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The role of serological titres in the diagnosis of ocular toxoplasmosis

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Current clinical practice limits the role of Toxoplasma serology in the diagnosis of ocular toxoplasmosis to being useful only when negative, which usually excludes the diagnosis (Rothova et al. 1986; Holliman et al. 1991; Burnett et al. 1998; Garweg et al. 2011). A cross-sectional and longitudinal analysis was performed at Massachusetts Eye and Ear Infirmary (MEEI) with a retrospective chart review to determine whether toxoplasmosis gondii IgG antibody titres using the IMMULITE 1000 (Siemens Medical Solutions Diagnostics, Flanders, NJ, USA) enzyme-linked immunosorbent assay (ELISA) methodology differed among Toxoplasma IgG-positive patients with active ocular toxoplasmosis, inactive ocular toxoplasmosis and non-toxoplasmic uveitis. A total of 212 patients were identified to have positive toxoplasmosis IgG serologies performed at MEEI. Forty-six subjects were excluded for being immunocompromised, having insufficient clinical data available, or not having uveitis. The non-uveitis diagnoses included otolaryngologic diagnoses, optic neuropathy and peripapillary oedema. In total, we identified 166 patients who had uveitis and positive serum Toxoplasma gondii IgG tested at our institution.

The demographic and clinical characteristics for the three groups are summarized in Table 1. Our study found that the mean level of Toxoplasma IgG was significantly different between the groups: 162.7 ± 97.3 IU/ml in patients with active chorioretinitis, 143.7 ± 107.5 IU/ml in patients with inactive chorioretinitis and 91.1 ± 88.0 IU/ml in non-toxoplasmic uveitis (p = 0.0002), suggesting a potential role of IgG titres in the diagnosis of ocular toxoplasmosis. To further explore whether the differences in Toxoplasma IgG levels could be clinically meaningful, we examined the sensitivity, specificity, negative predictive value and positive predictive value of Toxoplasma IgG titres at different cut-off values to define a significantly elevated Toxoplasma IgG titre: 5, 10 and 20 times the upper cut-off value for this assay (8 IU/ml) as well as 250 IU/ml, the clinically reported upper limit result for this assay (Table 2). Based on these data, when comparing patients with active chorioretinitis to non-toxoplasmic uveitis patients, a Toxoplasma IgG titre > 40 IU/ml had a sensitivity of 85.4% but a specificity of 42.3%. A Toxoplasma IgG titre > 250 IU/ml had a sensitivity of 45.1% and a specificity of 80.4%, limiting the clinical utility of the Toxoplasma IgG titres by the low sensitivity and specificity of the test.

Most cases of Toxoplasma chorioretinitis can be clinically diagnosed based on the fundus examination with

Table 1. Demographic and clinical data of participants in the cross-sectional analysis.

	Active toxoplasmosis chorioretinitis (*n* = 82)	Inactive toxoplasmosis chorioretinitis (*n* = 32)	Non-toxoplasmic uveitis (*n* = 52)	p Value*
Age in years, mean (range)	32.2 (14–68)	33.6 (8–76)	52.0 (21–88)	<0.0001
Males (%)	65.6	43.8	53.8	0.08
Toxoplasma IgG in IU/ml, mean ± SD (range)	162.7 ± 97.3 (4–321)	143.7 ± 107.5 (17–531)	91.1 ± 88.0 (8–250)	0.0002
Brazil-born, %	34.1%	21.9%	11.5%	0.01

SD = standard deviation.
* Determined with one-way analysis of variance (ANOVA).

Table 2. Toxoplasma IgG titres according to different cut-off values.

Toxoplasma IgG titre	Active toxoplasmosis chorioretinitis (n = 82)	Non-toxoplasmic uveitis (n = 52)	Sensitivity	Specificity	PPV	NPV
>40 IU/ml (5 times the positive cut-off value)	69	32	85.4%	42.3%	70.0%	64.7%
>80 IU/ml (10 times the positive cut-off value)	57	21	69.5%	61.5%	74.0%	56.1%
>160 IU/ml (20 times the positive cut-off value)	44	12	53.7%	76.9%	78.6%	51.3%
>250 IU/ml	37	9	45.1%	82.7%	80.4%	48.9%

PPV = positive predictive value; NPV = negative predictive value.

features of a focal chorioretinitis, often adjacent to a chorioretinal scar, and do not require serologic testing. However, when an ophthalmologist encounters a uveitis patient with findings that could be consistent with toxoplasmosis but are not entirely classic for this entity, they often ask whether the degree of Toxoplasma IgG elevation can help decrease or increase clinical suspicion for toxoplasmosis. While there is a difference in the mean titres between patients with toxoplasmosis chorioretinitis and non-toxoplasmic uveitis patients, there is still a great overlap in the titres from patients in both categories as evidenced by the ranges of values in Table 1, thus limiting its clinical utility.

Papadia et al. (2011) found that the mean toxoplasmosis IgG level ascertained by ELISA was significantly higher in 51 patients with active chorioretinitis (147.75 IU/ml) compared with 27 patients with other types of uveitis (18.35 IU/ml). Contrary to the findings of findings of Papadia et al., we found no significant difference in serum Toxoplasma IgG titres between the active and inactive Toxoplasma chorioretinitis groups. Our findings were consistent with those of an earlier study which examined this question with Sabin–Feldman dye titres (Rothova et al. 1986). To our best knowledge, this study design, examining ELISA-determined Toxoplasma IgG titres in uveitis, has not been previously employed. It should be noted that a significant difference in mean Toxoplasma IgG levels between the group with inactive Toxoplasma chorioretinitis and the non-toxoplasmic uveitis group was found. Therefore, our data overall suggest that a very high Toxoplasma IgG titre was associated with ocular involvement but not with ocular toxoplasmosis disease activity.

There are some limitations to our study. It is a retrospective study and relied on the accuracy of the medical record and clinicians' assessments of disease aetiology. Although the ELISA detection method we used is one of the most common commercially available methods, there are several other methods in clinical use around the world. Because there is variability between results from different ELISA kits, our results are not directly generalizable to clinicians using different methods. Also, the test was designed with prespecified cut-off values and was not designed for the different cut-off values that we investigated in our study. The inclusion of patients with an IgG titre reported as >250 IU/ml reduced the discrimination strength of the study, although exclusion of these patients from the analyses did not significantly alter the findings.

In summary, Toxoplasma IgG titres are higher on average in patients with toxoplasmosis chorioretinitis as compared with non-toxoplasmic uveitis who happen to be sero-positive for Toxoplasma. However, among uveitis patients at our institution with positive Toxoplasma IgG titres, no level of Toxoplasma IgG titre was both highly sensitive and specific so as to make it strongly predictive of ocular toxoplasmosis.

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