Epidemiological evidences from China assume that psychiatric-related diseases may be associated with *Toxoplasma gondii* infection

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Submitted: 2007-01-30 *Accepted: 2007-02-20*

Key words: **toxoplasmosis; antibody; psychiatric-related disease**

Neuroendocrinol Lett 2007; **28**(2):115–120 **PMID:** 17435677 NEL280207A03

Abstract

In recent years, the effect of *Toxoplasma gondii* infection on psychiatric-related aspects has been increasingly recognized. *T. gondii* has a high affinity for brain tissue where tachyzoites may form tissue cysts and persist life long. In recent years, 15 serological surveys about *T. gondii* infection and psychiatric diseases have been carried out in different areas in China. Studies showed that the prevalence of antibodies against *T. gondii* in psychotic patients was much higher than in normal persons; statistically differences were significant. Studies also reported that raising cats or enjoying the habit of eating raw or under cooked meet were potential risk factors for the infection of *T. gondii*. The epidemiological and serological evidence support the hypothesis that some psychiatric diseases such as schizophrenia or mental retardation might be linked to *T. gondii* infection.

INTRODUCTION

Toxoplasma gondii is a widespread apicomplexan parasite able to infect virtually all warm-blooded vertebrates. Between 22% and 84% of the population in both developed and developing countries was infected with this parasitic protozoan [1]. Ingestion of food or water contaminated with oocysts and ingestion of raw or undercooked meat contaminated with cysts are the main routes of postnatal transmission of *T. gondii*. In immunocompetent persons who infected with *T. gondii*, is characterized by reproduction of tachyzoites in cells of different tissues, and within months, tachyzoites disappear and tissue cysts form, mainly in the brain and muscles [2,3]. These cysts are believed to persist throughout the life of the immunocompetent hosts in whom psychotic diseases may be developed [4]. Toxoplasmic encephalitis, marked by dementia and seizures usually occurs in immunocompromised people, such as HIV-infected patients [5]. Congenital infection with the parasite occurs primarily by transmission of the tachyzoites from the mother and prenatal infection of *Toxoplasma gondii* is a high

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risk factor of schizophrenia in later life [6]. *In utero* infection with *T. gondii* may result in congenital defects, signs of the classic triad of toxoplasmosis (retinochoroiditis, intracranial calcifications, hydrocephalus). Evidence has shown that dopamine is one of the key neurochemicals related to human behavior [7]. An increased level of dopamine has been observed in mice experimentally infected with *T. gondii* [8]. Experimental studies *in vivo* have found that tachyzoites of *T. gondii* infect and multiply in both glia and neurons [9]. Results from the studies with brain slices organotype culture *in vitro* have shown that especially the glial cells are the targets of this parasite [10]. Studies have also indicated that astrocyte-specific structural protein, the glial fibrilliary acidic protein is beneficial for the formation of *T. gondii* cysts [11]. Many epidemiological investigations have been carried out to study the relationship between psychiatric diseases and toxoplasmosis [12–14].

Specific manifestation and etiological implication of psychiatric-related diseases

Brain is the most commonly affected site for prenatally infected toxoplasmosis. It may impact the development of mental faculties and produce abnormalities such as mental retardation, concentration disorder, and abnormal behavior [15,16]. Teenagers infected with the parasite may show a significant intellectual deficit [17,18]. Patients with latent toxoplasmosis also present specific changes in psychomotor performance. Their capacity for learning and memory decreases and their reaction time is significantly prolonged [19]. Infected subjects have lower IQ ($p=0.003$) and a lower probability of achieving a higher education ($p<0.0001$) [20]. This lower IQ has also been observed in children ranging from 3 to 13 years old with subclinical congenital toxoplasmosis [21]. Reports have also indicated that acute toxoplasmosis may cause psychiatric symptoms such as delusions and hallucinations [22,23].

There are suggestions that infectious agents may play some role in the etiology of schizophrenia and bipolar disorder. A large number of epidemiological and clinical studies carried out from 1953 to 2003 have shown that *T. gondii* infection may contribute to some cases of schizophrenia [22,24]. The clinical deterioration of schizophrenia suggests a disruption in cortical development in a patient's early life. Evidence has shown maternal exposure to toxoplasmosis can increase the risk factors of schizophrenia in adult offspring [25]. Experimental studies in mice also indicated that *T. gondii* could alter host's behavior and neurotransmitter function [26]. 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 [27,28]. In man, evidence suggests that infection with *T. gondii* associate with alterations of behavior and psychomotor skills [22]. By examining 19 studies 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 [13].

Serological investigation of T. gondii infection in patients with psychiatric-related disease in China

Fifteen investigations on the relationship between *T. gondii* infection and psychiatric diseases have been carried out in different areas in China as demonstrated in the map (Figure 1). Studies showed that serologically positive rates of *T. gondii* infection were much higher in psychotic patients than in normal persons, although the seroprevalence varied among different geographical areas and among different ethnic groups (Table 1). For example, the average infection rate of *T. gondii* in normal people in Sinkiang was 9.28% [23]; it was much higher by comparable with the infection rate of *T. gondii* in the Han nationality (6.02%) [44]. These significant differences may be due to the people in Sinkiang enjoying barbecue meat in which some parts may be raw. 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 excluding one study reported that sero-positive rate in patients with psychosis was somewhat high but there was no significance compared with control groups [37]; still the general results from the table 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 [24].

In the studies, antibodies against *T. gondii* were detected by ELISA, IFAT, or McAb-Sandwich-ELISA in patient and control groups. If the titer of antibody against *T. gondii* in the patient's serum was 1:8 or higher, it was considered to be seropositive. However, a titer of anti-*T. gondii* antibody of 1:1 600 or higher indicated acute *Toxoplasma* infection. Interestingly, Yu reported that there was a very high seropositive rate to *T. gondii* in both patients and normal people in a county hospital where most of the patients were from villages with poor living conditions and poor sanitation [34]. As Torrey et al. mentioned, psychosis seems to be endemic in some rural, lower socioeconomic areas in Ireland [43]. Li et al. reported that patients with psychosis who had close contact with cats displayed a significantly high percentage of antibodies to *T. gondii* (17/52) than that of the patients without such close contact (24/202) [33]. Interestingly, a significant difference of anti-*T. gondii* antibody was not found between men and women in the regions investigated in China [34,38].

Results from many studies have indicated that the incidence of *T. gondii* infection in psychiatric inpatients

Table 1. Serological studies of *T. gondii* antibody in patients with psychosis in China.

Area	Year of sampling	Methods used by test	Patients & symptoms	Seropositive rate (%)	Control groups	Seropositive rate (%)	p-value	Ref.
Urumqi	1987–93	IHA	Inpatients with psychosis	6.37 (43/674)	Inpatients from non-psychosis departments	1.53 (4/260)	<0.025	[23]
Guangxi	1990–91	IEST	Inpatients with mental disease	24.14 (182/754)	Normal persons employed in service work from same region	5.86 (17/290)	<0.01	[29]
Guangzhou	<1996	IHA	Inpatients with schizophrenia	10.80 (10/93)	–	–	–	[30]
Fujian	<1996	IHA	Inpatients with psychosis	28.36 (38/134)	Employees of hospital and their family members	8.33 (5/60)	<0.01	[31]
Hubei	1997–98	ELISA	Inpatients with schizophrenia	16.14 (41/254)	General population	10.35 (41/396)	<0.05	[32]
Jiangsu	1997–98	ELISA	Inpatients with schizophrenia	43.84 (64/146)	Normall persons for routine physicals	16.07 (9/56)	<0.05	[33]
Guangxi	1997–99	ELISA	Psychiatric inpatients or clinical patients	9.2 (38/413)	Normal persons from same region	4.27 (5/117)	>0.05	[34]
Zhangjiakou	1999–2000	IHA	Inpatients with schizophrenia	7.66 (17/222)	Healthy persons for routine physicals	1.28 (1/78)	<0.05	[35]
Shandong	<2001	IFAT	Inpatients with primary epilepsy	14.77 (13/88)	Students from Jining Teachers College	5.56 (8/144)	<0.01	[36]
Shantou	<2002	ELISA or IHA	Inpatients with schizophrenia	10.58 (11/104)	Practice students and employee	3.8 (8/210)	<0.05	[37]
Zhejiang	<2003	IHA	Inpatients with psychosis	14.17 (64/455)	Normal persons from same region	1.80 (9/500)	<0.01	[38]
Wuhan	2000–2004	ELISA	Patients with first-episode-schizophrenia	13.7 (82/600)	Normal persons	3.0 (6/200)	<0.05	[39]
Shantou	2003–2004	ELISA	Inpatients with schizophrenia	13.1 (19/145)	–	–	–	[40]
Dalian	2004	ELISA	Inpatients with psychiatric-related diseases	39.8 (37/93)	Students	10.3 (9/87)	<0.01	[41]
Dalian	2005	ELISA	Inpatients with psychosis	25.53 (24/94)	Normal persons for routine physicals	10.34 (9/87)	<0.05	[42]

IEST, Immuno-Enzyme Staining Test; ELISA, enzyme-linked immunosorbent assay; IEST, immuno-enzyme staining test; IHA, indirect haemagglutination test; IFAT, indirect immunofluorescent antibody test.

was 3 to 5 times more than that of the normal persons (Table 1). These results suggest that some psychiatric symptoms may be caused by *T. gondii* infection. But, some people 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 contracting *T. gondii* [36]. But the causality 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% [44]. In recent years in China, more families have been keeping cats as pets in cities, and more families in villages keeping cats to kill rats for protecting their crops. Keeping cats is a very effective way to decrease the population of rats, and thus it was suggested that every family in a village should keep cats to kill rats [45–48]. However, people are not aware of the potential danger of disseminating diseases by cats.

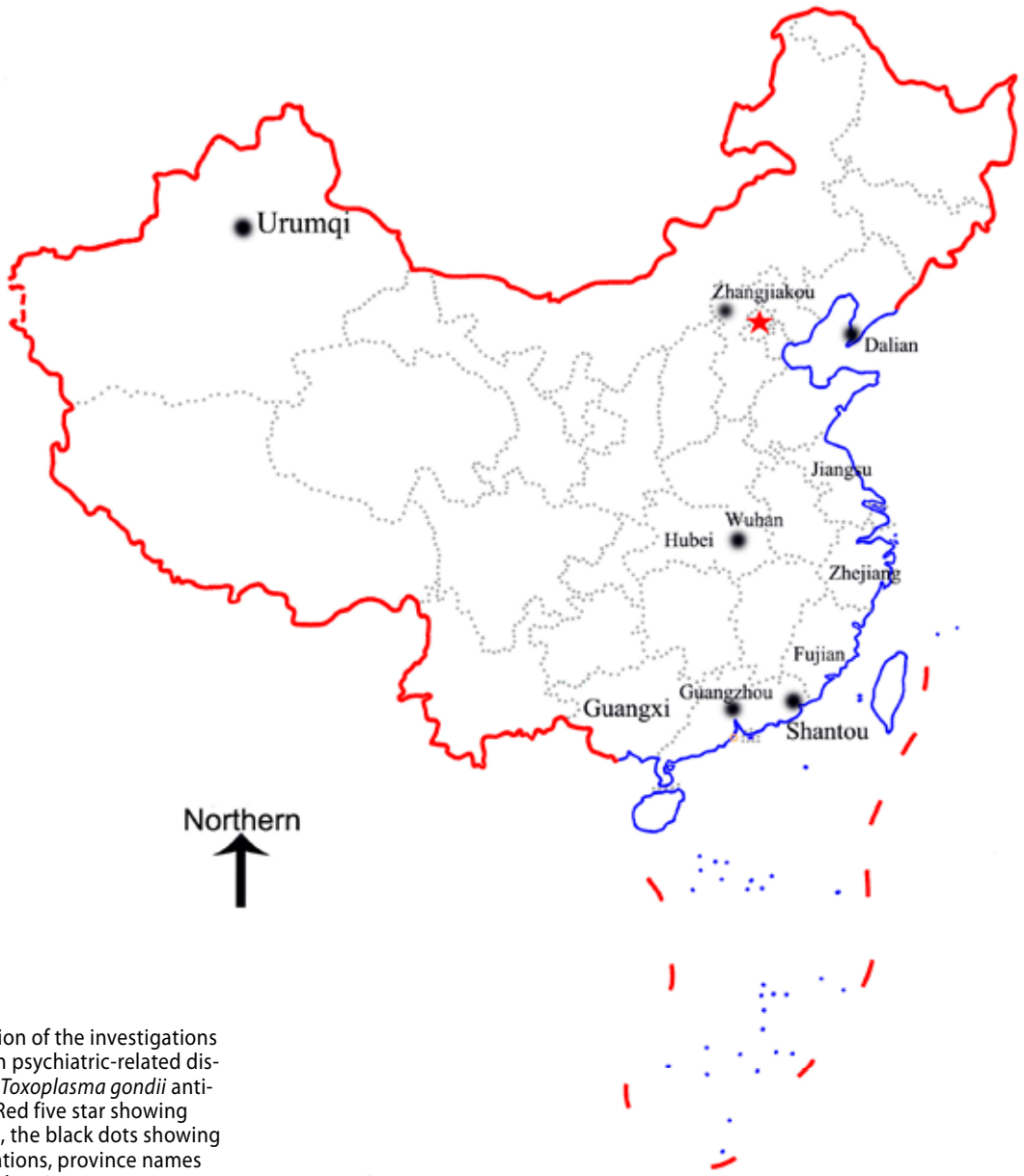

Figure 1. Distribution of the investigations on patients with psychiatric-related diseases and their *Toxoplasma gondii* antibody in China. Red five star showing Beijing location, the black dots showing related city locations, province names shown in related regions.

CONCLUSION

T. gondii is of special interest due to its high affinity for brain and life-long time infection in it. Numerous studies indicated that *T. gondii* was a candidate infectious agent replicating within the human central nervous system and to alter behavior in experimental animals [49]. Some patients with central nervous system diseases had a great exposure to cats in early childhood [50, 51]. The clinical and epidemiological investigations indicate that there are some links between *T. gondii* infection and pathological effects on patients.

Seroprevalence investigations among psychiatric patients performed in various regions of China indicated that there was a positive association between *T. gondii* infection and psychiatric-related diseases. These results are in accordance with the results of Yolken and colleagues, who found that, compared with control subjects, individuals with first-episode schizophrenia had significantly increased levels of IgG, IgM, and IgA class antibodies to *Toxoplasma* proteins [12]. By skin test, reactivity to *T. gondii* has also been found to be elevated in individuals with schizophrenia in different populations [52].

Studies on patients with toxoplasmosis indicated that the effect of latent *T. gondii* infection on human personality and behaviour associated with activity of the

dopaminergic system [53,54]. In the Temperament and Character Inventory questionnaire, Hosak et al. indicated that shifts in personality factors correlated with concentration of particular neurotransmitters in brain tissue and *T. gondii* produced an increase in dopamine concentration [55]. These results are consistent with the studies indicating that brain infection with *T. gondii* could result in behavioral aberrant in experimentally infected animals [56, 57]. Skallova et al. reported that discreased levels of Novelty Seeking was associated with *Toxoplasma gondii* infection [58]. That agrees with another psychomotor study on military conscripts with latent toxoplasmosis also showed that serologically positive subjects had significantly lower psychomotor performance in Novelty Seeking scores [59]. Moreover, Webster et al. found that anti-psychotics and mood stabilizing drugs commonly used for treating schizophrenia and affective disorder had the ability to inhibit the replication of *T. gondii* in cells [60].

These studies imply that psychiatric-related diseases are the diseases of brain structural or functional abnormalities, that the etiologic agents may be infectious microorganisms such as *T. gondii*. We suggest that patients with psychiatric symptoms detection of *T. gondii* antibody should be attached a certain importance.

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