Ocular toxoplasmosis - an update and review of the literature

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Ocular toxoplasmosis is the most common cause of posterior uveitis worldwide. The infection can be acquired congenitally or postnatally and ocular lesions may present during or years after the acute infection occur. Current treatment controls ocular infection and inflammation, but does not prevent recurrences. We present a review and update on ocular toxoplasmosis and address misconceptions still found in the current medical literature.

Key words: ocular toxoplasmosis - diagnosis - treatment and ocular lesions

Ocular toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii*. Infections may be acquired congenitally or through the ingestion of uncooked and infected meat, contaminated vegetables or water (Silveira et al. 1988).

T. gondii infects up to a third of the world's population and is responsible for the majority of infectious uveitis (intra ocular inflammation) cases. In some countries, up to 50% of all cases of posterior uveitis in a given population are attributable to toxoplasmosis (Soheilian et al. 2004, Vallochi et al. 2005).

The population structure of *T. gondii* is highly clonal. There are three predominant clonal lineages in North America and Europe, namely I, II and III. The lineages are based on murine model virulence studies (Howe & Sibley 1995). It has been suggested that the type II clonal lineage of *T. gondii* may be responsible for the majority of acquired ocular lesions, while type I may be more frequently seen in congenital toxoplasmosis. Recently, it has been shown that type I as well as atypical strains may play an important role in acquired infection (Howe & Sibley 1995, Belfort-Neto et al. 2007).

Type II strains appear to be responsible for the majority of symptomatic human cases in France and the United States (Nowakowska et al. 2006), while types I and III are found in only 10% and 9% of *Toxoplasma* isolates from patients, respectively (Howe et al. 1997).

In Brazil, type I strains appear to be responsible for ocular infections in human patients (Vallochi et al. 2005). De Moura et al. (2006) showed that parasites isolated from contaminated water in the Southern state of Paraná were type I. Another recent publication analyzing samples from Brazilian patients suggests a cloning diversity when compared with strains from North America and Europe (Khan et al. 2006). The city of Erechim, in the South of Brazil, has a 17% prevalence of ocular toxoplasmosis, and type I *T. gondii* predominates (Jones et al. 2006). The genotypes of *T. gondii* strains isolated from São Paulo and Erechim (Brazil) were highly atypical when compared with the previously described cloning lineages reported in the literature (Khan et al. 2006).

Genotyping of *T. gondii* in 24 chickens from the Amazon, Brazil, indicated that 14 were type I and 10 were type III, confirming that strains in Brazil are divergent from European or North American strains (Dubey et al. 2006).

In Erechim, samples from porcine tongues and diaphragms were obtained in both large and small abattoirs and tested for *T. gondii*. The results indicated a high prevalence of infection and suggested that unusual genotypes of *T. gondii* are also found in Brazil among domesticated pigs (Belfort-Neto et al. 2007). In that area, according to an epidemiological survey, risk factors for acquiring toxoplasmosis include eating undercooked meat, working in the garden or yard more than once per week, eating raw, cured, dried or smoked meat and being a male (Jones et al. 2006).

The genetic makeup of *T. gondii* is more complex than the three-strain theory and unusual genotypes may contribute to various clinical outcomes of toxoplasmosis in different localities. Variant alleles have also been associated with severity of pathology. The study of parasite genetic backgrounds is important for understanding the establishment of ocular disease (Vallochi et al. 2008).

Ocular manifestations and diagnosis

Toxoplasmic retinochoroiditis is often seen in settings of congenital or postnatally acquired disease as a result of acute infection or recurrence (Nussenblatt & Belfort 1994, Montoya & Remington 1996). This disease typically affects the posterior pole of a single eye and the lesions can be solitary, multiple or satellite to a pigmented retinal scar (Fig. 1).

Active lesions present as grey-white focuses of retinal necrosis with adjacent choroiditis, vasculitis, haemorrhage and vitreitis (Figs 2-4). Cicatrization occurs from

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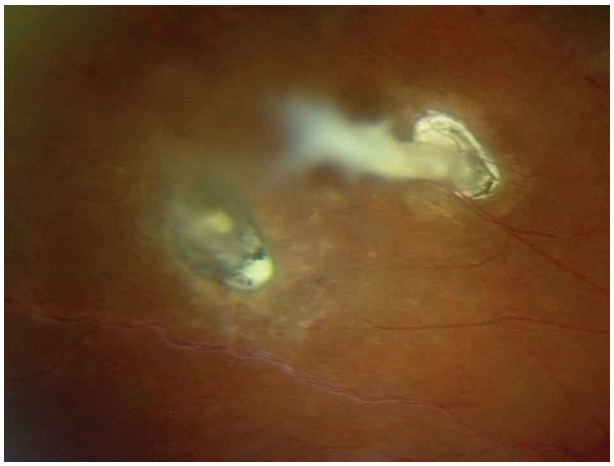

Fig. 1: inactive old ocular toxoplasmosis lesions with vitreous strand and vasculitis.

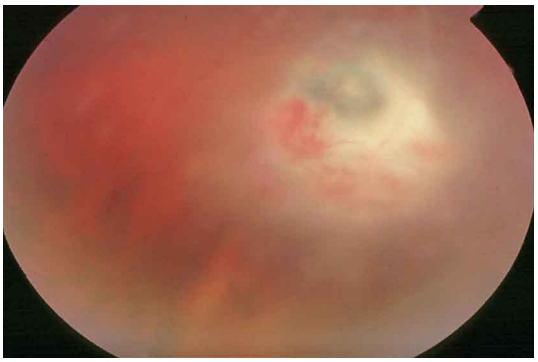

Fig. 2: retinal scar with typical features of recurrent ocular toxoplasmosis.

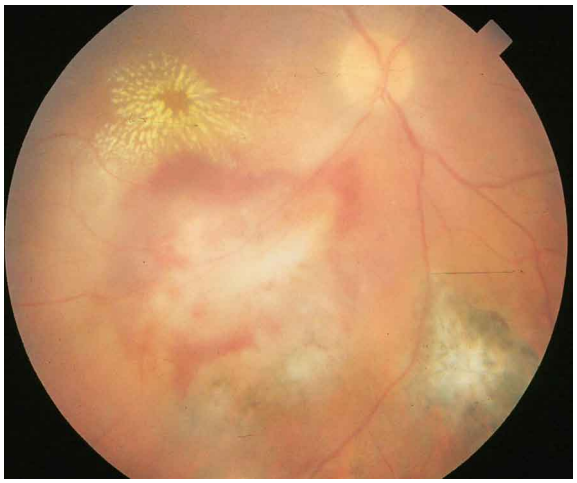

Fig. 3: ocular toxoplasmosis with old pigmented scar and recurrence inferior to the macula.

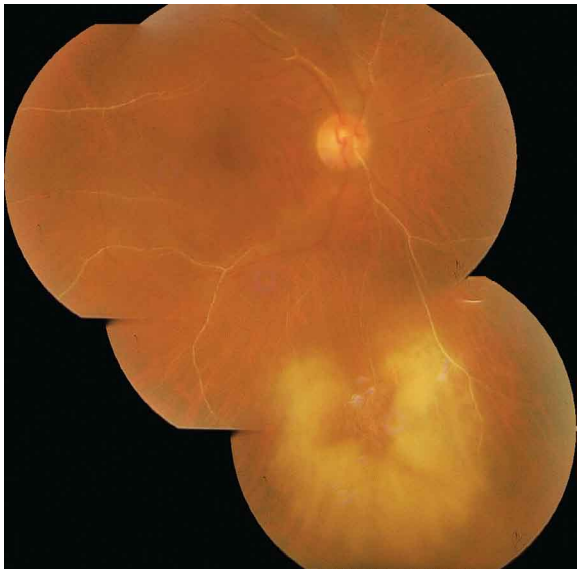

Fig. 4: inferior area of retinochoroiditis and diffuse vasculitis.

the periphery towards the centre, with variable pigmentary changes. Anterior uveitis is another common finding, with mutton-fat keratic precipitates, cells and flare, and posterior synechiae (Nussenblatt & Belfort 1994).

The retina is the primary site of *T. gondii* infection in the eye, but the choroid, vitreous and anterior chamber are also involved. The choroid is secondarily affected, although choroidal lesions do not occur in the absence of retinal infection. An intense secondary iridocyclitis may also be present (Nussenblatt & Belfort 1994, Holland 2004). In addition, the optic nerve head can also be involved in ocular toxoplasmosis (Eckert et al. 2007) (Fig. 5).

Elderly or immunosuppressed patients may present with more aggressive bilateral or multifocal disease (Fig. 6). Elderly patients recently infected with *T. gondii* may have a higher prevalence of ocular involvement. Other atypical presentations include punctate outer retinal toxoplasmosis, retinal vasculitis, retinal vascular occlusions, rhegmatogenous with serous retinal detachments, unilateral pigmentary retinopathy mimicking retinitis pigmentosa, neuroretinitis and additional forms of optic neuropathy, peripheral retinal necrosis and scleritis (Smith & Cunningham 2002, Bonfioli & Orefice 2005).

Ocular complications seen more frequently in children, include choroidal neovascularisation, cataract, glaucoma, optic nerve atrophy and retinal detachment (Bosch-Driessen et al. 2000). An association between ocular toxoplasmosis and Fuchs' heterochromic cyclitis has been described (Toledo de Abreu et al. 1982) and confirmed by several researchers (Schwab 1991, La Hey & Baarsma 1993, Ganesh et al. 2004).

The appearance of toxoplasmic retinochoroiditis lesions varies. The duration and intensity may be related to the host, parasite, or environmental factors (Holland et al. 1996). The genotype of the infecting parasite appears to be an important determinant of disease severity in immunocompetent patients (Holland 2004).

Retinal vasculitis and associated inflammatory reactions may be the lone ophthalmic disorder during the early stages of a newly acquired *T. gondii* infection. Later development of retinitis or scars consistent with toxoplasmic retinochoroiditis in the same eyes suggests that the initial isolated inflammation may have been caused by the parasites. These cases may have implications for understanding the original source of retinal infection in patients who have recurrent toxoplasmic retinochoroiditis and could have implications for novel treatments of newly acquired *T. gondii* infections (Silveira et al.2001).

Recurrent toxoplasmic retinochoroiditis is not associated with systemic symptoms and the risk of recurrence may be influenced by patient age. Ocular lesions may first develop many years after *T. gondii* infection and are often asymptomatic (Nussenblatt & Belfort 1994).

Transplacental transmission of *T. gondii* to the foetus during pregnancy is another important route of infection. The mother can transmit toxoplasmosis to the foetus if infected primarily by *T. gondii* during pregnancy or a few months prior to conception (Montoya & Liesenfeld 2004). The foetal infection can result in visual loss, hearing loss, mental and psychomotor retardation, seizures, haematological abnormalities, hepatosplenomegaly and/or death (Montoya & Remington 2008). Retinochoroidal scars are the most characteristic manifestation of a congenital or prenatal infection (Mets & Chhabra 2008) (Fig. 7). Mothers who become infected during the first trimester of gestation have a decreased risk of congenital transmission, but more severe consequences for the foetus when compared with the third trimester (Montoya & Remington 2008). Paediatricians, parents and elder children with congenital infections should be aware that late-onset retinal lesions can occur many years after birth, but the overall ocular prognosis of congenital toxoplasmosis is satisfactory when the infection is identified early and treated accordingly (Wallon et al. 2004).

Severe bilateral impairment occurred in 9% of children with congenital toxoplasmic retinochoroiditis. Half of the children with a posterior pole lesion and one in six of those with peripheral lesions alone were visually impaired in the affected eye (Tan et al. 2007). Numerous children with congenital toxoplasmosis have substantial retinal damage at birth and consequent loss of vision. Nevertheless, vision may be remarkably good, even in the presence of large macular scars. Active lesions become quiescent with treatment and may recur at any age (Mets et al. 1997).

In one study evaluating 430 children treated for congenital toxoplasmosis, ocular involvement was present in 30% of the cohort after a median follow-up of 12 years. The overall functional prognosis of congenital toxoplasmosis was better than would be predicted on the basis of literature findings, with only two of the 130 children suffering bilateral visual impairment (Kodjikian et al. 2006).

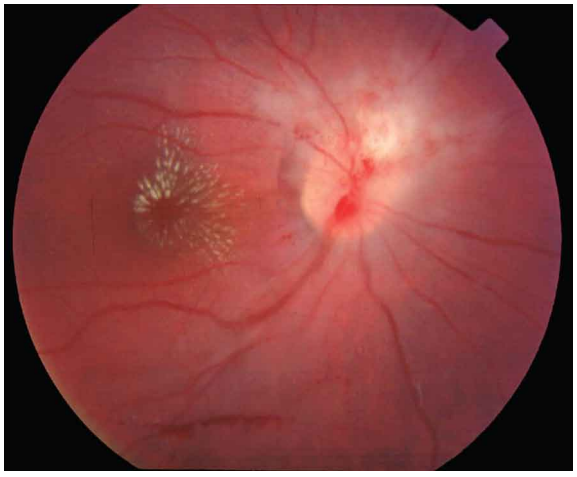

Fig. 5: optic disk involvement with macular exudates in a case of ocular toxoplasmosis.

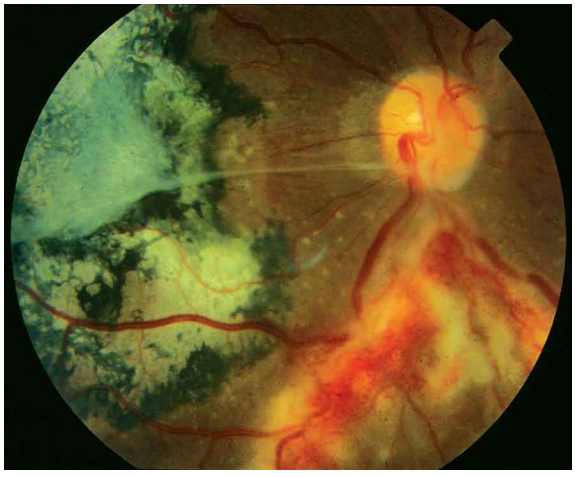

Fig. 6: toxoplasmic scar and active CMV retinitis in a patient with AIDS.

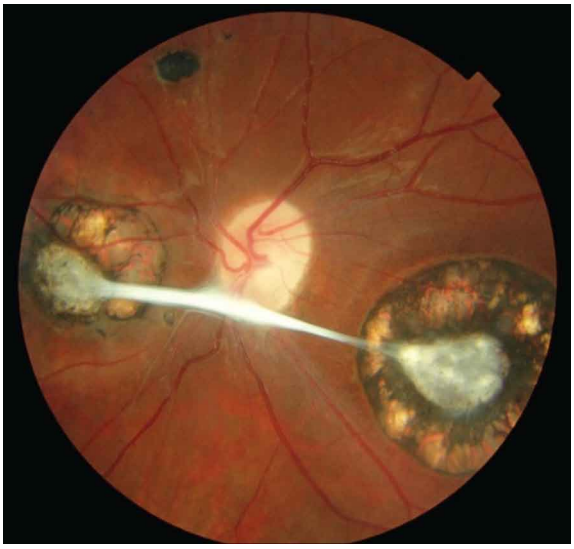

Fig. 7: retinal scars linked by vitreous strand in congenital toxoplasmosis.

Although it is classically known that only during acute infection the mother could transmit the infection to the foetus, there are a few reports supporting the possibility that chronically infected women may be transmitting the disease congenitally (Silveira et al. 2003).

The diagnosis of ocular toxoplasmosis is typically clinical. There is no reliable diagnostic test to identify toxoplasmic uveitis. The presence of anti *T. gondii* IgG antibodies does not confirm the toxoplasmic aetiology, but a negative IgG generally discards the possibility. Such antibodies can often persist at high titers for years after the acute infection and there is a high prevalence of such antibodies in the general population (Ongkosuwito et al. 1999).

Pathological diagnosis of ocular toxoplasmosis can be established by identifying the cysts in biopsies stained with haematoxylin and eosin, polyclonal or monoclonal antibodies by immunohistochemistry (Rao & Font 1977), or by polymerase chain reaction (PCR) (Brezin et al. 1990). Histologically, ocular toxoplasmosis typically presents as extensive granulomatous inflammatory infiltration of the choroid and areas of necrosis of Bruch's membrane (Belfort et al. 2008, unpublished observations).

T. gondii DNA has been identified in ocular tissue sections of patients with presumed toxoplasmic retinochoroiditis using PCR techniques, even when typical tissue cysts are not identified during histopathologic examination (Brézin et al. 1990, Ongkosuwito et al. 1999).

Examination of vitreous fluid using PCR in patients where toxoplasmosis is considered in the differential diagnosis but in whom the presentation is atypical, is a useful diagnostic aid (Montoya et al. 1999, Rothova et al. 2008). To facilitate genotyping of *T. gondii* in vitreous fluid of patients with severe or atypical ocular toxoplasmosis, PCR followed by restriction fragment length polymorphism assays were developed (Grigg et al. 2001).

One study compared three biological methods, immunoblotting/Western blotting, the calculation of the Goldmann-Witmer coefficient and PCR for the diagnosis of ocular toxoplasmosis in the aqueous humor and serum samples. The authors showed that the combination of all three techniques improved the sensitivity of diagnosis to 97% (Fekkar et al. 2008).

Alternatively, nested-PCR (nPCR) can be a reliable diagnostic technique for ocular toxoplasmosis because of the amount of specimen required, speed, cost effectiveness, high sensibility and high specificity to detect of *T. gondii* DNA in the intraocular fluids (Calderaro et al. 2006, Mahalakshmiet al. 2006).

More recently, real-time PCR has been replacing nPCR as a rapid and sensitive technique for quantitatively evaluating ocular samples for the presence of infectious pathogens (Lin et al. 2000, Dworkin et al. 2002, Rothova et al. 2008).

Laboratory confirmation of the diagnosis is also thwarted by marked individual variations in the time elapsing between the onset of clinical symptoms and the activation of specific antibody production. This difficulty results in a high proportion of false negative results (Garweg 2005).

Treatment of ocular toxoplasmosis

Ocular toxoplasmosis therapy includes antimicrobial drugs with or without the presence of corticosteroids. Several drugs have been proposed including pyrimethamine, sulfadiazine, spiramycin, clindamycin and trimethoprim-sulfamethoxazol (Pleyer et al. 2007, Antoniazzi et al. 2008).

Results of a study comparing three drug combinations: (i) association of pyrimethamine, sulphadiazine and corticosteroids; (ii) association of clindamycin, sulphadiazine and corticosteroids; (iii) association of cotrimoxazole (trimethoprim and sulphamethoxazole) and corticosteroids, showed no difference in the resolution of inflammatory activities. However the most common side effects were associated with pyrimethamine medication and included hematologic complications, such as thrombocytopenia and leucopenia, despite folinic acid supplementation (Rothova et al. 1989). The same group studied in 1993 showed a reduction in size of the retinal inflammatory lesion for 49% of the pyrimethamine-treated patients (17 of 35) compared to 20% of the untreated patients (8 of 41). However, the most frequent occurrence of side effects was also associated with pyrimethamine medication (26%, 9 of 35) (Rothova et al. 1993).

The combination of pyrimethamine, sulfadiazine and corticosteroids, which is considered "classic" or specific therapy for ocular toxoplasmosis, is the most common drug combination currently used to treat toxoplasmosis (Montoya & Liesenfeld 2004).

Patients with active toxoplasmosis may also be treated with trimethoprim-sulfamethoxazole (Bactrim), with or without adjunctive clindamycin and prednisone for 4-6 weeks. Trimethoprim-sulfamethoxazole appears to be a safe and effective substitute for sulfadiazine, pyrimethamine and folinic acid in treating for the treatment of ocular toxoplasmosis (Opremcak et al. 1992, Soheilian et al. 2005).

The pyrimethamine and azithromycin drug combination was shown to be similar to the standard treatment with pyrimethamine and sulfadiazine. However, the frequency and severity of adverse effects was significantly lower with the regimen containing pyrimethamine and azithromycin. Multidrug therapy containing the combination of pyrimethamine and azithromycin appears to be an acceptable alternative treatment for sight-threatening ocular toxoplasmosis (Bosch-Driessen et al. 2002).

The causes of recurrences in ocular toxoplasmosis remain unknown. The causes may be related to the rupture of the dormant retinal cyst (Abreu et al. 1987) or toxoplasma circulating in peripheral blood (Silveira et al., unpublished observations). Recurrent toxoplasmic retinochoroiditis remains a major health crisis and can be associated with severe morbidity if the disease extends to structures critical for vision, including the macula and optic disk. Severe morbidity may also occur if there is damage to the eye from inflammation or if there are complications such as retinal detachment or neovascularisation. In patients with frequent recurrences, long-term intermittent treatment with trimethoprim (160 mg)/sulfamethoxazole (800 mg), one tablet three

times a week reduced the rate of recurrent toxoplasmic retinochoroiditis from 23.8-6.6% (Silveira et al. 2002).

Traditional short-term treatment of active toxoplasmic retinochoroiditis lesions does not prevent subsequent recurrences. Various short-term therapeutic approaches had no effect on visual outcomes or future recurrence rates, with the exception of a poor visual outcome for patients who received corticosteroids without anti parasitic drugs (Bosch-Driessen et al. 2002). Studies have yet to confirm the relationship between systemic corticosteroid use and reactivation of toxoplasmosis (Morhun et al. 1996).

Intravitreal clindamycin injection and possibly steroids may be indicated for patients that have contraindication of systemic therapy specific for toxoplasmosis (Aggio et al. 2006, Sobrin et al. 2007). Sobrin et al (2007) showed that intravitreal clindamycin injection, alone or in conjunction with pars plana vitrectomy, was associated with resolution of toxoplasmic retinochoroiditis. On the other hand, intravitreal injections of clindamycin and dexamethasone (Kishore et al. 2001) with subconjunctival injections of clindamycin (Colin & Harie 1989) appear to be an interesting useful alternative in the choice of an anti-toxoplasmic ocular therapy.

Treatment with spiramycin should be initiated immediately after diagnosis of recently acquired maternal infection (Montoya & Liesenfeld 2004). The literature shows the lack of efficacy of short-term treatments for ocular disease as well as the long-term prenatal treatments on foetal transmission rate and the severity of congenital disease (Rothova 2003).

Ocular toxoplasmosis remains a disease in which most concepts are unfortunately not based on scientific evidence. Treatments often change according to induction and seduction of speakers and investigators instead of objective findings based on reasoning and deduction. Little is known, and much less of what is known is true.

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