

Toxoplasmosis can be a sexually transmitted infection with serious clinical consequences. Not all routes of infection are created equal[☆]



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ABSTRACT

Toxoplasma gondii infects about 30% of the human population. Common sources of infection are oocysts in cat faeces contaminating drinking water or unwashed vegetables, undercooked meat containing tissue cysts, and organ transplants from infected donors containing tissue cysts. However, very often, it is not possible to identify any potential source of infection in mothers of children with congenital toxoplasmosis. Here we present a hypothesis suggesting that toxoplasmosis is transmitted from infected men to non-infected women during unprotected sexual intercourse, which can result in the most serious form of disease, congenital toxoplasmosis. Arguments for the hypothesis: (1) *Toxoplasma* tachyzoites are present in the seminal fluid and tissue of the testes of various animals including humans. In some species infection of females by artificial insemination with semen from infected males has been observed. (2) Up to two thirds of *Toxoplasma* infections in pregnant women cannot be explained by the known risk factors. (3) Prevalence of toxoplasmosis in women in child-bearing age covaries with the incidence of sexually transmitted diseases in particular countries. (4) In some countries, an increased incidence of toxoplasmosis has been reported in women (but not men) aged 25–35 years. This second peak of infection could be associated with women having regular unprotected sex after marriage. (5) Toxoplasmosis triggers schizophrenia in predisposed subjects. Onset of schizophrenia is about 2–3 years earlier in men than in women. However, this difference in the onset can be found only between *Toxoplasma*-infected patients. The increased onset of schizophrenia in infected women could be associated with the already mentioned second peak of toxoplasmosis incidence. (6) The prevalence of toxoplasmosis decreases in developed countries in last 20 years. This trend could be a result of decrease in promiscuity and increase in safe sex practices, both associated with the AIDS pandemics. (7) In women, probability of being *Toxoplasma*-infected correlates positively with the amount of unprotected sex with the child's father before the conception. Evidence against the hypothesis: Questionnaire study showed negative association between *Toxoplasma* infection and the number of earlier partners with whom the woman had unprotected sex. If our hypothesis turns out to be true, then sexual route of transmission, even if rare, could be responsible for a large part of cases of congenital toxoplasmosis. Women should be warned that having unprotected sex with men of positive or unknown toxoplasmosis status should be avoided during pregnancy.

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Introduction

Toxoplasma gondii, a protozoan parasite that reproduces sexually in the intestine of cats and asexually in tissues of any

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warm-blooded animal, currently infects about one third of the human population [1]. After a short acute phase resembling a common viral or bacterial infection, the acute toxoplasmosis promoted by rapidly reproducing tachyzoites goes into a life-long latent phase in most of the immunocompetent humans. In immunocompromised subjects, such a spontaneous switch does not occur and the disease often results in encephalitis and death [2]. Latent toxoplasmosis with the typical presence of slowly dividing bradyzoites in tissue cysts was considered asymptomatic for a long time. However, studies published in the past 20 years have shown that the latent form of the disease brings about specific changes in the human personality and behaviour, consequently increasing the risk

of traffic and work-place accidents, suicide, brain tumours, schizophrenia, obsessive-compulsive disorder, epilepsy, and possibly also other conditions, including various heart diseases [3]. The most serious form of toxoplasmosis is congenital toxoplasmosis – a result of transmission of parasites from an acutely infected mother to the foetus. When such a transmission occurs in the first trimester of pregnancy, it can lead to abortion or serious congenital anomalies in new-borns. In the third trimester of pregnancy, infection with a common genotype II strain of *Toxoplasma* results in less serious disorders, mostly causing “only” more or less serious defects of the visual or hearing apparatus [2,4].

The most important sources of postnatal infection are resistant oocysts in cat faeces contaminating drinking water or unwashed vegetables, raw or undercooked meat of intermediate hosts containing tissue cysts, blood transfusion containing blood cells with tachyzoites of the parasite, or organ transplants from *Toxoplasma*-infected donors containing tissue cysts with bradyzoites [2]. However, very often, it is not possible to identify any potential source of infection in mothers of children with congenital toxoplasmosis. Latent toxoplasmosis can re-enter a new acute phase during pregnancy due to pregnancy-associated immunomodulation, namely the suppression of the cellular arm of the immune system [5,6]. Here we discuss and present evidence for an alternative hypothesis suggesting that toxoplasmosis can be relatively often transmitted from infected men to noninfected women during unprotected sexual intercourse.

Arguments for the hypothesis

The tachyzoites of *T. gondii* are known to be present in the seminal fluid and tissue of the testes of various animals including humans [7], goat [8], and swine [9], for review, see [10]. In some animal species like rabbits [11], sheep [12,13], and dogs [14], infection of females by artificial insemination with semen from infected males has been observed. It is not clear whether the tachyzoites are present only during or immediately after the acute phase of infection or whether they could appear there also during latent phase of toxoplasmosis, for example, after an infection-associated or therapeutic immunosuppression.

The efficiency of educational campaigns aiming to decrease the risk of congenital toxoplasmosis is surprisingly low. Up to two thirds of *T. gondii* infections in pregnant women cannot be explained by the known risk factors [15,16].

Correlation analyses have shown that the prevalence of toxoplasmosis in women in child-bearing age significantly covaries with the incidence of sexually transmitted diseases (mainly gonorrhoea, syphilis, and chlamydia) in particular European countries, see Fig. 1. It can be speculated that this correlation is possibly due to a common risk factor, namely the unprotected sex.

In some countries, an increased incidence of toxoplasmosis has been reported in women aged 25–35 years [17]. This increase is generally interpreted to result from handling raw meat while cooking after getting married. However, it can also be interpreted as a result of the fact that married women are likely to have unprotected sex more often than younger single women.

About fifty studies have shown a strong connection between toxoplasmosis and schizophrenia [18–20]. A prospective study has even reported *Toxoplasma* infection to cause schizophrenia in genetically predisposed subjects and toxoplasmosis-associated schizophrenia to be a distinct, more severe form of this serious mental disease [21,22]. It is well known that the onset of schizophrenia is about 2–3 years earlier in men than in women. However, a recent study has shown that this difference in the mean onset can be found only between *Toxoplasma*-infected men and women [21]. The most parsimonious explanation for this difference between

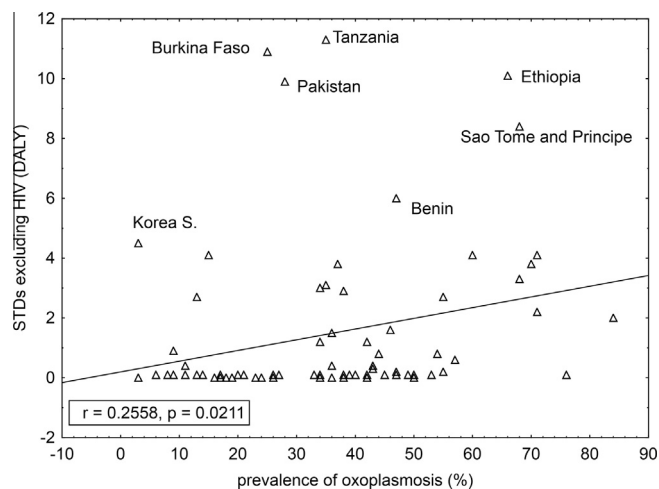


Fig. 1. Correlation of prevalence of toxoplasmosis with STD attributed DALY for 88 WHO-member countries. The y-axis shows the number years of ‘healthy’ life lost by virtue of being in a state of poor health or disability due STD (except AIDS) per 100,000 inhabitants in 2004.

sexes in *Toxoplasma*-infected schizophrenics but not in *Toxoplasma*-free schizophrenics is that the already mentioned second peak of toxoplasmosis incidence in 25–35 old women increases mean onset of schizophrenia in *Toxoplasma*-infected women. Again, the second peak of toxoplasmosis incidence in women can be associated with women having regular unprotected sex after marriage.

Except, for example, in China, Mexico, or Korea, the prevalence of latent toxoplasmosis is currently decreasing in most of the countries [1]. It has been declining at a rate of about 1% per year in most European countries and in the USA over the past two decades. There is no widely accepted explanation for this rapid decrease but higher hygienic standards in the food processing industry and improved personal hygiene practices in general may be a clue. An alternative explanation, however, is a possible decrease in promiscuity and increase in safe sex practices, both associated with the AIDS pandemics [23].

A questionnaire study performed on a sample of 302 Prague women who were pregnant in 2008–2009 has shown that the probability of being *Toxoplasma*-infected correlates positively with the amount of unprotected sex with the child’s father before the conception: partial Tau = 0.072, $p = 0.061$, partial Kendall regression, covariate age of women. In 69 *Toxoplasma*-infected women, the amount of unprotected sex with the child’s father before the conception correlated positively with the concentration of anti-*Toxoplasma* antibodies: partial Tau = 0.178, $p = 0.031$, partial Kendall regression, covariate age of women. This suggested that especially the women with recent infection had a lot of unprotected sex with their partners. Of course, these statistical associations could also be explained alternatively, namely by decreased fertility and therefore decreased probability of conception in infected women. However, such a decreased fertility of infected women has never been noted.

T. gondii is known to manipulate the behaviour of its animal and human hosts in order to increase the probability of its transmission from an infected to an uninfected host [24–26]. Most of the observed behavioural changes are probably related to an enhanced synthesis of dopamine caused by the expression of two tyrosine hydroxylases encoded in the genome of *T. gondii* [27,28]. However, it is known that *Toxoplasma* also increases the concentration of the steroid hormone testosterone in infected human and rat males [29,30]. The increased level of testosterone is known to be associated with higher sexual activity in males, which has also been

confirmed in *Toxoplasma*-infected male rats [31]. It can be argued that such a rise could be adaptive for parasites transmitted by predation (e.g. for *Toxoplasma*) because increased sexual activity raises the risk of predation accident. However, it can be extremely adaptive for any sexually transmitted parasite.

Arguments against the hypothesis

The questionnaire study mentioned earlier/above has shown an extremely strong negative association between *Toxoplasma* infection and the number of previous partners with whom the woman had unprotected sex, partial $\tau = -0.125$, $p = 0.001$, covariate age of women. This observation contradicts the expectations of the hypothesis of sexual transmission of toxoplasmosis. It can be speculated that latent toxoplasmosis-associated changes in the woman's personality [32,33] or a decreased concentration of testosterone in infected women [29] could later result in a lower number of sexual partners (or number of sexual partners reported/misreported in the questionnaire) in *Toxoplasma*-infected women.

Conclusions

We are aware that all arguments above in favour of the hypothesis of sexual transmission of toxoplasmosis are only indirect and all compiled phenomena have also alternative ad hoc explanations. However, taken together, they provide rather a strong support for the hypothesis about the frequent sexual transmission of toxoplasmosis. The hypothesis provides several predictions that can be experimentally tested and several important implications for medical practice. For example, the hypothesis predicts that a husband's toxopositivity should increase the probability of his wife being toxopositive while a wife's toxopositivity should have a much lower effect on the probability of her husband being toxopositive. And most importantly, mothers of children with congenital toxoplasmosis, i.e., women who became infected around the time of conception, should have increased probability of having a toxopositive partner, probably with serological and possibly also clinical indices of acute or postacute toxoplasmosis.

Toxoplasma is a very successful parasite which can infect humans in many different routes. However, not all routes are created equal. Some routes of infection are very effective, especially the ingestion of oocysts, probably responsible for most infections during childhood. Infection by oocysts reportedly has much more serious impacts on the host's health than the ingestion of tissue cysts in raw or undercooked meat [34]. However, even less frequent infection with tachyzoites contained in the seminal fluid, possibly only during an acute or postacute phase men infection, could have much more serious consequences, namely congenital toxoplasmosis, as it occurs during unprotected sex at the critical time of conception. If the hypothesis of sexual transmission of toxoplasmosis turns out to be true, then preventive repetitive screening of toxonegative pregnant women for toxoplasmosis should focus on the subpopulation of women with a toxopositive husband. Moreover, all women should be warned that not only contact with cat faeces, eating unwashed vegetables, drinking suspicious water, and eating raw or undercooked meat but also having unprotected sex with men of positive or unknown toxoplasmosis status should be avoided during pregnancy.

Conflict of interest statement

Authors have no conflict of interest.

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