TOXOPLASMOSIS AND RISK OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND MAJOR DEPRESSIVE DISORDER: A REVIEW ARTICLE

By

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Abstract

Toxoplasmosis is a worldwide disease caused by *Toxoplasma gondii* which is an obligate intracellular parasite that affects warm-blooded mammals including man. *T. gondii* neurotropic nature made it a potential causative agent for psychiatric and behavioral disorders. *T. gondii* uses a complicated mechanism to gain access to the brain, where it invades different brain cells, including astrocytes and neurons forming cysts. Attention deficit hyperactivity disorder (ADHD) represents a neuropsychiatric alarming concern due to its indefinite etiopathogenesis among children. Depression as major depressive disorder (MDD) is a common and serious psychiatric illness that negatively affects feeling, thinking and acting. Owing to the high prevalence of toxoplasmosis and the increased incidence of ADHD and MDD in recent years, this review studied the relationship between toxoplasmosis and each of ADHD and MDD.

Keywords: *Toxoplasma gondii*, Psychiatric disorders, Mental disorder, Attention deficit hyperactivity disorder, Depression, Major depressive disorder.

Introduction

Toxoplasmosis, a parasitic infection caused by the protozoan *T. gondii*, was identified as a “new disease” in Egypt (Ruge, 1952). Since then, many studies were published indicating its importance in Egypt (Taman and Alhusseiny, 2020). Attention-deficit hyperactivity disorder is a neurodevelopmental disorder, with symptoms such as inattention and hyperactivity (Afsharpaiman et al, 2017). Major depressive disorder, also referred to as depression, is often accompanied by loss of interest and decreased self-esteem (Arling et al, 2009). Association between *T. gondii* infection, neuropsychiatric disorders, and personality changes was suggested in the early 1990s (Havlícek et al, 2001).

Review and Discussion

Toxoplasmosis is found worldwide, and is estimated to have infected up to one-third of the global population (de Bles et al, 2021). It is a highly prevalent zoonosis where the definitive host of *T. gondii* is cat, which harbors the sexual parasitic cycle in the feline intestine and spreads infectious oocysts via feces, while the asexual reproduction of the parasite takes place in a broad spectrum of intermediate hosts, including humans who represent dead-end hosts of *T. gondii* (Imam et al, 2022). Human infection is often via the ingestion of sporulated oocysts detected on vegetables or in water and soil and eating raw or uncooked meat of infected animals. The nosocomial transmission was associated with blood transfusion, needle-stick injury and hematopoietic stem cell transplantation (Hussein et al, 2022). In pregnant women congenital transmission occurred (Al-Agroudi et al, 2016). *T. gondii* infection in effective immune response, fast-replicated tachyzoites were cleared, but some parasites are converted into bradyzoites persisted in cysts, predominantly in brain; astrocytes, microglia and neurons, or in muscle tissues (Weiss and Kim, 2000). Acute infection presents as mild flu-like symptoms, largely controlled by a healthy immune system (Kamal et al, 2023).

Clinically silent or latent infection in immunocompromised patients; AIDS, organ transplantation, and on chemotherapy, toxoplasmosis causes risky reactivated infection (Nissapatorn, 2017). Also, latent infection caused fatal encephalitis (Robert-Gangneux and Darde, 2012).

A fascinating effect of the neurotropic apicomplexan parasite on rodent’ behavior was
its ability to cause them to lose their natural aversion to cat odors (Vyas et al., 2007), with behavioral showed evidence that latent toxoplasmosis may lead to behavioral changes, the so-called manipulation hypothesis (Webster and McConkey, 2010). There was a less fear by rodents toward cats, which are the only definitive host, and so this cunning intracellular parasite manipulated its host, increasing the parasite’s chance to be transmitted by cats (Tyejbi et al., 2019).

*Toxoplasma gondii* was one of the causes of mental disorders (Sutterland et al., 2015). Its role in developing psychiatric illnesses was directly by affecting neurons, glial cell, and brain structures, or indirectly by causing a specific immune response, releasing proinflammatory cytokines and neurotoxic factors (Del Grande et al., 2017). An *in-vivo* study showed that *T. gondii* in mammalian dopaminergic cells repeatedly raised dopamine-dependent potassium secretion (Prandovszky et al., 2001). Staining infected rats' brains with dopamine-specific antibodies resulted in strong staining of cysteine-containing regions, and tyrosine hydroxylase, a limited enzyme in dopamine production, was within intracellular cysts. They concluded that *T. gondii* plays an important role in increasing dopamine metabolism in neurons, a process that led to neurologic and psychiatric disorders, such as ADHD (Akaltun et al., 2018a).

The attention-deficit hyperactivity disorder (ADHD), as one of the common neurodevelopmental disorders, is a chronic condition with onset before 12 years of age (Afshar-paiman et al., 2017). It is neurodevelopmental disorder that occurs by developed and developing countries and was more common in males than females (Rommelse et al., 2017). The clinicians increased recognition of this disorder is more likely today than in before. ADHD affected about 3-7% of school-aged children (Arabgol et al., 2009), but the adult ADHD has a worldwide prevalence of 2.8% (Fayyad et al., 2017). In Egypt, the incidence was up to 21.8% (Azzam et al., 2021). The ADHD clinical presentation was primarily inattentive, primarily hyperactive-impulsive, or both, depending on the symptoms' nature (WHO, 2018). Hyperactive-impulsive symptoms are associated with peer rejection, aggression, impaired concentration, and motor restlessness impairing both academic performance and interpersonal relationships (Rommelse et al., 2017).

Pathogenesis of ADHD is considered multifactorial. Population-based registry studies in children and adults suggested that infections were associated with an increased risk of mental disorders by a direct influence on the nervous system, immune activation, or inflammatory mediators. But, studies focused on relationship of infective agents and ADHD were scarce (Shehata et al., 2016). A wide range of functional and structural brain anomalies had been found to be associated with the disorder, especially in the dopaminergic system (Dunn et al., 2019). Also, for most people with ADHD, many genetic and environmental risk factors could accumulate causing disorder (Younis et al., 2023). Smoking (Becker et al., 2008), obesity (Buss et al., 2012), Stress (Bronson and Bale, 2014), and mothers' infection (Terasaki and Schvarz, 2016), could be among the factors that have been mentioned in various studies.

Toxoplasmosis might be associated with an increased risk of developing ADHD (Elzeky et al., 2022). Attention disorders, in ADHD, were associated with minimal brain damage and many disturbances in neurotransmitter levels, particularly disturbances in the level of dopamine (Akaltun et al., 2018a), which were recorded in toxoplasmosis (Nessim et al., 2023). Studies comparing infected and uninfected humans in terms of personality traits, behavior, and psychomotor performance as well as intelligence suggested the applicability of manipulation hypothesis of *T. gondii* to man (Martinez et al., 2018). Parasite influenced, deregulated dopamine metabolism and disease susceptibility to host' genes (Prandovszky et al., 2011). Dopaminergic neurotransmission pathway was strongly related to ADHD developing (Volkow,
2009). *T. gondii* cysts by settling and damaging brain, as well as performing changes in dopaminergic systems and neurotransmitters, may be involved in ADHD severity (Akaltun et al, 2018a). Behavioral changes of *T. gondii*-infected rodents resembled patients’ clinical symptoms of ADHD (Carter, 2013). Also, resemblance between toxoplasmosis-induced changes and ADHD showed elevated activity levels (Flegr, 2002), deficits in motor performance (Gulinello et al, 2010), less anxiety (Afonso et al, 2012), increased novelty-seeking behavior (Donfrancesco et al, 2015), and increased injury risk (Lindemann et al, 2017).

Alvarado-Esquivel et al. (2017) found that children with ADHD were more likely to have been exposed to *T. gondii* than those without ADHD. The study of 151 children with ADHD and 149 healthy controls, measured serum IgG antibodies to *T. gondii* levels, showed children with ADHD had higher levels IgG antibodies than healthy controls, suggesting that they had a higher rate of exposure to the parasite. Alvarado-Esquivel (2019) investigated the relationship between toxoplasmosis and ADHD in 100 adults and 100 healthy controls; found that adults with ADHD had higher levels of IgM antibodies to *T. gondii* than healthy controls, indicating that they had a more recent infection with the parasite. They also found that the severity of ADHD symptoms positively correlated with levels of IgM antibodies, suggesting that the parasite may be a contributing factor to the development of ADHD.

No doubt, the immune response to *T. gondii* contributed to ADHD development. Toxoplasmosis activates immune system, led to the cytokines production such as interferon-gamma and other immune molecules. These molecules affected brain function, behavior, and contributed to the ADHD symptoms development (Miman et al, 2010). Also, parasite affected the brain neurotransmitters levels, such as dopamine and serotonin (Prandovszky et al, 2011), which play a role in the ADHD developing (Del Campo, 2011). Tryptophan is a precursor for serotonin synthesis, required for *T. gondii* growth decreased the concentration of this amino acid, thus, decreasing serotonin level (Cerávolo et al, 1999). Inattention, reduced behavioral inhibition, and increased impulsivity caused by decreased serotonin via tryptophan depletion (Banerjee and Nandagopal, 2015). Also, tryptophan catabolism products play a marked role in increasing brain oxidative stress and apoptosis (Schwarz et al, 2012). The interferon-gamma and tumor necrosis factor-alpha were important on controlling the tachyzoites proliferation in acute and chronic stages of infection (Suzuki, 2002). The interferon-gamma induced the release of indolealmine 2, 3-dioxygenase, which has a role in tryptophan catabolism (Tan et al, 2012). So, concentrated indolealmine 2, 3-dioxygenase increased during *T. gondii* infection leading to decreased serotonin synthesis recorded in ADHD (Banerjee and Nandagopal, 2015). *T. gondii* alters the neurotransmitters levels in animals and possible effects may occur in humans (Kamal et al, 2022). Also, *T. gondii* could affect the expression of about 3000 host genes throughout its life cycle (Faraone et al, 2015). Remarkably, the expression of 17.7% of 237 ADHD susceptibility genes is affected by the *T. gondii* infection (Carter, 2013). Furthermore, it was clarified that the primary common emphasis in ADHD was on calcium signaling pathway and number of other metabolic pathways, such as tyrosine, tryptophan, and histidine, and number of recovered gene in this pathway was 44 (Liao et al, 2010). The calcium-signaling pathway is activated by voltage or receptor-gated ion channels, processes modulating intracellular stores, and phosphatidylinositol signaling system (Deckelbaum and Torrejon, 2012). The calcium channel blockers, calmodulin antagonism, or extracellular calcium reduce cell invasion by *T. gondii* (Song et al, 2004), and that calcium signaling being essential for cellular and developmental changes supporting *T. gondii* parasitism (Triana et al, 2018).
Alexandra et al. (2020), they investigated the seropositivity, serointensity, and avidity of latent toxoplasmosis in 140 adult ADHD patients and examined the influence of those variables on ADHD symptomatology. 20% were anti-T. gondii IgG seropositive without any anti-IgM. Seropositivity was associated with 2.8-fold increase in the ADHD odds in a confounder-adjusted multivariable analysis, which showed a significant association with T. gondii positivity, elevated IgG, with stronger anti-T. gondii IgG avidity. All severity increased in Toxoplasma-seropositive ADHD patients compared to seronegative ones with ADHD. They concluded that there was a high rate of T. gondii seropositivity in adults with ADHD, with a clinical impact of latent T. gondii on related symptoms in a serointensity- and avidity-dependent manner.

Major depressive disorder (MDD) is a common psychiatric disorders and serious illness (Li et al., 2021), and listed as the third largest cause of disease burden by the WHO since 2008, and may rank the first by 2030 (Dadi et al., 2020). Globally, an estimated 5% of adults suffer from depression, women were found to be more affected by depression than men (Institute of Health Metrics & Evaluation, 2023). MDD is often associated with loss of interest, decreased self-esteem, cognitive performance, suppressed energy level, feelings of worthlessness, and changes in weight, with attempt for suicide (Pratt and Brody, 2008). It is a mental disorder characterized by at least two weeks of feeling low mood and disappointment (Halonen and Weiss, 2013). Also, it led to a variety of emotional and physical problems and decreased function ability to work and home. MDD is the commonest mental disorder among behavioral disorders, coupled with remarkable morbidity and mortality (American Psychiatric Association, 2013).

No exact pathological theory explained pathogenesis, as MDD is a multifactorial disease caused by social interaction, psychological, and biological aspects (Li et al., 2021). Undoubtedly, latent toxoplasmosis caused behavioral disorders in both mice and humans (Elshafey et al, 2023). Studies of toxoplasmosis effect on depression were inconsistent. T. gondii caused chronic brain inflammatory process and contributed to both depression and its’ serious complication, suicidal behavior (Hlaváčová et al, 2021). Ozkan et al. (2020) reported that the MDD patient became better post toxoplasmosis treatment, which caused depression in immune system increasing suicidal behaviors by inducing monoamine neurotransmitters. Toxoplasmosis in mice increased the level of dopamine (Henriquez et al, 2009) and decreased serotonin synthesis in brain (Dalimi and Abdoli, 2012). Increase in dopamine release in neuronal cultures showed cysts (Prandovszky et al, 2011). T. gondii 2 genes encode tyrosine and phenylalanine hydroxylases catalyzed the conversion of phenylalanine to tyrosine, converted into dopa, the first step in dopamine production modified behavior (Gaskell et al, 2009).

The MDD and toxoplasmosis showed that depression was associated with microbias as human herpes-virus, HBV, Chlamydiaceae, and Borna disease virus (Wang et al, 2014). But, both Chegeni et al. (2019) and de Bles et al. (2021) didn't find significant relationship between toxoplasmosis and neither of depression nor affective disorders.

Bahceci et al. (2021) showed a correlation between anti-T. gondii IgG positivity and depression with suicidal thoughts. Also, Liu et al. (2022) recorded a high seroprevalence of T. gondii infection in psychiatric patients and that age was an influencing factor. But, Fernandes et al. (2020) reported that MDD didn't associate with anti-T. gondii IgG and IgM. The depressed patients had a lower seroprevalence of T. gondii as compared to controls, and they concluded that toxoplasmosis is not a risk factor for depression.

Studies in rodents and humans have linked T. gondii to various neuropsychiatric diseases associated with a dysfunctional dopaminergic system, such as bipolar disorder type I, schizophrenia, depression and Parkinson’s
disease (Fabiani et al, 2015), and mood disorders (Torrey and Yolken, 2003). Also, the mood stabilizers and antipsychotics used in bipolar disorder treatment inhibited T. gondii replication (Webster et al, 2006). Based on the fact that the main neurobiological changes caused by latent toxoplasmosis in man were consistent with the neuropsychiatric disease' pathophysiology as schizophrenia and mood disorders (Fabiani et al, 2015). Toxoplasmosis role in developing schizophrenia was proved by a longitudinal study (Niebuhr et al, 2007). Changes in brain morphology characterizing schizophrenia, such as gray matter reduction in frontal and temporal cortices, caudate, median cingulate, and thalamus were found typically for T. gondii-seropositive schizophrenia patients (Horáček et al, 2012). So, T. gondii-seropositive patients expressed more prominent positive schizophrenia symptoms (Holub et al, 2013), and had a 15-times higher possibility of having a continuous disease course than T. gondii-free patients (Celik et al, 2015).

T. gondii seropositivity was related to mental illnesses such as schizophrenia, bipolar disorder, generalized anxiety disorder, obsessive-compulsive disorder, suicide, aggression, and impulsivity (Akgül et al, 2021). But, De Witte et al (2015) didn't find significant relation between psychiatric disorders and toxoplasmosis. Anti-T. gondii antibody prevalence of ranged from 10 to 80% (Pan et al, 2017). Toxoplasmosis in psychiatric disorders became a heading topic (Hamdani et al, 2018).

Chronic T. gondii infection led to cortical neurodegeneration and resulted in interaction of complement and microglia, thereby dividing and clearing degenerate neurons (Li et al, 2019). Seroprevalence of toxoplasmosis in bipolar disorder patients significantly differed from that in the general population (Chaudhury and Ramana, 2019). However, Şirin et al. (2021) reported that bipolar disorder was not associated with toxoplasmosis. T. gondii was considered an etiological factor in some schizophrenia cases (Torrey et al, 2007). Akgül et al. (2021) suggested that toxoplasmosis may be an underlying component of schizophrenia pathophysiology. Liu et al. (2022) found that Mania, schizophrenia, bipolar disorder, depression and recurrent depressive disorder were associated with high anti-T. gondii antibodies positivity. In a cross-sectional study in (China), they showed that the anti-T. gondii IgG and IgM antibodies in psychiatric patients and in the general population were both at low levels, but the positivity rate of anti-T. gondii IgG antibody in psychiatric patients was higher than that in general population, indicating that psychiatrist must pay attention to T. gondii detection in psychiatric patients. Also, they recorded no significant difference in the positivity rates of anti-T. gondii IgM antibody between the general population and psychiatric patients indicating no difference in acute/recent T. gondii infection among the general population and psychiatric patients. However, these results disagreed with Chen et al. (2019) in China, who showed that anti-T. gondii IgG & IgM antibodies were both significantly higher in psychiatric patients than in control. El-Beshbishi et al. (2018) in Egypt found high of anti-IgG positivity in neurologically disabled non-syndrome children. Sapmaz et al. (2019) reported that toxoplasmosis affected susceptibility and depression severity in children, adolescents and pregnant women.

**Conclusion**

The relationship between toxoplasmosis and some psychiatric disorders, like ADHD and MDD, must be in consideration. Avoiding Toxoplasma gondii infection is a must to manage afflicted patients.

**References**


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