Anti-\textit{Toxoplasma gondii} Antibodies in Patients With Schizophrenia—Preliminary Findings in a Turkish Sample

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Schizophrenia is a serious neuropsychiatric disease of uncertain etiology. We investigated the seropositivity rate for anti-\textit{Toxoplasma} IgG and IgM antibodies by enzyme-linked immunosorbent assay (ELISA) in patients with schizophrenia to ascertain a possible relationship between \textit{Toxoplasma gondii} and schizophrenia. We selected 100 patients with schizophrenia, 50 with depressive disorder, and 50 healthy volunteers to investigate the seropositivity rate of anti-\textit{Toxoplasma} antibodies by ELISA. The seropositivity rate for anti-\textit{Toxoplasma} IgG antibodies among schizophrenia patients (66%) was significantly higher than among patients with depressive disorder or healthy volunteers (\(P < .01\)). Thus, there might be a causal relationship between toxoplasmosis and the etiology of schizophrenia.

\textit{Key words:} schizophrenia/\textit{Toxoplasma gondii}/ELISA

Introduction

\textit{Toxoplasma gondii}, worldwide in distribution, is closely related to other coccidia. This organism is an obligate intracellular parasite and is found in 2 forms in humans. The actively proliferating trophozoites or tachyzoites are usually seen in the early, more acute phases of the infection in immune competent individuals. The resting bradyzoites or tissue cysts are primarily found in muscle and brain, probably as a result of the host immune response.\(^1\)

The fact that a large number of humans are seropositive suggests that the majority of infections are mild, with most people exhibiting few (eg, a cold or light case of the flu) or no symptoms. On the other hand, studies have shown higher rates of symptomatic infection in immune compromised individuals such as those with HIV infection.

Schizophrenia is a pervasive, neuropsychiatric disease of uncertain cause that affects approximately 1% of the adult population in the United States and Europe. An increased occurrence of schizophrenia in family members of affected individuals suggests that genetic factors may play a role in its etiology, and specific genes have been proposed as being responsible for predisposing to schizophrenia. Environmental factors are also important. Epidemiological studies, eg, have established that winter-spring birth, urban birth, and perinatal and postnatal infections are all risk factors for the disease developing in later life. These environmental studies have rekindled interest in the possible role of infectious agents in schizophrenia.\(^2\)

Several parasitic infections may cause convulsions, most of which are easily detected by cerebrospinal fluid (CSF) analysis, serum testing, and magnetic resonance imaging (MRI).\(^3,4\) \textit{T. gondii} can form dormant microscopic cysts in the brain, which cannot be detected with MRI or routine CSF analysis. \textit{T. gondii}, in its dormant, tissue cyst form, is generally not associated with symptoms. In the case of immunosuppression, however, reactivation of the bradyzoites causes a potentially lethal disease, toxoplasmosis.\(^5\) About 20\% of the US population is seropositive for IgG antibodies for \textit{T. gondii}, making this one of the most prevalent protozoan infections and probably the only chronic parasitic infection lasting a human lifetime without any known consequences.\(^6\) In Turkey, the rate of seropositivity has been reported to be 23.1\% in Izmir\(^7\) and 36\% in Kayseri.\(^8\) A positive antibody titer is thought to reflect the persistence of parasites in the CNS or other body sites.\(^9\) Tissue cysts containing bradyzoites may spontaneously rupture, thus releasing parasites that cause antibody titers to remain elevated.\(^3,10\)

To investigate a possible association between \textit{T. gondii} infection and schizophrenia, we selected patients from the schizophrenia population and tested them with micro enzyme-linked immunosorbent assay (ELISA) for \textit{T. gondii} antibodies. We assumed that a positive antibody
titer (IgG) reflects chronic infection and the presence of tissue cysts within the CNS or other body tissues.

Methods

Patients and Their Sera

In this study, 100 patients with schizophrenia were selected from among patients who applied to Elazig Neuropsychiatry Hospital. Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, was used for clinical diagnoses. All patients had a normal MRI of the brain; no family history of schizophrenia; no history of head trauma, brain surgery, or previous meningitis/encephalitis; and no history of alcoholism. The patients were also not immunodeficient and did not have other immunologic abnormalities, a preexisting medical condition, a neurological disease, or other substance abuse.

Control groups consisted of 50 patients with depressive disorder (another psychiatric disorder) and 50 healthy volunteers. The healthy volunteer group was chosen from among patients who applied to Elazig Neuropsychiatry Hospital. Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, was used for clinical diagnoses. 11 All patients had a normal MRI of the brain; no family history of schizophrenia; no history of head trauma, brain surgery, or previous meningitis/encephalitis; and no history of alcoholism. The patients were also not immunodeficient and did not have other immunologic abnormalities, a preexisting medical condition, a neurological disease, or other substance abuse.

Control groups consisted of 50 patients with depressive disorder (another psychiatric disorder) and 50 healthy volunteers. The healthy volunteer group was chosen from among health care workers and from among the relatives/visitors of the patients. The patients and controls were living in the urban and rural region in and near Elazig, Turkey. They were screened to rule out physical and other psychiatric diseases. The patient and control groups were matched by sex (50 women and 50 men in the schizophrenia group, 26 women and 24 men in the healthy volunteer control group); socioeconomic status; dietary habits (especially with regard to eating or drinking uncooked/undercooked meat, milk, or eggs); and age (the mean age was 37.25 ± 6 among the schizophrenia group, 37.17 ± 11.54 among the healthy volunteers). They were also matched with regard to having come from an urban or rural environment. After matching, we verified that the case and control groups did not differ significantly with respect to these factors (P > .05). The length of illness of the patients was 3 months to 8 years.

Serological Technique

Five milliliters of blood was taken under sterile conditions. Blood samples were then centrifuged at 1000 r.p.m., and the sera were stored at −20°C until the analysis. We used the micro ELISA technique for T. gondii. A commercial ELISA kit (BIO-RAD, France) was used for detection of anti-T. gondii IgG and IgM antibodies. This technique was performed according to the manufacturer’s instructions.

Statistical Analysis

SPSS V.9.0 for Windows pocket program was used.

Results

In the present study, 66 of the 100 (66%) cases with schizophrenia, 12 of the 50 (24%) cases with depressive disorder, and 11 of the 50 (22%) healthy volunteers were positive for IgG titers (Table 1). IgM titer was positive for only 1 individual in the schizophrenia group and negative in the control groups by ELISA. The positive optical density values for anti-T. gondii IgG antibodies were converted into international units according to the test procedure.

The percentage of anti-T. gondii IgG antibody positivity in the schizophrenia patients (66%) was greater than in both control groups, ie, the depressive disorder group (24%) and the healthy volunteers (22%). The results are statistically significant between the schizophrenia group and the control groups (P < .01).

We also investigated the relationship between length of illness and T. gondii antibody seropositivity and observed that the seropositivity rate did not differ significantly with length of illness (P > .05). The types of schizophrenia of the patients were paranoid (n = 30), disorganized (n = 26), undifferentiated (n = 23), and residual (n = 21). We compared the types of schizophrenia and seropositivity rate but did not observe any significant difference with these parameters (P > .05).

Discussion

Toxoplasmosis can vary from an asymptomatic, self-limiting infection to a fatal disease, as is sometimes seen in patients with congenital infections or in debilitated patients in whom underlying conditions may influence the outcome of the infection. In immunocompromized patients, the infection most often involves the nervous system, with diffuse encephalopathy, meningoencephalitis, or cerebral mass lesions. 12 Neuropathologically, studies of T. gondii have shown that glial cells, especially astrocytes, are selectively affected in vitro. 13,14 Postmortem studies of brains from individuals who had schizophrenia have reported many glial abnormalities, 15 including decreased numbers of astrocytes. 16 It has been also shown that Toxoplasma infections may affect levels of dopamine, norepinephrine, and other neurotransmitters, which are known to be

| Table 1. Results of Anti-T. gondii IgG Antibodies Analysis in Schizophrenia Patients and in Control Groups (Depressive Disorder and Healthy Volunteers) |
|-------------------------------------------------|-----------------|------|
| Schizophrenia                                   | 66 (66%)        | 100  |
| Depressive disorder                             | 12 (24%)        | 50   |
| Healthy volunteers                              | 11 (22%)        | 50   |
affected in people with schizophrenia. There is also evidence of focal inflammation with disrupted tissue cysts in mice. Reactivation of the cysts could depolarize cells being entered or exited. The tissue cysts mature slowly and have been shown to eventually lyse in the immunocompetent host, thereby reestablishing chronic infection and, in the process, producing microscopic scars (glial nodules). Studies have documented that serologically Toxoplasma-positive people may have psychiatric changes even if the toxoplasmosis is clinically unapparent. Studies in which personality questionnaires have been administered to healthy adults have indicated that serum antibodies to T. gondii are associated with alterations in behavior and psychomotor skills. Few data exist concerning the clinical correlates of T. gondii infection in persons with schizophrenia.

In recent years, serological studies on patients with schizophrenia have been carried out showing that anti-T. gondii antibodies were higher in patients than in all the selected control groups. In our study, the seropositivity rate for anti-Toxoplasma IgG antibodies in schizophrenia patients (66%) indicates that chronic Toxoplasma infection is greater than in controls, ie, than in the depressive disorder group (24%) and the healthy volunteers (22%) (P < .01). Concerning the question of whether the patients could have acquired Toxoplasma after the onset of the illness, perhaps by eating or drinking undercooked meat or eggs or unpasteurized milk served in the hospital, hospital management informed us that these types of exposures are unlikely to have occurred. Anti-Toxoplasma IgM antibodies, which indicate an acute infection, were positive in only 1 individual in the schizophrenia group and negative in the control groups. Additional comprehensive studies are needed on the possible association between T. gondii and the symptoms and clinical course of schizophrenia and other psychiatric diseases. A positive correlation between toxoplasmosis and schizophrenia or any other psychiatric disease may lead to new approaches for the treatment of these diseases.

References