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Toxoplasmosis: new challenges for an old disease

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Abstract

More than a century after the identification of *Toxoplasma gondii*, major issues need to be addressed for the optimal management of ocular disease. Toxoplasmic retinochoroiditis is the main cause of posterior uveitis in several geographical areas. The parasite establishes a love–hate relationship with the eye, manipulating the immune response and inducing variable initial lesions and further relapses. It is now well established that most cases are acquired after birth and not congenital. The severity of the disease is mainly due to the parasite genotype and the host immune status. Diagnosis is based on clinical features, but may be confirmed by biological tools applied to ocular fluids. Combining several techniques improves the diagnostic yield in equivocal cases. Therapeutic management is the most important challenge. Even though evidence-based data on the efficacy of anti-parasitic drugs are still missing, new strategies with a good safety profile are available and may be proposed earlier during the course of the disease, but also in selected cases, to reduce sight-threatening relapses. Revisiting the therapeutic options and indications may be an important step towards long-term maintenance of the visual function and avoidance of major complications.
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Introduction

Ocular toxoplasmosis is a retinochoroiditis due to *Toxoplasma gondii*, an obligate intracellular protozoan. Even though the parasite was identified more than a century ago, infection remains a potential blinding condition in all age groups, starting before birth. Diagnosis is usually easy to obtain, even though laboratory investigations may be necessary. The most controversial issue is therapeutic management. New antibiotics induce lesser side effects than the classical regimens, although their efficacy has never been clearly demonstrated. Indications and strategies must be adapted to each situation. However, due to their better tolerance profile, more cases are treated with antiparasitic drugs and corticosteroids. The results of a recently published survey highlight significant differences in epidemiology, diagnosis, and treatment of the disease.[1]

History and parasite life cycle

The protozoan parasite *Toxoplasma gondii* was described in 1908–1909 by Nicolle and Manceaux[2,3] at The Pasteur Institute in Tunis, Tunisia, and concomitantly by Splendore[4] in San Paolo, Brazil. Both groups were investigating *Leishmania* and viruses. Nicole was working on a rodent, *Ctenodactylus gundi*, which lives in the foothills and mountains of southern Tunisia. Chatton and Blanc[5] found that gundis were not infected naturally, but acquired infection in captivity. The first case of ocular toxoplasmosis was reported in 1923,[6] but the association was definitely accepted in 1939.[7] *T. gondii* has a wide host range, but it has retained the definitive host specificity restricted to felids. The full life cycle of the parasite was not discovered until 1970, with the identification of the sexual phase of the parasite in the small intestine of the cat.[5]

Seroepidemiological studies on isolated islands in the Pacific have shown an absence of *T. gondii* on islands without cats, confirming the important role of the cat in the natural transmission of *T. gondii.* Felines are the only definitive hosts,[8] and excreted infectious oocysts can last in the environment up to 18 months. Three parasitic strains have been identified. Type II strain is mainly isolated in Europe and

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North America, whereas type III and recombinant I/III strains are common in South America.

Risk factors and epidemiology

Up to one third of the world's human population is infected by the parasite, accounting for the parasite latency. Most of seropositive patients do not develop a symptomatic disease.[9] Congenital transmission, carnivorism, and fecal–oral transmission are well described. Ingestion of contaminated water should not be underestimated. Immune deficiency and strain variability are the major risk factors for an aggressive form of infection.[10–12] Ocular toxoplasmosis occurs in 2 and 18% of seropositive individuals in the United States[13] and Southern Brazil, respectively. Age is a major factor to consider, with new interesting and controversial data.[14–16] The disease seems more severe at the extremes of age. New data indicate that nearly two third of cases are postnatally acquired. The risk of maternal infection during pregnancy is 0.2 to 1%, with a transplacental transmission rate of 40 to 50%. Early transmission during pregnancy is rare, but has catastrophic consequences. The prevalence of congenital toxoplasmosis is 1–10/10 000 live births in the United States and 1/3000 live births in France. Significant visual impairment occurs in 9, 29, and 87% of congenital cases in the United States, Europe, and Brazil, respectively. Older patients may have a higher risk of ocular involvement with more severe lesions. Due to an impaired immune reaction, lesions are more extensive in older patients with a prolonged course of infection. In a large study performed in the Netherlands, it was reported that patients older than 40 years of age at the time of an active episode were at higher risk of recurrence after an active episode than younger patients (RR 1.74 (1.06–2.86), $P = 0.03$).[16] Interestingly, another study from Switzerland reported informations on recurrences,[14] which appear controversial compared with the Dutch study. To explain this discrepancy, it is important to consider that risk of recurrence differs after episodes associated with initial infection and recurrent episodes. It is important to consider that 20% of patients develop recurrences.

Clinical findings

In most of the cases, the diagnosis of toxoplasmosis is based on clinical features. Systemic signs are usually absent. However, cervical lymphadenopathy or a mononucleosis-like infection may occur. Floaters, blurred vision, or visual loss are the main complaints. A unilateral yellow–white necrotizing retinochoroiditis with fuzzy borders is generally associated with an adjacent scar and variable degree of vitreous haze ('headlight in the fog' aspect). Intraocular inflammation may involve other structures such as retinal vessels, the optic disc, and the anterior segment with a granulomatous uveitis. Branch retinal vein occlusion occurs in nearly 8–10% of cases, and may be associated with retinal ischemia and neovascularization with intravitreal hemorrhage. A serous retinal detachment may explain a severe visual loss associated with an extrafoveolar lesion. High intraocular pressure is usually associated with severe intraocular inflammation or a peripheral lesion. An immune deficiency must be excluded in case of bilateral infection. Differential diagnosis includes other types of infectious retinochoroiditis or retinitis such as toxocariasis, viral-induced necrotizing retinopathies, syphilis, diffuse unilateral subacute neuroretinitis, and aspergillus endophthalmitis. Extensive toxoplasmosis with peripheral involvement mimicking an acute retinal necrosis is the most challenging situation, especially in the elderly. Non-infectious entities such as Behçet's disease, multifocal choroiditis and panuveitis, serpiginous choroiditis, and punctate inner choroidopathy should also be considered. Finally, atypical presentations may be due to a primary intraocular lymphoma.

Diagnostic procedures

Clinical examination is the current gold standard for the diagnosis of ocular toxoplasmosis. In equivocal cases of retinochoroiditis, laboratory tools may help the clinician to establish the definite diagnosis. A negative blood ELISA serology would exclude toxoplasmosis, but a positive result does not mean an ocular infection. Ocular fluids are the most reliable samples, which can be tested for local specific antibody production or for *T. gondii* DNA by PCR analysis. Local antibody production (LAP) can be detected with an immunoblotting technique and quantified by calculating the Goldmann–Witmer coefficient. A coefficient above 2 to 3 is considered as positive. It has been well established that as opposed to ocular viral infections, LAP is a more sensitive method than PCR for the diagnosis of ocular toxoplasmosis. However, PCR yield may be superior to antibody detection methods in immunocompromised patients and those with an extensive retinochoroiditis. The combination of the three methods improves diagnostic sensitivity.[17] The interval between symptom onset and sample collection has been reported to influence the results of biological diagnostic tests. Therefore, LAP is difficult to detect before the second week after onset, and PCR becomes negative later during the course of infection.

Treatment

Mimicking a trench war, toxoplasmic lesions may progress from the periphery towards the posterior pole with an end-stage blinding condition (Figure 1). An evidence-based systematic review disclosed that there is a lack of evidence to support routine antibiotic treatment for acute toxoplasmic retinochoroiditis.[18,19] The ideal drug for ocular toxoplasmosis must be parasitocidal, destroying cysts, reaching optimal concentrations in the posterior segment, and having an acceptable tolerance profile. None of the current available drugs fulfill all these criteria. Until recently, because of the rare but well-documented allergic and life-threatening reactions that can be associated with antibiotics, and because of the usually self-limited nature of the disease, treatment used to be proposed to patients with lesions within the vascular arcades of the posterior pole (zone 1), dense vitritis, or severe ocular inflammation requiring corticosteroids, retinal vein occlusion, papillitis with visual-field defects, and retinal detachment. It is also highly recommended in immunodeficient patients.

The classic treatment of ocular toxoplasmosis consists in pyrimethamine (100 mg loading dose the first day, followed by 50 mg daily), sulfadiazine (1 g every 6 or 8 h), folinic acid (5 mg daily), and systemic corticosteroids (iv methylprednisolone in sight-threatening cases and/or oral prednisone 1 mg/kg daily). Monitoring of blood cell count is mandatory during the treatment, and the patient must be aware of possible allergic reactions or crystalluria. Compliance remains an important issue, as the treatment often requires more than 10 pills daily. Quadruple drug therapy (classic regimen plus clindamycin), clindamycin, trimethoprim and sulfamethoxazole, spiramycin, minocycline, azithromycin, atovaquone, and clarithromycin are other alternatives to the classical regimen. The mean duration of treatment is 6 weeks, but longer regimens may be needed in immunocompromised hosts or more virulent strains.

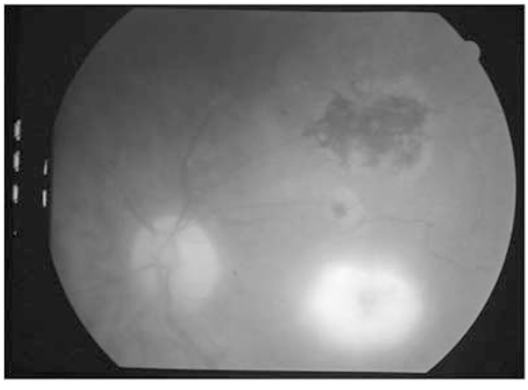

Figure 1 Patient presenting with recurrences of ocular toxoplasmosis with final macular involvement and subsequent permanent visual loss of the left eye.

Soheilian *et al*[20] have reported on the results of a randomized trial of intravitreal clindamycin and dexamethasone versus oral pyrimethamine, sulfadiazine, and prednisolone in patients with ocular toxoplasmosis. Both strategies seem to be equivalent. The intravitreal regimen may be an option during pregnancy or in patients with systemic intolerance to antibiotics.

It is important to consider that an increasing number of ophthalmologists choose to propose well-tolerated molecules such as azithromycin to nearly all patients with ocular toxoplasmosis.

Secondary prophylaxis is another major issue in one-eye patients and those with frequent recurrences or macular threat. Silveira *et al*[21] have shown that the rate of relapse was 6.6% in a group of patients treated with trimethoprim (160 mg)/sulfamethoxazole (800 mg) once every 3 days, and 23.8% in a group of patients without prophylaxis. The study was performed during a period of 20 months.[21]

Unmet medical needs

More knowledge is needed on the genetic of the parasite. Unusual genotypes and variant alleles may induce more severe clinical presentations and longer infections with more relapses. Despite their limitations, animal models may be helpful.

The natural history of ocular toxoplasmosis needs to be better defined by taking into account factors related to the parasite and the host. Clinical presentations, relapse rates, responses to antibiotic treatment, and to corticosteroids vary among patients. The ocular immune reaction has a major role, but its mechanisms need to be better defined. It is important to determine whether the treatment needs to be adapted to the strain virulence, and to the host's characteristics, such as age or immune functions.

Prospective, randomized placebo-controlled trials are needed to establish the efficacy and safety of the different antiparasitic drugs and corticosteroids.

Long-term secondary prophylactic treatment seems to be promising, but these results need to be confirmed by a placebo-controlled trial.

Conclusions

Ocular toxoplasmosis is a potential blinding condition associated with severe morbidity. Old concepts on the pathophysiology and therapeutic management of the disease may be revisited in the near future. In the absence of well-designed, placebo-controlled trials on the

efficacy of antiparasitic drugs, well-tolerated regimens are more widely proposed to patients with all forms of ocular toxoplasmosis.

Conflict of interest

The authors declare no conflict of interest.

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