Effect of Specific Seropositivity and IgG-Avidity on Visual Outcomes and Recurrence in Active Ocular Toxoplasmosis: A Preliminary Study

Aktif Oküler Toksoplazmoziste Spesifik Seropozitifliğin ve IgG Aviditenin Görsel Sonuçlar ve Nüks Üzerine Etkisi: Bir Ön Çalışma

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ABSTRACT

Purpose: To evaluate the effect of serology and avidity on visual prognosis and recurrence in cases with active ocular toxoplasmosis (OT).

Methods: Twenty eyes of 16 patients with active OT between were included. All patients underwent a full ophthalmic examination including optical coherence tomography. The anti-toxoplasma antibodies and IgG-avidity were investigated with the ELISA method.

Results: Baseline central macular thickness (CMT) was thicker in eyes with toxoplasma IgM-positive than with IgM-negative (272.8 vs. 210.1µm, p=0.04, Cohen's d=1.63). However, baseline CMT in eyes with low IgG avidity was not statistically different from eyes with high IgG avidity although a high effect size coefficient was present (442.0 vs. 227.0 µm, p=0.40, Cohen's d=2.95). No difference was present between recurrent and non-recurrent cases in terms of CMT (263.0 vs. 295.9 µm, p=0.66, Cohen's d=0.25). While no statistically significant difference was present between the final VA and the IgM positivity and IgG avidity (p>0.05; Phi coefficients of 0.56 and 0.44, respectively) and recurrence and the IgM positivity and IgG avidity (p>0.05; Phi coefficients=0.41 and 0.26, respectively), the effect size coefficients were clinically significant. There was a strong positive correlation between the final VA and the baseline VA and CMT (r=0.92 and r=0.79 respectively; p<0.01).

Conclusions: Significant linear relationships were observed between baseline CMT, final VA and recurrence and toxoplasma IgM-positivity and IgG-avidity. The final VA was correlated with the baseline VA and CMT.

Key words: Anti-Toxoplasma IgG; anti-Toxoplasma IgM; IgG-avidity test; recurrence; ocular toxoplasmosis.

ÖZ

Amaç: Aktif oküler toksoplazmozisli (OT) olgularda görsel prognoz ve nüks üzerine seroloji ve avidite etkisini değerlendirmek.

Yöntem: Aktif OT'li 16 hastanın 20 gözü çalışmaya dâhil edildi. Tüm hastalara optik koherens tomografi dâhil olmak üzere tam oftalmolojik muayene yapıldı. Anti-toksoplazma antikorları ve IgG avidite ELISA yöntemi ile araştırıldı.

Bulgular: Bazal santral makula kalınlığı (SMK) toksoplazma IgM-pozitif olan gözlerde IgM-negatif olanlardan daha kalındı (272.8 vs. 210.1µm, p=0.04, Cohen's d=1.63). Ancak yüksek etki büyüklüğü katsayısı mevcut olmasına rağmen, düşük IgG aviditeli gözlerdeki bazal SMK yüksek IgG avidite gözlerden istatistiksel olarak farklı değildi (442.0 vs. 227.0µm, p=0.40, Cohen's d=2.95). Nüks olan

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ve olmayan olgular arasında SMK açısından fark yoktu (263.0 vs. 295.9µm, p=0.66, Cohen's d=0.25). Son GK ile IgM pozitifliği ve IgG avidite arasında (p>0.05, Phi katsayıları sırasıyla 0.56 ve 0.44) ve nüks ile IgM pozitifliği ve IgG avidite arasında (p>0.05; Phi katsayıları sırasıyla 0.41 ve 0.26) istatistiksel olarak anlamlı fark yokken, etki büyüklüğü katsayıları klinik açıdan anlamlı idi. Son GK ile başlangıç GK ve SMK arasında güçlü bir pozitif korelasyon vardı (sırasıyla r=0.92 ve r=0.79, p<0.01).

Sonuç: Başlangıç SMK, son GK ve nüks ile toksoplazma IgM-pozitifliği ve IgG avidite arasında anlamlı doğrusal ilişki gözlendi. Son GK; başlangıç GK ve SMK ile korele idi.

Anahtar kelimeler: Anti-Toksoplazma IgG, anti-Toksoplazma IgM, IgG-avidite testi, nüks, oküler toksoplazmozis

INTRODUCTION

Ocular toxoplasmosis (OT) is a disease caused by the *Toxoplasma gondii (T. gondii)* parasite that can cause blindness.[1,2] Although the diagnosis of toxoplasmosis is based on clinical evaluation, laboratory tests may help making a definite diagnosis. The presence of Anti–T. IgG antibodies may not validate toxoplasmosis etiology as these can persist at high titers for years but negativity excludes the diagnosis of toxoplasmosis.[3] Anti–T. gondii IgM antibodies can indicate newly acquired, systemic or probable ocular infection despite a high false positivity rate as they persist at high titers for years.[4]

The avidity test is the binding strength of the antibody with a multivalent antigen and measures the avidity of IgG antibodies specific to *T. gondii*. While IgG antibodies formed against the agent in the primary infection at the first encounter with the antigen show low avidity, they mature later and gain high avidity. High and low avidity tests are especially helpful for the differential diagnosis in acute infection, reactivation-reinfection, pregnant women, and immunosuppressed patients.[5] The effect of serology and avidity specific to ocular toxoplasmosis on the visual prognosis and recurrence has not been evaluated before in the literature. The aim of this study was to evaluate the effect of serology and avidity on the visual prognosis and recurrence in cases diagnosed with OT.

METHODS

A total of 20 eyes of 16 patients diagnosed with active OT at the Izmir Kâtip Celebi University Ataturk Training and Research Hospital's Uvea-Behçet Division at the Department of Ophthalmology between January 2007 and March 2015 were retrospectively evaluated in this study. This study was approved by the Izmir Katip Celebi University Ethics Committee (10.09.2015-decision no: 177).

Patients with uncertain diagnosis, inactive disease or insufficient data were excluded from the study. Ocular toxoplasmosis was diagnosed based on the clinical (visual symptoms with acute onset, focal retinochoroidal inflammation that heals with a characteristic scar) and serologic findings of toxoplasma infection.[7] Recurrent ocular toxoplasmosis lesions were also defined as "usually single and active retinal lesions associated with old retinochoroidal scars".

A detailed ocular and medical history was obtained from each patient at the first examination. An average of 5 ml of peripheral blood was drawn from each patient during the acute attack. Peripheral venous blood was centrifuged at 3000 x g for 10 minutes and the sera were separated. Clinical samples were delivered to the microbiology laboratory within a maximum of 4 hours. Sera were kept at -20°C until they were serologically evaluated. Serum IgM and IgG anti-toxoplasma antibodies of the cases were studied with the macro ELISA method by using a commercial kit (Immulite® 2000 XPi™ Immunoassay System (Siemens, Germany)) in accordance with the manufacturing company instructions. Index ≥ 8 were evaluated as positive, 6.5-8 as intermediate, and ≤ 6.5 as negative for anti-T. gondii IgG. Index < 0.6 cases were evaluated as negative, 0.6-1.5 as intermediate, and >1.5 as positive for anti-T. gondii IgM. The avidity value of the patients where Anti-T. gondii IgM and IgG were found together was investigated with the ELISA method via the Anti-T. gondii IgG avidity kit (DIA. PRO, Milan, Italy). The avidity index was accepted to be low if ≤ 30 and high if >30.

We requested erythrocyte sedimentation rate, liver and kidney function tests, chest X-ray, tuberculin skin test, serum angiotensin-converting enzyme levels and serologic tests for syphilis, brucellosis and human immunodeficiency virus (HIV) infection to rule out other etiologies in patients without a typical old scar. Suspicious cases were excluded from the study as the analysis of specific antibodies or *T. gondii* DNA in intraocular fluids is an invasive procedure.

All patients were underwent a visual acuity (VA) test, intraocular pressure measurement, biomicroscopic examination and ophthalmic examination including indirect ophtalmoscopic examination and optic coherence tomography measurements. Cases were also evaluated angiographically when necessary. Antibiotic treatment regimens for OT were prescribed according to the systemic state of the patient, the localization and severity of the active lesion, drug tolerance, and the preference of the patient. Oral steroid treatment (1 mg/kg/day prednisolone) was added when necessary. The patients were called for follow-up at 2-week intervals in the acute period until recovery and then once every 6 months.

Statistical analysis

We checked whether the parametric test assumptions of a normal distribution and homogenous variance were provided by evaluating both the variables themselves (single-sample Kolmogorov-Smirnov test) and also these variables in groups (Shapiro-Wilk test and Levene test). We found that continuous variables including the baseline central macular thickness (CMT), baseline VA, baseline lgM and lgG levels, lgG avidity, and follow-up VA did not have a normal

distribution individually, but baseline lgM positivity, avidity positivity and the presence of recurrence had a normal distribution and homogenous variances based on groups. The independent samples *t*-test was used for the group comparisons.

Linear relationships between constant variables were investigated with the Pearson correlation coefficient and the relationships between nominal variables were investigated with chi-square tests while group rate comparisons were made using Z tests to which the Bonferroni correction was applied. The Wilcoxon signed rank test was used for baseline and follow-up logMAR levels comparison. For the assessment of effect sizes, the phi coefficients were reported together with chi-square tests. $P < 0.05$ was used as the criterion for statistical significance and the IBM SPSS Statistics ver. 22 statistical software program was applied for the analyses.

RESULTS

There were 6 males and 10 females; the mean presentation age was 32.9 ± 10.4 (17-50) years and the mean follow-up duration 31.9 ± 28.6 (4-101) months (Table 1). Visual acuity at final examination (VA) (logMAR) (0.26 ± 0.51) had decreased statistically significantly compared to the baseline (0.37 ± 0.62) ($p = 0.03$).

Central macula thickness at first examination was higher in eyes with positive anti-toxoplasma IgM antibody than eyes with negative IgM (272.8 vs. 210.1, $p = 0.04$, Cohen's d = 1.63). On the other hand, CMT was not statistically different in eyes with low IgG-avidity and eyes with high IgG-avidity although a high effect size coefficient was present (442.0 vs. 227.0, $p = 0.40$, Cohen's d = 2.95) (Table 2). There was no difference between recurrent and non-recurrent eyes in terms of CMT, but a low effect size coefficient was present (263.0 vs. 295.9, $p = 0.66$, Cohen's d = 0.25).

Although no statistically significant association was present between the final VA and IgM positivity and IgG-avidity ($p > 0.05$, effect size = 0.203 and 0.443, respectively), or recurrence and the IgM positivity and IgG-avidity, the effect size coefficient ($p > 0.05$, effect size = 0.224 and 0.199, respectively) was observed to be clinically significant (Table 2).

Final VA and baseline VA and CMT were statistically significant and highly positively correlated (r = 0.92 and r = 0.79 relatively; $p < 0.01$). Final VA and IgM and IgG positivity (r = 0.144; $p = 0.594$ and r = 0.416; $p = 0.109$ respectively) and IgG-avidity (r = -0.129; $p = 0.661$) showed a low, intermediate and low degree of correlation respectively (Table 3). These correlations may have been found not to be significant due to inadequate statistical strength related to small sample size.

DISCUSSION

Toxoplasmosis is the most common cause of posterior uveitis and constitutes 80% of the cases in certain regions.[7] Although observing clinical findings of OT is the gold standard in diagnosis, ELISA tests identifying anti-*T. gondii* IgG and IgM antibodies can also be used, especially in suspicious cases, considering the specificity and sensitivity of the laboratory tests. IgG antibodies usually emerge in the second week of the infection, peak at 6-8 weeks and remain positive for life. IgM antibodies are accepted as an indicator of recent infection and can be detected within two weeks.[8] On the other hand, IgM antibodies usually disappear earlier in

Table 1. *Demographic, clinical and serological characteristics of the patients with active ocular toxoplasmosis*

Gender	6 males (37.5%) / 10 females (62.5%)
Age (mean ± SD, range) (years)	32.9 ± 10.4 (17-50)
Laterality*	9 right, 11 left
Serum anti-*Toxoplasma* antibodies	
IgG +	12/12 (100%)
IgM +	5/12 (41.7%)
IgG-avidity index	
Low Avidity (≤ 30)	2/11 (18.2%)
High Avidity (>30)	9/11 (81.8%)
Serum anti-*Toxoplasma* antibodies (IU/mL)	
IgG (mean ± SD, range)	79.7 ± 81.3 (23.8 - 250.0)
IgM (mean ± SD, range)	0.21 ± 0.27 (0.03 – 0.89)
IgG-avidity index (mean ± SD, range)	64.3 ± 31.8 (11.8 – 100.0)
Follow-up (month) (mean ± SD, range)	31.9 ± 28.6 (4-101)
Baseline central macular thickness (μm) (mean ± SD, range)	280.7 ± 127.8 (141 – 600)
Baseline visual acuity (logMAR) (mean ± SD, range)	0.37 ± 0.62 (0 – 2.00)
Final visual acuity (logMAR) (mean ± SD, range)	0.26 ± 0.51 (0 – 2.00)
Recurrence	6/16 (37.5%)

Table 2: *Association of anti-toxoplasma IgM and anti-toxoplasma IgG-avidity with central macular thickness, final visual acuity and the presence of recurrence*

		CMT	*P*-value	Effect Size (Cohen's d)	Final VA	*P*-value	Effect Size (r) [c]	Recurrence	*P*-value	Effect Size (r) [c]
Anti-*T. gondii* IgM avidity	positive	272.8 ± 11.9	0.044[a]	1.63	0.66 ± 0.40	0.416[b]	0.203	0.73 ± 0.39	0.371[b]	0.224
	negative	210.1 ± 51.6			0.81 ± 0.29			0.94 ± 0.12		
Anti-*T. gondii* IgG avidity	low	442.0 ± 223.4	0.401[a]	2.95	1.10 ± 1.27	0.467[b]	0.443	0.18 ± 0.31	0.523[b]	0.199
	high	227.0 ± 54.1			0.76 ± 0.34			0.12 ± 0.29		

[a]: t-test
[b]: Mann-Whitney U
[c]:Effect size for Mann-Whitney U: $r = \frac{Z}{\sqrt{N}}$ (Cohen's guidelines for "r" are that a large effect is 0.5, a medium effect is 0.3, and a small effect is 0.1)
CMT, central macular thickness; VA, visual acuity (logMAR).

Table 3: *Correlations of clinical and serological parameters of patients with active ocular toxoplasmosis*

Parameters	Baseline VA	Baseline CMT	Baseline IgM	Baseline IgG	Baseline IgG avidity
Baseline CMT	**0.860****				
	0.000				
Baseline IgM	0.141	0.455			
	0.604	0.159			
Baseline IgG	0.258	0.312	**0.633****		
	0.334	0.350	*0.009*		
Baseline IgG avidity	-0.425	**-0.613***	-0.093	0.558	
	0.130	*0.045*	0.774	0.060	
Final VA	**0.922****	**0.791****	0.144	0.416	-0.129
	0.000	*0.001*	0.594	0.109	0.661

Statistically significant correlations are shown in bold.
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
* or ** r value (correlation coefficient).
P value; statistically significant correlations are shown in italics.
VA, visual acuity (logMAR); CMT, central macular thickness.

acute infection but can be found in the serum for months-years especially in the case of re-infection and reactivation.[9]

The IgG avidity test can be used to identify the beginning of the infection during the diagnosis when IgM antibodies do not increase in individuals with congenital toxoplasmosis and reactivation where anti-*T. gondii* IgM antibodies cannot be detected in the initial period of the infection, and especially for initial infection in pregnant women with IgM positivity, to finalize the diagnosis and to differentiate old and new infection.[10] It is a reliable method where high anti-*T. gondii* IgG avidity results indicate that the infection has been active a minimum of 3-4 months ago, especially in cases in the first trimester of pregnancy who are IgM negative and IgG positive.[11] According to the test kit of our hospital, the high avidity in our cases indicated that the infection had been active before 16 weeks and avidity elevation in a single serum sample was sufficient for diagnosis. Low avidity does not definitely mean infection by itself. Repeated long-term low or borderline levels of avidity may be found in some patients. Therefore, although the avidity test is a meaningful confirmatory test in the determination of antibodies with high avidity, it cannot be used as a confirmatory test by itself as low or borderline avidity results may be interpreted incorrectly.[12] Yazar et al.[13] reported low avidity in 4.7%, high avidity in 70.8% and suspect values in 24.5% of their cases in a study on 695 toxoplasma seropositive pregnant women. Bahar et al.[14] reported low avidity in nine (29.1%), high avidity in 14 (45.1%) and borderline avidity in 8 (25.8%) of 31 pregnant women with the anti *T. gondii* IgG avidity test in another study which was conducted in pregnant women. Gungor et al.[12] evaluated the results of the avidity test requested from all clinic and services and found 13 low avidity (15.5%), 61 high avidity (72.6%), and two intermediate values (2.4%).

The avidity test can be important in the differential diagnosis of new/chronic ocular toxoplasmosis infection lesions. A study conducted on ten patients has found that high IgG avidity values made it more probable for ocular toxoplasmosis to be congenital and less probable that it was a reactivation of chronic acquired infection in immunocompetent

patients.[15] Mattos et al.[16] investigated the contribution of various laboratory methods to the diagnosis of 184 clinically suspicious OT patients by dividing them into 2 groups and reported that anti-*T. gondii* IgG antibodies were positive and anti-T. gondii IgM antibodies were negative with high avidity in 135 patients (73.3%) [49 patients with OT (100%) vs. 86 patients from the other group including cataracts, other disease related vitreous or retinal detachment, type 2 diabetes, vascular occlusions, age-related macular degeneration, glaucoma, toxocariasis, cytomegalovirus infection, corneal transplant, non-toxoplasmosis uveitis, hypertensive retinopathy macular changes, lack of light perception and choroidal melanoma (63.7%)]. The authors reported that the parasites circulating in the blood of immunocompetent patients could be related to the reactivation of the ocular disease. In our study, only patients with active OT were investigated and low avidity was found in two patients (18.2%) and high avidity in nine patients (81.8%), close to the rates above. We also evaluated CMT at the first examination in our study and found it to be thicker in patients with positive anti-toxoplasma IgM antibody than those who were IgM negative (272.8 vs. 210.1). On the other hand, CMT was not statistically significantly different when the eyes with low IgG-avidity were compared with those eyes with high IgG-avidity, although high effect size was detected in CMT and IgG avidity.

Suresh et al.[17] found that VA was better than 6/36 in thirty-two (45.1%) and worse than 6/60 in twenty-eight (39.4%) of 71 patients with seropositive toxoplasmosis. However, 18 of these patients had a recently acquired and/or active OT infection. All the patients in our study were diagnosed with active OT and the final VA was ≤ 6/60 in 2 eyes (11.1%) while it was over 20/50 in the other eyes (88.9%). A highly positive correlation was found between the final VA and the baseline VA and CMT. On the other hand, the effect size power between final VA and the IgM and IgG positivity and IgG-avidity was observed to be clinically remarkable, but not statistically significant. We believe the lack of statistical significance might have been due to the small sample size.

Ocular toxoplasmosis is usually a recurrent disease and two thirds of the patients can present with recurrence.[18] Recurrence-related risk factors have been reported as the early stage after an acute attack, age < 40 years, pregnancy and cataract surgery.[2,19,20] On the other hand, gender, the presence of retinal scar at the first attack, whether the patient received treatment at the first attack and whether the infection was postnatal/congenital have been reported not to affect recurrence.[2] Binquet et al.[21] have reported that the gestational age at the time of contamination, and the antibody load at birth to be risk factors for lesion formation in their study where they investigated the prognostic factors in the development of ocular lesions in 327 children with congenital toxoplasmosis. Although no statistically significant difference was present between recurrence and the IgM positivity and IgG-avidity in our study, we accepted the findings as clinically significant due to the high effect size. On the other hand, recurrence was found not to be associated with CMT.

The limitations of this study should be underlined: In the present study the number of cases was limited. Secondly, to create a homogeneous group according to the host's immune response, clarity of the optic media, location of the lesion, presence of complications, recurrences and finally the time of diagnosis would be extremely difficult. We therefore used "preliminary study" in the title. As a next study, the authors planned to expand the study to obtain a larger sample and to complete clinical data including recurrence index that correct for duration of follow-up, time to resolve inflammation and response to antibiotic therapy. On the other hand, the strong aspect of the current study is that the present study was designed to explore for the first time in the literature whether the association between serology and visual acuity and recurrence in ocular toxoplasmosis. The linear relationship between final VA and baseline CMT, and the correlation between IgM positivity and initial CMT could help in making the clinical decision.

In conclusion, the IgG avidity test can be used in the diagnosis of toxoplasmosis. High IgG-avidity in patients with a healthy immune system indicates infection reactivation and low IgG-avidity in the early stage that gradually increases during follow-up aids the clinician in the differential diagnosis of ocular toxoplasmosis. Significant linear relationships were observed to be present between the baseline CMT, final VA and recurrence and the toxoplasma IgM antibody positivity and IgG-avidity in this study. The final VA showed a significant correlation with baseline VA and CMT. We consider that this cohort study should be conducted in larger series, so that the relationship between seropositivity specific to toxoplasmosis, IgG avidity with recurrence and final VA can be accurately revealed.

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