Rate of recurrence of toxoplasmosis retinochoroiditis at a tertiary eye centre in Auckland

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ABSTRACT

AIM: Our aim was to examine rate of recurrence of toxoplasmosis retinochoroiditis and risk factors for recurrence. No New Zealand epidemiological data on recurrence rates of toxoplasmosis retinochoroiditis have been previously published.
METHODS: Retrospective chart review of all patients with toxoplasmosis retinochoroiditis presented to Auckland District Health Board Department of Ophthalmology between 2006–2019.
RESULTS: One hundred and twenty-six eyes of 115 patients were included with a median age at initial diagnosis of 36.7 years (IQR 23.7–53.8). Fifty-nine patients were female (51.3%), and 16 patients (13.9%) were immunosuppressed. Twenty-six of the 86 patients tested (30.2%) were IgM positive at presentation. Mean follow-up was 6.1 years and 73 recurrences occurred during the follow-up period in 36 patients (31.3%). Treatment was initiated in 87.4% of cases, with oral cotrimoxazole or clindamycin the most common options. Recurrence occurred in 14.8% in the first year (95% CI 10.3%–21.0%), and the risk of recurrence was increased 2x for every previously documented recurrence (HR 2.00; p<0.001). There was no statistically significant increased risk of recurrence with age, IgM positivity, immunosuppression or macular involvement.
CONCLUSIONS: Toxoplasmosis retinochoroiditis had a 14.8% risk of recurrence in the first year, with each previous recurrence increasing the risk by two-times.

Toxoplasmosis gondii is a ubiquitous parasitic protozoan that causes blindness worldwide. Although cats are its primary hosts, toxoplasmosis commonly infects humans and can infect any nucleated mammalian cell.[1] An estimate in 2004 suggested one third of the human population was infected with toxoplasmosis.[2] Positive toxoplasmosis serology varies between 20–85% in the world,[1] with differences largely due to cultural differences in cooking patterns and cleanliness of water supply. The most common pathological clinical presentation of toxoplasmosis is acute retinochoroiditis[1]—inflammation of the retina and choroid in the eye. This results in scarring of these structures and can lead to permanent vision loss left untreated.

Ocular toxoplasmosis typically has a recurring course[2] that can be explained by the lifecycle of the parasite. The slow-growing bradyzoite forms of toxoplasmosis can remain dormant for prolonged periods throughout a person's lifetime. Bradyzoites covert into fast-growing tachyzoites, which utilise cells of nucleated hosts to replicate. These manifest clinically with unilateral necrosis of the retina with secondary inflammation of surrounding choroid, vitreous and retinal vessels. The necrosis often occurs adjacent to a pigmented retinochoroidal scar. No cure for ocular toxoplasmosis is known, and current treatments aim to reduce inflammation, scar size, and rates of recurrence.

Knowledge of recurrence rates and risk factors for recurrence can guide treatment. Recurrence rates of ocular toxoplasmosis range from 40–79%,[3] with the highest rate of recurrence of toxoplasmosis being in the first year. Higher rates of recurrence have been reported to occur in the elderly or very young, people with existing retinal scars,[4] people affected with Brazilian strains of *T. gondii* compared to European or American strains,[5] IgM positive patients treated with intravitreal therapy compared to classic oral therapy,[3] lack of long-term antibiotic prophylaxis,[6] and immunosuppressed people. Treatment with prophylactic antibiotics for secondary prevention has been shown to reduce recurrence rates.[5] However, the only absolute indications for this are congenital toxoplasmosis, infection during pregnancy and immunocompromised status.[3] In immunocompetent individuals, an active episode of ocular toxoplasmosis can resolve without treatment. Thus, the decision to treat with antibiotics for secondary prophylaxis is controversial despite its tendency to relapse.[7]

Given the high variability between geographic locations of seroprevalence and prevalence of different strains of toxoplasmosis, local epidemiological data is important. Currently, no known studies have looked at rates of recurrence in the New Zealand population. The aim of this study was to explore rates and risk factors for recurrence of toxoplasmosis retinochoroiditis in a New Zealand population.

Methods

Patients with toxoplasmosis retinochoroiditis were identified from a database of patients with uveitis seen in Uveitis Clinic (acute clinic and specialist clinic) at Auckland District Health Board, a publicly-funded specialty eye clinic for the Auckland Region, between 2006 and 2019. To be seen in this clinic: patients with possible uveitis are referred from general practitioners, optometrists, and other ophthalmologists in public or private, or triaged from the acute eye clinic. The catchment group is therefore Auckland residents who have acute toxoplasmosis retinochoroiditis, or those who have dormant toxoplasmosis retinochoroiditis and choose to have publicly-funded follow-up appointments in Auckland. Patients with follow-up in private clinics and patients from outside Auckland were excluded. Ethics Committee approval was obtained before data collection (AH 1339).

Data was collected on a standardised pro forma including demographic characteristics, immunosuppression, presentation, toxoplasmosis serology, treatment, complications and recurrence of disease. The best-corrected visual acuity results were converted to logMAR units for analysis. For visual acuities of counting fingers or worse, the following conversion was used: counting fingers 2.0 logMAR; hand movements 2.3 logMAR; light perception 2.6 logMAR; no light perception 2.9 logMAR.

Statistical analysis

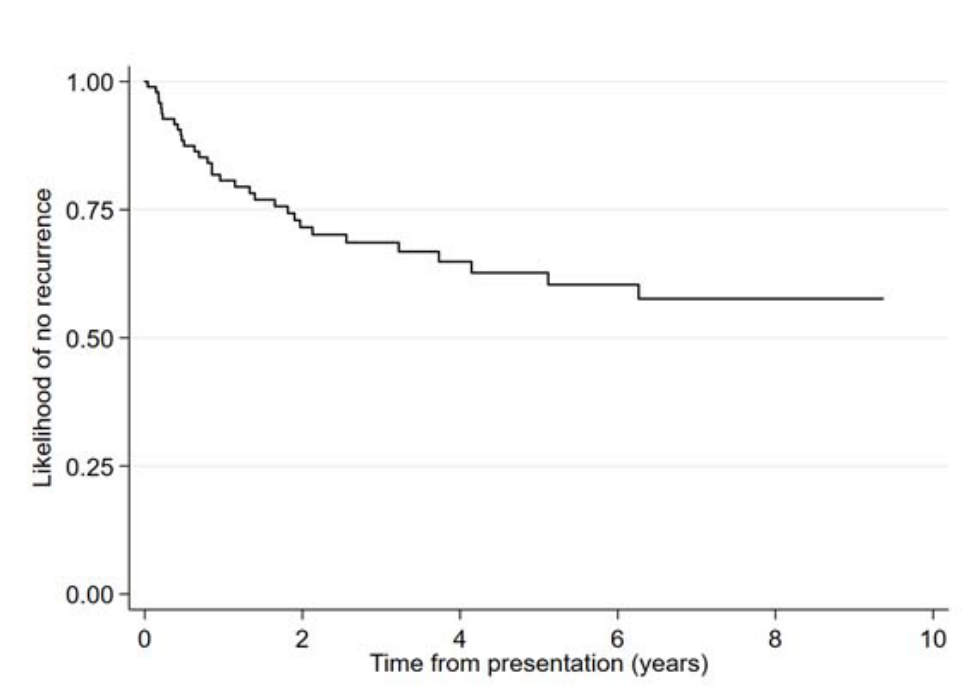
Data was entered into a spreadsheet before analysis. Risk factors for recurrence of toxoplasmosis retinochoroiditis were calculated using a marginal Cox Regression model with a robust sandwich estimate to allow for correlations between eyes. A p value <0.05 was considered significant. Data was analysed using STATA version 15 (StataCorp 2017, College Station, TX).

Results

Rate of recurrence

Toxoplasmosis was identified in 126 eyes of 115 patients, representing 4.3% of the 2659 patients in the uveitis database at the time of the study. During the study period, 199 episodes of retinochoroiditis were observed. Mean follow-up was 6.1 years, with

Figure 1: Cumulative hazard of recurrence of toxoplasmosis retinochoroiditis.



a total of 696.9 eye-years follow-up. During the follow-up period, 73 recurrences were observed amongst the 43 eyes of 37 patients. In the 126 eyes: 43 had at least one recurrence; 20 had at least two recurrences; 7 had at least three recurrences; 5 had at least four recurrences; 3 had at least five recurrences; 1 had at least six recurrences; and none had seven or more recurrences. No patients with unilateral active disease at initial presentation, and a previously unaffected contralateral eye, developed recurrence in the unaffected eye.

Cumulative incidence of recurrence is reported in Figure 1. Specifically, this shows the cumulative incidence for any recurrence from a population perspective based on the number of individuals who had one or more recurrences out of the total population after specified time intervals. The cumulative hazard of recurrence declined over time and was greatest at 1 year. The likelihood of no recurrences at 1, 2 and 3 years was 14.8% (95% CI 10.3–21.0%), 25.5% (95% CI 19.5–32.9%) and 33.4% (95% CI 26.4–41.6%), respectively.

Patient demographics

Demographic characteristics are reported in Table 1. Age at first presentation ranged between 1.8 to 85.2 years, with a median age of 36.7 years (IQR 23.7–53.8). Fifty-nine patients (51.3%) were female. Sixteen patients were immunosuppressed (13.9%), which included three patients who were HIV positive, four patients receiving chemotherapy, two patients with chronic lymphocytic leukaemia, two patients receiving immunosuppression for rheumatological disorders, and one patient with splenectomy.

Presentation

Visual acuity, intraocular pressure, presence of cells in the anterior or vitreous chambers, proportions of active lesions being macular and peripapillary, and presence of retinochoroidal scars at initial presentation are listed in Table 2. In presentations with recurrence of toxoplasmosis within our study period, active lesions were macular in 70.0% of the recurrent presentations during our study period, peripapillary in 4.7% and more peripheral in the remainder.

Table 1: Demographic characteristics.

	All patients N = 115 (%)	**Patients with ≥1 recurrences N = 37 (%)**	**Patients with 0 recurrences N = 78 (%)**
Median age at first presentation (years)	36.7; IQR 23.7–53.8	36.3; IQR 26.0–57.1	37.2; IQR 21.6–53.8
Female	59 (51)	18 (49)	41 (53)
Ethnicity			
European	67 (58)	23 (62)	44 (56)
Asian	17 (15)	8 (22)	9 (12)
Pacific Islander	17 (15)	3 (8)	14 (18)
Māori	6 (5)	1 (3)	5 (6)
Other	7 (6)	2 (5)	5 (6)
Unknown	1 (1)	0 (0)	1 (1)
Immunosuppressed	16 (14)	7 (19)	9 (12)
HIV	3 (3)	3 (8)	0 (0)
Serology done	85 (74)	25 (68)	60 (77)
IgM positive *	27 (32)	8 (32)	19 (32)
IgG levels > 100 *	53 (62)	15 (60)	38 (63)

* expressed as a percentage of patients with serology tested

Table 2: Ophthalmic clinical features at presentation of ocular toxoplasmosis.

	Initial presentations in eyes with ≥1 recurrence **N = 43 (%)**	**Initial presentations in eyes with 0 recurrences** **N = 83 (%)**	**Recurrent presentations** **N = 73 (%)**
Median best-corrected visual acuity	6/9; IQR 6/7.5–6/27	6/15; IQR 6/7.5–6/120	6/9; IQR 6/7.5–6/18
Intraocular pressure ≥24 mmHg	2 (5)	16 (19)	11 (15)
Presence of cells in the:			
Anterior chamber	24 (56)	47 (57)	45 (62)
Vitreous chamber	34 (79)	62 (75)	69 (95)
Location of active lesion(s):			
Macular	12 (28)	27 (33)	30 (41)
Peripapillary	3 (7)	14 (17)	2 (3)
Retinochoroidal scars present at initial presentation in this study	20 (47)	39 (47)	–

Table 3: Treatments initiated in active ocular toxoplasmosis.

	Initial presentations in patients with ≥1 recurrence **N (%)**	**Initial presentations in patients with 0 recurrences** **N (%)**	**Recurrent presentations** **N (%)**
Treatment initiated	31 (72)	72 (87)	71 (97)
Unknown if treatment initiated	1 (2)	3 (4)	0 (0)
Antibiotics given:			
Oral	28 (65)	64 (77)	59 (81)
Cotrimoxazole *	11 (39)	35 (55)	25 (42)
Clindamycin *	8 (29)	9 (14)	29 (49)
Triple therapy *	4 (14)	6 (9)	0 (0)
Mixed *	5 (18)	12 (19)	5 (8)
Intravitreal clindamycin	3 (7)	4 (5)	4 (5)
1 injection	0 (0)	0 (0)	4 (5)
≥1 injection			
Steroids given	30 (70)	68 (82)	67 (92)
Oral #	24 (80)	58 (85)	53 (79)
Intravitreal #	0 (0)	1 (1)	5 (7)
Topical #	20 (67)	54 (79)	41 (61)
Prophylactic antibiotics	6 (14)	21 (25)	22 (30)

* expressed as a percentage of patients given oral antibiotics in respective groups; # expressed as a percentage of patients given steroids in respective groups (individual percentages do not total 100, as some patients were given steroids via multiple routes).

Treatment

Treatment was initiated at presentation in 174 cases (87.4%). Of the 151 cases treated with oral antibiotics, antibiotic choice was documented in 149 (98.7%). Cotrimoxazole was the most common choice, followed by clindamycin and classic triple therapy (Table 3). In the remainder, different variations of combination therapy were utilised. There was no statistical difference in recurrence between clindamycin versus cotrimoxazole (p=0.70) and classic triple therapy versus cotrimoxazole (p=0.20). Intravitreal therapy with clindamycin was utilised in 15 cases. Eleven eyes received one intravitreal injection, one eye received two injections, two eyes received three injections, and one eye received four injections. No oral antibiotics were given to 75% of those who received more than one intravitreal antibiotic injection.

Oral steroid was given in 135 cases (67.8%) and intravitreal dexamethasone in 6 cases (3.0%). Topical steroid was given in 115 cases (57.8%). Long-term prophylaxis was commenced in 49 cases (24.6%). Cases involving immunosuppressed patients were significantly more likely to receive prophylactic treatment (68.0% vs 19.3%, p<0.001). There was no statistically significant difference in risk of recurrence between those given and those not given prophylactic antibiotics (p=0.38).

Treatment was commonly initiated if patients had congenital toxoplasmosis, multiple central lesions or vision-threatening features, such as significant vitritis or vasculitis, were symptomatic of floaters or blurry vision, the location of the active retinochoroidal lesion was macular, peripapillary or on the arcades, or if risks of vascular occlusion or retinal detachment were significant for the individual, although reasons were not always documented.

Risk factors of recurrence

The only statistically significant risk factor associated with increased risk of recurrence was previous recurrence (HR 2.00, p<0.001) (Table 4). Demographic characteristics like age, gender and immunosuppression, and serological parameters like IgM positivity and IgG levels >100 AU/mL had no statistically significant association with risk of recurrence. Presenting features like best-corrected visual acuity or ocular hypertension (intraocular pressure ≥24 mmHg) at initial presentation, and initiation of treatment had no statistically significant association with risk of recurrence of ocular toxoplasmosis.

Table 4: Risk factors for recurrence.

	Hazard ratio	95% CI	p value
Age	1.01	0.99–1.04	0.17
Female	0.78	0.35–1.76	0.43
Immunosuppression	1.81	0.65–4.72	0.15
IgM positive	1.11	0.40–3.13	0.82
IgG >100 AU/mL at presentation	0.91	0.35–2.07	0.83
Best corrected visual acuity of affected eye	0.70	0.39–1.18	0.082
Intraocular pressure ≥24 mmHg	0.89	0.43–2.54	0.74
Presence of cells in anterior chamber	1.52	0.96–1.86	0.29
Presence of cells in vitreous chamber	1.15	0.85–7.54	0.54
Previous recurrence	2.00	1.29–2.98	<0.001
Treated	0.94	0.35–2.78	0.89

Discussion

Toxoplasmosis retinochoroiditis is a common cause of posterior uveitis in New Zealand.[8] In our study, toxoplasmosis retinochoroiditis recurred in 32% (37/115) of patients; the highest rate of recurrence was within the first year of initial presentation. Previous recurrence was the only statistically significant risk factor for recurrence.

The three main strengths of this study were having a large catchment size, a relatively captive population to study, and relatively long follow-up periods. A moderately large number of patients with toxoplasmosis retinochoroiditis in a single area were identified. Because there is only a single emergency eye clinic for Auckland City, most acute episodes of toxoplasmosis retinochoroiditis for the region would have been captured in this study. Although episodes managed in private optometry and ophthalmology centres were excluded, practitioners in these centres would likely have been referred to the centralised emergency eye clinic for further assessment and acute management. Thirdly, patients could be followed up for longer periods (mean follow-up time was 6.1 years in our study). The 199 episodes of toxoplasmosis retinochoroiditis captured in our study are likely the majority of acute episodes that occurred for our study patients during the study period. Unlike studies where episodes are self-reported, these episodes were all clinically diagnosed episodes of recurrence.

This study also had limitations. Episodes where patients self-treated themselves, or that occurred while patients were residing outside of the Auckland Region, would not have been clinically-diagnosed, and thus no episode of active toxoplasmosis retinochoroiditis would have been recorded. Although this is likely a low number of active episodes, this may underestimate the true incidence of active episodes of toxoplasmosis retinochoroiditis. Secondly, heterogeneity of treatment criteria between clinicians may have reduced statistical differences between groups of patients with recurrences and without recurrences, and thus potentially reduces identification of other significant risk factors for recurrence.

Ocular toxoplasmosis is known to have a clustering pattern of recurrence. In our study, the rate of recurrence per person over the mean follow-up period was 0.11 recurrences/person-year (based on 73 recurrences for 115 patients over a mean follow-up of 6.1 years). Recurrence was observed in 15% in the first year and a cumulative rate of 25% in the first two years. Some patients who had no recurrences may have experienced asymptomatic or mild first episodes previously, for which no medical attention was sought. This may help explain why 63% of patients with no recurrences in our study had IgG levels more than 100 AU/mL, and 47% of patients with no recurrences in our study had retinochoroidal scars at initial presentation. Our reported recurrence rates would therefore be conservative rates of recurrence.

The rate of recurrence found in this study sits on par with some retrospective studies[9–11] but is much lower than the rate of recurrence amongst other studies, which quote recurrence rates between 0.24 and 0.35 recurrences/person-year.[12–14] Apart from the possible underestimation of true first episodes of toxoplasmosis retinochoroiditis, there may be other reasons for the differences between studies. Given the more aggressive strain of toxoplasmosis in Brazil,[5] it would make sense that the prospective study conducted in the Rio de Janeiro population found higher rates of recurrence within its study group[12] although in another area of Brazil, recurrence rates from a separate randomised controlled trial conducted in Campinas found lower rates of recurrence than our reported rate—even in its placebo arm.[6] Thus, we can only generalise that the differences in recurrence rates between studies are likely explained by a combination of differences in toxoplasmosis pathogenicity, study methodologies, population demographics and presenting features, and treatment regimens.

All isolates of toxoplasmosis globally can be divided into different haplotype groups, and haplotype prevalence can vary geographically.[16] This study did not look at specific strains, and no known studies detail the prevalence of strain types found in New Zealanders or New Zealand-origin wildlife, domesticated or farm animals. However, strains found in South America are more likely to cause more severe disease and recur more frequently than European or North American strains.[5] The recurrence rate of toxoplasmosis retinochoroiditis may be indicative of the haplotype mix in the Auckland population.

Methodological differences can under- or over-estimate the incidence of recurrence, which may also help explain some of the differences in recurrence rates between studies. Some studies counted only one eye in bilateral cases, while others excluded immunosuppressed individuals or individuals with no serological data. These factors can underestimate true rates of recurrence. Several previous studies have only included those with long follow-up periods,

which results in selection of patients that have either had more severe disease or several recurrences.[10,13,15] Heterogeneity between studies makes comparing recurrence rates between studies difficult.

There is consistency of some risk factors for recurrence with other studies. This study found an increased risk of recurrence with previous recurrence, consistent with other studies.[4] This study did not find an increased risk with age or immunosuppression, contrary to the findings of many other studies, which found higher rates of recurrence in the elderly[17,18] and people with immunodeficiency. While most studies show an increased risk of recurrence with advanced age, one study[19] found that patients younger than 20.9 were at higher risk of recurrence than patients above 20.9 years. Notably, this study is at risk of non-response bias (55% of patients identified with ocular toxoplasmosis did not respond) and also found that the interval between successive episodes was stable between the first three recurrences. The latter reported outcome seems to be an isolated finding in the current literature, which is more suggestive of increased time between disease-free intervals. On the contrary, like other studies,[11,13,19] gender, IgM and IgG status were not associated with increased risk of recurrence in this study. Notably, pregnancy has been reported as a risk factor for recurrence in other studies, [20] but there were no pregnant patients in this study.

Differences in the numbers of individuals treated with appropriate treatments may also contribute to differences in recurrence rates. For example, IgM-positive patients treated with classic oral therapy rather than intravitreal therapy had lower rates of recurrence in one randomised trial.[21] Some studies have shown that treatment with prophylactic antibiotics, such as trimethoprim/sulfamethoxazole every 2–3 days for 12 months or more, can reduce the rate of recurrence of ocular toxoplasmosis by up to 74–95%.[5,6,15] In this study, there was no statistically significant association between either initiation of treatment, or use of prophylactic antibiotics, with risk of recurrence of toxoplasmosis retinochoroiditis. This may be because there were insufficient numbers of patients given long-term prophylaxis (long-term prophylaxis was commenced in less than 25% of cases). Further studies that are adequately powered may be able to elucidate this.

In summary, this study demonstrated recurrence rates of 15% in the first year, and showed that having a previous recurrence was associated with an increased risk of recurrence in a New Zealand population. This study will help guide discussions with patients regarding long-term rates of recurrence.

COMPETING INTERESTS
Nil.

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