

Is Underdiagnosed, Chronic, Latent Infection with *Toxoplasma gondii* Responsible for the Development of Several, Common Neurological and Psychiatric Disorders? Assessment of Manipulation Theory. Review and Metanalysis of the Available Literature

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Received: July 25, 2018; **Published:** August 22, 2018

Abstract

Toxoplasmosis is an important, widespread, parasitic infection caused by *Toxoplasma gondii*. It is well known the danger of re-activation of the latent infection in immunosuppressed individuals (e.g. AIDS patients). Although the chronic infection in immunocompetent patients or seropositive patients, usually considered as asymptomatic or relatively benign, is now suspected to be a risk factor for a variety of neurological and psychiatric disorders. We aimed to conduct a systematic review and meta-analysis of the available literature to estimate the wide range of CNS morbidity due to latent chronic infection with *Toxoplasma gondii*, which may be underdiagnosed.

Keywords: *Toxoplasmosis; Toxoplasma gondii; Latent Chronic Infection; Protozoal Infection; Neurological Disorders; Psychiatric Disorders; Manipulation; Riskier Behavior*

Introduction

Toxoplasmosis is one of the most common parasitic diseases worldwide. Although estimated that one third of the world's population are infected with *Toxoplasma gondii*, but the most common form of the disease is latent (asymptomatic).

In the United States and most European countries, the seroprevalence increases with age and exposure. For example, in the United States, 5 - 30% of individuals 10 - 19 years old and 10 - 67% of those > 50 years old have serologic evidence of exposure; seroprevalence increases by ~1% per year. In Central America, France, Turkey, and Brazil, the seroprevalence is higher [1].

Toxoplasmosis is one of the commonest opportunistic infections in immunocompromised individuals. Humans are mainly infected by consumption of undercooked meat containing tissue cysts or by ingestion of food and water contaminated with oocysts from infected cat feces. In a healthy host, the infection usually remains asymptomatic. In immunocompromised individuals, toxoplasmosis presents with meningeal and encephalitic symptoms or with signs of solitary or multiple mass lesions. Patients may present with altered mental status, fever, seizures, headaches, and focal neurologic findings, including motor deficits, cranial nerve palsies, movement disorders, dysmetria, visual-field loss, and aphasia. Although lesions can occur anywhere in the CNS, the areas most often involved appear to be the brainstem, basal ganglia, pituitary gland, and corticomedullary junction. Involvement of the pituitary gland can give rise to panhypopituitarism and hyponatremia from inappropriate secretion of vasopressin [1,2].

Citation: Chatzintounas Thomas. "Is Underdiagnosed, Chronic, Latent Infection with *Toxoplasma gondii* Responsible for the Development of Several, Common Neurological and Psychiatric Disorders? Assessment of Manipulation Theory. Review and Metanalysis of the Available Literature". *EC Neurology* 10.9 (2018): 835-844.

Both *in vitro* neuropathologic studies of *T. gondii* in cell cultures and postmortem studies on the brains of schizophrenic patients have shown many glial abnormalities, especially in astrocytes. The fact that patients with schizophrenia have abnormal neurotransmitters, especially dopamine, glutamate, and gamma aminobutyric acid (GABA), is well known. Animal studies of *T. gondii* have demonstrated that this organism can lead to altered behavior and affect dopamine, norepinephrine, and other neurotransmitters [3,4]. Recent studies have indicated that the genome of *T. gondii* has two genes encoding tyrosine hydroxylase; this enzyme affects dopamine biosynthesis [5].

The pathology may present as solitary or multiple necrotizing abscesses, coagulative necrotic granulomas, and microglial nodular encephalitis. *Toxoplasma* organisms within cysts or freely dispersed in the parenchyma are demonstrated in sections stained with H&E (haematoxylin and eosin) stain or by the Wright-Giemsa stain, but most reliably using immunohistologic methods.

Congenital toxoplasmosis is acquired transplacentally, either from an acute or reactivated infection of the mother. Characteristic clinical features are microcephaly, mental retardation, seizures, variable neurologic deficits, and chorioretinitis. Pathologic features are microencephaly, extensive coagulative necrosis with calcifications, and hydrocephalus [2].

Furthermore, except by ingestion of food and water contaminated with oocysts, other ways of contamination include blood transfusion, and solid organ or hematopoietic cell transplantation [6,7]. After ingestion, sporozoites and bradyzoites released from oocysts and cysts invade intestinal cells and are converted to tachyzoites [8]. Actively proliferating tachyzoites or trophozoites are usually seen in cells of different tissues in the acute phases of infection. Within weeks or months, tachyzoites disappear, and the resting bradyzoites in tissue cysts appear in various tissues, mainly in the brain and muscle [9,10]. These cysts may remain throughout the life of the host. If the host becomes immunosuppressed, the infection can be reactivated [11].

Neurological and Psychiatric Disorders in Latent Chronic Infection

The systematic review of the available literature revealed the wide spectrum of CNS morbidity due to latent chronic infection with *Toxoplasma gondii*. We found many common neurologic symptoms and signs, psychiatric disorders or altered cognition and behavior in patients not only immunosuppressed (e.g. AIDS patients), but immunocompetent or seropositive also.

Although latent chronic infection with *Toxoplasma gondii* in immunocompetent or seropositive humans is generally considered relatively benign, the parasite is never cleared from the nervous system, but cell-mediated immune response suppresses pathogenic activity. This “no harm done” assumption is now being reconsidered, as growing evidence links *T. gondii* as a risk factor for several neurological and psychiatric disorders associated with serological evidence of *Toxoplasma gondii* exposure.

Risk factor for or Possible Neurological Manifestations

(Due to latent chronic infection with *Toxoplasma gondii*)

- Toxoplasmic encephalitis (in AIDS patients) [12,27]
- Mollaret meningitis - acute monosymptomatic aseptic meningitis [13,14]
- Cerebral toxoplasmosis - intracranial inflammatory granuloma [15-17,36]
- Tourette's syndrome [18]
- Chronic motor or vocal tic disorder [18]
- Recurrent headaches - migraine [19-23]
- Epilepsy [19,24-27]
- Brain tumors (ependymoma and glioma) [28,29]
- Anosmia [30]

- Alzheimer's disease [19,31-33]
- Parkinson's disease [19,31,34-37]
- Choreic movements - Hemichorea [37-40]
- Choreoathetosis [41]
- Mental retardation [19,42,43]
- Obstructive hydrocephalus [17,44]
- Ventriculitis [45]
- Myelitis - myelopathy [46-49]
- Myopathy [47]
- Polymyositis [50-52]

Risk factor for or Possible Psychiatric Manifestations

(Due to latent chronic infection with *Toxoplasma gondii*)

- Obsessive-compulsive disorder (OCD) [19,53,54,62]
- Schizophrenia (increased incidence) [3-5,7,10,11,19,31,38,55-57]
- Depression [19,58]
- Bipolar disorder [42,57,59]
- Suicidal behavior - suicidal self-directed violence (SSDV) [19,60,65]
- Generalized anxiety disorder [58,61,62]
- Risk of traffic accidents [19,63,64]
- Aggression and impulsivity [65,66]
- Addiction [57]

Discussion

Although there are controversial or contradictory results in some studies, apparently from differences in design and assessment of results, it is clear the obvious correlation of *Toxoplasma gondii* latent, chronic infection with a wide spectrum of neurological and psychiatric manifestations.

The neurological manifestations depends on which parts of the CNS are affected by the protozoal infection. So in immunocompromised individuals, toxoplasmosis presents usually with meningeal and encephalitic symptoms or with signs of solitary or multiple mass lesions. Chronic latent neuroinflammation caused by the parasite may be responsible for the development of several neurodegenerative diseases, manifesting mainly with extrapyramidal signs and symptoms. There is also the hypothesis that, *T. gondii* could increase the risk of brain cancer, because it is a long-lived parasite that encysts in the brain, where it provokes inflammation and inhibits apoptosis.

The pathophysiology and development of behavioral changes and psychiatric manifestations originates from brain dysfunction, as a result of the inoculation of cysts in specific anatomic structures of the brain, such as in hippocampus and amygdala [67,68], where *Toxoplasma* tissue cysts can persist for extended periods of time. Some other alterations may also play role in etiology of various mental disorders, including neurotransmitters alterations (particularly dopamine) [3,4,69], inflammatory responses in brain [70], tryptophan metabolism and kynurenic acid formation [71,72]. Furthermore, recent discoveries suggest that *Toxoplasma* may also increase susceptibility to human brain diseases including cognition and behavior through immune activation, as a secondary result of interference with gastrointestinal mucosa and changes in the intestinal microbiome. Numerous studies have documented alterations in functioning and inflammation in the intestines of individuals with psychiatric disorders. Also antibodies to *T. gondii* have been associated with markers of intestinal inflammation in patients with psychiatric disorders [73-75].

The diagnosis is usually suspected on the basis of MRI findings of multiple lesions throughout the CNS, although sometimes only a single lesion may be seen. These lesions demonstrate ring or homogeneous enhancement on contrast MRI or on double dose contrast CT, with evidence of surrounding edema in many cases, because of inflammation and central necrosis. Calcifications may be found in the parenchyma and beneath the ventricles. The diagnosis of cerebral toxoplasmosis is rather difficult because the clinical manifestations are non-specific and it mimics several other infectious diseases or tumors in the CNS of immunocompromised patients. The differential diagnosis includes primary CNS lymphoma and, less commonly, tuberculous, fungal or bacterial abscesses, herpes simplex encephalitis, cryptococcal meningitis and progressive multifocal leukoencephalopathy [1].

Infection may be diagnosed by visualisation of the protozoa in biopsy material (histologic examination of lymph nodes) or isolation of *T. gondii* from blood or other body fluids. The diagnosis is confirmed with serial serologic tests on serum and CSF. Serology has become the routine method of diagnosis. The presence of circulating IgA favors the diagnosis of an acute infection. In general, toxoplasma-specific IgG antibody appears 2 to 3 weeks after acute infection and often persists lifelong. Presence of toxoplasma-specific IgM antibody suggests infection within the last two years. In immunocompromised individuals a positive IgG assay indicates distant infection, while a negative one argues strongly against reactivation. Molecular approaches can directly detect *T. gondii* in biologic samples independent of the serologic response [1]. A specific PCR performed on amniotic fluid may determine if a foetus has become infected [2]. Meningeal involvement is uncommon, and thus CSF findings may be unremarkable or may include a modest increase in cell count and in protein - but not glucose - concentration [1]. The definitive diagnostic procedure is brain biopsy, when treatment fails but with controversial results.

Because untreated cases have a fatal outcome, empirical therapy is justified [1,2]. Treatment includes pyrimethamine and sulfadiazine (folinic acid is added in an immunosuppressed host) in acute cases and for maintenance therapy. If allergic to sulfa drugs clindamycin may be used [1,2].

The chances of primary infection with *T. gondii* can be reduced by avoiding to eat undercooked meat (specifically lamb, beef and pork) and by avoiding direct contact with oocyst-contaminated material (i.e. a cat's litter box). Hands should be washed thoroughly after working in the garden, and all fruits and vegetables should be washed. Blood intended for transfusion into seronegative, immunocompromised individuals should be screened for antibody to *T. gondii*. Preventive measures should be taken especially during pregnancy, in order to reduce the risk of contracting a primary infection, particularly in countries with high prevalence of toxoplasmosis.

Pearls, other Issues and Future Directions in Research

“Manipulation Hypothesis”

The “manipulation hypothesis” or “Mind control” like influence of *T. gondii* upon human behavior needs to be explored in depth. Many organisms throughout the nature uses the above technique for transmission and reproduction. The Cordyceps fungus, for example, infects ants before making them travel to the top of the tree canopy where they die. Then after the reproduction of the fungus, their offsprings float down to the forest floor to infect more ants [76]. The same happens from *T. gondii* influence to rats and mice in order to make sure that they will come into contact with cats. They lose their inhibition of cats and cat urine and become more exploratory and spend more time in daylight, with diminished predator vigilance. This behavior promotes predation by and finally transmission to the definitive feline host, where it can undergo sexual reproduction and complete its life cycle [77].

Consistent with this hypothesis are studies indicating an association between the exposure to *T. gondii* and other risk taking behaviors in humans, such as increased risk of traffic accidents [19,63,64] and impulsivity [65,66]. How this tiny organism can cause such extreme reactions, could be explained by influencing the levels of neurotransmitters such as dopamine and the inoculation of cysts (bradyzoites) in specific anatomic regions of the brain, such as amygdala, which has been shown to control fear response [67,68,78]. The resultant riskier

behaviour and neuropsychiatric disorders could also be associated with changes in the intestinal microbiome, as a result of intestinal inflammation, which in turn can affect the production of another neurotransmitter (serotonin) in the colon, with subsequent influence in behavior [73-75,79].

Having all these in mind ethical and philosophical issues arise. We must be more prone, to excuse the odd and unpredictable manner that other people may act, from unseen external influences. We also must wonder if all our ideas, motivations and decisions are really self-produced and to estimate in which manner, all the above could influence our way of thinking, our way of acting, our society or even politics.

Anti-parasitic Properties of Antipsychotic Agents - Potential Clinical Applications on Human Seropositive Individuals

CNS-acting medications, particularly antipsychotic agents, are often prescribed to seropositive individuals due to the relatively high coincidence of schizophrenia and other mental disorders with *T. gondii* infection. As we said earlier, analysis of the *T. gondii* genome has discovered two genes that encode tyrosine hydroxylase, an enzyme that produces a precursor to making dopamine, called L-DOPA [3,5]. In addition, there is experimental evidence to support how this could affect behaviour, by demonstrating the anti-parasitic properties of these antipsychotic agents in vitro trials, probably working in part via parasite inhibition. Dopamine levels are found high in infected mice, and their altered behaviour can be reduced if an antagonist of dopamine (like haloperidol - a well-known dopamine D2 antagonist) is administered. Furthermore, valproic acid, a mood-stabilizing drug with well documented and broad use for the treatment of epilepsy and bipolar disorder, was found to reverse loss of fear to predator odor, with unknown mechanism of action. However, there are no animal experiments analyzing the ability of antipsychotic agents to reduce morbidity, acute disease spread or to satisfy the imperative need to diminish the activity of disease especially in the cyst stage [79,80].

Several questions arise about potential clinical applications of the aforementioned data on human seropositive individuals. Would have been better to give haloperidol or valproic acid in seropositive individuals, having in this way dual effect, both in the control of psychiatric manifestations and in limiting also the possible underlying parasitic infection? Further research regarding the potential efficacy of the second-generation anti-psychotic agents is needed also. On the contrary other clinical trials are needed, in order to confirm the effectiveness of anti-*T. gondii* medications (pyrimethamine, sulfadiazine, or clindamycin) as adjunct therapies for schizophrenia or other psychiatric manifestations in seropositive individuals.

Conclusion

Although latent, chronic infection with *Toxoplasma gondii* in immunocompetent or seropositive humans was generally considered relatively benign, the systematic review of the available literature revealed that latent, chronic infection could be a risk factor for a wide spectrum of several neurological and psychiatric manifestations, including altered cognition and behavior as a possible consequence.

The increased seroprevalence of *T. gondii* worldwide and the obvious correlation of *T. gondii* latent, chronic infection with CNS morbidity, should not be underestimated. Suggestions should be made to doctors to include *T. gondii* serology in their daily clinical practice, especially in countries where seroprevalence is higher. In this way, the enriched and more thorough clinical and laboratory evaluation of patients, could reveal chronic, latent infection, eliminating the danger of serious consequences in immunocompromised individuals or in pregnant women. Special caution should be given when blood transfusion, and solid organ or hematopoietic cell transplantation is going to be performed.

People with altered cognition and behavior - even in mild form - should undergo serology evaluation, if previous differential diagnosis of other causes was negative. Seropositive individuals must follow periodic assessment of their intellectual and mental state by medical personnel (medical interview and easily performed, specific tests and scales must be included). This could help in prevention of riskier behaviour and in initiation of treatment in early stages of neuropsychiatric disorders.

People must be informed about the potential dangers arisen after infection with *T. gondii*, especially pregnant women and immunocompromised patients. Informative lectures should be held for the public, as well as specific instructions for personal hygiene, which will emphasize the necessity of preventive measures. These include: avoiding to eat undercooked meat (lamb, beef and pork), avoiding direct contact with cat's litter box, careful hand washing after working in the garden, while all fruits and vegetables should be washed thoroughly.

Further research and clinical trials are needed, in order to confirm the effectiveness of anti-*T. gondii* medications in psychiatric manifestations or the anti-parasitic properties of antipsychotic agents or other medication (such as valproic acid) not only *in vitro* trials or animal experiments. In this way the imperative need to diminish the hazardous effects of reactivated infection, will be confronted more effectively.

Acknowledgments

The authors thank Asima Husain, MD for her help in preparing the IRB submission, and Kelli Grant for her help in producing the CPRS database search. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs. This work was supported in part by the National Institutes of Health (NS91006, PI: Frances Jensen and NS080565, PI: Brian Litt) and the Mirowski Family Foundation via the University of Pennsylvania Center for Neuroengineering and Therapeutics. The funding sources were not involved in the study design, collection, analysis or interpretation of the data, nor in the writing of the article or decision to submit for publication.

Conflicts of Interest

The authors declare no conflict of interest exists, financial or otherwise, with respect to this work.

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Volume 10 Issue 9 September 2018

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