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Toxoplasma Immunomodulation Related to Neuropsychiatric Diseases

Mammari Nour and Halabi Mohamad Adnan

Abstract

Toxoplasma gondii (*T. gondii*) causes toxoplasmic encephalitis resulting from reactivation of latent toxoplasmosis. It is the most frequent clinical manifestation, characterized by multiple necrotizing brain lesions. Bradyzoite tissue cysts activate an immune response that has a major impact on controlling parasite persistence in the brain. The immune mechanisms stimulated in the brain cause a local inflammatory mediated by Th1 immune reaction cytokines. Several studies have linked this process to that active during different neuropsychiatric disorders, such as Schizophrenia. In addition to the immune reaction activated in the brain, this latter has the capacity to stimulate neurotransmitter production. *T. gondii* induces high concentrations of dopamine and tyrosine hydroxylase in the central nervous system and has also been shown to increase kynurenine/tryptophan ratio and elevated Kynurenic acid level, mainly in astrocyte cells. This imbalance plays a role in the pathophysiology of Schizophrenia. Results of different studies explain in this chapter support the idea that *Toxoplasma* is an etiological factor in Schizophrenia.

Keywords: *Toxoplasma gondii*, neuropsychiatric disorders, schizophrenia, immunity, neurotransmitter

1. Introduction

Toxoplasmosis is one of the most common parasitic zoonosis in the world. Its causative agent, *Toxoplasma gondii*, is an obligate intracellular protozoan, which has developed several potential pathways for the transmission between different host species. *T. gondii* is able to establish a persistent infection within the brain. In this case, the immunocompetent subject will harbor latent *Toxoplasma* cysts in his central nervous system (CNS). Chronic *Toxoplasma* infection is asymptomatic although studies suggest that it may be a factor associated with chronic neurological conditions (Schizophrenia, Parkinson, bipolar diseases, etc.) [1, 2]. When the infection occurs in a pregnant woman, contamination of the fetus is possible with varying consequences depending on the stage of embryogenesis and the degree of maturity of the immune system. The neurological disorders (hydrocephalus, microcephaly, mental retardation, intracranial calcification) or ocular (retino-choroiditis) of congenital toxoplasmosis reflect the neurological tropism of this parasite [3]. Similarly, during a progressive degradation of the immune system functions following infection with the human immunodeficiency virus (HIV) or immunosuppressive treatment, the brain is the preferred target for the reactivation

of latent *Toxoplasma* cysts [4, 5]. Parasite multiplication in the CNS induces a local inflammatory reaction resulting in brain damage and a strong synthesis of neurotransmitters which are involved in necrotizing brain lesions and in neurological disorders. The relationship between *T. gondii* infection and the development of the bipolar disorder (BD) has long been investigated, Evidence studies suggest that this infection may be related to neuropsychiatric disorders, especially Schizophrenia. Immune response has a major role in the persistence of *T. gondii* cysts in the brain. The protective immune reaction against *Toxoplasma* is very complex. During primary infection, the components of the nonspecific immune response occur first. *T. gondii* tachyzoites reach the intestinal lumen, enter the intestinal cells, and multiply in the cells of the lamina propria [6]. At this stage, infected enterocytes activate an immune response to limit parasite multiplication [7]. This response mainly involves neutrophils, macrophages, monocytes and dendritic cells via the secretion of different chemoattractant proteins. Secondarily, cellular immune response is specifically activated against the parasite [8]. It is essentially an immune response Th1-type. This response is marked by interleukin (IL)-12 production by antigen presenting cells, and interferon-gamma (IFN-γ) production by CD4+ T cells, CD8+ T cells, and natural killer (NK) cells (**Figure 1**). The Th1-type reaction most often induces a local inflammatory reaction, hence the interest of activating a Th2-type immune reaction that inhibits the activation of the Th1 immune response. The Th2 response is mediated primarily by two interleukins IL-4 and IL-10 [6] (**Figure 1**). This immune regulation seems to be of great interest in reducing the inflammatory reactions responsible for most lesions, but it makes the soil favorable to parasite multiplication. Despite the immune responses against *T. gondii*, this parasite has the ability to escape and spread via the bloodstream to infect different organs. In the central nervous system, tachyzoites have the ability to cross the blood-brain barrier (BBB), infect different types of nerve cells, and become encysted bradyzoites that persist throughout the life of the host. Several studies have shown in the mouse model the importance of IFN-γ in this control [9]. Among the parasitic factors, the genotype also has a role in the influence of the evolution of *Toxoplasma* infection. Type I strains are associated with high virulence in mice, whereas type II or III strains are considered avirulent for mice. Type I tachyzoites have the ability to cross epithelial barriers and reach immune-privileged sites more rapidly than type II
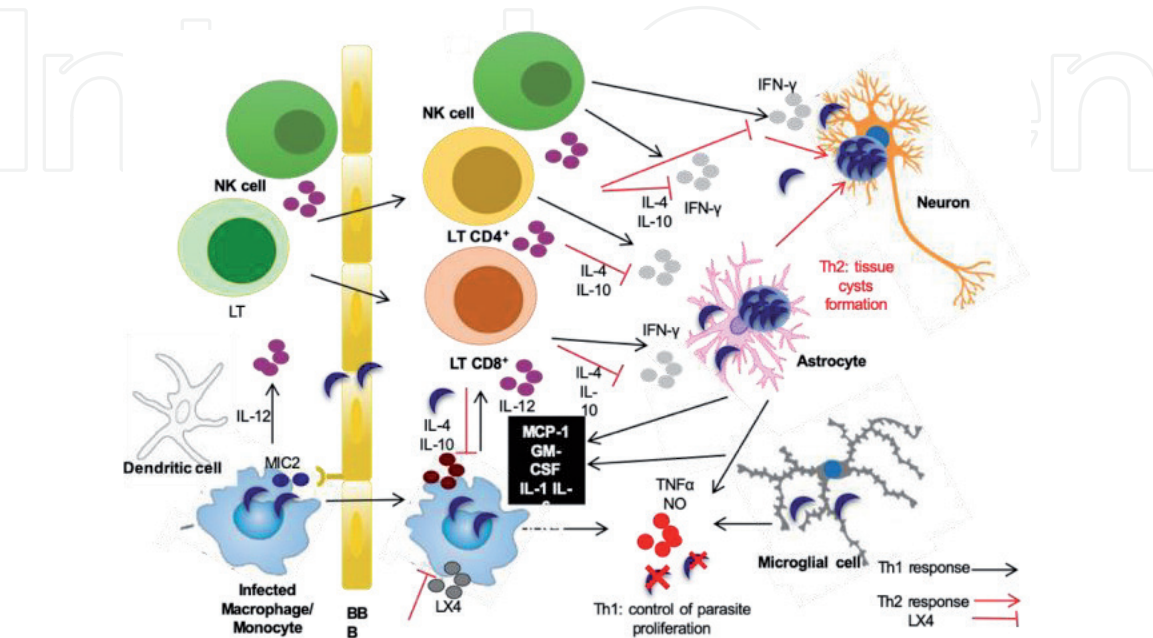

Figure 1.
Diagram showing the cerebral immune response during a cerebral toxoplasmosis infection in mice.

strains [10]. In human, several studies have reported severe acquired toxoplasmosis due to atypical strains in immunocompetent individuals. An overrepresentation of other atypical strains has been observed in patients with ocular toxoplasmosis [11]. The influence of the parasite strain on the development of the infection or the cerebral pathology remains however unknown.

2. The cerebral anti-*Toxoplasma* immune reaction

2.1 The central nervous system immunity

The central nervous system is closely linked to the immune system at several levels. The cerebral parenchyma is separated from the periphery by the BBB, the integrity of which is maintained by tight endothelial junctions. This barrier under normal conditions prevents the entry of mediators such as activated leukocytes, antibodies, complement factors, and cytokines. The myeloid cell line plays a crucial role in the development of immune responses at the central level, it includes two main subtypes: microglial cells, distributed in the cerebral parenchyma; perivascular macrophages located in the capillaries of the basal lamina brain and the choroid plexus. In addition, astrocytes, oligodendrocytes, endothelial cells, and neurons are also involved in the immune response in the CNS. By modulating synaptogenesis, microglial cells are more particularly involved in the restoration of neuronal connectivity following inflammation. These cells release immune mediators, such as cytokines, that modulate synaptic transmission and alter the morphology of dendritic spines during the inflammatory process after injury. Thus, the expression and release of immune mediators in the cerebral parenchyma are closely related to the plastic morphophysiological changes in the dendritic spines of neurons. Based on these data, it has been proposed that these immune mediators are also involved in the learning and memory processes. Microvasculature is a key element of brain damage. Endothelial cells are an important source of immune mediators such as a nitric oxide (NO), which are involved in the process of immune cell adhesion [12, 13]. A recent study shows that *T. gondii* invasion of neural tissue is mediated by epidermal growth factor receptor (EGFR), enhancing invasion likely by promoting survival of the parasite within endothelial cells [14]. Damage to the BBB can lead to increased permeability, which facilitates leucocyte access to the brain parenchyma. The release of mediators of endogenous inflammation and neurotoxins and the promotion of phagocytosis of cellular debris [6, 14]. Excessively activated microglial cells can cause major histocompatibility complex class II (MHCII) expression. This molecule facilitates the involvement of these cells in immune responses. Activation of microglial cells strongly influences the profile of cytokines released by two distinct mechanisms: recognition receptors and activation of the immune response [13, 15]. Activation of monocytes and macrophages is an important part of the innate immune response; it induces the production of pro-inflammatory cytokines and chemokines such as IL-8, monocyte chemoattractant protein1 (MCP-1), macrophage inflammatory proteins (MIP-1α and MIP-1β). Regulatory cytokines can also be activated within the CNS, such as IL-4 and IL-10 [8]. Expression of MHCII and adhesion molecules (CD11a, CD40, CD54, CD80, CD86) in activated microglial cells indicates that these cells can acquire antigen presenting activity and participate in the activation of T cells [16]. This suggests the existence of a network of complex interactions linking microglial cells, astrocytes and T cells; which creates a balance between the Th1/Th2 signals, which defines the immune response of the CNS. The role of astrocytes in the CNS is even more complex than that of microglial cells. Astrocytes are divided into two main subtypes: fibrous astrocytes located in the white matter; protoplasmic astrocytes located in the gray matter. These contribute to

the formation of the BBB [6, 15]. Astrocytes also act as neuroprotectants by secreting neurotrophic and releasing potentially toxic pro-inflammatory molecules.

2.2 The mechanism of *T. gondii* invasion in the brain

In the brain, dendritic cells and monocytes are the most permissive cells for initial *Toxoplasma* infection [17]. These cell populations probably play an important role in the spread of the parasite, including in the brain. The CD11c+ CD11b− dendritic cells infected promote the diffusion of *T. gondii* of the lamina propria to the mesenteric lymph nodes. Monocytes CD11c+ CD11b− are the main cell population that contains tachyzoites in the blood [17]. *T. gondii* was detected in mononuclear cells + of infected mice 1 day after receiving an intravenous injection of CD11b+ cells [18, 19].

The transepithelial migration capacity of tachyzoites is implicated in the passage of the parasite across the BBB. This could be done through the interaction of the intercellular adhesion molecule 1 (ICAM-1) of the BBB cells with the parasite MIC2 protein [20]. This interaction is important for transmigration of tachyzoites, as demonstrated *in vitro* in monolayers of several different cell lines [20] (**Figure 1**).

Macrophages are also responsible for the spread of *T. gondii* in the brain [21, 22]. The migration of infected macrophages into the CNS is mediated by the uPA/uPAR pathway and the expression of metalloproteinases 9 (MMP9) [23]. In the mouse brain during the acute phase of infection, *T. gondii* tachyzoites are able to infect all brain cells, mainly microglial cells, astrocytes and neurons. However, microglial cells tend to react against the parasite. These cells inhibit the growth of *T. gondii* and can, therefore, function as important inhibitors of *T. gondii* propagation in the CNS by mechanisms independent of NO and IFN-γ; but this does not prevent *T. gondii* from being able to encyst in these cells [15, 24]. Astrocytes and rat neurons are also suitable to host cells for the intracerebral proliferation of the PLK (type II) *T. gondii* strain [24]. These cells can harbor tachyzoites and cysts during the two respective phases of *Toxoplasma* infection [25]. Astrocytes also have the ability to control the proliferation of tachyzoites during the acute phase of infection for the local control of this opportunistic pathogen [26]. In neurons, the presence of tachyzoites or bradyzoites alters the functioning of infected neurons. These modifications will favor the persistence of the parasite [27, 28].

2.3 The regulation of the cerebral immune mechanism during *T. gondii* infection

After *T. gondii* has entered the CNS through the BBB, a cerebral immune response is triggered against the parasite. Experimental data on animal models show that the Th1-type immune response is activated against *T. gondii* to control the replication of the parasite in the brain. In the murine model, this immune response leads to the production of IFN-γ after infection with the ME49 (type II) strain [29–31]. This cytokine is the main mediator of parasite resistance in the murine model. IFN-γ produced by brain-resident cells is crucial for facilitating both the protective innate and T cell-mediated immune responses to control cerebral infection with *T. gondii*. Mice deficient for the IFN-γ receptor or those that are neutralized by an anti-IFN-γ antibody, are unable to control acute *Toxoplasma* infection [32]. During this host response, other cytokines and chemokines are produced. These may promote the infiltration of immune cells to the site of infection [33]. T cells and IFN-γ are essential for maintaining the latency of chronic infection in the brain and the prevention of reactivation of latent infection. The protective activity of T lymphocytes (CD4+, CD8+) results in the production of IFN-γ (**Figure 1**). The protective activity of these cells has

been demonstrated in a transfer of immune cells T, which conferred protection against the reactivation of cerebral toxoplasmosis in an IFN-γ deficient mouse [34]. However, the presence of TCD4 and TCD8 cells appears to be critical for the long-term maintenance of the latency of chronic *Toxoplasma* infection in the brain. In addition, mRNA encoding IFN-γ was also detected in the brains of *T. gondii*-infected and NK-cell deficient mice. This suggests that IFN-γ could be produced by non-T cells and non-NK cells. This production is important for the maintenance of chronic toxoplasmosis in the brains of mice [35]. Microglial cells and macrophages are identified as the major non-T and non-NK cells that express IFN-γ in the brains of *T. gondii*-infected mice [36]. Therefore, it is possible that the production of IFN-γ by these cells plays an important role in the prevention of cerebral toxoplasmosis. Microglial cells play an important role on the one hand in the innate defense system that limits parasite proliferation and on the other hand by regulating the production of chemokines that facilitate the accumulation of T lymphocytes at the parasite multiplication site. Murine astrocytes have also been implicated in inhibiting the growth of type II *T. gondii* strain *in vitro*. Astrocytes infected with ME49 (type II) *Toxoplasma* strain, produce IL-1, IL-6 and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) [37]. During the innate immune response, dendritic cells, macrophages, and neutrophils produce IL-12 in response to *T. gondii* infection. This cytokine is essential for the production of IFN-γ. Neutralization of IL-12 with antibodies to this cytokine resulted in 100% mortality in mice infected with an avirulent strain of *T. gondii*, mortality was associated with decreased production of IFN-γ [38]. In addition, IL-12 is also important for maintaining IFN-γ production by T cells during chronic infection. The production of IL-12 is regulated by Lipoxin A4 (LXA4), in order to avoid pathogenic inflammatory reactions in the brain during the chronic phase of *T. gondii* infection. This has been demonstrated by the high production of LXA4 in the serum of mice during chronic *Toxoplasma* infection 5-Lipoxygenase (5-LO) is an essential enzyme in the production of LXA4, 5-LO deficient mice succumbed to infection during the chronic phase, thus presenting a cerebral inflammatory reaction [39]. LXA4 is important for the downregulation of pro-inflammatory responses during the chronic phase of *T. gondii* infection. Studies have shown that lipoxins activate two receptors (AhR and LXAR) in dendritic cells. This activation triggers the expression of the suppressor of cytokine signaling (SOCS)-2. SOCS-2 deficient mice succumb to chronic *T. gondii* infection. This is accompanied by a strong production of IL-12, IFN-γ, and reduction of cerebral cysts [40]. Although Th1 immune responses play a critical role in resistance to *T. gondii* infection, Th2-like immune responses are also implicated in protective immunity. IL-4 plays a major role in the development of the cellular immune response and in the differentiation of T cells into Th2 cells. During the chronic phase of *Toxoplasma* infection, IL-4 inhibits the production of pro-inflammatory mediators to prevent the development of local inflammations, promoting the persistence of cysts in the brain. Mice deficient in IL-4 die during the late phase of infection [41]. In these mice, a histological study reveals local areas of acute inflammation associated with the multiplication of tachyzoites in the brain. These results indicate that IL-4 is protective against the development of toxoplasmic encephalitis by preventing the formation of cysts and the proliferation of tachyzoites in the brain. The action of IL-4 during the chronic phase of infection is enhanced by the production of IL-10 by T cells [41]. IL-10 also exerts an immunomodulatory role in regulating the Th1-type inflammatory immune response [42]. Mice deficient in IL-10 and treated with sulfadiazine develop fatal inflammatory responses in the brain during the late stage of infection [43]. IL-10 is important for the survival of mice during the acute and chronic phases

of infection. This is confirmed by the neutralization of this cytokine in *T. gondii*-infected mice [44] and following vaccination of the mice with *T. gondii* antigens (E/SA) [45].

3. The role of *T. gondii* in the etiopathogenetic of psychiatric diseases

Any infectious agent can affect neurons and brain structures after activation of the proinflammatory immune response and neurotransmitters, thus causing psychosis. Among the different infectious agents, *T. gondii* has received more attention for its location in the CNS. Many studies have suggested that toxoplasmosis is a risk factor for the development of behavioral changes and neuropsychiatric disorders such as depression, Schizophrenia, Alzheimer and Parkinson diseases. During an acute infection, the parasite is mainly present in peripheral tissues and blood, but also has access to the brain via immune circulating cells, as is explained in the part of *Regulation of the cerebral immune mechanism during T. gondii infection*. An early feature of *T. gondii* brain infection is the activation of glial cells, particularly astrocytes and microglia [24, 25, 46]. *Toxoplasma* cysts reside in the brain during latent infection. In individuals with acquired immune deficiencies, e.g., AIDS, or undergoing prolonged immunity, suppressive treatments, reactivation of the infection can lead to toxoplasmic encephalitis, also calling for cerebral toxoplasmosis. In recent years it has been shown that the latent toxoplasmosis, although often rejected as asymptomatic and clinically unimportant, can modify host behavior in human and rodents. This parasite has the capacity to be an etiological factor for some neuropsychiatric diseases [47].

A bunch of data hypothesizes that latent toxoplasmosis may be a risk factor for the depression. The low-grade inflammation caused by the chronic *Toxoplasma* infection it could be related to the development of behavioral symptoms, but the results have been varied multifactorial [48]. Regarding, the possible relationship between *Toxoplasma* infection and depression, study shows that specific *Toxoplasma* IgG titer levels correlated positively with depression [49]. One study found that this infection affected susceptibility to depression and severity of depressive symptoms in pregnant women [50]. Another study showed that male subjects infected with *Bartonella henselae* displayed more severe depressive symptoms when co-infected with *T. gondii* [51] but Pearce and collaborators, Sutterland and collaborators concluded that there is not any relationship between *T. gondii* infection and depression [52, 53]. Psychiatric patients with primarily severe or very severe depression are displaying more severe symptoms when are infected with *T. gondii*. In this recent study, results suggest that *Toxoplasma* infection can be related to anxiety, burnout and potentially to the severity of depression [48]. The possible link between *T. gondii* infection and Parkinson diseases is controversial. Tissue cysts of *T. gondii* reside especially in the amygdala, olfactory bulbs, hippocampus, cortical regions, and hypothalamus and could actively inhibit neuronal function in chronically infected mice [54]. Tachyzoite infection of neurons resulted in a dysregulated Ca^{2+} influx upon stimulation with glutamate, the major excitatory amino acid in the CNS leading either too hyper- or hypo-responsive neurons. Other experiments indicate that tachyzoites deplete Ca^{2+} stores in the endoplasmic reticulum that may contribute to the altered behavior of the host [54]. In addition, alteration of neurotransmitter pathways, degradation of dopamine-producing nerve cells and neurogenic inflammation induced by *T. gondii* infection are mentioned as etiology that could eventually lead to Parkinson disease [55]. Regarding the effect of *Toxoplasma* on the production of dopamine (DOPA) in the brain, studies have shown that this parasite-induced high concentrations of DOPA and tyrosine hydroxylase (TH)

in CNS [56]. Parkinson disease is associated with lower levels of DOPA. So, the association between *Toxoplasma* infection and neuropsychiatric disorders could be strongly related to Schizophrenia but not Parkinson's disease [57]. Evidence suggests that *T. gondii* could be an etiological factor for Schizophrenia. Clinically, latent toxoplasmosis and Schizophrenia both induce similar alteration in brain morphology: gray matter atrophy, loss of brain parenchyma, ventricle system enlargement, CD4+ and CD8+ T cell influx, pro-inflammatory immune system infiltration, dendritic retraction in basolateral amygdala accompanied by reduced corticosterone secretion, which may deal with *T. gondii*-induced behavioral change [47, 58, 59]. Indeed, the relationship between chronic or acute *Toxoplasma* infection and Schizophrenia seems to exist. Researches in this field are increasing to determine the existence of this association by epidemiological, medical and biological studies. The following section presents an overview of the explanations published.

3.1 The cerebral immune response activated during schizophrenia and *T. gondii* infection

In cerebral toxoplasmosis, the balance between host immunity and defense mechanisms in the event of parasite escape is the basis of asymptomatic infection. Inflammation and immune deregulation have consistently been observed in both *Toxoplasma* infection and Schizophrenia. In the acute phase of infection, Th1 proinflammatory reaction is promoted by cytokines released in CNS to control parasite multiplication, this reaction was controlled by activation of Th2 immune reaction to minimize local cerebral inflammation. This immune response enhances the multiplication of parasite and promotes persistence of *Toxoplasma* tissue cysts in neuronal and glial cells. In Schizophrenia, an imbalance Th1 and Th2 reaction have shown with major activation of Th2 immune response and production of IL-6 and IL-10 [60]. IFN-γ, IL-12, TNF-α, IL-4 and IL-10, together with IL-1 and IL-1β, IL-2, IL-6, granulocytes (GM-CSF and GSF), IL-17 and IL-23 are variably expressed by astrocytes, microglial cells, neuron, TCD4+ and TCD8+ cells [9, 13, 31, 41–43] (**Figure 1**). All these immune mediators have shown to be markers for acute exacerbations of Schizophrenia [60]. This immune system can influence mood and behavior through their ability to modulate neurotransmission; therefore, the idea that latent infection is clinically asymptomatic may be associated with neuropsychiatric disorders. Since tachyzoites induce inflammatory tropism in host cells more than bradyzoites, the proliferation of tachyzoites in the brain after cyst rupture may be related to the onset of Schizophrenia and other mental illnesses [61]. In people with acute Schizophrenia, the display of symptoms has increased responses to cytokines. With regard to cytokine-induced effects, the role of IL-1β and IFN-γ in the activation of astrocytes have a major role. These immune proteins induce activation of astrocytes and microglia cells to inhibit tachyzoite replication by producing high levels of NO. In addition, experimental studies in rodents have shown that TCD8+ cells play a central role in long-term immunity to *Toxoplasma*. Depletion of CD8+ T cells may cause reactivation of latent disease in later phases of chronic toxoplasmosis. Interest in the potential correlation to this observation is the regulation of TCD8+ lymphocytes typically observed in ischizophrenic patients [62]. After a short acute toxoplasmosis phase, the infection becomes latent and becomes encysted in the central nervous system and muscle tissue, probably throughout the life of the infected host. Evidence suggests that the parasite affects the synthesis of neurotransmitters, particularly DOPA, in infected individuals, which could lead to neurological and psychiatric disorders [63]. In addition to the studies that directly indicated the association between *Toxoplasma* infection and the increased incidence of Schizophrenia,

some indirect evidence also highlighted the role of *T. gondii* in the etiology of Schizophrenia. More knowledge about the pathogenesis of the disorder would lead to more effective prevention and treatment strategies.

3.2 The neurobiological studies related to *T. gondii* infection to schizophrenia disease

There are differences in *T. gondii* infection; the acute phase and the chronic and phase. Cerebral cysts are formed in the cerebral hemispheres, hippocampus, amygdala, basal ganglia, cerebellum, cerebral cortex, brainstem, and olfactory bulb, and a variety of brain cells that may be infected, including neurons, microglia and mainly astrocytes [46] (**Figure 1**). Encysted *T. gondii* bradyzoites are capable of inhibiting apoptosis and modulates some signaling pathways such as nuclear factor (NF-κB), mitogen-activated protein kinase (MAPKinase), phosphoinositide 3 kinase (PI3K)/ PKB/Akt and c-Jun N-terminal kinases (JNK); so that they can persist in host cells for long periods of time [64]. As cysts develop, the host cell degenerates and can break, releasing bradyzoites that can differentiate into tachyzoites, invade and kill surrounding cells, if uncontrolled by the immune system. Especially in immunocompromised patients, the infection is severe, sometimes with hydrocephalus, acute necrotizing encephalitis, and glial nodules formation. Lesions in the brain can manifest as behavioral symptoms by interfering with brain function in the area surrounding the lesion via mass effects or paracrine secretions. This explains the observation of high-concentration tissue cysts in the amygdala and nucleus accumbens, containing dopamine in limbic regions of the brain known to be an important control of motivation, pleasure, dependence, reward, and fear [47]. Other effects are more intriguing; Alteration of the neurotransmitter involves the production of homologous proteins to aromatic amino acid TH and dopamine (DOPA) 2 receptor (D2R) compounds with an increase in DOPA synthesis, tryptophan (TRP) degradation and the decrease in serotonin synthesis [56, 65].

The most likely mechanism of action in Schizophrenia affects neurotransmission in specific brain areas such as the thalamic-cortical limbic circuit of DOPA, 5-hydroxytryptamine (5-HT), gamma-aminobutyric acid (GABA), and glutamate. As a result, schizophrenic patients show abnormal levels of these neurotransmitters. Studies show an increase in DOPA release in the limbic system [47, 66]. In addition, *T. gondii* involves in the etiopathogenesis of Schizophrenia affecting neurotransmitters, especially DOPA [67]. The production *T. gondii* bradyzoites leads to induce liberation of TH, the enzyme that catalyzes the conversion of L-tyrosine (L-Tyr) to L-dihydroxyphenylalanine (L-DOPA) [68] and then L-DOPA is converted to DOPA by the enzyme DOPA decarboxylase. Dopamine is shown to be an essential product that stimulates proliferation and enhance infection and conversion of *T. gondii* in the brain [68]. After the synthesis of DOPA, it is transformed into phenylalanine (Phe) and tyrosine (Tyr) via the activity of phenylalanine hydroxylase (PAH). the elevation of the Phe/Tyr ratio and the alteration of PAH activity is related to the activation of the Th1-type immune response, which is activated during *T. gondii* infection. The increase in DOPA production was originally thought to be a product of inflammation of brain tissue (**Figure 2**). Blood levels of Phe and Tyr were increased in *T. gondii*-positive individuals with aggressive personality traits, and in particular those with overt history of aggression and suicidal behavior, so this mechanism could explain the link between Toxoplasmosis and Schizophrenia [69]. The increased concentration of DOPA in specific parts of the brain of patients is presumed to be responsible for the positive symptoms of this mental disorder. However, studies
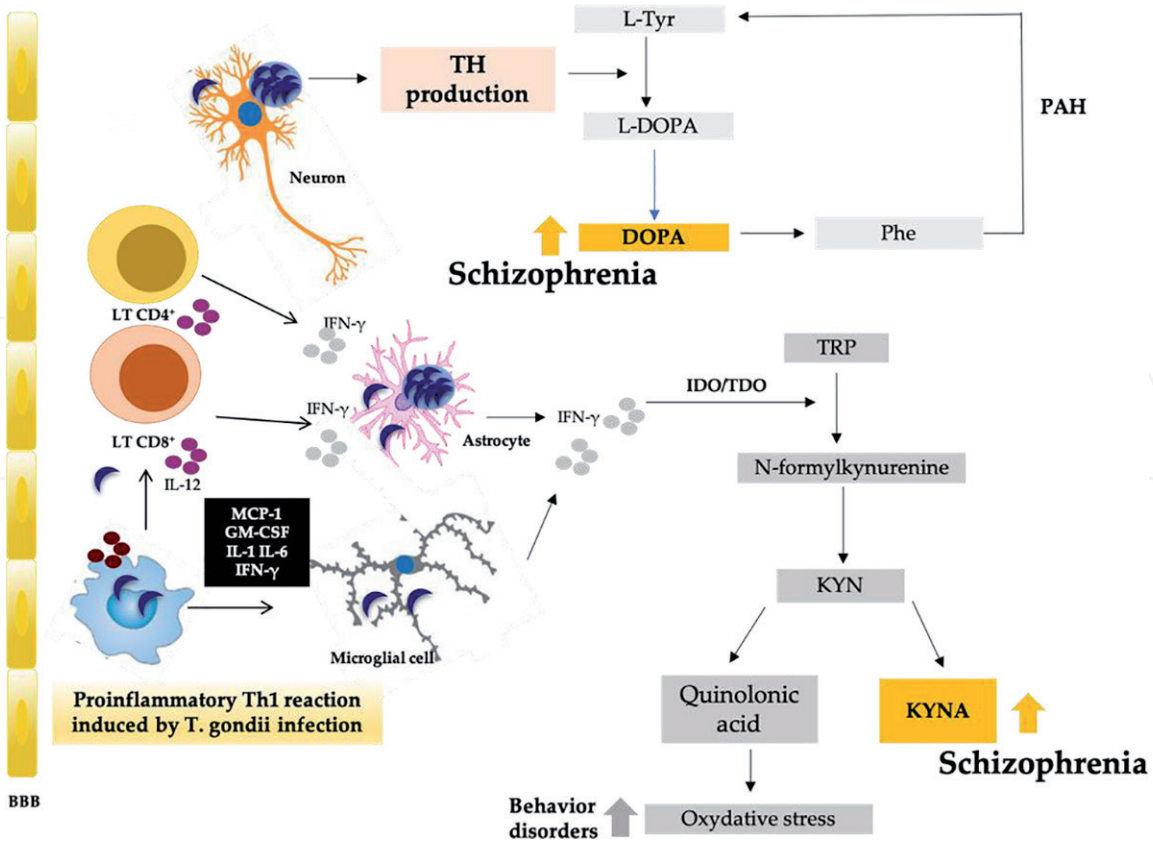
Figure 2.
Diagram showing the neurobiological pathway related to T. gondii *infection to schizophrenia disease.*

have identified two genes for limiting the TH synthesis in the genome of *T. gondii*; these genes expressed in the brain are responsible for DOPA overproduction in *T. gondii* tissue cysts that is responsible for the positive symptoms of some Schizophrenia patients [70].

In addition to DOPA, studies have also evaluated alterations of the kynurenine pathway (KYN) and involvement of TRP [71, 72]. In immunocompetent hosts, infection with *T. gondii* leads to the production of IFN-γ and production of indoleamine 2,3-dioxygenase (IDO), which converts the TRP to KYN and inhibits *T. gondii* growth. The metabolism of Tryptophan generates kynurenine and 3-hydroxykynurenine. The imbalance of these catabolites plays a role in the pathophysiology of Schizophrenia with positive and negative symptoms, which are reversible in response to antipsychotic treatment impact on such imbalance [71]. Additionally, alterations of the KYN pathway have also been shown with an increased KYN/TRP ratio and elevated kynurenic acid (KYNA) levels [73]. Activation of the KYN pathway following *T. gondii* infection may be part of a biological defense strategy against *T. gondii* infections. In the brain, this metabolism pathway takes place mainly in astrocytes that release newly produced KYNA into the extracellular environment, where it can influence surrounding neurons. KYNA synthesis is initiated also by tryptophan dioxygenase (TDO), this enzyme has shown that is elevated in the brains of Schizophrenia patients particularly in astrocytes and glial cells [74]. *T. gondii* infection in the CNS is accompanied, in response to parasite invasion or an inflammatory reaction, by strong activation of astrocytes and glial cells, resulting from high KYNA synthesis in these stimulated cells [75]. This reaction promotes high production of TDO or IDO in the brain and enhances proinflammatory cytokine expression in the site of *T. gondii* infection. These neurobiological data relating *Toxoplasma* infection to neuropsychiatric diseases.

4. Conclusion

The question that *Toxoplasma* infection could be the etiological cause psychological diseases and behavioral disorders is still under study. Recent studies try to prove this relationship. Study of Lindgren and collaborators demonstrated a significant association between *T. gondii* seropositivity and psychotic symptoms [76]. Vlatkovic and collaborators find an increased prevalence of *T. gondii* infection in a patient with Schizophrenia [77]. So, increased risk of developing toxoplasmosis infection prior to the onset of Schizophrenia was reported in several epidemiological, neurobiological and parasitological studies. One day this association will be a new method of diagnosis, treatment, and prevention of development of Schizophrenia. Therefore, health education on personal and nutritional hygiene given to patients and healthy people, especially early age, can help reduce the risk of contact with infectious agents and subsequently could decrease the incidence of behavior disorders.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this chapter.

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References

[1] Dalimi A, Abdoli A. Latent toxoplasmosis and human. Iranian Journal of Parasitology. 2012;**7**:1-17

[2] Buoli M, Serati M, Caldiroli A, et al. Neurodevelopmental versus neurodegenerative model of schizophrenia and bipolar disorder: Comparison with physiological brain development and aging. Psychiatria Danubina. 2017;**29**:24-27

[3] Syn G, Anderson D, Blackwell JM, et al. Epigenetic dysregulation of host gene expression in *Toxoplasma* infection with specific reference to dopamine and amyloid pathways. Infection, Genetics and Evolution. 2018;**65**:159-162

[4] Soleymani E, Babamahmoodi F, Davoodi L, et al. Toxoplasmic encephalitis in an AIDS patient with normal CD4 count: A case report. Iranian Journal of Parasitology. 2018;**13**:317-322

[5] Marra CM. Central nervous system infection with *Toxoplasma gondii*. Handbook of Clinical Neurology. 2018;**152**:117-122

[6] Halonen SK, Weiss LM. Toxoplasmosis. Handbook of Clinical Neurology. 2013;**114**:125-145

[7] Długońska H. *Toxoplasma gondii* and the host cells. Annals of Parasitology. 2014;**60**:83-88

[8] Hunter CA, Sibley LD. Modulation of innate immunity by *Toxoplasma gondii* virulence effectors. Nature Reviews. Microbiology. 2012;**10**:766-778

[9] Mammari N, Vignoles P, Halabi MA, et al. Interferon gamma effect on immune mediator production in human nerve cells infected by two strains of *Toxoplasma gondii*. Parasite: Journal de la Société Française de Parasitologie. 2015;**22**:39

[10] Ajzenberg D. Type I strains in human toxoplasmosis: Myth or reality? Future Microbiology. 2010;**5**:841-843

[11] Delhaes L, Ajzenberg D, Sicot B, et al. Severe congenital toxoplasmosis due to a *Toxoplasma gondii* strain with an atypical genotype: Case report and review. Prenatal Diagnosis. 2010;**30**:902-905

[12] Konradt C, Ueno N, Christian DA, et al. Endothelial cells are a replicative niche for entry of *Toxoplasma gondii* to the central nervous system. Nature Microbiology. 2016;**1**:16001

[13] Mammari N, Vignoles P, Halabi MA, et al. In vitro infection of human nervous cells by two strains of *Toxoplasma gondii*: A kinetic analysis of immune mediators and parasite multiplication. PLoS ONE. 2014;**9**:e98491

[14] Corcino YL, Portillo J-AC, Subauste CS. Epidermal growth factor receptor promotes cerebral and retinal invasion by *Toxoplasma gondii*. Scientific Reports. 2019;**9**:669

[15] Schlüter D, Barragan A. Advances and challenges in understanding cerebral toxoplasmosis. Frontiers in Immunology. 14 February 2019;**10**. DOI: 10.3389/fimmu.2019.00242. [Epub ahead of print]

[16] Goverman J. Autoimmune T cell responses in the central nervous system. Nature Reviews. Immunology. 2009;**9**:393

[17] Tosh KW, Mittereder L, Bonne-Annee S, et al. The IL-12 response of primary human DC and monocytes to *Toxoplasma gondii* is stimulated by phagocytosis of live parasites rather than host cell invasion. Journal of Immunology (Baltimore, Md. : 1950). 2016;**196**:345-356

[18] Courret N, Darche S, Sonigo P, et al. CD11c- and CD11b-expressing mouse leukocytes transport single *Toxoplasma gondii* tachyzoites to the brain. Blood. 2006;**107**:309-316

[19] Lambert H, Hitziger N, Dellacasa I, et al. Induction of dendritic cell migration upon *Toxoplasma gondii* infection potentiates parasite dissemination. Cellular Microbiology. 2006;**8**:1611-1623

[20] Barragan A, Brossier F, Sibley LD. Transepithelial migration of *Toxoplasma gondii* involves an interaction of intercellular adhesion molecule 1 (ICAM-1) with the parasite adhesin MIC2. Cellular Microbiology. 2005;**7**:561-568

[21] Suzuki Y, Claflin J, Wang X, et al. Microglia and macrophages as innate producers of interferon-gamma in the brain following infection with *Toxoplasma gondii*. International Journal for Parasitology. 2005;**35**:83-90

[22] Ploix CC, Noor S, Crane J, et al. CNS-derived CCL21 is both sufficient to drive homeostatic CD4+ T cell proliferation and necessary for efficient CD4+ T cell migration into the CNS parenchyma following Toxoplasma gondii infection. Brain, Behavior, and Immunity. 2011;**25**:883-896

[23] Schuindt SHS, OBC d L, Pimentel PM de O, et al. Secretion of multi-protein migratory complex induced by *Toxoplasma gondii* infection in macrophages involves the uPA/uPAR activation system. Veterinary Parasitology. 2012;**186**:207-215

[24] Lüder CG, Giraldo-Velásquez M, Sendtner M, et al. *Toxoplasma gondii* in primary rat CNS cells: Differential contribution of neurons, astrocytes, and microglial cells for the intracerebral development and stage differentiation. Experimental Parasitology. 1999;**93**:23-32

[25] Contreras-Ochoa CO, Lagunas-Martínez A, Belkind-Gerson J, et al. *Toxoplasma gondii* invasion and replication within neonate mouse astrocytes and changes in apoptosis related molecules. Experimental Parasitology. 2013;**134**:256-265

[26] Hidano S, Randall LM, Dawson L, et al. STAT1 signaling in astrocytes is essential for control of infection in the central nervous system. MBio. 8 November 2016;**7**. DOI: 10.1128/mBio.01881-16. [Epub ahead of print]

[27] Song HB, Jung B-K, Kim JH, et al. Investigation of tissue cysts in the retina in a mouse model of ocular toxoplasmosis: Distribution and interaction with glial cells. Parasitology Research. 2018;**117**:2597-2605

[28] Halonen SK. Use of human neurons derived via cellular reprogramming methods to study host-parasite interactions of *Toxoplasma gondii* in neurons. Cell. 23 Sept 2017;**6**. DOI: 10.3390/cells6040032. [Epub ahead of print]

[29] Hwang YS, Shin J-H, Yang J-P, et al. Characteristics of infection immunity regulated by *Toxoplasma gondii* to maintain chronic infection in the brain. Frontiers in Immunology. 2018;**9**:158

[30] Lieberman LA, Hunter CA. Regulatory pathways involved in the infection-induced production of IFN-γ by NK cells. Microbes and Infection. 2002;**4**:1531-1538

[31] Sa Q, Ochiai E, Tiwari A, et al. Cutting edge: IFN-γ produced by brain-resident cells is crucial to control cerebral infection with *Toxoplasma gondii*. Journal of Immunology (Baltimore, Md. : 1950). 2015;**195**:796-800

[32] Scharton-Kersten T, Caspar P, Sher A, et al. *Toxoplasma gondii*: Evidence for interleukin-12-dependent

and-independent pathways of interferon-gamma production induced by an attenuated parasite strain. Experimental Parasitology. 1996;**84**:102-114

[33] Schlüter D, Deckert M, Hof H, et al. *Toxoplasma gondii* infection of neurons induces neuronal cytokine and chemokine production, but gamma interferon- and tumor necrosis factor-stimulated neurons fail to inhibit the invasion and growth of *T. gondii*. Infection and Immunity. 2001;**69**:7889-7893

[34] Kang H, Suzuki Y. Requirement of non-T cells that produce gamma interferon for prevention of reactivation of *Toxoplasma gondii* infection in the brain. Infection and Immunity. 2001;**69**:2920-2927

[35] Kang H, Suzuki Y. Requirement of Non-T cells That Produce Gamma Interferon for Prevention of Reactivation of *Toxoplasma gondii* infection in the brain. Infection and Immunity. 2001;**69**:2920-2927

[36] Wang X, Suzuki Y. Microglia produce IFN-γ independently from T cells during acute Toxoplasmosis in the brain. Journal of Interferon & Cytokine Research. 2007;**27**:599-605

[37] Halonen SK, Chiu F-C, Weiss LM. Effect of cytokines on growth of *Toxoplasma gondii* in murine astrocytes. Infection and Immunity. 1998;**66**:4989-4993

[38] Gazzinelli RT, Hieny S, Wynn TA, et al. Interleukin 12 is required for the T-lymphocyte-independent induction of interferon gamma by an intracellular parasite and induces resistance in T-cell-deficient hosts. Proceedings of the National Academy of Sciences of the United States of America. 1993;**90**:6115-6119

[39] Aliberti J, Serhan C, Sher A. Parasite-induced lipoxin A4 is an endogenous regulator of IL-12 production and immunopathology in *Toxoplasma gondii* infection. The Journal of Experimental Medicine. 2002;**196**:1253-1262

[40] Machado FS, Aliberti J. Impact of lipoxin-mediated regulation on immune response to infectious disease. Immunologic Research. 2006;**35**:209-218

[41] Suzuki Y, Yang Q, Yang S, et al. IL-4 is protective against development of toxoplasmic encephalitis. Journal of Immunology (Baltimore, Md. : 1950). 1996;**157**:2564-2569

[42] Ivanova DL, Denton SL, Fettel KD, et al. Innate lymphoid cells in protection, pathology, and adaptive immunity during apicomplexan infection. Frontiers in Immunology. 2019;**10**:196

[43] Wilson EH, Wille-Reece U, Dzierszinski F, et al. A critical role for IL-10 in limiting inflammation during toxoplasmic encephalitis. Journal of Neuroimmunology. 2005;**165**:63-74

[44] Jankovic D, Kullberg MC, Feng CG, et al. Conventional T-bet+Foxp3− Th1 cells are the major source of host-protective regulatory IL-10 during intracellular protozoan infection. The Journal of Experimental Medicine. 2007;**204**:273-283

[45] Abdollahi SH, Ayoobi F, Khorramdelazad H, et al. Interleukin-10 serum levels after vaccination with In vivo prepared *Toxoplasma gondii* excreted/secreted antigens. Oman Medical Journal. 2013;**28**:112-115

[46] Blanchard N, Dunay IR, Schlüter D. Persistence of *Toxoplasma gondii* in the central nervous system: A fine-tuned balance between the parasite, the brain and the immune system. Parasite Immunology. 2015;**37**:150-158

[47] Fabiani S, Pinto B, Bonuccelli U, et al. Neurobiological studies on the relationship between toxoplasmosis and neuropsychiatric diseases. Journal of the Neurological Sciences. 2015;**351**:3-8

[48] Bay-Richter C, Petersen E, Liebenberg N, et al. Latent toxoplasmosis aggravates anxiety- and depressive-like behaviour and suggest a role of gene-environment interactions in the behavioural response to the parasite. Behavioural Brain Research. 2019;**364**:133-139

[49] Suvisaari J, Torniainen-Holm M, Lindgren M, et al. *Toxoplasma gondii* infection and common mental disorders in the Finnish general population. Journal of Affective Disorders. 2017;**223**:20

[50] Nourollahpour Shiadeh M, Rostami A, Pearce BD, et al. The correlation between *Toxoplasma gondii* infection and prenatal depression in pregnant women. European Journal of Clinical Microbiology & Infectious Diseases. 2016;**35**:1829-1835

[51] Flegr J, Preiss M, Balátová P. Depressiveness and Neuroticism in bartonella seropositive and seronegative subjects-preregistered case-controls study. Frontiers in Psychiatry. 2018;**9**:314

[52] Pearce BD, Kruszon-Moran D, Jones JL. The relationship between *Toxoplasma gondii* infection and mood disorders in the NHANES III. Biological Psychiatry. 2012;**72**:290-295

[53] Sutterland AL, Fond G, Kuin A, et al. Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: Systematic review and meta-analysis. Acta Psychiatrica Scandinavica. 2015;**132**:161-179

[54] Haroon F, Händel U, Angenstein F, et al. *Toxoplasma gondii* actively inhibits neuronal function in chronically infected mice. PLoS ONE. 2012;**7**:e35516

[55] Ramezani M, Shojaii M, Asadollahi M, et al. Seroprevalence of *Toxoplasma gondii* in Iranian patients with idiopathic Parkinson's disease. Clinical and Experimental Neuroimmunology. 2016;**7**:361-365

[56] Skallová A, Kodym P, Frynta D, et al. The role of dopamine in *Toxoplasma*-induced behavioural alterations in mice: An ethological and ethopharmacological study. Parasitology. 2006;**133**:525-535

[57] Fallahi S, Rostami A, Birjandi M, et al. Parkinson's disease and *Toxoplasma gondii* infection: Sero-molecular assess the possible link among patients. Acta Tropica. 2017;**173**:97-101

[58] Mitra R, Sapolsky RM, Vyas A. *Toxoplasma gondii* infection induces dendritic retraction in basolateral amygdala accompanied by reduced corticosterone secretion. Disease Models & Mechanisms. 2013;**6**:516-520

[59] Hermes G, Ajioka JW, Kelly KA, et al. Neurological and behavioral abnormalities, ventricular dilatation, altered cellular functions, inflammation, and neuronal injury in brains of mice due to common, persistent, parasitic infection. Journal of Neuroinflammation. 2008;**5**:48

[60] Miller BJ, Buckley P, Seabolt W, et al. Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. Biological Psychiatry. 2011;**70**:663-671

[61] Tedford E, McConkey G. Neurophysiological changes induced by chronic *Toxoplasma gondii* infection. Pathogens (Basel, Switzerland). 17 May 2017;**6**. DOI: 10.3390/pathogens6020019. [Epub ahead of print]

[62] Bhadra R, Cobb DA, Weiss LM, et al. Psychiatric disorders in *Toxoplasma* seropositive patients—The CD8 connection. Schizophrenia Bulletin. 2013;**39**:485-489

[63] Del Grande C, Galli L, Schiavi E, et al. Is *Toxoplasma gondii* a trigger of bipolar disorder? Pathogens (Basel, Switzerland). 10 Jan 2017;**6**. DOI: 10.3390/pathogens6010003. [Epub ahead of print]

[64] Mammari N, Halabi MA, Yaacoub S, et al. *Toxoplasma gondii* modulates the host cell responses: An overview of apoptosis pathways. BioMed Research International. 2019:10

[65] Alsaady I, Tedford E, Alsaad M, et al. Downregulation of the central noradrenergic system by *Toxoplasma gondii* infection. Infection and Immunity. 2019;**87**:e00789-18

[66] Wang T, Sun X, Qin W, et al. From inflammatory reactions to neurotransmitter changes: Implications for understanding the neurobehavioral changes in mice chronically infected with *Toxoplasma gondii*. Behavioural Brain Research. 2019;**359**:737-748

[67] Xiao J, Prandovszky E, Kannan G, et al. *Toxoplasma gondii*: Biological parameters of the connection to schizophrenia. Schizophrenia Bulletin. 2018;**44**:983-992

[68] Gaskell EA, Smith JE, Pinney JW, Westhead DR, McConkey GA. A unique dual activity amino acid hydroxylase in *Toxoplasma gondii*. PLoS ONE 2009;**4**(3):e4801

[69] Mathai AJ, Lowry CA, Cook TB, et al. Reciprocal moderation by *Toxoplasma gondii* seropositivity and blood phenylalanine:tyrosine ratio of their associations with trait aggression. Pteridines. 2016;**27**:77-85

[70] Prandovszky E, Gaskell E, Martin H, et al. The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. PLoS ONE. 2011;**6**(9):e23866. DOI: 10.1371/journal.pone.0023866

[71] Notarangelo FM, Wilson EH, Horning KJ, et al. Evaluation of kynurenine pathway metabolism in *Toxoplasma gondii*-infected mice: Implications for schizophrenia. Schizophrenia Research. 2014;**152**:261-267

[72] Bay-Richter C, Buttenschøn HN, Mors O, et al. Latent toxoplasmosis and psychiatric symptoms: A role of tryptophan metabolism? Journal of Psychiatric Research. 2019;**110**:45-50

[73] Schwarcz R, Hunter CA. *Toxoplasma gondii* and schizophrenia: Linkage through astrocyte-derived kynurenic acid? Schizophrenia Bulletin. 2007;**33**:652-653

[74] Miller CL, Llenos IC, Dulay JR, et al. Expression of the kynurenine pathway enzyme tryptophan 2,3-dioxygenase is increased in the frontal cortex of individuals with schizophrenia. Neurobiology of Disease. 2004;**15**:618-629

[75] Wurfel BE, Drevets WC, Bliss SA, et al. Serum kynurenic acid is reduced in affective psychosis. Translational Psychiatry. 2017;**7**:e1115

[76] Lindgren M, Torniainen-Holm M, Härkänen T, et al. The association between *Toxoplasma* and the psychosis continuum in a general population setting. Schizophrenia Research. 2018;**193**:329-335

[77] Vlatkovic S, Sagud M, Svob Strac D, et al. Increased prevalence of *Toxoplasma gondii* seropositivity in patients with treatment-resistant schizophrenia. Schizophrenia Research. 2018;**193**:480-481