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Relationship between toxoplasmosis and schizophrenia: A review

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A - Research concept and design, B - Collection and/or assembly of data, C - Data analysis and interpretation, D - Writing the article, E - Critical revision of the article, F - Final approval of article

DOI: 10.17219/acem/61435

Article type: REVIEW PAPER

Submitted: 29.04.2015
Accepted: 19.01.2016
Published online: 21.09.2017
Abstract. A growing body of evidence suggests a correlation between schizophrenia and exposure to infectious agents. The majority of studied cases concerns the infection caused by T. gondii, an obligatory intracellular parasite that infects about one third of the entire human population, according to the available data. The acute stage of the disease, predominantly short-lived and transient, transforms into the latent and chronic phase in which the parasite localizes within tissue cysts, mainly in the central nervous system. The chronic toxoplasmosis, primarily regarded as benign and asymptomatic, might be responsible, in light of current scientific evidence, for a vast array of neuropsychiatric symptoms. Numerous epidemiological case-control studies show a higher prevalence of T. gondii infestation in individuals with various psychiatric and behavior disorders, including schizophrenia.

This paper tends to review the relevant studies that demonstrate links between schizophrenia and T. gondii infestation, of which the latter may be acquired in different developmental phases. Apart from epidemiological correlation studies, some papers on other associations were also presented, describing putative patophysiological mechanisms that might be at least partly responsible for chronic infection-induced neuromediator disturbances, together with morphological and functional alterations, e.g., low-grade neuroinflammation, which are likely to induce psychopathological symptoms.

Toxoplasmosis is only one of the putative infectious agents that derange correct brain growth and differentiation, alongside genetic and environmental factors. All of them may lead eventually to schizophrenia. A better knowledge of infection mechanisms and its influence on neurobiochemical and neuropathological pathways may enable more efficient therapy and the prevention of this devastating disease.

Key words: neuropsychiatric symptoms, schizophrenia, Toxoplama gondii.
External funds
None declared

Conflict of Interest
None declared

Acknowledgment
None declared

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Short title
Toxoplasma gondii and psychiatric disorders

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Introduction

Toxoplasmosis is an infectious disease caused by a parasitic protozoan Toxoplasma gondii, which affects approximately one third of entire human population. It is, therefore, the most common disease of infectious origin, more widespread than malaria, tuberculosis, and other infections and parasitoses, which are commonly regarded as serious global threats [1]. T. gondii is able to infect almost all species of mammals and numerous species of birds (warm-blooded animals), while the incidence of infestation in humans varies according to the geographical region, climate, and hygienic and nutritional habits [1,2]. In humans, two principal forms of infection occur: inherited - which is transmitted vertically from the mother to the fetus by means of placental tissues; and acquired – acquired mostly via the digestive route by ingesting undercooked meat dishes or accidental contact with cat feces, which is the unique definitive host of T. gondii [2].

A considerable number of health disorders and diseases has been found and studied in correlation with toxoplasmosis. They were presented in more detail elsewhere [1]. It was thought earlier that such a latent form of the disease does not lead to any serious sequelae and it is only the reactivation of infection due to individual disorders of immunity that poses a real threat [3]. However, a growing body of evidence suggests unequivocally that a persistent and dormant infestation might be responsible for various neurologic and psychiatric symptoms [4]. The majority of evidence comes from epidemiological case-control studies which denote a higher incidence of chronic T. gondii infection in individuals suffering from various psychiatric disorders, in comparison with healthy people (controls) [5,6,7]. The diagnosis of the infection is based on an analysis of specific antibody prevalence.

Schizophrenia is a severe psychiatric disorder with a lifetime prevalence of approximately 1%, regarded as the ninth most common cause of disability all over the world [4]. The disease manifests itself most often from late teens to early adulthood, although the psychotic episodes
can persist throughout the entire life of the patient. Schizophrenia is a heterogeneous disease and its origins are slowly being disclosed. Up to now, no unique causal agent has been detected; therefore, it is legitimate only to describe some factors that were shown to be positively correlated with schizophrenia. The known risk factors include: genetic predisposition, neurodevelopmental disturbances and environmental factors, including infectious agents [4,5].

The interest in infectious origins of psychiatric disorders can be traced back as early as to the nineteenth century. In 1896, Scientific American published an article with an expressive title: "Is insanity due to a microbe?" [5]. It prompted temporary attention in the study of the correlation between infections and psychiatric disorders in the beginning of the previous century. These theories then waned until the closing years of the previous millennium, when the correlation started to be examined again. In the second half of the twentieth century, a few dozen papers, studying the correlation between T. gondii infestation and psychiatric disorders (especially schizophrenia), were published. Moreover, several reports were issued dealing with other potential infectious factors, acting both at the pre- and perinatal period (influenza A virus, herpes simplex 2, poliomyelitis), and also after delivery - predominantly viruses and bacteria causing meningitis and encephalitis [6]. However, in the majority of cases the attention of scientists was focused on T. gondii infection [6,7].

Note that the very first report was based on studies conducted in Poland (Gdańsk) in 1953 and concerned the investigation of toxoplasmosis prevalence among psychiatric department patients. The rate of infection was significantly higher in patients compared with controls (52% vs. 25%; OR 3.19), but the application of now outdated diagnostic tests (skin tests) and the lack of precise inclusion criteria for both groups make this research useless for contemporary meta-analyses; it has only historic value [8].
Correlation between T. gondii infection and schizophrenia

Owing to the high affinity of T. gondii to the nervous tissue (predominantly the glia cells - astrocytes) and the established association with inborn cerebral disorders, the interest of researchers was for a long time directed at potential links between exposure to the parasite and the onset of severe psychiatric disorders [6,9]. As for schizophrenia, such correlation was established on base of the following studies:

1. Higher serological prevalence of T. gondii infection in schizophrenic patients.

In 2007, Torrey et al. published a review of available research material (also unpublished so far), which included not only English scientific magazines, but also the reports from the entire world, written in various national languages [6]. They identified 42 papers, issued over a 50-year span, 23 of which conformed strict inclusion criteria for conducting meta-analysis. The studies covered a total of 3,873 patients and 7,046 people from control groups. The combined odds ratio (OR) was 2.73 (2.10-3.60; p < 0.000) [6]. Seven of these reports dealt only with patients in the first episode of schizophrenia, but the results of this subgroup did not significantly differ from the entire material (2.54 vs. 2.73). Six included papers were not previously published and their combined OR was 2.16, compared to OR = 2.97 of the published reports [6]. This is consistent with the common research experience that the works of higher statistical and clinical significance are submitted for publication more readily than reports of lesser significance [5,6].

The above-mentioned study group published an update of the meta-analysis in 2012. Fifteen additional papers were included and the new combined odds ratio that was calculated on the basis of all studies, older and new ones, amounted to 2.71 (95% CI: 1.93-3.80) [7].

The results presented above suggest that some individuals with schizophrenia have an increased prevalence of antibodies to T. gondii. The odds ratio of 2.73 (2.71) may seem modest,
but it exceeds any other genetic or environmental factors found so far, showing without any
doubt that Toxoplasma is linked in some way to a great number of schizophrenia cases [7].
Moreover, new reports are still being published and they mostly replicate the earlier results
[10]. Taking T. gondii infestation into account is also crucial, since individuals with higher
titers of IgG antibodies often experience more severe symptoms of psychosis and it was
observed that infections in schizophrenic patients might be correlated with increased mortality
[6]. Dickerson et al. studied the prevalence of anti-T. gondii antibodies in 358 patients with
schizophrenia who subsequently underwent a follow-up for 5 consecutive years. It was noted
that mortality in seropositive patients was 8.6%, while that of seronegative ones was 1.7% (p < 0.003) [11].

2. Increased risk of schizophrenia in the offspring of mothers with serologic signs of infection
detected during pregnancy.

   A growing body of evidence points to maternal infection as a risk factor for
schizophrenia in children [12]. These infections include influenza, genitourinary system
infections, and also toxoplasmosis [13]. These microbes certainly cause inherited brain
malformations and a vast spectrum of cognitive and behavior disorders in childhood [14].
Furthermore, it has been known for many years that people exposed in utero to rubella, measles,
toxoplasma, herpes virus 2, and various other infections are more likely to suffer from
neurodevelopmental disorders, mental retardation, learning difficulties, sensory dysfunction
and structural brain malformations [14].

   As far as toxoplasmosis is concerned, cohort studies of blood samples taken from
mothers in the perinatal period revealed an over two-fold increase (OR 2.61; 1.0-6.82) of IgG
antibodies to T. gondii in mothers, whose children later developed schizophrenia. It is worth
noting that none of the studies detected an acute infection (which is confirmed, e.g., by the
presence of specific IgM antibodies), but only serological markers of earlier contact with the parasite (latent infection) [6,15].

3. Increased prevalence of antibodies to T. gondii in the newborns who later developed schizophrenia.

Research conducted in 2007 in Denmark studied blood samples obtained from earlier neonatal screening tests. The IgG and IgM anti-T. gondii antibody levels were measured and the results were attributed to respective adult patients, suffering from schizophrenia-spectrum disorders. Positive IgG antibodies were detected more often in people with schizophrenia (OR 1.79; p < 0.05) [16].

Assuming that no IgM antibodies suggesting an acute infection were detected but only those of IgG class that must have been transmitted from mothers via placenta (in children, the ability to secrete IgG antibodies appears no sooner than the third month after birth), the results of both studies mentioned above suggest one explanation - earlier maternal exposure to T. gondii may account for a risk factor of schizophrenia in the offspring [13,16].

4. The ability to destroy T. gondii cells in vitro by some antipsychotic and normothymic drugs.

Three independent studies detected a significant correlation between the first psychotic episode in schizophrenia and serological markers of toxoplasmosis (p < 0.001), suggesting that these patients must have acquired the infection earlier [6]. The difference was less marked in patients with a long-standing disease. An assumption was, therefore, made that antipsychotic drugs or other agents used by patients may decrease the titers of circulating antibodies to T. gondii [6]. It was discovered even earlier that some psychotropic drugs inhibited in vitro proliferation of the parasite in human fibroblasts. The first relevant study, performed by Jones-Brando et al., investigated the influence of twelve anti-psychotic and normothymic drugs on
proliferation of T. gondii cells [17]. Valproic acid in conjunction with haloperidol had the strongest inhibitory effect, while risperidone and trimethoprim were weaker inhibitors [17]. Since that time, several other studies have been published that examined the effect of different psychotropic drugs (including those mentioned above) on the proliferation of the parasite, generating various, sometimes contradictory results. The inhibitory action of the drugs on T. gondii growth depends on developmental form of the parasite, stage of infection and duration of illness, but available data suggests that some therapeutic agents used in schizophrenia (e.g., fluphenazine, thioridazine, trifluoperazine, zuclopenthixol, alongside with cyamemazine, olanzapine and loxapine) may exert their effect also in vivo, while their relieving of psychotic symptoms may, at least to some degree, depend also on the inhibition of the parasite metabolism [18,19]. Furthermore, a report exists in the literature that depicts a case of depression resistant to treatment with standard agents in a patient with T. gondii infection. A marked improvement was observed instantly after the parasite had been eradicated with trimethoprim and sulphadiazine [20].

Studies conducted on rats showed that haloperidol or valproic acid reversed behavioral changes induced by the T. gondii infection, such as decreased neophobia and transforming the innate aversion to cat odor into unnatural attraction, on par with standard anti-parasitic regimen. However, those drugs did not prevent acute infection or decrease the number of tissue cysts in the animal brain [18]. What is important, a chronic and occult toxoplasmosis induces specific behavioral changes also in humans, which are well described, especially by Flegr, Webster, et al. [18,21].
5. Neurotransmitter secretion disturbances due to T. gondii infection, which may induce psychotic symptoms.

In the natural course of schizophrenia and the manifestation of its symptoms, a pivotal role is attributed to the derangement of secretion or the action of several neurotransmitters, which actually forms the background of pharmacological therapy, directed not only at positive symptoms of the disease, but also at the negative ones [22]. The principal substances involved in pathogenesis of schizophrenia symptoms are: dopamine, serotonin (5-HT), GABA, glutamate, etc. [4,22] Symptoms of the disease, such as hallucinations and delusions, are eliminated or alleviated by dopaminergic D2-receptor-blocking agents; this constitutes the primary, but not exclusive mechanism, of neuroleptic drug action, especially those of the first generation [22].

Available data suggests that T. gondii may elicit or worsen the symptoms of neurodegenerative diseases and psychiatric disorders via the modulation of secretion or the effects of some neurotransmitters, predominantly dopamine [3,4]. The parasite genome includes two aromatic acid hydroxylase genes, which may possibly directly influence the biosynthesis of dopamine and/or serotonin [4]. In researches on mice, it has been shown that chronic (but not acute) infection with T. gondii elevates the local brain dopamine concentrations, as in patients suffering from schizophrenia [4,23]. Another putative mechanism may be a tryptophan metabolism disruption, which is a typical immunological reaction to a parasite infestation and it leads to accelerated tryptophan depletion by IFN-γ-inducible enzymes: indoleamine-2,3-dioxygenase (IDO) and tryptophan dioxygenase (TDO) [3,4]. Disruption of metabolism decreases the levels of tryptophan that is indispensable for T. gondii growth and replication, but also generates the accumulation of some harmful metabolites, particularly kynurenic acid (KYNA), an antagonist of N-methyl-D-aspartate- (NMDA) and nicotinic receptors [4,24]. High concentrations of KYNA, detected in cerebrospinal fluid of
schizophrenic patients, are one of the potential causes of cognitive disorders in schizophrenia [4]. The principal source of KYNA are astrocytes, the cells preferably chosen by T. gondii for replication [24]. To the best of the authors' knowledge, there is a lack of direct evidence so far that parasite-infected cells secrete high amounts of KYNA via IDO-mediated tryptophan degradation, but this seems highly probable, according to some authors [3,4].

6. The symptoms of toxoplasmosis in some patients with an acute infection.

The symptomatology of acute toxoplasmosis, which is a reactivation of chronic infection in immune-compromised patients, has been well described [25]. Case reports of patients suffering from AIDS with a relapse of latent infection indicate that as much as 60% of them report psychiatric disturbances, including: delusions, auditory hallucinations and thought disorders [4,25]. However, psychopathological symptoms are also relatively frequent in various stages of HIV infection and AIDS, which might be presumably caused by the virus itself, not by opportunistic infections [26].

Moreover, it has been observed that in some healthy and immune-competent individuals an acute infection may manifest itself with delusions and hallucinations, thus the symptoms specific mainly but not exclusively of schizophrenia. A study of 114 people with acquired toxoplasmosis detected fairly frequent and serious psychiatric disturbances in 24 of them [25]. In some case reports, the initial symptoms of toxoplasmosis were highly specific of schizophrenia and it was not until the follow-up of patients and the onset of neurological symptoms that the possibility of infection was considered. After anti-parasitic therapy, psychotic symptoms vanished in these subjects [25]. It is suggestive that T. gondii infestation may per se induce patophysiologic mechanisms in some individuals that change brain neurotransmitter levels, which eventually leads to psychopathological manifestations [3,4,21]. However, such changes should coincide with other known risk factors, because Toxoplasma per se cannot induce schizophrenia, but only influence liability to its development.
7. Parasite affinity to the brain cells.

T. gondii cells show high degree of neurotropism and after an acute stage of infestation, the parasite migrates within the brain tissue (predominantly gray matter), localizing in astrocytes, microglia and neurons [4,27]. The dormant form of T. gondii (bradyzoite) can persist in the host brain for many years, presumably until the end of its life [28,29]. Tissue cysts are not constant and passive in nature, but are rather active. They do not cause tangible symptoms in immune-competent individuals, but are subjected to continuous remodeling, vanishing in some brain regions and appearing in others [30]. Available neuroimaging methods cannot visualize single cysts; however, great expectations are put on novel magnetic resonance techniques (with the application of contrast solutions: gadolinium and ultrasmall superparamagnetic iron oxide particles (USPIO)) [29]. These obstacles make localizing cyst aggregates in humans particularly challenging (brain biopsy is indispensable), but the precious evidence is supplied by means of studying animal models and histological examination of human brains, made post mortem, which are very rare, unfortunately [29]. Given the results, it can be concluded that: 1) T. gondii is localized within the brain structures responsible for thought processes, emotions and sensorium: amygdalae, hippocampus, striatum, thalamus and cerebellum [27]; 2) latent toxoplasmosis and schizophrenia both induce similar, often discrete changes in brain morphology: gray matter atrophy, ventricle system enlargement and microscopic presence of inflammatory cells in perivascular spaces, around cerebral aqueducts and within the pia mater, features commonly detected also in neurodegenerative diseases [31]. Furthermore, considering that chronic and occult T. gondii infection causes discrete symptoms of low-grade neuroinflammation [30], inevitably linked to tissue cyst remodeling and, according to most available studies, additional combined treatment of schizophrenia with anti-inflammatory drugs (e.g., celecoxibe) elicits a better therapeutic response [32], another putative link can be drawn between the infection and psychiatric disorders. As for anti-inflammatory
treatment, it is most successful in the beginning stages of the disease (prodromal phase) and applying the therapy thereafter diminishes the percentage of positive reactions [32].

8. Other associations.

Some less important risk factors for schizophrenia include contact with cats in childhood, which may indeed generate an elevated risk [28,33]. It is true that not all reports confirm the correlation between T. gondii infection and the possession of domestic pets (especially cats) but they postulate maintaining a high level of personal hygiene and the appropriate management of cat litters [1,28]. It is worth mentioning that cat bites have been linked to cases of depression [33], which is a disorder different from schizophrenia but also attributed to disturbances of neuromediator balance [4]. Finally, the association between toxoplasmosis and schizophrenia is consistent with infection models in animals, pointing to constant and repetitive behavioral changes in animals with T. gondii infestation [34].

Critical remarks and summary

When creating links between the parasite and schizophrenia, at least some problematic issues should be taken into consideration. First, the majority of available records deals only with the serological markers of infection and T. gondii, which are not directly detected in body fluids or tissues [5,6]. However, it must be admitted that the countries with a particularly high rate of infection (France, Ethiopia) do not exhibit a significantly higher prevalence of schizophrenia (however, available data is equivocal and in the Scandinavian countries, where the rate of infection has consistently declined over several decades, a lower incidence of psychoses is noted) [6].

The most serious problem with plausibility is that the majority of patients with schizophrenia do not have measurable levels of antibodies to T. gondii [5,6]. Despite the higher
rate of infection in schizophrenia patients and their mothers, most people living in areas of low infection prevalence (e.g., USA) do not have detectable antibodies [1,6]. It is highly probable that schizophrenia is of heterogenous origins and infection by the parasite does not play a direct and deciding role in the etiology of most cases within the population [5,6]. However, it cannot be excluded that the circulation of specific antibodies slowly declines over time and exposure in the perinatal period or in early childhood will not result in their detectable levels several decades after [15,35,36]. Moreover, agents used in schizophrenia are able to inhibit the parasite proliferation, which lowers antibody titers in patients undergoing standard therapy [6,19].

Accumulating scientific evidence suggests that exposure to infectious agents during pregnancy and early childhood constitutes a risk factor of schizophrenia in adult life. The results are particularly meaningful for the parasite T. gondii; however, some other microorganisms that share the same pathogenic and biological traits may also be involved [6,7,37]. The mechanisms of the associations are most probably diverse and include direct infection, exposure to some common environmental factors, as well as maternal-fetal transfer of inflammatory mediators [6,37,38]. The individual susceptibility to various pathogens presumably depends on genetic constitution of the host, which is particularly important in schizophrenia, due to the strong correlation between the risk of the disorder onset and genetic factors (highly elevated risk in the offspring and siblings), which have unfortunately remained unidentified up to now [39]. The persistent and chronic inflammatory process in the brain, which most commonly occurs without tangible, specific symptoms (neuroinflammation), is currently being linked to a plethora of neuropsychiatric disorders, e.g., dementia syndromes and Parkinson’s disease. Some of those disorders correlate also with T. gondii infestation [1]. Moreover, the inflammatory component of schizophrenia might be presumably evoked by activation of brain cells (microglia, astrocytes), due to latent toxoplasmosis [37,38,40]. Lack of universal response to anti-inflammatory and anti-parasitic treatment in schizophrenia has also been regarded by some
authors as a proof against its infectious origin [32,37]. It should be noted though that the number of available studies is limited and their results inconclusive, which suggests further studies rather than definitive conclusions.

Summary

Currently proposed mechanisms of schizophrenia pathogenesis assume a simultaneous participation of genetic, infectious and environmental factors that act together and derange the correct growth and differentiation of the brain, i.e., neurodevelopmental theory of schizophrenia [37,38]. Toxoplasmosis is, therefore, not the unique presumed infectious agent, involved in its etiology; however, it is certainly the best studied and documented one. Better knowledge of neuropathogenic mechanisms might help identify common paths of damage and disruption, similar to other infections, which will enable more efficient therapy and prevention of schizophrenia.

Unfortunately, these ideas are almost universally disregarded within the psychiatric society in Poland. The origin of this almost hostile disregard remains largely unknown, especially in view of a complete lack of such prospective or epidemiological studies in our country. Each association is potentially worth following; therefore, the authors strongly argue that they do not claim to have depicted a universal theory but a mere pathway that probably merits further studies. According to current knowledge, Toxoplasma gondii has been clearly excluded as the causal factor of schizophrenia, although it is able to influence some metabolic and developmental pathways, leading, in consequence, to altered predisposition to the disease.
18. Webster JP, Lamberton PHL, Donnelly CA, Torrey EF. Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer and anti-parasite

