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Invited Review

New clinical and experimental insights into Old World and neotropical ocular toxoplasmosis

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ABSTRACT

Retinal lesions or other ocular manifestations are serious consequences of infection with the protozoan parasite *Toxoplasma gondii*. Whilst classically considered a consequence of congenital transmission, recent screening studies estimated that 2% of *T. gondii* seropositive persons in Europe and North America have retinal lesions, most of them persisting unnoticed. The situation is more dramatic in South America, probably due to the predominance of virulent strains. Some of these strains seem to exhibit ocular or neuronal tropism and are responsible for severe ocular lesions. Despite the medical importance, the physiopathological mechanisms have only recently begun to be elucidated. The particular immune-privileged situation in the eye has to be considered. Studies on French patients showed low or undetectable ocular parasite loads, but a clear Th1/Th17 type immune reaction. Suitable mouse models have appeared in the last few years. Using such a model, IL-17A proved to impair parasite control and induce pathology. In contrast, in South American patients, the parasite seems to be much less efficiently controlled through a Th2 type or suppressive immune response that favors parasite replication. Finally, several host genetic markers controlling immune response factors have been associated with ocular involvement of *T. gondii* infection, mainly in South America.

1. Introduction

While the apicomplexan parasite *Toxoplasma gondii* infects approximately one-third of the world's population, transmission frequency is very variable, owing to temperature and humidity variation, as well as local eating habits (Montoya and Liesenfeld, 2004). Following a multiplication phase, where the parasites disseminate throughout the body, the host's immune system takes control and eliminates most of the parasites, mainly by cellular, IFN-γ driven Th1 type responses (Pifer and Yarovinsky, 2011). However, *T. gondii* persists in cysts, mostly in muscles and the CNS. These cysts can reactivate when immunity weakens. Consequently, reactivation of cerebral cysts was a major cause of mortality in AIDS patients before the introduction of effective anti-viral therapies. The retina has also been identified as the location of dormant cyst forms in mice (Lahmar et al., 2010). Until recently, the presence of *T. gondii* in eye tissues was not considered to be a threat to health in immunocompetent persons, with the notable exception of congenital infection. However, thorough investigation of *T. gondii* seropositive individuals revealed a non-negligible prevalence of retinal lesions, with a life-long risk of recurrence, i.e. the appearance of new lesions (Delair et al., 2008). Despite this apparent medical importance, the physiopathology is still not well understood, which also thus far prevented the introduction of an efficient treatment (Holland, 2004). This review summarises the current knowledge, the active fields of research and the ideal therapeutic strategy.

2. Epidemiology

Toxoplasmic retinochoroiditis is the commonest form of posterior uveitis in many countries. Prevalence and incidence of ocular symptoms after infection depend on socio-economic factors and the circulating parasite genotypes (Holland, 2003; Furtado et al., 2013). Ocular toxoplasmosis (OT) is more common in South and central America, the Caribbean and parts of tropical Africa, compared with 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 (Petersen et al., 2012). The results obtained in a

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study comparing OT in Europe, North America and South America suggest that disease characteristics also vary in different areas of the world (Dodds et al., 2008), which obviously has fundamental consequences for treatment strategies (Sauer et al., 2011).

2.1. Europe and North America

There are few studies on the prevalence of OT. It is usually estimated through funduscopic screening by discovering chorioretinal scars, suspected to be toxoplasmic, in the general population, as the concerned individuals are often unaware of the presence of scars. A large retrospective study in a United States (US) medical center identified OT as the most common form of posterior uveitis in the 1990s (Rodriguez et al., 1996), which was confirmed for various countries. Generally, it is estimated that approximately 2% of *T. gondii* seropositive persons will develop retinal lesions (Holland, 2003). This led to the estimation that in 2009, 1,075,242 persons became infected in the US, resulting in 21,505 new cases of retinal lesions, of which 4,839 were symptomatic (Jones and Holland, 2010).

In Europe, Gilbert et al. (1999) placed the incidence of symptomatic OT at 0.8/100,000 persons per year, and the lifetime risk (to 60 years of age) at 18/100,000 British born individuals. *Toxoplasma gondii* infection was the main cause of posterior uveitis in 1,064 consecutive patients at a national uveitis referral center in Italy between 2002 and 2008, accounting for 6.9% of all uveitis cases (Cimino et al., 2010). A French multi-center study showed that retinal toxoplasmic lesions could more often attribute to acquired than to congenital infection (Delair et al., 2008). In Germany, a survey of 1,916 patients seen in a similar setting and almost concurrently, also found OT to be the most frequent diagnosis in patients with posterior uveitis and the cause of 4.2% of uveitis cases (Jakob et al., 2009). Acquired infections also may be complicated by recurrent retinochoroiditis, with recurrences being most common close to the time of acquisition (Delair et al., 2011).

The incidence of congenital infections varies with the geographical origin, in parallel with overall seroprevalence. A large retrospective study in the US estimated the number at approximately one in 10,000 live births (Guerina et al., 1994), whereas three in 10,000 live births were observed in France (Villena et al., 2010). A prospective cohort study on European children with confirmed congenital toxoplasmosis found retinal lesions in one of six of these children, who received treatment for at least 1 year, after the first 4 years of life (Tan et al., 2007). Curiously, some North American studies found retinal lesions in more than 70% of congenitally infected and untreated, and 58% of treated children (Mets et al., 1996; Phan et al., 2008). These discrepancies might be due to referral bias or divergent criteria for proven toxoplasmic lesions. In any case, even in countries with low *T. gondii* seroprevalence, such as the Netherlands, congenital toxoplasmosis causes considerable morbidity, with retinal lesions playing an important part (Havelaar et al., 2007).

2.2. South America

The enormous impact of toxoplasmosis on public health is best demonstrated by the incidence numbers of congenital OT. The estimated number of one case of congenital toxoplasmosis in 770 live births in Brazil (Vasconcelos-Santos et al., 2009) is 5–15-fold higher than what is seen in Europe and North America. A comparative prospective cohort study of congenitally infected children in Brazil and Europe showed that Brazilian children were at a five-times higher risk than European children of developing eye lesions. Two-thirds of Brazilian children infected with congenital toxoplasmosis had eye lesions by 4 years of age compared with one in six in Europe (Gilbert et al., 2008).

The burden of OT in South America is impressive not only in congenitally infected children, but also in adolescents and adults, most of whom have presumably acquired infection postnatally (Ajzenberg, 2011). Population-based studies of this age group showed that the prevalence of OT is higher in South America compared with North America. Initial studies found an OT prevalence as high as 17.7% in the Erechim region in southern Brazil (Glasner et al., 1992). However, the situation within South America seems to be much more heterogeneous than in Europe or North America. A survey of university students and employees in the Colombian town of Armenia (Quindio region) diagnosed OT in 6% of the study group, 20% of which had visual impairment. (De-la-Torre et al., 2007). The prevalence of congenital toxoplasmosis in this region was estimated at 0.5%. Although the academic study group might not be altogether representative of the overall population, this study suggests a predominance of postnatally acquired OT. The incidence of OT has been estimated to be three new episodes per 100,000 inhabitants per year (De-la-Torre et al., 2009), compared with 0.4 cases per 100,000 persons in British-born patients (Gilbert et al., 1999). Additionally, striking differences are seen even within Colombia. In military personnel operating in the jungle, *T. gondii* seropositvity was significantly higher than in those serving in Bogota, after only 1 year of service (80% versus 45%), but characteristic toxoplasmic chorioretinal lesions were only found in four soldiers that operated in the jungle (0.8%) and in one urban soldier (0.19%) (Gomez-Marin et al., 2012). Consequently, *T. gondii* strain distribution and OT frequency may vary considerably.

Assuming that half of the 41 million inhabitants of Colombia are chronically infected with *T. gondii*, we can estimate that 1 million people live with retinochoroidal scars and at least 200,000 suffer from unilateral legal blindness due to this infection in this country. If we transpose this scenario to the whole population living in tropical parts of South America, especially in Brazil, we have to become aware that the neglected tropical disease OT is in fact a leading cause of blindness in South America (De-la-Torre et al., 2007; Ajzenberg, 2011).

Some studies estimated the proportion of seropositive patients who will eventually develop retinal lesions. In Southern Brazil, 383 persons were reexamined to determine the rates of seroconversion and the incidence of toxoplasmic retinal lesions in individuals who were seronegative for *T. gondii* infection. In this series, 11 (8.3%) of 131 individuals who were seropositive without ocular lesions in 1990 were found to have typical lesions by 1997 (Silveira et al., 2001). The above-mentioned Colombian study (De-la-Torre et al., 2007) suggests that 11% of people with acquired infection develop ocular lesions.

3. Clinical appearance

3.1. Europe and North America

In young children, OT may be asymptomatic. Children who are able to vocalise may complain of decreased vision or ocular pain, while parents may note leukocoria or strabismus. Adults often present with floaters, which may be associated with altered vision. The ‘classic’ sign of infection includes retinal scars, white-appearing lesions in the active phase often associated with vitritis (Holland, 2000, 2004; Butler et al., 2013). Depending on the size and thickness of involved retina, the overlying vitreous and subjacent choroid are variably involved. Spontaneous resolution of active retinochoroiditis is the rule in immunocompetent patients, resulting in an atrophic, well-defined scar. Complications may include fibrous bands, secondary serous or rhegmatogenous retinal