Association between infection with *Toxoplasma gondii* and psychiatric disorders

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**Abstract:** Toxoplasmosis is one of the world’s most prevalent zoonoses. The causative agent, *Toxoplasma gondii* (Nicolle et Manceaux, 1908) is a facultative heteroxenic, polyxenic apicomplexan protist. There are several potential pathways of transmission within and between host species. Most infections with *T. gondii* result from close contact with pets/cats, ingestion of tissue cysts in undercooked meat of infected animals, and oocysts from food or water contaminated by feline faeces. Recently, epidemiological studies have shown that *T. gondii* infection plays a prominent role in the pathogenesis of several psychiatric disorders. This report reviews the association between *T. gondii* infection and patients with psychiatric disorders, particularly schizophrenia, depressive disorders and bipolar disorders.

**Keywords:** toxoplasmosis, mental disorders, schizophrenia, depressive disorders, bipolar disorders

Toxoplasmosis is a highly prevalent zoonosis. The disease can cause mortality and significant morbidity in immunocompromised patients and congenitally infected fetuses/neonates (Elsheikha et al. 2009, Mohamed and Hajissa 2016). Its causative agent, *Toxoplasma gondii* (Nicolle et Manceaux, 1908), is a zoonotic pathogen that infects warm-blooded animals, including humans (Parlog et al. 2015, Bay-Richter et al. 2019). *Toxoplasma gondii* is an obligate intracellular eukaryotic protist belonging to the phylum Apicomplexa (Tyebji et al. 2019). It comprises type I, II, and III genotypes; the first two are commonly isolated in humans (Kim and Weiss 2018). About one-third of the world’s population is estimated to be infected with *T. gondii*, with marked geographical variations (Montoya and Liesenfeld 2004, Fuglewicz et al. 2017). Humans may be infected via horizontal transmission from the ingestion of tissue cysts in undercooked meat of infected animals and oocysts from feline faeces contaminating food or water. The transmission also occurs vertically from the infected mother to her foetus and horizontally from infected men to his male or female sexual partner (Hlaváčová et al. 2021).

Seroprevalence of *T. gondii* infection varies among countries and correlates with various sociodemographic and risk factors, such as age, ethnicity, residence, pet ownership, water supply, and pregnancy (Alvarado-Esquível et al. 2011, Cong et al. 2015, Muflikah et al. 2018, Achaw et al. 2019). Areas with high prevalence include Latin America, Eastern and Central Europe, Middle East, South-East Asia, and Africa. The reported seroprevalence rates were 10–70% in Asia, 8–22% in the USA and UK, and 30–90% in Central America, South America, and continental Europe (Dubey 2002, Dubey and Jones 2008, Pappas et al. 2009, Minbaeva et al. 2013, Wilking et al. 2016, Abdollahian et al. 2017). A study conducted at the University of Malaya in Malaysia reported a *T. gondii* seropositivity rate of 20% (n = 62) among people who had close contact with animals, with antibody positivity rates of 18% IgG, 1% IgM, and 1% IgG and IgM (Brandon-Mong et al. 2015).

The presence of specific IgM and IgG antibodies alone cannot be used as indicators of recent infection, and IgG avidity can help assess whether the infection is recent. It is based on the maturity of the IgG immune response, i.e., how avidly the IgG antibody binds to *T. gondii* (see Fonseca et al. 2017). A low avidity IgG indicates an early infection (acute), while a high IgG avidity confirms infection of more than three months (chronic) (Berredjem et al. 2017, Fonseca et al. 2017, Chemoh et al. 2019).

The prevalence of *T. gondii* infection in humans has increased since most people are unaware of the risk factors of acquiring it, such as lifestyle and eating habits. Also, there is little awareness of the association of *T. gondii* infection with educational level and psychotic syndromes...

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(mental retardation and schizophrenia) (Muflikhah et al. 2018). *Toxoplasma gondii* infection does not cause serious illness in most adults and often there are no clinical manifestations. Latent *Toxoplasma* infection is usually asymptomatic in immunocompetent subjects (Borráz-León et al. 2021). However, blindness and mental retardation in children may result from congenital infection and in those with depressed immunity, the disease may be severe (Hammadnejat et al. 2010, Borráz-León et al. 2021).

In the acute phase of the infection, *T. gondii* can multiply in almost all tissues and then form long-lived cysts in muscle and liver tissues and nerve cells during the latent/chronic stage of the infection (Lyons et al. 2002). The infection is primarily subacute, with focal neurological symptoms that occur along with altered mental state, fever and headache. Subcortical or cortical brain lesions may be present in more than half of the patients with cerebral toxoplasmosis, resulting in hemiparesis, speech and walking difficulties (Luft et al. 2012).

Epidemiological studies have recently highlighted the prominent role of *T. gondii* in the pathogenesis of several psychiatric disorders, including in people who are unable to interpret details that typically correlate with cognitive and depressive illness, such as mental retardation and schizophrenia (Del Grande et al. 2017, Muflikhah et al. 2018). The first study of the association between *T. gondii* infection and the psychiatric patient was reported in Poland in 1953 (Kozar 1953). It has now been shown that *Toxoplasma* infection is associated with multiple neuropsychiatric conditions, posing exciting questions about how the parasite biology and its relationships with the brain and immune system could contribute to mental health disorders (Tyejbi et al. 2019).

**Toxoplasma gondii**

*Toxoplasma gondii*, one of the most polyxenous parasites, is a tissue cyst-forming coccidian that can infect both warm-blooded animals (mammals and birds) and humans (Tenter et al. 2000). In most regions of the world, *T. gondii* is widespread and is of veterinary and medical significance in the intermediate hosts, causing abortions or congenital diseases. Humans get infected via two principal ways, i.e., inherited and acquired. The latter is mainly due to ingestion of undercooked meat or accidental ingestion of oocysts in a cat’s faeces (Tenter et al. 2000). Inherited infection occurs when a pregnant woman is acutely infected and transmits it to her foetus. When this happens during the first trimester of pregnancy, it might result in an abortion or significant congenital defects in the newborn. Infection with the common *Toxoplasma* genotype II strain, especially in the third trimester of pregnancy, causes less severe outcomes such as vision or hearing defects (Tenter et al. 2000, Pappas et al. 2009).

*Toxoplasma gondii* is one of the most thoroughly investigated coccidians due to its great significance as a causative agent of zoonosis. *Toxoplasma gondii* can also manipulate the behaviour of its host (Prandovszky et al. 2011). The life cycle study of *T. gondii* in its intermediate hosts was completed more than 60 years after the first report of its asexual phase. The asexual phase occurs in various tissues of herbivorous or omnivorous intermediate hosts, while the sexual phase occurs in the intestine of definitive carnivorous hosts (Tenter et al. 2000).

Environmental susceptibility to oocysts is widespread as domestic cats, and other Felidae excrete the oocysts. Domestic cats are the leading cause of infection, as oocyst-forming is highest in them. The behavioural alterations in infected rodents increase the chances of the parasite being transmitted back to its definitive cat host (Prandovszky et al. 2011). After a cat ingests bradyzoites in tissue cysts (such as in an infected mouse), the sexual cycle ensues, and millions of oocysts are excreted. Unsporulated oocysts are shed in the cats’ faeces; the sporulation process occurs in the environment within one to five days and becomes infective. Intermediate hosts such as humans, rodents, sheep, cattle, pigs and birds ingest the sporulated oocysts in the contaminated soil, plants and water. The excystation process, whereby sporulated oocysts turn into sporozoites, occurs in the intermediate hosts’ lumen. The sporozoites invade the mucosa lumen and transform into tachyzoites; the blood then transports them to organs of the intermediate hosts such as the brain, eye, heart and liver. They actively multiply and turn into bradyzoites (within transformed host cells – the tissue cysts) when the host’s immune response develops. The tissue cysts localize in tissues for many years and are known as latent infection (Dubey et al. 1970, Tenter et al. 2000, Hill and Dubey 2002, Lyons et al. 2002, Dubey 2008, Webster and Dubey 2010, Dalimi and Abdoli 2012, Robert-Gangneux and Dardé 2012).

**Risk factors of Toxoplasma gondii infection**

*Toxoplasma gondii* infection has been related to various types of risk factors, such as close contact with cats or pets, cleaning up cat faeces or litter, consumption of undercooked meat, direct contact with soil, consumption of unpasteurised milk or milk products, eating unwashed vegetables or fruits, inadequate water supply and hygiene care (Cong et al. 2015, Muflikhah et al. 2018, Achaw et al. 2019). It is possible to infect animals such as cats, goats, sheep, chickens, ducks, and fowl by feeding them with food or water that was contaminated with *T. gondii* tissue cysts or oocysts. A few studies have shown that close contact of psychiatric patients with a pet/cat was substantially associated with the transmission of *T. gondii* (Alvarado-Esquivel et al. 2011, Cong et al. 2015, Achaw et al. 2019).

Other studies also reported that undercooked consumption of meat was substantially associated with *T. gondii* infection (Cong et al. 2015, Muflikhah et al. 2018). Infection with *T. gondii* can occur via cuts in the skin or accidental ingestion during human activities typically associated with their jobs, such as a farmer who comes in contact with soil, a chef who contacts uncooked meat and raw vegetables, meat sellers, and butchers. Contamination of uncooked meat is also related to environmental contamination with oocyst (Muflikhah et al. 2018).

However, other study found that undercooked meat consumption was not significantly associated with *T. gondii* infection (Alvarado-Esquivel et al. 2015). Previous studies

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found that farming (agriculture and gardening) and other activities that expose one to contaminated soil may be the most effective transmission route among psychiatric patients (Muflikhah et al. 2018, Achaw et al. 2019). However, in a hospital-based study in Durango City, Mexico, factors reported to be correlated with *T. gondii* infection in psychiatric patients were ingestion of uncooked raw fruits, frequency of consumption of meat, consumption of dried or refined milk, unpasteurised milk, or untreated water; while interaction with soil was found not to be correlated with *T. gondii* infection (Alvarado-Esquível et al. 2015).

There have been reports of the association between *T. gondii* infection and handwashing practices. In Indonesia, handwashing habits and water sources were significantly associated with *T. gondii* infection. Oocyst may contaminate water sources, generally used for cooking, bathing, washing and other activities. Contamination can spread through flowing water (rain or river) that can pollute the nearby areas. Spreading the region of exposure raises the risk of *T. gondii* infection. Consumption of contaminated water could occur directly from drinking water or accidentally swallowed during water activities in a polluted area (Muflikhah et al. 2018).

Sexual transmission has been confirmed in several animal species and indirect evidence suggests it also can be the risk factors to the humans. Studies in the Czech Republic found some evidence that toxoplasmosis can be transmitted by seminal fluid also in humans. Although seminal fluid rarely contains tachyzoites during acute toxoplasmosis and the risk appears minimal, transmission could occur by another form of the parasite, possibly even in the latent stage of toxoplasmosis (Flegr et al. 2014, Hlaváčová et al. 2021). The strong positive association between frequency of oral sex and toxoplasmosis suggests that bradyzoites in tissue cysts, rather than tachyzoites that cannot pass through the digestive tract, are probably responsible for the sexual transmission of toxoplasmosis (Kaňková et al. 2020). The transmission in the ejaculate, even if rare, can play a very important role in the etiology of congenital toxoplasmosis.

A recent study found that the seroprevalence of *T. gondii* infection in women with infected male partners (26%; n = 156) was higher than in women with uninfecte male partners (18%; n = 477; p = 0.045). Therefore, a partner’s seropositivity seems to be a risk factor for infection in women (n = 593; p = 0.045) but not in men (n = 573; p = 0.816) (Hlaváčová et al. 2021). Pregnant women should be advised against unprotected sex with men who are *T. gondii* positive or of unknown *T. gondii* serology status (Flegr et al. 2014).

**Psychiatric disorders**

Psychiatric disorders are increasingly important in developing countries such as Malaysia. National Health and Morbidity Survey (NHMS) in 2011 stated that psychiatric disease affects 12% of Malaysians aged 18 to 60. The incidence of mental health disorders among adolescents showed an increasing trend, from 11% in 1996 to 29% in 2015, according to NHMS (2015) (Institute for Public Health (IPH) 2015). In 2017, one in five adolescents was found to have depression, and is more common in males. Two in five women (42%) compared with men (37%) faced anxiety, and one in ten adolescents is stressed (Institute for Public Health (IPH) 2018). The World Health Organisation (WHO) has predicted depression as the world’s leading cause of disease burden by 2030.

Previously, the latent form of *T. gondii* infection was thought not to result in any significant sequelae, and only reactivation of the infection poses a real threat (McConkey et al. 2013). However, a growing body of evidence suggests that persistent and latent infection may be responsible for several neurologic and psychiatric symptoms (Henriquez et al. 2009, Borráz-León et al. 2021). Several findings have shown that *T. gondii* seropositivity is associated with personality changes and multiple psychiatric disorders, such as schizophrenia, suicide attempts, obsessive-compulsive disorder, bipolar disorder, and depressive disorder (Daryani et al. 2010, Alvarado-Esquível et al. 2011, Dalimi and Abdoli 2012, Cong et al. 2015, Del Grande et al. 2017, Muflikhah et al. 2018, Achaw et al. 2019, Borráz-León et al. 2021). Psychosis can be caused by infectious agents, like viruses, spirochetes, and protozoa. Upon activating the microbe-specific immune response, the infecting agent is released to the neurons. It can then directly or indirectly affect the neurons and brain structures (Bergink et al. 2014).

A systematic review and meta-analysis study focused on the relationship between *T. gondii* infection and obsessive-compulsive disorder (OCD), a common, chronic, and debilitating psychiatric condition (Nayeri et al. 2019a). Out of 389 people with OCD, 26% were positive for *T. gondii* infection. Meanwhile 17% of 9484 people did not have OCD were positive for *T. gondii* infection. Estimation of the random effect model indicated a significant common odds ratio [(OR) = 1.96, p = 0.119]. Thus, *T. gondii* infection could be associated with OCD (Nayeri et al. 2019a).

Another condition that can be related to *T. gondii* infection is Alzheimer’s disease (AD). It is an important neurologic disease characterised by beta-amyloid plaque deposition and irreversible loss of brain neurons (Nayeri et al. 2019b). A systematic review and meta-analysis study on *T. gondii* infection and AD were performed, involving eight reports and a total of 3,239 subjects (360 cases and 2,879 controls). Meta-analysis (random effect model) showed a significant result (OR = 1.53, p = 0.079). Thus, they considered *T. gondii* as a risk factor for the development of AD and exacerbation of its symptoms (Nayeri et al. 2019b).

Unnatural causes of death, such as traffic accidents (TA) or suicide attempts (SA), are a significant health burden worldwide (Sutterland et al. 2019). Latent infection with *T. gondii* has recently been proposed as a biological risk factor for TA and SA. A systematic study for evidence of an association between *T. gondii* infection and TA and/or SA was performed using PRISMA guideline in Medline, Pubmed, and PsychInfo. They found a significant association of antibodies against *T. gondii* with TA (OR = 1.69, p = 0.003) and SA (OR = 1.39, p = 0.006). Indication of publication bias was found for TA, but statistical adjustment for this bias did not change the OR (Sutterland et al. 2019).
Attention-deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric illnesses in children and adolescents, and it frequently persists into adulthood. A systematic review and meta-analysis study was conducted to investigate the association of *T. gondii* and ADHD (Nayeri et al. 2020a). The results showed a statistically non-significant association between exposure to *T. gondii* infection (based on *T. gondii* IgG detection) and increased risk of ADHD (OR = 2.02, *p* = 0.014). Furthermore, sensitivity analysis revealed stable results for the association between anti-*T. gondii* IgG antibody with ADHD. The limited number of studies in this field makes it still impossible to determine whether *T. gondii* is a risk factor for ADHD. It is crucial to have accurate information regarding the relationship between *T. gondii* and ADHD throughout the world to better understand the probable link between *T. gondii* infection and ADHD etiology (Nayeri et al. 2020a).

Infection with *T. gondii* has also been linked to a spectrum of psychiatric disorders, including autism spectrum disorders (ASD). A systematic literature review searched seven electronic databases on the prevalence of *T. gondii* antibodies among autism patients (Nayeri et al. 2020b). The result showed that latent *T. gondii* infection was associated with risk of ASD (OR = 1.93, *p* = 0.851). The results of Begg’s and Egger’s tests showed no publication bias (*p* = 0.851 and *p* = 0.297, respectively). However, there was no significant association between acute *T. gondii* infection and ASD (OR = 0.39, *p* = 0.910). Thus, the study demonstrated that *T. gondii* infection is not a significant risk factor for autism. However, another study by Flegr and Horáček (2020) reported a significant association between toxoplasmosis and autism (OR = 4.78).

**Depressive disorder**

A common condition and the leading cause of the global burden of chronic disease is depression. Depressive mood, lack of interest or pleasure, low motivation, a feeling of shame or low self-worth, impaired sleep or appetite, and poor concentration are common symptoms of mental disorders. It is commonly associated with significant morbidity and mortality (Hsu et al. 2014). In 2011, the World Mental Health Survey carried out in 17 countries found that, on average, one in 20 people experienced a depressive episode. Sometimes, depressive symptoms begin at a young age. The median prevalence of depression is approximately 40 years of age. However, this disorder may affect a person at any age and socio-economic background, but it is most prevalent in females. Depression is also associated with signs of anxiety. These symptoms may become chronic or recurring and lead to severe impairments in the ability of an individual to take care of daily tasks. Depression, at its worst, may lead to suicide (Marcus et al. 2012).

Many animal and human studies have postulated an inflammation-associated depression model. The hypothesis is that serotonin and glutamate biosynthesis are altered by immune-mediated cytokines and lead to depression or suicidal behaviour (Müller and Schwarz 2007). Inflammation can happen to a person who has an infectious disease and is associated with mood disorders. Microbial pathogens like *T. gondii* and cytomegalovirus may cause actual psychoses (Yolken and Torrey 2008). A reported mechanism of *T. gondii* in the development of depression is that the host immune response is triggered to produce proinflammatory cytokines (IL-6 and TNF). The cells become activated and produce IFN-γ that induces the activation of the enzyme, indoleamine-pyrrole 2,3-dioxygenase (IDO). The enzyme blocks *T. gondii* growth and causes tryptophan depletion.

The production of serotonin decreases in the brain, leading to depression (Webster and Mcconkey 2010, Dalimi and Abdoli 2012). Another study revealed that two *T. gondii* genes encode tyrosine and phenylalanine hydroxylases and catalyse phenylalanine to tyrosine. Tyrosine is converted into dopa, the precursor to dopamine, which specifically alters behaviour (Gaskell et al. 2009, Henriquez et al. 2009).

The Centers for Disease Control and Prevention (CDC) in the USA reported a 33% *T. gondii* seroprevalence rate worldwide (Hsu et al. 2014). Many incidences of depression were higher in patients with *T. gondii* infection, while seronegative patients were more likely to have no depression (Henriquez et al. 2009, Okusaga et al. 2011, Tedla et al. 2011, Zhang et al. 2012). A cross-sectional study conducted in Mecca, Saudi Arabia, reported a significant difference of anti-*T. gondii* IgG prevalence between patients with depression (26%, *n* = 39, *p* = 0.001) and healthy controls (15%, *n* = 55) (Al-Hussainy et al. 2015). Another case-control study in Durango, Mexico reported a significantly higher *Toxoplasma* seroprevalence in patients with major depressive disorder (MDD) (12%, *n* = 11) compared to controls (6.2%, *n* = 22), (OR = 2.14, 95% CI = 1.00–4.59, *p* = 0.04). They found that patients with a depressive episode and recurrent depressive disorders had similar *Toxoplasma* IgG prevalence rates. However, seropositivity rates of *Toxoplasma* IgM antibodies between the two groups were not statistically different (*p* = 0.27) (Alvarado-Esquivel et al. 2016b).

Another case-control study of 65 mixed anxiety and depressive disorder patients in Mexico showed a statistically significant difference in anti-*T. gondii* IgG prevalence between MDD and controls (OR = 4.03, *p* < 0.001) (Alvarado-Esquivel et al. 2016a). They reported that latent infection (IgG positive) rather than acute infection (IgM positive) was associated with MDD. They concluded that *T. gondii* infection might be related to moderate rather than severe depression.

However, several studies reported a non-significant difference in anti-*T. gondii* IgG antibody prevalence between depression and healthy control subjects. A study on the relationship between *T. gondii* infection and suicidal behaviour showed that 99 depressed individuals had higher anti-*T. gondii* IgG antibody level (adjusted geometric mean titre = 0.51) than 39 normal individuals (adjusted geometric mean titre = 0.4); the difference was, however, non-significant (*p* = 0.19) (Arling et al. 2009). However, they did not find a significant association between depressed individuals and *T. gondii* seroprevalence. A study in Egypt reported *T. gondii* IgG prevalence of 20% (24/118) and 12% (7/60) among depressed and control groups, respectively.
which was not statistically significant (El-Aal et al. 2016). Similar finding was observed in another study (Gale et al. 2014). The findings may be due to several limitations in interpreting results associated with a cross-sectional study design.

Another cross-sectional study in the USA reported no association between depression and latent *Toxoplasma gondii* infection regardless of whether they treated latent infection as a binary (i.e., presence/absence) or continuous variable (i.e., titre levels) (OR = 1.00, p = 0.868) (Gale et al. 2016). In Finland, there was also no significant difference in the prevalence of subjects with anti-*T. gondii* IgG antibodies between MDD patients (5.1%) and controls (4.8%) (Suvisaari et al. 2017). *Toxoplasma gondii* infection is also not a risk factor for MDD based on the findings of a systematic review and meta-analysis involving 1,657 MDD patients and 19,565 control individuals, but only 1,311 MDD patients and 6,015 controls without depression were involved in the review of cross-sectional studies. The result indicated that the pooled OR in MDD patients in case-control and cross-sectional studies was not significant (OR = 1.55) (Chegeni et al. 2019). However, more research is needed to determine the detailed association between *T. gondii* and dysthymia or mild to moderate depression.

It is also possible that pre-existing MDDs are associated with exposure to *T. gondii* due to raw meat consumption or outdoor exposure to the soil in some individuals, which can be associated with *T. gondii* (see Pearce et al. 2012). On the other hand, the differences in the findings could be due to differences in ways of determining “depression” (criteria or methods of measurement) among the studies (Alvaredo-Esquivel et al. 2016b).

**Bipolar disorder**

A chronic and persistent psychiatric disease, bipolar disorder (BD) is one of the leading causes of disability and death worldwide, affecting 2.4% of the world’s population (Merikangas et al. 2011). The etiology of BD is unknown; however, increasing evidence indicates that abnormal immune-inflammatory processes play a role. According to clinical findings, BD patients are at risk for chronic autoimmune disorders (Fries et al. 2019, Misiak et al. 2020). BD causes are multifactorial, originating from a complex relationship between genetic variation and environmental risk factors (Dakkak 2017). The affected individual has difficulties at work, social events, interpersonal relationships, and other significant areas. In different aspects of an individual’s well-being and socio-economic achievements, the condition may contribute to irreparable harm. BD is also characterised by manic and depressive cycles (Marcus et al. 2012). The intervention of infectious agents, particularly *T. gondii*, has received increasing attention in major psychosis development (Torrey et al. 2007, Yolken and Torrey 2008, Del Grande et al. 2017, Bay-Richter et al. 2019).

*Toxoplasma gondii* may be involved in BD development via its neurotropism, i.e., a predilection for encystation in the brain’s neurons, glial cells and astrocytes (Del Grande et al. 2017). Damage to brain tissue occurs due to the enlarged foci of necrosis and microglial nodules. In infants, obstruction of the aqueduct of Sylvius or foramen of Monro may cause periaqueductal, periventricular vasculitis and hydrocephalus. It may result in severe necrosis in the cortex and basal ganglia and also in periventricular areas. Also, toxoplasmic encephalitis occurs when multiple brain abscesses are present (Montoya and Liesenfeld 2004, Fekadu et al. 2010). Therefore, *T. gondii* has the potential to influence human behaviour as a direct effect on brain tissue.

Several studies have also observed neuroinflammation in *post-mortem* brain samples of BD patients, including microglial activation and elevated cytokine levels (Giridharan et al. 2020). Some immune-inflammatory alterations have been found in the peripheral bloodstream of BD patients. The role of pro- and anti-inflammatory cytokines in the pathophysiology of BD seems to be the focus of several studies in this field. Cytokines are small molecules that regulate immune responses as well as infection and injury. Cytokines can cross the blood-brain barrier (BBB) and impact serotonin catecholamine-related pathways, as well as the hypothalamus-pituitary-adrenal (HPA) axis. Chemokines (a subgroup of cytokines) may have neuromodulator and neurotransmitter-like actions and regulate neurogenesis, which is relevant to neuropsychiatric disorders (Giridharan et al. 2020, Borráz-León et al. 2021).

According to recent meta-analyses, some cytokine alterations found in BD patients become evident during symptomatic relapses associated with cognitive deficits, and this represents one of the main psychopathological characteristics of BD (Munkholm et al. 2013, Borráz-León et al. 2021). Another systemic review and meta-analysis study was performed in Poland that examined the levels of chemokines in peripheral blood of BD patients (n = 1221) and healthy controls (n = 663) (Misiak et al. 2020). The following chemokines were analysed: interleukin-8 (IL-8), monocyte-chemoattractant protein-1 (MCP-1), eotaxin-1, eotaxin-2, and interferon-γ-induced protein 10 (IP-10). The levels of IL-8 (p < 0.001), MCP-1, eotaxin-1 (p = 0.001) and IP-10 (p < 0.001) were significantly higher in BD patients as compared with controls. They suggested that chemokine alterations in BD might be related to mood state (Misiak et al. 2020).

A study in France reported that *T. gondii* IgG positivity was significantly higher in BD patients (77%, n = 80/110) than controls (48%, n = 41/106) (p = 0.005) (Hamdani et al. 2013). In another study, 9.1% (6/66) patients with BD and 5.6% (22/396) controls had anti-*T. gondii* IgG antibodies. In the third National Health and Nutrition Survey (NHANES III) in the USA, a higher incidence of BD was observed in *T. gondii*-positive than in *T. gondii*-negative subjects (OR = 2.4, p < 0.05) (Pearce et al. 2012). A case-control study among 171 BD patients and 80 controls in Ethiopia found that the *T. gondii* IgG antibodies prevalence was higher in individuals with BD (OR = 3.0) than in unaffected controls (Tedla et al. 2011). However, a study by Khademvatan et al. (2013) in the Golose Education Hospital, Ahvaz, Iran, reported no significant difference between *T. gondii* IgG level in BD (32%, 37/117)
and healthy individuals (27%, 53/200). Similarly, another study in the northern Mexican city of Durango also reported no statistically significant difference in *T. gondii* seroprevalence between these two groups (OR = 1.7, *p* = 0.26) (Alvarado-Esquível et al. 2019).

The potential exposure of *T. gondii* association between BD and depression has not been thoroughly investigated. *Toxoplasma* has different genotypes in terms of virulence, and their geographical recurrence may also vary (Khademvatan et al. 2013).

**Schizophrenia**

The term ‘schizophrenia’ refers to a group of psychotic reactions linked to mental disabilities and characterised by perception, thinking, affectivity, and behavioural changes. Its etiology is unknown and healing treatments are unavailable (Tardy et al. 2014, Muflikhah et al. 2018). Acute toxoplasmosis has been observed to resemble mental disorders when it is accompanied by positive psychiatric symptoms such as hallucinations and delusions (Flegr 2015). Based on this, serological surveys in psychiatric hospitals found that the prevalence of latent toxoplasmosis in patients, particularly those with schizophrenia, was often higher than in the normal population. It was once thought that schizophrenic patients had a higher chance of having *T. gondii* infection. Numerous studies have shown that, although schizophrenia symptoms typically do not appear until late adolescence or early adulthood, the disease process has its origin in earlier stages of brain development, and the psychotic episodes remain throughout the entire life (Gogtay et al. 2011, Fuglewicz et al. 2017).

People with schizophrenia have a daily habit that can lead to infection, such as low hygiene practices. Their outside activities could also lead to eating without recognising whether the food is safe or not (Muflikhah et al. 2018). A study found that schizophrenia patients were more exposed to cats than healthy controls (Dubey 2008). Indeed, *T. gondii*’s ability to invade the perinatal brain is correlated with this aspect of schizophrenia pathogenesis (Torrey and Yolken 2003). Some factors include variations in genetic vulnerability, mode of infection (tissue or oocyte), or duration of infection (in utero, adolescence or adulthood). Besides, personality traits associated with schizophrenia have been suggested to increase the *T. gondii* infection rate (Henriquez et al. 2009).

*Toxoplasma gondii* may contribute to the etiology of schizophrenia. There are four significant considerations related to this. Firstly, genes are known to affect the vulnerability of mice (Torrey et al. 2007, de Barros et al. 2017). In mice, more than five progressive generations with a pseudo genetic pattern have been transplacentally transmitted by *T. gondii* (see Beverley 1959). Therefore, 35-50% concordance between monoygotic twins in the genetic component of *T. gondii* linked to schizophrenia (Torrey et al. 2007).

Second, schizophrenia can cause abnormalities of neurotransmitters. For example, studies on animal have shown the impact of *T. gondii* on the abnormalities of neurotransmitters based on the level of dopamine and serotonin (Stibbs 1985). The mechanism(s) triggering behavioural changes in the host is unknown. However, two lines of published evidence suggest that the parasite alters neurotransmitter signal transduction: disruption of parasite-induced behavioural changes with psychiatric medications (specifically dopamine antagonists) and finding direct or indirect evidence of the increased level of dopamine (or the enzyme involved in the synthesis of dopamine, the tyrosine hydroxylase encoded by the parasitic genome) in the brain tissue of the infected hosts (Flegr et al. 2003, Prandovszky et al. 2011, Burgdorf et al. 2019). Dopamine metabolism problems have a significant effect on human behaviour. A variety of neurological disorders, including schizophrenia, attention deficit hyperactivity disorder, tic disorders, Torett’s syndrome, and dyskinesias, have been linked to dopamine dysfunction (Prandovszky et al. 2011).

A study found that infection of mammalian dopaminergic cells with *T. gondii* increased the levels of K+-induced release of dopamine by several folds, with a direct association between the number of infected cells and the quantity of dopamine released (Prandovszky et al. 2011). Infected mice’s brain sections were immunostained with a dopamine antibody, and they revealed many encysted parasites. *Toxoplasma gondii* causes a significant increase in dopamine metabolism in neural cells. The rate-limiting enzyme for dopamine synthesis (tyrosine hydroxylase) was discovered in intracellular tissue cysts in brain tissue with antibodies specific for the parasite encoded tyrosine hydroxylase. These findings point to a mechanism of parasite-induced behavioural alterations. The effects on dopamine metabolism that have been reported could be useful in interpreting reports of psychobehavioral changes in *T. gondii* infecting humans (Prandovszky et al. 2011).

Third, schizophrenia is a neurodevelopmental disorder associated with *T. gondii*. This might be a cause of perinatal infections and remaining latent for a long time before reactivation (Torrey et al. 2007). Fourth, the association between *T. gondii* infection and schizophrenia in animal models reliably suggests behavioural changes in *T. gondii*-infected animals (Webster 2001).

Many epidemiological studies in schizophrenia patients have reported increased *T. gondii* seropositivity (Torrey et al. 2007, Yolken and Torrey 2008, Okusaga et al. 2011, Fuglewicz et al. 2017). Increased *T. gondii* IgG titres were observed in people with schizophrenia (n = 950) (OR = 1.59, *p* = 0.03) (Okusaga et al. 2011). A prospective cross-sectional study in Germany comparing schizophrenia (n = 277) and healthy volunteers (n = 214) found that *T. gondii* serointensity was substantially higher in patients, but the serofrequency between the two groups was comparable. Serointensity was found to be significantly associated with C-reactive protein levels. Furthermore, the routes of infection appear to be also different between patients and healthy volunteers. The authors suggested that the *T. gondii* infection is related to schizophrenia in patients due to environmental factors and interactions among psychiatric vulnerability, immunomodulation, neurotransmitter systems, and genetic background (Hinze-Selch et al. 2007).
A recent study was conducted by Flegr and Horáček (2020) using 6,367 subjects tested for toxoplasmosis. The typical symptom associated with toxoplasmosis was anxiety, and the typical toxoplasmosis-associated disorders were autism (OR = 4.78), schizophrenia (OR = 3.33), attention deficit hyperactivity disorder (OR = 2.50), obsessive compulsive disorder (OR = 1.86), antisocial personality disorder (OR = 1.63), learning disabilities (OR = 1.59), and anxiety disorder (OR = 1.48). Toxoplasmosis may have a significant part in the etiopathogenesis of mental health disorders, and it has the second strongest association to schizophrenia, after autism (Flegr and Horáček 2020). Previous studies have shown that patients with psychosis have substantially elevated T. gondii IgG antibodies levels compared with controls. (Tamer et al. 2008, Alvarado-Esquivel et al. 2011, Achaw et al. 2019). In Iran, 73% (n = 80) of schizophrenia patients and 62% (n = 99) of healthy control persons were seropositive for anti-T. gondii IgG/IgM antibodies (Daryani et al. 2010). A Mexican case-control study found a significantly higher seroprevalence of anti-T. gondii IgG antibodies in schizophrenia patients (20%, n = 10/50) compared to controls matched by gender, residence place, age, and ethnic group (5%, n = 8/150) (OR = 4.44, p = 0.003) (Alvarado-Esquivel et al. 2011). A study conducted at the University of Gondar Hospital, Northwest Ethiopia, reported a significantly higher T. gondii IgG prevalence among psychiatric patients (34%, 51/152) compared to the control group (16%, 25/152) with p = 0.001 (Achaw et al. 2019).

Similar findings were observed in a case-control study conducted in Weinai, Eastern China. They reported that psychiatric patients have a substantially higher prevalence (p = 0.038) of T. gondii infection (17.3%, 77/445) compared to healthy controls (12.4%, 55/445). The types of psychiatric disorders were affective disorder (OR = 15.39, p = 0.745), somatoform disorder (OR = 8.33, p = 0.476), schizophrenia (OR = 32, p = 0.001), mental and behavioural disturbance due to alcohol intake (OR = 18.87, p = 0.184), mental and behavioural disturbance due to drugs intake (OR = 11.54, p = 0.901), obsessive-compulsive disorder (OR = 24.14, p = 0.068), mild depression (OR = 13.04, p = 0.923), moderate depression (OR = 15.39, p = 0.535), MDD (OR = 7.69, p = 0.390), mental retardation (OR = 22.50, p = 0.070), Alzheimer’s disease (OR = 15.15, p = 0.640), and dementia in Alzheimer’s disease with early-onset (OR = 16.67, p = 0.588). In schizophrenia patients, a high prevalence (32.35%, 11/34), of latent T. gondii was reported (Cong et al. 2015).

In Iran, the prevalence of anti-T. gondii infection was 46.9% (164/350) and 34.3% (n = 120/350) in psychiatric in-patients and controls, respectively. The types of psychiatric disorders with anti-T. gondii IgG+/IgM+ were personality disorder (0.9%/0%), posttraumatic stress disorder (1.1%/0%), mental retardation (0.9%/0%), schizoaffective (2.9%/0.3%), schizophrenia (18.6%/2.6%), delusional disorder (1.1%/0%), mental disorder (2.3%/0.3%), bipolar affective disorder (9.4%/1.4%), and MDD (5.1%/3.3%). The highest seropositivity rate was found among schizophrenia patients (46.3%, n = 162/350). The significant association between schizophrenia and toxoplasmosis was found for both IgG+ (p = 0.019) and IgM+ (p = 0.001) seropositivity (Abdollahian et al. 2017). IgM commonly becomes negative within 4–12 weeks of infection, so an elevated risk of schizophrenia might not be associated with it (Tamer et al. 2008, Hamidinejat et al. 2010).

Variation in results among the studies may be attributed to various factors, such as differences in control group selection, genetic susceptibility, and the use of antipsychotic drugs. Antipsychotic medications have been shown to inhibit T. gondii tachyzoite replication in schizophrenia-treated patients (Goodwin et al. 2011). Schizophrenia patients treated with anti-psychotic drugs showed increased anti-T. gondii IgG antibody compared to the placebo group (non-schizophrenia) but lower than schizophrenia patients without anti-psychotic treatment (Leweke et al. 2004).

CONCLUSION

The association of the neurotropic T. gondii parasite with an increased risk of psychiatric disorders, especially schizophrenia, is indicated by a substantial body of literature. A possible association between T. gondii and other psychiatric disorders has not been thoroughly explored. There is growing but still limited information on the relationship between T. gondii infection and risk factors in psychiatric disorders. Variations in the characteristics of the patients examined, including the severity and duration of the illness, the prevalence of associated psychiatric disorders, or the duration of the infection (acute or chronic), can define the various outcomes (Alvarado-Esquivel et al. 2019). More studies on the association between T. gondii infection and different kinds of psychiatric disorders would help further understand the etiology of psychiatric disorders and contribute to the preventive measures and treatment approaches.

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