Toxoplasma gondii in Individuals With Schizophrenia: Association With Clinical and Demographic Factors and With Mortality

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Background: Increased rates of exposure to Toxoplasma gondii have been found in individuals with schizophrenia as compared with control groups, but the correlates of Toxoplasma exposure in schizophrenia have not been defined. Methods: We measured IgG class antibodies to Toxoplasma gondii in 358 individuals with schizophrenia. We correlated Toxoplasma antibody status with clinical and demographic variables and examined the effect of Toxoplasma seropositivity on mortality in a follow-up period of up to 5 years. Results: Individuals with schizophrenia who had serological evidence of Toxoplasma infection were more likely to be female but did not differ in age, race, total symptom score, or other demographic or clinical characteristics. However, we found that serological evidence of Toxoplasma was associated with a significantly increased risk of dying of natural causes during the follow-up period (Cox proportional hazard ratio of 4.70; 95% confidence interval, 1.27–17.31, \( P = .020 \)) adjusted for age, gender, and other clinical and demographic variables. Conclusions: Toxoplasma infection may confer an increased risk for mortality from natural causes in schizophrenia. An understanding of the pathogenesis of Toxoplasma infections in individuals with schizophrenia might lead to new approaches to the management of this disorder.

Key words: infection/parasite/mortality

Introduction

Schizophrenia is a serious neuropsychiatric disorder of uncertain etiology with a lifetime prevalence of approximately 1% in the United States. While a number of genetic risk factors for schizophrenia have been found, most have relatively low odds ratios.1,2 In addition to genetic factors, environmental exposures have been identified as increasing risk for the disease. Toxoplasma gondii is a protozoan of the family apicomplexa, with a worldwide distribution and neurotropic effects. Previous studies indicate that increased levels of maternal antibodies to T. gondii are associated with increased rates of schizophrenia in the offspring.3,4 Other studies, summarized by Torrey1 in this issue, indicate that the prevalence of antibodies to T. gondii is higher in individuals with schizophrenia than in control groups. However, clinical correlates of serological evidence of Toxoplasma in schizophrenia have not been the subject of systematic investigation.

Schizophrenia is associated with excess mortality from natural as well as unnatural causes. It is estimated that individuals with schizophrenia have approximately a 20% reduced life expectancy compared with the general population.5 The causes of premature death in this population are not known with certainty. Cigarette smoking, obesity, hypertension, and substance abuse, all of which are more prevalent in individuals with schizophrenia, have been cited as possible contributing factors.6 In one recent study, the risk of mortality remained increased among individuals with schizophrenia even after controlling for these potential risk factors for premature death.7 Associations between specific infectious agents and premature death in schizophrenia have not been previously investigated.

The purpose of this study was to evaluate the clinical and demographic correlates of serological evidence of infection with Toxoplasma in schizophrenia. We also examined the association between Toxoplasma status and subsequent mortality in the cohort in a follow-up period of up to 5 years.

Materials and Methods

The study population consisted of individuals who met the following criteria: (1) a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder meeting criteria in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition; (2) age between 13
We employed solid-phase immunoassay techniques to study procedures were explained. All participants provided written informed consent after Medical Institutions following established guidelines. Committee for Clinical Investigation of Johns Hopkins issue.

A duration of observation was calculated for each patient as the time between the original assessment and December 31, 2004, or the date of death. These data were used to determine the rate of mortality in the individuals who had serological evidence of Toxoplasma infection as compared with those who did not have serological evidence of Toxoplasma. The effect of Toxoplasma seropositivity on mortality was calculated using the method of Kaplan and Meier. The effect of other clinical and demographic variables on mortality was evaluated using Cox proportional hazards regressions. These variables included age at study entry, race, gender, level of education, duration of schizophrenia illness, cigarette smoking, and a diagnosis of diabetes at initial evaluation. Two individuals who died of unnatural causes during this period were censored from these analyses, leaving 358 individuals to be evaluated.

Demographic Characteristics of the Study Samples

The sample of 358 individuals with schizophrenia had a mean age of 40.5 years (SD = 11.0) at the time of assessment. A total of 266 individuals in the sample (74.3%) were Caucasian and 221 (61.7%) were male. The mean level of educational achievement in the sample was 12.5 years (SD = 2.5). The mean age of illness onset was 21.2 years (SD = 7.2), and the mean duration of illness at the time of assessment was 19.4 years (SD = 11.0). A total of 351 (98.1%) schizophrenia participants were receiving regular antipsychotic medication at the time of the initial study assessment. A total of 277 participants (77.4%) were receiving atypical antipsychotic medications: 120 (33.5%) were receiving olanzapine, and 89 (24.9%) were receiving clozapine. A total of 224 (62.6%) of the individuals were current cigarette smokers at the time of the assessment, and 43 (12.0%) had a history of diabetes. The mean RBANS cognitive total score was 67.6 (SD = 14.2), and the mean PANSS symptom total was 71.3 (SD = 13.7). The individuals were evaluated for a mean of 43.4 months (SD = 20.3).

Results

We found serological evidence of Toxoplasma infection in 58 (16.2%) of the 358 individuals with schizophrenia in our study population. The individuals who had serological evidence of Toxoplasma were more likely to be female ($\chi^2 = 5.3, P = .021$) compared with individuals without serological evidence of infection. The individuals who had serological evidence of Toxoplasma did not differ from those who did not in terms of age, race, or educational level. They also did not differ in terms of disease-related variables such as age of illness onset, duration of illness, PANSS total symptom score, RBANS total cognitive score, cigarette smoking, diabetes, or the receipt of an atypical antipsychotic agent or olanzapine or clozapine at the time of evaluation (all $P > .05$).
We examined the rate and cause of mortality in the cohort; as depicted in table 1, 10 persons died of natural causes in the follow-up period. A total of 5 of the 10 individuals who died of natural causes during the study period had serological evidence of Toxoplasma infection. As depicted in table 2, the overall mortality rate was thus 8.6% for individuals with serological evidence of Toxoplasma infection compared with 1.7% for individuals without serological evidence of Toxoplasma infection ($\chi^2 = 8.6, P < .003$). Expressed in terms of time of observation, the mortality rate for individuals with schizophrenia who had serological evidence of Toxoplasma infection was 2.10 deaths/1000 person-months of observation compared with a rate of 0.38 deaths/1000 person-months of observations in individuals with schizophrenia who did not have serological evidence of Toxoplasma infection.

We further explored the independent contribution of Toxoplasma seropositivity on mortality, controlling for demographic and clinical parameters that might contribute to mortality in this population, utilizing Cox proportional hazard analyses. This analysis indicated that serological evidence of Toxoplasma infection was associated with a hazard ratio of dying from natural causes related to Toxoplasma infection = 4.70 (95% confidence interval = 1.27 – 17.31, $p = 0.020$), independent of age, race, gender, level of education, smoking status at baseline, and diabetes diagnosis at baseline.

### Discussion

Previous studies summarized in the meta-analysis by Torrey in this issue indicate that the prevalence of antibodies to T. gondii is higher in individuals with schizophrenia than in control groups and suggest that infection with Toxoplasma may confer a risk for schizophrenia. Our current study extends this finding by investigating the correlates of Toxoplasma seropositivity within a schizophrenia sample.

![Figure 1. Kaplan-Meier Survival Estimates for Individuals With Schizophrenia Who Have Serological Evidence of Toxoplasma Infection (Toxo = positive) or Who Do Not Have Serological Evidence of Toxoplasma Infection (Toxo = negative). “Observed” represents the actual values; “predicted” represents survival estimates adjusted for race, gender, level of education, age at study entry, duration of illness, smoking status, and diagnosis of diabetes. The x-axis represents the number of days of the follow-up period. It is of note that the values shown at the end of the x-axis are based on small numbers of individuals and thus have wide confidence intervals.](https://academic.oup.com/schizophreniabulletin/article-abstract/33/3/737/1882694)
We found that schizophrenia individuals who had serological evidence of infection differed from those who did not in that they were more likely to be female, but they did not differ in terms of psychiatric symptom severity, cognitive functioning, or whether or not they had received atypical antipsychotic agents. Most population-based studies have not found differences in Toxoplasma by gender. The reasons for the gender difference in our study are not known. It is of note that Lindova et al found gender-related personality differences in Toxoplasma-seropositive individuals. Gender differences in Toxoplasma seropositivity in schizophrenia should be the focus of future studies. The absence of an age effect for Toxoplasma seropositivity in our sample is also curious and may represent a type 2 error that would be corrected with a larger sample size.

We found that individuals with schizophrenia who had serological evidence of Toxoplasma infection had an almost 5-fold increased rate of death from natural causes during the follow-up period compared with individuals with schizophrenia without serological evidence of infection. This difference was found when controlling for age, race, gender, and other demographic factors that might affect mortality. The reasons for the increased mortality associated with Toxoplasma infection are not known with certainty. To our knowledge, there have not been any studies linking Toxoplasma seropositivity to adult mortality in the general population. It is of note that Toxoplasma infection has been associated with an increased rate of automobile accidents in 2 different populations. There were not a sufficient number of accidents in our population to perform analyses. The relationship between Toxoplasma infection and accidental deaths should be the subject of future investigations.

We could not identify the timing of Toxoplasma infection in our population. The finding of Toxoplasma IgG antibodies in adults can be the result either of infection acquired around the time of birth or infection acquired later in life, so we did not know the sequence of Toxoplasma exposure and our participants’ schizophrenia prodrome and psychosis onset. Increased mortality in Toxoplasma individuals may be related to organ system disease or immune suppression, which can occur with Toxoplasma infection, although we do not have evidence from our own sample to support this explanation. It is possible that there is an interaction between Toxoplasma exposure and cardiac risk factors that lead to mortality; however, only 1 of the 5 deaths among Toxoplasma-positive individuals in our sample was due to cardiac disease. It is possible that other deceased individuals also suffered from cardiac disease but that this did not appear as the stated cause of death in the NDI. The number of decedents in the sample is relatively small, so our findings should be confirmed in larger samples. It will also be important to determine the association between Toxoplasma status and other mortality risk factors. In addition, further studies should be performed in individuals in other populations in order to further define the relationship between Toxoplasma infection and mortality.

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References