

Clinical pattern of ocular toxoplasmosis treated in a referral centre in Serbia

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CLINICAL STUDY

Abstract

Purpose To analyze the clinical pattern of ocular toxoplasmosis (OT) in a referral centre in Serbia.

Patients and methods The medical records of consecutive patients admitted for OT to the single referral centre for uveitis in Serbia between 2006 and 2010 were retrospectively analyzed. OT was diagnosed on the basis of typical fundus lesions and positive serology for *Toxoplasma*.

Results In a total of 457 uveitis patients, OT was the third leading cause, with 59 patients (12.9%). Most OT cases (73%) were monocular. An active primary retinal lesion was observed in 36% and recurrent OT in 64% patients.

Localization of lesions was central/paracentral (44%), juxtapapillary (27%), peripheral (19%), and multifocal (10%). Other ocular manifestations of inflammation included vitritis (44%), anterior uveitis (19%), and retinal vasculitis (10%).

Complications included choroidal neovascularization in two and exudative retinal detachment with cataract, glaucoma, and cystoid macular oedema in one patient each.

The detection of *Toxoplasma*-specific IgM antibodies in a single patient indicates a low rate of OT concomitant with acute infection.

After treatment, the mean best-corrected visual acuity (BCVA) increased significantly. However, 14 (24%) patients ended up legally blind in the affected eye, of which 2 (3%) with bilateral blindness, all with a very poor BCVA (0.047 ± 0.055) at presentation. Visual impairment and treatment outcome were both associated with central localization of lesions ($P < 0.0001$ and $P = 0.006$, respectively).

Conclusion OT is a significant cause of posterior uveitis in Serbia. Patients should be aware of the recurring nature of OT and react immediately if symptoms occur.

Eye (2012) 26, 723–728; doi:10.1038/eye.2012.20; published online 24 February 2012

Keywords: ocular toxoplasmosis; uveitis; clinical pattern; epidemiology; Serbia

Introduction

Toxoplasma gondii is a cosmopolitan protozoan parasite that has been estimated to infect one-third of the global population. Although generally mild and self-limiting in immunocompetent individuals, *Toxoplasma* infection may cause life-threatening disease in the fetus and in the immunosuppressed host. Historically, ocular disease was the first clinical entity to be associated with toxoplasmosis¹ and has long been a well-known consequence of congenital infection.

Ocular toxoplasmosis (OT) most often presents as focal retinochoroiditis, which is considered to be triggered by the reactivation of dormant parasites in the retina.² Lesions can occur anywhere in the fundus and may be vision-threatening if localized in the posterior pole. Toxoplasmosis is actually the most common cause of infectious posterior uveitis worldwide.² Formerly considered to result mainly from congenital infection,³ OT has in the past decades been well established to occur both after congenital and acquired infection.^{1,2,4–7} Indeed, a greater frequency of acquired than congenital infection in the origin of OT has been reported in several clinical series, both in Europe and in South America.^{4–6} However, it appears that congenital infections cause a more severe OT.⁶ The geographic differences in the epidemiology of OT reflect the genetic variability in the parasite strains occurring in the respective regions; that is, strains from South America, responsible for the often severe clinical course of toxoplasmosis on this continent, are often type-1, or recombinant, and generally divergent from those in Europe and North America where a vast majority of all

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Received: 17 October 2011

Accepted in revised form:

15 January 2012

Published online:

24 February 2012

isolates belongs to type-2.^{8–11} In Serbia, the seroprevalence of toxoplasmosis is currently estimated at 30–35%¹² and type-2 genospecies has been isolated.¹³

As fetal infection may only develop following maternal primary infection in pregnancy, congenital toxoplasmosis is a preventable disease; therefore, the incidence of OT of congenital origin may be expected to decrease in line with successful prevention strategies implemented in a particular milieu. However, acquired infection, which is often inapparent and therefore clinically unrecognized, and the recognition of its role in the origin of OT, is responsible for the currently increased interest in the study of OT.

Because the frequency and characteristics of OT have never been reported for Serbia, we conducted a study to analyze the clinical pattern of OT in a Serbian referral centre.

Patients and methods

A retrospective analysis of the medical records of consecutive patients admitted for OT to the Uveitis Department of the Institute for Eye Diseases in Belgrade between 01 January 2006 and 31 December 2010 was performed. This department is the single referral centre for uveitis in Serbia. All patients underwent complete ophthalmological examination, including clinical history, visual acuity (VA) assessment (measured by Snellen chart at 6 m and converted to decimal notation), applanation tonometry, slit lamp examination, and fundus examination with the three-mirror lens. In addition, fundus photography, fluorescein angiography, and optical coherence tomography were performed if clinically appropriate.

OT was diagnosed on the basis of clinical findings in the fundus and positive serology for *Toxoplasma*. Active OT was defined as the presence of an active whitish focal retinochoroidal lesion in either eye; if no associated pigmented retinochoroidal scars were present in either eye, it was considered primary OT and conversely, if there was a scar in either eye, OT was considered recurrent (termed satellite if localized at the borders of the scars). In patients with two or more episodes, the last episode of active OT was the one analyzed.

Detection of IgG and IgM antibodies specific for *T. gondii* was performed using an ELISA test (Enzygnost Toxoplasmosis IgG and Enzygnost Toxoplasmosis IgM tests, Siemens Healthcare Diagnostics, Marburg, Germany) according to the manufacturer's instructions. The test for IgG antibody was quantitative and the results were expressed in IU/ml, whereas the one for IgM antibody was qualitative.

The study has followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Clinical Centre of Serbia.

Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Methods used included Student's *t*-test for comparison of numerical variables and χ^2 or Fischer's exact test (as appropriate) for categorical variables. The level of statistical significance was 0.05.

Results

A total of 457 patients were admitted for uveitis during the study period, in whom OT was diagnosed in 59 (12.9%) patients. OT was the third leading cause of uveitis after anterior serofibrinous uveitis ($n = 131$, 28.7%) and retinal vasculitis ($n = 75$, 16.4%). Of all the uveitis patients, above one-half (53%) had posterior uveitis ($n = 243$). Of these, OT accounted for 24.3% and was the second most common cause after retinal vasculitis. Importantly, OT was the most common cause of infectious uveitis.

Toxoplasma-specific IgG antibodies were detected in all patients, at a mean concentration of 96.4 ± 15.8 IU/ml, ranging from 10–350 IU/ml. Specific IgM antibody was detected in a single patient, who was thus considered as acute infection.

Baseline demographic and clinical characteristics of patients with OT are shown in Table 1. The annual number of OT cases was 12, 10, 10, 11, and 16, respectively, for the period 2006–2010. Most (76%) patients were admitted for OT only once; among the 14 who were admitted twice or more, the mean follow-up (\pm SD) was 4.2 ± 2.8 years (ranging from 1 to 9 years).

Female patients were slightly predominant (58%). Patients were relatively young (mean 34.9 ± 16.6 years), with 76% younger than 45 years.

Of the 59 cases of OT, 43 (73%) were monocular and 16 (27%) binocular. In all the binocular cases, active OT was present in one eye and old scars were observed in the other. The eye with active OT was used to classify the localization of retinochoroidal lesions. In the analysis of the lesion localization, juxtapapillary lesions were considered central if within the vascular arcades and peripheral if outside, and similarly, multifocal lesions were considered central if at least one lesion was within the vascular arcades and peripheral if all foci were out of the vascular arcades.

According to medical history data, the current OT episode was the first one the patients were aware of in 42% and a recurrence in 58%. However, on clinical examination, active primary retinal lesions were observed in 36% and one or more satellite lesions in 64%. Although patients with primary OT were older (38.0 ± 20.2 years) than those with recurrent OT (33.2 ± 14.3), this difference was not significant ($P = 0.291$).

Table 1 Clinical and demographical characteristics in a series of 59 patients with OT

Variable	Number	Range	%
Sex			
Male	25		42.4
Female	34		57.6
Age in years (mean ± SD)			
<30	26	13–74	44.1
30–44	19		32.2
45–59	8		13.6
>60	6		10.2
Toxoplasma-specific antibodies			
IgM	1		1.7
IgG	59		100.0
IgG (mean ± SE, IU/ml)	96.4 ± 15.8	10–350	
Affected eye			
Monocular	43		72.9
Right eye	19		
Left eye	24		
Binocular	16		27.1
Type of lesion at 1st exam			
Primary active lesion	21		35.6
Satellite lesion	38		64.4
Localisation of lesions			
Juxtapapillar	16		27.1
Paracentral	15		25.4
Central	11		18.6
Peripheral	11		18.6
Multifocal	6		10.2
OT accompanied by			
Vitritis	26		44.1
Anterior uveitis	11		18.6
Retinal vasculitis	6		10.2
Complications of OT			
CNV	2		3.4
Retinal detachment + cataract	1		1.7
Secondary glaucoma	1		1.7
CMO	1		1.7
VA^a (mean ± SD)			
Right eye			
At admission	0.69 ± 0.40	0.02–1.0	P = 0.009
At the end	0.75 ± 0.35	0.02–1.0	
Left eye			
At admission	0.68 ± 0.37	0.0–1.0	P = 0.005
At the end	0.77 ± 0.36	0.0–1.0	
Days of stay in hospital (mean ± SE)	12.9 ± 0.6	6–17	
Number of hospital admissions			
1	45		76.3
2	9		15.3
3	3		5.1
4	0		0.0
5	1		1.7
6	1		1.7
Time lapse from first to last admission (years)	4.1 ± 0.9	1–9	

^aVisual acuity measured by Snellen chart at 6 m and converted to decimal notation.

Table 2 Clinical characteristics and outcome of patients with OT according to BCVA at presentation

BCVA of the affected eye	At admission ≤0.3	At admission >0.3	P-value
No. of patients	24	35	
Localisation of lesions			
Juxtapapillar	6 ^b	10 ^c	<0.0001 ^a
Central/paracentral	15	11	
Peripheral	0	11	
Multifocal	3 ^b	3 ^c	
Presence of			
Vitritis	14	12	0.068
Anterior uveitis	5	6	0.721
Retinal vasculitis	2	4	0.699
Complications of OT			
CNV	2	0	NA
Retinal detachment	1	0	
Secondary glaucoma	0	1	
CMO	1	0	
BCVA ^d at admission (mean ± SD)	0.06 ± 0.07	0.74 ± 0.21	<0.0001
BCVA at the end of treatment (mean ± SD)	0.25 ± 0.32	0.90 ± 0.13	<0.0001
P-value ^e	0.006	<0.0001	

Abbreviation: NA, not applicable because of low numbers.

^aBetween all patients with central and peripheral lesions taken together.

^bLocalized inside the vascular arcades (central and/or paracentral ± interpapillo-macular).

^cLocalized out of the vascular arcades (juxtapapillar and/or peripheral).

^dVisual acuity measured by Snellen chart at 6 m and converted to decimal notation.

^eBetween admission and end of treatment in groups of BCVA ≤ and >0.3.

In addition to the OT-defining lesions, the clinical presentation quite frequently included other manifestations of ocular inflammation. In contrast, complications were rare (Table 1).

Treatment was initiated immediately after diagnosis and included systemic Clindamycin 20–30 mg/kg for 3 weeks and/or a combination of pyrimethamine 2 × 25 mg 4–8 weeks with sulfadiazine 50–75 mg/kg and folic acid (leucovorin) 5 mg/day.

Best-corrected VA (BCVA) was the main parameter of the visual function. At admission, BCVA >0.3 was observed in 35 patients (Table 2) and ≤0.3 (moderate and severe visual impairment) in 24 patients, of which BCVA was ≤0.1 (0.04 ± 0.03) in as many as 21. At the end of treatment, BCVA was improved in all; in those with initial BCVA >0.3, vision improved to almost normal

Table 3 Clinical characteristics of OT patients with unilateral or bilateral blindness at the end of treatment

BCVA of the affected eye	≤0.1	>0.1	P-value
No. of patients	14 (of which 2 bilateral)	45	
Localisation of lesions			0.006 ^a
Juxtapapillar	1	15	
Central/paracentral	12	14	
Peripheral	0	11	
Multifocal	1 ^b	5 ^c	
Presence of			
Vitritis	8	18	0.259
Anterior uveitis	3	8	0.759
Retinal vasculitis	1	5	0.668
Complications of OT			
CNV	1	1	NA
Retinal detachment	1	0	
Secondary glaucoma	0	1	
CMO	0	1	
BCVA ^d at the admission (mean ± SD)	0.047 ± 0.055	0.60 ± 0.34	<0.0001
BCVA at the end of treatment (mean ± SD)	0.050 ± 0.037	0.82 ± 0.24	<0.0001
P-value	0.808	<0.0001	

Abbreviation: NA, not applicable due to very small numbers.
^aBetween groups of patients with central and peripheral lesions taken together.
^bLocalized in the posterior pole (interpapillo-macular).
^cLocalized out of the vascular arcades (juxtapapillar and/or peripheral).
^dVisual acuity measured by Snellen chart at 6 m and converted to decimal notation.

levels and was obviously significantly ($P < 0.0001$) better than in those with initial BCVA ≤ 0.3 . However, the improvement in these latter ($P = 0.006$), as well as in those with initial BCVA ≤ 0.1 (0.24 ± 0.32 ; $P = 0.01$), was clinically meaningful in only 10 patients, whereas 14 (24%) remained legally blind in the affected eye (Table 3). Of these, there were 2 (3%) cases of bilateral blindness (defined as BCVA of the better eye ≤ 0.1), whereas unilateral legal blindness (BCVA of the affected eye ≤ 0.1) was observed in 12 (20%) patients. Patients who ended up with unilateral or bilateral blindness had extremely poor BCVA (0.047 ± 0.055) at admission, which did not improve with treatment ($P = 0.808$). Both moderate and severe visual impairment at admission and poor treatment outcome depended on the lesion localization ($P < 0.0001$ and $P = 0.006$, respectively), occurring only in case of lesions within the vascular arcades, whereas other ocular inflammation manifestations had no effect.

Discussion

Globally, there are wide variations in the distribution of OT among all uveitis cases, with the smallest percentage of OT observed in Japan (0.7%)¹⁴ and the highest in South America (39.8%).¹⁵ Europe, North Africa, and USA range between these two extremes (2.9–14%).^{16–21} Thus, the data presented here from a Serbian referral centre showing OT in 12.9% of all patients admitted for uveitis, and in 24.3% of those with posterior uveitis, fit within those for Europe.

In our series, primary OT was observed in one-third and recurrent disease in two-thirds of all patients. Primary OT at first presentation has been reported at rates of 28–42.5%.^{5,6,22,23} The greater frequency of recurrent disease may be accounted for by old peripheral lesions that go unnoticed by the patient; this is also supported by our clinical findings of a combination of active lesions and old retinochoroidal scars at a greater frequency than the patients were aware of.

Patient age is one of the several host factors that are believed to influence the severity of OT, and OT tends to be more severe at the extremes of age.²⁴ Patients with OT are generally young adults, and in our study group, 76% of the patients were younger than 45 years. Similar results were found in other studies,^{5,18,22,23,25} for instance, Bosch-Driessen *et al*⁵ showed that the mean age at first presentation of OT was 29.5 years and that patients with primary ocular lesions were significantly older than those with combinations of active lesions and old scars. Also, Garweg *et al*²⁵ reported that the mean age at the first occurrence of OT was 23.9 years and patients with only one episode were older at first manifestation than those with two episodes (29.6 and 17.9 years, respectively). However, in our series, although patients with active primary OT were older than patients with recurrent OT, the difference was not significant.

Even greater age differences have been reported according to the origin of OT; that is, in the study of Delair *et al*,⁶ patients with OT of congenital origin were only 9.1 (± 8.8) and those with acquired origin 21.7 (± 12.6) years old. We were not able to distinguish between congenital and acquired origin of OT, but detection of Toxoplasma-specific IgM antibodies in a single patient would indicate ophthalmic manifestations coinciding with acute infection in 5% among patients with primary OT. The proportion of OT concomitant with acute toxoplasmosis based on the detection of serological markers of acute infection (specific IgM/IgA antibodies) has varied in different reports from 0% in a series in Turkey²⁶ to 11% in the Netherlands.⁵

At a rate of 73%, monocular presentation was clearly predominant and was within the range (64.3–86.4%) reported in other studies.^{18,22,23}

Localization of retinal lesions was predominantly within the vascular arcades, whereas peripheral lesions and those multifocal outside the vascular arcades were less common. This resulted in an end-of-treatment unilateral legal blindness in 24% patients, all of which had central lesions. Predominance of OT lesions within the vascular arcades has been commonly observed,^{5,18,22,23} for instance, of up to 84.2% of unilateral and 75% of bilateral cases in Italy,¹⁸ in a tertiary setting like ours where patients without visual impairment are infrequent, and of 73% in a Colombian cohort study.²² In contrast, in a population-based study in Brazil, peripheral lesions predominated (58.5%).²⁷ However, with regard to visual outcome, unilateral legal blindness occurred in as many as 37.8% patients in the Colombian study.²² This is substantially higher than the results reported in Europe; the rate of 24% that we found was virtually the same as the one reported by Bosch-Driessen *et al*,⁵ whereas Scherrer *et al*²⁸ found moderate to severe impairment (VA <0.3 or 0.05, respectively) in 27.5% of cases, which correlated with the central localization of lesions. These opposing results obviously reflect the general differences in the clinical evolution and severity of *Toxoplasma* infection in South America *vs* Europe and USA due to the above-mentioned differences in the respective parasite genotypes.

Ocular symptoms of inflammation did not differ, in type or in rate, from previous reports.^{22,26} However, the rate of vitritis was lower than generally reported,^{22,26,29,30} which may suggest that the level of vitreous haze was not always reliably recorded, particularly if low.

Complications of OT were not very marked. The 1.7% of cataract was similar to the findings of Balasundaram *et al*³⁰ and Tugal-Tutkun *et al*,²⁶ but considerably lower than the 13% reported by Bosch-Driessen *et al*;⁵ the comparatively high rate of complications in the latter series is presumably due to the longer follow-up. Interestingly, although raised IOP is often associated with an OT episode,^{23,29,30} glaucoma as a complication is rare; that is, in the study of Tugal-Tutkun *et al*, although an IOP rise was seen in 8% patients during active OT, there was no case of glaucoma as a complication,²⁶ nor was it seen in the series of Balasundaram *et al*.³⁰ In our series, one case was complicated by glaucoma secondary to OT.

In conclusion, OT was found to be a common cause of posterior uveitis in patients in Serbia. Given its vision-threatening potential, patients with OT should be aware of the recurring nature of their disease and react immediately in case of visual symptoms. In addition, because of the recently recognized significance of acquired toxoplasmosis in the origin of OT, public health campaigns to increase general public awareness of this infection are needed. Further research should focus on distinguishing between congenital and acquired infections in the origin of OT.

Summary

What was known before

- The course and manifestations of ocular toxoplasmosis (OT) have long been known. However, the recent advent of information on the genetic structure of *Toxoplasma*, as well as the increasing understanding that OT may develop after acquired infection as often as after intrauterine infection, call for revisiting of this issue in the literature. Accordingly, clinical studies of OT have recently been published.^{15,18,22,23}

What this study adds

- Although our study did not show that the course, presentation, and complications differ much in Serbia from other European countries, this is in contrast with the recent data from South America, which is important in itself. In addition, focusing on OT is important because of a still very high rate of poor outcomes. In our study legal blindness occurred in one-fourth of all the OT cases.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by a project (Grant no. III41019) from the Ministry of Education and Science of Serbia.

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