Ocular involvement in toxoplasmosis

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Toxoplasmosis is a major and preventable cause of severe visual handicap and blindness in young people. Congenital toxoplasmosis, as well as toxoplasmosis in immunocompromised patients, is a serious, sometimes fatal disease.1 Toxoplasmic encephalitis has gained importance as a leading cause of AIDS related mortality.

*Toxoplasma gondii*, the aetiological agent of human and animal toxoplasmosis, is ubiquitous in nature. The organism is an obligate intracellular parasite and its definitive host is the cat. Oocysts, which are excreted in cat faeces, are highly resistant and may remain infective for more than 1 year. Usually only young cats are infected for a short period of time. The infected cat is not the primary source of infection for humans but is a very important cause of contamination of the environment (soil, fruit, and vegetables and thus other infected animals which become intermediate hosts).

*Toxoplasma gondii* is the most important protozoan cause of intraocular inflammation owing to its widespread distribution throughout the world, the frequency of ocular involvement, and the seriousness of the symptoms it may cause. Toxoplasmosis was first recognised in patients with congenital disease: in 1923 Janku in Prague presented the first report on a boy who became blind at the age of 3 months and died of hydrocephalus; a granulomatous inflammation of the eye with protozoal in the retina was found.2 Wolf subsequently verified the aetiology by recovering the *Toxoplasma* and transmitting the infection to animals.3 Retrospective analysis of specimens has demonstrated the disease in a large number of patients with neonatal encephalitis, thus emphasising the possibility of toxoplasmosis in such cases.3

The major problem in diagnosing ocular toxoplasmosis in adults was the difficulty of establishing the presence of the parasite in ocular lesions. Helenor Wilder provided proof by demonstrating organisms with the morphological characteristics of *Toxoplasma gondii* in the eyes of patients with chorioretinitis, who had undergone enucleation because of blindness and pain.4

Human infection may occur by either the congenital or the acquired route. Acquired disease usually develops after ingestion of oocysts or tissue cysts and almost all cases (in immunocompetent individuals) are asymptomatic. The prevalence of seropositivity due to a previous *Toxoplasma* infection varies among different populations, depending on eating habits, climate, etc. In the Netherlands the majority of the population has already been infected by the age of 40 years.5

Congenital infection can occur when a pregnant woman becomes infected; during the parasitaemia, *Toxoplasma* crosses the placenta and invades the tissues of the developing fetus. The risk and severity of infection in the child depend on the time of gestation in which the mother acquires the infection.6 The severity of congenital infection is greatest when the disease is acquired during the early stages of pregnancy. The frequency of transmission to the fetus is highest during the third trimester, when contact between the maternal and fetal circulations is more likely to occur.6 Overall, about 40% of children of infected mothers will also become infected. Of these infected children only a small proportion will exhibit clinical symptoms directly after birth. However, long term follow up has shown that about 80% of these infected children will eventually develop neurological and/or ocular sequelae.7-11 Once maternal immunity has developed, it is believed that all subsequent fetuses will be protected against congenital toxoplasmosis. However, a case of repeated fetal infections acquired from the same mother with presumed chronic toxoplasmic endometritis has been reported.12 Toxoplasmic scars present in multiple siblings have also been documented, but whether these scars were caused by acquired or congenital disease remains unclear.13 Ocular recurrence during pregnancy in three patients did not cause an infection of the fetus.14

Until recently it has been assumed that ocular toxoplasmosis represents a (frequently late) manifestation of congenital disease.15 In 1973 Perkins, who performed a retrospective review of patients with acquired toxoplasmosis, showed that only 3% had associated ocular disease. Furthermore, an epidemiological study on a South Pacific island, where 90% of the population over 22 years of age had already been infected by *Toxoplasma*, revealed virtually no cases of either congenital or ocular disease.16 Population surveys showed that the number of acquired infections increased with age, while the ocular disease affected mainly young individuals—the age of onset lying between 10 and 20 years of age. In contrast, recent reports support the view that acquired infection may lead to ocular disease and may even be a more important cause of ocular involvement than previously thought.17-22 Although absence of retinal lesions was noted in patients with an acute stage of acquired toxoplasmosis, ocular involvement may not become manifest until several years after initial seroconversion.18 In a large population based household study in southern Brazil, the incidence of ocular toxoplasmosis was 18%, which is extremely high.21 The authors argued that ocular toxoplasmosis in the affected area was not of congenital origin, since systemic congenital toxoplasmosis is uncommon there. Furthermore, in the same area, IgM antibodies were found in fewer than 1% of cord blood specimens and the ocular lesions were also documented in multiple siblings.19-21 The epidemiological pattern revealed a paucity of ocular lesions in young children and an increase in the prevalence of ocular lesions during adolescence, a phenomenon which has also been noted in congenital disease.21-22 Several hypotheses have been presented on the role of acquired toxoplasmosis in ocular disease, addressing the importance of infection at an early age, long term antigen exposure and the role of reinfecions, strain differences between parasites, as well as genetic differences between hosts.

Immunocompromised patients may develop lethal disseminated toxoplasmosis and/or toxoplasmic encephalitis.
Ocular disease, which is not common in such cases, may be atypical with such features as bilateral multifocal lesions. AIDS patients with (ocular) toxoplasmosis usually require continuous, lifelong treatment.\textsuperscript{22,23} Toxoplasmic retinochoroiditis in AIDS is probably due to (reactivation of) acquired disease, although in some cases it may result from pre-existing congenital ocular lesions.\textsuperscript{22}

Clinical manifestations
The ocular lesions primarily affect the retina. The hallmark of ocular toxoplasmosis is focal necrotising retinitis, ultimately resulting in characteristic atrophic scars. Old inactive atrophic scars sometimes help to establish the correct diagnosis of a former ocular disease, but such a finding does not present a therapeutic dilemma (Fig 1). It is active retinitis which poses diagnostic and therapeutic problems. Funduscopy may be difficult because of the inflammatory reaction in the vitreous – the lesions resemble ‘headlights in the fog’ (Fig 2). The active lesions may vary in size but are usually oval or circular. Frequently reactivation is situated adjacent to an old atrophic scar with hyperpigmentation along the borders, indicating an old infection (satellite formation; Fig 3). During active inflammation the retina is thickened and cream-coloured due to necrosis and associated oedema. Overlying inflammatory cells and sometimes dense infiltrates
are observed in the vitreous (Fig 4). Retinal vasculitis and sometimes a haemorrhage may surround an active lesion (Fig 4). Fluorescein angiography demonstrates early masking with late fluorescence from the active lesion. Anterior uveitis, sometimes associated with granuloma formation and a secondary rise in intraocular pressure, may also be noted. This anterior segment reaction is thought to represent either an 'overspill' from the posterior segment or a secondary immunological reaction, but *Toxoplasma* has also been observed in the iris of a patient with AIDS.24

Ocular toxoplasmosis is a self-limiting disease (in patients with a normal immune system) and, without treatment, the inflammation gradually subsides and the lesion usually heals in 6–8 weeks. The healing process is indicated by decreased protuberance and sharper borders of the retinal lesion associated with the beginning of pigment clumping. The typical scar is atrophic with hyperpigmented borders, sometimes resembling a coloboma. A visual field defect corresponding to the interruption of the retinal fibre layer may ensue. In the event of treatment these scars may be
atypical with a fragmentary aspect (Fig 5). The characteristic picture of a juxtapapillary lesion (Jensen's retinitis, Fig 6) is well known and may cause an arcuate visual field defect, which may be symptomatic if it involves an area which affects the ability to see objects close by. Sometimes papillitis with secondary optic atrophy develops.

Clinical presentation of ocular toxoplasmosis as multiple grey-white punctate lesions located deep in the retina has been described by Friedman and Knox. Resolution of these lesions may leave a typical toxoplastic scar.

The disease is bilateral in 40% of cases (however, in immunocompetent individuals it is almost never active simultaneously in both eyes); the finding of a typical scar in the contralateral eye may contribute to the diagnosis.

The most common symptoms of patients with toxoplasmic chorioretinitis are black floating spots in the affected eye. Blurred vision caused by inflammatory debris is common (Fig 4). If the visual axis or macula is involved, vision may be severely reduced. Ocular pain and redness may occur when severe iridocyclitis is present.

The most important complication of ocular toxoplasmosis is permanent loss of visual acuity. When the lesion is peripheral, the prognosis is excellent. However, if the lesion is located near the macula, associated macular oedema may affect the central acuity. Finally, the retinal lesion may involve the macula directly, which causes definite loss of central visual acuity.

Other complications include subretinal and choroidal neovascularisation (Fig 7), chorioretinal anastomoses, retinal and choroidal occlusion. Retinal detachment with vitreous strands and a hole adjacent to an old scar is rare.

Structural ocular anomalies, such as microphthalmos, nystagmus, strabismus, vitreous organisation, and optic atrophy are the ocular signs most often associated with severe retinal involvement in patients with manifest congenital disease.

Ocular toxoplasmosis in the immunocompromised host, especially in AIDS patients, is an important although uncommon disease. Clinical manifestations are variable and atypical, which often makes the diagnosis difficult. Multifocal and bilateral retinal lesions are found regularly (Fig 8). Furthermore, full thickness retinal necrosis with formation of retinal tears and detachment may develop. These features can be confused with cytomegalovirus (CMV) retinopathy, but a prominent anterior chamber and vitreous inflammatory reaction should alert the clinician to the possibility of toxoplasmosis. T gondii may co-infect the retina with other organisms; CMV retinopathy and toxoplasmosis in the same eye have been reported in a patient with AIDS. An interesting association between ocular toxoplasmosis and Fuchs' heterochromic cysts has often been reported. A patient with definitive congenital and ocular toxoplasmosis, who developed Fuchs' heterochromia at the age of 13 years, has been described.

Pathogenesis

Chronic toxoplasmosis, whether congenital or acquired postnatally, may include ocular involvement. The causative factors, except immunosuppression are not yet well defined, nor is it known how frequently a postnatal infection predisposes to ocular disease. Toxoplasma invades the human retina, where it may transform into the cystic form (bradyzoites). Primary and recurrent toxoplastic retinitis is thought to occur when the cyst ruptures and liberated parasites (tachyzoites) multiply in the surrounding cells, causing a subsequent inflammatory reaction in the retina and choroid. Neither humoral nor cell mediated immunity are fully protective.

The histopathological pattern of the ocular lesion is a focal granulomatous necrotising retinitis, although the necrosis may also involve retinal pigment epithelium and choroid. Cysts and free parasites are usually found in a superficial part of the retina, where granulomas with central necrosis are formed. The central necrotic portion is surrounded by epithelioid cells and varying numbers of giant cells, lymphocytes, and plasma cells. In a case report on an AIDS patient free parasites were found in the iris without involvement of other ocular structures.

The cause of the cyst rupture and the subsequent retinal necrosis is unknown. Various theories have been postulated: hormonal effects, multiplication of T gondii causing mechanical rupture, release of toxins of lytic enzymes by the parasite, cell mediated defence reactions, hypersensitivity to the organism, or products released by the inflammatory process. Kaufman demonstrated that after a period of 3 months, an anterior chamber reaction could be elicited by injection of inactivated Toxoplasma via various routes, but Nozik and O'Connor were unable to reactivate retinitis in their rabbit studies. There is evidence that the most pathogenic strains of Toxoplasma comprise a single clonal lineage, regardless of host or geographical origin, which may have clinical implications (examination of isolates from pregnant women or patients with AIDS in relation to the severity of their disease).

Histological studies have shown that in murine congenital ocular toxoplasmosis the inflammatory response is directed toward the photoreceptor layer of the retina and not to the Toxoplasma cysts, which could suggest an autoimmune mechanism for the retinal damage. However, the data on humoral and cellular responses to retinal antigens are contradictory and not conclusive. Nussenblatt et al, who found a positive cellular response to bovine retinal antigen in patients with ocular toxoplasmosis, introduced a provocative hypothesis that the inflammatory retinal disease is at least in part caused by an autoimmune response. In contrast, Kijlstra et al observed no differences in the humoral and cellular responses to human retinal S and human interphotoreceptor retinoid binding protein (IRBP) antigens between patients with active ocular toxoplasmosis and patients with other types of uveitis. The role of an eventual reinfection with Toxoplasma parasites has not yet been investigated systematically.

HLA typing of patients with ocular toxoplasmosis did not reveal an association with a specific phenotype, and no correlation was observed between any HLA phenotype and in vitro responsiveness to purified Toxoplasma antigen or bovine retinal S antigen.

One may conclude that the initiating events of toxoplastic retinitis are not known nor has the role of immunological processes in the pathogenesis of tissue destruction in this infective type of uveitis been established.

Diagnosis

Until serological tests were developed, the diagnosis of toxoplasmosis depended on histological examination and animal inoculation. In reality, the diagnosis of ocular toxoplasmosis has remained mainly clinical, despite the development of serological tests; it appeared that these tests were positive for a considerable percentage of the general population and are not necessarily indicative of ocular involvement.

In the case of acute acquired toxoplasmosis, which rarely causes ocular disease, the antibody titres are usually very high, and therefore serology is indispensable for this diagnosis. The diagnosis of ocular toxoplasmosis may be very difficult. The conclusive diagnosis of active toxoplasmosis depends on the isolation of Toxoplasma from body fluids or tissues while the patient actually has the disease, but this is
Ocular involvement in toxoplasmosis rarely possible in ocular disease. The high incidence of IgG antibodies against *Toxoplasma* in the population can be explained primarily by past acquired infections; therefore a positive IgG test is not discriminatory for ocular disease and may not even be related to the eye lesion. The importance of serological testing in a given situation depends on the age of the patient and the probability that he/she has already undergone infection. Most authors agree that a positive result by any of the accepted serological methods is compatible with the diagnosis of ocular toxoplasmosis. A negative test is thought to rule out the diagnosis of ocular toxoplasmosis, and therefore ophthalmologists have often urged that tests should be performed with undiluted serum. On the other hand, a case of congenital toxoplasmosis, and even histologically proved toxoplasmic retinitis with negative serum titres for antibodies against *Toxoplasma*, have been described. Therefore, although the absence of circulating antibodies does not exclude ocular toxoplasmosis, it does make this diagnosis improbable. Possibly a combination of the results of several serological methods is more valuable in these cases.

Since the assessment of *Toxoplasma* antibodies in the blood of patients is of limited use, demonstration of the local synthesis of *Toxoplasma* antibodies in the eye by intraocular fluid analysis, as described by Domsits, is a valuable diagnostic tool. Intraocular antibody production is considered to have taken place if the relative amount of specific antibodies compared with total immunoglobulin level found in the aqueous exceeds the relative amount of these antibodies in the serum (Goldmann-Witmer coefficient). The results obtained by this method of paired aqueous and serum analysis have provided helpful information, even in clinically doubtful cases. However, false negative results may be obtained in the event of high serum titres and during the initial stage of the disease. The occasional multiply positive results may be further analysed by determination of the C' coefficient.

The diagnosis of congenital disease in newborns is established by detection of specific IgM or IgA antibodies or demonstration of stable or rising titres of IgG antibodies for a period of several months after birth. This is complicated by the fact that IgM antibodies are not formed in a large percentage (30%) of neonates and maternal IgG may persist for a long time. Differentiation between maternal and neonatal IgG by advanced immunological methods is not yet possible as a routine procedure. Tests based on antigen detection are more valuable in situations in which one cannot depend on a serological response. The application of the polymerase chain reaction, in which the parasite's DNA is detected, may be expected to change the diagnostic repertoire in the future. Clindamycin, a semisynthetic antibiotic, has a weaker antitoxoplasmic effect in animals than pyrimethamine, but has been found to be efficacious in human ocular toxoplasmosis. This drug has relatively few side effects. In addition a clindamycin associated triple combination (clindamycin with sulphadiazine and corticosteroids) has been administered with success to patients with ocular toxoplasmosis. According to scattered case reports cotrimoxazole (trimethoprim with sulphamethoxazole) appears to be effective in humans.

Spiramycin is not indicated for ocular disease but is recommended for treatment during pregnancy. It reduces the frequency of placental infection in infected mothers, penetrates into the fetal circulation and is not teratogenic. A possible case of teratogenicity of pyrimethamine in humans has been reported. Azithromycin, a derivative of erythromycin which was active in vitro against the cystic form of the parasite, is a promising new drug currently being tested for clinical use. Since ocular toxoplasmosis is a self-limiting disease and the diagnosis is established mainly on clinical grounds, it is difficult to evaluate the efficacy of the various therapeutic regimens used. The beneficial role of therapy has been reported in many non-controlled studies, but a controlled trial in 1964 demonstrated no difference in outcome between the patients on pyrimethamine and those receiving a placebo. The incidence of recurrence of retinitis after therapy has been reported to be lower than that without treatment, however no data from controlled studies are available.

Recently a prospective multicentre study of 149 patients with ocular toxoplasmosis was performed to evaluate the efficacy of currently used therapeutic strategies in the Netherlands. Three triple drug combinations – that is, (1) pyrimethamine, sulphadiazine, and corticosteroids; (2) clindamycin, sulphadiazine, and corticosteroids; and (3) cotrimoxazole (trimethoprim and sulphamethoxazole) and corticosteroids, were compared. Patients with peripheral retinal lesions received no systemic therapy. No difference in the duration of inflammatory activity was observed between the treated and untreated patients. The most important factor predicting the duration of inflammatory activity was the size of the retinal focus itself (independent of therapy); large retinal lesions were associated with a longer duration of activity. Patients on pyrimethamine triple drug therapy developed significantly smaller scars than those receiving other therapeutic modalities or those without treatment. However, pyrimethamine was also associated with the most frequent and severe side effects. The follow up period of 3 years disclosed a recurrence rate of almost 50%, which was independent of therapy.

The most widely used therapeutic regimens are listed in Table 1. Treatment usually lasts 4 weeks, eventually longer depending on the clinical picture. In the case of pyrimethamine (a folic acid antagonist), folic acid supplementation (which humans but not the parasite can utilise) should always be instituted. During therapy platelet counts should be determined at least weekly.

There appears to be a clear role for antiparasitic therapy in the treatment of ocular toxoplasmosis in immunosuppressed patients. Resolution of disease activity has been seen following treatment with pyrimethamine, either alone or in combination with sulphadiazine or clindamycin. Continued treatment with at least one antiparasitic drug appears to be necessary to maintain disease quiescence. Continued therapy is very difficult in patients with AIDS, however, because of pre-existing bone marrow suppression and the frequent allergies to sulphonamides that occur. Severe diarrhoea in AIDS patients during prolonged low dose clindamycin therapy has also been reported.

It is important to emphasise that systemic corticosteroids

Therapy

Not all cases of ocular toxoplasmosis require treatment since the ocular disease is ultimately self-limiting and the available therapeutic agents are not only ineffective against the tissue cysts but may also cause severe side effects. The major aim of therapy is still to stop multiplication of parasites during the active stage of retinochoroiditis. The classic indications for treatment of ocular toxoplasmosis include: (1) lesions in the papillomacular area which threaten visual acuity; (2) large retinal lesions (>2 disc diameters) with marked vitritis; and (3) all lesions in immunocompromised patients. But which antiparasitic drug should then be chosen?

Classic treatment includes a synergistic combination of pyrimethamine and sulphonamides. A triple combination with pyrimethamine (pyrimethamine with sulphadiazine and corticosteroids) is considered to be the most effective therapy for toxoplasmosis, but many toxic side effects and recurrences have been reported.
Table 1  Therapy for ocular toxoplasmosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Pyrimethamine triple drug therapy</td>
<td>4x 125 mg/day</td>
<td>for 2 weeks</td>
</tr>
<tr>
<td>Clindamycin triple drug therapy</td>
<td>4x 150 mg/day</td>
<td>for 2 weeks</td>
</tr>
<tr>
<td>Co-trimoxazole triple drug therapy</td>
<td>2x 960 mg/day</td>
<td>for 2 weeks</td>
</tr>
</tbody>
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should never be used exclusively, only in therapeutic combination with a specific antiparasitic therapy, since several cases of fulminant ocular toxoplasmosis have been described after the use of corticosteroids without antiparasitic drugs. It is reported that corticosteroids are contraindicated since the disease may be exacerbated.

In view of the results, it seems that an important means of controlling ocular toxoplasmosis is prevention of congenital infection. This is achieved by preventing maternal infection during pregnancy. Induction of protective immunity against toxoplasmosis using purified parasite antigens (p30) vaccine has been achieved in mice and is an important step forward in the development of an effective vaccine to protect humans or domestic animals (thus blocking an important route of transmission). Since vaccine is not yet available, the major approach to prevent the disease is the dissemination of adequate information about how to avoid the infection (for example, cooking meat and not eating it until it is well done, washing fruit and vegetables, wearing gloves when working in the garden, and not touching the cat litter). Secondary prevention includes the detection of active infection during pregnancy and its treatment. This requires repeated serological screening of pregnant women by means of uniform and quick tests performed in reliable laboratories that provide a rapid and accurate interpretation; here the problems of cost benefit analysis are obvious. The recent possibility of antenatal diagnosis will lead to improved decision making regarding treatment of the mother and eventual termination of the pregnancy in antenatally confirmed cases.

There are several examples in Europe (for example, Portugal, Spain) where the preventive strategy has been incorporated in a general programme for all women of childbearing age. It should be kept in mind that for a preventive programme to be successful it is necessary that diagnosis of the maternal infection should be reliable and also that eventual treatment be effective. Unfortunately, these aims have not yet been achieved. In the Netherlands, the preventive measures were analysed in a Toxoplasma infection prevention study. It was provisionally concluded that primary prevention (information about the sources of the disease, hygienic measures) contributed markedly to the success of the preventive programme. The secondary prevention (detection of recent infection – that is, seroconversion – during pregnancy) of limited value because of the above-mentioned problems and the low incidence of infection in the study. Only large scale studies will be able to provide conclusive evidence on the best way to assess this serious but preventable ocular disease.

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doi: 10.1136/bjo.77.6.371

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