Chapter 7

Risk Factors, Pathogenesis and Diagnosis of Ocular Toxoplasmosis

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1. Introduction

Ocular toxoplasmosis (OT) is a major cause of posterior uveitis worldwide but its incidence and prevalence are difficult to establish precisely. In 1993, a survey in a French Hospital Service of Ophthalmology showed that OT was seen in less than 1 per thousand outpatients [1]. In a study performed in Germany, toxoplasmosis accounted for 4.2 % of all cases of uveitis at a referral centre [2]. Around 5000 people develop symptomatic OT each year in the United States [3]. OT is a complication of both acute acquired and reactivated congenital in immunocompetent but particularly in immunocompromissed individuals and its severity can be influenced by variation in parasite isolates, parasitic load, route of infection and host-related factors such as immune function, age and pregnancy. Diagnosis is usually based on ophthalmological examination and is confirmed by the response to specific treatment, but also by biological assays including local antibody production, PCR and western blot. All these points will be detailed below.

2. A complication of acquired and congenital infections

Classically, retinochoroiditis secondary to acquired toxoplasmosis was considered an exceptional event in immunocompetent individuals, and was usually defined as a periodic reactivation of latent cysts associated with undiagnosed congenital infections. But recent data, based on ophthalmological examination, seem to establish that acquired infection might be responsible for most cases. This fact was particularly demonstrated by outbreaks reported in Canada, Brazil and India. In Canada, amongst 100 individuals infected during a water-borne outbreak, 19 had OT [4]. In southern Brazil 17.7% of 1,042 individuals examined had OT with lesions in 0.9% of 1- to 8-year-olds and in 21.3% of all individuals older than 13, suggesting that in this population, the disease was a sequel of postnatal rather

than congenital infection [5]. In India, Balasundaram et al. [6] described ocular involvement due to toxoplasmosis in 248 patients who had active retinochoroiditis and toxoplasmic serology suggesting recently acquired disease. Delair et al. [7] analysed 425 cases of OT, 100 (23.5%) were acquired, 62 (14.6%) were congenital, and 263 (61.9%) were of unknown origin. At the time of the study, the mean age of the patients with congenital OT was 9.1 +/- 8.8 years, and 21.7 +/- 12.6 years in the patients with the acquired disease ($p < 0.001$). Bilateral OT was only found in 4% of acquired cases and in 43.5% of congenital cases ($p < 0.001$) and in acquired infections, visual acuity was significantly less impaired than in congenital infections. In the United Kingdom, 50% of OT in children was acquired after birth and no clear clinical distinction could be made between acquired and congenital toxoplasmosis (CT) [8]. However, other authors have identified clinical presentations specific to each group. Montoya et al. (1996) observed that patients with post-natal acquired toxoplasmic retinochoroiditis had mostly unilateral lesions without old scars or involvement of the macula [9]. In case of congenital origin, the risk of ocular disease depends on the trimester of pregnancy when infection occurred, and on whether or not treatment was administered to the mother during pregnancy. In one study, a period exceeding 8 weeks between maternal infection and the beginning of treatment, female gender, and especially cerebral calcifications were risk factors for retinochoroiditis [10]. No significant association was found in other cohort studies between gestational age at maternal infection, prenatal treatment and the risk of developing OT [11, 12].

3. Occurrence depends on host genetic background and immune status

In mice, the severity of ocular damage is linked to many factors related to either host immunity or the parasite, such as inoculum size, infective stage (oocysts versus cysts), route of infection and the genotype of the infecting strain. However, these data are not well documented in humans. The acquired immune deficiency syndrome (AIDS) epidemic has dramatically reminded that effective host immunity was essential to limit the severity of ocular lesions. AIDS patients without highly active antiretroviral therapy can develop extensive and recurring lesions [13]. Similar lesions may also be encountered during the use of immunosuppressive drugs [9, 14]. Many studies have focused on elderly patients [15-17]. These patients can have large and multiple ocular lesions with severe vitritis and prolonged disease, in some instances similar to lesions encountered in immunocompromised individuals, although they are otherwise healthy. Indeed, both cellular and humoral immune responses are modified with advancing age and probably contribute to the higher severity of OT in older patients [16]. A cross-sectional household study involving 499 individuals was undertaken in Minas Gerais state of Brazil, where infection with *T. gondii* is endemic. The frequency of OT increased significantly with age as approximately 50% of individuals above 60 years of age had lesions and older patients had a higher risk of OT following recently acquired infection compared to younger patients [18]. The factors responsible for recurrences are unknown, but trauma, hormonal changes and cellular or humoral immunosuppression appear to contribute to the release of parasites from tissue cysts. Bosch-Driessen et al. reported an increased incidence of recurrences after cataract surgery and during pregnancy [19]. The hormonal and immunological changes in pregnant

women can cause recurrences and these authors described four women having such recurrences in every pregnancy [19]. Garweg et al. [20] reported that recurrence occurred in approximately in 4 out of 5 patients and that the risk was higher two years after the first episode. Holland et al. [21] confirmed that the risk of recurrence was the highest immediately after an episode of active disease and that recurrence had a tendency to occur in clusters. Mice with different genetic backgrounds will have different susceptibilities to the parasite [22]. In humans, an increased frequency of the HLA-Bw62 antigen was observed in patients with severe OT [23]. In mother-child pairs from Europe and North America, ocular disease in CT was associated with polymorphisms in ABCA4 encoding the ATP-binding cassette transporter and in COL2A1 encoding type II collagen [24]. Evidence will be shown below that polymorphism in cytokine genes is also an important factor triggering OT occurrence.

4. Specific parasitic genotypes could be involved

Currently, it is assumed that the population of *T. gondii* consists of 3 3 predominant clonal lineages, which differ at the DNA sequence level by 1% or less [25] but microsatellite analysis has shown the high diversity of that genus [26]. In Europe and the United States, type II is the most common cause of systemic *Toxoplasma* infection [27]. As early as 2001 Grigg et al. [28] suggested a possible correlation between severe retinal disease and atypical genotypes in immunocompetent patients as, in acquired OT, an unusual abundance of type I, or recombinant genotypes I/III were found. In Brazil, genetic studies have shown that genotypes of *T. gondii* involved in acquired OT were atypical, belonging to genotypes different from genotype II [29]. The differences in the frequency, size and multiplicity of retinochoroidal lesions may be explained by more virulent parasite genotypes that predominate in Brazil, but are rarely found in Europe. Khan et al. [30] compared 25 clinical and animal isolates of *T. gondii* from Brazil to previously characterised clonal lineages from North America and Europe. Genotypes of *T. gondii* strains isolated from Brazil were highly divergent when compared (by multilocus nested PCR analysis combined with sequencing of a polymorphic intron) to the previously described clonal lineages found in Europe. These atypical genotypes may also explain the high frequency (20% of 97 cases) of ocular involvement in the above mentioned Canadian outbreak where an atypical cougar isolate was suspected, and the 100-fold higher incidence of OT in patients born in Africa compared to patients born in Britain [31,32]. The distribution of genotypes was different in immunocompromised patients who reactivate a type II strain (if acquired in Europe), or a non–type II strain (if acquired in Africa or South America). However, direct genotyping of strains from aqueous or vitreous fluids of 20 French patients showed a predominance of the type II genotype in OT [33] so the possible link of OT with some specific genotypes is not yet clear.

5. Immune privileged status and cytokine responses are key factors in toxoplasmic retinochoroiditis

The pathogenesis of OT is directly linked to the anatomical characteristics of the eye resulting in an immune privileged status. The presence of the hemato-retinal barrier and the

absence of lymphatic vessels limits the passage of inflammatory cells and lymphocytes and of antibodies and complement components [34]. In addition, the ocular characteristics of the distribution and the functions of antigen presenting cells are also of importance. For example, corneal epithelium is deprived of Langerhans cells and the dendritic cells of the ciliary epithelium are not activated by GM-CSF and do not stimulate T lymphocytes [35, 36]. There is a low expression of classical MHC class IA molecules which reduce the lytic activity of CD8+ lymphocytes usually stimulated by the MHC I molecules. MHC II molecules are not expressed in the eye, which limits CD4+ lymphocyte activation. Increased expression of surface molecules like CD46, CD55 and CD59 will also inhibit complement activation [37]. A local production of immunosuppressive cytokines, such as TGF-β, limits B and Th1 lymphocyte activation but activates Th2 lymphocytes [34, 38, 39]. Finally, retinal cells express surface molecules involved in apoptosis such as TNF- Related Apoptosis Inducing Ligand (TRAIL) and Fas ligand (FasL). FasL interacts with FasR (Fas receptor) carried by the inflammatory cells, inducing their apoptosis. This would control the entry of Fas-expressing lymphoid cells and limit the alteration of ocular cells by these cells [40, 41]. Whereas the mechanisms that underlie retinal damage in OT are yet not fully understood, the immune response might directly affect the pathogenesis of toxoplasmic retinochoroiditis and some cytokines have been shown to be fundamental to either control or block a protective response against *T. gondii* in experimental models. As early as 1998, Gazzinelli & Denkers [42] stated that initiating a strong T-cell-mediated immunity was crucial in the immune defense against *T. gondii*. High levels of gamma interferon (IFNγ) were induced by the parasite during initial infection as a result of early T-cell as well as natural killer (NK) cell activation. Induction of interleukin-12 by macrophages is a major mechanism driving early IFNγ synthesis. They also stated that "while part of the clinical manifestations of toxoplasmosis results from direct tissue destruction by the parasite, inflammatory cytokine-mediated immunopathologic changes may also contribute to disease progression". In animal experiments, many authors have described that IFNγ and TNFα, which enhance macrophage activation and induce production of other cytokines such as IL-12, give rise to a type Th1 immune response that plays a crucial role in parasite control [43]. These two cytokines could play a major role in immunological responses that control parasite proliferation by induction of indoleamine 2,3-dioxygenase production in retinal pigment epithelial cells [44]. Moreover, Gazzinelli et al. [45] observed that compared to control animals, mice treated with IFNγ or TNFα antagonists or antibodies against T cells (CD4 and CD8), showed more severe lesions characterized by exacerbated ocular damage and increased parasite detection in the eye. Conversely, a shift to a Th2 immune response with production of anti-inflammatory cytokines including IL-10, TGF-β and IL-4 promoted parasite survival, and was required to maintain immune privilege in the eye and prevent immune tissue destruction [46]. IFNγ and TNFα are also inhibitors of parasite replication in retinal pigment epithelial cells [47]. In humans, the participation of inflammatory mediators in physiopathology of OT is not yet clear. Nevertheless, a study by Yamamoto et al. [48] showed that asymptomatic patients secreted significantly more IL-12 and IFNγ in response to *T. gondii* antigens than patients with ocular damage. Conversely, acquired OT was associated with high levels of IL-1 and TNFα. They also observed that in comparison with

non-infected subjects, IL-2 and IFNγ production by peripheral blood mononuclear cells in response to *T. gondii* was decreased in subjects with congenital infection, suggesting a status of parasite tolerance. Ongkosuwito et al. [49] measured the levels of six chemokines directly in aqueous humor samples from patients presenting with viral or toxoplasmic uveitis. Interestingly, IL-6 titers in patients with OT correlated with the degree of activity of toxoplasmic chorioretinitis. This cytokine is now described as essential in Th17 differentiation and Th17 cells are involved in inflammatory and autoimmune uveitis, supporting the hypothesis that the host immune response takes part in ocular damage [50]. The expansion of IL-17 producing cells in human OT has been demonstrated by Lahmar et al [51] who monitored cytokine patterns in serum and aqueous humor of subjects suffering from OT, infectious or non-infectious uveitis and cataract. High levels of IL-17 were reported in aqueous humor samples from 70 % patients presenting OT. Similar findings were also reported in patients suffering from other ocular inflammatory diseases showing that inflammatory processes could play a major role in the establishment of ocular damage in the chronic stage of OT. Due to large inter-individual variations of cytokine levels within each group of patients, no correlation was found between cytokine titers and clinical presentation. In addition, increased levels of pro-inflammatory mediators MCP-1, IL-8 and IL-6 were found in intraocular fluid samples from OT, but these variations were not specific for toxoplasmic uveitis [51]. IL-12 enhances TNF production and synthesis was higher in OT than in other ocular diseases in accordance with the importance of the Th1 response in mouse models. The Th2 cytokines (Il-4, IL-5, IL-10), which counterbalance inflammatory processes, were up-regulated and consequently the authors were unable to define the respective roles of Th1 and Th2 responses in the pathogenesis of human OT. As observed in experimental autoimmune uveitis, it is now proposed that eye damage may be induced by pathogenic responses mediated by Th-17 cells producing TNFα [52]. Conversely, host hypersensitivity pathways in the eye might be counterbalanced by IL-27 secretion up-regulated by IFNγ from Th1 cells [52]. A possible association between polymorphisms in cytokine genes and OT was searched for in patients. Specific IL1, IL10 and IFNγ alleles were preferentially found in patients with OT. No such association was found with TNFα gene polymorphisms [53-56]. A putative summary of the role of the different cytokines and T cells in defense against the parasite but also in the occurrence of tissue lesions is summarized in figure 1.

6. Diagnosis is based on clinical signs and some selected biological assays

The diagnosis is usually based on ophthalmological examination showing unilateral, whitish, fuzzy-edged, round, focal lesions surrounded by retinal edema (figure 2). Cells are found in the vitreous, particularly overlying the active lesion. In the area surrounding the active retinitis, one may see hemorrhage, as well as sheathing of the retinal blood vessels. Fluorescein angiography of the active lesion demonstrates early blockage with subsequent leakage of the lesion. Cells in the anterior chamber may also be noted and may appear to be either a granulomatous or non granulomatous uveitis. The discovery of healed pigmented

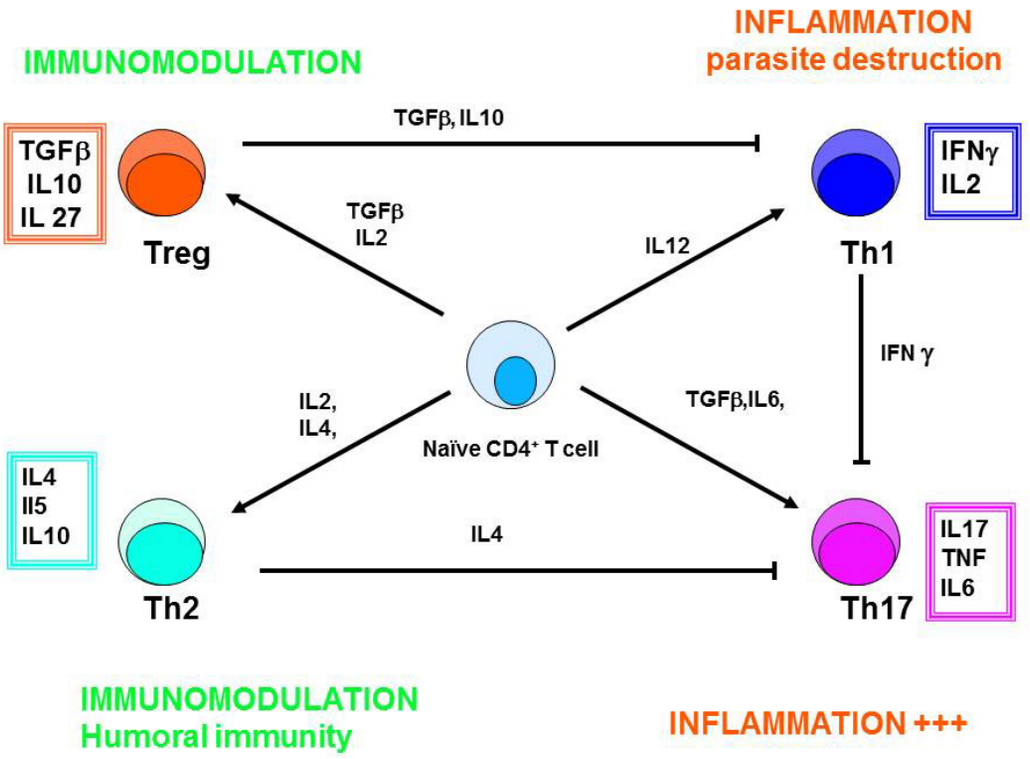

Figure 1. T cells and cytokines involved in ocular toxoplasmosis and parasite destruction

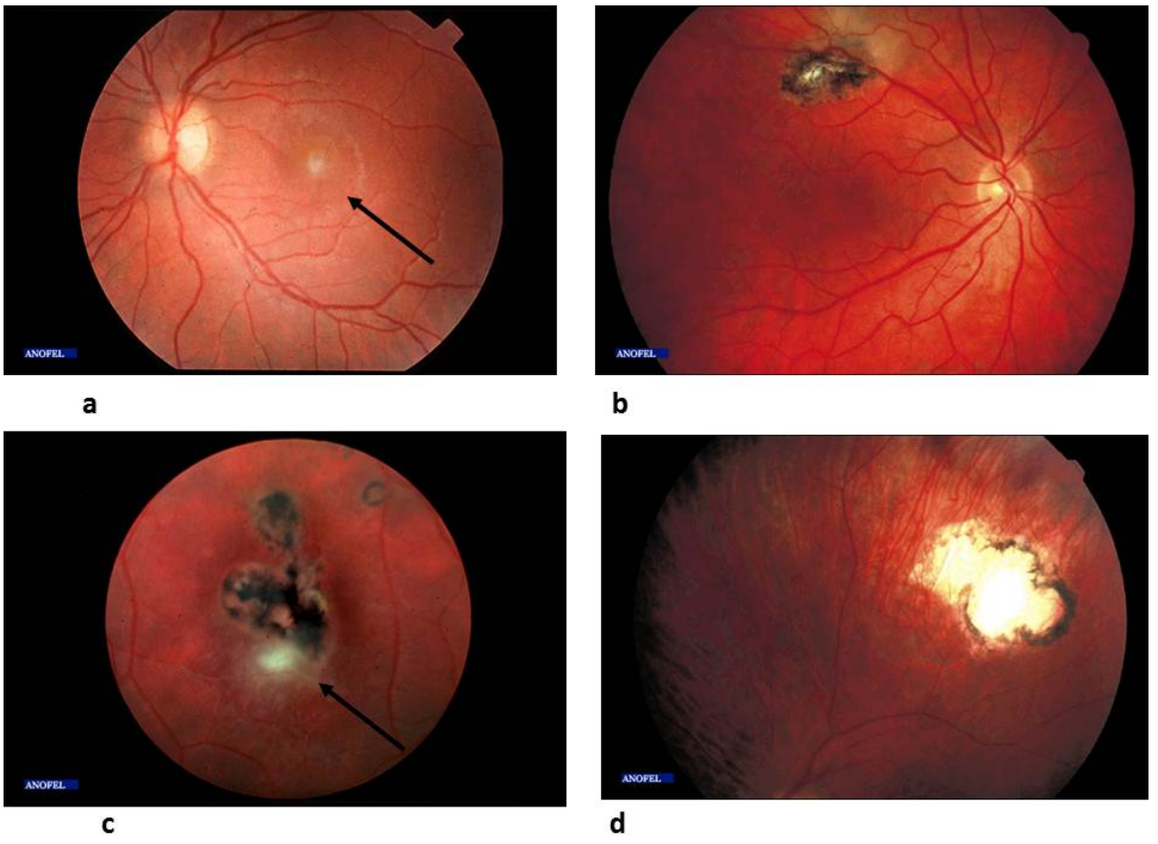

Figure 2. Eye fundus aspects of ocular toxoplasmosis. a: active lesion; b, d: scar; c: active lesion and scars (source A.P. Brézin and Anofel)

retinochoroidal scars facilitates the diagnosis [57, 58]. OT is also confirmed by a favorable clinical response to specific therapy. However, diagnosis and treatment can be delayed in patients with atypical lesions (unusual and complicated forms) or patients showing an inadequate response to antimicrobial therapy as particularly observed in elderly or immunocompromised patients [13, 17]. In such cases, rapid identification of the causative agent requires aqueous humor sampling by anterior chamber paracentesis [59]. Laboratory diagnosis is based on the comparison of antibody profiles in ocular fluid and serum samples in order to detect intraocular specific antibody synthesis, based on the Goldmann-Witmer coefficient (GWC) or on the observation of qualitative differences between eye fluid and serum by immunoblotting (IB) [60]. The GWC is based on the comparison of the levels of specific antibodies to total immunoglobulin in both aqueous humor and serum. Recent studies have shown the usefulness of PCR applied to aqueous humor, in combination with serologic tests, for the diagnosis of OT [61-68]. However, although this combined approach improves diagnostic sensitivity, the volume of the ocular fluid sample may not be adequate for PCR, IB, and GWC. We showed [68] that a combination of all three methods had a 85% sensitivity and a 93% specificity for the diagnosis of atypical or extensive toxoplasmic retinochoroiditis. The sensitivity of GWC alone for atypical uveitis (based mainly on aqueous humor samples) ranges from 39% to 93% [60, 63, 65, 67, 69-71]. Discrepancies could be explained by differences in (i) the interval between symptom onset and paracentesis, (ii) the characteristics of the uveitis (typical or atypical), (iii) underlying immunological status, and (iv), the chosen GWC positivity threshold, which ranges from 2 to 8 in the literature. The specificity of the GWC is usually high if the retinal barrier has not been impaired. IB on aqueous humor has sensitivities ranging from 50 to 81% for the diagnosis of atypical [60, 65] and typical [66, 68, 69] OT. Apparently the sensitivity of IB increases with the length of the interval between onset of symptoms and paracentesis. The sensitivity of real-time PCR ranges from 36 % to 55% [63, 67, 68]. The sensitivity was higher with a real-time PCR assay targeting the *T. gondii* repeat element of 529 base pairs [68] than with real-time PCR targeting the B1 gene (40% and 36% respectively). Real-time PCR has been shown to be more sensitive on a variety of samples when the 529-bp repeat element rather than the B1 gene was used as a target [71]. In contrast to the IB and GWC results, the results of PCR are not influenced by the interval between symptom onset and paracentesis. The total size of acute retinal foci is larger in PCR-positive patients [64, 67, 68]. PCR seems more informative than the GWC and IB for immunocompromised patients [62, 64]. The rate of detection of specific intraocular antibodies seems related to the interval between symptom onset and paracentesis. Early sampling is often associated with negative GWC results and with low IB sensitivity. The sensitivity of the GWC increases when sampling is performed at least 10 days after symptom onset, and IB was positive for 72% of cases 30 days after symptom onset [68]. Several studies have examined the influence of this interval on GWC results. Fardeau et al. [64] reported that the GWC was useless during the first 2 weeks but that its sensitivity increased sharply when anterior chamber puncture was performed between the 3rd and 8th week after symptom onset. Garweg et al. [69] showed that GWC sensitivity increased from 57% to 70% when puncture was performed at 6 weeks instead of 3 weeks. As stated above, PCR sensitivity was not influenced by this interval. Combining the three biological

techniques increases the sensitivity and the specificity but sometimes the volume size of the sample is so small that it is not possible to perform all three. On the basis of the presented results, we propose an algorithm for choosing the test with the best sensitivity according to ophthalmologic findings and delay after onset of the disease (figure 3). When paracentesis is performed during the 10 days following symptom onset, real-time PCR is most suitable, especially if the patient is immunocompromised or if the total size of the foci is large (> 2 optic disc diameters). Beyond 10 days, the best choice is the GWC if old scars are present and/or if the reaction in the anterior chamber is mild to severe, or PCR if the total size of foci is large (>2 optic disc diameters); IB should be preferred when paracentesis is performed more than 30 days after symptom onset.

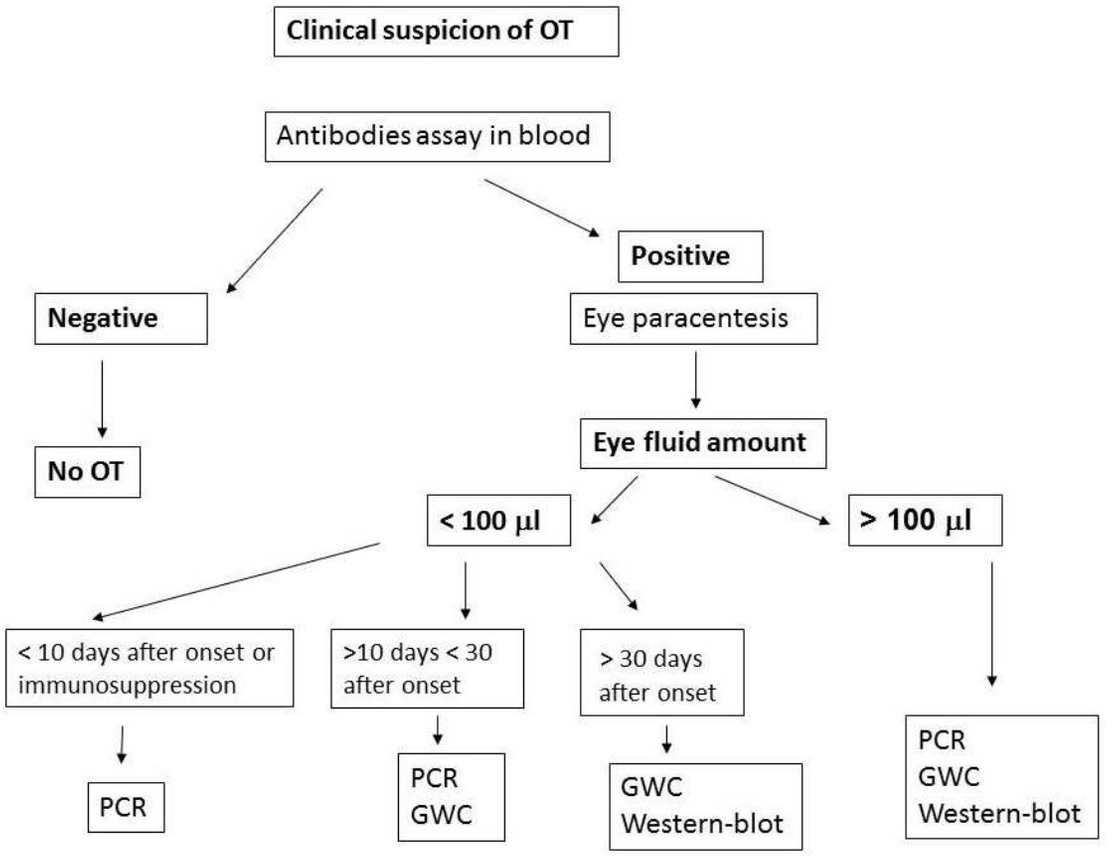

Figure 3. Algorithm for the biological diagnosis of ocular toxoplasmosis (in severely immunosuppressed patients a negative serology does not exclude OT which can be then confirmed by PCR)

7. Efficient treatments are available but there is no real mean of prevention

There is no real consensus on the treatment of retinochoroiditis [72-75]. Some experts will treat only patients in which the lesions are near the macula or the optic nerve and when there is an important hyalitis with an impairment of the optical acuity. The non-treated patient will be regularly checked. Other experts will treat all the lesions whatever their

localizations and this is now possible because the recommended association pyrimethamine/azythromycine is better tolerated and has a better compliance than pyrimethamine associated to sulfadiazine [76, 77]. Corticosteroids (prednisone at 0.5 to 1mg/kg/d) are constantly administered for several weeks, except for immunocompromised patients [73, 78]. Pyrimethamine in adults is used at 100mg/d for several days then decreased at 50mg/d. It should be associated with sulfadiazine at 75mg/kg/d divided in 4 doses or better with azythromycine 250 mg/d. The total length of the treatment will be of 3 to 6 weeks, sometimes more, depending on the initial size of the lesion. In patients intolerant to treatment, clindamycine at 450-600 mg/d should be associated [79]. The treatment of congenital retinochoroiditis in newborns is based on sulfadiazine (50mg/kg/d in 2 doses) associated with pyrimethamine at 1mg/kg/d for 6 to 12 months. Fifteen mg folinic acid is given every 3 days. The prophylaxis of congenitally acquired OT is based on national programs of prevention of CT (e.g. France, Austria) but their efficiency is discussed [80-82] and depends on the local epidemiology and virulence of strains [83]. Peyron et al. [84] stated that "treating CT has little effect on the quality of life and visual function of the affected individuals". However, Kieffer et al. [10] showed that a period exceeding 8 weeks between maternal infection and the beginning of treatment was a risk factor for retinochoroiditis; therefore emphasizing the need to prevent and treat CT. Evidence for the effectiveness of prenatal or postnatal treatment for CT is still needed. Randomised controlled trials and cohort studies are in progress to provide information on prognosis, especially disability [85]. There is no radical prevention of acquired toxoplasmosis besides hygienic rules in preparing meals. Eating well done or deeply frozen meat should be particularly recommended in regions where highly pathogenic isolates are prevalent. In HIV patients, drug prevention of toxoplasmosis has been successfully used for years and is now less needed since the use of efficient HAART.

8. Conclusions

Acquired or CT can be complicated by OT. The diagnosis relies on clinical aspects, responses to specific treatment and results of biological assays. The incidence and the prevalence of this complication are both difficult to establish precisely and depend on the parasite prevalence in the general population, and are affected by different factors such as type of exposure to the parasite, genetic background of the different parasites and the host, and the type of immune response elicited by the parasite. Prevention of CT (though still discussed), and a rapid specific treatment of acquired cases could be the key measures to avoid severe visual impairment but evaluation of these procedures is urgently needed.

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