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Serum Immunoglobulin Levels in Schizophrenic Disorders

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Abstract:
Background*: Schizophrenia is regardes as a psychiatric disorder with unknown etiology. Genetic factor, environmental insults and their interactions are purposed etiologies in the disease development. Also there are many studies which discuss about immunologic aspects of schizophrenia.*
Materials and Methods*: The aim of the study was to determine the serum concentrations of immunoglobulins of schizophrenic patients and to find out the relationship between immunoglobulin concentrations and the duration of illness. The study included 134 schizophrenic patients (main group) and 50 healthy subjects (control group). Schizophrenic patients were selected from the Psychiatric Hospital in Skopje. The age and the sex distributions of schizophrenic patients were similar to those of control group. All the patients used adequate neuroleptic drugs. Serum immunoglobulin concentrations were determined by turbidimetry method using immunoglobulin kit.*
Results*: Mean serum IgG, IgM and IgA value was found to be significantly higher in schizophrenic patients compared with controls (p<.01). The concentration of IgM increased significantly (P=.001) in schizophrenic patients while the concentration of IgG (P=.000) and IgA (P=.002) were found to be decreased. A positive relationship was noted in the levels of Immunoglobulins IgA, IgM and IgG and duration of illness*.
Conclusion: *These results demonstrate a definite link between schizophrenic disorders and the immune changes during the illness. The results confirm the immuniological theory of the disease.*
Key Word*: schizophrenia, immune system, immunoglobulin levels, duration of illness, neuroleptic treatment.*

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I. Introduction

Schizophrenia is regarded as a psychotic disorder with unknown etiology characterized as derangements in cognition, perception and expression of reality that can lead to complications such as the lack problems in rational, communication behavior and speech, excessive isolation, withdrawal delirium and hallucinations. The person usually hears voices, see scenes and touch's things that often cannot understand (Van Haremet al., 2008).

The aetiology of schizophrenia has always been one of the most burning topics in psychiatric research. The heterogonous features of this disease have led to different hypothesis and scientific approaches (Vetlugina et al., 2013). Genetic factors, environmental insults and their interactions are purposed aetiologies in the disease development. Surveys show that one of the principle risk factor for schizophrenia is genetic susceptibility and some genes may make people more at risk for this disease (Levy et al., 1995). However, genetics has proven to be the most important, that is supported by findings of twin, family and adoption studies (Hanson & Gottesmain, 2005).

Researchers have focused on the interaction of the central nervous system (CNS) and immune system in patients with schizophrenia over the past three decades such as viral diseases in the foetus which will cause immunity against parts of the brain and increase the risk of schizophrenia (Brasov et al., 2007). In fact, schizophrenia is caused by changes in the immune system and the central nervous system (CNS) to produce antibodies against antigens and can disrupt neuronal function (Barguest & Barguest, 1993; Crow, 1999).

Over viewing the immunological studies a great number of partly contraversional results can be found in the literature. Some authors report on functional and histological abnormalities of lymphocytes as well as on changes in the reactivity of natural killer cells (Rothermundt et al., 2001; Vasileva et al., 2011). Other presented evidence for antiviral antibody titres in serum. Some of these data give hints for very specific immunological alterations in schizophrenia, which may confirm a immunological dysfunction as a possible etiologic cause (Lobachyova, 2011).

New immunological examination techniques have led to numerous interesting observations concerning, the cellular and immunological systems of schizophrenic patients. In schizophrenic patients rise of serum concentration of IgA, IgM and IgG has been reported (Tiwari et al., 1990). A significant higher incidence of

antibodies with affinity for dopamine was found in the group of psychiatric patients compared with healthy control group. Several factories including autoimmune factors have suggested the etiopathology of schizophrenia (Taylor, 2000).Some studies reported that positive emotions produce a significant increase in IgA level and negative emotions are associated with a decrease in the IgA level (Delis et al., 1999). Moe et al. (2003) found that the concentration of immunoglobulin's (IgA, IgM and IgG) was reduced in schizophrenic patients who have been taken narcoleptics for long period of time.

II. Material And Methods

Study objectives

The main objectives of the present study were to investigate the serum immunoglobulin levels of schizophrenic disorder patients and to find the relationship between immunoglobulin, neuroleptic therapy and duration of illness.

Participants

The study group included 134 patients with schizophrenia (67 males and 67 females, mean age 31.5) and 50 healthy controls (25 males and 25 females, mean age 30.5). All patients were recruited from Psychiatric Hospital in Skopje and healthy controls from volunteer's subjects. The clinical diagnosis of schizophrenia was conducted in accordance with DSM-V criteria (American Psychiatric Association, 2013). Before the very inclusion in the research, each respondent was informed about the objective of the research, the procedures during the research were explained to the respondent, as well as the advantages and disadvantages of the respondent's participation in the research. The criteria for inclusion of the respondents included: patients (male/female) diagnosed with schizophrenia according to the criteria of DSM-V; patients diagnosed with schizophrenia from 18 to 60 years of age, patients in the acute stage of schizophrenia without prior antipsychotic therapy, and patients with chronic schizophrenia who had taken neuroleptic drugs. The criteria for exclusion of the respondents included: patients diagnosed with schizophrenia under the age of 18 and patients diagnosed with schizophrenia and a comorbid psychiatric disorder.

In total, 70 patients were admitted to a psychiatric hospital for the first time and have never taken neuroleptic drugs. The other 64 patients had taken psychotropic drugs irregularly during the remission, although proper to entering the hospital. The study samples were filled questionnaires based on age, sex, education level, marital status and duration of illness.

The psychopathological status of the patients was assessed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1976). The BPRS total score was 60(SD=11) on admission and 48(SD=14) on re-examination.

Blood analysis

Five ml venous blood specimen was collected from each of the patients and controls. The blood samples were transported to the Institute of Clinical Biochemistry laboratory where were isolated samples centrifugation (3000 rps, 30 min at 4°C) and stored at -80°C until analysis of immunoglobulins.

The serum immunoglobulins (IgA, IgM and IgG) level in patients and control were determined by immunoturbidimetry method using immunoglobulin kits. In this method anti-human antibodies were mixed with samples confirming IgA, IgM and IgG that formed insoluble antigen-antibody complexes. These complexes caused an absorbance change depending upon the immunoglobulin concentration thus was quantified by a calibrator.

Statistical analysis

SPSS software package (Version 17.0) was used to analysis the data. Descriptive statistics were used to all variables. Comparison of immunoglobulins of schizophrenic patients and controls were performed by one-way ANOVA and Pearson correlations. In this study, the signifiance levels were accepted as .01 or .05.

III. Results

Table 1 shows the general information of the schizophrenic patients and control subjects. It was shown that average age of patients and control groups were (31.5) and (30.5) years respectively. Most of the patients have been married (68.65%) and have finished secondary or higher education (70.15%). In the control group 50.00% of subjects have been married, while 60.00% of them have finished secondary or high education.

Table1. Demographic and clinical characteristics of patients with schizophrenia

Parameter	Patients (N=134)	Mean (SD)	Control (N=50)	Mean (SD)
Gender				
Female	67 (50.00%)		25 (50.00%)	
Male	67 (50.00%)		25 (50.00%)	
Age range	18 - 55	31.5 (6.3)	18 - 50	30.5 (5.9)
Marital status				
Married	92 (68.65%)		25 (50.00%)	
Unmarried	42 (31.35%)		25 (50.00%)	
Education				
Primary	40 (29.85%)		20 (40.00%)	
Secondary	54 (40.30%)		18 (36.00%)	
Higher	40 (29.85%)		12 (24.00%)	
Duration of disease				
Schizophrenia				
First admission:	70 (52.25%)			
Second admission	64 (47.75%)	After 12 months		

Serum immunoglobulin levels are presented in Table 2. Mean valued of serum IgA, IgM and IgG concentrations of patients with schizophrenia were M=1.33 g/L, M=1.73 g/L and M=6.66 g/L while these were M=2.76 g/L, M=1.22 g/L and M=13.34 g/L in control subject respectively.

Table2. Serum immunoglobulin concentrations of schizophrenic patients and controls

Immunoglobulin (g/L)	Patients N=134 Mean (SD)	Control N=50 Mean (SD)	F	p-value
Ig A	1.30 (0.22)	2.76 (0.58)	77.123	.002
Ig M	1.73 (0.76)	1.22 (0.12)	64.213	.001
Ig G	6.66 (0.95)	13.34 (2.47)	101.235	.000

Concentrations of IgA and IgG in schizophrenic patients decreased significantly (p=.002 and p=.001), while the concentration of IgM in schizophrenic patients increase significantly (p=.000) compared with control subjects.

Range and distribution of immunoglobulins in patients compared to healthy subjects are shown in Figure 1. From this figure we can clearly see that schizophrenic patients represent a population in which immunoglobulin levels are shifted upward from normal. As one may expect in such population, there are some valued which lie outside the normal range.

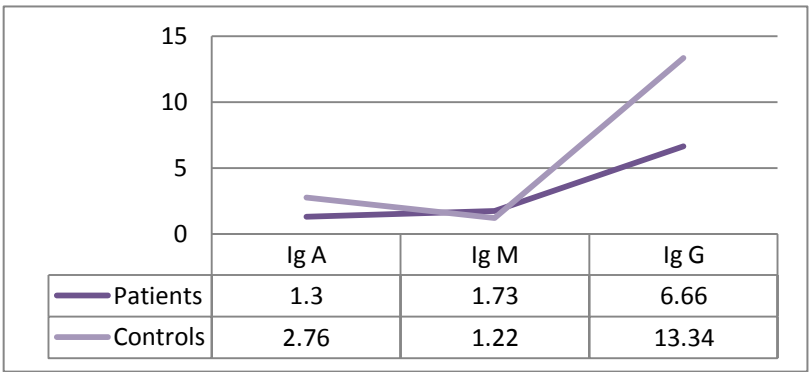

Figure1. Serum immunoglobulin concentrations of schizophrenic patients and controls

In our study we observed that patients in acute phase of schizophrenic disorder had higher concentration of immunoglobulin IgA, IgM and IgG in serum compared with patient group who have taken psychotropic drugs for 12 months (Table 2). As can be seen from this table, there was positive and significant correlation between the level of IgA, IgM, IgG and duration of disease (r=.234, p<.01; r=.314, p<.01 and r=381, p<.01).

Table3. Mean serum immunoglobulin levels according to the duration of psychosis

Immunoglobulin (g/L)	Schizophrenia: First admission (N=70) Mean (SD)	Schizophrenia: Second admission (N=64) Mean (SD)	r
Ig A	1.40 (0.50)	1.18 (0.47)	.234**
Ig M	1.83 (0.84)	0.99 (0.35)	.314**
Ig G	8.49 (1.80)	7.06 (1.03)	.381**

**Correlation is significant at the level 0.01 level

Figure 2 illustrates the overall scores for the level of immunoglobulin IgA, IgM and IgG among schizophrenic patients and neuroleptic treatment. There is an interesting trend, which warrants father investigation for humoral immunity in schizophrenia to rise with psychotrophic treatment.

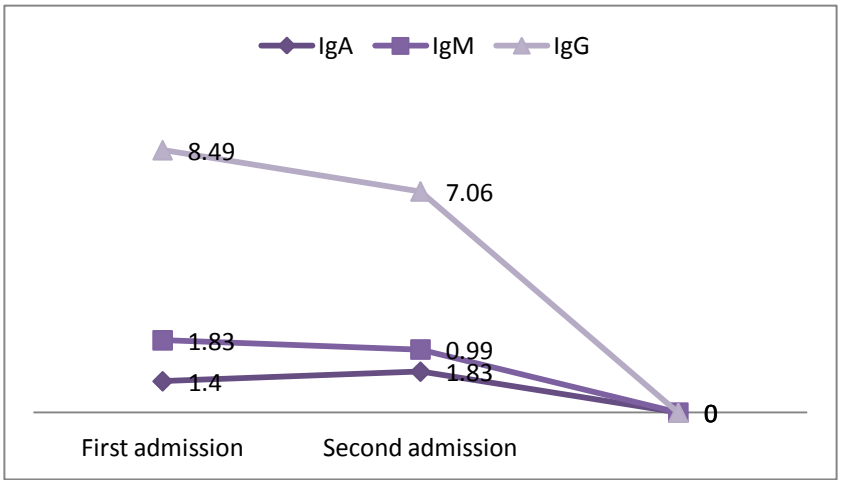

Figure2. Mean serum immunoglobulin levels according to the neuroleptic treatment

IV. Discussion

Although the etiology of altered immunological function in schizophrenia is unknown several possibilities as have been proposed. They include a reaction to viral like substance in some schizophrenic patients (Dickenson et al., 2009), a manifestation of an autoimmune disease (Krause et al, 2010) and the result of pharmacological treatment (Lagos et al., 1985).

The most accessible and extensively studied components of the immune system are the immunoglobulins. Studies of immunoglobulins have produced contradicting findings. Balata and Iscrulescu (2002) demonstrated significantly higher serum IgA and IgM in psychiatric patient group, while the elevation of serum IgA was confirmed by others (Chong Thin & Wing Foe, 1993).

By applying humoral cell-mediated immunological tests, we were able to observe several differences between schizophrenic patients before and during neuroleptic treatment and healthy subjects. The schizophrenic patients in an acute stage of their disease generally showed in comparison with controls a increase level of IgM, but decrease level of IgA and IgG. The neuroleptic treated schizophrenic patients showed in comparison to the acute schizophrenic patients, a significant decrease in their concentration of immunoglobulins. Elevations of immunoglobulins levels in the schizophrenic patients, who have been treated with psychotropic drugs during one year, may be one of the most clinical significance of this research. The low levels of IgG and IgG1 observed here can mark the stable phase of the disease and/or related to the duration of the disease.

In schizophrenic patients, presence of antibodies against central nervous system neurotransmitter such as dopamine, serotonin, cardiolipin, antigens cytoplasmatic and nuclear antigens, has been showed. This finding supported the increase of dopamine. Antibodies against antigens of the central nervous system (CNS), are produced both in normal subjects and patients with schizophrenia, but schizophrenia can cause changes in the central nervous system and one of these brain's antigens, leading for further increase in the amount of the natural antibodies, including IgM (Boas, 2000). Sane et al. (2001) found increasing of IgM and decreasing of IgG in schizophrenic patients who have never been treated with psychotropic medication.

Our results may be consisted with the notion that neuroleptic medication may suppress the immune response. Neurolleptics affect the immune system is supported by several lines of evidence. Antinuclear antibodies have also been associated with long term neuroleptic treatment. It is well documented that neuron target reactions include the exchange of materials which are able to influence the metabolism, genetic expression and viability of target cells. The changes in the target cell, tissue and organ may have profound

effects on neurons in brain and antigen-antibody complexes cross the blood-brain barriers more easily (Leary & McLean, 2002).

V. Conclusion

The present study attempted to show further light on the involvement of the humoral immunological; system in the pathology and course of schizophrenia. Toward this end, we studied schizophrenic patients before they received neuroleptic treatment and schizophrenic patients who showed clinical improvement in response to neuroleptic therapy. In fact several factors such as age, race, sex, diagnostic criteria, duration of disease, hospitalization and drugs influence immunological system (Müller et al., 2015).

The link between the immune reactivity, clinical course and cause of the disease has now been revealed. Based on the analysis of numerous studies the association between schizophrenia with and autoimmune processes was discovered. New immunological examination techniques, have led to numerous interesting observations concerning the humoral, cellular and immunological systems of schizophrenic patients.

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