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Evaluation of the Relationship between Serum Levels of Igg and Igm Immunoglobulins Associated with Toxoplasma Gondii Infectious and the Incidence of Schizophrenia Disease in Schizophrenia Patients Admitted to the Tehran Razi Hospital

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Abstract

Schizophrenia is a disease that known by unknown foundations and main underlie of genetics and environmental factors. Acute infection with Toxoplasma gondii can cause similar psychotic symptoms of schizophrenia so that in adults, serum antibody levels against T. Gondii are associated with changes in behavior and psycho-motor skills. Therefore, the aim of this study was to determine the relationship between the sera level of IgG and IgM immunoglobulins associated with Toxoplasma Gondii infectious and schizophrenia. Accordingly, the subjects of this study were included 84 patients of both genders include male and female who were hospitalized to the Tehran's Razi Hospital based on the diagnosis of schizophrenia and 84 healthy subjects as the control group. the gender, age, marital status and hospitalization history information of all the subjects were obtained by a questionnaire and the sera assayed according to the ELISA kits procedure and by Antibody capture method. The mean of IgG but not IgM immunoglobulins in schizophrenic group was only increased significantly compared to the control groups. Also there is a significant inverse correlation between hospitalization time and level of sera IgG based on the Pearson test but there is no significant difference between the sexes (male and female) in terms of the IgG and IgM antibody level based on Independent T-test. Regarding the results, it can be concluded that the increased mean levels of antibodies against Toxoplasma, reflecting the association of Toxoplasma gondii infection and the incidence of schizophrenia.

Keyword: Schizophrenia, Toxoplasma Gondii Infection, IgG, IgM

Introduction

Schizophrenia has been known as a severe psychiatric disorder that affects the individual's mental functions as well as one of the 20 diseases that have resulted in physical disability in different societies, and this perturbation is known by unknown foundations and main underlie of genetics and environmental factors in along with abnormalities in thinking, temperament, and behavior (Organization, 2014; Khademvatan et al., 2014; Scharko, 2011). according to the reports, the prevalence of schizophrenia is about 1 percent, and if Be considered the Spectrum Disorders of schizophrenia, it will be between 0.6 and 1.9 percent. its prevalence is equal in men and women, but in both sexes the onset and course of the disease are different (Canu et al., 2015). Among the environmental elements, can be noted to infections caused by microorganisms including viruses, bacterial and at least one protozoa (Brown AS, Susser, 2002; Debnath & Chaudhuri, 2006; Yolken & Torrey, 2008). Toxoplasma gondii is a non-genetic agent and a coccidian protozoa from the family of apicomplexa that after enter to the human body especially to pregnant women, parasitic infection can lead to deafness syndrome, retina damage, seizure and mental retardation. Also, in people with the immune system diseases, such as AIDS, may cause symptoms in the CNS (Smit et al., 2017; Hamdani et al., 2015; Arling et al., 2009). In animals, infection with Toxoplasma gondii causes a change in the behavior and function of the nerve. The individual response to Toxoplasma infection is determined by the immune status, host and organism genetic composition as well as the time of infection and disease. It has also been shown that exposure to Toxoplasma influence memory loss and learning and behavioral changes (Torrey et al., 2012). because the toxoplasmosis life cycle in the body of cats and other warm-blooded that known as its definitive hosts is completing. so it can infect humans, and followed by the many kinds of deviations such as abortion, and the ethics and behavior of schizophrenia(Khademvatan et al., 2014; Torrey et al., 2012). Acute infection with Toxoplasma gondii can cause similar psychotic symptoms of schizophrenia Although Its diagnosis due to the lack of non-invasive methods was limited in the past, today via the increasing expansion of diagnostic science, it is possible through complemented tests, such as computer tomography (CT), magnetic resonance imaging (MRI), and anti-toxoplasmosis serum antibody testing(Torrey et al., 2012) In addition, Toxoplasma gondii infection causes the slow activation of glial cells, especially astrocytes also increase the expression of

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indolamine, 2,3-dioxygenase, and Kynurenine, and affect dopamine act as the main neurotransmitter involved in the pathogenesis of schizophrenia in mouse brain (Brown et al., 2004; Leweke et al., 2004; Doyle & Deakin , 2002). on the other hand, numerous drugs that have been found in the treatment of schizophrenia and bipolar disorder are also used to treat Toxoplasma gondii (Jones-Brando et al., 2003). In epidemiological studies, various patterns have been used to determine the relationship between Toxoplasma and schizophrenia. In most studies, the prevalence of Toxoplasma in schizophrenic patients and the control group has been compared (Hamidinejat et al., 2010; Omar et al., 2015). Studies have shown that in adults, serum antibody levels against T. Gondii are associated with changes in behavior and psycho-motor skills {8}. There is numerous serological evidence of Toxoplasma gondii infection in people with schizophrenia disorders (Torrey et al., 2012; Yolken et al., 2001).

People with schizophrenia disorder have been discriminated in the community and are associated with a significant decline in quality of life (Fontanil et al., 2017). The onset of this disease usually occurs in the late adolescence between the ages of 18 and 25 and is characterized by a set of signs and symptoms that include perception, thinking, feeling, cognitive impairment, and communication problems. Also, for a variety of reasons, such as reducing the life expectancy, abnormal lifestyle, conflict with related illnesses, and the risk of suicide, mortality within this group subjects are 20 to 25 times more than usual people (Khademvatan et al., 2014; Santos, 2017). On the other hand, due to the role of Toxoplasma in the development of schizophrenia and the controversial information in this field (Scharko, 2011), further research is essential on the relationship between infection of toxoplasmosis and schizophrenia disorder. Therefore, the aim of this study was to determine the relationship between Toxoplasma gondii infection and schizophrenia by measuring the level of immunoglobulins associated with Toxoplasma infection in Razi Psychiatric Hospital in Tehran.

Methods of Implementation

The subjects of schizophrenia group of this study included 84 patients of both genders include male (n=42) and female (n=42) who were hospitalized to the Tehran's Razi Hospital based on the diagnosis of schizophrenia by a neurologist. The sampling method was randomized so that the subjects of patient group were selected among all patient's hospitalization to the Razi mental hospital. then requested from The families of the subjects to complete the questionnaire containing the information: gender, age, marital status and hospitalization history after signing and confirmation of the consent form. Also, 84 subjects of both gender include male (n=42) and female (n=42) without any history of diabetes, high blood pressure and a specific disease history were selected as the control group. Diagnostic criteria for patients with schizophrenia, including age 20 ≥, the onset of the disease more than at least 1 year, the use of an antipsychotic drug during the study and receive informed consent from the patient or patient's family for the control group were age 20 ≥, receiving informed consent from the subjects, and Exit criteria for the both patient and control subjects include clinical or laboratory findings Suggest a significant neurological or organoleptic disease., mental retardation, dependence or drug abuse (except nicotine and caffeine), high risk of suicide, pregnancy and lactation, Kidney disease, and inability to communicate.

Sampling and Sample Preparation

After receiving the consent form from the subjects, 5 ml of the blood samples collected and then centrifuged at 15 °C for 15 minutes and then stored in -20 °C. The progression of schizophrenia as independent variables and changes in antibody levels against toxoplasma gondii (IgG) and (IgM) in the blood of the subjects were considered as dependent variables {18}.

antibodies level assay

In this study all of the sera assayed according to the ELISA kits (AUTOBIO) procedure and by Antibody capture method. Briefly, patients and controls sera were diluted 1:1 in the kit diluent. After shaking and the end of the incubation period, the plate was washed and the conjugate solution was added and re-shaken and incubated again. The microtiter wells were Rinse again and 50 µl of chromogen solution and 50 µl of the Substrate were added to each microtiter wells and incubated. After the incubation time, 50 µL of stopping solution was added to each microtiter wells and the optical absorption was read at 450 nm and 620 nm or 630 nm as reference filters by using an ELISA.

Data Analysis

For analyzing the data was used to the SPSS software. descriptive statistics were used to assess calculated IgM and IgG antibodies. for check the normality of the data was used the Kolmogorov-Smirnov test (K-S), and to compare the difference between the mean of the groups the one-way ANOVA test was followed by the Tukey test. also to show correlation the Pearson correlation test and independent t-test for comparing the mean of the two groups was used. data is expressed as mean ± SD and probability p-values < 0.05 were considered statistically significant.

Results

The results of measuring the immunoglobulin G (IgG) blood level

Blood samples-evaluated immunoglobulin G (IgG) levels in different research groups show that The mean of IgG in men's schizophrenic group was increased significantly (0.5762) compared to the control group of men (0.2810). The mean of IgG level in the schizophrenic group female indicated a significant increase (0.5167) compared to the male subjects of the control group (0.2810), but it was not significant in comparison with schizophrenic group male (0.5762) as well as female subjects of the control group (0.4429) (Figure 1-A).

The results of measuring the Immunoglobulin M (IgM) blood level

The examination results of blood samples-evaluated immunoglobulin M (IgM) levels of different research groups represented in Figure 1-B show that, statically There was no significant difference between immunoglobulin M (IgM) mean quantity in diverse study groups at the level of $P< 0.05$.

correlation between the duration of hospitalization of schizophrenic patients with IgG antibodies against toxoplasmosis

As shown in Figure 2-A, according to the value of sig (0.039), there is a significant inverse correlation (-0.22) between hospitalization time and level of immunoglobulin G (IgG) blood samples were taken from the subject based on the Pearson test.

correlation between the duration of hospitalization of schizophrenic patients with IgM antibodies against toxoplasmosis

We appraised the correlation between Increasing duration of hospitalization of schizophrenic patients and IgM antibody level due to toxoplasmosis Infection. Pearson test results (0.122) show that there is no significant correlation between these two variables (Figure 2-B).

The results of the IgG antibody level assessment in terms of the gender

To establish whether between males and females there is a difference in IgG antibody level Independent T-test was performed. The results show that there is no significant difference in terms of the IgG antibody level of yielded blood samples from subjects (Figure 3-A).

The results of the IgM antibody level assessment in terms of the gender

Independent T-test results showed that, statically in the $P< 0.05$ level there is no significant difference between the sexes (male and female) in terms of the IgM antibody level of derived blood samples from the subjects (Figure 3-B).

Discussion

To find a trustworthy perspective to diagnose and treat schizophrenia disease, which is one of the most common causes of hospitalization among Mental patients, its need to go significantly deeper into the possible contributing factors to its development such as the common infectious agents. Our results have shown that the Toxoplasma gondii Infection has been linked with the schizophrenia, which it can be a good indicator for diagnosis of disease and appropriate medicine selection. It is believed that Toxoplasma gondii plays a key role in the ethics and behavior of schizophrenia patients (Khademvatan et al., 2014). Thorry and colleagues in a case report declared an increase in the level of antibodies against Toxoplasma gondii following the symptoms of schizophrenia (Torrey et al., 2012). in accordance, the results of this study showed a significant increase in blood IgG but not IgM levels in both males and females of the schizophrenic groups compared to the control groups of each one. The differences of both studies can be due to many factors, which have been considered as the limitations of our study, such as the prenatal period (family history, gene polymorphism, parental age, mother's flu, prenatal stress, physical abnormalities, the time of birth in winter and summer, the geographical location of the birthplace, childbirth conflicts) and the infant associated risk factors Including hit the skull (Torrey et al., 2012; Guet al., 2001; Leweke et al., 2004). Our data is also in agreement with the previous studies and the distinguished increase in blood IgG antibody level, but IgM antibody level is not consistent with the reported of other studies in the schizophrenia patient (Yolken, 2001; Mortensen et al., 2007). this inconsistency can be explained by the lake of adequate sample size as well as different methods for measuring blood levels of antibodies in various studies. Another possible explanation for this is that the contrary to the previous study, which was involved people who are in the early phase of schizophrenia, the current study involved people with a history of several years of schizophrenia and the duration of hospitalization has been studied (Yolken, 2001). Considering the nature of mental illnesses, judgments about the epidemiology relevance of schizophrenia with Toxoplasma has considerations, of which the most important is the possibility of toxoplasma contamination after the onset of the disease. Moreover, the fact that hospitalization time is important. because of the disease onset, the patient's health habits may change and

may be more exposed to infections, including toxoplasma. In some studies, the effect of this factor has been reduced through patient's examination during the earlier phase of the disease (Guet al., 2001; Yolken, 2001 ; Leweke et al., 2004; Bachmann et al., 2005).

The present study showed that there is no significant correlation between IgM antibody levels due to toxoplasmosis infection and increase in hospitalization time. we showed also that there is a significant correlation between increasing the hospitalization time and the levels of the IgG antibody. The presence of the specific IgG antibody without IgM against Toxoplasma gondii is a symptom of chronic infection and individual immunity (Paquet et al., 2013). therefore, ignoring the effect of hospitalization time on the level of antibodies IgG can be another possible cause of the contradiction between the previous studies and the present study (Khademvatan et al., 2014; Garcia, 1979). numerous studies have compared the prevalence of Toxoplasma in schizophrenic patients and the control group (Leweke et al., 2004; Yolken et al., 2001; Gu et al., 2001; Bachmann et al., 2005; El-Sahn et al., 2005; Alvarado-Esquivel et al., 2006; Wang et al., 2006; Amminger et al., 2007). Our study results are confirmed by results of some of the studies but its inconsistent with others. The contradiction can be due to laboratory measurement methods, sample sizes, and the non-inclusion of age and gender factors.

Our findings showed that There was no significant difference between the levels of characteristic antibodies IgG and IgM against Toxoplasma gondii in both sexes and our data is in accordance with the previous studies (Hamidinejat et al., 2010). Therefore, in most studies, the gender segregation of subjects in patient groups cannot be convincing and homogeneously can be used from both sexes. proposed that the risk of schizophrenia strengthens via Toxoplasma infection (Hamidinejat et al., 2010). our data are in agreement with the other studies and the suggested role of Toxoplasma infection on the risk of schizophrenia (Brown et al., 2004; Buka et al., 2001; Brown et al., 2005).

Regarding the results of present study, it can be concluded that the increased mean levels of antibodies against Toxoplasma, reflecting the association of Toxoplasma gondii infection and the incidence of schizophrenia. nevertheless, there is a need for further studies with varied and more samples size as well as newer measuring methods and tools.

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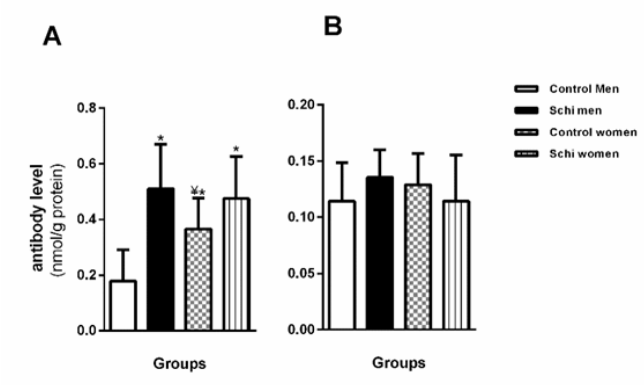

Fig. 1. Comparison of antibody levels averages between different groups. A) Comparison of IgG antibodies averages between different groups. B) Comparison of IgM antibodies averages between different groups. The results of the ANOVA and Duncan post hoc tests. data are expressed as means ± SD. *(P<0.05) significantly different when compared with control alone. ¥ (P< 0.05) significantly different between control groups.

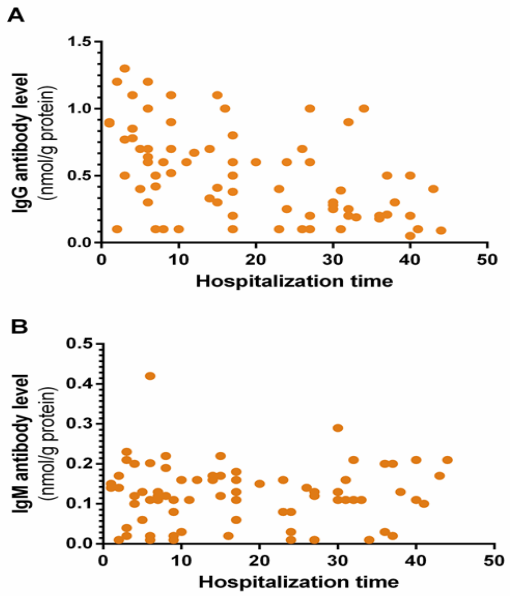

Fig. 2. The correlation between the hospitalization time of schizophrenic patients and the antibodies index. A) negative correlation between the hospitalization time of schizophrenic patients and IgG level. B) there is no correlation between the hospitalization time of schizophrenic patients and IgG level. The results of the Pearson's correlation coefficient (r) test.

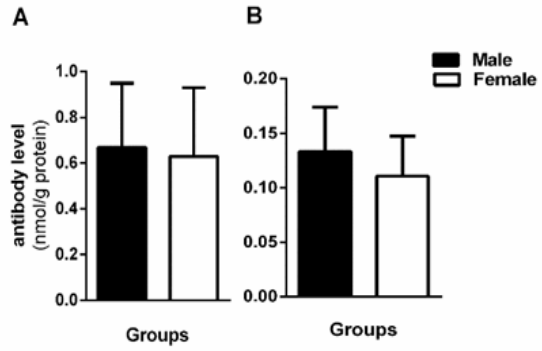

Fig. 3. The difference between the male and female of schizophrenic patients in terms of the A) IgG and B) IgM antibody levelS derived from independent t-test. data are expressed as means ± SD.