Ocular Toxoplasmosis in the United States: Recent and Remote Infections

Jeffrey L. Jones,1 Valerie Bonetti,2 Gary N. Holland,3 Cindy Press,2
Steven R. Sanislo,4 Rahul N. Khurana,2 and Jose G. Montoya2,4

1Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia; 2Palo Alto Medical Foundation, Toxoplasma Serology Laboratory, 3Ocular Inflammatory Disease Center, Jules Stein Eye Institute and Department of Ophthalmology, David Geffen School of Medicine, University of California, Los Angeles, 4Byers Eye Institute, Stanford University School of Medicine, California

We tested all samples from patients with ocular toxoplasmosis sent to the Palo Alto Medical Foundation Toxoplasma Reference Laboratory from June 2004 through August 2010 for serologic evidence of recent Toxoplasma gondii infection. Of 205 patients aged 10–96 years, 11.7% had recent infection. Many people develop ocular disease soon after T. gondii infection.

Keywords. toxoplasmosis; Toxoplasma gondii; ocular; eye.

Toxoplasmosis is one of the most common causes of posterior uveitis [1] and can lead to variable degrees of vision loss, including blindness. In the United States, an estimated 21,000 persons develop ocular lesions from Toxoplasma gondii each year, and >4800 develop symptomatic ocular disease (data from a study done in the early to mid-2000s) [2]. Care of patients with ocular toxoplasmosis causes a substantial burden on the US healthcare system, with >250,000 visits to ophthalmologists for active or chronic disease over a period of 2 years estimated from a survey in 2002 [3].

Traditional teaching has been that the majority of ocular toxoplasmosis is associated with congenital disease. Clinicians now accept the fact that the majority of reactivations are associated with postnatally acquired infections, the first episode of ocular involvement having gone unnoticed, either because it was associated with minimal symptoms or because it occurred in preverbal children [4]. It is estimated that approximately 2% of T. gondii–infected individuals in the United States develop ocular toxoplasmosis; however, in some settings, such as epidemics with atypical genotypes, the prevalence of ocular disease soon after infection may be as high as 20% [4, 5].

METHODS

Our study evaluated all T. gondii antibody–positive serum samples from persons in the United States diagnosed clinically with ocular toxoplasmosis that had been sent to the Palo Alto Medical Foundation Toxoplasma Reference Laboratory (PAMFRL) to confirm infection between June 2004 and August 2010. PAMFRL is the only Toxoplasma testing reference laboratory in the United States. The methods for determining recent T. gondii infection have been described, and can determine if infection occurred within the previous 6 months [6, 7]. In brief, all samples were tested with the T. gondii Sabin-Feldman dye test and immunoglobulin M (IgM)–enzyme-linked immunosorbent assay (ELISA). Samples that had been found to be both immunoglobulin G (IgG) and IgM antibody positive were tested further with the immunoglobulin A (IgA) ELISA, immunoglobulin E (IgE) ELISA, and differential agglutination (AC/HS) test. An acute serological profile (ie, positive Sabin-Feldman dye test, positive IgM ELISA, an acute pattern in the differential agglutination test, and positive IgA and IgE ELISA tests) correlates 100% with an infection acquired within 6 months in seroconversion studies of pregnant women in Europe and in serological studies of patients with lymphadenopathy in the United States [6, 7]. In addition, all case patients had a low Toxoplasma avidity test result consistent with a recent infection [8, 9]. We did not use commercial Toxoplasma IgM tests alone to determine acute T. gondii infection because up to 27% of Toxoplasma IgM tests can remain positive for ≥2 years [10]. In analyzing our study data, exact confidence intervals for binomial proportions and the t test were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Of 205 patients with serologic evidence of T. gondii infection, 110 (54%) were female. The median age for those with recent infection and chronic infection were 52 years (range, 15–80
years) and 44 years (range, 10–96 years), respectively (P = .19, t test with Satterthwaite approximation). Samples from 24 (11.7% [95% confidence limits, 7.7%, 16.9%]) patients were found to have serological test results indicating recent infection (ie, IgG-positive/IgM-positive and a serological panel including IgA, IgE, AC/HS, and avidity test consistent with recent infection); the remaining 181 (88.3%) were IgG positive/IgM negative, indicating that they had ocular disease associated with chronic infection from the more distant past.

DISCUSSION

In this referral population, 11.7% of patients with ocular disease had recently acquired T. gondii infection. Because the youngest person in the study was 10 years old, all recently acquired infections occurred after birth (in the 6 months prior to T. gondii testing, as defined in the “Methods” section), whereas chronic infections may have occurred after birth or congenitally (but >6 months previous to T. gondii testing). Patients with chronic infections were probably tested by their physicians when active ocular lesions were noted (representing reactivations, the most common clinical presentation), but for these patients it is not known when the ocular disease first developed or over what interval reactivation occurred.

It has been assumed that most retinal lesions among T. gondii-infected individuals are associated with remote infections [4], with clinically apparent lesions first arising from occult tissue cysts that had been present in retinal tissue since the systemic infection occurred [11]. Retinal disease can recur multiple times, as satellite lesions adjacent to retinochoroidal scars, which represent the residua of past infections. In contrast, as many as 10%–20% of patients infected in several reported epidemics of T. gondii infection have developed clinically apparent toxoplasmic retinochoroiditis within a few weeks of the outbreaks [5]. These initial retinal infections present as “primary lesions” (those not arising from the borders of scars). The hypothesis is that the higher incidence of early ocular involvement in epidemics vs the general population is related to infection with atypical strains of parasite [5]. Numerous genotypes are circulating in the United States [12], and atypical genotypes have been found to be associated with ocular toxoplasmosis in the United States, even among those with sporadic disease [13].

Our study has a number of limitations. The samples may not be representative of all people with ocular toxoplasmosis in the United States. Ophthalmologists are trained to recognize the classic appearance of satellite lesions adjacent to chronic retinochoroidal scars as being diagnostic for ocular toxoplasmosis, and might be less likely to seek serologic confirmation of infection in such cases. Because other presentations of ocular toxoplasmosis are less well understood, serologic testing might be obtained more often for people with primary lesions or for those lesions that represent more severe disease. Clinicians therefore may be more likely to seek confirmation of infection for lesions that occur at the time of initial infection, because all such patients will have primary lesions; being the first episode of retinal disease, none will already have scars. It should be noted, however, that primary lesions alone are not a reliable sign of recent infection; up to 20% of patients who present with primary lesions have serologic profiles consistent with remote T. gondii infection [14]. The PAMFRL records do not provide information about whether patients tested had satellite recurrences or primary lesions. These potential biases could increase the observed prevalence of ocular toxoplasmosis associated with recent infection. An additional potential limitation is that the diagnosis of ocular toxoplasmosis was made by physicians who referred serum for testing, and the authors did not independently validate the diagnosis.

Nevertheless, the results of our study indicate that >10% of people with ocular disease developed it soon after acquiring T. gondii infection, a phenomenon previously thought to be uncommon in the general population. These results also suggest that patients identified both clinically and serologically as having had a recent T. gondii infection should be questioned about known risk factors for infection, and about close family members or associates who may have had systemic and/or ocular symptoms similarly suggestive of infection (ie, persons who may have had a common exposure leading to infection). Potentially infected persons thus identified could then be examined and tested; this is particularly important for those who are pregnant or immunosuppressed [15]. Household members who are infected with the same genotype as a person with ocular involvement may be at increased risk for ocular disease because, as noted above, a higher rate of ocular disease has been reported in epidemics associated with atypical genotypes [5]. Recent evidence from a study in Brazil in an area with atypical genotypes and a high rate of T. gondii–related ocular disease suggests that systemic treatment of recently infected persons may decrease the occurrence of early ocular involvement (T. E. F. Arantes et al, manuscript submitted). However, this forthcoming study does not present the type, dose, or duration of treatment, and clinical trials would be needed to fully establish the regimen and effectiveness of prophylactic treatment after acute T. gondii infection to prevent ocular disease.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Financial support. Funding for this study was provided to the Palo Alto Medical Foundation by the CDC.

Potential conflicts of interest. R. N. K. reports that he has been a consultant for Allergan and Genentech, has grants pending from Allergan and
Regeneron, and has received payment for lectures from Genentech and Regeneron. G. N. H. reports that he has been a consultant for Genentech, Novartis International, Staten, and Xoma LLC, and has received funding for clinical trial participation from Xoma LLC. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References