REVIEW ARTICLE

Toxoplasma gondii: the changing paradigm of congenital toxoplasmosis

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SUMMARY

Researchers have learned much concerning the population biology of *Toxoplasma gondii* over the past 2 decades. It is now apparent that many atypical genotypes exist besides the typical 3 genotypes (type I, type II and type III) first described from samples from Europe and the United States. These genotypes can differ in pathogenicity and transmissibility from the typical genotypes that have been used in the majority of scientific research over the past 70 years. These differences impact much of what we used to believe as facts about congenital toxoplasmosis (CT) and will be important in developing new recommendations for prevention of CT and the monitoring of women at risk for developing CT. The present review highlights new information on *T. gondii* genotypes and how this information will change the way we convey information about CT to pregnant women, physicians and students.

Key words: *Toxoplasma gondii*, congenital toxoplasmosis, genotypes, pregnancy.

INTRODUCTION

Toxoplasma gondii is a zoonotic apicomplexan with a worldwide distribution (Dubey, 2010). It has a complex life cycle and causes a wide variety of symptoms in infected individuals. Infection in humans follows a course of active replication of the parasite and dissemination of the infection throughout the body followed by encystment in the brain, retina, and other organs as latent tissue cysts. Congenital toxoplasmosis (CT) has long been recognized because of the devastating results it can have on the infected fetus including miscarriage, mental retardation, visual, and hearing problems (Weiss and Dubey, 2009). Until recently, it was believed that transmission of *T. gondii* to the fetus occurred predominantly in women who acquired their primary infection during gestation (Remington *et al*. 2006). Only in rare cases was congenital transmission of *T. gondii* found to occur in chronically infected women whose infection became reactivated because of immunosuppression from AIDS or treatment with corticosteroids for underlying disease (Remington *et al*. 2006).

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Old beliefs

The old thinking on CT was that women of childbearing age that had antibodies to *T. gondii* were immune and would not transmit the infection to their fetus. Women that did not have antibodies indicative of exposure to *T. gondii* were therefore considered to be at risk of acquiring the infection during pregnancy and transmitting it to their offspring. The risk of a fetus becoming infected with *T. gondii* and the severity of outcome of infection was believed to be related to the trimester in which the mother was exposed to *T. gondii* (Dunn *et al*. 1999). Exposure early in pregnancy (1st trimester) results in fewer fetal infections but the severity of disease is more pronounced than if infection occurs later in pregnancy (3rd trimester) when more transmission is likely to occur, but the disease is usually less severe. Most pregnant women do not experience symptoms of infection (Remington *et al*. 2006) and have no reason to seek medical attention so infection goes undiagnosed. Exposure to raw or undercooked meat containing viable tissue cysts, produce or water contaminated with oocysts, and exposure to kittens (source of oocysts) are risk factors for *T. gondii* infection (Dubey, 2010).

These beliefs were the foundation for the following recommendations for detection of CT in pregnant women in countries where CT is a recognized

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problem. Prevention of CT and its detection became national policy in France in the late 1970s and requires: (i) the detection and follow-up of *T. gondii* serologically negative (non-immunized) women as soon as possible during pregnancy; (ii) appropriate counselling and education aiming at limiting the risks of maternal exposure to both tissue cysts and oocysts); (iii) the detection and treatment of toxoplasmosis as early as possible aiming to prevent or limit transmission to the fetus and the severity of CT; (iv) post-natal examination for signs of CT using monthly ultrasound examinations in cases of maternal seroconversion during surveillance; (v) combined sulfadiazine-pyrimethamine treatment during pregnancy if CT is proven; and (vi) clinical, radiological and serological surveillance of neonates and infants at risk (Sterkers *et al*. 2010; Villena *et al*. 2010).

Toxoplasma gondii *and CT in humans: a changing paradigm*

A new concept of congenital human toxoplasmosis has been evolving over the last few decades and can be attributed to the findings of the different genotypes of *T. gondii* that are present in various areas of the world (Howe and Sibley, 1995; Su *et al*. 2010). There are 3 major genotypes (Howe and Sibley, 1995) that account for 95% of the isolates in North America and Europe and the remaining 5% of isolates are termed atypical (or exotic) because they do not fall into the 3 major clonal lineages but this concept is changing and greater genetic diversity is now realized (Khan *et al*. 2011). The *T. gondii* genotypes differ in their pathogenicity for mice, and prevalence in humans. The low linkage disequilibrium among genetic loci of these atypical isolates suggests that they have undergone frequent sexual recombination (Su *et al*. 2010; Khan *et al*. 2011).

The Type II genotype of *T. gondii* is responsible for most cases of CT in Europe and the United States. CT in *T. gondii* seropositive mothers (immune) from Europe indicates that atypical genotypes can overcome the acquired resistance from the original infecting genotype (Elbez-Rubinstein *et al*. 2009). A recent study demonstrated that severe CT could occur in children of non-immune mothers infected in the 3rd trimester (Delhaes *et al*. 2010), which is a rare occurrence in CT caused by the typical genotypes.

Congenital toxoplasmosis in humans occurs in 4 major ways

It is now recognized that CT can occur by 4 different ways. The first way that transmission of *T. gondii* to the fetus can occur is in women who acquire their primary infection during gestation (Remington *et al*. 2006). Most of our knowledge is based on women from Europe that are most frequently infected with typical genotypes (usually Type II). The relationship between stage of pregnancy when infection occurs and the potential for infection and disease in the offspring are based on medical information from these women. The general thinking is that as pregnancy progresses, the chance of fetal infection increases but the chance that severe disease developing in the fetus decreases (Remington *et al*. 2006; Dubey, 2010). We know less of the primary infection with atypical *T. gondii* genotypes during pregnancy and the predicted outcome of CT in the infected infants (Ajzenberg *et al*. 2002; Cneude *et al*. 2007; Demar *et al*. 2007; Delhaes *et al*. 2010). Congenital toxoplasmosis caused by atypical genotypes is more severe than CT caused by typical genotypes (Delhaes *et al*. 2010). Six of 8 atypical CT cases were severe and resulted in medical termination of pregnancy or death a few days after birth. Three of the 8 cases were acquired during the 3rd trimester (Delhaes *et al*. 2010). It currently appears that, unlike the typical genotypes, infections with atypical genotypes in the 3rd trimester can result in severe CT. Atypical genotypes are associated with more severe ocular disease in children with CT from Brazil than Europe (Gilbert *et al*. 2008).

A second way is transmission by immunocompetent women infected shortly before pregnancy. This is associated with acquisition of infection a few months before pregnancy and is thought to be due to persistent parasitaemia that continues after the pregnancy is established (Marty *et al*. 1991; Pons *et al*. 1995; Vogel *et al*. 1996; Dollfus *et al*. 1998; Villena *et al*. 1998; Boumahni *et al*. 2004). Little is known of differences in duration of parasitaemia between typical and atypical genotypes and what role it has in causing CT.

A third way of transmission is by true reactivation of CT in HIV-infected mothers (Desmonts *et al*. 1990; Marty *et al*. 1994, 2002; Bachmeyer *et al*. 2006; Azevedo *et al*. 2010) or mothers that have immunologically altered immune function due to systemic lupus erythematosus or malignancies of their haematological systems (Desmonts *et al*. 1990). The importance of *T. gondii* genotype and the likelihood that reactivation will occur in immunosuppressed pregnant women is currently unknown.

The fourth way of transmission is in a mother immune to a typical genotype challenged by an atypical genotype during pregnancy and subsequently transmitting the atypical genotype to their offspring (Fortier *et al*. 1991; Gavinet *et al*. 1997; Hennequin *et al*. 1997; Kodjikian *et al*. 2004; Lebas *et al*. 2004; Elbez-Rubinstein *et al*. 2009). These cases are in mothers that live in a country where type II genotypes of *T. gondii* predominate and exposure to *T. gondii* is thought to be from atypical genotypes acquired by visiting or consumption of products from a country that has predominantly atypical genotypes. The ability of a previous infection with an atypical

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genotype of *T. gondii* and the protection it induces to challenge with typical or other atypical genotypes of *T. gondii* is not currently known. This fourth mode of transmission is contrary to the widely held belief that if a woman is infected with *T. gondii* prior to pregnancy then she is immune to re-infection and will not transmit the infection to her developing child. This is the basis for maternal screening of pregnant women for *T. gondii* in countries where it is practiced.

New challenge

Serological tests currently available for clinical use cannot differentiate between typical and atypical genotypes of *T. gondii*. Maternal testing methods and recommendations for *T. gondii* need to be re-evaluated in light of recent clinical evidence to include the potential for exposure to atypical genotypes during pregnancy. Educators need to revise the information they teach on CT to medical, veterinary, graduate and undergraduate students.

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