Treating ocular toxoplasmosis - current evidence

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The current treatment of ocular toxoplasmosis is controversial. The mainstay of treatment has been pyrimethamine and sulphonamides with or without systemic corticosteroids, but the actual evidence that antibiotics have a beneficial effect in recurrent toxoplasmic retinochoroiditis is unsupported by randomised placebo controlled trials. Thus far there have only been three studies looking at the efficacy of antibiotic treatment, all of which were methodologically weak and two of which were perfomed more than 30 years ago. All studies reported adverse effects from treatment. There is an urgent need for further randomised, double blind, placebo controlled studies for lesions in all parts of the retina and to test the efficacy of adjunctive corticosteroid treatment.

Key words: ocular toxoplasmosis - treatment - current evidence

Historical introduction

Toxoplasmosis affecting the eye was first described in 1938 in a postmortem study of an infant with severe encephalomyelitis and bilateral retinochoroiditis (Wolf et al. 1939). Subsequent reports of congenital toxoplasmosis confirmed its association with retinochoroiditis. Thereafter it was recognised that infants could be born with asymptomatic disease and only identified by the presence of a later flare up. It was suspected that many cases of chorioretinitis in older children and adults might also be a result of acquired toxoplasmosis, but this was not confirmed until the introduction of the toxoplasmin skin test (1947) and subsequently the methylene blue dye test (1948). The pendulum subsequently swung back to the belief that almost all toxoplasma disease in the eye was a result of congenitally acquired infection, a dogma that has recently been strongly challenged (Gilbert & Stanford 2000).

Early studies of the treatment of ocular toxoplasmosis were disappointing despite evidence that, in experimental models, infections were responsive to a combination of sulfadiazine and pyrimethamine (Eyles & Coleman 1955). Contemporaneous work suggested that there was an effect in human ocular toxoplasmosis (Ryan et al. 1954) and apparently confirmed by Perkins in an early placebo controlled randomised study (Perkins et al. 1956). However, it is difficult to assess whether the patients treated in these studies actually had ocular toxoplasmosis as a number were classified by the presence of uveitis and a positive dye test result, but not by the presence of active retinochoroiditis. Although this treatment was subsequently largely embraced by the ophthalmological community, Hogan (1958) surmised that "the outcome of these therapeutic studies often was disappointing".

The situation remained largely unchanged through the 1960s and 1970s. Clindamycin was enthusiastically embraced as part of treatment regimes in the 1980s (Tabbara & O'Connor 1980) since it appeared that the drug was concentrated in ocular tissue and might penetrate tissue cyst walls (Tabbara & O'Connor 1975). In experimental models, the drug reduced the number of tissue cysts (McMaster et al. 1973) but subsequent clinical experience showed no effect on disease recurrence (Lakhanpal et al. 1983). In the 1990s, azithromycin (Rothova et al. 1998) and atovaquone (Pearson et al. 1999) were both introduced but have not gained widespread acceptance. Also there appears to be an increasing popularity of the trimethoprim/sulphamethoxazole combination, offering as it does the combination of a dihydrofolate reductase inhibitor and a sulphonamide. Small scale uncontrolled studies apparently showed accelerated rates of resolution and improved acuities in patients on the combination (Opremcak et al. 1992) and, more recently, it has been given as long term prophylaxis to prevent recurrences in high risk patients (Silveira et al. 2002). There is however considerable uncertainty in the field as to which is the best combination of drugs to use reflected by the fact that a survey of members of the American Uveitis Society found that they used a total of nine separate drugs in a possible 24 different regimes (Holland & Lewis 2002). Such uncertainty is reinforced by the paucity of placebo-controlled studies, with the few that there are all suffering from methodological problems (Stanford et al. 2003).

Available agents

The ideal drug for the treatment of ocular toxoplasmosis should be parasitocidal, should concentrate in the eye, should be able to penetrate cyst walls and be effective against both bradyzoites and tachyzoites, and should have no adverse effects. Unfortunately, none of the available anti-toxoplasma agents fulfil these requirements. In particular, all have side effects and none have yet been shown to reduce the incidence of recurrent disease convincingly. The principles of antibiotic treatment are to reduce the duration and severity of symptoms of

acute intraocular inflammation, the risk of permanent visual impairment (by reducing the size of the eventual retinochoroidal scar) and the risk of recurrent episodes (Holland & Lewis 2002, Stanford et al. 2003). Common indications include lesions within the macular arcades since they may threaten the fovea and thus central vision and lesions close to the optic disc, as the subsequent scars cause full thickness retinal loss and thus loss of nerve fibres subserving distal retina. This leads to large field defects when the inflammation has settled (Stanford et al. 2005, Scherrer et al. 2007). Finally, antibiotic therapy is indicated for retinochoroiditis in the immunosuppressed as, if left untreated, a fulminant progressive retinochoroiditis will result (Holland et al. 1988). Relative indications for treatment include a marked vitreous reaction, disease in an only eye and disease presenting in the elderly as this appears to be more aggressive than in the young. Some physicians will only treat lesions in a sight threatening position, whereas others treat all lesions (Holland & Lewis 2002). Since the goal of therapy is to alter the natural history of the disease, it is worth examining studies where this has been reported. Rothova et al. (1993) carried out a prospective non-randomised study looking at the efficacy of therapy for ocular toxoplasmosis in 149 patients divided into four groups. Group 1 received pyrimethamine, sulfadiazine and corticosteroids; group 2, clindamycin, sulfadiazine and corticosteroids; and group 3, trimethoprim, sulphamethoxazole and corticosteroids. The fourth group (patients with peripheral lesions only) was not treated systemically. Overall the study found that duration of disease related to the size of the initial inflammatory focus regardless of treatment, that pyrimethamine was slightly better at reducing the size of the retinal scar than other agents, but that it also had the highest occurrence of adverse events and that there was no difference in the recurrence rates at three years in any of the groups (Rothova et al. 1993). They found no evidence that their therapy altered the inflammatory activity of the disease, despite the use of systemic corticosteroids, that patients who presented late (from 48 h to more than one week after the onset of symptoms) fared differently to those who presented early and that there was no difference whether the patient were presenting for the first time or with recurrent disease.

The lack of substantial effect in the Dutch study and the uncertainty about the effectiveness of the agents used, coupled with concern about adverse drug reactions prompted a systematic review of antibiotic therapy for ocular toxoplasmosis (Stanford et al. 2003). This found only three randomized controlled studies (a total of 173 participants), all of which were methodologically poor and two of which had been carried out more than 35 years ago. None reported the effect of treatment on the long term visual outcome and no evidence was found for a beneficial effect on either duration of disease and severity of signs. All reported that treatment was associated with adverse effects. One study found weak evidence that long-term prophylaxis might reduce the recurrence rate over 20 months. The first study by Perkins et al. (1956) looked at the response of patients with acute uveitis to Daraprim and also analysed a subgroup with posterior uveitis and a positive dye test. It is not clear whether these patients actually had toxoplasma retinochoroiditis. Perkins et al. (1956) reported that 76% of treated patients had improved intraocular inflammation compared with 50% in the control group: relative risk 1.76 (0.98, 3.19), but based on *post-hoc* analyses of groups, defined by positive serology. In the second study, patients received a combination of pyrimethamine and trisulfaprimidine or lactose capsules. All patients were treated with corticosteroids and 1/10 in each group had long term vision limitation (Acers 1964). In the final study (Silveira et al. 2002), patients were given trimethoprim/sulfamethoxazole every three days and compared with those who received nothing. Eligible patients had to have had two or more recurrent attacks in the previous five years. Recurrences developed in four treated patients against 15 controls at 14 months: relative risk of one or more recurrence by 14 months = 0.27 (95% CI: 0.1-0.71). The authors concluded that such prophylactic treatment might be of benefit in those patients predicted to be at high risk of recurrence. However, the investigators were not blind to the treatment and there was a high rate of loss to follow up in both arms of the study. The results of the systematic review highlighted the urgent need for prospective, randomised, placebo controlled trials in patients with active retinochoroiditis in any part of the retina and for the prevention of chronic recurrent disease. The review has subsequently been updated and no further relevant trials have been found.

The authors of the review also raised the possibility that the drugs themselves might have no effect. Stage conversion from tachyzoite to bradyzoite may occur within days (Dubey et al. 1998) and intact impermeable cysts may form within two weeks (Luder et al. 1999). It is possible that this transition will have occurred by the time patients present with symptoms, since these are usually due to the inflammatory reaction produced by the disease rather than by retinal necrosis *per se*. Therefore, the institution of drug treatment at this stage would be predicted to have little effect as a number of parasites would have converted to bradyzoites or be encysted, both stages being resistant to available agents.

Use of corticosteroids

Corticosteroids have a long history in the treatment of toxoplasma retinochoroiditis and have usually been given to try and limit the inflammatory reaction that accompanies the disease. In the early days they were often given without antibiotic cover, with apparently no problem. However, there are clearly documented cases where the use of corticosteroids on their own led to fulminant toxoplasmic endophthalmitis due to excessive parasite proliferation (O'Connor & Frenkel 1976). 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 (Holland 2004).

Treatment in the immunosuppressed

An absolute indication for treatment of toxoplasma retinochoiditis is its appearance in the immunosuppressed. Active toxoplasmic retinochoroiditis in patients with AIDS will rapidly resolve on treatment (Holland et al. 1988, Cocherau-Massin et al. 1992). Whether long-term maintenance therapy may be discontinued with immune recovery following the use of anti retroviral drugs, as is now the case following cytomegalovirus infections, awaits evidence from clinical trials.

Prophylactic treatment of congenital infection to prevent subsequent retinochoroiditis

The commonest consequence of congenitally acquired infection is the occurrence of retinochoroiditis in the childhood years. The principles of pre-natal treatment are to prevent mother to child transmission or, if fetal infection has occurred, to limit the cell damage caused by the parasite. Current therapies include spiramycin and pyrimethamine and sulphadiazine but, as with post-natally acquired disease, there is doubt as to whether these therapies are effective (Gras et al. 2001, Freeman et al. 2008). Given the low risk of developing retinochoroidal lesions if none are present in early infancy may not justify the prolonged use of postnatal treatment or repeated ocular examinations during childhood.

Surgical options

A number of surgical options are required in the treatment of toxoplasma retinochoroiditis. For some time, particularly in continental Europe, argon laser photocoagulation was applied around old scars (Spalter et al. 1966, Rodriguez 1981). The rationale for this treatment was that quiescent cysts had been observed pathologically in retina adjacent to chorioretinal scars. Furthermore disease recurrence usually occurred at the edge of an old scar perhaps indicating reactivation of these cysts. Since *Toxoplasma* is a heat sensitive organism, it seemed logical to try and destroy the parasite with laser therapy. Unfortunately, the treatment had no effect on the recurrence rate and has now been abandoned. Laser treatment of active disease carries a risk of complications and is rarely advised. Intraocular surgery may be required for the removal of cataract or epiretinal membranes or, occasionally, to clear an opaque vitreous gel.

The next 100 years

Since both the development of a suitable vaccine to prevent infection and of a safe cysticidal drug to eradicate current infections seems unlikely to occur in the near future, the current emphasis in reducing ocular toxoplasmosis is in prevention of the acquisition of disease. In developed countries, improvements in animal husbandry, freezing of meat products before sale and improvements in water supply have all contributed to a progressive reduction in the incidence of disease. Similar effects may be expected in developing countries. In addition a greater understanding of the relationship between the host and the parasite will lead to new drug discovery. Recent genetic studies have classed *Toxoplasma*

gondii strains into one of three clonal lineages: types I, II and III, all of which seem to be able to cause human disease (Howe & Sibley 1995). The type II strains predominate in Europe and in North America, whilst type III and recombinant I/III strains predominate in South America. It is clear that in experimental models the strain type relates to virulence, but this is not proven in man. The demonstration of infection with a more virulent strain might justify more toxic or prolonged treatment (Holland 2004) and further investigation of the genome of the different strains may predict antibiotic sensitivity (Meneceur et al. 2008). Currently prospective placebo controlled trials are needed to answer whether the use of antibiotics in active ocular disease is doing more harm than good and to compare the effect of concomitantly administered corticosteroids. Studies are required that examine the effect of treatment on duration of acute symptoms and signs as well as permanent visual impairment (both central acuity and field of vision). Furthermore, the preliminary studies that indicated that long-term antibiotic prophylaxis might reduce the recurrence rate in susceptible patients need to be repeated in a placebo-controlled manner. These studies should include patients likely to have been infected by different strains of the parasite (e. g., in a North American or European population) and, in South America, include patients presenting de novo rather than those with recurrent disease. Since long-term treatment is likely to be associated with a high risk of adverse effects it should be reserved for patients with a high risk of recurrence. The characteristics most predictive of recurrent disease are yet to be identified by prospective studies although there are preliminary findings that suggest this risk is higher in those who are younger at age of first episode and declines with each 10 year recurrence free period (Holland et al. 2008). If antibiotics are found to be effective then studies determining treatment type and timing are also required. This will also include the evaluation of intravitreal therapy. The last 100 years have improved our knowledge of this ubiquitous parasite; it is hoped that the next 100 will lead to its eradication.

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