High risk of psychosis may be associated with toxoplasmosis☆

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Abstract

Many parasites induce characteristic changes in their host. The effect of *Toxoplasma gondii* (*T. gondii*) infection on the cerebrum and neuropsychiatric patients has been increasingly emphasized in recent years. *T. gondii* has a high affinity for brain tissue where tachyzoites may form tissue cysts and persist for a life long time. Some psychiatric symptoms such as schizophrenia and mental retardation may be induced by the infection of *T. gondii*. Furthermore, experiments demonstrated that some antipsychotics and mood stabilizers used to treat phychosis displayed the function of inhibiting *T. gondii* replication. Investigations from various regions in China also support that psychosis in some patients is associated to *T. gondii* infection. [Life Science Journal. 2007; 4(4): 38 – 41] (ISSN: 1097 – 8135).

Keywords: *Toxoplasma gondii*; psychosis; antipsychotic medications

1 Introduction

Toxoplasma gondii (*T. gondii*) is an intracellular parasite that infects virtually all warm-blooded vertebrates including humans. It is estimated that about 30% – 60% of the population in both the developed and the developing countries are infected with this parasite through the ingestion of food and water contaminated with cysts or oocysts[1]. An immunocompetent person who infected with *T. gondii*, is characterized by reproduction of tachyzoite in cells of different tissues[2] and within weeks or months, tachyzoites disappear and tissue cysts form in various tissues, mainly in brain and muscles. These cysts are believed to persist throughout the life of the immunocompetent hosts in whom psychotic manifestation may be induced. Many epidemiological studies focused on patients with CNS diseases have been carried out in recent years, and increasing evidence supports the hypothesis that *T. gondii* infection may be an etiological factor for the development of psychosis in some patients[3–5].

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2 Dopamine Modulation and Etiological Implication of Psychosis

Many reports indicated that *T. gondii* might be an etiological agent in some cases of psychosis. Stibbs (1985) suggested that *T. gondii* infection might contribute to the increase of the dopamine level in mice brain[6]. Evidence showed that dopamine is one of the key compounds related to psychosis such as schizophrenia, and bipolar disorder in laten toxoplasmosis patients[7,8]. Dopamine releasing in the nucleus accumbens by activating the retrohippocampal region can disrupt the fornix section of brain as evolve to develop a psychosis[9]. It has long been recognized that amphetamine abuse can produce schizophrenia-like symptoms, which involves an increased release of dopamine in response to the methamphetamine. Moreover, abnormal behavioral responses to directly acting dopamine agonists have been demonstrated[10]. The clinical deterioration of schizophrenia is suggested a disruption on the frontal cortex where is known to play an important role in emotional processing and decision-making. Pathopsychomotor manifestation can be induced by the chronic action of the changed dopaminergic baseline in frontal cortical dysfunction patients. For those healthy and immu-

nocompetent subjects subtle change of the serodopamine concentration are less susceptible to develop psychosis. In contrast, continued prolonged excessive dopaminergic activation is posited to induce neuronal degeneration in dopamine system, leading to a hypodopaminergic state and psychotic symptoms[7].

The central nervous system (CNS) is the most commonly affected site of the latent toxoplasmosis and this infection may exert a certain extent impact on the development of mental faculties. Patients with latent toxoplasmosis present specific changes in psychomotor performance. Their capacity of learning and memory decreases and the time to simple reaction is significantly prolonged. The infected subjects had lower IQ ($P = 0.003$) and lower probability of achieving a higher education ($P < 0.001$)[11]. This lower IQ was also observed in children aging from 3 to 13 years old with subclinically congenital toxoplasmosis[12]. These clinical evidence indicate that *T. gondii* infection in central nervous system may cause mental damage. Experimental studies in mice also indicated that *T. gondii* could alter host's behavior and neurotransmitter function[13]. Webster and colleagues performed a series of studies on the effect of *T. gondii* on rat's behavior and their results showed that the infected rats were significantly more active than the uninfected control animals[14,15]. In man, evidence suggests that infection with *T. gondii* associate with alterations of behavior and psychomotor skills. By examining 19 cases of *T. gondii* antibodies in patients with schizophrenia and affective disorders from the publications worldwide, Torrey and Yolken considered that *Toxoplasma gondii*, as an infectious microorganism might be an etiological agent in some cases of psychosis[3].

3 Surveying the Situation of *T. gondii* Infection in Patients with Psychosis in China

A large number of epidemiologic and clinic studies collected from 1953 to 2007 have shown that *T. gondii* infection may contribute to some cases of psychosis[16]. In animals, experimental infection indicated that *T. gondii* can alter their behavior and neurotransmitter levels[17]. In humans, however, clinic evidence showed that the acute infection with *T. gondii* can produce psychotic symptoms similar to those displayed by persons with schizophrenia. Recently, similar investigations on the relationship between *T. gondii* infection and psychosis have also been done in different areas in China (Figure 1). In these studies, antibodies against *T. gondii* were detected by ELISA, IFAT, or McAb-Sandwich-ELISA on patients with schizophrenia and bipolar disorder and normal[18–25]. Studies indicated that serum antibodies against *T. gondii* were associated with the alterations of behavior and psychomotor skills[26]. Clinic evidence showed that the seropositivity of *Toxoplasma* in children has associated with tiredness and intelligent development in some ways[25]. These results are in accordance with the results reviewed by Torrey and Yolken[3].

Figure 1. Distribution of the investigations on patients with psychosis and their *Toxoplasma gondii* antibody in China. Red five star showing Beijing location, the black dots showing related city locations, province names shown in related regions.

In most of the studies, CCMD-2R (classification and diagnosis criteria of medical psychiatric diseases that is mostly used in China as ICD and DSM of the United States) was used as the diagnostic criteria in psychotic patients. Patients with obvious neuropathological changes were excluded. Results from these studies showed that the prevalence of antibodies against *T. gondii* in psychotic patients was much higher than in normal persons, with significant differences of $P < 0.05$ or $P < 0.01$ between them (Figure 2). The general results from the histogram are in accordance with the results reviewed by Torrey and Yolken and they also showed that seropositivity to *T. gondii* in children is associated with mental retardation and attention deficits. It was suggested that if the titer of antibody against *T. gondii* in the patient's serum was at 1 : 8 or higher, it was considered a seropositive to *T. gondii*. However, if the titer of anti-*T. gondii* antibody was at 1 : 1600 or more, it indicated the acute *Toxoplasma* infection.

Results from these studies have indicated that the incidence of *T. gondii* infection in psychiatric inpatients was 3 to 5 times more than that of the normal persons. These results suggest that some psychiatric symptoms may be caused by *T. gondii* infection. But, some researchers consider that the higher incidence of *T. gondii* in psychiatric patients may be due to their lower senses, incapable of self-dependent and weaker function of cell immunity, thus they have a higher opportunity of infecting *T. gondii*[26]. But the cause needs further study and throws more light on it.

It has been estimated that there was only one cat in each 50 to 60 families in China in past years. Based on the results from nationwide surveys, the average rate of *T. gondii* infection among normal peoples is about 6.02%. Recent years in China, more families have been keeping cats as pets in cities, and more families in villages keeping cats for protecting their crops from rats. Keeping cats is a very effective way to decrease the population of rats, and it was suggested that every family in a village should keep cats to kill rats[27,28]. However, people are not aware of the potential danger of disseminating diseases by cats.

4 Conclusion

The clinical and epidemiological studies mentioned above showed that there are some positive correlation between *T. gondii* infection and pathological effect on patients. There are some reasons based on:

First, sero-prevalence investigation in various regions of China indicates there is a positive correlation between *T. gondii* infection and psychosis. That is confirmed the results of Yolken and his colleagues' found that as compared with the control subjects, the individuals with first-episode schizophrenia had significantly increased levels of IgG, IgM, and IgA class antibodies to *Toxoplasma* proteins[29].

A second finding is *T. gondii* has a high affinity for brain tissues. Couzinet developed an *in vitro* model for studying of brain cells and the development of *T. gondii* in central nervous tissues. Result showed glial cells in central nervous structure are the targets contracted by *T. gondii*[30]. Flegr suggests *T. gondii* has a high affinity to brain by interacting with specific genes may induce functional changes in it[31].

Third, studies indicated that any changes in the neurotransmitter levels could induce changes in personality-profile[29]. In the Temperament and Character Inventory questionnaire, Hosak *et al* indicated that shifts in person ality factors correlated with concentration of particular

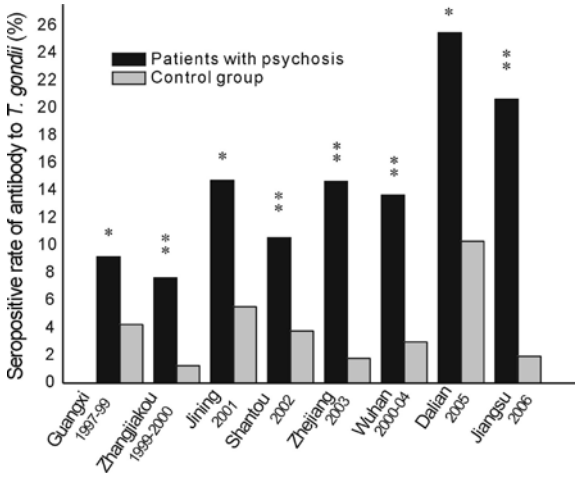

Figure 2. Serological studies of *Toxoplasma gondii* antibody in patients with psychosis and control subjects between 1997 and 2006 in different areas in China (*vs.* control, *: $P < 0.05$; **: $P < 0.01$, respectively).

neurotransmitters in brain tissue and *T. gondii* produced an increase in dopamine concentration[32]. These results are consistent with the studies indicating that brain infection with *T. gondii* can result in behavioral aberrant in experimentally infected animals[33].

Fourth, Benjamin and Ebstein reported that the level of the factor Novelty Seeking was associated with certain alleles of dopamine transporter and receptors. A psychomotor study on 875 military conscripts with latent toxoplasmosis showed positive subjects have significantly lower psychomotor performance in Novelty Seeking (NS) scores[34]. Jones-Brando and his colleagues demonstrated several commonly used medications of antipsychotics such as Fluphenazine HCl, Chlorpromazine and Clozapine, for treating schizophrenia and bipolar disorder have the ability to inhabit the replication of *T. gondii*[35].

Such studies imply that psychosis is the diseases of brain structural or functional abnormalities, which the causation of the diseases may be infectious microorganisms such as *T. gondii*. We suggest that patients with CNS symptoms detection of etiologic agents should be attached a certain importance, and development of medications with the function of anti-specific infectious microorganisms in CNS may have a promising significance.

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