frequency of autoantibodies against CNS antigens was evaluated by rats' biochip mosaics of cerebellum tissue (Euroimmun, Germany). When multiple Biochips coated with different substrates are arranged in one reaction field, antibodies against various organs or infectious agents can be investigated simultaneously. Comprehensive antibody profiles can be quickly established (multiplex), and the results are verified reciprocally on different substrates (Euroimmun, Germany).

Diluted samples were added to BIOCHIP slides and incubated in RT for 30 min. After washing, fluorescein-labeled goat antibodies against human IgA, G, and M are used, set for 30 minutes, and then observed by fluorescence microscopy. Classification of samples into positive or negative ways was based on the intensity and immunofluorescence pattern of cerebral tissue.

**Enzyme-linked Immunosorbent Assay (ELISA)**

IL-35 was evaluated by an ELISA kit (ZellBio GmbH, Germany) with intra-assay coefficients of variability (CV) of < 10% and inter-assay CV of<12%. In this assay, we added 40 µL of the sample(s), 10 µL of Biotin-IL-35-Ab, 50 µL of the standards, and 50 µL of Streptavidin-HRP and let them react for 60 minutes at 37℃. After washing, we added 100 µL of chromogen solution and incubated it for 10 minutes at 37°C. Then, 50 µL of the stop solution was added, and the OD was read; using the ELISA reader (Dynex DS2, USA) at 450 nm.

**Statistical Analysis**

The age of patients was indicated as mean±SD. Student t-test was used to compare the age of patients between two groups. The normality of variables was assessed using the Kolmogorov-Smirnov test. The chi-square ($\chi 2$) test or Fisher's exact test was used to compare the frequency of autoantibodies between two groups, and a comparison of IL-35 was performed by an independent-samples t-test. Finally, data were statistically analyzed using SPSS 23 (SPSS Inc., Chicago, IL, USA). A *p*-values≤0.05 were considered to be statistically significant.

## RESULTS

**The Demographic Information**

Forty patients with SCZ (20 males, 20 females; mean age: 40.30±10.09 years; BMI: 23.65±3.32) and 40 healthy subjects (20 males, 20 females; mean age: 40.23±10.23 years; BMI: 22.89±3.23) were included in this study. There were no significant differences in age, gender, BMI, smoking, and alcohol use between the control and schizophrenia patients (Table 1). Other clinical data of patients with schizophrenia showed in Table 1.

**Autoantibodies Against CNS Antigens**

Autoantibodies against NMDAR, MAG, Myelin, AQP4, MOG, VGKC, AMPAR, GABABR, DPPX, IgLON5, Glycine R, and Ach R were evaluated by indirect immunofluorescence assay.

**Table 1. Demographic information of schizophrenia patients and healthy subjects**

| Characteristics | Patients | Controls | *p* |
|---|---|---|---|
| Age (year) | 40.23±10.23 | 40.30±10.09 | 0.974 |
| Gender [male (%)] | 50 | 50 | 1.00 |
| BMI (kg/m2) | 22.89±3.23 | 23.65±3.32 | 0.306 |
| Smoking [Yes, n (%)] | 13 (32.5) | 11 (27.5) | 0.626 |
| Disease status [Chronic, n (%)] | 40 (100) | - | - |
| Duration of the disease | 8.65±4.1 | - | - |
| PANSS-Positive | 16±3.5 | - | - |
| PANSS-Negative | 11.2±2.2 | - | - |

Values are presented as mean ± SD.

PANSS: Positive and Negative Syndrome Scale



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In this method, 9 patients have had a positive pattern (22.5%). Six patients had antibodies against NMDAR with a positive pattern in the Purkinje layer of the cerebellum ($p$=0.026) (Figure 1A). The negative control of NMDAR is shown in Figure 1B. Three patients (7.5%) had antibodies against MAG. These antibodies were seen in the white matter of the cerebellum against myelin sheath ($p$=0.241) (Figure 1C). The negative control of MAG is shown in Figure 1D. There were no antibodies against Myelin, AQP4, MOG, VGKC, AMPAR, GABABR, DPPX, IgLON5, Glycine R, and Ach R in patients. No antibody is detected in healthy controls (Table 2).

**Table 2. Frequency of autoantibodies against central nervous system antigens in schizophrenia patients and healthy subjects**

| Variables | | Case (n=40) | Control (n=40) | *p* |
|---|---|---|---|---|
| NMDAR | Positive [n (%)] | 6 (15) | 0 (0) | 0.026 |
| | Negative [n (%)] | 34 (85) | 40 (100) | |
| MAG | Positive [n (%)] | 3 (7.5) | 0 (0) | 0.241 |
| | Negative [n (%)] | 37 (92.5) | 40 (100) | |
| Glycine R | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| DPPX | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| GABAR | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| AMPAR | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| Ach R | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| VGKC | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| Myelin | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| IgLON5 | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| MOG | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |
| AQP4 | Positive [n (%)] | 0 (0) | 0 (0) | --[a] |
| | Negative [n (%)] | 40 (100) | 40 (100) | |

--[a] No statistics are computed

NMDAR: N-methyl-D-aspartate receptor, MAG: myelin-associated glycoprotein, Gly R: glycine receptor, DPPX: antidipeptidyl peptidase-like protein-6, GABARB1: γ-butyric acid receptor type B1, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors, AchR: acetylcholine receptor, VGKC: voltage-gated potassium channel, IgLON5: immunoglobulin-like cell adhesion molecule 5, MOG: myelin oligodendrocyte glycoprotein, AQP4: aquaporin-4.

**IL-35 Serum Levels**

IL-35 (Interleukin 35) is a main anti-inflammatory cytokine that regulates immune system function. The results of our study showed that serum levels of IL-35 were significantly decreased in patients with schizophrenia compared to healthy individuals ($p$<0.0001) (Figure 2). The fold changes in serum IL-35 levels in schizophrenia patients were 2.24 less than in healthy subjects.

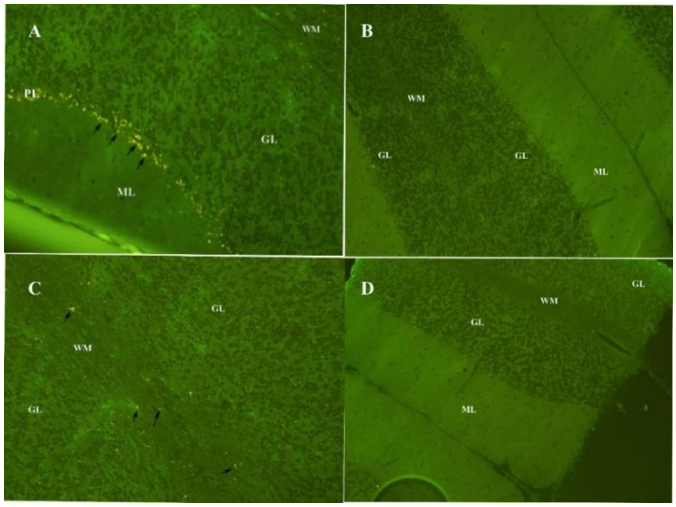
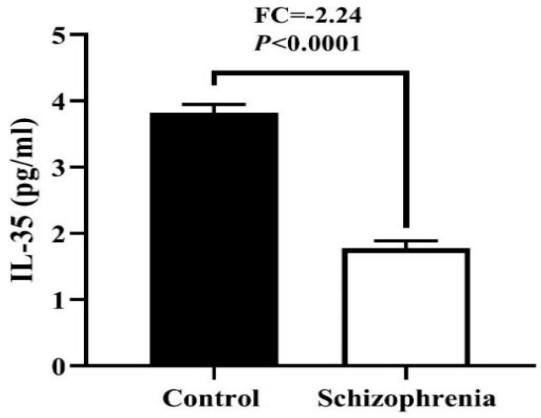



**Figure 1. Our study has indirect immunofluorescence (IF) patterns of auto-antibodies of central nervous system antigens. A: NMDAR positive pattern, Fluorescent- IgGs bind to NMDAR on the postsynaptic membrane of Purkinje layer in the cerebellum (arrows). B: Negative control of NMDAR. C: MAG positive pattern, antibodies bound to MAG on myelin sheath in white matter (arrows). D: Negative control of MAG. (GL: Granular layer, ML: Molecular layer, WM: White matter, PL: Purkinje layer).**

**Figure 2. IL-35 serum levels in patients with SCZ and healthy subjects. IL-35 serum levels in patients with SCZ were**




**significantly lower than the healthy subjects by -2.24-fold ($p$<0.0006). An independent-samples t-test was used to compare the IL-35 concentration between patients with SCZ and healthy subjects. $p$-value≤0.05 was considered a significant value. (FC: fold change; IL-35: Interleukin 35; SCZ: Schizophrenia)**

## DISCUSSION

Schizophrenia is a severe psychological disorder associated with various positive and negative symptoms and cognitive disorders.[24] In schizophrenia, a decrease in the molecules involved in the tight junction (Claudin5, Cadherin5) and an increase in adhesion molecules (ICAM1, VCAM1) can lead to abnormalities

in the BBB and result in the decline in BBB integrity and increased permeability. Following BBB disruption, the immune mediators enter the brain. On the other hand, activated microglia can disrupt BBB function via pro-inflammatory cytokine secretion, including IL-1α, IL-1β, IL-6, and TNF-α.[10,12] So, these cytokines can play a role in the pathophysiology of schizophrenia.[17,25] In addition to microglia, following BBB damage, entry of the peripheral immune system cells (monocytes, macrophages, and T&B lymphocytes) into the brain can mediate more inflammation in the CNS. Brain antigens exposed to B lymphocytes can produce antibodies against them that support the role of autoimmunity in SCZ.[8,19,26]

The main results of this study show a decrease in the serum levels of IL-35 in patient groups compared to healthy subjects. IL-35 is a regulatory and anti-inflammatory cytokine produced by resting and activating Treg cells and Breg cells. This cytokine can inhibit Th1, Th17, and Th2-dependent immunity and enhance Treg and Breg-dependent responses. In addition, it can regulate inflammatory factors and inhibit GATA3 (GATA Binding Protein 3) and IL-4. Also, it can convert Th2 cells to Treg and induce iTreg cell proliferation[21,22,27] IL-35 has been studied in immune-related diseases[22] and psychic patients,[27] but not specifically in schizophrenic patients. A study showed that gene expression levels of IL-35 were significantly lower in depressed patients than in healthy controls.[27] Some studies also reported a decrease in serum levels of IL-35 in rheumatoid arthritis (RA) patients. These authors found that IL-35 enhanced Tregs' suppressive function and suppressed T cells' IL-17 and IFN-γ production.[28,29] Also, decreased IL-35 has been observed in some diseases such as allergic asthmatics and systemic lupus erythematosus (SLE).[30,31]

Elevated inflammatory cytokines such as IL-6 and IL-1 and IL-23 in SCZ can decrease Treg cells (Foxp3) and induce Th17 responses by transcription factor ROR γt.[32,33] Because Treg cells are IL-35-producing cells, a decrease in Treg cells in patients can be one of the possible causes of a reduction of IL-35 in patients with schizophrenia.

Recently, the role of autoimmunity in psychiatric patients has been emphasized.[8,19,26,34,35] The CNS has been considered an immune-privileged organ in which immune cells do not have access to brain antigens. BBB damage can lead to immune response and autoimmune conditions.[12,14,16,36] Therefore, investigation of autoantibodies that react against brain proteins is considerable.

Our results showed autoantibodies against NMDA receptors in 15% of patients (6/40). In schizophrenic patients, one of the most essential antigens targeted by autoantibodies is the NMDA receptor. The NMDA receptor is an ionotropic receptor that plays a central role in synaptic plasticity, memory formation, and CNS function in normal conditions. Its highest density is in the hippocampus and on the surface of the dendritic membrane of Purkinje cells. Impaired memory and learning are symptoms of schizophrenic patients that may be due to hypofunction of NMDA receptors.[37-40] Our results suggested that NMDA receptor autoantibodies can cause clinical symptoms in SCZ. Previous studies[41,42] confirmed our data about NMDA receptor antibodies. Masopost et al, in contrast, showed no autoantibodies against NMDA receptors in patients with first-episode psychosis.[43]

MAG, MOG, and myelin produced by oligodendrocytes contribute to myelin sheath formation. MAG plays an essential role in the development and function of the nervous system, so degenerative disorders are associated with this glycoprotein. In our study, 7.5% of SCZ patients had autoantibodies against MAG. Parshukova et al, reported antibodies against the myelin-based protein (MBP) in schizophrenic patients, consistent with our study. They stated that antibodies against myelin and MAG and myelin sheath degradation could play an important role in CNS diseases such as SCZ and multiple sclerosis.[34]

Chia-Hsiang Chen et al, reported that no autoantibodies against (GABARB1), protein 2-like protein-related protein (AMPAR1,2), leucine-rich glioma inactivated protein-1 in schizophrenic patients.[44] Another study showed no autoantibodies against CNS antigens in psychotic patients.[26] Hoffman et al reported low antibodies against α7AChR in less than 1% of patients.[45] They had suggested that the seroprevalence autoantibodies against neuronal antigens or proteins might be very low in these patients. So, experiments with living cells are more sensitive than with fixed cells. This study detected no antibodies against MOG, myelin, AQP4, VGKC, AMPAR, GABABR, DPPX, IgLON5, Gly R, or AChR. However, some studies have reported conflicting results; this can be due to the low seroprevalence of autoantibodies, different methods of evaluation, and different stages of the disease.

In conclusion, the results of this study showed that the serum level of IL-35 in patients with SCZ was lower than the healthy controls, which may be due to a

decrease in Treg and Breg cells. On the other hand, the destruction of BBB causes immune cells to react with brain antigens, which leads to the production of some autoantibodies that can be involved in the pathophysiology and symptoms of this disease.

Therefore, our findings suggest that decreased serum IL-35 levels and autoantibodies against NMDAR antigen may be involved in the pathogenesis of SCZ.

## CONFLICT OF INTEREST

All authors approved this manuscript. No competing interests were declared.

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