zoonotic diseases

MDPI

Review

Reconsidering Toxoplasmosis Prevention and Treatment Due to Its Relation to Neuropsychiatric Disturbances

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Simple Summary: Toxoplasmosis is a widespread zoonotic disease caused by *Toxoplasma gondii*, which is taxonomically classified as an apicomplexan protozoon. In immunocompetent adults, the infection is generally asymptomatic or accompanied by mild symptoms (fever and asthenia, mimicking a flu-like illness). In immunocompromised individuals or following vertical transmission, the disease may be characterized by severe clinical manifestations. Because the parasite exhibits life-long persistence, we reviewed the current literature, primarily focusing on epidemiological and neurobiological aspects, with the aim of verifying the effects of infection on the risk of developing neuropsychiatric disorders.

Abstract: Toxoplasmosis is a parasitic, foodborne infection caused by *Toxoplasma gondii*. The infection can be transmitted through various routes, including the following: (i) the consumption of vegetables, fruits, or drinking water containing sporulated oocysts; (ii) the consumption of raw or undercooked meat; (iii) transmission from mother to fetus; (iv) through blood transfusion; and (v) transplantation of solid organs, bone marrow, or hematopoietic stem cells. Infection is generally asymptomatic or exhibits a mild clinical presentation in those with adequate immune function; however, the clinical outcomes becomes more severe in both fetal and immunocompromised individuals. In this work, we reviewed the current literature, primarily focusing on epidemiological and neurobiological aspects. Using the PubMed database, we conducted a search by combining the following terms: "*Toxoplasma gondii*" or "Toxoplasmosis" and "neuropsychiatric" "diseases" or "disorders" or "psychiatric" "diseases" or "disorders" or "neurological" "diseases" or "disorders" or "neurobehavioral disorders" or "behavioral disorders" or "schizophrenia" or "bipolar disorder" or "autism spectrum disorder" or "Parkinson's disease" or "Alzheimer's disease". No language or time restrictions were applied in the literature review, which was concluded in April 2024. Although the literature does not yet provide definitive answers, current data should be considered sufficient to change attitudes toward toxoplasmosis prevention and treatment measures. The focus should be not only with regard to seronegative pregnant women and immunocompromised patients, but also to people particularly prone to developing neuropsychiatric diseases.

Keywords: toxoplasmosis; neuropsychiatric disorders; prevention; tryptophan

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1. Distribution and Global Burden of Toxoplasmosis

Toxoplasmosis is a worldwide zoonotic disease caused by the apicomplexan protozoon *Toxoplasma gondii*. The disease affects around two billion people globally. In industrialized

countries, however, its seroprevalence is significantly declining, primarily due to changes in human habits in terms of prevention measures (see transmission routes) [1].

Infection may be transmitted through the following routes: (i) the consumption of vegetables, fruits, or water contaminated with sporulated infective oocysts; (ii) the ingestion of meat (raw or undercooked) from infected animals; (iii) vertical transmission of tachyzoites; (iv) blood transfusion; and (v) solid organ or hematopoietic stem cell transplantation [1].

Foodborne toxoplasmosis accounts for around 10.3 million cases of the disease. Congenital and acquired toxoplasmosis induces a burden of 1.68 million disability-adjusted life years (DALYs) [2].

2. Clinical Impacts of Toxoplasmosis on Different Populations, the Pathogenesis of Infection and the Neurotropism of *Toxoplasma gondii*

When infected, immunocompetent adults (both males and females) are generally asymptomatic or exhibit a mild clinical presentation. The clinical presentation in immunocompromised individuals or fetuses is that of potentially severe disease [1]. When infection is caused by more virulent strains of *T. gondii*, primarily present in Latin America, even immunocompetent individuals may exhibit serious illness, with fatal outcomes [3].

The persistence of the parasite in the tissues of the host for the duration of their life is a relatively recent concept. In fact, in 1953, scientists referred to the concept of "long periods of life" to indicate the duration of parasite survival in the host and it was only in 1965 that the field began to consider the possibility of parasite persistence during the entire life span of an individual. However, it was in 1997, when Innes referenced the concept of "for life", that the field accepted that toxoplasmosis is "forever" [4].

Encysted *T. gondii* bradyzoites are capable of inhibiting cellular apoptosis; they can therefore persist in host cells, including at the central nervous system (CNS), for long periods of time. As cysts grow, the host cell undergoes morphological changes and may rupture, thereby releasing bradyzoites, which can differentiate into tachyzoites and invade surrounding cells. At the juncture of these two stages (bradyzoites and tachyzoites), there is a delicate balance mediated by inflammatory cytokines [5].

Evidence exists to support the neurotropism of *T. gondii*. Shortly after entering the intestinal tract, *T. gondii* tachyzoites rapidly disseminate systemically to ultimately establish latent infection in the CNS [6], with a preferential distribution in cerebral hemispheres [7].

Lesions occurring in the brain can manifest as behavioral symptoms by interfering with brain functions in the region surrounding the lesion via mass effects or paracrine secretions and the induction of endocannabinoids through the brain cannabinoid receptor type 1 activity on the basal ganglia, substantia nigra, globus pallidus, caudate nucleus, and putamen [7].

There is evidence to support the above findings with regard to the observation of high concentrations of tissue cysts in the amygdala and nucleus accumbens, dopamine-containing limbic brain regions recognized as vital for motor control (in particular, the basal ganglia), motivation, pleasure, addiction, reward, and fear. Despite this, the results of a recent study using the mouse model showed no clear region-dependent cyst distribution within the hippocampus or amygdala, implying that cysts do not directly cause behavioral changes through perturbation of the surrounding tissue.

Other more intriguing effects are the alterations of neurotransmitter pathways involving the production of proteins homologous to aromatic amino acid tyrosine hydroxylase and to dopamine 2 receptors. This might lead to an increase in dopamine synthesis and tryptophan degradation, as well as a decrease in serotonin synthesis, the induction of the immune response, and the activation of inflammatory cytokines [7,8] (see Table 1).

Table 1. Neurobiological findings in support and against a link between toxoplasmosis and neuropsychiatric disorders.

		Toxoplasmosis	Schizophrenia	Bipolar Disorder	Autism Spectrum Disorders	Parkinson's Disease	Alzheimer's Disease	Behaviour Problems	References
Cerebral areas involved		Not sufficient data							[6,7]
Neurobiological pathway	Endocannabinoid system (induction of endocannabinoids)	Not sufficient data				Beneficial effects of cannabinoids	Beneficial effects of cannabinoids		[7,8]
	Neurotrasmitter system	Decreased DOPA pathway	Decreased DOPA pathway («negative symptoms») Increased DOPA pathway («positive symptoms»)	Increased DOPA pathway	Decreased DOPA pathway	Decreased DOPA pathway	Decreased DOPA pathway	Not sufficient data	[7,8]
		Glutamate (NMDAR) &GABA pathway					blockade of NMDAR function leads to neuronal apoptosis and degeneration		[7,8]
		TRP degradation	Imbalance of TRP metabolites plays a role in pathophysiology of schizophrenia with positive and negativesymptoms				TRP and metabolites inhibit various enzymes participating in the biosynthesis of β-amyloid	Not sufficient data	[7,8]
	Endocrine function	HPA induction					Not sufficient data		[7,8]
		Decreased testosterone levels in acute infection and increased in men and decreased in women, during latent	Low testosterone levels in males	Not sufficient data	Pre-natal exposure to high testosterone levels	Not sufficient data		Not sufficient data	
	Cytokine pathway	Increased pro-inflammatory/ neurotoxic cytokines Decreased anti-inflammatory/ neuroprotective effects				IL-5 decreased			[5,7,8]
		Cytokines-mediated enhancement of phagocytosis and degradation of soluble Aβ	Not sufficient data	Not sufficient data	Not sufficient data	Not sufficient data	Accumulation of β-amyloid (possible beneficial effect of Toxplasma infection?)	Not sufficient data	[5,7,8]

Green: Supporting findings; Red: Findings against; Blank: Not sufficient data.

After entering the CNS and invading parenchymal cells (microglia, astrocytes, and neurons), the parasite induces alteration in the numbers of CD4+ T cells (Tregs, Th1, Th2, and Th17) and the levels of some cytokines in the peripheral blood. In the CNS, the cytokine IFN-γ is able to activate the astrocyte production of chemokines (CXCL9 and CXCL10), which facilitate the recruitment of CD4+ T cells into the CNS across the blood–brain barrier after *T. gondii* infection. In the brain parenchyma, cytokines released by different T cells can induce the transformation of microglia into M1 (pro-inflammatory/neurotoxic) or M2 (anti-inflammatory/neuroprotective) types. IFN-γ, IL-12, TNF-α, IL-4, and IL-10, together with IL-1 and IL-1β, IL-2, IL-6, granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-17 and IL-23 are variably expressed by microglia cells, astrocytes, and infiltrating CD4+ and CD8+ T cells, and may influence mood and behavior through their ability to modulate neurotransmission [7,8].

In light of the above findings, the idea that latent infection is clinically asymptomatic should be reconsidered [7].

In Table 1, the main characteristics of toxoplasmosis, schizophrenia, bipolar disorder, autism spectrum disorder, Parkinson's disease (PD), Alzheimer's disease (AD), and behavioral problems, as regards the cerebral areas involved, and neurobiological aspects of the endocannabinoid system, neurotransmitter system, endocrine function, and cytokine pathway are compared, highlighting their differences.

Independently of the mechanism involved, behavioral changes potentially induced by *Toxoplasma* parasites, either in experimentally infected rodents or in infected humans, have been reported, and infection with *T. gondii* has been described as being associated with the occurrence of neuropsychiatric diseases in genetically predisposed individuals [9].

Neuropsychiatric disorders with a possible link to toxoplasmosis are schizophrenia, bipolar disorder, autism spectrum disorder (ASD), PD, AD, and behavioral changes (anxiety, fear or panic, confusion, suicide, traffic accidents, crime, violence, and masochism).

Starting from these assumptions, we reviewed the current literature, focusing primarily on epidemiological and neurobiological aspects, in an attempt to answer the following fundamental questions: (i) Are *Toxoplasma* seropositive individuals more susceptible to neuropsychiatric disorders than the general population?; (ii) Does prenatal exposure to *Toxoplasma* facilitate the occurrence of neuropsychiatric disease, such as autism?; (iii) Is there a relationship between the stage of *Toxoplasma* infection and the development of psychiatric disorders?; (iv) Should we change attitudes toward toxoplasmosis prevention and treatment measures?

Using the PubMed database, we searched the literature by combining the following terms: "*Toxoplasma gondii*" or "Toxoplasmosis" and "neuropsychiatric" "diseases" or "disorders" or "psychiatric" "diseases" or "disorders" or "neurological" "diseases" or "disorders" or "neurobehavioral disorders" or "behavioral disorders" or "schizophrenia" or "bipolar disorder" or "autism spectrum disorder" or "Parkinson's disease" or "Alzheimer's disease".

The search was concluded in April 2024.

Assumptions from the Literature Search and Discussion

(i) Are *Toxoplasma* seropositive individuals in the general population more susceptible to underlying neuropsychiatric diseases and behavioral changes?

"How and why Toxoplasma makes us crazy" is the provocative title of a review by Flegr [10]. This interpretation resulted in some criticism of the Czech researcher, who was awarded the Ig Nobel Prize in Public Health in 2014 (https://en.wikipedia.org/wiki/List_of_Ig_Nobel_Prize_winners (assessed on 31 March 2025) based on his discovery of a correlation between cat ownership and the increased risk of developing schizophrenia.

A recent survey carried out in the UK on pregnant women and individuals in the early (age 13, N = 6705) and late (age 18, N = 4676) stages of adolescence clearly demonstrated the opposite finding, i.e., that cat ownership does not significantly increase the risk of underlying psychiatric disturbances [11].

Over the years, epidemiological findings have provided support for and against the link between toxoplasmosis and neuropsychiatric disorders (see Table 2).

Table 2. Epidemiological findings in support and against a link between toxoplasmosis and neuropsychiatric disorders.

Factors	Toxoplasmosis	Ref.	Neuropsychiatric Disorders	Ref.
Genetic/familial	Increased risk of infection in members of the same family, likely due to interaction between genetic and environmental factors; a trans-placental transmission of the parasite up to 5 generations was shown in mice	[12]	In schizophrenia: higher risk in first-degree relatives affected, but no single gene involved definitely identified In autism spectrum disorder: Twin and family studies demonstrate a strong genetic component	[13,14]
Age of onset	Seroconversion peak among 15 and 35 years, early among males	[15]	In schizophrenia: major clinical manifestation among 20 and 30 years, with early onset among males In autism spectrum disorder: conditions typically diagnosed after the second year of life. Males are affected more than women (4:1)	[14,16]
Seasonal variation	Patients born in winter or spring show a higher probability of contracting infectious diseases, including toxoplasmosis	[17]	In schizophrenia: the birth season (winter or spring) seems to correlate with risk of schizophrenia development In autism spectrum disorder: the risk was highest for fall births (i.e., conceived in the winter) and lowest for spring births (i.e., conceived in the summer)	[14,17,18]
Stillbirth	Increased	[15]	In schizophrenia: Increased	[15]
Socio-economic status	Lower	[15]	In schizophrenia: lower In autism spectrum disorder: higher	[14,15]
Residence area	Conflicting data exist on the association between prevalence for toxoplasmosis and residence area	[15]	In schizophrenia: An association may exist with being born or living during childhood in an urban area and the onset of schizophrenia	[19]

Table 2. *Cont.*

Factors	Toxoplasmosis	Ref.	Neuropsychiatric Disorders	Ref.
Geographical correlation	Countries with a low prevalence of anti T. gondii antibodies generally show a low prevalence of schizophrenia. Subjects from Papua, New Guinea, where domestic and wild cats are rare show low (≤2%) prevalence rates for toxoplasmosis. In countries such as France, Ethiopia and Brazil, where prevalence rates of toxoplasmosis are high and schizophrenia prevalence is similar to the general population	[15]	In schizophrenia: countries with a low prevalence of anti T. gondii antibodies generally show a low prevalence of schizophrenia. In subjects from Papua, New Guinea, schizophrenia is poorly disseminated. In countries such as France, Ethiopia and Brazil, where prevalence rates of toxoplasmosis are high and schizophrenia prevalence is similar to the general population In autism spectrum disorder: Worldwide prevalence is about 1%	[13,14]
Contact with cats	The seropositivity to *T. gondii* has increased together with the habit of keeping domestic cats. In particular, it is important the possession of a kitten under the age of one year	[9]	In schizophrenia, a positive correlation between schizophrenia and cat contact, especially during childhood is likely: schizophrenic patients show a higher frequency of exposure to cats in childhood (43%) compared to control subjects (34%) families in which members later developed schizophrenia or bipolar disorder, were more likely to have owned a cat. The number was higher (52%) during the period from birth up to 13 years old compared to controls (42%). In autism spectrum disorder: Cat ownership does not increase the risk to underlie psychotic disturbances	[14,20]

In several countries, the positivity rate of *Toxoplasma* is noted as being significantly higher in individuals with schizophrenia than in healthy subjects [9].

In a study carried out in France within the national Fonda Mental Expert Center (FACE-SZ) Cohort, Fond et al. [21] demonstrated that toxoplasmosis infections are almost three times more frequent in individuals with schizophrenia (SZ) than in the general population.

Another large-scale study conducted in Denmark, involving 81,912 individuals from the Danish Blood Donor Study, examined, for the first time, the impact of the temporality of pathogen (*T. gondii* and Cytomegalovirus) exposure. This study revealed a total positivity rate of about 26% and a significant association between toxoplasmosis and schizophrenia and related disorders (O.R. = 1.47), as well as suicides or suicide attempts (O.R. = 1.13) [22].

Contopoulos-Ioannidis et al. conducted a meta-analysis of 66 studies (including those cited previously in references [8,11,12]) involving 11,540 patients and 69,491 controls, ultimately demonstrating that many studies reported the existence of a positive association between *Toxoplasma*-IgG seropositivity and an increased risk of SZ. It is important to point out, however, that these contributions exhibit significant methodological limitations [23].

In another study, Galvàn-Remirez et al. showed that individuals with SZ have a significantly higher seroprevalence of toxoplasmosis than controls (51.7% vs. 27.97%) [24].

Banihashem et al. [25] and Ademe et al. [26] showed a marginally higher seroprevalence of toxoplasmosis in individuals with SZ than in controls (87.2% vs. 80.9% and 56% vs. 50.7%, respectively).

At a global scale, data on the association between SZ and *Toxoplasma* infection are consistent.

More recently, research has focused on the relationship between toxoplasmosis and bipolar disorder [27], showing a positive correlation in most cases [28–34], with some exceptions [35–39].

A significant number of studies have focused on the fact that *T. gondii* can affect the intermediate hosts (non-feline mammals) at different levels [40–44].

In their case-control study, Alvarado-Esquivel et al. [45] showed that interstate truck drivers may be at an increased risk of *T. gondii* infection and that *T. gondii* exposure may impact their neurological function. Anti-*T. gondii* IgG antibodies were found in 23 (12.0%) of the 192 truck drivers and in 13 (6.8%) of the 192 controls (OR = 21.0; 95% CI: 1.23–358.38; $p = 0.002$). The seroprevalence of *T. gondii* infection was higher in drivers with reflex impairment than in those without this impairment (4/13, 30.8% vs. 19/179, 10.6%, respectively; $p = 0.05$) and in drivers with hearing impairment than in those without this impairment (3/7, 42.9% vs. 20/185, 10.8%, respectively; $p = 0.03$). Multivariate analysis of the employment and behavioral characteristics of the truck drivers showed positive associations between *T. gondii* exposure and trips to southern Mexico (OR = 3.11; 95% CI: 1.02–9.44; $p = 0.04$) and the consumption of horse meat (OR = 5.18; 95% CI: 1.62–16.55; $p = 0.005$) [45].

The cross-sectional cohort study by Flegr et al. [46] observed that infected and non-infected subjects differ in their sexual behavior, fantasies, and preferences; infected subjects are more often aroused by their own fear, danger, and sexual submission although they practice more conventional sexual activities than *Toxoplasma*-free subjects. The authors suggest that the latter changes could be related to a decrease in the personality trait of novelty seeking in infected subjects, which is potentially a side effect of the increased concentration of dopamine in the brain of these individuals.

In their case-control study, Stock et al. [47] concluded that "...the presumed chronic increase in dopaminergic signaling in latent toxoplasmosis may boost behavioral performance in challenging cognitive control situations but may at the same time reduce the sensitivity towards motivational effects of rewards".

In a more recent study, Flegr et al. [48] remarked on *Toxoplasma* infection's negative impact on quality of life, especially on mental health.

The results of a report on 102 autopsy cases showed a correlation between the occurrence of risky behavior leading to death and the presence of higher proportions of positive parasite DNA within the brain. This correlation was not observed between parasite DNA presence and excessive alcohol consumption [49].

Another case-control study showed that *T. gondii*-seropositive males exhibited better self-regulation compared to *T. gondii*-seronegative males, and the opposite conclusion was true for females (behavioral regulation interaction $\gamma = 0.267$, 95% CI (0.093, 0.441)) [50].

Studies on *T. gondii* seropositivity and frailty (the consequence of cumulative decline in many physiological systems during a person's lifetime), accounting for age ($p = 0.0002$), point to this direction as well [51].

Suicidal behavior is a specific field of focus in research. In their systematic review and meta-analysis, Postolache et al. [52] demonstrated a significant association between suicide attempts/death by suicide and latent *T. gondii* infection.

A new field of research is the association between *Toxoplasma* seropositivity and AD and PD. The first reported (AD) link is, at present, a supposition based on a neurobiological hypothesis; however, no supporting epidemiological data appear to exist. More data relating to PD exist, at present, with some equivalence, numerically speaking, between the strengths and limitations of studies [53–58].

In a study involving the use of the murine model of AD, Möhle et al. showed that chronic *Toxoplasma gondii* infection enhances β-amyloid phagocytosis and degradation by recruited monocytes [59].

In a case-control study, Miman et al. showed that the seropositivity rates for anti-*T. gondii* IgG antibodies in PD patients and control groups were 42.3 and 22.5%, respectively, and this difference was statistically significant ($p = 0.006$) [53].

In another case-control study, Ramezani et al. also published results supporting such an association (82.5% vs. 65%) [54].

In a study by Fallahi et al. [55], based on PCR assay results, the prevalence of *Toxoplasma* infections was 19.3% in the case group and 10.4% in the control group, with the difference reaching statistical significance (OR = 3.02; 95% CI = 1.46–6.27; $p = 0.002$).

A statistically significant association was also found between PD and cat ownership ($p = 0.03$), in addition to the consumption of undercooked eggs ($p = 0.004$) [56].

The association between acute infection by *Toxoplasma* and PD risk is not supported by the results of Alvarado-Esquivel et al.'s study [57] or those of a systematic review and meta-analysis by Zhou et al. [58].

In regard to ASD, Prandota [60] addressed the question of whether neuropathological changes and clinical features of ASD would be similar to those reported in congenital and chronic cerebral toxoplasmosis in humans and in mice. In fact, the structures that underlie major neuropathological changes are similar in both conditions. More recently, Abdoli and Dalimi [61] hypothesized that the increased risk of ASD in *Toxoplasma*-positive individuals is ascribed to higher levels of testosterone induced by a latent infection.

Elzeky et al. [62] showed that *Toxoplasma* seroprevalence and nested PCR positivity were significantly higher in patients with neurodevelopmental disorders versus controls.

Hassan et al. found that data do not show an association between autism and toxoplasmosis and/or CMV infection. Despite this, taking into account the fact that autistic children are at a high risk of contracting such infections, further studies with a larger sample size are recommended [63].

In light of the above findings, we can affirm that pathogens such as *T. gondii*, together with others (viruses, for example), encountered either during fetal development or adult life, may modify neuronal cells, rendering them more prone to facilitate the occurrence of neuropsychiatric disorders.

(ii) Does prenatal exposure to Toxoplasma facilitate the occurrence of neuropsychiatric manifestations?

The relationship between toxoplasmosis and conditions such as ASD has received particular attention from researchers. For example, a study carried out in Finland showed an inverse relationship between autism in children with maternal infection [64]. In their study, Spann et al. came to similar conclusions [65]. However, it is recognized that fetal *T. gondii* infection impacts brain development, with clinical patterns potentially manifesting during postnatal life [66]. Further studies aimed at investigating the relationship between maternal *T. gondii*, the immune response to this parasite, and ASD will provide new strategies for disease prevention [67].

(iii) Is there a relationship between the stage of Toxoplasma infection and the development of psychiatric disorders?

To date, no specific relationship between the time of infection during the course of human life and the phase of *Toxoplasma* infection (i.e., acute, chronic, acute or chronic for reactivation) and the development of neuropsychiatric disorders has been clearly demonstrated.

A crucial point is the presence of the circulating parasite, possibly due to reactivation, in patients affected by neuropsychiatric disorders, with contrasting results presented in the current literature. For instance, in one study, parasitic DNA was found in a significant percentage of a cohort of 101 patients affected by SZ (32 patients compared to 36 healthy controls) by amplifying the B1 gene [68]. In contrast, Galli et al., examining a cohort of 63 patients affected by bipolar or schizoaffective disorders based on DSM-5 criteria, did not detect parasitic DNA in the parasite-specific IgG-positive patients, despite the use of different molecular methods, including a real-time amplification method [69].

It was only in one study, by Del Grande et al., that circulating DNA, through the use of a nested PCR by amplifying the MAG-1 gene, was detected in a patient affected by bipolar disorder and toxoplasmic chorioretinitis, which was treated with long-term corticosteroids [70].

Recently, *N*-Methyl-D-Aspartate Receptor (NMDAR) autoantibodies were found during experimental toxoplasmosis infection in mice, which were associated with behavioral and pathological changes in animals. These antibodies are elicited by tissue cysts; in fact, evidence shows that they are significantly correlated with MAG1 antibody levels ($r = 0.96$), which are a serologic marker of cyst burden. NMDAR autoantibody seroreactivity might represent a useful pathological biomarker of chronic toxoplasmosis. Such experimental results should be confirmed in clinical samples to better explain and confirm the possible mechanisms underlying the occurrence of neuropsychiatric disorders in some *Toxoplasma*-infected individuals [71].

The fact that there is evidence of different time periods of first contact with the parasite and different phases of infection, and that genetic predisposition could exist leads to the consideration of the need for changing attitudes and, ideally, guidelines for the prevention and treatment of toxoplasmosis.

(iv) Should we change attitudes toward toxoplasmosis prevention and treatment measures?

Prevention is primarily based on appropriate food habits, avoiding raw meat, including cured meat (containing tissue cysts) and mollusks, in addition to avoiding insufficiently washed vegetables and fruits (contaminated with oocysts), and using gloves when gardening and when handling raw meat.

In addition, pregnant women should not clean litter boxes when cats are present in the house.

Veterinarians are increasingly aware of the need to detect and treat animals for toxoplasmosis.

With regard to vaccine development, only one approach using an attenuated live S48 strain of the parasite has been licensed for use in animals (sheep) in Europe and New Zealand [72].

In humans, if needed, anti-toxoplasmic treatment is usually administered for a period of 2–4 weeks followed by a re-evaluation of the patient's condition. The combination of pyrimethamine, sulfadiazine, and folinic acid for 4–6 weeks is the most typical drug regime [73].

Most immunocompetent patients exhibit mild, self-limited symptomatology; for this reason, acute toxoplasmosis does not generally need to be treated. When symptoms persist and cause discomfort or serious illness develops, appropriate treatment should be given [74]. In addition, all cases of active infection during pregnancy must be treated [75].

From the results of studies focusing on autism, early treatment for maternal *T. gondii* infections could decrease the risk of autism development in their offspring; however, thorough examination of more samples and different techniques should be employed

to confirm this assumption. In addition, there is a need for more research to explain the mechanism responsible for the development of autism as a result of toxoplasmosis infection [65].

Regarding the anti-Toxoplasma drug's potential usefulness in the treatment of neuropsychiatric diseases in *Toxoplasma* seropositive patients, researchers have begun to consider whether there is a relationship between anti-toxoplasmic drugs and psychiatric disorders. For example, Jones-Brando et al. [76] found that drugs used in the treatment of SZ and bipolar disorder inhibited the in vitro replication of *T. gondii*. A total of 12 neuroleptic compounds were tested, and of these compounds, the antipsychotic haloperidol and the mood stabilizer valproic acid were the most effective in inhibiting parasite growth in vitro (76). Another study tested agents used to treat schizophrenia, such as haloperidol, clozapine, fluphenazine, trifluoperazine, and thioridazine, showing that some of these agents, such as fluphenazine, thioridazine, and trifluoperazine, have the ability to inhibit *T. gondii* proliferation in cell cultures [77].

The above results address the question of whether it might be useful to treat seropositive patients affected by SZ or bipolar disorder with anti-toxoplasmic drugs. In patients with chronic SZ, trimethoprim used as adjuvant treatment did not produce superior results compared to the placebo [78].

Four randomized controlled trials have shown that none of the antiparasitic drugs given to patients with SZ induced modifications in psychopathology [79].

Independent of common use and guideline-based attitudes, an important answer resulting from all of the aforementioned assumptions is as follows:

There is no scientific evidence that supports the use of antiparasitic drugs in the treatment of neuropsychiatric diseases in seropositive patients; however, further research is required.

Another important issue is in regards to the treatment of asymptomatic patients once an acute infection is serologically detected.

Anti-*Toxoplasma* primary prophylaxis, mainly with the use of trimethoprim/sulfamethoxazole, is a well-established strategy in other clinical settings for high-risk immunocompromised patients. From speculations regarding SZ, prevention of intermittent subclinical reactivations of *T. gondii* in the brain of Toxoplasma seropositive patients with SZ could be a benefit in the SZ treatment course [23].

3. Conclusions

The papers reviewed in this study appear to provide evidence confirming the existence of a relationship between toxoplasmosis and neuropsychiatric disorders.

The majority of studies published to date are case-control studies comparing patients affected by neuropsychiatric disorders with healthy individuals.

Studies on larger cohorts of patients, involving the use of more in-depth methods, the improvement of statistical methods, and the ability to replicate results in distinct populations are needed to verify the relationship clearly and possibly to understand the pathogenesis of such a relationship.

The consequent implications in terms of therapy and prevention are obvious.

To date, the prevention of toxoplasmosis has only been addressed with regard to seronegative pregnant women and immunocompromised individuals [1].

This attitude may change in the future if the focus is shifted to also protect individuals with a high likelihood of developing neuropsychiatric diseases based on genetic predisposition and even treating infected NMDAR-ab-positive patients.

It is therefore important that in-depth studies in this field are conducted. In the words of Bill Hutchinson, "any organism that shares our brain with us is worthy of study" [80].

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