Recurrence characteristics in European patients with ocular toxoplasmosis

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ABSTRACT

Background: The risk of function loss after each episode of ocular toxoplasmosis (OT) supports efforts to improve our understanding of the disease.

Patients and methods: 139 patients with OT were contacted retrospectively and requested to complete a questionnaire addressing course and activity of their disease. This information was compared with that retrieved from their medical records. Sixty-three patients completed the questionnaire and were included in the study. They were allocated according to their median age to one of two groups (group 1: $<$20.9 years; group 2: $\geqslant$20.9 years).

Results: The mean reported age at the time of first ocular manifestation was 23.9 (median 20.9, range 0 to 70.5; SD 12.9) years. The clinical diagnosis was made 3.5 years later ($p = 0.0008$). The follow-up time was 6.5 (median 5.0; range 0.5 to 49.9; SD 7.6) years. The recurrence rate was higher in patients below 20.9 years (66%; $n = 35$) than in older patients (39%; $n = 28$; χ^2 test, $p<0.05$). Patients reporting only one episode were older at first manifestation (29.6 (median 25.6; range 10.6 to 70.5; SD 14.3) years; $n = 29$) than those reporting two episodes (17.9 (median 19.5; range 5.9 to 33.9; SD 7.8) years; $n = 15$ ($p<0.05$)). The proportion of patients who developed a recurrence was 54–63% after each episode without a tendency to enlarge, and the interval between successive episodes remained stable between 1.0 and 1.7 years for the first three recurrences.

Conclusion: Younger OT patients carry a higher risk of developing a recurrence than older ones. After each episode, two-thirds of all OT patients will develop another one.

Several key issues relating to ocular toxoplasmosis (OT) are still under debate. The pertinent literature yields heterogeneous and conflicting information respecting the characteristics of the disease and its recurrence. Beyond cases with a *Toxoplasma*-positive serology, the incidence of ocular involvement is estimated at 1.5–3%[1] but may be much higher for specific geographic and genetic backgrounds. Among Brazilians, for example, a peak incidence of 17.7% has been reported.[2 3] And black people who were born in West Africa, but are living in Britain, are prone to a 100-fold higher incidence than white individuals who were born in Britain.[1] These findings may reflect not only genetic, behavioural and cultural differences but also the socio-economic situation of the affected individuals.[4] Recurrences occur in nearly four out of every five persons who have been followed up for more than 5 years.[5 6] The risk of a recurrence appears to be higher during the first year of an active episode of retinochoroiditis (cumulative incidence until end of the first year 21%, until end of the second year 27%).[7] Recurrences may be attributable to senescent changes in tissue cysts, with an ensuing release of parasites or antigens, to trauma, to hormonal fluctuations, to transient humoral or cellular immunoreactivity,[8] to pregnancy or to cataract surgery.[9 10] The development of severe, progressive and atypical lesions may be exacerbated by age, pregnancy and immunosuppression, but specific triggers for reactivation have not been identified.[10–17]

Most patients with an active OT lesion have been reported to be between 30 and 40 years of age. And in more than 25% of clinically diagnosed cases, the retinal lesions are primary ones, occurring in the absence of old scars.[1 5 18 19] Patients with primary OT tend to be older than those with active lesions and old scars. According to serological characteristics, more than 10% of European and North American patients[1 5 18] and the overwhelming majority of Brazilian ones[2 20 21] are in an acute phase of systemic infection.

Available data do not correspond closely with the clinical behaviour of the disease in our own OT patients. We therefore conducted a retrospective study to evaluate age at the onset of OT, the number of recurrences and the interval between single episodes in a mid-European population of patients.

PATIENTS AND METHODS

Our case series consisted of 119 consecutive patients who had been reviewed from the onset of symptoms at the Department of Ophthalmology, University of Bern (Switzerland), and of 20 who had been referred to the Department by private ophthalmologists. With the approval of the Local Institutional Ethical Committee, the patients were contacted retrospectively and asked to complete a mailed questionnaire addressing the course and the activity of their disease, with emphasis on the dates of the first manifestation and recurrences. Only questionnaires that had been fully answered were included in the study. The information supplied by the patients was compared with that retrieved from their clinical records. Neither the mode of infection (acquired or congenital) nor serological criteria were considered. But all individuals were seropositive for *Toxoplasma* antibodies, and all patients had been offered a 6-week antiparasitic treatment with pyrimethamine and sulfonamides under the control of haematological and serological parameters, which was completed in more than 90% of instances.

The patients were allocated to one of the two groups according to their median age at the time of

the first ocular manifestation (table 1). For the descriptive data analysis, we calculated the median values (for graphic presentation), the means (for the statistical evaluation), SD, and the minimal and maximal values. Differences between sets of quantitative data were analysed using the Student t test and Wilcoxon two-sample test for smaller groups. For the bivariate analysis, the χ^2 test was applied. For all comparisons, the level of significance was set at $p = 0.05$. The median recurrence-free survival time between the first and subsequent episodes was determined using the Kaplan–Meier estimate, which was calculated according to the logrank test.

RESULTS

Sixty-three questionnaires were correctly completed and thus available for analysis. Forty of the 63 patients were female (63%) and 23 male (37%). Bilateral involvement occurred in 14 instances (22%). The mean follow-up time was 6.5 years (median 5.0 years; range 0.5 to 49.9 years; SD 12.9 years). The mean reported age at the time of the first ocular manifestation of the disease was 23.9 years (median 20.9 years, range 0 to 70.5 years; SD 12.9 years). According to the medical records, which were available for 59 patients, the clinical diagnosis was made 3.5 years later, at a mean age of 27.4 years (median 25.7 years; range 10.6 to 73.4 years; SD 12.7 years ($p = 0.0008$)). The gender of the patients had no influence either on the reported age at the time of the first ocular manifestation or on unilateral versus bilateral involvement at this juncture.

The patients were allocated to one of two groups according to their median age at the time of the first ocular manifestation: group 1 <20.9 years: group 2 ≥20.9 years. Thirty-five patients fell within the first category (56%) and 28 within the second (44%). The rate of recurrence was higher in group 1 (younger patients (66%)) than in group 2 (older individuals (39%)) (χ^2 test: $p<0.05$ (table 1)). If the level of discrimination was set at 30 years of age, the difference in the recurrence rates between younger and older individuals was even more pronounced, 67% vs 15%, respectively (χ^2 test: $p = 0.001$).

Patients reporting only one episode (n = 29) had a mean age of 29.6 years (median 25.6 years; range 10.6 to 70.5 years; SD 14.3 years) at the time of its manifestation. Patients reporting two (n = 15) or more episodes (n = 19) were younger at the time of the first manifestation (two episodes: mean age 17.9 years; median years 19.5 years; range 5.9 to 33.9 years; SD 7.8 years); more than two episodes: mean age 19.0 years; median 20.0 years; range 0.0 to 38.0 years; SD 8.6 years ($p<0.05$)).

No differences were observed either in the interval between single episodes (fig 1) or in the portion of patients who developed a recurrence after their last episode had healed for the first three recurrences (fig 2): 54% of the patients had one recurrence. Fifty-six per cent of them had a second recurrence 1.0 year after the last episode. Sixty-three per cent of those with three episodes (n = 19) developed their third recurrence 1.6 years after the last and 4.3 years after the first episode, and 33% of those with four episodes (n = 2) developed their fourth recurrence 5.1 years after the first episode (fig 3). Most of the recurrences occurred within the first, second or third year of the first manifestation (cumulative incidences: 32%, 53% and 64%, respectively (n = 34)).

Table 1 Recurrence rates of ocular toxoplasmosis in the two age brackets

Age of patient at the time of the first ocular manifestation	No of patients experiencing recurrences	No of patients with no recurrence	Total no of patients
<20.9 years	23	12	35
≥20.9 years	11	17	28
Total	34	29	63

Patients younger than 20.9 years at the time of the first ocular manifestation tended to develop recurrences more frequently than older patients (66% vs 39%, respectively; $p<0.05$).

DISCUSSION

Patients who were younger than 21 years at the time of the first manifestation of OT carried a higher risk of developing recurrences than older individuals. Hence, the median age of our patients at the time of the first episode is 8.5 years younger than the average age reported over all episodes in the literature.[5] Most likely because younger individuals are more likely to develop recurrences, the time elapsing between the initial ocular manifestation and later recurrences is longer than that calculated from the mean age of our patients (mean age at first episode 23.9 years; age at first recurrence 24.8 years; age at third recurrence 27.3 years) and differs from calculated averages for all recurrences. Our overall recurrence rate of 54–67% falls within the literature range for Europeans: 57–79%.[5 7] In contrast to common belief,[22] the proportion of patients with recurrences was, however, not influenced by the number of episodes.

In 17.5% of our patients, the ocular disease pattern was characteristic of a primary infection, namely, no scars existed at the time of the first diagnosis. This value lies at the lower end of the literature range for Europeans.[5] That nine of the 11 patients with primary OT (14.3% of all patients) were younger than 30 years (mean age: 25.9 years) accords with the published age incidences of primary OT for European and North American populations.[1 5 18 23] At the time of the first ocular manifestation, patients with a primary disease tended to be older than those with pre-existing scars at their first examination. This finding likewise accords with existing data,[5] with the expectation that older patients carry a higher risk of ocular involvement due to a recently acquired infection with *Toxoplasma gondii*.[24–27]

Our observation that younger patients were more prone to developing recurrences than older ones (table 1) implies that age, in addition to the mode of infection (congenital or acquired), could have an impact on the recurrence behaviour of the disease.[28] Corresponding to a decrease in the seroprevalence of the disease, one would expect a decrease in the incidence for cases of acquired OT since the 1960s and, in consequence, also an upward shift in the age bracket for newly acquired infection with *Toxoplasma* since this time. However, no

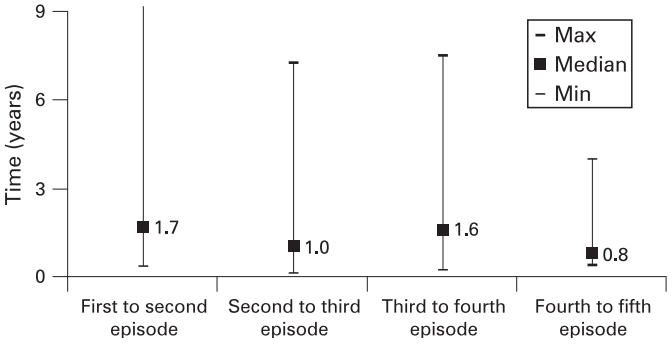

Figure 1 Plot of the time elapsing between successive episodes of ocular toxoplasmosis (up to 5). The interval between successive episodes was not influenced by their number.

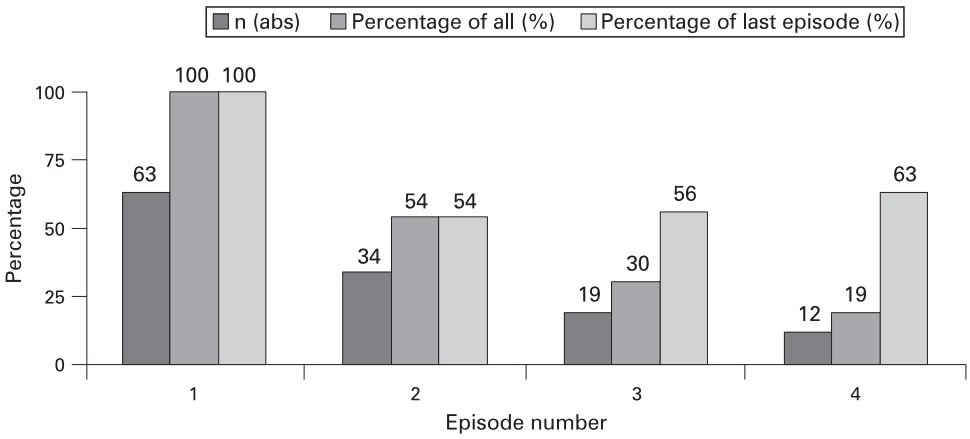

Figure 2 Frequency of ocular toxoplasmosis episodes in our case series. The number on the x axis displays the episode number, the black columns (n (abs)) represent the absolute number of individuals experiencing an episode, the darker grey columns the portion of all patients, and the light grey columns the portion of patients from the last episode experiencing a new one. 46% of patients remained free of recurrences. 54% (n = 34) developed a second, 30% (n = 19) a second and 19% (n = 12) a third episode. The proportion of patients with recurrences was not influenced by the number of episodes.

such shift has been reported.[29] This may be partially explained by age- and genetic-background-related differences in the recurrence behaviour of OT patients.

However, neither age nor genetic background is likely to explain per se a difference in recurrence frequencies between younger and older individuals. Therefore, the congenital way of infection, the route of infection, the host–parasite relationship, and systemic and local immunotolerance factors have been discussed. None has been identified to play a key role in animal models.[30] This may allow the conclusion that recurrence behaviour is a multifactorial phenomen. Clinically, we have observed that local antibody production may be detected markedly after the manifestation of first clinical symptoms, namely in congenitally attracted disease with a low inflammatory response. Moreover, a marked variability in local and systemic antibody levels is known from patients with recurrent disease of presumably congenital origin. Patients with acquired disease, in contrast, manifest more uniformly a marked inflammatory response and usually harbour high levels of specific antibodies.[31] In a rabbit model of acquired ocular toxoplasmosis, we have shown that high levels of local antibodies may persist over several months.[32] Based on these observations, one might argue that patients with a stronger immune response and persisting high local antibody concentrations, that is otherwise healthy young patients with acquired disease, may achieve a better protection against reactivation, but this has as yet to be shown. Moreover, the active infection is widely controlled by cellular immunity, and the influence of the humoral immune response in the control of the active infection and recurrences is uncertain. On the other hand, the host–parasite relationship and the contribution of host genetics as well as the impact of the route of infection onto reactivation are not widely understood.[30 33] Moreover, the regulation and restoration of ocular immune privilege during and after active infection may be related to the development of early recurrences and may well differ between congenital and acquired disease.[30] But again, published evidence does not support speculations in either direction so far.

The risk for a recurrence is generally assumed to be highest during the first year of the primary ocular manifestation[23] implying a decrease over time. Our data do not confirm this tenet: 53% of our patients developed a recurrence within the first 2 years of the primary ocular manifestation. However, an inspection of the recurrence behaviour revealed that 54–67% of our patients experienced a recurrence after their last episode had healed (fig 2) and that the interval between any episode and the next recurrence tended to decrease as the number of episodes increased (p = 0.008; fig 4). Since the proportion of recurrences in our case series lies within the reported range for acquired OT, we are not in a position to speculate on whether the recurrence behaviour is influenced by the mode of infection (acquired or congenital).[7]

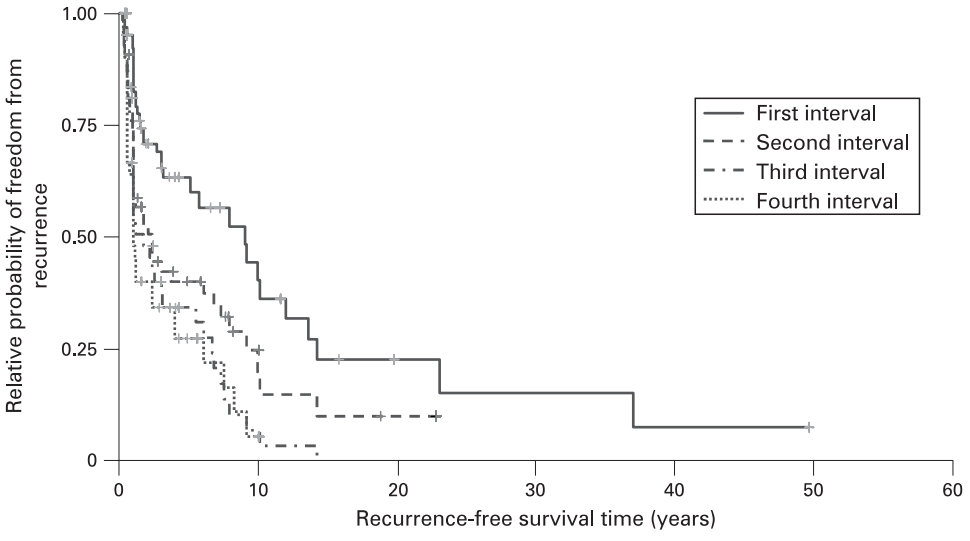

Figure 3 Kaplan–Meier analysis of the interval between the ocular manifestation and a recurrence. The median times from ocular manifestation to successive episodes were: 9.0 years from first to the second episode (n = 34), 2.3 years from second to the third episode (n = 19), 1.7 years from third to the fourth episode (n = 12) and 1.0 years from fourth to the fifth episode (n = 4).

That younger individuals harbour a higher risk of recurrences during the first year of primary ocular manifestation is interesting because it might imply an age-stratified treatment. It has to be kept in mind that none of the antiparasitic treatments does achieve an eradication of the dormant parasite tissue cysts, and none has been shown to result in a better functional outcome, fewer recurrences or a longer time to recurrence. The use of antiparasitic therapy is therefore not unequivocally deemed necessary but associated with significant side effects.[27 34] On the other hand, an antibiotic interval prophylaxis of recurrences has proven effective in Brazilian patients with frequent recurrences.[3] In the absence of a sufficient efficacy of antiparasitic therapies but an effect of antiparasitic prophylaxis on recurrences, it might therefore be concluded that younger patients with frequent recurrences (ie, more than two per year) and those with a macula at risk due to a parafoveal lesion should be considered candidates for an antiparasitic prophylaxis for up to 1 year after an active disease episode. In the future, treatment studies might consider the time to recurrence and number of recurrences after stratification for patient age as outcome measures for a treatment effect. Prophylaxis studies, at least in European patients, would be expected to gain strength if they focus on a 12-month prophylaxis and a 12-month observation period after ocular manifestation or first recurrence.

To some extent, our data have been influenced by a selection bias, since 76 patients had to be excluded (no response or incomplete answering of the questionnaire). The prevalence of females may also have contributed to this selection bias, since women tended to show more interest in the clinical examination and are more flexible regarding appointments for clinical assessment in our series. Interestingly, but probably unrelated to a selection bias, our patients reported their first episode of OT to occur more than 3 years before the first consultation and diagnosis (as documented in the medical records). And in some instances, the discrepancy spanned more than 10 years. This finding indicates that great care must be exercised in interpreting information derived from these different sources.

In summary, we have shown that younger OT patients carry a higher risk of developing recurrences than older patients, and that after each episode, a constant proportion of individuals (50–70%) develop a further one. The interval between the first ocular manifestation and a recurrence tends to decrease as the number of episodes increases. Our data afford new insights of OT in Europeans,[35] and may help to anticipate the results of treatment–effect studies.

Competing interests: None.

Ethics approval: Ethics approval was obtained from the Local Institutional Ethical Committee.

REFERENCES

1. **Gilbert RE,** Dunn DT, Lightman S, *et al*. Incidence of symptomatic *Toxoplasma* eye disease: aetiology and public health implications. *Epidemiol Infect* 1999;**123**:283–9.
2. **Silveira C,** Belfort R Jr, Muccioli C, *et al*. A follow-up study of *Toxoplasma gondii* infection in southern Brazil. *Am J Ophthalmol* 2001;**131**:351–4.
3. **Silveira C,** Belfort R Jr, Muccioli C, *et al*. The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis. *Am J Ophthalmol* 2002;**134**:41–6.
4. **de Amorim Garcia CA,** Orefice F, de Oliveira Lyra C, *et al*. Socioeconomic conditions as determining factors in the prevalence of systemic and ocular toxoplasmosis in Northeastern Brazil. *Ophthalmic Epidemiol* 2004;**11**:301–17.
5. **Bosch-Driessen LE,** Berendschot TT, Ongkosuwito JV, *et al*. Ocular toxoplasmosis: clinical features and prognosis of 154 patients. *Ophthalmology* 2002;**109**:869–78.
6. **Hovakimyan A,** Cunningham ET Jr. Ocular toxoplasmosis. *Ophthalmol Clin North Am* 2002;**15**:327–32.
7. **Bosch-Driessen EH,** Rothova A. Recurrent ocular disease in postnatally acquired toxoplasmosis. *Am J Ophthalmol* 1999;**128**:421–5.
8. **O'Connor GR.** Factors related to the initiation and recurrence of uveitis: XL Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1983;**96**:577–99.
9. **Bosch-Driessen LH,** Plaisier MB, Stilma JS, *et al*. Reactivations of ocular toxoplasmosis after cataract extraction. *Ophthalmology* 2002;**109**:41–5.
10. **Garweg JG,** Scherrer J, Wallon M, *et al*. Reactivation of ocular toxoplasmosis during pregnancy. *Br J Obstet Gynaecol* 2005;**112**:241–2.
11. **Holland GN,** Engstrom RE Jr, Glasgow BJ, *et al*. Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1988;**106**:653–67.
12. **Holland GN,** O'Connor GR, Diaz RF, *et al*. Ocular toxoplasmosis in immunosuppressed nonhuman primates. *Invest Ophthalmol Vis Sci* 1988;**29**:835–42.
13. **Holland GN.** Ocular toxoplasmosis: a global reassessment. Part II: disease manifestations and management. *Am J Ophthalmol* 2004;**137**:1–17.
14. **Johnson MW,** Greven GM, Jaffe GJ, *et al*. Atypical, severe toxoplasmic retinochoroiditis in elderly patients. *Ophthalmology* 1997;**104**:48–57.
15. **Jones JL,** Muccioli C, Belfort R Jr, *et al*. Recently acquired *Toxoplasma gondii* infection. *Brazil Emerg Infect Dis* 2006;**12**:582–7.
16. **Labalette P,** Delhaes L, Margaron F, *et al*. Ocular toxoplasmosis after the fifth decade. *Am J Ophthalmol* 2002;**133**:506–15.
17. **Morhun PJ,** Weisz JM, Elias SJ, *et al*. Recurrent ocular toxoplasmosis in patients treated with systemic corticosteroids. *Retina* 1996;**16**:383–7.
18. **Friedmann CT,** Knox D. Variations in recurrent active toxoplasmic retinochoroiditis. *Arch Ophthalmol* 1969;**81**:481–93.
19. **Rothova A.** Ocular manifestations of toxoplasmosis. *Curr Opin Ophthalmol* 2003;**14**:384–8.
20. **Glasner PD,** Silveira C, Kruszon-Moran D, *et al*. An unusually high prevalence of ocular toxoplasmosis in southern Brazil. *Am J Ophthalmol* 1992;**114**:136–44.
21. **Silveira C,** Belfort R Jr, Burnier M Jr, *et al*. Acquired toxoplasmic infection as the cause of toxoplasmic retinochoroiditis in families. *Am J Ophthalmol* 1988;**106**:362–4.
22. **Lum F,** Jones JL, Holland GN, *et al*. Survey of ophthalmologists about ocular toxoplasmosis. *Am J Ophthalmol* 2005;**140**:724–6.
23. **Holland GN.** Ocular toxoplasmosis: a global reassessment. Part I: epidemiology and course of disease. *Am J Ophthalmol* 2003;**136**:973–88.
24. **Holland GN.** Reconsidering the pathogenesis of ocular toxoplasmosis. *Am J Ophthalmol* 1999;**128**:502–5.
25. **Jones JL,** Kruszon-Moran D, Wilson M, *et al*. *Toxoplasma gondii* infection in the United States: Seroprevalence and risk factors, *Am J Epidemiol* 2001;**154**:357–65.
26. **Joynson DH.** Epidemiology of toxoplasmosis in the U.K. *Scand J Infect Dis* 1992;**84**(Suppl):65–9S.
27. **Portela RW,** Bethony J, Costa MI, *et al*. A multihousehold study reveals a positive correlation between age, severity of ocular toxoplasmosis, and levels of glycoinositolphospholipid-specific immunoglobulin A. *J Infect Dis* 2004;**190**:175–83.
28. **Gilbert R,** Tan HK, Cliffe S, *et al*. Symptomatic *Toxoplasma* infection due to congenital and postnatally acquired infection. *Arch Dis Child* 2006;**91**:495–8.
29. **Smith KL,** Wilson M, Hightower AW, *et al*. Prevalence of *Toxoplasma gondii* antibodies in US military recruits in 1989: Comparison with data published in 1965. *Clin Infect Dis* 1996;**23**:1182–3.
30. **Jones LA,** Alexander J, Roberts CW. Ocular toxoplasmosis: in the storm of the eye. *Parasite Immunol* 2006;**28**:635–42.
31. **Garweg JG,** Jacquier P, Böhnke M. Early aqueous humor analysis in patients with human ocular toxoplasmosis. *J Clin Microbiol* 2000;**38**:996–1001.
32. **Garweg JG,** Boehnke M. The antibody response in experimental ocular toxoplasmosis. *Graefes Arch Clin Exp Ophthalmol* 2006;**244**:1668–79.
33. **Garweg JG.** Determinants of immunodiagnostic success in human ocular toxoplasmosis. *Parasite Immunol* 2005;**27**:61–8.
34. **Stanford MR,** See SE, Jones LV, *et al*. Antibiotics for toxoplasmic retinochoroiditis: an evidence-based systematic review. *Ophthalmology* 2003;**110**:926–31.
35. **Scherrer J,** Iliev ME, Halberstadt M, *et al*. Visual function in human ocular toxoplasmosis. *Br J Ophthalmol* 2007;**91**:233–6.