Ocular toxoplasmosis in an immunocompetent 8-year-old child: a new active lesion or a late manifestation of a congenital toxoplasmosis?

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1. Introduction

Infection with the protozoan *Toxoplasma gondii* is one of the most frequent parasitic infections worldwide and the common infection of the retina in the general population. We describe a case report of a chorioretinitis in an immunocompetent 8-year-old patient as a consequence of a underdiagnosed neonatal toxoplasmosis. The boy was successfully managed with pyrimethamine and sulfadiazine. The present case we would like to empathize the importance of considering toxoplasma gondii as a possible cause of chorioretinitis in children living in developed countries and we provide a detailed reviewed of the literature about treatment of *Toxoplasma gondii* infection.

**KEYWORDS**

Chorioretinitis, *Toxoplasma gondii* infection, Children
in 10%–20% of cases; on the contrary, immunocompromised children often show fulminant and rapidly fatal infection. Congenital infection causes a wide variety of manifestations, most of all chorioretinitis and central nervous system lesions, and may also interests heart, lungs and gastrointestinal tract[3]. The severity depends on the time of infection during pregnancy: if the infection is acquired in the first trimester of pregnancy, the maternal–foetus transmission would be less probable (about 17%) but with a severe decorse and damage to several organs, such as visual or hearing impairment, learning disabilities or mental retardation; if acquired late in pregnancy, the transmission would be much more likely (rate transmission is about 65%) but it will be mild or asymptomatic at birth. Transmission of infection in weeks 10–24 results in the highest severity of clinical disease, whereas transmission in the period of 26–40 weeks results in subclinical disease which manifests latter in life. If left untreated, 85% of children with subclinical disease develop signs and symptoms of the disease including chorioretinitis or developmental delays. The transmission and severity of infection in the child may be modified by providing treatment to the mother during pregnancy. Treatment of children with congenital infection can also alter the course of disease, although relapses of chorioretinitis are still seen in treated children[4]. Despite a lack of published evidence for effectiveness of current therapies, most ophthalmologists elect to treat patients with ocular toxoplasmosis that reduces or threatens to impact vision. Classic therapy consists of oral pyrimethamine and sulfadiazine, plus systemic corticosteroïd. Substantial toxicity of this drug combination has spurred interest in alternative antimicrobials, as well as local forms of drug delivery. At this time, however, no therapeutic approach is curative of ocular toxoplasmosis[5].

2. Case report

An 8–year-old child came at the attention of our Pediatric Infectious Disease Unit. During our evaluation obstetrical and perinatal history were investigated and maternal history suggested toxoplasmosis during late pregnancy. Serological tests documented maternal negative serology at 32nd week of pregnancy. Delivery occurred at 40th week of gestation without complications, except for the occurrence of maternal laterocervical lymphoadenopathy. The newborn was in good clinical conditions. Work-up for congenital toxoplasmosis with serological tests, brain ultrasonography and funduscopy weren’t performed at birth. During the first years of life he showed a regular growth at 50’ centile and normal cognitive development. No symptoms of visual impairments were reported by parents. At 4 years of age, an ophthalmologist evaluation was performed for suspected decrease in visual activity: visual acuity was 7/10 in the right eye and 8/10 in the left eye, and fundus examination showed a dystrophic macula with vitreal retraction in the right eye. Optical coherence tomography (OCT) didn’t reveal any morphological or structural alteration of the retina, then no pharmacological treatment was proposed. Funduscopy was then performed yearly, without revealing more alterations. At 8 years of age, a macular lesion associated with mild visual impairment was identifed at the right eye. The OCT exam confirmed an inactive macular lesion compatible with ocular toxoplasmosis (Figure 1). The child came then at the attention of our Pediatric Infectious Disease Unit for an assessment. Serological tests were performed using Chemiluminescence Immunoassay LIAISON® Toxo IgM and IgG test, DiaSorin Laboratories, Saluggia, Italy, and showed toxoplasma IgG 34.0 IU/mL (negative results <7.2 IU/mL, positive results >8.8 IU/mL) and toxoplasma IgM <3 AU/mL (negative results <6 AU/mL, positive results >8 AU/mL). At the same time, ophthalmological evaluation confirmed the macular lesion at the right eye and identified a small pigmented scar in the peripheral retina of the left eye. Given the clinical and serological data compatible with ocular toxoplasmosis, an antibiotic therapy was recommended, but refused by parents. Two years later, the child showed significant visual impairment at the right eye. OCT examination revealed a grey–white focus in the nasal retina of the right eye with vasculitis, haemorrhage and vitreitis, consistent with a newly active lesion. The antibiotic therapy consisting in pyrimethamine (25 mg/d) sulfadiazine (1.5 g twice/d) and deltacortene (15 mg twice/d) was administered for 2 months, leading to a progressive resolution of inflammation and scarring of the lesion, with simultaneous improvement of visual acuity in 8 weeks.

3. Discussion

The apicomplexan parasite T. gondii was discovered
about hundred years ago and was soon recognized as a pathogen responsible for congenital infection[6]. Prevalence of congenital infection ranges from 0.1 to 0.3 per 1 000 live births. Benefits of antenatal treatments remain today controversial and, despite antenatal and postnatal treatment, chorioretinitis can occur at any age (prevalence >20% at 10 years of age), so long-term ophthalmological follow-up remains necessary[7]. Differentiating prenatal from postnatal toxoplasmosis in older children or adults could be difficult if clear signs of intrauterine infection, such as intracranial calcifications, hydrocephalus, and microcephaly, are not present at birth. Retinochoroiditis is the most frequently described ocular manifestation of congenital toxoplasmosis[8]. Despite the poorness of comparative studies between different modalities and the lack of a randomized controlled trial, is generally well agreed on that macular lesions, lesions involving the optic nerve, and cases with intense inflammation should be treated. The goal of antimicrobial treatment is limiting irreversible damage to the retina and optic nerve that can lead to permanent blindness, since nowadays no drug has been shown to cure infection in the human host. In terms of therapy for active retinochoroiditis in older children and adults, however, it makes no difference how the infection was acquired. The therapy is also recommended in infected newborns, immunocompromised patients and also in case of atypical presentations[9]. Eye lesions can develop years after birth, whether children have been treated antenatally or not, but the frequency of recurrence of episodes or the severity of the lesions may differ. In up to 80% of infants infected with *T. gondii* who do not receive treatment, ocular lesions will develop by the time they reach childhood or early adolescence[10]. Currently, The World Health Organization and the Centers for Disease Control and Prevention recommend pyrimethamine, sulfadiazine, and folic acid as the standard of care for persons with congenital toxoplasmosis[11]. These medications were proven to be effective in a randomized prospective study called the National Collaborative Chicago Based Congenital Toxoplasmosis Study. This study found that treatment with the three aforementioned medications significantly decreased adverse signs and symptoms associated with congenital toxoplasmosis, including ocular and central nervous system symptoms and sensorineural hearing loss[12]. This combination of medications also is recommended by the American Academy of Pediatrics.

### 3.1. Pyrimethamine and sulfadiazine

For more than 60 years, the standard therapy for toxoplasmosis has been “triple therapy” with sulfadiazine, pyrimethamine, and prednisone, considered the most effective therapy against *T. gondii* by experimental and *in vitro* studies[13–15]. Pyrimethamine (infants: 1 mg/kg once daily for 1 year; children: loading dose: 2 mg/kg per day divided into 2 daily doses for 1–3 d, maximum 100 mg/d) and sulfadiazine (children >2 months: loading dose: 75 mg/kg; treatment dose: 120–150 mg/kg per day; divided every 4–6 h, maximum dose: 6 g/d) act at different steps in the synthesis of tetrahydrofolate (pyrimethamine inhibits dihydrofolate reductase, and sulfadiazine is a competitive antagonist of p-aminobenzoic acid), and thereby impact nucleic acid synthesis by *T. gondii* with a combined effect[16]. Pyrimethamine may cause gastrointestinal, dermatological and haematological side effects (neutropenia more frequently, but also leukopenia and thrombocytopenia), so weekly monitoring of blood cells is recommended throughout the course of treatment. In addition, patients are prescribed folic acid (5 mg every 3 d). Sulfadiazine, as well as other sulfonamides, carries a risk of multiple hypersensitivity reactions, most commonly skin rashes. At this time, debate exists about the appropriate length of therapy. Although some studies argue that in some patients 3 months of therapy may be sufficient to eradicate the parasite and prevent longterm effects[7], the National Collaborative Chicago Based Congenital Toxoplasmosis Study and the American Academy of Pediatrics recommend treatment of pyrimethamine, sulfadiazine, and folic acid often up to 1 year[12,18]. However, most treatment recommendations suggest that decisions about the length of the therapy should be based on patient response, the severity of symptoms and the age of the patient at the time of diagnosis.

### 3.2. Trimethoprim and sulfamethoxazole

An alternative to classic treatment, trimethoprim–sulfamethoxazole (TMP) can be an option due to its low cost, wide availability and tolerability. This drug combination (TMP pediatric dose: 6–12 mg/kg per day in divided doses every 12 h) has a similar mode of action to pyrimethamine and sulfadiazine on tetrahydrofolate synthesis. The prospective trial published by Soheilian et al. in 2005, showed that inflammation resolved in all patients treated with TMP, and reduction in the size of the lesion was similar to the group treated with the classic therapy, without significant differences in post–treatment visual acuity. Trimethoprim and sulfamethoxazole may also have a role in the prevention of recurrent attacks of ocular toxoplasmosis[19]. Silveira et al. found that TMP taken orally every 3 d for 20 months, significantly reduced the risk of recurrent toxoplasomic retinochoroiditis from 23.8% in untreated control subjects to
As well as for sulfadiazine, also trimethoprim and sulfamethoxazole carry a higher than normal risk of inducing Steven–Johnson syndrome and toxic epidermal necrolysis, but the absolute risk of developing either is extremely low.

### 3.3. Clindamycin

Clindamycin is a lincosamide antibiotic that interferes with translation of the apicoplast, an unusual plastid-like organelle in *T. gondii*. For patients with sensitivity to sulfadiazine, clindamycin (pediatric dose: 8–25 mg/kg per day in 3–4 divided doses) can be used in combination with pyrimethamine as an alternative. This drug is often added to triple therapy, which is then referred to as “quadruple therapy”: in a retrospective study it is reported 81% of eyes responded within 3 weeks of starting quadruple therapy[21]. On the other hand, the comparative study by Rothova et al. showed less reduction in lesion size in patients treated with clindamycin, sulfadiazine and corticosteroid when compared to patients who took classic therapy[22]. Clostridium difficile colitis is a recognized potential complication of oral clindamycin, and diarrhoea required cessation of drug. In a prospective randomized single-blind clinical trial, the efficacy of intravitreal clindamycin plus dexamethasone was compared to conventional oral therapy with pyrimethamine, sulfadiazine, folinic acid and prednisone in active toxoplasmic retinochoroiditis: both therapies were shown to be equally effective against active toxoplasmic retinochoroiditis, although the former is apparently safer and particularly suitable for in patients with recurrent infection or in whom systemic drug toxicities are a concern, but to date studies of intravitreal clindamycin therapy in pediatric populations are lacking[23]. On the other hand, the local approach is not recommended in immunocompromised patient[24].

### 3.4. Atovaquone and azithromycin

Although some reports describe convincing activity of these drugs against encysted parasites these agents do not appear to prevent recurrent toxoplasmic retinochoroiditis in the human host. In 1999, the study of Pearson et al reported improvement of active retinitis within 1 to 3 weeks, considering visual acuity the main outcome measure[25]. A retrospective study of 41 adult patients treated with atovaquone for toxoplasmic retinochoroiditis documented reactivation in 44% of patients, during an average follow-up of 39 months[26].

### 3.5. Pyrimethamine and azithromycin

The efficacy of the multidrug regimen with pyrimethamine (infants dose: 1 mg/kg once daily for 1 year; dose for children: loading dose 2 mg/kg per day divided into 2 daily doses for 1–3 d, maximum: 100 mg/d, treatment dose 1 mg/kg per day divided into 2 doses for 4 weeks, maximum 25 mg/d) and azithromycin (children ≥6 months 10 mg/kg on first day, maximum 500 mg/d, followed by 5 mg/kg per day once daily, maximum 250 mg/d) is demonstrated to be similar to the standard treatment with pyrimethamine and sulfadiazine. However, the frequency and severity of adverse effects is significantly lower with a regimen containing pyrimethamine and azithromycin. The therapy appears to be an acceptable alternative for treatment of sightthreatening ocular toxoplasmosis[27]. In a recent study, the therapy with only azithromycin, compared to sulfadiazine and pyrimethamine combination of therapy, was shown to be effective and well-tolerated for the treatment of active, non–vision–threatening toxoplasmic retinochoroiditis[28].

### 3.6. Corticosteroids

In healthy adult, the host immune response contributes substantially to the intraocular inflammation that follows tachyzoite replication within the retina. For this reason, systemic corticosteroids are routinely added to the anti-microbial cocktail in immunocompetent adults with toxoplasmic retinochoroiditis. A recent systematic review did not identify evidence from randomized controlled trials for the role of corticosteroids in the management of ocular toxoplasmosis. Several questions remain unanswered by well-conducted randomized trials in this context, including whether use of corticosteroids is more effective than use of anti-parasitic therapy alone, when corticosteroids should be initiated in the treatment regimen (early versus late course of treatment), and which dosage and duration of steroid use is best[29].

However, up to date, there is little in the literature to support or refuse the use of steroids in the treatment of toxoplasmosis, with the exception of the only therapy with systemic steroids without antiparasitic treatment, that has been shown to negatively affect outcomes of toxoplasma retinochoroiditis and should not be undertaken.

As discussed above, dexamethasone has been successfully combined with clindamycin as intravitreal therapy. The effective use of intravitreal use of triamcinolone acetoniode, is reported, but very poor outcome due to uncontrolled infection is also described. On the other hand, topical corticosteroid is widely prescribed for anterior uveitis in ocular toxoplasmosis. However, prospective head to head studies of antibiotics with and without steroids are required. The role of corticosteroids will become clearer with a better understanding of the phenotype of the infecting parasite and...
the ocular inflammatory response it induces.

3.7. Prevention

Prenatal screening is still effective to select women for prenatal therapy aiming to decrease vertical transmission and to identify foetuses/newborns with congenital disease that could benefit from pre and/or post-natal antiparasitic therapy[30]. Prevention messages include hygienic measures related to cats, cooking meat well, washing vegetables, and hand washing. Drinking water is recently emerged as a new risk factor in some countries including Brazil, India and Canada, depending on the source of the water supply network (surface or ground water) and on the sanitary level or the use of well water[31]. Serologic screening in pregnancy is based on the early detection of infection in the mother to allow early treatment in order to reduce vertical transmission and foetal sequelae. Such screening is performed in some countries (e.g. in France it is based on initial serology during the first trimester of pregnancy followed by monthly testing in seronegative women). Other countries (Austria, Belgium, Italy, Lithuania, and Slovenia) have also serologic screening but the frequency of follow-up serologic testing varies from one to three monthly. In other countries (United Kingdom, Norway, and Finland), the screening is not recommended[32,33].

Despite many advances in the management of ocular toxoplasmosis, important clinical questions remain, especially with regard to treatment. Moreover, the search for a safe drug with effective cysticidal activity in humans, which theoretically would eliminate disease recurrences, has not been fruitful to date. Additional prospective clinical trials, which randomize patients to various treatment strategies, including no intervention, are indicated.

Conflict of interest statement

The authors declare no conflict of interest.

Comments

Background

Infection with the protozoan T. gondii is one of the most frequent parasitic infections worldwide and a common infection of the retina in the general population. Approximately 25%–30% of the world human population is infected by Toxoplasma.

Research frontiers

A case was reported that a chorioretinitis in an immunocompetent 8-year-old boy as a consequence of a underdiagnosed neonatal toxoplasmosis and he was successfully managed with pyrimethamine and sulfadiazine.

Related reports

Retinchoroiditis is the most frequently described ocular manifestation of congenital toxoplasmosis. Despite the poorness of comparative studies between different modalities and the lack of a randomized controlled trial, it is generally well agreed on that macular lesions, lesions involving the optic nerve, and cases with intense inflammation should be treated.

Innovations & breakthroughs

Neonatal toxoplasmosis identified with chorioretinitis in an immunocompetent little boy, and he was successfully treated with pyrimethamine and sulfadiazine.

Applications

The importance of considering T. gondii as a possible cause of chorioretinitis in children should be empathized in developed/developing countries.

Peer review

This case depicts the ocular toxoplasmosis in an immunocompetent 8-year-old child and the highlights the importance of considering T. gondii as a possible cause of chorioretinitis in children living in developed/developing countries.

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