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DISEASE OF THE YEAR

Epidemiology of Ocular Toxoplasmosis

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ABSTRACT

Retinal infection with *Toxoplasma gondii* is the most important cause of posterior uveitis, whereby prevalence and incidence of ocular symptoms after infection depend on socio-economic factors and the circulating parasite genotypes. Ocular toxoplasmosis is more common in South America, Central America, and the Caribbean and parts of tropical Africa as compared to Europe and Northern America, and is quite rare in China. Ocular disease in South America is more severe than in other continents due to the presence of extremely virulent genotypes of the parasite. Drinking untreated water is considered the major source of *Toxoplasma* infection in developing countries, whereas in the Western world the consumption of raw or undercooked meat (products) is the most important cause. Since acquired infection with *T. gondii* is currently a more important cause of ocular toxoplasmosis compared to congenital infection, prevention should be directed not only toward pregnant women but toward the general population.

Keywords: epidemiology, genotypes, risk factors, *Toxoplasma*, uveitis

Toxoplasmosis occurs worldwide, but the incidence is higher in tropical areas and decreases with increasing latitude. This is probably due to the poor survival of the oocyst stage of the parasite under freezing conditions. In most individuals, a *Toxoplasma* infection does not lead to immediate clinical symptoms and light symptoms associated with the infection are often misdiagnosed. Following infection the parasite evades the immune system by forming cysts in muscle and nervous tissues such as the brain and retina. Reactivation of these cysts and the ensuing immune response can lead to irreversible function loss when occurring in delicate tissues such as the retina. The prevalence of retinochoroidal inflammation (commonly named posterior uveitis) caused by infection with *Toxoplasma gondii* in a population is dependent on the overall prevalence of infection in the population and the genotypes of the local strains of *T. gondii*. Currently, *T. gondii* is considered the most common infection of the retina and accounts for approximately 20–60% of cases presenting with posterior uveitis.[1,2,3,4,5]

Most patients presenting with a first episode of ocular toxoplasmosis are in their second to fourth decade of life; severity of ocular lesions has been reported to be worse in older patients.[6,7] An example of the high prevalence of toxoplasmosis as a cause of uveitis comes from a recent French study of 121 patients where it was found that infection with *T. gondii* was the etiology in 14% of cases. The main remaining etiologies were sarcoidosis (11.6%), spondylarthritis or HLA B27-associated uveitis (13.2%), and herpes virus infections (9.1%).[8] A lower incidence was reported in a study of 3080 patients with uveitis from Italy where it was found that infection with *T. gondii* was the etiology in 2.8% of all cases.[9] This latter study emphasized the high rate of recurrences of ocular disease (79% of cases) and furthermore showed that the time lapse between recurrences shortens with ongoing disease.

CONGENITAL VERSUS ACQUIRED INFECTION

Ocular toxoplasmosis has long been regarded as a disease that was mainly caused by congenital infection, while symptomatic ocular infection acquired after birth was considered rare. This paradigm was challenged by data from Brazil,[10] showing that *Toxoplasma*

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eye disease acquired after birth was much more common compared to congenital infection. This concept was confirmed by other groups and probably applies to many other areas of the world as well.[11]

The age of first onset of ocular symptoms is one of the clinical characteristics that might be expected to help distinguish between prenatal and postnatal *T. gondii* infection. Four studies from the United States and Europe of cohorts identified by pre- or neonatal screening found that 15–25% of children with congenital toxoplasmosis had ocular toxoplasmosis at birth.[12,13,14,15]

A study from France found that most eye lesions in congenitally infected children developed before the age of 5 years and almost always before the age of 10 years.[16] Reports of new lesions in previously unaffected, congenitally infected children were thought to be rare and possibly be due to failure to detect lesions during earlier examinations. Such cases were reported from a follow-up study of referred cases of congenitally infected children from the United States, where 2 out of 54 patients followed for 1–5 years developed new eye lesions.[17] Two studies from France reported late recurrent *T. gondii* eye disease in 2 out of 37 patients after the age of 10 years,[18] and another study found that 2 out of 49 children followed for up to 11 years developed new eye lesions.[19] Thus, the first appearance of new lesions after 2 years of age in children with no previous lesions cannot be excluded.[20,21,22]

In acquired *T. gondii* infection a retinochoroidal scar forms after 6–8 weeks,[23] and new lesions can appear for the first time as early as 2 months after the onset of infection,[24] or as late as 5 years.[25]

The life-time risk of acquiring retinochoroiditis due to congenital *T. gondii* infection has been calculated to range between 6.4 and 80 per 100,000 population.[11] Using the data from the outbreak of waterborne toxoplasmosis in Victoria, British Columbia,[26,27] of ocular symptoms in 0.3% of infected individuals, and assuming that no new lesions developed after 1 year postinfection, the estimated lifetime risk of ocular toxoplasmosis due to acquired infection ranges from 30/100,000 to 160/100,000,[11] higher than the incidence of ocular toxoplasmosis due to congenital infection.

It is generally not considered possible to distinguish congenital and acquired *T. gondii* infection from the morphology of retinal lesions alone or whether lesions are unilateral or bilateral.[5] One study, however, found that the macula was involved more often in patients with congenital infections (11/24 eyes: 46%), compared to patients with known acquired infection (4/19 eyes: 21%).[28]

DISEASE BURDEN

Recently, infection with *T. gondii* with ocular symptoms has been estimated to cause a disease burden in society equal to infections with *Salmonella*.[29] The use of disability-adjusted life years (DALYs) allows comparison of the burden of disease between different infections. A study from The Netherlands analyzed a random sample of 10,008 dried blood spot filter paper cards from babies born in 2006 for *Toxoplasma gondii*-specific IgM antibodies.[30] A total of 388 children were found infected, equivalent to an estimated 2300 DALYs (range 820–6710 DALYs),[30] where chorioretinitis was the symptom contributing most DALYs.[31] These studies have not yet been confirmed by other groups and the methods used to calculate the DALYs associated with ocular disease were not published in detail and may have been exaggerated.

SOCIO-ECONOMIC AND PARASITE FACTORS

Socio-economic factors play an important role in the infection of humans with *T. gondii*. A good example is the use of untreated water in many developing countries. A study from Brazil clearly showed that using untreated surface water for consumption is a risk factor for infection with *T. gondii*.[32] Waterborne outbreaks of *T. gondii* infections from contaminated water reservoirs have been described from Brazil and India and even in a developed country such as Canada.[26,27,33,34] These outbreaks were due to drinking water contaminated with *T. gondii* oocysts. The proportion of patients infected with *T. gondii* who developed ocular symptoms probably depended on the genetic background of the *T. gondii* strains involved in these outbreaks. Whether *T. gondii* oocysts are more virulent for humans than tissue cysts (bradyzoites) is a question that cannot be easily addressed experimentally and remains unsolved.[35] It is currently assumed, however, that oocyst infection caused by waterborne outbreaks of *T. gondii* is an underestimated problem.[36]

Apart from socio-economic factors it has become clear over the past 15 years that parasite factors also play an important role in infection. *T. gondii* can now be divided into different genotypes. These genotypes are distributed unevenly between continents. The genotype of the parasite determines pathology, with some genotypes being responsible for more severe disease than others.[37]

The epidemiology of *T. gondii* infections in different parts of the world will be reviewed with emphasis on prevalence and incidence of infection, ocular symptoms, and risk factors of infection.

Europe

Seroprevalence in Europe varies. It is high (up to 54%) in Southern European countries, and decreases with increasing latitude to 5–10% in northern Sweden and Norway.[38,39] The age-specific prevalence has been decreasing in Europe over the past 3–4 decades.[40]

A study of pregnant women from France over the period 1995–2003 found that the overall prevalence decreased by 19% in the investigated period and was 43.8% in 2003, with the highest prevalence in the southwest of France.[41] The birth-prevalence of congenital toxoplasmosis in France was estimated to be 3.3 infected newborns per 10,000 live births and the birth-prevalence of symptomatic congenital toxoplasmosis was estimated to be 10 times lower or 0.34 cases per 10,000 liveborns.[42]

A case series of 139 patients with ocular toxoplasmosis from Switzerland found a mean age of first reported symptoms of 23.9 years. The mean age was 29.6 years in patients reporting only one episode and 17.9 years in patients reporting more than one recurrence; the highest recurrence rate was found in patients below 20 years.[43]

A study from the United Kingdom based on active reporting from ophthalmologists identified 83 patients aged 10–54 years, with a mean age of 29 years.[44] The incidence of symptomatic ocular toxoplasmosis was estimated to be 0.4 cases per 100,000 population per year in British-born patients and the lifetime risk of disease to be 18 cases per 100,000 population.[44] In the Netherlands the overall seroprevalence dropped from 40.5% in 1995/1996 to 26.0% in 2006/2007.[45] In women of reproductive age the seroprevalence went from 35.2% in 1995/1996 to 18.5% in 2006/2007.

In Turkey, ocular *T. gondii* infection has been described in a case series of 109 patients with a mean age of 25.7 years at the time of diagnosis.[46] Eighty percent of the patients had previous scars at presentation and it was not known whether the ocular toxoplasmosis represented acquired or congenital infection. Surveillance of toxoplasmosis in pregnant women in the Russian Federation found that 4.2% of pregnant women had *T. gondii*-specific IgM antibodies.[47]

North America

In the United States data are collected regularly through the NHANES study (National Health and Nutrition Examination Study). The NHANES III 1999–2004 study reported a *T. gondii* seroprevalence of 15.8% in the age group 12–49 years. The *T. gondii* seroprevalence was higher among non-Hispanic black persons than among non-Hispanic white persons (age-adjusted prevalence 19.2 vs. 12.1%). No statistically significant differences were found between *T. gondii* antibody prevalence in NHANES II 1999–2000 and NHANES I (1988–1994).[48] A study of risk factors for acute infection with *T. gondii* in the United States found that consumption of raw and undercooked meat and unpasteurized goat's milk and exposure to kittens were the main risk factors.[49] *T. gondii* was found in only 7 out of 6282 samples of meat from retail stores in the United States.[50]

A recent review based on the NHANES data stated that "toxoplasmosis is the most common retinal infection in the United States."[51] The same review estimated that the risk of experiencing ocular symptoms within the first year of a *T. gondii* infection was approximately 2%.[1] This may be influenced by the predominant genotype in the United States.

An early case series found that 1.2% of 1669 patients with acquired toxoplasmosis developed retinochoroidal lesions and reported a higher risk (2.6%) in patients with neurological or systemic signs and symptoms.[52] In an outbreak in British Columbia, Canada, of waterborne toxoplasmosis the rates of symptomatic chorioretinitis were between 0.2 and 0.7% based on the assumption that between 2894 and 7718 individuals acquired infection during the outbreak.[26,27] Later, cougars at Vancouver Island were found to harbor *T. gondii* and the contamination of the water reservoir could also have been due to fecal deposition in the reservoir by these animals.[53]

South America and Central America

T. gondii is a common infection in South America, and a study from Brazil found that seroprevalence was high in people from poor socio-economic conditions probably due to waterborne transmission.[32] Another study found a seroprevalence of 73% in slaughterhouse workers and suggested that fresh meat is an important source of infection in Brazil.[54] A study of children from Guatemala found that infection with *T. gondii* often took place before the age of 5 years, at which time 43% were seropositive.[55] A seroprevalence of nearly 60% has also been found in Amerindians from Venezuela.[56]

A high prevalence of ocular toxoplasmosis was first described from southern Brazil[10,57–59] and it is now well recognized that ocular toxoplasmosis is more prevalent in South America, Central America, and the Caribbean compared to North America and Europe.[60,61] It has been estimated that infection with *T. gondii* is responsible for up to 30% of infectious uveitis in Brazil.[10,62,63] Even within Brazil the prevalence of chorioretinitis in adults may vary from 2% in northern Brazil[64] to 25% in southern Brazil.[65] A study from Columbia found that 6% of healthy adults had retinal scars and *T. gondii*-specific IgG antibodies.[66,67]

A striking difference in the distribution of *T. gondii* genotypes between different parts of the world with an abundance of so called "atypical strains" has been described.[68–70] A high prevalence, 80%, of ocular toxoplasmosis has been found in newborns with congenital toxoplasmosis in Brazil,[71] and a study from Rio de Janeiro found that 3% of acutely infected adults had chorioretinitis within 2 years of infection.[72]

A higher prevalence of congenital toxoplasmosis has been found in Brazil compared to Europe followed by a higher rate of chorioretinitis in newborns and a higher rate of ocular disease in Brazilian infants after birth compared to European infants.[73] Severe, disseminated *T. gondii* infection with multiorgan involvement, including eye symptoms. has been described from French

Guiana due to highly virulent strains circulating in a forest-based cycle involving wild felids.[74] Most patients reported forest-related activities, such as ingestion of surface water, consumption of undercooked game meat, and hunting.

Asia

The seroprevalence in Asian countries varies. A study from Korea found an IgG-specific prevalence in pregnant women of 0.8%,[75] and a study of HIV-positive patients from Taiwan found a seroprevalence of 10.2%.[76] A recent study from India found a seroprevalence of *Toxoplasma*-specific IgG antibodies of 45%,[77] and a study of HIV-infected patients from Japan found an overall seroprevalence of 44.8%, and the majority of these patients were aged 25–34 years.[78] A study of 640 pregnant women in Thailand found a seroprevalence of 28.3%.[79]

A study from Malaysia showed that people belonging to the Indian ethnic group had a seroprevalence of 55.3%, whereas ethnic Chinese had a seroprevalence of 19.4%.[80] Few studies have been published from China, but one study reported a 3.7 times increased risk of being *T. gondii*-IgG positive in patients with posterior uveitis.[81] Another study found only 2 cases of ocular toxoplasmosis among 1752 patients in Guangdong Province, Southern China.[82]

Outbreaks of ocular toxoplasmosis have been described from Tamil Nadu, southern India.[34,83] In both studies it was hypothesized that the main route of infection was the municipal drinking water, as the majority of cases were located in areas supplied by one water reservoir and there were almost no cases from areas supplied by a second reservoir.

A study of the seroprevalence of *T. gondii*-specific IgG antibodies from northern India found an overall prevalence of 51.6% in males and 89.2% in females.[84] In contrast, a study from Chandigarh found an overall seroprevalence in adults of 15%,[85] probably indicating huge differences in the prevalence and incidence of infections with *T. gondii* in India.

A case series from Indonesia included 173 patients with ocular toxoplasmosis, mostly young adults. Bilateral involvement was found in 32.4% of all patients and visual acuity categorized as blind in 13.9%.[86] A case series from Thailand found *T. gondii* uveitis the most common single cause of posterior uveitis in 8.7% of HIV-negative patients.[87] In Malaysia, the seroprevalence of toxoplasmosis in different groups was 58% (258/443), with a seroprevalence in the age group 21–40 of 28.4%, of which 32 cases were clinically diagnosed with ocular toxoplasmosis.[88]

Africa

A study from Sao Tomé (West Africa) found a seroprevalence of 21.5% in children below 5 years of age,[89] and a study from Sudan found a seroprevalence in pregnant women from Khartoum of 34.1%.[90] Of 1828 HIV-positive patients from Bobo-Dioulasso, Burkina Faso, 25.4% had positive *T. gondii* serology.[91] Immigrants to the United Kingdom born in West Africa had a 100-fold higher incidence of symptomatic eye disease due to *T. gondii* compared to white people born in Britain.[44] Another study found that infection with *T. gondii* accounted for 43% of patients with uveitis and visual impairment in Sierra Leone, West Africa.[92]

A study of *T. gondii* seroprevalence among immigrant women in Spain found that seroprevalence in women from Sub-Saharan Africa was twice as high as in age-matched European women.[93] A study from Tanzania found a seroprevalence approaching 60% in persons over 60 years.[94] A study of *T. gondii* genotypes of isolates from Africa found that genotype III dominated but atypical strains were also found.[95,96] Thus, there is little doubt that *T. gondii* is prevalent in Africa and probably causes a high burden of visual disability. A study of 472 patients with uveitis from Tunis, North Africa found that infection with *T. gondii* was the most frequent cause of posterior uveitis, 38% (51/472).[97]

Australia

Until recently almost nothing was known about the genetic diversity of *T. gondii* in Australia. Type II strains have been reported from a human patient and a domestic dog.[98] Furthermore, a greater diversity of genotypes have been described in marsupials in the same study.[99] Toxoplasmosis was the highest recognizable etiology in 20% of posterior uveitis patients visiting a uveitis clinic in Sydney.[1]

RISK FACTORS FOR INFECTION WITH *TOXOPLASMA GONDII*

Oocysts are an important reservoir of infection contaminating the environment, including surface water.[100] Using an assay based on a recombinant, sporozoite antigen, TgERP, which allows distinction between persons infected with oocysts or tissue cysts, it was recently shown that 78% of North American mothers of congenitally infected infants had a primary infection with oocysts.[101] Further application of this technique in epidemiological surveys may yield an important breakthrough in the study of the risk factors for *Toxoplasma* infection.

Until now, outbreaks and epidemiological surveys examining risk factors in infected and noninfected persons were the most useful way of assessing the relative importance of different sources of *T. gondii* infection in humans. Soil contact through gardening allows contact with infective oocysts deposited by any recently infected cat.[102,103] Oocysts take 1–5 days to become infective, but

they can remain infective in soil and probably water for up to 1 year, depending on ambient temperature and humidity. A waterborne outbreak of infection with *T. gondii* was first described in American soldiers in Panama and was attributed to drinking water from a contaminated stream.[100] An outbreak that involved at least 426 people in the town of Santa Isabel do Ivai, in Parana state, Brazil, was traced to a contaminated drinking water cistern,[35] and about 10% of the diagnosed cases developed ocular symptoms.

Infection with *T. gondii* from contaminated dust has been described in a few outbreaks. One outbreak was attributed to inhalation or ingestion of dust or dirt contaminated with oocysts from cat feces,[102] where 3 out of 10 patients developed eye disease.[103]

A systematic sample of 1157 women of reproductive age, aged 15–49 years in Belgrade, Serbia, found a seroprevalence of 77%.[104] Consumption of undercooked meat and exposure to soil (farming, gardening) were found to be associated with *T. gondii* infection, but cat ownership was not. A prospective case-control study from Norway 1992–1994 found that eating raw or undercooked meat and meat products, poor kitchen hygiene, cleaning the cat litter box, and eating unwashed raw vegetables or fruits were associated with increased risk of *T. gondii* infection.[105] From 1991 through 1994 a prospective risk factor study in pregnant women infected during pregnancy and controls was performed in Italy. Eating cured pork or raw meat at least once a month increased the risk of *T. gondii* infection threefold (OR: 3.1; 95% CI: 1.6–6.0).[106] A case-control study from France found the following risk factors: poor hand hygiene (OR = 9.9; 95% CI: 0.8–125), consumption of undercooked beef (OR = 5.5; 95% CI: 1.1–27), having a pet cat (OR = 4.5; 95% CI: 1.0–19.9), frequent consumption of raw vegetables outside the home (OR = 3.1; 95% CI: 1.2–7.7), and consumption of undercooked lamb (OR = 3.1; 95% CI: 0.85–14).[107]

A European multicenter case-control study in 6 centers in Belgium, Denmark, Italy, Norway, and Switzerland included 252 cases and 708 controls.[108] The study found that contact with raw or undercooked beef, lamb, or other sources of meat, as well as with soil, were independent risk factors for *T. gondii* seroconversion during pregnancy. In addition, travel outside of Europe, the United States, and Canada was a risk factor for seroconversion. The population attributable fraction showed that 30–63% of seroconversions were due to consumption of undercooked or cured meat products and 6–17% were a result of soil contact, but ownership of a cat was not a risk factor.[108]

An epidemiological study from the Netherlands showed that *Toxoplasma* seropositivity was associated with living in the northwestern part of the country, living in urban areas, low educational level, consumption of raw pork, and keeping a cat. For younger seropositive participants, risk factors included keeping sheep or cattle, consumption of raw unwashed vegetables, and putting sand in the mouth.[45]

Information about how to avoid toxoplasmosis in pregnancy could be a cost-effective approach to preventing congenital toxoplasmosis.[109,110] Based on the knowledge of these identified risk factors for primary toxoplasmosis, pregnant women should be appropriately advised by their obstetricians and primary care providers on how to lower the risk of congenital toxoplasmosis by avoiding risk factor exposure. Emphasis on prevention is badly needed because currently available antibiotic therapy seems to have little effect on mother-to-child transmission, and whether treatment affects the clinical manifestations in the newborn with congenital toxoplasmosis (CT) is still under debate.[111]

SURVEILLANCE, CONTROL, AND PREVENTION

Notification of congenitally infected children would help determine the burden of congenital disease in countries that either perform screening or do not. A case definition needs to be used to be able to compare data. Also, posterior uveitis due to infection with *T. gondii* should be notifiable to determine the burden of infection and also here a strict case definition which includes the use of appropriate serological methods is needed.[23]

Control and prevention has so far primarily been directed toward prevention of food-borne infection. Surveillance of *T. gondii* in meat is important and the long-term aim must be to provide the consumer with *T. gondii*-free products. This is particularly a challenge with so-called "green" products, where animals must be allowed outside access, where risk of acquiring *T. gondii* is difficult to control.[112] Health education has not proven effective and should probably be reserved for a setting with well-documented risk factors. Pregnant women especially should be informed about consuming well-cooked meat and observing hygiene when gardening and when keeping cats. With the emerging knowledge that acquired *T. gondii* infection is the major cause of ocular toxoplasmosis and that congenital infection represents only a small proportion of cases, it could be argued not only that preventative strategies should be targeted at pregnant women but that an approach is also needed for the entire population. Governments should be persuaded to provide their citizens with safe drinking water and the meat industry should guarantee their consumers a *Toxoplasma*-safe product.

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