Antibodies to Infectious Agents in Individuals at Ultra-High Risk for Psychosis


Background: While there is evidence that some cases of schizophrenia may be associated with microbial infections, the role of microbial agents has not been investigated in people with emerging psychosis.

Methods: Participants were 105 help seeking ultra-high risk individuals. Psychiatric measures included the Brief Psychiatric Rating Scale and the Scale for the Assessment of Negative Symptoms. Serum IgG antibodies against human herpesviruses and Toxoplasma gondii were determined using immunoassay methods. Multiple linear regression with adjustment for age and sex was applied to test associations between serum antibodies and psychiatric measures.

Results: Higher levels of serum IgG antibodies against Toxoplasma gondii in Toxoplasma-positive individuals were significantly associated with more severe positive psychotic symptoms. No significant association was observed between antibody levels and psychiatric measures in individuals positive for human herpesviruses.

Conclusions: In some individuals infection with Toxoplasma gondii may be an environmental factor contributing to the manifestation of positive psychotic symptoms.

Key Words: Human herpes viruses, onset of psychosis, positive symptoms, schizophrenia, toxoplasma gondii, ultra-high risk

A growing body of serological studies suggests that some cases of schizophrenia may be associated with exposure to microbial infections (Buka et al 2001; Brown et al 2001, 2004, 2005; Leweke et al 2004; Yolken et al 2001). Recent studies in people with schizophrenia have focused on members of the human herpesvirus family and the protozoan organism Toxoplasma gondii because of their ability to establish persistent infection within the central nervous system as well as the occurrence of neurological and psychiatric symptoms in some individuals infected with these agents (Torrey and Yolken 2003; Yolken 2004). While microbial agents have been investigated in patients with established schizophrenia, the role of infectious agents for the onset of psychotic symptoms is unclear. We examined the relationship between serum antibodies against human herpesviruses and Toxoplasma gondii and measures of psychopathology in individuals at ultra-high risk for psychosis.

Methods and Materials

Participants

All participants (n = 105; 39.0% male) (mean age = 19.1 years, SD = 3.2) were consecutively admitted to the Personal Assistance and Crises Evaluation (PACE) clinic in Melbourne, Australia, between April 2001 and December 2004. The criteria for identification of the ultra-high risk cohort and the rationale for these criteria have been previously described (McGorry et al 1998). The participants met the criteria for at least one of three groups at intake, characterized by specific state and/or trait risk factors for psychosis. The three groups were: 1) trait plus state risk factors (i.e., genetic risk plus decrease in functioning), 2) attenuated symptoms, and 3) brief, limited intermittent psychotic symptoms. The criteria met by the subjects were as follows: trait plus state, 21.0%; attenuated symptoms, 85.7%; brief, limited intermittent psychotic symptoms, 9.5%. All participants were between the ages of 14 and 29 years, had not experienced a previous psychotic episode (treated or untreated), and reported English as the preferred language. The present study was approved by the North-Western Mental Health Program Research and Ethics Committee (Melbourne, Australia). All participants provided written informed consent, including parental consent for those less than 18 years of age.

Measures

The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), the Scale for Assessment of Negative Symptoms (SANS) (Andreasen 1982) and the Global Assessment of Functioning (GAF) (DSM-IV) were used to assess psychopathology and functioning. Serum IgG class antibodies were measured to Herpes Simplex Virus Type 1 (HSV-1), Herpes Simplex Virus Type 2 (HSV-2), Cytomegalovirus (CMV), Epstein Barr Virus (EBV), Varicella-Zoster Virus (VZV), and Toxoplasma gondii using previously described immunoassay methods (Buka et al 2001; Yolken et al 2001). For each assay, a result was defined as positive or negative based on comparison with the reactivity of specific antibody standards assayed along with the blood samples. In the case of antibodies to the herpesviruses, these standards consisted of samples with defined levels of reactivity to the specific herpesvirus antigens (Sauерbrei and Wutzler 2004). In the case of antibodies to Toxoplasma gondii, this standard consisted of samples corresponding to 10 international units of antibody (Cubitt et al 1992; Rigsby et al 2004). Blood samples and psychopathology measures were obtained within 3 weeks after acceptance to the PACE clinic. All serological tests were carried out at the Stanley Laboratory of Developmental Neurovirology, Baltimore, Maryland.

Statistical Analysis

Multiple linear regression analyses with adjustment for age and sex were applied to investigate associations between IgG antibodies against infectious agents and psychiatric measures. First the predictive effects of seropositivity versus seronegativity were determined. If significant, subsequent analyses were carried out in seropositive individuals using continuous antibody concentrations as predictors.
of psychiatric measures. A significance level of .05 was used for all statistical tests, and two tailed tests were applied.

Results

Mean values (SD, range) for psychiatric measures in 105 ultra-high risk individuals at entry to the program were as follows: BPRS total, 27.2 (8.6, 8-50); BPRS psychotic subscale, 6.8 (2.7, 0-14); SANS total, 31.7 (16.8, 0-87); GAF 56.2 (8.2, 38-75). Numbers (%) of individuals who tested positive were 45 (42.2%) for HSV-1, 33 (31.4%) for HSV-2, 50 (47.6%) for CMV, 76 (72.4%) for EBV, 91 (86.7%) for VZV, and 18 (17.1%) for *Toxoplasma gondii*. Being *Toxoplasma*-positive was significantly associated with more severe positive psychotic symptoms, and more severe psychiatric symptoms in general, whereas being EBV-positive was significantly associated with less severe positive psychotic symptoms (Table 1).

When linear regression analyses were performed in *Toxoplasma*-positive individuals (*n* = 18), IgG antibodies against *Toxoplasma* accounted for 35.9% of the variation in BPRS psychotic subscale scores (B = 2.083, *p* = .014) after adjusting for the effects of age and sex. The positive correlation between IgG antibody levels to *Toxoplasma gondii* and psychotic symptoms is illustrated in Figure 1. No significant associations were observed between antibodies against Toxoplasma and BPRS total, SANS total, or GAF in Toxoplasma-positive individuals.

Linear regression analyses in EBV-positive individuals (*n* = 76) revealed no significant association between IgG antibodies against EBV and any applied psychiatric measures.

Discussion

The findings suggest that the onset of positive psychotic symptoms in some ultra-high risk patients may be specifically associated with *Toxoplasma gondii* infection. Elevation of IgG antibodies to *Toxoplasma gondii* may reflect an active primary infection, reactivated infection, or a persistent immune response to a dormant infection (Brown et al 2005). IgM in contrast to IgG class antibodies are a specific indicator of recent infection. In 77 individuals (73.3%) of the present study sample in which both IgM and IgG levels to *Toxoplasma gondii* were obtained, no significant

### Table 1. Associations between Psychiatric Measures and Seropositivity for Specific IgG Class Antibodies in 105 Individuals at Ultra-High Risk for Psychosis Adjusted for Age and Sex

<table>
<thead>
<tr>
<th></th>
<th>BPRS (Psychotic Subscale)</th>
<th>BPRS (Total Scale)</th>
<th>SANS (Total Scale)</th>
<th>GAF</th>
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<tr>
<td></td>
<td>B&lt;sup&gt;a&lt;/sup&gt; p Value</td>
<td>B&lt;sup&gt;a&lt;/sup&gt; p Value</td>
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<td>B&lt;sup&gt;a&lt;/sup&gt; p Value</td>
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<tr>
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<td>-.71 .68</td>
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<td>-.90 .58</td>
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<td>-.02 .99</td>
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<td>.46 .78</td>
</tr>
<tr>
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<td>2.8 .10</td>
<td>2.5 .46</td>
<td>.68 .67</td>
</tr>
<tr>
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<td>-3.1 .10</td>
<td>-2.8 .46</td>
<td>-1.2 .51</td>
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<tr>
<td>VZV</td>
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<td>.35 .87</td>
<td>.55 .91</td>
<td>1.9 .42</td>
</tr>
<tr>
<td><em>T. gondii</em></td>
<td>1.9 .005</td>
<td>4.3 .047</td>
<td>-1.5 .73</td>
<td>-69 .75</td>
</tr>
</tbody>
</table>

HSV-1, Herpes Simplex Virus Type 1; HSV-2, Herpes Simplex Virus Type 2; CMV, Cytomegalovirus; EBV, Epstein Barr Virus; VZV, Varicella-Zoster Virus; *T. gondii, Toxoplasma gondii*; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for Assessment of Negative Symptoms; GAF, Global Assessment of Functioning.

<sup>a</sup>Regression coefficient from multiple regression procedure.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Positive correlation between IgG antibody levels to *Toxoplasma gondii* and psychotic symptoms in 18 Toxoplasma-positive ultra-high risk individuals.
association ($r = -.40, p = .73$) between IgM and IgG levels was detected, and *Toxoplasma gondii* IgM antibody levels were not associated with any psychiatric measure in seropositive individuals. It is therefore unlikely that recent primary infections account for the observed finding. This view is supported by epidemiological data indicating that early contact with cats, a main reservoir of *Toxoplasma gondii*, is a risk factor for the development of schizophrenia (Torrey and Yolken 1995), and compelling serological evidence showing prenatal exposure to *Toxoplasma gondii* increases the risk for subsequent schizophrenia (Brown et al 2005).

*Toxoplasma gondii* infects about 15-85% of people worldwide; the rate varies widely by location, age and other factors (Walzer and Genta 1989). Psychotic symptoms might occur only in a small proportion of infected individuals, presumably those more susceptible to neuropsychiatric effects of the infection. Susceptibility factors may include timing of primary infection, co-infections, and genetic disposition. In some individuals positive psychotic symptoms may be an effect of reactivated dormant *Toxoplasma gondii* microcyts on the brain. This view is consistent with descriptions of delusions and hallucinations in acute toxoplasmosis (Kramer 1966), as well as reports of increased IgG concentrations to *Toxoplasma gondii* associated with neuropsychiatric abnormalities (Sever et al 1988), and findings that individuals with first-episode schizophrenia are characterized by increased levels of IgG antibodies to *Toxoplasma gondii* as compared to control subjects (Leweke et al 2004; Yolken et al 2001). The mechanism of the effect of *Toxoplasma gondii* on the brain is unknown. However, there is evidence from research in rodents with chronic toxoplasmosis (Stibbs 1985), and findings on temperament features in toxoplasma-positive mice, i.e. increased novelty seeking, suggesting that *Toxoplasma gondii* increases dopamine levels in the brain. Dopamine increase could explain the emergence of positive psychotic symptoms, and represent a link between toxoplasmosis and psychotic disorders (Plegr et al 2003). The timing of *Toxoplasma gondii* infections in individuals with recent onset psychiatric diseases is the subject of ongoing evaluations by our group.

Unlike individuals with recent onset schizophrenia, we found no evidence to support an involvement of human herpesviruses, in particular CMV (Leweke et al 2004), in the etiology of psychiatric symptoms in ultra-high risk patients. Conversely, EBV-positive individuals were characterized by less psychotic symptoms compared to EBV-negative individuals. The reason for this finding is unclear. Secondary analyses conducted in EBV-positive patients, however, failed significance. The fact that we did not find increased levels of antibodies to human herpesviruses indicates that the increase in antibodies to *Toxoplasma gondii* was not simply a consequence of a nonspecific increase in antibody levels due to immunological activation.

A strength of the present study is that all individuals experienced a first manifestation of psychotic symptoms, making it less likely, compared to patients who met criteria for psychotic diagnosis, that elevated antibodies were a consequence of psychopathology. A limitation of the present study is its cross-sectional design. Although there is cumulative evidence for an involvement of *Toxoplasma gondii* in the emergence of psychotic disorder we can not rule out that the present findings were due to chance and results require confirmation in other samples.

Longitudinal research is warranted to address the question of whether *Toxoplasma gondii* infection is involved in the transition to schizophrenia and other psychotic disorders in ultra-high risk populations. The establishment of an etiological link between reactivation of *Toxoplasma gondii* and the onset of psychosis would provide a rationale for drugs with anti-*Toxoplasma gondii* activity (e.g., trimethoprin-sulfamethoxazole or azithromycin) in the treatment of psychotic symptoms and/or disorders that may have implications for their prevention.

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