

CLINICAL MANIFESTATIONS OF OCULAR TOXOPLASMOSIS IN YOGYAKARTA, INDONESIA: A CLINICAL REVIEW OF 173 CASES

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Abstract. Toxoplasmosis was the most common cause of primary retinochoroiditis. The majority of cases of ocular toxoplasmosis were congenital. However, cases of acquired ocular toxoplasmosis have been reported. The clinical manifestations of congenital ocular toxoplasmosis were choroidal coloboma, strabismus, nystagmus, ptosis, microphthalmia, cataract and enophthalmia. The purpose of this study was to determine the clinical presentation and visual outcome of 173 patients with ocular toxoplasmosis at Dr Sardjito Hospital, Dr Yap Eye Hospital, and private practice during the last six years. A total of 173 subjects were studied - 98 males and 75 females. The ages at which first diagnosis was established ranged from 3 months to 68 years, frequently in young adults and occurring mostly in students. The most-reported chief complaint was blurred vision in 70.5% and floaters in 6.1% of cases. The most frequent clinical manifestations were chorioretinitis (71.2%), macular scars (22.4%), squint (6.4%), congenital cataract (2.8%), nystagmus (6.4%) and atrophic optic papilla (2.8%). Bilateral involvement was found in 32.4% of all patients. The therapeutic outcome showed improvement, especially visual acuity in acute cases (25.6%). However, visual acuity categorized as blindness was 13.9%. The results of the study imply that suddenly blurred vision in the quiet eye in the young adult, squint, and nystagmus in children could be chorioretinal inflammation and scar caused by *Toxoplasma gondii*.

INTRODUCTION

Ocular toxoplasmosis is an intraocular inflammation that has the potential to cause blindness. Toxoplasmosis is caused by the protozoan *Toxoplasma gondii*. Posterior segment abnormality was the most important factor resulting in blindness and visual impairment in children and young adults. Some of the damage was caused by an antiretinal auto-immune mechanism (Whittle *et al*, 1998). Toxoplasmosis is the most common cause of posterior uveitis in the world, in some countries accounting for more than 80% of cases.

In the US, seropositivity to toxoplasmosis was reported in 30-60% of the adult population,

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while fetal infection was found in 4,200-16,800 per year (Fernandez and Orefice, 1996). In Brazil and France, seropositivity to toxoplasmosis was found in 42-83% and 90%, respectively (Orefice and Bonfioli, 1999). Anti-toxoplasmosis prevalence in humans in Indonesia was 2-63%, and the variation depended on the city in which the sample was taken (Gandahasada, 2000). In animals, the reported prevalence of anti-toxoplasmosis was as follows: in cats 35-73%, pigs 11-36%, goats 11-61%, dogs 75%, and other livestock <10% (Gandahasada, 2000). If a pregnant woman contracted a primary infection of *Toxoplasma gondii*, the risk that the baby would also become infected was as high as 40%. The manifestations of infection were stillbirth, miscarriage, premature delivery, or the baby suffering from congenital toxoplasmosis. Classical features of congenital toxoplasmosis were hydrocephalus, brain calcification and chorioretinal scar (Mets *et al*, 1996).

Congenital ocular toxoplasmosis comprised

80-98% of all ocular toxoplasmosis. Most of those experienced reactivation in the 2nd and 3rd decades. The most common site was the macular area, which comprised about 76% of the cases (Mets *et al*, 1996). Perkins (1973) suggested that the prevalence of infection increased in relation to the increase in age, but in fact the infection occurred in the 2nd and 3rd decades. If the *T. gondii* infections were acquired, therefore the numbers of cases would increase according to age. Invasion through the optic nerve would cause juxtapapillary retinochoroiditis. Relapse could be caused by more than one thing, but the latest theory suggests that toxoplasmosis reinfection is caused by infection with another, new strain of toxoplasma (Araujo *et al*, 1997). Location of recurrent infection occurred on the edge of the retinochoroid scars, forming one or multiple satellite lesions in the remote area. The lesion could be as deep as the retinal layers expanding to the choroid, sclera and vitreous. In some cases, the lesion could spread out into the optic nerve papilla and anterior uvea, resulting in cataract. Disturbance of macular function during developmental age could result in squint and nystagmus (Nunuk and Suhardjo, 1988).

Signs and symptoms of ocular toxoplasmosis vary with age. Children were generally referred to an ophthalmologist complaining of decreased visual acuity, strabismus, nystagmus, leucocoria, choroidal coloboma and microphthalmia (Da Mata and Orefice, 2002). The typical complaint in ocular toxoplasmosis, in adolescents and adults, was blurred vision, floaters and sometimes with pain, photophobia, conjunctival hyperemia if the anterior segment was involved. The most common cause of visual loss in ocular toxoplasmosis was a macular scar, but other causes for substantial visual loss included dragging of the macula secondary to peripheral lesion, retinal detachment, macular edema, optic atrophy, cataract, glaucoma, opacification of the media, amblyopia and phthisis. Surprisingly, the presence of a large congenital macular scar can be associated with remarkably good vision (Mets *et al*, 1996).

Acquired toxoplasmosis was rare, and about 70% of the cases of immunocompetent patients were asymptomatic. The most common manifestations were lymphadenopathy, fever, headache,

malaise, pharyngitis, fatigue and night-sweats. Most acquired toxoplasmosis was asymptomatic, so that the true incidence of ocular toxoplasmosis in this setting was unclear, but current estimates range from 2-20% (Glasner *et al*, 1992; Couvreur and Thulliez, 1996). Toxoplasmosis in AIDS patients was rare, about 1-3% (Jabs *et al*, 1989). If there were retinochoroiditis toxoplasmosis, it was often correlated with encephalitis and brain abscess (Henin *et al*, 1987).

The latest reports disagree with the traditional pathogenesis of eye toxoplasmosis. Considerable research was developed based on research in Erechim, a small city in a farming area in Rio Grande do Sul, south of Brazil (Glasner *et al*, 1992). Almost all of the population in Erechim was seropositive, in contrast with a report from the South Pacific. The study in Erechim found a very high frequency of ocular abnormality and almost 18% of the population had retinochoroidal scars. Some families also had siblings who suffered from ocular toxoplasmosis. This finding was different from the study by Perkins (1973), who reported, in southern Brazil, that ocular toxoplasmosis increased in relation to increased age (Glasner *et al*, 1992).

Two opinions have stimulated a review of ocular toxoplasmosis in Yogyakarta. The review was carried out in two referral eye clinics in Yogyakarta, which may be deemed representative of the whole of Indonesia, since many tribes from all over Indonesia live in Yogyakarta. Yogyakarta was the old capital of the State of Indonesia, 55 years ago. Now, Yogyakarta, a city of over 600,000, is the capital of Yogyakarta Province and representative of Indonesia. The majority occupations are farmer, handicraft maker and student.

The purpose of this study was to determine clinical features; demography as a risk factor; management and some complications of ocular toxoplasmosis. It was hoped that the result would be useful for comparison with previous studies outside Indonesia.

MATERIALS AND METHODS

This study was a descriptive retrospective cohort study. The data were collected from the

Uveitis Subdivision and the Vitreo-retina Subdivision of Dr Sardjito Hospital, Dr Yap Eye Hospital and private practice medical records of the last 6 years. Diagnosis was established by clinical and laboratory examinations. The laboratory examinations were IgG and IgM for toxoplasmosis obtained from patients' blood sera. Congenital toxoplasmosis was established by finding IgM in an infant's serum, and if it were not found, the examination would be repeated 2-3 months later. Acquired toxoplasmosis was established if there were increasing IgG titers in the 3-week serial examination. Each case was followed up continuously for 3 months to track the development of the disease.

Data included age, sex, occupation, chief complaint, visual acuity, clinical features, bilateral involvement, therapeutic outcome, side-effects of treatment and complications. Drug therapies administered were a combination of pyrimethamine/sulfadoxine (Fansidar), dexamethasone, and folinic acid. In special conditions, trimethoprim/sulfamethoxazole, spiramycin, clindamycin were administered as substitute therapy. Because of the length of the therapy (up to 6 weeks), side-effects need to be considered, such as leukopenia or thrombocytopenia. All of the data were tabulated and analyzed descriptively and statistically.

RESULTS

In the last 6 years, there were 173 ocular toxoplasmosis cases, consisting of 98 (56.65%) males and 75 (43.35%) females. The age when diagnosis was established ranged from 3 months-68 years, but mostly in the 2nd and 3rd decades. In

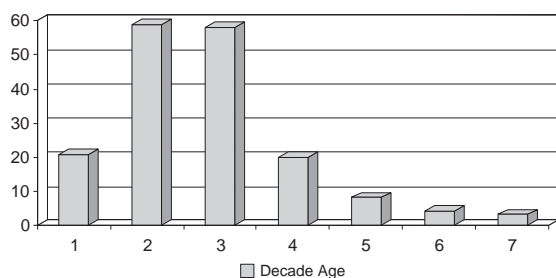


Fig 1—Ocular toxoplasmosis by age.

Table 1
Occupations of the patients.

Occupation	Total	%
Farmer	82	47.39
Breeder	15	8.67
Civil servant	25	14.45
Army/Police	2	1.24
Vendor	15	8.67
Student	33	19.08
Other	1	0.58

Table 2
Chief complaints of ocular toxoplasmosis (173 cases).

Symptom(s)	Total	%
Blurred vision	122	70.52
Floaters	11	6.36
Squint	11	6.36
Nystagmus	15	8.67
Congenital cataract	5	2.89
Diplopia	2	1.16
Pain	4	2.31
Red eye	3	1.73

this study, ocular toxoplasmosis in males and females was not significantly different.

Table 1 shows that ocular toxoplasmosis was found most in farmers. The open disposal system, or the farmers' habit of using manure without any pre-processing, were believed to be the causes of the high incidences in farmers and breeders.

The chief complaint that caused patients to attend hospital was blurred vision, with 122 cases (70.5%) (Table 2). Pre-school children and school-aged children were brought to the doctor by their parents because of a request by a schoolteacher, congenital cataract, squint or nystagmus. Pain and red-eye complaints were present if the inflammation process had spread out into the anterior segment, such as the anterior uvea, sclera and trabecular meshwork.

Abnormality was commonly found in the posterior segment, especially in the macular area (Table 3). Three of the neuroretinitis cases were

Table 3
Ocular toxoplasmosis manifestations in the posterior segment (173 cases).

Clinical features	Total	%
Chorioretinitis	121	69.4 ^a
Macular scar	39	22.54 ^a
Juxtapapillary scar	27	15.61 ^a
Peripheral chorioretinal scar	11	6.36 ^a
Neuroretinitis	9	5.20 ^b
Papillitis	2	1.16 ^a
Atrophy of the optic papilla	2	1.16 ^a

^aSome cases had more than one abnormality, such as atrophy of the optic papilla, chorioretinal scar and vitreitis.

^bThere were 3 cases of acquired toxoplasmosis.

Table 4
Ocular complications caused by congenital toxoplasmosis (N=170).

Complications ^a	Total	%
Squint	11	6.47
Congenital cataract	5	2.94
Nystagmus	11	6.47
Granulomatous uveitis and Fuchs	4	2.35
Secondary glaucoma	1	0.59
Retinal detachment	1	0.59

^aAll of the cases had chorioretinal abnormality, especially macular.

young adults, 19-23 years old, who were assumed to have acquired toxoplasmosis; they had a history of fever, and present regional lymphadenopathy. Among the abnormalities that threatened vision were neuroretinitis, papillitis, atrophy of the optic papilla, macular scar and juxtapapillary scar.

Table 4 shows that toxoplasmosis occurring in the chorioretina could spread out into the anterior segment and cause marked inflammation. The squint and nystagmus were the reasons why the patients should be examined by an ophthalmologist. Visual acuity in the squint patient was poor even if it was treated properly. Nystagmus was usually seen in the bilateral cases, and in this study

Table 5
Non-ocular complications of congenital toxoplasmosis (N=170).

Complications	Total	%
Intracerebral toxoplasmosis	3	1.77
Hydrocephalus	2	1.18
Encephalitis	1	0.59

Table 6
Visual impact of ocular toxoplasmosis.

Visual acuity (WHO criteria)	Frequency (N=173)	%
Good vision	28	16.17
Visual impairment (20/400 - < 20/200)	121	69.95
Blindness (<20/400)	24	13.88

we found 58 cases (32.4%) were bilateral. The retinal type was non-rhegmatogenous and surgical treatment was not needed.

Almost all non-ocular complications of congenital toxoplasmosis affected the brain and bilateral chorioretinitis occurred in all of them. The encephalitis case occurred in a 23-year-old woman who finally died. Hydrocephalus cases were detected with the help of a pediatrician and a neurosurgeon (Table 5).

The decrease of visual acuity to blindness happened in cases of atrophy of the optic papilla, severe macular scar, extensive juxtapapillary scar, secondary glaucoma, retinal detachment and congenital cataract. However, absolute blindness (no light perception) was not found, which might be correlated with a previous abnormality, such as segmental papillitis (Table 6).

Not all patients received a specific therapy. Some of them just received roborantia, such as vitamin B, vitamin C and anti-oxidant. New medications, such as azithromycin, were not used. Improvement of visual acuity occurred especially in acute or relapse cases and those involving the macula or optic nerve papilla. Steroid was used directly, but in some cases steroid was given a

Table 7
Success and side-effects of therapy.

Medication regimen	No. of patients	Increase of V.A	Side effect: gastrointestinal problems
Pyrimethamine, trisulfa, steroid	62	26	4
Trimethoprim/sulfamethoxazole, steroid	46	19	1
Spiramycin, steroid	18	14	-
Clindamycin, steroid	16	14	-
Roborantia	31	-	-

few days after specific therapy. The side-effects found were gastrointestinal disturbances, such as nausea, vomiting, cramps, pain, and occasionally diarrhea. Nausea may have been caused by the long-term use of sulfa, and the pain was because of the use of steroid. The success and side-effects of therapy are shown in Table 7.

DISCUSSION

Congenital toxoplasmosis did not always show an increase in IgM, especially in the case of chorioretinal scar. Almost all of these had positive IgG. The prevalence of anti-*T. gondii* usually increased with age. A survey in Jakarta, Indonesia showed the prevalence of anti-*T. gondii* in ocular patients to be 77%; 60% of these had chorioretinal abnormality and 17% other forms of eye disease (Gandahasada, 1990). Smith and Ganley (1972) found 0.6% of people in Maryland had a chorioretinal scar, consistent with previous episodes of toxoplasmic retinochoroiditis. Anti-*T. gondii* titer positive was an important factor in determining whether the lesion found was active or inactive. An active process in toxoplasmic chorioretinal infection was perceived with vitreous cell, satellite lesion and exudates.

Congenital toxoplasmosis occurred if a pregnant woman contracted a primary infection. Tissue damage caused by the parasite could be stopped with humoral or cellular host immunity. The severity of eye damage in congenital infection was reported to be up to 85% without treatment (Wilson *et al*, 1980). In contrast, the severity of eye damage in acquired toxoplasmosis was low, about 1-3% (Holland *et al*, 1996). In the 1977 epidemic of acquired toxoplasmosis in Atlanta,

Georgia, only 1 (3.6%) of 28 infected people who underwent follow-up examination four years later had eye damage (Akstein *et al*, 1982). Chorioretinitis was thought to be a hypersensitive reaction phenomenon in young adults and teenagers, but some suggested tachyzoite reproduction in the chorioretina (Frenkel, 1985). Holland (1999) proposed that relapsed retinochoroiditis toxoplasmic scar was more frequent in acquired cases than in residual congenital infection.

The most common symptom was a decrease in visual acuity (70.52% of patients), caused by macular lesion, optic papilla, juxtapapillaris, the presence of vitreous cell and inflammation in the anterior segment. Nystagmus, squint and disturbance of reading activity were the reasons for parents bringing their children to an ophthalmologist; other objective symptoms reported were retinal phlebitis, vitreitis, anterior uveitis and scleritis (Vaughan *et al*, 1992).

Bosch-Dreissen *et al* (2000) reported the clinical course and prognosis of 150 ocular toxoplasmosis patients, 6% with retinal detachment and 5% with retinal tear. Retinal detachment and retinal tear in active ocular toxoplasmosis initiated with severe intraocular inflammation. The study showed that the visual prognosis was worse for five patients. This study found one case of non-rhegmatogenous retinal detachment without surgical therapy.

Lafaul *et al* (1999) suggested that the presence of peripheral hypertrophy of the chorioretinal scar was a sign of congenital toxoplasmosis with choroidal vascularization. Proliferate protrusion of the sensory retinal layer and a secondary scar caused by congenital toxoplasmosis might be

caused by vitreitis, tractional or exudative retinal detachment. Laser photocoagulation could be performed in such cases.

The impact upon visual acuity in toxoplasmosis infection was very significant. Only 28 cases (16.17%) still had good vision, which means that almost 85% of ocular toxoplasmosis cases have visual disturbances. Some work that needs good visual acuity, such as reading, driving and writing will thus be disturbed. Considering that the frequency of relapse was high, relapse cases with good visual acuity will become worse if not treated immediately. Most of the cases in this study were relapse cases, especially in the 2nd and 3rd decades. For that reason, routine examination every six months during the vulnerable age is necessary. Ongkosuwito *et al* (1999) showed that 50% of the source of infection for primary toxoplasmic retinochoroiditis was from outside the eye. The first reactivation was usually mild and sometimes asymptomatic. The next reactivation was moderate and caused marked ocular abnormality. In some cases, relapsing retinochoroiditis toxoplasmosis was assumed to be due to a hidden focal infection, not from the sequel of congenital infection (Bosch-Driessen and Rothova, 1999). Clinical variants of toxoplasmosis include neuroretinitis, papilledema, multiple pseudoretinitis, anterior uveitis, Fuchs iridocyclitis, and unilateral pigmentary retinopathy (Da Mata and Orefice, 2002). Multiple pseudoretinitis was indicated with active and simultaneous retinal lesions that were actually a single lesion in the edematous retina. If this condition healed it would not leave any scar. Fuchs iridocyclitis was found in one case, a woman 31 years old with secondary glaucoma and posterior capsular cataract. The most common complication found in ocular toxoplasmosis was secondary glaucoma due to an inflammatory reaction and it could be managed with anti-inflammatory agents. We found only one case like this. Other complications found were vitreal bleeding and epiretinal membrane but no phthisis bulbi was found.

Although the necessity for treatment of ocular toxoplasmosis is still controversial, it still needs to be considered, given the likely spread of lesions to vital areas, such as the optic macula, papilla and temporal arcade. In this situation, we

preferred to give medication rather than not, because we must consider the risk of new infection in Indonesia, such as: immunological status that correlates with poor nutritional status, the 2nd and 3rd decades were the vulnerable age for infection in tropical areas, poor hygiene, sanitation and food hygiene, that are still below standard. Furthermore, an economic crisis has been taking place in Indonesia during the last four years.

Based on a physician survey in the US, uveitis specialists appear to be more likely to treat patients with ocular toxoplasmosis (Holland and Lewis, 2002). The results of treating primary active case and relapse case were satisfactory. Visual acuity usually increased and in some cases visual acuity even reached 6/6. Most of the cases were of the congenital type (170/173 cases). Steroids were used in the management of ocular toxoplasmosis if there were signs of acute inflammation *ie*: exudates, vitreous cell, edema, etc. Side-effects of medication were caused by sulfa. Long-term intermittent treatment with trimethoprim/sulfamethoxazole can reduce the rate of recurrent toxoplasmic retinochoroiditis (Silviera *et al*, 2002); however, sulfamethoxazole can be a potent allergen. In the future, clindamycin and spiramycin appear more promising in the management of ocular toxoplasmosis.

In summary, our study provides evidence that the majority of the clinical features of ocular toxoplasmosis in Indonesia were chorioretinitis, macular lesion and juxtapapillary lesion in the retina. Based on the symptoms, the chief complaints were blurred vision, squint and nystagmus. Many children with congenital toxoplasmosis have substantial retinal damage at birth and consequent loss of vision. Nonetheless, vision may be remarkably good in the presence of large macular scars. Active lesions become quiescent with treatment.

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