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Oral sex: A new, and possibly the most dangerous, route of toxoplasmosis transmission

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A B S T R A C T

Toxoplasmosis is a parasitic disease widespread in the temperate zone. The definitive hosts of *Toxoplasma gondii*, which causes the disease, are cats. All warm-blooded vertebrates, including humans, can be intermediate hosts. A person is usually infected by ingesting oocysts, e.g. by consuming along with vegetables some contaminated soil, by drinking contaminated water, or by ingesting tissue cysts contained, for instance, in poorly cooked meat. Less common is congenital transmission or transmission via organ transplant from an infected donor. Recently, it has been suggested that toxoplasmosis could also be transmitted sexually from infected men to uninfected women. In this article, we discuss and present evidence for an alternative hypothesis, which suggests that toxoplasmosis could be transmitted by oral sex (via fellatio) from an infected man to an uninfected person (male or female), especially if the uninfected individual swallows the infected ejaculate. This hypothesis finds support in the following facts and findings: (1) *Toxoplasma* has been found in male ejaculate. (2) In several animal species, presence of the parasite in the seminal fluid of infected males can lead to infection of uninfected females during mating. (3) A higher prevalence of toxoplasmosis has been reported in both homosexuals and promiscuous individuals, i.e. in populations which practice a broader spectrum of sexual activities, including oral sex. (4) In heterosexual couples, a partner's infection seems to be a risk factor for infection in women but not in men. (5) A higher prevalence of toxoplasmosis in females compared to males has been observed in adolescents aged 10 to 14, where oral sex, including fellatio, is highly prevalent among those who have not yet engaged in penetrative intercourse. (6) On a theoretical level, one could expect that when an uninfected person swallows ejaculate containing *Toxoplasma* tissue cysts, this results in a similar infection pattern to ingestion of *Toxoplasma*-contaminated undercooked meat. (7) Approximately two-thirds of *Toxoplasma* infections in pregnant women cannot be explained by any of the known risk factors. (8) In both women and men who report practicing fellatio with men, there is a higher prevalence of toxoplasmosis than in corresponding controls. If our hypothesis is correct, an effective public health campaign with emphasis on early sexual education about the risks of unprotected oral sex will be necessary, especially in pregnant women and HIV-positive people. This route of toxoplasmosis transmission could be experimentally verified by force-feeding laboratory mice with the ejaculate of infected men.

Introduction

Toxoplasmosis, the result of an infection by a coccidian protist *Toxoplasma gondii (T. gondii)*, is probably the most widespread human parasitic infectious disease in industrialized countries. This parasite causes major opportunistic infections in HIV infected people. The prevalence of latent toxoplasmosis in populations ranges from 20% to 80%, depending on various environmental and socioeconomic factors, including the number of cats in the environment, latitude, moisture, hygienic standards, and cooking habits [1]. *T. gondii* enters host cells by actively penetrating host cell membranes or by phagocytosis. It spreads through the host body via infected mobile cells, such as dendritic cells and monocytes [2]. Using this Trojan horse strategy, it can enter immune-privileged organs such as the testes, eyes, and brain. In these organs, it infects various cell types, including neurons, Purkinje cells, and microglial cells [3]. Invasion and growth rate vary depending on the strain of *T. gondii* and the type of host cells.

Acute toxoplasmosis, characterized by rapid replication of tachyzoites in the body, can be accompanied by influenza-like symptoms such as cervical lymphadenopathy, fever, malaise, night sweats, and myalgia [4]. In immunocompetent hosts, the acute phase usually spontaneously evolves into a latent phase characterized by the presence of slowly dividing bradyzoites contained in tissue cysts in various organs of the host. Bradyzoites remain in the body for the rest of host's life and likely do not elicit any inflammatory response [5]. Latent toxoplasmosis seems asymptomatic, but it has been shown that it can be accompanied by specific changes in psychomotor performance, behavior, and personality profile [6–8]. The strongest effect of latent toxoplasmosis is probably its effect on human reproductive function [9]. In particular, women with latent toxoplasmosis have more sons [10–12] and their children exhibit slower prenatal [13,14] as well as postnatal development [15].

The most harmful form of toxoplasmosis is congenital toxoplasmosis. In pregnant women with acute toxoplasmosis, the parasite (rapidly dividing tachyzoites) can infect the placenta and, after a delay, the fetus as well. If such transmission occurs during the first trimester, it

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can lead to spontaneous abortion or serious congenital anomalies in the newborn child. Approximately 20% of infants born with a congenital infection are severely affected. Around 70% are asymptomatic at birth but go on to develop various clinical conditions affecting the visual or auditory system (e.g. chorioretinitis) and/or exhibit slower neurological and mental development. Only about 10% of children with congenital toxoplasmosis show no symptoms of the infection [1,16].

Toxoplasmosis is transmitted to humans by ingestion of food or water contaminated with cat feces containing *Toxoplasma* oocytes, or by eating undercooked meat containing tissue cysts with slowly dividing bradyzoites [1]. The infection can be also transmitted by the most active form of the parasite, the tachyzoites, but this form is present in the host only during acute infection and disappears soon after the host develops an immunity to the parasite. An important difference between tachyzoites and bradyzoites is that bradyzoites are resistant to gastric enzymes and are therefore infectious orally, while tachyzoites are destroyed by gastric enzymes [17].

Recently, it has been suggested that toxoplasmosis could also be transmitted sexually [18]. The authors of this hypothesis have presented several pieces of an indirect evidence in support of *T. gondii* transmission from infected men to uninfected women during unprotected sexual intercourse. The problem with this hypothesis is that *Toxoplasma* tachyzoites are present in the blood and other body fluids of infected subjects only during the short acute stage of the infection and tissue cysts containing bradyzoites, which persist in many organs throughout the host's life, are adapted to entering the body of a new host orally. In the following, we discuss and present evidence for an alternative hypothesis, which suggests that toxoplasmosis can be transmitted via oral sex, namely by fellatio, rather than by penetrative sexual intercourse.

The issue of pathogen transmission via oral sex is increasingly important given the common notion that "oral sex is not sex" [19], because virginity, as it is traditionally defined, is not lost, and the likelihood of pregnancy is removed. Oral sex is also considered a safe version of sex. However, its safeness (without using a mechanical barrier) only concerns the elimination of the risk of conception, not the risk of transmission of infections. In fact, many widespread infections, including the papilloma virus infection and candidiasis, are frequently transmitted by this route.

The hypothesis

Transmission of toxoplasmosis from an infected man to an uninfected person (male or female) occurs during oral sex (fellatio) when the uninfected individual swallows the ejaculate of the infected man.

Evaluation of the hypothesis

T. gondii DNA has been found in the semen of experimentally infected male rabbits [20] and male goats [21]. *T. gondii* cysts were observed eight weeks after infection in the epididymis and semen of infected male rats [22]. Moreover, immunohistochemical analysis detected the presence of *T. gondii* in both testicular samples and the epididymis of dogs with acute toxoplasmosis. Tachyzoites were found in semen samples and their viability was demonstrated by artificial insemination of four *Toxoplasma*-negative female dogs, all of which seroconverted by day seven after inoculation [23]. In another study, immunohistochemical results revealed the presence of *T. gondii* in the epididymis and seminal vesicles of pigs. These findings were confirmed by DNA detection of *T. gondii* in pig semen [24]. In another study, a bioassay found *T. gondii* in the testes and seminal vesicles of all twelve examined young steers [25]. The parasite was also isolated from semen samples of experimentally infected steers and detected both by Indirect Fluorescent Antibody Technique and directly, in the form of *T. gondii* brain cysts, in mice inoculated subcutaneously with semen aliquots from bovine ejaculates [25].

Presence of the parasite in the seminal fluid of infected males may lead to the infection of uninfected females during mating. Sexual transmission of toxoplasmosis has been observed in several animal species. In rats and sheep, females and their offspring have acquired the infection via mating with infected males [22,26]. In goats, *T. gondii* has been sexually transmitted during natural mating with infected males [27]. Female dogs, rabbits, and sheep have been infected after artificial insemination with infected semen [23,28]. It ought to be noted, though, that in all these animal experiments, the males had been infected recently and tachyzoites were therefore probably only temporarily present in their body fluids.

The first study related to the sexual transmission of toxoplasmosis in humans was carried out in 1971, and that study found the parasite in the ejaculate of several men [29]. Generally speaking, when it comes to sexual transmission of toxoplasmosis in humans, we can only look for indirect evidence because the ethics of direct testing would be highly problematic. Nevertheless, a recent analysis of infection patterns in couples had shown that some women have probably been infected with *T. gondii* by their male partners. Authors of that study analyzed various risk factors for toxoplasmosis, including sexual partners' infection status, and it seems likely that partner's infection is a risk factor for infection in heterosexual women, but not in heterosexual men. These results [30] strongly support the hypothesis of sexual transmission of toxoplasmosis from men to their sexual partners.

A positive correlation has been observed between the prevalence of toxoplasmosis in women of childbearing age and the incidence of sexually transmitted diseases (mainly gonorrhea, syphilis, and chlamydiosis) in WHO-member countries [18]. The authors of that study suggested that unprotected sexual intercourse may well represent a shared risk factor for the transmission of these diseases and toxoplasmosis. Moreover, the probability of *T. gondii* infection in pregnant women increases with the amount of unprotected sex with her infected partner prior to pregnancy [18]. Similarly, a high prevalence of toxoplasmosis was reported in promiscuous people in Mexico [31] and in sex workers [32]. In this context, it should be noted that sexually transmitted infections are transmitted from person to person during various types of sexual contact, not only through penile-vaginal intercourse. Higher sexual activity is associated with various sexual practices, including oral sex. It is also well known that oral-genital and oral-anal sex may lead to the transmission of a wide variety of both non-viral [33] and viral sexually transmitted infections [33,34]. During oral sex, partners often intentionally or unintentionally swallow the man's ejaculate. It should be borne in mind, meanwhile, that if an uninfected person swallows ejaculate containing *T. gondii* tissue cysts, one could expect a similar infection pattern as, for instance, after eating undercooked meat containing tissue cysts with bradyzoites.

Other results indirectly supporting this hypothesis come from studies on homosexual men. A high prevalence of toxoplasmosis has been reported among homosexuals in Indonesia [35]. Among men who have sex with men, unprotected oral and anal sex was associated with the highest risk of HIV transmission [36]. Similarly, a higher *Toxoplasma*-seropositivity (67.8%) has been observed in HIV-infected people than in immunocompetent adults (30.9%) in India [37] and especially in sub-Saharan Africa. A recent systematic review and *meta*-analysis [38] comprising 25,989 HIV-infected persons from 34 countries showed a suspiciously high prevalence of toxoplasmosis in various regions: 25.1% in Asia and the Pacific (where the prevalence in general population is mostly low), 44.9% in sub-Saharan Africa, 49.1% in Latin America and the Caribbean, and 60.7% in North Africa and the Middle East. In the Czech Republic, the prevalence of positive *Toxoplasma* serology was 40.2% in HIV-infected men [39] compared to 31% prevalence of toxoplasmosis in the general population of men over 19 years of age [40]. It can be hypothesized that HIV-infected subjects' impaired immunity (and not, e.g., the more active sex life of male homosexuals) is responsible for the increased prevalence of toxoplasmosis in this population. This explanation, however, is challenged by the fact that the

same study found virtually no difference in toxoplasmosis prevalence between HIV-positive and immunocompetent women (43.5% in HIV-infected and 42% in the general population).

Approximately two thirds of *T. gondii* infections in pregnant women cannot be explained by any of the known risk factors [41,42]. We could speculate that some pregnant women abstain from sexual intercourse or are not advised to engage in penile-vaginal sex during pregnancy for health reasons. It is possible that these women could start to practice oral sex or practice it more often to sexually satisfy their partners. If the sexual partner is infected, women could acquire toxoplasmosis, which could lead to primoinfection in pregnancy, and consequently to an increased risk of congenital toxoplasmosis in the fetus [1,16].

Generally, it is assumed that females perform fellatio more often than males do. In many countries, there is a higher prevalence of latent toxoplasmosis in women than in men. For example, in clinically healthy people in China, seroprevalence was 14% for women and 10.7% for men [43]. Similarly, in urban areas of Slovakia, seroprevalence of toxoplasmosis is 32.4% for women and 22.4% for men [44]. In the Czech Republic, an epidemiological survey conducted between 1971 and 1996 showed a toxoplasmosis prevalence of 34.1% for women and 26.3% for men [40]. A similar pattern has been observed in the most recent epidemiological study performed on a sample of 1,865 Czech internet users, which showed a 34.5% prevalence of toxoplasmosis in women and just 24% in men [45]. These differences in prevalence between genders first emerge in the age group of 10–14 and culminate in age groups of 20–39 [40] and 20–24 [45]. It ought to be noted, though, that the difference in toxoplasmosis prevalence after the age of 14 could be linked to first sexual experiences, especially with oral sex, which in many countries – including Czechia – tends to precede penile-vaginal sex [46,47]. The subsequent increase in prevalence could be linked to increasing sexual activity and lifelong accumulation of “past sexual partners”. Oral sex is commonly practiced by sexually active couples (both opposite-sex and same-sex) of various ages, including adolescents. Because the risk of acquiring sexually transmitted diseases through oral sex is believed to be lower than during anal or vaginal sex, people could erroneously believe that unprotected oral sex is a safe or low-risk sexual practice. People engage in oral sex both as part of foreplay or following penetrative intercourse. It has been shown that a high percentage of boys aged 15–19 reported receiving oral sex (47%) and among men aged 15–24, 24% had oral sex before their first penile-vaginal intercourse [46]. One study which focused on the practice of oral sex among people aged 16–21 in the United Kingdom [47] reported that fellatio and cunnilingus are highly prevalent among young people (70%), regardless of whether they had had any previous experience with penetrative intercourse. The study showed that 22% of those who had not yet engaged in penetrative intercourse had already practiced some form of oral sex. Moreover, only 17% of respondents who experienced fellatio once and 2% who received fellatio more than once reported consistent use of a condom [47]. Reduced pleasure and lack of motivation, desire, and forethought were reported as the main reasons for not using condoms during fellatio, while hygiene and avoiding the dilemma of spitting or swallowing the ejaculate were reported as reasons for using condoms.

Empirical data

A recent anonymous survey [48] performed on a sample of Czech internet users showed that all forms of oral sex, including man-man fellatio, were rather common in Czechia. Approximately 93% of 8,984 women in the sample had performed fellatio on their male partner at least once, while among the 7,928 men in the sample, the proportion of individuals who admitted to giving fellatio to another man was nearly 22%. About 1,000 men and 1,500 women who answered questions about oral sex also indicated whether they had been tested for toxoplasmosis and the result of their laboratory test, i.e. whether they were infected with *Toxoplasma* or not. Partial Kendall correlation tests controlled for subjects’ age showed no significant effect of fellatio on the risk of *T. gondii* infection (women: Tau = 0.023, p = 0.134, men: Tau = -0.015, p = 0.481). It is known, however, that toxoplasmosis has a strong negative impact on the frequency of all forms of sexual behavior and especially on the frequency of less conventional forms of sex [48,49]. We have therefore repeated the analyses and controlled for both age and the frequency of passive forms of oral sex, i.e. cunnilingus from male partner in women (reported by 94% women) and fellatio from another man in men (reported by 24% of men). In women, providing oral sex had a significant positive effect on the risk of being infected with *Toxoplasma* (Tau = 0.036, p = 0.016). In men, the effect was only slightly weaker (Tau = 0.029) and statistically nonsignificant (p = 0.177), probably due to the much lower number of subjects who reported engagement in these activities: only 265 (31 *Toxoplasma*-infected) men reported man-man fellatio, while 1,830 women (356 *Toxoplasma*-infected) reported woman-man fellatio.

Limitations

Sexual transmission of *T. gondii* has been convincingly established in animals (see above). Based on a number of arguments [18], it can be assumed that this mode of transmission can also take place in humans. Unfortunately, it is very hard to disentangle the available indirect evidence which supports transmission through sexual intercourse from that which supports transmission by oral sex. Moreover, the proposed hypothesis of transmission through oral sex assumes that the ejaculate is swallowed.

The positive association between oral sex and toxoplasmosis is a convincing argument for the hypothesis. The observed effect size of the association was relatively weak. It must be stressed, however, that the observed effect size of around 0.03 probably underestimates the importance of this route of *Toxoplasma* transmission, because fellatio is a necessary but not sufficient precondition of penile-oral transmission of *Toxoplasma*. To wit, participants were asked in the questionnaire only how often they provided fellatio, not how often they provided fellatio and swallowed the ejaculate. Subjects who did not swallow ejaculate (especially those whose partners used a condom) were in fact not at risk of penile-oral transmission of *Toxoplasma*. Their presence in the subset of subjects who provided fellatio thus strongly decreases the observed strength of the toxoplasmosis–fellatio association

Consequences of the hypothesis and discussion

It is difficult to estimate how common infection through oral sex might be. In several animal species, *T. gondii* has been found in addition to the ejaculate in the testes, epididymis, and in seminal vesicles [22,25,50]. It is therefore possible that the parasite enters the ejaculate continuously with spermatozoa or with the secretion from seminal vesicles.

Various forms of oral sex occur frequently in different animal species, including bonobos [51], orangutans [52,53], lemurs [54], and fruit bats [55]. It is therefore possible that pathogen presence in the ejaculate is actually an effective evolutionary adaptation for a horizontal spread of primarily food-transmitted diseases (not only toxoplasmosis) in host populations.

It is not known how often the parasites are present in the ejaculate of infected men, what form they take, and how much enters the ejaculate. It is also not known how many ingested parasites are required for infection to take hold. It is known that bradyzoites are better adapted to oral infections and they are far less susceptible to destruction by proteolytic enzymes than the tachyzoites [17]. A study which examined the effect of trypsin and pepsin on *T. gondii* tachyzoites in vitro and in vivo showed that some tachyzoites can survive in acid trypsin solution for one hour in vitro. Nevertheless, relatively high doses (over 1,000 zoites) of *T. gondii* tachyzoites were needed to infect mice and cats by the oral route. Mice and cats were probably infected

by tachyzoites which entered the pharynx mucosa or those which survived digestion in the intestines [56]. We can also speculate that the parasite's route doesn't necessarily lead through the stomach and intestine after infection via oral sex. For example, local lesions in the oral epithelium could be the main site of entrance of *Toxoplasma gondii* into the bloodstream.

It has already been established that other protozoa can be transmitted orally. Oral transmission is the most important route of transmission of *Trypanosoma cruzi* in some geographical regions [57]. A high efficiency of metacyclic forms of *T. cruzi* in establishing infection by oral route is associated with the expression of gp82, a stage-specific surface molecule that binds to gastric mucin and to epithelial cells [58]. Using bioluminescence and quantitative real-time PCR to evaluate the presence of T. cruzi Dm28c luciferase (Dm28c-luc), parasites in orally infected mice indicated the nasomaxillary region as the site of parasite invasion in the host, becoming consistently infected throughout the acute phase [59].

In future studies, it would be important to prove the hypothesis experimentally. For obvious reasons, it is not possible to perform the infection experiment on humans. However, experimental rodents, e.g. sensitive strains of mice or rats could be force-fed with ejaculate of infected men and then examined serologically, histologically for the *Toxoplasma* infection. It would be also crucial to find out which form of *Toxoplasma* (tachyzoites, bradyzoites, tissue cysts, eventually another specialized or yet unknown form of the parasite) is present in the ejaculate of latently infected males. The ejaculate of the infected men should be stained with stage-specific antibodies, such as anti-Bag-1 or processed with the RNAScope staining technique [60]. Such studies are currently underway.

Toxoplasmosis is a very widespread parasitosis which affects about one third of world's population. The importance of its most serious form, congenital toxoplasmosis, is now increasing because protective immunity, acquired by latent infection, is decreasing among young women in most developed countries. At the same time, the popularity of all less traditional forms of sex, including oral sex, is on the rise. If our hypothesis is correct and *Toxoplasma* can be transmitted from infected men to noninfected individuals by fellatio, the clinical impact of penile-oral transmission of toxoplasmosis is thus also increasing. Paradoxically, the observed decrease of seroprevalence of toxoplasmosis in developed countries could thus escalate the risk of serious health complications during pregnancy.

Currently, we can only speculate whether *Toxoplasma gondii* is the only alimentary transmitted pathogen adapted to this type of transmission or whether the infectious stages of other pathogens, including viruses, could also be present in the ejaculate of seemingly healthy men. Many people are aware of the health risks of unprotected penetrative intercourse. Various emerging evidence, however, suggests that in the case of diseases usually transmitted by the alimentary route, unprotected oral sex could also pose a high risk. If oral sex with infected men is indeed an important risk factor for acquiring toxoplasmosis, an effective public health campaign focused on awareness of the risks of unprotected oral sex should be designed and aimed at young people, pregnant women, and HIV-positive patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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