

# Clinical Manifestations of Ocular Toxoplasmosis at a Referral Center in Iraq

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## ABSTRACT:

### BACKGROUND:

Ocular toxoplasmosis is an important cause of posterior uveitis worldwide including Iraq.

### OBJECTIVE:

To study the clinical manifestations of ocular toxoplasmosis at a referral center in Iraq.

### PATIENTS AND METHODS:

Nine months prospective case series study was performed in the outpatient clinic at Ibn Al Haetham teaching eye hospital in Baghdad, Iraq. The diagnosis was mainly clinical supported by serological tests.

### RESULTS:

In this study 20 patients were diagnosed with Ocular toxoplasmosis. Primary active, recurrent & an inactive diseases were reported in: 8 patients (40%), 7 patients (35%) & 5 patients (25%) respectively. Unilateral disease was seen in 13 patients (65%), while bilateral disease was seen in 7 patients (35%). The macula was involved in 15 eyes (55.5%). Visual acuity at presentation was:  $\leq 6/36$  seen in 15 eyes (55.5%). Complications –reported at a rate of (75%)- were include: High IOP, macular edema, optic disc swelling, Choroidal neovascularization & branch retinal vein occlusion.

### CONCLUSION:

The commonest type of presentation of ocular toxoplasmosis seen in this study was the primary active retinitis, followed by recurrent disease. Poor visual outcome seen at the end of treatment course was mainly due to macular involvement.

**KEYWORDS:** ocular toxoplasmosis, recurrent, primary active disease.

## INTRODUCTION:

Toxoplasmosis is caused by the parasite *Toxoplasma gondii*, a single-cell obligate intracellular apicomplexan parasite.<sup>1</sup> Cats are the definitive hosts, while mice, livestock, birds and humans represent the intermediate hosts. It is estimated to infest at least 10% of adults in northern temperate countries and more than half of adults in Mediterranean and tropical countries.<sup>2</sup> Toxoplasmosis is an important cause of posterior uveitis worldwide including Iraq & neighboring countries. In Iraq, ocular toxoplasmosis was the most common infectious uveitis and the leading cause of unilateral posterior uveitis.<sup>3</sup> There are two types of human infection by *Toxoplasma gondii*: congenital & acquired.

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Congenital infection is caused by trans-placental transmission of *T gondii* during pregnancy, while acquired infection may be caused by either one of the following: consumption of undercooked meat infected by tissue cysts, ingestion of water, fruit, or vegetables contaminated with oocytes, accidental contact with cat litter, feces, or soil containing oocytes, blood transfusion or organ transplantation.<sup>4</sup>

Clinical manifestations of ocular toxoplasmosis: Symptoms: Ocular toxoplasmosis in young children may be asymptomatic while older children who are able to vocalize may present with reduced vision or ocular pain.<sup>5</sup> Unilateral acute or sub-acute onset of floaters, blurring and photophobia are the main presenting features in adults.<sup>2</sup> The mean age for

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the first presentation of symptomatic infection is 29.5 years but the exact age of onset is difficult to ascertain, however, 72% of patients are discovered to have pre-existing retinochoroidal scars which indicates a prior subclinical disease.<sup>6,7</sup>

Signs:

The prevalence and clinical manifestations of ocular toxoplasmosis may vary with different racial/ethnic groups and in different geographic areas which may be due to cultural factors that cause different exposures in terms of parasitic stage, amount of inoculum, or age of infection.<sup>6</sup> Ocular toxoplasmosis is unilateral in about (72%–83%), whether occurring as primary or reactivated disease.<sup>8</sup> Despite the fact that the anatomic macula comprises only about 5% of the total retinal area, it tends to be more commonly affected than the other areas of retina.<sup>6</sup> The typical presentation is characterized by a single inflammatory nidus of fluffy white necrotizing retinitis or retinochoroiditis associated with a pigmented scar ('satellite lesion'). The focus of retinitis is usually full thickness, with or without limited involvement of either outer or inner retina. The overlying vitreous and subjacent choroid are variably involved depending upon the thickness and the size of involved retina. Severe vitritis will result in the classic 'headlight in the fog' sign.<sup>5,6,9,10,11</sup> Healing in immunocompetent persons may occur spontaneously within 4–8 weeks (hastened by anti-protozoal therapy) ended with a scar replacing the inflammatory focus. This scar is usually smaller than the initial focus of retinitis, with variable degree of pigmentation and choroid atrophy which may relate to the degree of retinal pigment epithelial damage during the active phase and subsequent reactive hyperplasia of the retinal pigment epithelium (hypopigmented scar may develop when severe retinochoroiditis causes destruction of the retina and adjacent choroid, exposing the underlying sclera).<sup>6,10,12</sup> 'Spill-over' anterior uveitis is common. It may be granulomatous or nongranulomatous and it commonly indicates severe vitritis and frequently associated with

elevated intraocular pressure (elevated IOP occurs in up to 20% of patients).<sup>1,2,9</sup> The atypical presentation of ocular toxoplasmosis may include:<sup>12,13</sup>

- 1) Optic nerve involvement: It may be occasionally seen. (Jensen) retinochoroiditis is characterized by juxtapapillary choroiditis, a varying degrees of papillitis and a typical sector shaped visual field defect.<sup>12,14,15</sup>
- 2) Vasculitis: which is more commonly venous, but may be arterial. Vasculitis may be either close to or distant from the focus of active retinitis. Kyrieleis arteriolitis refers to accumulation of periarterial exudates.<sup>2,12,13</sup>
- 3) Punctate outer retinal toxoplasmosis which usually presents in young patients featuring clusters of small (25–75 µm diameter) grey–white lesions with little associated vitritis but the macular involvement and disc oedema are common.<sup>2,16,17,18</sup>
- 4) Neuroretinitis is another atypical but rare event.<sup>6,12</sup>

5) Scleritis: <sup>6,12</sup>

6) Anterior uveitis, vitritis & retinal vasculitis in the absence of retinochoroiditis: may be seen in the acute phase of acquired disease.<sup>5</sup>

7) Pigmentary retinopathy: It was reported in patients with bilateral recurrent ocular toxoplasmosis & the changes here are unilateral and in some patients involve only a portion of the fundus.<sup>12</sup>

8) Other atypical presentations may include: Retinal vascular occlusion, Roth spots, optic disc granuloma & serous retinal detachment.<sup>6,12</sup>

Reported complications of ocular toxoplasmosis: They develop in nearly 44% of patients, and about 10-18% of them may require at least one intraocular surgery).<sup>7</sup> Complications may include: Raised intraocular pressure, macular oedema, cataract, preretinal membrane, isolated retinal tear, retinal detachment, retinal vascular occlusion, vitreous haemorrhage & choroidal neovascularization.<sup>5</sup>

Recurrence of active retinochoroiditis: It have been reported to occur in 79% of 76 patients followed for over 5 years.<sup>7</sup> Infection appears to recur with increased incidence

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from the same location along the scar border.<sup>6</sup> Pregnancy and cataract surgery have both been associated with an increased risk of reactivation.<sup>7</sup> In patients with AIDS and reduced CD4-positive T cell count, recurrence is the rule in the absence of long-term anti-parasitic therapy.<sup>17</sup> The risk of reactivation in patients with inactive toxoplasmic retinal scars who receive treatment with systemic corticosteroid for other indications is probably very low.<sup>5</sup> Systemic manifestations of toxoplasmosis: Congenital toxoplasmosis has systemic manifestations that differ considerably from those of acquired disease. Congenital toxoplasmosis develops in 30% to 50% of infants whose mothers are first infected during pregnancy, and 70% to 90% of affected infants develop retinochoroiditis which is bilateral in approximately 85% of cases.<sup>1,10</sup> The risk of congenital toxoplasmosis is highest in the third trimester (i.e. 72% at 36 weeks versus 6% at 13 weeks gestation), but if the infection is contracted during the first trimester, the systemic manifestations will be more severe.<sup>19</sup> Spontaneous abortion may occur, or the newborn may show such abnormalities as: microcephaly, hydrocephaly intracranial calcifications etc.<sup>20</sup> There is no significant risk of infecting the fetus if the mother acquires the disease before pregnancy or develops a reactivation of ocular toxoplasmosis, this is because of the presence of protective maternal immune response.<sup>5</sup> Postnatally acquired ocular toxoplasmosis in an immunocompetent subjects do not usually have systemic symptoms, however, in about 10% of them non-specific symptoms, such as fatigue, fever and myalgias may be reported.<sup>18</sup> whoever, epidemic infection usually results in symptomatic systemic disease (seen in about 94%).<sup>21</sup> The risk of ocular involvement in acquired toxoplasmosis was thought to be 3%, however the current estimates range from 2-20%.<sup>22,23</sup>

Serological testing for *Toxoplasma gondii*: The diagnosis of ocular toxoplasmosis is mainly clinical, supported by serological tests. Serological testing for *Toxoplasma gondii* plays a little role in the diagnosis of ocular

toxoplasmosis.<sup>5</sup> Its primary use is in the exclusion of ocular toxoplasmosis as the cause of posterior uveitis if specific antibody is absent from the serum (i.e. It confirms the exposure to the parasite).<sup>5,24</sup> The presence of anti-*T. gondii* IgG antibodies (ABs) will support the diagnosis of toxoplasmic retinitis but in the presence of appropriate clinical context. IgG (ABs) appear 2 weeks after infection and the typically remain detectable for life but at different levels. Rising titer of specific IgG (ABs) over a period of 3-week has been used as an indicator of recent infection. IgM (ABs), will increase early during the acute stage of the infection, and will typically remain detectable for less than one year.<sup>1,25</sup>

### **PATIENTS AND METHODS:**

This study is a descriptive prospective case series study. It was performed at the outpatient clinic at Ibn Al-Haetham teaching eye hospital after an ethical board approval has been obtained from the Iraqi board for medical specialization. The prospective clinical and laboratory medical data were collected for all patients seen in this study during June 2017 and February 2018 (9 months). An informed consent was obtained from all patients or their legal tutors. An ophthalmic history was taken at each visit along with complete ocular examination. The diagnosis of ocular toxoplasmosis was mainly clinical depending on the presence of characteristic lesions in the fundus supported by serological tests. Active ocular toxoplasmosis was defined by the presence of an active creamy-white focal fluffy necrotizing retinitis or retinochoroiditis. Primary ocular toxoplasmosis was defined as an active focal retinitis without associated pigmented retinochoroidal scars in either eye while the recurrent infection was defined as an active lesion in the presence of old pigmented retinochoroidal scars in either eye. An inactive lesion was defined as (in patients who have no known history of trauma, surgery, uveitis or laser therapy) an atrophic, well-defined retinal scar which often has a variable degree of pigmentation but a hypopigmented scar may also develop. Juxtapapillary lesions were defined as lesions that touched or covered the optic disc margin, & in this study, if a lesion touched the optic disc on the temporal side, it was classified as juxtapapillary,

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rather than macular. 26 peripheral lesions were defined as lesions located outside the temporal vascular arcades). All patients in this study were examined for the presence of anti-toxoplasma IgM and IgG (ABs) using an ELISA technique. Serological criteria for the acute primary toxoplasma gondii infection included the presence of specific IgM (ABs), while positive IgG (ABs) (any positive titre) without IgM (ABs) represents the chronic phase of systemic infection. Follow-up schedule was supposed to be at 1-week interval until the resolution of each active episode and then calling for follow-up visits six monthly or whenever new symptom develop. Statistical data were entered and analyzed using the statistical package for social sciences (SPSS) version 24. Descriptive statistics of variables were presented as mean, standard deviation, frequencies (No.) and simple percentages (%). Due to small sample size chi square test was inapplicable, therefore, Fisher's exact test (a statistical test used as an alternative to chi squared) was used to assess the significance of differences in qualitative variables (frequencies count and proportions), such as age group across gender and toxoplasma-specific antibodies across the primary active, recurrent & inactive diseases respectively. Students' t test was used to compare quantitative mean age of males against females. Level of significance of  $\leq 0.05$ , considered as significant difference. Finally results and findings presented in tables and figures using the MS word software, 2010.

### RESULTS:

The total number of patients who were diagnosed with ocular toxoplasmosis during June 2017 & February 2018 was 20 patients (27 affected eyes). The mean age of the 20 patients was  $33.6 \pm 9.2$  (Range: 8-60) y, with 70% of the patients aged 30y or more. Touch with indoor cats was reported in two patients, eating poorly washed vegetables was reported in another two patients & drinking unfiltered water was reported in one patient. Seventeen patients (85%) were found to live in urban areas, while only three patients (15%) were living in rural areas. Eight patients (40%) had primary active disease, seven patients (35%) had recurrent disease and five patients (25%) had inactive disease. In the 15 patients with an active disease, blurring of vision was the commonest chief complaint as it was reported in 14 patients (93.24%). Twelve patients (79.92%) with active disease were presented 1-3 days after the onset of symptoms, while the remaining 3 patients (19.98%) were initially misdiagnosed and mismanaged & so they had delayed presentation (2-3 weeks after the onset of symptoms). The remaining 5 patients with inactive disease: two had central lesions (presented with decreased vision) & 3 cases were detected by routine clinical examination. Twelve eyes (44.4%) had best corrected visual acuity between (6/6-6/18), while 15 eyes (55.5%) had best corrected visual acuity  $\leq 6/36$ . Unilateral ocular toxoplasmosis was reported 13 patients (65%), while bilateral disease was reported in 7 patients (35%). See table 1.

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**Table 1: laterality of ocular toxoplasmosis lesions.**

No.	%	
Cases with Bilateral lesions	7	35%
Bilateral old scars	3	15%
Satellite lesion in one eye + old scar in the other eye	3	15%
Active retinitis in one eye + satellite lesion in the other eye	1	5%
Cases with unilateral lesions	13	65%
Old scar	2	10%
Primary active retinitis	8	40%
Active retinitis + peripheral scar	1	5%
Satellite lesions	2	10%
Total number and percentage	20	100%

**Total No. & percentage of ocular toxoplasmosis lesions (retinochoroiditis, scars) & their localization in the retina:** were as follow: **table 2.**

**1) Central (Macular) lesions** were 15 in number (53.55 %) including: 6 (21.42%) old scars, 4 (14.28 %) primary active retinitis, 4 (14.28%) satellite lesions & 1(3.57%) central active retinitis (associated with peripheral scar).

**2) Juxtapapillary lesions** were 4 (14.28 %) including: 2 (7.14%) primary active lesions and 2 (7.14%) old scars.

**3) Peripheral lesions** were 9 (32.13%) in number including: 4 (14.28%) old scars , 2 (7.14%) primary active retinitis , 2 (7.14%) satellite lesions & 1(3.57%) active retinitis (associated with central satellite lesion in the other eye).

**Other additional clinical features who were reported in the 16 affected eyes with active disease: They were include:**

1) **Vitritis:** was reported in all 16 affected eyes (100%).

2) **Anterior chamber cells:** was reported in 12 eyes (75%).

3) **Keratic precipitates:** They were small-medium in size (granulomatous) and were reported in 3 patients (18.75%).

**The complications of ocular toxoplasmosis (seen in 8 eyes out of the 16 affected eyes with active disease):** Twelve (75%) complications from ocular toxoplasmosis have been reported in 8 (50%) eyes and in some affected eyes there was more than one complication. They were included the following:

High IOP (> 21mmHg) was seen in 3 eyes (18.75%), macular edema and optic disc swelling each one of them was reported in 2 eyes (12.5%), while each of (Choroidal neovascularization with retinal hemorrhage) and branch retinal vein occlusion was reported in 1 eye (6.25%). The reported complications after resolution were include: Cataract which was seen in 2 eyes (12.5%) and epiretinal membrane which was seen in 1 eye (6.25%).

**Table 2: Total Number & percentage of ocular toxoplasmosis lesions & their localization in the retina.**

Active retinitis + satellite lesion or scar	Satellite lesions	primary Active retinitis	Old scar	Number & %	localization of lesions:-
1(3.57%)	4(14.28%)	6(21.42%)	4(14.28%)	15(53.55%)	Central
-	-	2(7.14%)	2(7.14%)	4(14.58%)	Juxtapapillary
1(3.57%)	2(7.14%)	4(14.28%)	2(7.14%)	9(32.13%)	Peripheral
<b>Total Number &amp; %</b>	<b>28</b>	<b>8 (28.56%)</b>	<b>12(42.84%)</b>	<b>6(21.42%)</b>	<b>2(7.14%)</b>

### DISCUSSION:

In this study, the mean age of patients at presentation was (33.6 ± 9.2 year) which is nearly similar to the mean age that was reported by Bosch-Driessen et al (29.5 years).<sup>7</sup> However, no statistically significant differences have been found between both gender regarding the age, in both comparison for age categories or mean age, (P>0.05). Touch with indoor cats at home, eating poorly washed vegetables and drinking unfiltered water were reported in 5 patients with active disease. Such risk factors were reported to be positively associated with acute toxoplasmosis.<sup>1</sup> The commonest presenting complaint in patients with active disease was the blurring of vision (seen in 95%) which is comparable to what was documented by Abraham et al.<sup>(32)</sup> Ocular toxoplasmosis has different modes of presentation (including typical and atypical presentation) and not all the types have been documented in this study because of the short time and small number of patients. Unilateral presentation (13 cases 65%) was more frequent than bilateral presentation (7cases 35%) which actually falls within the range (64.3-64.4%) that was reported by other studies.<sup>(27,28,30,31)</sup> Patients with primary active retinitis (8 cases "53.28%" out of 15) were slightly more common than those patients with recurrent disease (in whom pre-existing retinochoroidal scars were discovered which indicates a prior subclinical disease) (7cases "46.62%"). This rate of occurrence of primary lesions is higher than the rate reported by other studies 72%.<sup>7,32</sup> In more than half of the cases (15 eyes "55.5 %" out of 27 eyes), the macula was involved and similar results were found in other studies.<sup>(27,29,31)</sup> Such higher incidence of macular involvement seen in this study was an important cause of impact of ocular toxoplasmosis on vision. Vitritis associated with peripheral active lesions, epiretinal membrane & macular edema were an additional causes of poor vision seen in this study. Vitritis and anterior uveitis with different grades were a major additional clinical features seen in patients with active disease, while keratic precipitates were seen in three patients. Similar findings were also reported by Justine R. Smith et al.<sup>(12)</sup>

High IOP, macular edema, optic disc swelling, BRVO, CNV, cataract and Epiretinal membrane were the main complications seen in 8 eyes (50%) with active disease, with an incidence rate of 75% (where more than one complication was reported in some affected eyes) & generally the rate of occurrence of individual complication was comparable to the results reported by other studies.<sup>(5,6)</sup>

### CONCLUSION:

The commonest type of presentation of ocular toxoplasmosis seen in this study was the primary active retinitis, followed by recurrent disease. Poor visual outcome seen at the end of treatment course was mainly due to macular involvement.

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