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REVIEW

Toxoplasmosis and psychosis: environment makes a difference

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Abstract

Psychotic symptoms are the hallmark of one of the most debilitating serious mental illnesses, schizophrenia. They are also evident in certain forms of depression, bipolar disorder, delirium, and other neuropsychiatric disorders. Thus, differential diagnosis can sometimes be difficult to perform. Further, schizophrenia is believed to be, in part, related to genomic risk, with many variants already identified to contributing to genomic risk. However, most models include a likely role for environmental risk factors as well. We will explore the relationship between Toxoplasmosis, as one such environmental risk and schizophrenia.

Keywords: Toxoplasmosis gondii, Psychosis, Schizophrenia, Dopamine, Cats, Feline.

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Introduction

Psychosis

Psychosis burdens many people worldwide. In the United States, approximately 100,000 young people experience psychotic symptoms each year, and three in 100 people will experience symptoms at some time in their lives. Psychosis is characterized primarily by symptoms of either delusions, hallucinations or thought disorder [1,2]. These include seeing or hearing things that are not there or believing things that are not true or might be perceived as strange. Psychotic episodes in childhood are strong predictors of schizophrenia later in life [3].

Psychiatric illnesses that include psychotic symptoms such as schizophrenia, schizoaffective disorder, bipolar disorders with psychotic features, depression with psychotic features and even anxiety disorders like obsessive compulsive disorder (OCD), where poor insight can have a delusional feature to it, are felt to be a result of a combination of factors including environmental, such as trauma or substance abuse, and genetic. One such environmental factor that has recently been explored in leading to psychotic symptoms is the contribution of parasitic infections. *Toxoplasma gondii* infection has been associated with psychiatric illnesses however, research on the causal pathway is limited and therefore not clearly developed. As research has shown, Toxoplasmosis could be related to developing a psychotic disorder or alternatively Toxoplasmosis could cause psychotic symptoms by affecting similar brain regions and clinical manifestations might mimic a disorder like schizophrenia. Schizophrenia may well be a syndrome with many forms. If one were to consider an infection related form a careful diagnosis might lead to increased treatment options. While many people throughout the world are infected with *Toxoplasma gondii* and the prevalence of psychosis is rare in comparison, *T. gondii* should at least be considered as contributing factor in people who may have been exposed to *T. gondii*. However, the combination of genomic risk for schizophrenia and an infection is a possible model for a gene-environment type cause for illness.

The brain is one common area where *T. gondii* cysts form, affecting a large variety of cells with different functions. This could help us understand the etiology of psychiatric illnesses. One biological mechanism: *T. gondii* effects on hippocampus and amygdala. Evidence in mice shows higher cyst density by invading microglia, astrocytes and neurons, and structural changes in mice infected with *T. gondii*, which can lead to abnormalities in these regions [4]. Another hypothesis that could explain the biological plausibility is the interference of *T. gondii* with neurotransmitter function. Dopamine, a neurotransmitter known for its many functions including in behavior and cognition, memory and mood, also plays a role in the development of schizophrenia and psychosis. Typically, in patients with psychotic symptoms, there is an overproduction of dopamine and many antipsychotic medications used today block dopamine. Both *in vivo* studies in mice and *in vitro* studies have shown that *T. gondii* can stimulate the production of dopamine through enzymes involved in the dopamine synthesis pathway [5,6]. As mentioned previously, *T. gondii* infection can present clinically as psychosis.

Toxoplasmosis

Infection with the single-cell protozoan parasite *Toxoplasma gondii* causes a disease known as Toxoplasmosis. Felines are the definitive host and are the only animals capable of shedding the oocyst in their feces which thereby transmits the parasite to other intermediate hosts. It is estimated that one-third of the world's population has been infected with *T. gondii*, with seroprevalence varying throughout the world. The differences observed in prevalence rates throughout the world may be attributed to environmental factors such as food production practices, water treatment, climate, topography, cat feces-related hygiene, occupational and non-occupational soil exposure, and culinary practices, all of which vary widely between countries. High prevalence of *T. gondii* has been found in countries where consumption of raw or undercooked meat is common, such as France (47% prevalence), Tanzania (46% prevalence) and Nigeria (23.9% prevalence). In these regions there is an abundance of stray cats and in some the tropical climate is favorable to the survival of the oocyst, which is essential for transmission [7,8]. In the United States, the prevalence is 11%. Approximately 60 million people are infected with *T. gondii* and it is the third leading cause of food borne illness in the United States [9]. Toxoplasmosis contributes to over 300 deaths and 4,000 hospital visits each year [10]. Anywhere between 400 to 4,000 cases of congenital toxoplasmosis infection are reported each year in the United States [10]. Among those born with congenital toxoplasmosis 9% of cases have significant visual impairment. The rates of visual impairment from congenital toxoplasmosis in the three to four years after birth are much lower in the United States as compared to Europe (29%) and Brazil (87%) [7,11].

Transmission of *Toxoplasma gondii* to humans can occur in a variety of ways. The first is food-borne infection, which can occur by eating contaminated meat (especially pork, lamb or beef), ingestion of cysts after touching contaminated raw or undercooked meat and not washing hands thoroughly, or by eating food prepared with utensils or cookware that are contaminated and/or not properly cleaned. Animals can act as intermediate hosts and become infected by ingesting oocyst-contaminated food, water or soil that can then be transmitted to humans after consumption. Evidence from epidemiologic studies suggests that in places such as Ethiopia and France, where seroprevalence is high and eating raw beef is customary, tissue cysts are the main sources of infection [12]. Another method of transmission can occur through contact with cat feces, since they are the definitive host of the parasite and can shed the oocyst. Direct contact with cat feces

most often occurs when changing a cat's litter box [13]. Cat ownership has increased by approximately 50% in the last 20 years in the United States, increasing the contact between humans and cats [12]. The United States ranks highest among cat populations, followed by China, Russia, Brazil and France [14]. Evidence suggests that at any given time, about 1% of cats are shedding oocysts [12]. They excrete oocysts for an average of 8 days, which, under favorable environmental conditions, can be a substantial source of potential infection for humans [12]. Transmission can also occur through contact with cat feces by ingestion of soil or unwashed fruits or vegetables contaminated with the parasite [13].

Additionally, vertical transmission from mother to child (congenital) can occur through the placenta and, although rare, receiving a contaminated organ transplant or blood transfusion is also a possible model of transmission [8,15]. Congenital toxoplasmosis causes the highest burden of disease among humans who are infected with *T. gondii* [16]. According to the World Health Organization, the highest global incidence per 1000 live births and burden of congenital toxoplasmosis is in the following member sub regions: AMR(D) [3.4 (2.5-4.1)] which includes Bolivia and Peru, EMR(B) [2.5 (2.1-2.9)] which includes Iran, Lebanon, Syria, and United Arab Emirates, and AFR(E) [2.4 (2.2-2.5)] which includes Botswana, Central African Republic, Ethiopia, Kenya and South Africa [17]. Transmission patterns vary worldwide depending on environmental conditions. Exact transmission rates distinguishing foodborne transmission (tissue cyst) from direct cat-to-human transmission (oocyst) are unknown since people may be unaware of their exposure or have difficulty recalling risk factors that led to the infection.

Vulnerable Populations

The disease mainly affects the central nervous system, placing certain groups of individuals at higher risk over others. The vulnerable population for toxoplasmosis includes infants whose mothers have been infected immediately before or during pregnancy as well as patients who are immunocompromised, i.e. HIV positive patients, chemotherapy patients, those taking immunosuppressive medication, and organ transplant recipients [7,18]. *Toxoplasma* infection is a leading cause of death among patients concurrently infected with HIV [19].

Signs and symptoms of infection vary based on the health status of the infected individual. Healthy individuals who are infected may not be aware of their infection since their immune system is strong enough to prevent illness [18]. Those who are symptomatic upon initial infection may experience "flu like" symptoms such as aches and pains, swollen lymph nodes, fever or fatigue that typically resolve within a few weeks if left untreated [9]. Regardless of the presentation of symptoms during acute infection, chronic infection may lead to reactivation of disease later on, which, when coupled with an already weakened immune system, can lead to severe morbidity or mortality [10]. For example, immunocompromised individuals are more prone to symptoms of encephalitis, which most often result from reactivation of a previous infection [9,18].

Toxoplasma gondii can be very harmful in pregnant women because the parasite can cross the placenta. Most pregnant women who acquire infection are asymptomatic and rarely experience symptoms such as low-grade fever, abnormal lymph nodes or changes to their vision. However, congenital infection can result in miscarriage, stillbirth, or severe illness in the infant [20]. It is estimated that the prevalence of congenital toxoplasmosis is 1 per 1,000 live births in the United States, 1 per 770 live births in Southeast Brazil, and 1 per 3,000 live births in France [21-23]. Fetal transmission and the associated risks are highly dependent on maternal parasitemia, gestational age at infection, and maternal immune response to *T. gondii* [24]. Although the risk of infection by vertical transmission is present throughout pregnancy given exposure to the parasite by the mother, the most severe cases occur when maternal infection occurs early in the gestational period (first trimester). However risk of passing Toxoplasmosis to your child is highest in the third trimester [20,25]. Ultrasound findings may reveal symptoms of infection during gestation; otherwise the infant is diagnosed after birth based on clinical presentation of symptoms of infection [26]. A wide range of clinical disease can occur in children who are congenitally infected. The most common presentation of congenital infection is ocular disease or blindness, which has been shown to affect between 12%–30% of children. Congenital infection has also been known to cause intracranial calcifications, hydrocephaly, microcephaly, psychomotor and developmental delay in infants identified by both prenatal and postnatal screening programs. Infants congenitally infected are treated with antibiotics for up to one year [18,19].

Toxoplasma gondii infection is diagnosed by either serologic testing, genetic testing through polymerase chain reaction (PCR) or through isolation of the parasite in body tissue or fluids [27]. Serologic testing is the most common diagnostic test used, and is done to test for the presence of IgG and IgM antibodies. The presence of IgG antibodies against *Toxoplasma* reveals a previous exposure with the parasite, however does not indicate when it occurred, whereas IgM antibodies against *Toxoplasma* indicate an acute or recent infection. Distinction between acute and latent infection is most important in cases where the woman is pregnant or the individual is immunosuppressed. Antibody testing against *Toxoplasma* is readily available in most developed countries and routinely tested for in pregnant women where the prevalence of infection is high [10]. However, despite the wide use of serologic testing, it can fail to detect IgG and IgM antibodies during the active phase of *T. gondii* infection since antibodies might not be detected until up to several weeks after the initial infection. Testing the amniotic fluid by polymerase chain reaction

(PCR) can be used to confirm the diagnosis of the fetus in order to prevent unnecessary treatment [25]. Additionally, the presence of antibodies may go unnoticed in patients who are immunocompromised, since titer levels may be undetectable. Although the PCR method of detection is more sensitive, it is more time consuming and costly and therefore not used as often as serological testing [28,29].

Relationship between *Toxoplasma gondii* and Psychosis

There have been several studies looking at the association between parasitic infections and mental illness however the findings are mixed. A meta-analysis of 16 independent case- control studies from 2015 included patients with serum *T. gondii* IgM antibodies with acute psychosis either with schizophrenia or psychotic spectrum disorders and healthy controls. Study location varied and included countries such as Mexico, Turkey, Iran, Germany, China, and the United States. Among all the studies there was a significantly higher risk of IgM Toxoplasma gondii antibodies in acute psychosis as compared to controls (7.6% vs. 5.7%, OR = 1.68, 95% CI = 1.23 – 2.27, P = 0.001). However other aspects of the results were heterogeneous. In the studies that looked at schizophrenia only, there was a stronger association with *T. gondii* IgM antibodies (8.7% vs 4.6%, OR = 2.54, 95% CI: 1.63-3.96; p < 0.001) [30].

In another meta-analysis comparing 23 studies which includes patients with both first episode schizophrenia and those in all clinical phases there was an increased prevalence of *T. gondii* antibodies among individuals with schizophrenia [31]. In another meta-analysis of eight studies, seven of which were done on serological markers, and one from post-mortem brain tissue, there was a significant association between *T. gondii* infection and schizophrenia. Those who were exposed to *T. gondii* infection had a 2.7 times greater odds of having schizophrenia as compared to controls (OR = 2.70; 95% CI: 1.34-4.42) [32].

In a study published in 2015, a comparison of 50 studies from countries including Turkey, China, Iran, Mexico, USA, Vietnam, Peru, Spain and Ethiopia was done, which looked at if *T. gondii* was associated with bipolar disorder, schizophrenia, and addiction. There was a significant association between *T. gondii* infection and schizophrenia (OR = 1.81, 95% CI: 1.51 – 2.16, p < 0.00001). Even after controlling for publication bias, an association was still present (OR = 1.43, 95% CI: 1.21 – 1.70). All studies looked at IgG antibodies, except for one which looked at post mortem brain samples. The sample sizes ranged from 11 patients to 1,301 patients. Among these studies, seven looked at the association between *T. gondii* infection before schizophrenia symptoms. They showed an increased odds of *T. gondii* before schizophrenia onset (OR = 1.30, 95% CI: 1.05 – 1.61, p = 0.017). There was no significant association with IgM antibodies, which indicates a recent infection, present. Additionally, for the schizophrenia studies, there was a higher association between *T. gondii* and schizophrenia in Africa, South America and Asia respectively. The lowest associations were seen in Europe and North America. Bipolar disorder was also associated with T. gondii infection in a total of 11 studies (OR = 1.52, 95% CI: 1.06 – 2.18, p = 0.02. Specific subtypes of bipolar disorder were not mentioned. There were two studies that looked at obsessive compulsive disorder, one with a sample size of 42 patients and the other with a sample size of 12 patients (OR = 3.4, 95% CI: 1.73 – 6.6.8, p < 0.001). Although the findings for OCD are significant, they should be interpreted with caution since they are small sample sizes and did not clearly separate the OCD diagnosis from Generalized Anxiety Disorder [33].

A case control study in Nigeria compared the seroprevalence of *T. gondii* infection among those with a psychiatric diagnosis and those without. Study participants were between the ages of 18–64 years and had similar demographic characteristics. There were 140 cases and 140 controls recruited to participate and were matched on gender. Findings show that there was a significantly higher number of IgG antibodies, indicating a past infection, for psychiatric patients as compared to controls (OR: 2.04; 95% CI: 1.12-3.74, p < 0.02). Those who had a psychiatric diagnosis and had *T. gondii* IgG antibodies had a greater odds of being older in age (t = 10.76, df = 278, p < 0.001) and being female (OR = 4.6, 95% CI: 2.01 – 10.68, p < 0.001) [34].

A recent study in the United Kingdom sought to test whether prenatal and childhood cat ownership were associated with an increased risk of developing psychotic experiences (PEs) in early and late adolescence. Using the Avon Longitudinal Study of Parents and Children (ALSPAC), researchers followed women who were expected to give birth between 1991 and 1992. In this study 6,705 children at age 13 and 4,676 children at age 18 were included who had data on psychotic episodes. By contrast, findings revealed that cat ownership in pregnancy was not associated with psychotic symptoms at ages 13 or 18 years. These findings persisted even after adjustment for potential confounding factors including ethnicity, social class, housing type, maternal education and crowding index. Although the study above is one of the few that follows children longitudinally to see if psychiatric symptoms develop, cat ownership is not the only way one can become infected with *T. gondii.* As mentioned previously consumption of contaminated food is another source of infection. Another limitation is that the exposure variable (cat ownership) is limited from pregnancy to age 4 years, due to sensitivity of neurodevelopment. However, data shows that different regions of the brain have high variability in development. Therefore, by limiting the exposure age to four years old might be leaving out a significant population [35].

Treatment

Toxoplasmosis can be treated using medications such as pyrimethamine and sulfadiazine, including in pregnant

women. For those with a co-morbid diagnosis of psychosis and Toxoplasmosis, antipsychotics have recently shown to have anti-protozoal effects. Specifically, fluphenazine and zuclopenthixol have high anti-toxoplasmic activity.[36] Daraprim is also available for those who are congenitally infected as well as those who are immunocompromised, including HIV infected patients.[37] These findings are applicable to clinicians who are treating patients for psychosis that have been previously infected with *T. gondii*.

Conclusion

Both *Toxoplasma gondii* and mental health disorders with psychotic features exist in all areas of the world. There are differences in the rates of Toxoplasmosis in different countries and we have illustrated the importance of food handling practices as well as cat control in rates of infection. *T. gondii* infection is typically seen in the brain and can persist for many years. Both physical and mental manifestations of *T. gondii* should be considered during treatment. Importantly, clinicians that see patients with psychotic symptoms should be aware of the possible association between *T. gondii* infection and psychosis. Psychiatric assessments should consider testing for possible parasitic infection and may want to consider testing to see if the infection is acute or chronic. Additionally, clinicians should consider following up with a psychiatric assessment after exposure to parasitic infection. Such assessments can be done over a period of time given that the time between exposure and presentation of mental illness can be variable. Failure to recognize the etiology of psychotic symptoms can make your diagnosis and treatment incomplete or erroneous. Since patients with psychosis might present for psychiatric care much later than the onset of their symptoms, understanding the etiology of the disease might be more challenging. Future investigations are necessary to further understand the association between *T. gondii* infection and psychosis, exploring the role parasitic infections may play in mental illness.

Abbreviations

AFR(E): Africa; ALSPAC: Avon Longitudinal Study of Parents and Children; AMR(D): Americas; CI: Confidence Interval; EMR(B): Eastern Mediterranean; HIV: Human Immunodeficiency Virus; OCD: Obsessive Compulsive Disorder; OR: Odds Ratio; PCR: Polymerase Chain Reaction; PE: Psychotic Episode.

Competing interests

The authors declare no conflict of interest.

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