# OCULAR TOXOPLASMOSIS: BRIEF LITERATURE REVIEW

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**ABSTRACT**

Toxoplasmosis in humans is a zoonotic parasitic disease caused by a ubiquitous protozoan, *Toxoplasma gondii. Toxoplasmosis* is an opportunistic infection that can cause serious damage in immunocompromised patients.While in the non-immunocompromised individuals it is most often latent and asymptomatic, about one-third of the world's population is estimated to be infected. Toxoplasmosis is the most common cause of posterior uveitis in non-immunocompromised individuals and the second most common cause of chorioretinitis after cytomegalovirus infection in people with HIV / AIDS. The infection can be acquired congenitally or postnatally and ocular lesions may present during or years after the occurance of the acute infection. Molecular biology techniques to diagnose ocular toxoplasmosis have been available for many years and are now accessible as standard laboratory tests in many countries. Aqueous humor or vitreous evaluation to detect parasite DNA by polymerase chain reaction or specific antibodies may provide evidence for diagnosis. Oral pyrimethamine and sulfadiazine plus corticosteroids are an effective therapy for ocular toxoplasmosis. Recent data supports the use of other treatment options, including intravitreal antibiotics. The aim of the present review is to discuss briefly the new diagnostic and treatment approaches for ocular toxoplasmosis.

**Keywords:** *ocular toxoplasmosis; diagnosis; treatment*

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## INTRODUCTION

*Toxoplasma gondii* is an ubiquitous obligate intracellular parasite, which infects both humans and warm-blooded animals as a zoonotic pathogen widespread in nature (1,2). Approximately one-third of humans worldwide are estimated to be chronically infected with *T. gondii* (2,3). Ocular toxoplasmosis is the most frequent cause of posterior uveitis, presenting with a unilateral chorioretinal lesion associated with vitritis (4, 5). Although ocular toxoplasmosis in adult life was presumed to be the recurrence of the congenitally acquired infection, more recent reports indicate that acquired infections may account for a larger portion of ocular involvement than congenital toxoplasmosis (6, 7). Visual symptoms during acute toxoplasma retinochoroiditis are typically secondary to vitritis or less frequently from the involvement of the macula or optic nerve. Vision loss may become permanent due to formation of a macular scar or optic atrophy, and up to 24% of patients may have 20/200 vision or less in at least one eye (8, 9). A toxoplasmosis scar can be associated with severe visual field loss when it occurs close to the optic disk (10).Felidae are the definitive hosts for *T. gondii*, and humans and other mammals act as intermediate hosts. The transmission occurs by many routes, including ingestion of raw or undercooked meat infected with tissue cysts, ingestion of food and water contaminated with oocysts, ingestion of eggs and milk contaminated with tachyzoites, blood transfusion, organ transplantation or transplacental transmission (11).

Accurate diagnosis depends heavily on the characteristic clinical features of this disease, but atypical presentations, especially in immunocompromised patients, may create diagnostic challenges and lead to misdiagnosis and inappropriate treatment (12). The aim of the present review is to discuss briefly the new diagnostic and treatment approaches for ocular toxoplasmosis.

## EPIDEMIOLOGY

*T. gondii* is a common parasite that infects almost all mammalian species including humans. Approximately 25–30% of the human population is infected with *T. gondii* (13). However, seroprevalence varies widely, from 10 to 80% between different geographic areas and countries and even within countries. Reports of low seroprevalence in the range of 10–30% come from Southeastern Asia, North America and Northern Europe with (14). Prevalence between 30 and 50% has been reported for Central and Southern Europe, whereas high seroprevalences are observed in Latin America and in tropical African countries (15).

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 (16). 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 (16-17). Type II strains appear to be responsible for the majority of symptomatic human cases in France and the United States (18), while types I and III are found in only 10% and 9% of *Toxoplasma* isolates from patients, respectively (19).

Most patients present with uveitis secondary to ocular toxoplasmosis in their second to fourth decade of life. Disease severity is typically higher in older patients (20, 21). In a study by Nguyen et al. (22) toxoplasmosis was the most common etiology of uveitis in patients referred to a tertiary center and had a prevalence of 14% among all other etiologies. A survey of 1,916 patients from Europe found ocular toxoplasmosis to be the most frequent diagnosis in patients with posterior uveitis and the cause of 4.2% of uveitis cases (23). Multiple studies from different regions of the globe have identified ocular toxoplasmosis as the most common form of posterior uveitis (24).

The incidence of congenital infection ranges from 1/770 to 1/10,000 and largely depends on the geographical region (25–27). Most cases of congenital toxoplasmosis are asymptomatic, and initially remain unrecognized. Severe cases resemble other acute intrauterine infections such as rubella or cytomegalovirus. Low birth-weight, hydrocephalus, prematurity, seizures, enlargement of liver or spleen, and jaundice may occur. Evidence of retinal infection may be found in 75-80% of the infected babies. The disease affects both eyes in 85% of cases (27). In pediatric cases, ocular disease is the most common manifestation of congenital toxoplasmosis, with 95% of patients showing signs of chorioretinitis in the presence of systemic findings, and occurs in the absence of systemic involvement in 26% of children (28, 29). The majority of ocular toxoplasmosis infections are acquired orally, either by consuming or handling raw meat containing tissue cysts, or by drinking water contaminated with oocysts (11).

## CLINICAL FEATURES

Most of the acute systemic toxoplasmosis cases in healthy hosts tend to be subclinical, but some may present with mild flu-like symptoms. If parasites reach an eye and they yield a focus of inflammation, the lesion progresses to retinitis and involves the choroid secondarily. Is The release of rhoptry protein kinase from the parasite is a key-point in the pathogenesis of *T. gondii* infection of. The former interacts with JANUS kinase - an enzyme that is part of the signal transducer and transcriptional activator - STAT (JAK-STAT) pathway, which reduces cytokine production and leads to an ineffective local immune response l (30). Host immune responses appear to induce conversion of the parasitic forms from tachyzoites to bradyzoites and their encystment (31). The cyst may remain inactive in the scar or nearby for a long time. However, when the cyst ruptures with release of organisms into the surrounding retina, retinitis may be reactivated (32). The reactivation of retinitis is known to develop at the border of old scars and is attributed to the rupture of tissue cysts which are located within old lesions **(Fig. 1)**. Sometimes however, new lesions are found at locations distant from old scars. In general, the hallmark of the ocular lesion is retinitis, adjacent to an inactive retinochoroidal scar. Necrosis of the retina and choroid with destruction of the surrounding tissues is found within the active lesion. The inflammatory response is mononuclear cell reaction in nature, and

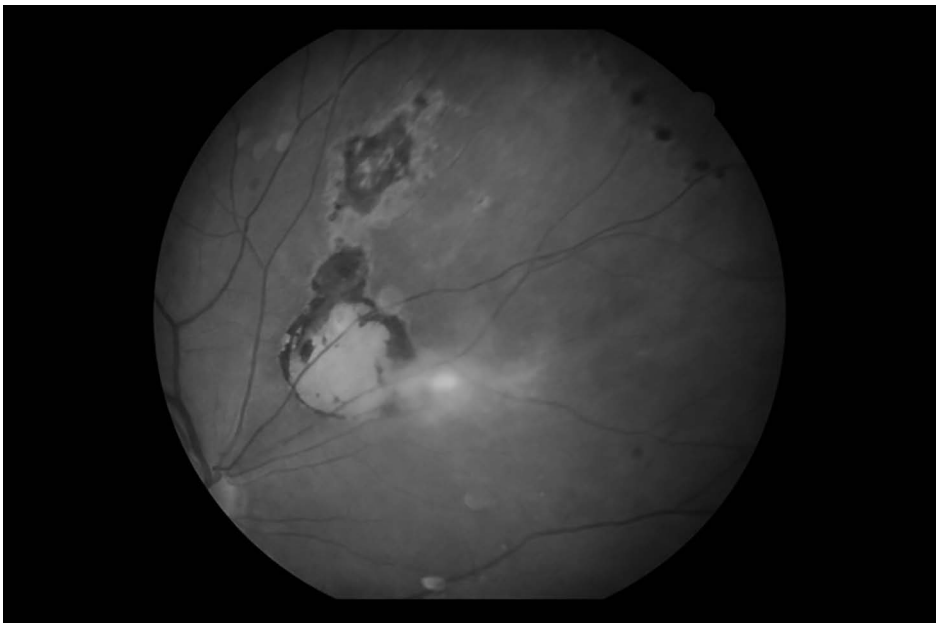

**Fig.1.** *Reactivation of toxoplasmic retinitis at the border of an old scars.*

consists of lymphocytes and macrophages at the edge of the lesion. Viable and intact cysts may be present, either adjacent to the scars or within the area of retinal necrosis, and rarely tachyzoites may be identified in the extracelluar space (33). Ocular toxoplasmosis often presents with classic ophthalmic findings, and the diagnosis is reached by clinical examination without any laboratory confirmation of *T. gondii* infection (34). Seropositivity for T. gondii infection indicates previous systemic exposure to the parasite, though this finding is not sufficient to confirm the diagnosis of ocular toxoplasmosis. Visual impairment may be secondary to a macular lesion, while lesions located at the peripheral retina often lead to vision loss secondary to severe vitreous inflammation (35, 36). Although the optic nerve is not commonly affected its damage may cause visual field loss and color vision deficiency. The involvement of the vitreous body in the inflammation leads to blurry vision, an important symptom of ocular toxoplasmosis. When the parasite becomes inactive, retinochoroidal scars are formed and from their size and location depends the severity of visual field deficits. Classical ocular manifestation of toxoplasmosis is a nidus of fluffy white, focal necrotizing retinitis or retinochoroiditis adjacent to a variably pigmented chorioretinal scar. Often the active lesion is obscured by severe vitritis producing the classic 'headlight in the fog' sign (37) **(Fig. 2)**. The severity of anterior uveitis may range from minimal reaction to an intense inflammation, masking the posterior

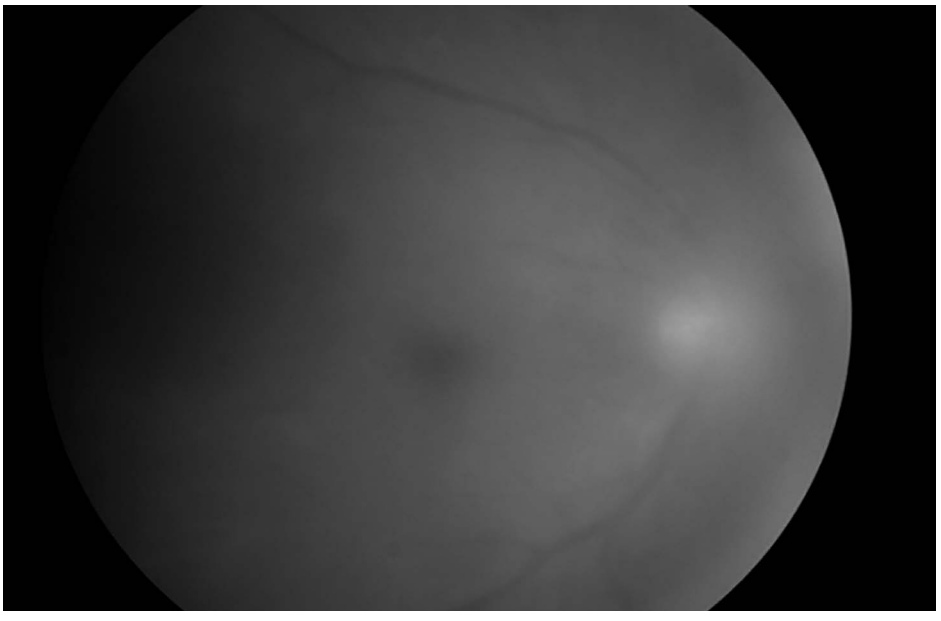

**Fig.2.** *An active lesion is obscured by severe vitritis producing the classic 'headlight in the fog' sign.*

segment involvement. Anterior uveitis may be either granulomatous or nongranulomatous inflammation. In children with congenital toxoplasmosis, cataract may be associated with retinochoroiditis and may follow severe iridocyclitis (36). Other common clinical signs of ocular toxoplasmosis include satellite lesion adjacent to an inactive retinochoroidal scar, retinochoroidal scar, focal or widespread vasculitis, and inflammatory ocular hypertension syndrome (38). Atypical findings include multifocal retinochoroiditis, low-grade or absent vitreal infiltration, an active lesion more than 2 disk diameters without an associated retinochoroidal scar, absence of a retinochoroidal scar, bilaterality, optic disk involvement, choroiditis without retinitis, hemorrhagic vasculitis, serous retinal detachment, andretinal neovascularization (38). Spectral-domain optical coherence tomography (SDOCT) imaging is an important diagnostic tool to identify the morphological features of the vitreoretinal changes in ocular toxoplasmosis (40-41). The stage of the disease is determinant for the SD-OCT findings of chorioretinal lesions. In children with congenital toxoplasmosis, cataracts may occur as a complication of retinochoroiditis, and may follow severe iridocyclitis. Cataract may cause severe amblyopia in children and may need to be removed surgically (42). Inflamation of the vitreous is usually more intense near the lesion of active retinochoroiditis. In cases of intense vitritis, epiretinal membranes may develop and vitreoretinal traction adjacent with consequent retinal detachment to the area may occur (**Fig. 3 and 4)**. A bright white reflex seen when one shines the light of the indirect ophthalmoscope into the back of the eye - headlight in the fog sign which results from severe vitritis.

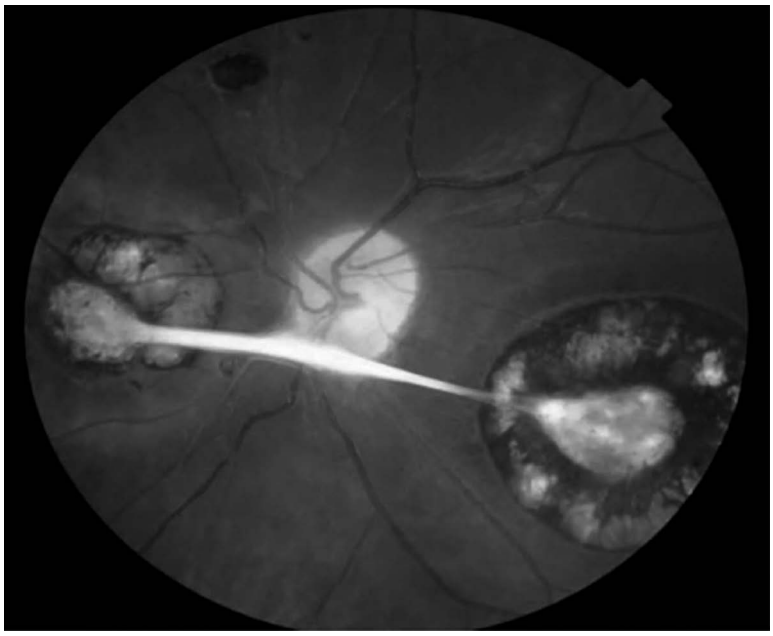

**Fig. 3.** *Severe vitritis with formation of epiretinal membranes that may develop vitreoretinal traction with consequent retinal detachment to the area.*

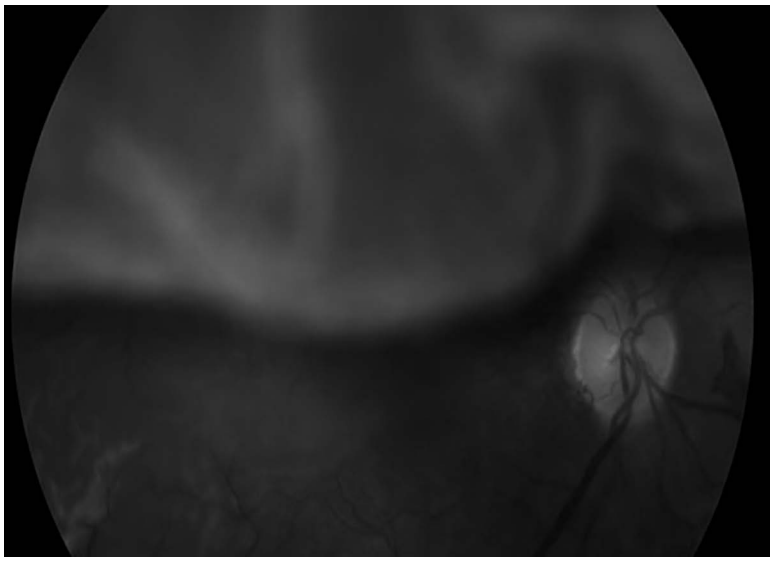

**Fig. 4.** *Retinal detachment as a result of severe toxoplasmic vtritis.*

## DIAGNOSIS

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 (43). *T. gondii* antibody titers in ocular fluids or polymerase chain reaction (PCR) of aqueous and vitreous samples are other newer tools with high sensitivity and specificity to confirm the diagnosis (44, 45). Many diagnostic laboratories are capable of measuring IgG and IgM antibody levels using enzyme-linked immunosorbent assay (ELISA) or immunofluorescent antibody commercial kits. ELISA has an advantage over the immunofluorescent antibody testing because it permits automation for simultaneous testing of large numbers of samples and the results are objective. The Sabin-Feldman dye test, the classic gold standard serology test, uses live *T. gondii* tachyzoites to detect IgG antibodies (46). It as high sensitivity and specificity, but this test is not frequently performed, owing to the risk for laboratory-acquired infections. Serum IgM and IgG antibodies to *T. gondii* develop within 1–2 weeks after infection (47). Patients suspected of acute toxoplasmosis may initially be analyzed for IgG serology, and if the result is positive for IgG, IgM antibody levels may be measured. IgM levels rise within the first week and become undetectable after 6–9 months. Elevated levels of antibodies alone should not be considered as an evidence of recent infection, nor should low serum IgG levels be considered as inactive disease. If the laboratory testing is unequivocal, serological tests should be repeated in 15–21 days (46).

Asymptomatic patients with IgG reactivity alone may have latent infection with a history of primary exposure. This serological pattern is most important for immunosuppressed patients, including HIV infection and transplant recipients, and defines the risk for reactivation of the disease (12). In patients with reactivation disease, IgM and IgG responses may not be seen. In immunocompromised patients with seronegativity but strong clinical evidence, further tests to exclude *Toxoplasma* infection should be performed. These include IgG antibody testing or *T. gondii* PCR of thevitreous and aqueous humor. Serology is also used to assess the risk of transplacental transmission. IgG serology is performed in women considering pregnancy routinely in countries with endemic toxoplasmosis (48) . Elevated levels of IgG before pregnancy in immunocompetent women indicate a low risk for transplacental transmission. 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 (43). Those with undetectable IgG levels are advised to avoid undercooked meat consumption or cat feces. Negative IgM serology excludes infection in the last 6 months; if positive, it may persist up to 2 years after exposure to T. gondii . The IgG avidity test provides information about the time of exposure if IgG and IgM serologic tests are reactive. An IgG avidity test resulting in high-avidity IgG antibodies in the sera of first trimester embryos indicates that the infection was acquired before conception, because high-avidity IgG antibodies take 3–4 months to appear (49). Low-avidity IgG antibodies could not confirm the diagnosis of recent infection, due to their persistence for many months afte rthe acute infection (12,48). Detection of Toxoplasma -specific antibodies or DNA of the parasite in ocular specimens is the main basis for diagnosis (13). Intraocular antibody production is established by the Goldmann-Witmer coefficient (GWC), which compares the Toxoplasma -specific antibodies in ocular fluids and in serum (50). Although a ratio >1 should indicate intraocular antibody production, this may also occur in healthy controls, and therefore a ratio of at least 3 is rather used to confirm diagnosis (51).The contribution of PCR to the diagnosis is more controversial. In immunocompetent patients with clinical diagnosis of ocular toxoplasmosis, DNA of T. gondii could be amplified by PCR techniques only in 30– 40% cases (52, 53). However, in immunocompromised individuals, T. gondii DNA was amplified in 75% of the clinically diagnosed patients (53). Montoya et al. (54) reported that the diagnostic value of PCR in

intraocular specimens for T. gondii chorioretinitis was 67%. The sensitivity of PCR in patients meeting clinical diagnostic criteria for toxoplasmic chorioretinitis was lower in other studies, ranging from 27 to 36% (51, 54, 55) . Despite low sensitivity, the specificity of PCR is 100% (56) . The sensitivity of PCR also depends on the immune status of the patient. When the clinical symptoms first manifest in immunocompetent patients, the intraocular inflammatory response reduces the parasitic burden in the aqueous humor and vitreous, thus decreasing the amount of target DNA for PCR amplification. To improve the sensitivity of PCR, Sugita et al. (57) established a 2-step PCR protocol as a novel PCR technique for the diagnosis of ocular toxoplasmosis. In the first step, this technique uses a qualitative multiplex PCR approach to detect the Toxoplasma genome in the ocular sample. In the second step, quantitative real-time PCR is used to measure the genomic DNA of T. gondii. By using this 2-step PCR method, it was possible to detect an exceedingly small amount of nucleic acid in small amounts of an ocular sample with a sensitivity of 85%.

## TREATMENT AND MANAGEMENT

There is no treatment for inactive toxoplasmosis. In immunocompetent patients, Toxoplasma - related chorioretinitis is usually a self-limited infection and generally resolves spontaneously in a period of 4–8 weeks (58). However, the highly variable severity of ocular toxoplasmosis raises significant issues regarding appropriate therapeutic strategies, mand even the need for any treatment at all, in this self-limiting disease (59). Traditionally, antibiotics and corticosteroids have been the mainstay of pharmacologic therapy against T. gondii. Treatment is given to reduce the risk of permanent visual impairment (aiming to reduce the size of the retinochoroidal scar), the risk of recurrence, and the severity and duration of acute symptoms. Antibiotics are usually given for 6 to 8 weeks. Steroids are also sometimes used to decrease the severity of intraocular inflammation symptoms (60). The aim of the treatment of gestational toxoplasmosis is to prevent fetal infection (61). Antibiotics used for the treatment have included trimethoprim-sulfamethoxazole, pyrimethamine, sulfadoxine, sulfadiazine, clindamycin, tetracyclines, clarithromycin, azithromycin, atovaquone, minocycline, spiramycin, rifabutin, trimetrexate, lincomycin, dapsone, sulfafurazole, ciprofloxacin, doxycycline, miokamycin, erythromycin, macrolide, sulfonamide, sulfamerazine, nifurtimox, methotrexate, alone or in combination (60, 62–65). The most frequent chemotherapeutic regimen for ocular toxoplasmosis consists of pyrimethamine and sulfadiazine, plus corticosteroids. Trimethoprim/sulfamethoxazole plus oral prednisolone is an alternative treatment option. This treatment was shown recently to have similar efficacy to classical therapy in a randomized clinical trial (66, 67). Other treatment option is intravitreal clindamycin injection and dexamethasone which is a promising approach (67-69). Intravitreal drug administration bypasses ocular barriers, and thereby delivering a high drug concentration directly to the intraocular tissues, avoiding systemic exposure and its risk of complications. Clindamycin 1.5 mg, given intravitreally, was non-toxic to the retina and had a half-life of 5.6 days. Following 1 mg intravitreal clindamycin injection, its concentration remained≥1.6 μg/ml during about 40 hr, which was higher than the 50% inhibitory concentration for T. gondii (67, 70).

However, the potential toxicity of, or intolerance to, many drug combinations has prompted research for alternative treatment regimens with better adverse events profiles. Azithromycin is an acid-stable, orally administered macrolide antibiotic, structurally related to erythromycin, with a similar antimicrobial spectrum (71). In vitro and in vivo efficacy of azithromycin against T. gondii has been demonstrated in several animal models, as well as for the treatment of T. gondii encephalitis in patients with AIDS (72, 73). The efficacy of azithromycin alone (74) or in combination with pyrimethamine (75) and trimethoprim/ sulfamethoxazole (76) in the management of active toxoplasmic retinochoroiditis has been demonstrated in previous studies. Aprospective randomized clinical trial compared the effects of two treatment regimens, pyrimethamine and azithromycin versus pyrimethamine and sulfadiazine, for the treatment of sight-threatening (near optic disk or fovea) ocular toxoplasmosis. The efficacy of the multidrug regimen

with pyrimethamine and azithromycin was similar to the standard treatment with pyrimethamine and sulfadiazine. The frequency and severity of adverse effects were significantly lower in patients receiving pyrimethamine and azithromycin. This data supports multidrug therapy with the combination of pyrimethamine and azithromycin as an acceptable alternative for the treatment of sight-threatening ocular toxoplasmosis (77). As in other ocular infections, the host immune response promotes intraocular inflammation against tachyzoites within the retina. The role of corticosteroids is to suppress the accompanying inflammation and minimize chorioretinal damage. The timing of initiation and the appropriate dose of corticosteroids are important to balance the suppression of the immune response to the parasite while minimizing the disease severity (78). Corticosteroid therapy without antiparasitics may lead to large retinal lesions even in immunocompetent patients (79, 80). The baseline indications for the use of corticosteroids include severe vitreous inflammation, decreased vision, proximity of lesions to the fovea or optic disk and the large size of the active lesion (65). The preferred oral corticosteroid drug is prednisone. In a survey by Holland and Lewis (65), 17% of physicians reported using oral corticosteroids for all immunocompetent patients with ocular toxoplasmosis regardless of clinical findings. Corticosteroids were started simultaneously with antiparasitic drugs by 36% of the respondents in this survey, while 64% deferred the start of corticosteroid therapy 1–7 days after starting antiparasitic therapy, with the majority waiting steroid initiation. Corticosteroid therapy is contraindicated in immunocompromised patients lacking the normal inflammatory response to the parasite (80). Most ophthalmologists prefer topical steroids for ocular toxoplasmosis patients. The main indications for use of topical corticosteroids are ocular pain, redness, photophobia, moderate to severe anterior chamber inflammation, and elevated intraocular pressure (21, 65). The treatment of ocular toxoplasmosis during pregnancy requires special consideration due to the potential adverse effects of antiparasitic agents on the fetus (48). If the mother acquires Toxoplasma infection during or immediately prior to pregnancy, there is a significant risk of placental transmission, and the risk increases with gestational age. Dunn et al. (81) reported an overall vertical transmission rate of 29%. The risk of transmission in early pregnancy was low, 6% at 13 weeks of gestation, and increased significantly in the second and third trimesters of pregnancy reaching 72% at 36 weeks. Although the transmission rate is low, toxoplasmosis severity and morbidity are much higher in infants acquiring the infection in the early gestational period (81). If a pregnant woman becomes infected up to 18 weeks into the pregnancy or within the 6 months prior to conception, treatment with the macrolide antibiotic spiramycin is recommended. Spiramycin does not readily cross the placenta, and there is no evidence for spiramycin teratogenicity. Alternatively, local intervention with intravitreal clindamycin and dexamethasone could be considered to prevent the possible teratogenic effects of systemic pyrimethamine and sulfadiazine. If the maternal infection is acquired 18 weeks or later after conception, treatment with pyrimethamine, sulfadiazine and folinic acid is advised (48).

## CONCLUSIONS

Ocular toxoplasmosis is mainly acquired postnatally. Although food is considered as the main source of infection, contaminated water should also be considered as a mechanism of acquisition of the disease. Diagnosis is based on the clinical picture and, in particular, on the presence of retinochorioiditis accompanied by inflammation of the vitreous body . Old retinochoroidal scars may be also observed. Laboratory confirmation relies on the analysis of serum or intraocular samples for antibody detection, but PCR is becoming more widely available for direct identification of the parasite DNA in the eye, and sensitivity of PCR is improving with new methods of detection. The combination of pyrimethamine, sulfadiazine, and corticosteroid provides an effective therapeutic approach. Alternative regimens may include treatment with trimethoprim- sulfamethoxazole alone, intravitreal injection of clindamycin with dexamethasone, or combination of azithromycin with pyrimethamine. All have shown efficacy in

the therapy of ocular toxoplasmosis. The use of the trimethoprim-sulfamethoxazole combination is now preferred by many due to better patient compliance, faster resolution of chorioretinitis, and improved visual acuity. Trimethoprim-sulfamethoxazole is recomended for long-term prophylaxis in patients with frequent relapses. The intravitreal injections of clindamycin and dexamethasone as local agents in the vitreous cavity and retina permit avoiding most systemic side effects.The combination of pyrimethamine and azithromycin has been reported to have very good therapeutic efficiency and fewer side effects in comparison with the combination of pyrimethamine and sulfadiazine. Continuous progress in improving diagnosis and treatment is very important to minimize the vision loss from ocular toxoplasmosis. An in-depth clinical and pathophysiological knowledge of the disease can lead to more effective approaches for its prevention and treatment. In case of surgical treatment, the application of antibiotics for prevention or treatment of the complications should be considered..

In summary, the time of toxoplasma infection leading to ocular disease is rarely known. However, current evidence suggests that many more people are affected by postnatal than by prenatal toxoplasmosis. This has major public health implications. Considerable expertise and expenses are concentrated on screening and health information to reduce the risks of toxoplasmosis due to prenatally acquired infection, principally to reduce the risks of ocular morbidity in the long term. Primary preventive strategies should include children and adults at risk of ocular disease as a result of postnatal infection and should not be confined only to the pregnant women.

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