THE GEEK CHRONICLES
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Opinion Article Chronicles of Clinical Reviews and Case Reports Open Access

The prevention of neurological disorders associated to latent toxoplasmosis must begin in early ages

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ARTICLE INFO

2025 Volume 2
https://www.doi.org/ccrcr.2025.tgc.0353

Article History
Received: Feb 17, 2025
Accepted: Mar 4, 2025
Published: Apr 18, 2025

Citation: Luis Fonte, María Ginori, Kirenia Oliva, Pedro Casanova, Doris Ginorio, Yaxsier Rodríguez. (2025). The prevention of neurological disorders associated to latent toxoplasmosis must begin in early ages. *Chronicles of Clinical Reviews and Case Reports*, The Geek Chronicles, 1, 1-7.

Keywords: Toxoplasma gondii; Latent Toxoplasmosis; Neurological Disorders; Prevention; Early Ages.

ABSTRACT

The association between latent toxoplasmosis and the development of neurological disorders constitutes a health problem of unknown dimensions. In the absence of effective drugs against bradyzoites of Toxoplasma gondii and vaccines against the parasite, other actions targeting different phases of its life cycle are in use to prevent and control the transmission. Since the prevalence of latent toxoplasmosis is already high at the end of adolescence, and bearing in mind the possible adverse consequences related to the presence of the silent form of the infection, the implementation of those prevention measures must begin at early ages.

Toxoplasma gondii and toxoplasmosis. A brief overview

Toxoplasma gondii is an apicomplexan parasite able to replicate in any nucleated cell of a wide range of animals [1]. *T. gondii*, owing to its high transmissibility and prolonged presence in its host, is regard as one of the most successful microorganisms on the life scale, affecting around 30% of the world's population (prevalences from 10% to 90% have been documented) [1,2].

The life cycle of *T. gondii* occurs in two stages and different scenarios*:* (i) the sexual phase, which takes place in cells of the intestine epithelium of the definitive hosts. In this site, non-sporulated oocysts are generated and then expelled in the stool; (ii) the asexual phase, which commences with the intake of the oocysts by the intermediary hosts (animals wherein the sexual phase cannot progress). The sporozoos arising from the swallowed oocysts invade the intestine epithelial cells and become tachyzoites, which propagate virtually to all organs, with particular tropism towards muscles, the retina and the central nervous system (CNS). Once in those final localizations, they turn into bradyzoites, which are structured into cysts inside several cell types, primarily muscle cells and CNS neurons. The bradyzoites are relatively resistant to immune responses and, in an apparently silent form, survive in their cellular niches until host death [3]. Humans acquire *T. gondii* infection mainly by three routes: (i) ingestion of sporulated oocysts in contaminated water or food, (ii) intake of tissue cysts in raw or undercooked meat containing them, and (iii) parasite transmission to the fetus [3].

The clinical course of *T. gondii* infection depends mainly on the immune competence of the host [4,5]. In healthy persons, the primary infection is commonly asymptomatic or shows moderately with general clinical manifestations, included fever, and lymph node inflammation [5]. In immune depressed persons, as those suffering of acquired immune deficiency syndrome, the symptoms and signs of the primary infection are more severe or a reactivation of a latent toxoplasmosis can occur [5]. If the primary infection happens during pregnancy, there will be a high risk of parasite transmission to the fetus, given that it is not immunologically ready to fight back such an attack [5]. This could result in miscarriage, fetal defects (for example, intracranial calcifications, hydrocephalus and microcephaly), and complications in newborns (for instance, chorioretinitis, blindness, deafness and mental retardation) [6]. Depressed.

Using the serologic detection of anti-*T. gondii* antibodies as a diagnostic tool, numerous studies have demonstrated that the proportion of infected persons increases with age [7-11]. In addition, those surveys also found that the proportion of individuals with antibodies against the parasite is already high from early ages. For instances, studies to estimate the seroprevalence of anti-*T. gondii* antibodies in Iran, Cuba and Bosnia and Herzegovina found 25.6%, 20.3% and 10.9%, respectively, in individuals under 20 years, and 33%, 29.7% and 30.9%, respectively, in general population (7,8,9).

Latent toxoplasmosis affects neurological functions of intermediary hosts

During many years, chronic infection by *T. gondii* has been considered clinically silent [3]. In general, two arguments have been used to support that assumption: (i) the absence of clinical manifestations in almost all the individuals who were seropositive for *T. gondii,* and (ii) the primary demonstration of the quiescent character of the bradyzoites present in the CNS of chronically infected individuals. However, in the course of the last three decades, a growing number of studies in rodents, which -like humans- act as intermediary hosts of *T. gondii*, have evidenced that chronic infection by this protozoan can alter important neurological functions of those animals: memory, learning, locomotion and, very significantly, behavioral [6,12-14].

In relation with those studies, the most captivating are some works showing conduct variations of chronically infected rodents. For instance, the expansion of moving spaces; the more confident movements around open areas; and more surprisingly, the development of a potential attraction to cat urine [15-17]. According to the hypothesis advanced by Lefèvre et al. in 2009 [18], those behavioral changes constitute a refined evolutive gain that allows the immature parasite (*T. gondii* bradyzoite) to live in an intermediary host (rodent) that subsequently will be ingested by the definitive host (cat). As a result, the parasite completes its life cycle and perpetuates its existence. The human is not the best intermediary host for *T. gondii* because our species does not have a natural predator. Nevertheless, and in line with that hypothesis, a relatively recent study on chimpanzee, a living primate still predated by a feline species, showed that *T. gondii* infection decreases the animal phobia for leopard urine [19].

Numerous studies in humans, using different designs and anti-*T. gondii* antibody detection tests, have shown an association between latent and a decline of cognitive functions (working and verbal memory impairments [6,20], reduced sensitivity towards motivational effects of rewards [21], and damaged of executive functioning [6], mood variations (major depression disorder [5] and bipolar disorder [5,22,23]), behavioral changes (higher frequency of suicidal attempts [24,25], traffic accidents [26] and promiscuity [6]), psychiatric diseases (schizophrenia [6,25], obsessive-compulsive disorders [6,27]) and degenerative diseases (Alzheimer disease [6,28], multiple sclerosis [29,30] and Huntington disease [31]).

From a more holistic perspective, the results of a very recent systematic review and meta-analysis offer generic support for the existence of the aforementioned associations. Of 49 studies containing 21,093 participants and conducted in 18 countries, the global pooled seroprevalence of *T. gondii* IgG antibody was 38.27% among neuropsychiatric patients and 25.31% in healthy controls [5]. Interestingly, and apart from that review, some works have found a direct relationship between the length of *T. gondii* infection, measured by the decrease in serum antibody titers against the parasite, and the depth of several personality changes [32].

Several mechanisms, or combinations of them, have been alluded to explain the association of *T. gondii* chronic infection and neurological disorders: alterations of neuron morphology and functions induced by the parasite (e.g., mental maladies like schizophrenia, bipolar and obsessive-compulsive disorders are associated with a lowering of spines density and dendritic functions induced by the infection [33-34]), neurotransmission impairments caused by the chronic infection (e.g., it has been reported higher levels of dopamine and lower levels of serotonin and norepinephrine in the brain of mice chronically infected [35]), hormonal changes within the context of the infection (e.g., in persons with bipolar disorder have been shown lesser levels of corticosterone production [5]), and inflammation caused by the immune response to *T. gondii* (e.g., some studies in mice show that the immune response control the replication of bradyzoites inside the cysts creating an adjacent proinflammatory environment [5,36]).

On the other hand, it is necessary to remark that most of the studies mentioned earlier have been of association type. Thus, the development of drugs capable of acting on *T. gondii* bradyzoites or the obtaining of vaccines against the protozoan are necessary. Both approaches would allow, with the elimination of the cause, the disappearance or attenuation of the neurological disorders.

At present, the most effective therapeutic option for *T. gondii* infection involves the combined use of pyrimethamine and sulfadiazine [37]. However, in addition to increased *T. gondii* resistance [38], it has been proven that this combination is effective against tachyzoites and practically ineffective against tissue-encysted bradyzoites [39]. Consequently, vaccination seems to be the most promising alternative to control latent *T. gondii* infections [40,41]. Nevertheless, Toxovax™, the only

commercially available vaccine against *T. gondii*, has lonely been authorized to prevent abortion caused by the parasite in sheep [40,41]. In this scenario, and taking into consideration the associations mentioned above, the development of new drugs and effective vaccines against toxoplasmosis is a pressing need.

The prevention of toxoplasmosis, including its latent form, must be faced from a One Health approach that incorporates diverse types of measures that target different phases of the life cycle of *T. gondii*. Among them, it should be mentioned the implementation of education programs for evading contact with infectious stages of the parasite; the execution of actions to ensure food and water safety; the securing of drugs for the treatment of active infections; the promotion of procedures for preventing livestock infection; and the development of vaccines both to prevent shedding of oocysts by definitive hosts and to prevent infection of humans [39].

Generally, the application of that set of measures, or part of them, requires considerable resources and is often not sustainable. This is a difficulty that other parasite control programs have gone through, for example, soil-transmitted helminthes [42]. One of the most effective ways to achieve this sustainability is the prioritized implementation of prevention and control actions on those population groups at greater risk of being infected by the parasite and in which it could have its deleterious effects for a longer period [43].Taking into account that the prevalence of *T. gondii* infection is already high from early ages, as the surveys mentioned above demonstrated, the prevention of latent toxoplasmosis must begin in children and adolescents in order to avoid possible subtle alterations at those ages, when the mental disorders and illnesses that usually appear in older people have not developed.

Conclusions

The relatively recent demonstration of association between latent toxoplasmosis and the development of neurological disorders evidences a health problem of unknown dimensions: a third part of the planet's population is at risk of developing incapacitating neurological conditions, with all that they mean in terms of human suffering and social burden. In the absence of effective drugs against bradyzoites of *T. gondii* and vaccines against the parasite, other actions targeting different phases of its life cycle are in use to prevent the transmission. Since the prevalence of latent toxoplasmosis is already high at the end of adolescence, and bearing in mind the possible adverse consequences related with the presence of the silent form of the infection, the implementation of those prevention measures must begin at early ages.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Funding

No fund

Acknowledgements

Not applicable

Author contributions:

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of Interest:

The authors declare that the preparation of the manuscript was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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