

## Association between latent toxoplasmosis and clinical course of schizophrenia – continuous course of the disease is characteristic for *Toxoplasma gondii*-infected patients

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**Abstract:** The aim of the present study was to investigate the association between various clinical aspects of schizophrenia and seropositivity against *Toxoplasma gondii* (Nicolle et Manceaux, 1908). We selected 94 patients with schizophrenia and investigated the seropositivity rate for anti-*T. gondii* IgG antibodies by ELISA. Clinical parameters of schizophrenic patients such as illness type and status, clinical course, awareness of the illness and need for electroconvulsive therapy (ECT) were compared with their serological status. Anti-*T. gondii* IgG antibodies were detected in 43 (46%) of schizophrenic patients. Chronic patients had a rate of 34 (72%) seropositivity, whereas 9 (22%) of the patients with partial remission showed evidence of latent toxoplasmosis. Of continuous patients, 35 (81%) were found to be seropositive and this rate was significantly more than in the other groups. The rate of latent toxoplasmosis was detected significantly higher in patients who lack awareness of schizophrenia (36, i.e. 72%) than the patients who were aware of their illnesses (7, i.e. 16%). Anti-*T. gondii* IgG antibodies were detected in 38 (70%) of ECT performed patients while this percentage was 13% in the ones who had never been treated with ECT. This difference was also statistically significant. We showed that *Toxoplasma*-infected subjects had 15× higher probability of having continuous course of disease than *Toxoplasma*-free subjects. Our results put forth the possibility of latent toxoplasmosis to have a negative impact on the course of schizophrenia and treatment response of schizophrenic patients.

**Keywords:** toxoplasmosis, schizophrenia patients, prognosis, serology

*Toxoplasma gondii* (Nicolle et Manceaux, 1908) is an intracellular apicomplexan parasite that can infect a wide range of hosts including humans. It can be contracted by humans through exposure to soil, water, undercooked meat and cat faeces that contain various life cycle stages of the parasite (Jones et al. 2001). It can invade and multiply in almost every cell type in its host. It stays dormant in tissue cysts consisting of thousands of bradyzoites and these tissue cysts play a key role in the life cycle of the protist. The tissue cysts have been shown to cause significant and continuous damage to neural tissues in rodents (Vyas et al. 2007).

*Toxoplasma gondii* can also reach human central nervous system as a result of its permissibility (Carruthers and Suzuki 2007, Torrey et al. 2007), and remain latent as tissue cysts. There is increasing evidence demonstrating that the localisation of these latent forms within the central nervous system is associated with mood and behaviour alteration in humans (Yolken et al. 2009). As such, stud-

ies are currently focusing on the possible relationship between chronic toxoplasmosis and behavioural pathologies as well as chronic illnesses of the central nervous system (Yolken et al. 2009).

The presence of latent tissue cysts in the brain is believed to cause changes in its functioning that potentially leads to schizophrenia and other neurological disorders in humans. This is engendered by the compression damage caused onto brain tissue, as well as the alteration of brain physiology due to the effects on neurotransmitter activity (Henriquez et al. 2009, Webster and McConkey 2010, Goodwin et al. 2011, Strobl et al. 2012). A standard computer-based assessment, which was employed to compare reaction times between infected and uninfected individuals, demonstrated that infected individuals had lower performance and concentration levels than uninfected individuals (Novotná et al. 2008).

Schizophrenia is a neuropsychiatric disorder with a worldwide prevalence of 4–7/1000 persons and with

a devastating impact on patients and their families. There are various factors influencing the incidence and prevalence of schizophrenia such as sex, urbanicity and migrant status. Although the prevalence of the illness is lower in developing countries, there is no evidence to suggest that the incidence differs due to economic status of the nations (McGrath et al. 2004, Saha et al. 2005, 2006, Yolken et al. 2009). Development of schizophrenia is mainly associated with genetic and environmental factors like exposure to pathogens, physical stress and foetal starvation during pregnancy, being known as a factor that increases individuals' predisposition (Susser and Lin 1992, Yolken et al. 2001). An immune basis for the illness, including mutations in the immune system that contributes to the alteration of the neurotransmitter physiology, has also been proposed Muller and Schwarz (2006). Other studies have shown that patients with schizophrenia experience structural and physiological changes in their brains even when they have never been treated with antipsychotics (Torrey 2002).

Psychotic symptoms involving delusions and hallucinations can be observed in patients with acute toxoplasmosis and AIDS patients with reactivated *T. gondii* infections. Such symptoms, however, are sometimes misinterpreted as symptoms of schizophrenia (Wang et al. 2006). Although *T. gondii* seropositivity is more frequent among schizophrenic patients, it is still not apparent either it is a cause or a consequence. Some studies strongly suggest that infection with *T. gondii* is a significant risk factor for the development of schizophrenia (Torrey and Yolken 2003, Cetinkaya et al. 2007, Henriquez et al. 2009, Torrey et al. 2012, Flegr 2013, Flegr et al. 2014).

To date, only a few studies have been undertaken about the effects of latent toxoplasmosis on the clinical characteristics of the schizophrenic patients. In a preliminary prevalence study, a relationship between seropositivity and a greater cognitive impairment in schizophrenia was found, whereas no significant association between serological status and Positive and Negative Syndrome Scale (PANSS) scores (Kay et al. 1987; Boronov et al. 2002). Wang et al. (2006) reported that seropositive schizophrenic patients had higher scores of the positive, cognitive and excitement components and lower scores of negative component of PANSS than the seronegative ones. A more recent finding indicates that latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls (Horáček et al. 2012). Lately, it was reported that *T. gondii*-infected patients spent more days than the uninfected ones in the hospital during their last stay. Also, their mean daily doses of antipsychotics were higher. They concluded that latent toxoplasmosis in schizophrenia may lead to more severe positive psychopathology and perhaps less favourable course of schizophrenia (Holub et al. 2013).

The association between schizophrenia and toxoplasmosis has been investigated in many studies, but the impact of this association on the prognosis of the illness is not en-

lightened. The aim of the present study was to investigate the association between latent infection with *T. gondii* and the clinical course in schizophrenic patients. We hypothesised that toxoplasmosis has a negative impact on the prognosis and treatment of schizophrenic patients.

## MATERIALS AND METHODS

### Patients and clinical measure

Patients consisted of 94 individuals who were admitted to the Department of Psychiatry at Inonu University Faculty of Medicine, and a nursing home in Malatya, Turkey with the diagnosis of schizophrenia in 2011 and 2012. Among patients, 32 (34%) were women and 62 (66%) were men and their median age was 40 years (range, 17–90 years; standard deviation 16 years). At the time of admission, none of the patients showed clinical evidence of immunodeficiency.

Clinical schizophrenia diagnoses were established by two psychiatrists upon the Turkish version of the Structured Clinical Interview for the Structured Clinical Interview for DSM-IV (Çorapcıoğlu et al. 1999). The subjects from the university hospital were follow-up patients who were not in a psychotic episode, whereas the residents of the nursing home were chronic patients requiring medical care. Some clinical data on the patients such as illness status, clinical course, awareness of the illness, electroconvulsive therapy, compliance with medication and illness type were chosen as indicators of prognosis to compare with the anti-*Toxoplasma gondii* serological status. All the patients were recorded in respect to illness status (chronic, partially cured, cured to a great extent), clinical course (first episode, single past episode and full remission, single past episode and partial remission, episodic without residual symptoms between episodes, episodic with residual symptoms between episodes, continuous), awareness of the illness (absent, present), electroconvulsive therapy (ECT) (performed, not performed), compliance with medication (not compliant, irregular or applies by persuasion, irregular with help, regular by self), illness type (catatonic, disorganised, paranoid, residual and undifferentiated). They all agreed to participate in the study. Written informed consents were obtained from all of the subjects after the study procedure had been explained. The study protocols and the consent forms were approved by Inonu University Ethics Committee.

### Serum collection and laboratory assay

Latent toxoplasmosis is a life-long illness in humans and, therefore, the presence of anti-*T. gondii* IgG antibodies is considered as a reliable indicator of viable bradyzoites in tissue cysts that persist in infected individuals (Montoya and Liesenfeld 2004). For this reason, the blood samples were obtained from the patients by venipuncture to investigate anti-*T. gondii* IgG antibodies. Sera were separated from whole blood and were stored at -80 °C until tested. The levels of class specific immunoglobulin G (IgG) antibodies against purified *T. gondii* antigens in serum samples were measured using enzyme-linked immunosorbent assay (ELISA) performed according to manufacturer instructions (Cobas Core, Roche, Langen, Germany).

### Statistical analysis

The data are represented as count and percentage. To compare the groups according to *T. gondii* seropositivity, Pearson chi-square and likelihood ratio tests were used. When the as-

**Table 1.** The relationship between toxoplasmosis and continuous course of schizophrenia determined by using a logistic regression with dependent variable continuous course and independent variable toxoplasmosis.

| Factor           | Toxoplasmosis   | Age               | Sex              | Population        |
|------------------|-----------------|-------------------|------------------|-------------------|
| t (89)           | 4.318           | 1.387             | -0.532           | 2.813             |
| P                | < 0.001         | 0.169             | 0.596            | 0.006             |
| O. R. (C. I. 95) | 15.0 (4.3–52.2) | 11.6 (0.35–392.5) | 0.71 (0.20–2.56) | 6.46 (1.73–24.13) |

t – t-value; P – P-value; O. R. – odds ratio; C. I. – Confidence Interval.

**Table 2.** Comparison of various clinical parameters of schizophrenia with serological status against *Toxoplasma gondii*.

| Clinical parameters        | Total count                                  | Anti- <i>Toxoplasma</i> IgG |                | P       |         |
|----------------------------|--|-----------------------------|----------------|---------|---------|
|                            |  | negative C (%)              | positive C (%) |         |         |
| Illness status             | chronic*                                     | 47                          | 13 (28)        | 34 (72) | < 0.001 |
|                            | partial remission                            | 41                          | 32 (78)        | 9 (22)  |         |
|                            | remission to a great extent                  | 6                           | 6 (100)        | 0 (0)   |         |
| Clinical course            | first episode                                | 1                           | 1 (100)        | 0 (0)   | < 0.001 |
|                            | single past episode and full remission       | 2                           | 2 (100)        | 0 (0)   |         |
|                            | single past episode and partial remission    | 10                          | 9 (90)         | 1 (10)  |         |
|                            | episodic without residual symptoms inbetween | 15                          | 12 (80)        | 3 (20)  |         |
|                            | episodic with residual symptoms inbetween    | 23                          | 19 (83)        | 4 (17)  |         |
| continuous*                | 43   | 8 (19)                      | 35 (81)        |         |         |
| Illness awareness          | present                                      | 44                          | 37 (84)        | 7 (16)  | < 0.001 |
|                            | absent                                       | 50                          | 14 (28)        | 36 (72) |         |
| ECT                        | performed                                    | 54                          | 16 (30)        | 38 (70) | < 0.001 |
|                            | not performed                                | 40                          | 35 (88)        | 5 (13)  |         |
| Compliance with medication | with help                                    | 83                          | 42 (51)        | 41 (49) | 0.051   |
|                            | by self                                      | 11                          | 9 (82)         | 2 (18)  |         |
| Illness type               | paranoid                                     | 41                          | 24 (59)        | 17 (42) | 0.611   |
|                            | undifferentiated                             | 10                          | 4 (40)         | 6 (60)  |         |
|                            | residual                                     | 12                          | 6 (50)         | 6 (50)  |         |
|                            | disorganized                                 | 17                          | 11 (65)        | 6 (35)  |         |
| catatonic                  | 14   | 6 (43)                      | 8 (57)         |         |         |

\* shows the statistically significant group due to the post-hoc analysis; ECT – Electroconvulsive Therapy.

sumptions of the asymptotic method could not be met, the exact significance of Pearson chi-square test was used. We used binary logistic regression analysis for estimation of odds ratios and their confidence intervals. In all analysis we considered the significance level as 0.05.

## RESULTS

In the present study, 43 of the 94 (46%) cases with schizophrenia were positive for anti-*Toxoplasma gondii* IgG antibodies. There was no significant difference between genders in respect to the seropositivity rate ( $P = 0.874$ ). Anti-*T. gondii* IgG was detected in the sera of 33 (60%) out of 55 patients from the nursing home, whereas 10 (26%) of 39 patients from the university hospital were seropositive. This difference was significant ( $P = 0.001$ ; OR = 4.4; 95% C.I. = 1.8–10.7).

Results of comparison of various clinical parameters of schizophrenia with serological status against *T. gondii* are presented in Table 1. Considering the seropositivity in groups with different illness status, *T. gondii* seropositivity rate among ‘chronic’ patients was found to be 72%

(OR = 9.3; 95% C.I. = 3.5–24.7) whereas it was 22% in partial remission group and no case was positive in remission to a great extent group. Prevalence of toxoplasmosis detected in patients with chronic illness was significantly higher than the ones in partial remission and in remission to a great extent groups ( $P < 0.001$ ).

When the relationship between the clinical course of the illness and past *T. gondii* infection was examined, we observed that *T. gondii* infection was significantly more prevalent among the ‘continuous’ group than the others ( $P < 0.001$ ). No *T. gondii* seropositivity was detected among the ‘first episode’ or ‘single past episode and full remission’ groups. When the ‘single past episode and partial remission’ group with 1 (10%) seropositivity was referred, 3 (20%) ( $P = 0.512$ ; OR = 2.3; 95% C.I. = 0.2–25.4) patients of the ‘episodic without residual symptoms between episodes’ group and 4 (17%) patients of the ‘episodic with residual symptoms between episodes’ group had *T. gondii* infection. In contrast, 35 (81%) ( $P < 0.001$ ; OR = 39.4; 95% C.I. = 44.0–356.8) of the ‘continuous’ patients had anti-*T. gondii* IgG antibodies.

Since much higher frequency of *T. gondii*-infected subjects (81%) was observed in subset of 43 patients with continuous course of disease than in other 51 subjects (16%), we coded this form of disease with a binary variable 'continuous' and analysed differences between patients with and without continuous course of disease using a logistic regression with dependent variable continuous and independent variables toxoplasmosis, age, sex and population. The results showed that *T. gondii*-infected subjects had fifteen times higher probability of having continuous course of disease than *T. gondii*-free subjects (Table 1).

We also investigated the relationship between the patients' awareness of schizophrenia and toxoplasmosis seroprevalence in the study group. While anti-*T. gondii* IgG antibodies were detected in 7 (16%) of the patients with awareness, this rate increased to 36 (72%) among patients without awareness of the illness. This difference was significant ( $P < 0.001$ ; OR = 13.6; 95% C.I. = 4.9–37.6).

Additionally, the association between ECT and past *T. gondii* infection was also found to be significant ( $P < 0.001$ ; OR = 16.6; 95% C.I. = 5.5–50.2). The rate of seropositivity among ECT performed patients was 38 (70%), whereas it was 5 (13%) for patients to whom ECT was never performed. There was no significant difference between seropositive and seronegative groups in respect to treatment compliance ( $P = 0.051$ ).

The types of schizophrenia in the study group were catatonic ( $n = 8$ ), disorganised ( $n = 6$ ), paranoid ( $n = 17$ ), residual ( $n = 6$ ) and undifferentiated ( $n = 6$ ). The toxoplasmosis frequency among patients was compared with types of schizophrenia but no significant difference was observed ( $p = 0.611$ ). Apart from these findings, three patients with latent toxoplasmosis also had intellectual disabilities. The relationship between *T. gondii* infection and the above-mentioned criteria is shown in Table 2.

Theoretically, patients in the nursing home could have both increased probability of *T. gondii* infection and more serious course of schizophrenia. This could result in observed associations between toxoplasmosis and various variables describing seriousness of schizophrenia disease. To test this hypothesis, we performed logistic and ordinal regressions with independent variables toxoplasmosis, age, sex and population (nursing home yes/no) for binary (ECT, awareness) and ordinal (course, compliance, illness status) variables, respectively. The effects of toxoplasmosis remained significant, except for the compliance with medication (ECT:  $P < 0.001$ ; illness awareness:  $P < 0.001$ ; clinical course:  $P < 0.001$ ; compliance with medication:  $P = 0.993$ ; illness status:  $P = 0.008$ ).

## DISCUSSION

Schizophrenia, like multiple sclerosis and Parkinson's disease, is a chronic illness of the central nervous system and as such, infectious agents can also be blamed

as a potential etiological factor, perhaps in persons who also have an increased genetic susceptibility (Torrey and Yolken 2003, Çelik et al. 2013). In recent years, serological studies on patients with schizophrenia have been carried out showing that the rate of anti-*Toxoplasma gondii* antibodies were higher in patients than in all the selected control groups (Yolken et al. 2001, Çetinkaya et al. 2007, Tamer et al. 2008). We did not compare seropositivity rate in the study group with a healthy control group, which was out of the range of this study, but the overall anti-*Toxoplasma* IgG positivity in our patient study group was 46% and the difference between the seropositivity rates of two gender was not statistically significant. This value is slightly higher the seroprevalance rate reported from this region of Turkey, which is around 40% (Çelik et al. 2010, Doğan et al. 2012).

There have been only a few studies investigating the association between seropositivity against *T. gondii* and symptoms in schizophrenic patients. In one of these studies, a significant relationship between severe positive schizophrenia symptoms in ultra-high-risk individuals for psychosis and higher levels of anti-*T. gondii* IgG antibodies was observed (Amminger et al. 2007). Following this study, more severe positive, disorganised and excitement symptoms among schizophrenic patients with latent toxoplasmosis were reported (Holub et al. 2013). In the present study, while most of the chronic schizophrenic patients (72%) were seropositive, none of the treatment responsive patients had specific antibody against *T. gondii*. We interpret this finding as latent toxoplasmosis could have a negative impact on clinical course of schizophrenia. According to a previous studies, behavioral changes in *T. gondii*-infected individuals are likely to be related to increases in the levels of dopamine, a neurotransmitter that is assumed to play a significant role in schizophrenia (Skallová et al. 2006, Gaskell et al. 2009, Prandovszky et al. 2011, Hodková et al. 2007). Such elevations in dopamine concentrations possibly contribute to the worsening and deterioration of schizophrenia symptoms.

In the present study, anti-*T. gondii* IgG positivity among patients from the nursing home was 4.3× higher than the patients from the university hospital. The patients at the nursing home were unable to care for themselves and the onset time of schizophrenia could not be detected. As they were older than the ones from the university hospital, all the data were adjusted with age. It may be assumed that the patients at the nursing home possess bad hygiene practices and nutrition status and thus was easier for them to acquire toxoplasmosis. However, latent toxoplasmosis may also be considered to have a negative impact on the treatment of schizophrenia and quality of life. A continuous clinical course was observed fifteen times higher among seropositive patients, which was a finding independent from age, sex and population. Therefore, we propose that latent toxoplasmosis may affect the response



to the schizophrenia treatment, prolong hospital stay and as a result increase the cost of the illness.

Among schizophrenia patients, the insight is a multifaceted concept that includes the following aspects: awareness of the mental illness, awareness of symptoms, awareness of social consequences and awareness of the effects of treatment. Awareness levels are reported to be related to the severity and extent of the patient's symptoms (Lysaker et al. 1994). We investigated the awareness of illness as a subset of insight and our findings showed that latent toxoplasmosis was more prevalent (72%) among patients who lacked awareness. Therefore, we thought that absence of awareness showing a severe illness was related to specific *T. gondii*-IgG positivity.

ECT is still considered to be one of the effective therapeutic approaches, especially for the patients who has insufficient or partial response to medication (Abrams 2002). Anti-*T. gondii* IgG antibodies were detected in 70% of patients to whom ECT was performed. We think that the possible negative effect of latent toxoplasmosis on the clinical outcome of schizophrenia may have increased the need for ECT in these patients.

Based on our results, we identified a negative correlation between the clinical picture of schizophrenia and the presence of anti-*T. gondii* IgG antibodies in patients with latent toxoplasmosis. This is indicative of the fact that the presence of *T. gondii* may lead to some changes in the psychopathology, and also that *T. gondii* infections may be associated with worse prognosis among patients with schizophrenia. This observation can be considered as a re-

flection of the effect of *T. gondii* infections on schizophrenia's psychopathology in different individuals, and also of the cumulative effect that these infections have over time on the patients' symptoms.

The strongest aspect of the present study is that we compared the relationship between latent toxoplasmosis and the subtypes and clinical course of this illness with heterogenous forms, although the previous studies compared the relationship between toxoplasmosis and the severity of the illness. The major limitation of this study is the small size of the study group, which did not allow for interpretation of the whole dataset. Although schizophrenia is familial, environmental factors such as toxoplasmosis should be investigated in order to understand why the illness has various clinical courses. Therefore, new studies with greater sample sizes regarding this issue should be carried out.

As a result, there seems to be a relation between latent toxoplasmosis and the course of schizophrenia and treatment response. We assume that the effects of toxoplasmosis on schizophrenic patients should be further investigated for a longer period of time. Following future studies, novel treatment regimens might be considered to improve the prognosis of schizophrenia in seropositive patients.

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