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Ocular Toxoplasmosis: Lessons From Brazil

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This issue of the *Journal* highlights 2 articles from corresponding author Gary Holland[1,2] that represent new studies from a series of publications the *Journal* has published concerning ocular toxoplasmosis in Brazil.[3–13] Collectively, these Brazilian studies have contributed substantially to a reassessment of the pathogenesis of the disease and its clinical characteristics and provide compelling new perspective on the utility of proactive treatment strategies to manage disease.[14,15] The bigger question, however, is whether the lessons learned in Brazil are relevant to a readership outside of Brazil, where disease is less endemic. The simple answer is yes.

Studies in Brazil have quite simply revolutionized our perspective and the concepts that have emerged have largely been possible because the prevalence, severity, and risk of ocular involvement are much higher than in the United States and Europe.[5] Toxoplasmosis has a widespread distribution and a global human infection rate of ~30%.[16] Ocular toxoplasmosis is a significant disease, with the odds of developing disease ranging from a low of 1 in 357 in the United States, where the incidence rate for eye disease is approximately 1%–2% among seropositive individuals,[14] to a high of 1 in 6 individuals in highly endemic regions such as Erechim, Brazil, where eye disease can approach 20%[5] of infected people. It is this high prevalence of ocular disease in Brazil that provides sufficient statistical power to identify relationships and to observe uncommon events. Importantly, we have no reason to believe that the basic disease in Brazil is inherently different from ocular toxoplasmosis in the rest of the world.

Five Significant Lessons Learned from Brazilian Studies

Examples of how Brazilian Studies have Impacted the rest of the world include:

1. *An association of ocular toxoplasmosis with postnatally acquired Toxoplasma gondii infection*. For many years, the traditional teaching was that the majority of ocular patients were associated with congenital toxoplasmosis. In the early 1990s,

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however, studies of families in southern Brazil confirmed that postnatal infections were an important cause of ocular disease. If ocular disease was associated exclusively with congenital disease, siblings born after an affected child from a naturally vaccinated mother should not be at risk for ocular toxoplasmosis, yet many families in Brazil were found to have multiple affected siblings.[9] In response to these Brazilian observations, investigators throughout the world began to reassess the timing of infection in their own populations, and it is now well accepted that the majority of ocular disease in both the United States and Europe is the result of postnatal infections.[14,17] This knowledge has underpinned the necessity to develop public health strategies to limit postnatal infections in order to limit eye disease.

2. *The strain hypothesis: Development and disease severity is dependent on parasite genotype*. Studies from Brazil suggest that the increased risk of ocular involvement is attributable to the higher prevalence of nonarchetypal *T gondii* strains infecting food animals or contaminating water supplies there. These strains are different from the archetypal I, II, or III strains that cause the majority of infections in North America and Europe.[18] In support of these findings, studies in the United States and Germany have shown that ocular toxoplasmosis in these areas, when they occur, are typically caused by nonarchetypal strains that represent only a small minority of the strains found infecting the general population.[19,20] Furthermore, the findings published herein from the Santa Isabel do Ivaí outbreak also support the concept that individuals infected by parasites bearing atypical genotypes are at increased risk of ophthalmic disease.

3. *Pathogenesis and disease mechanisms*. While parasite genotype plays a major role mediating toxoplasmic infection of the eye, it certainly comes as no surprise that the host immune response is important as well. Work in Brazil has evaluated the role of polymorphisms in CCR5, TLR2, TLR4; identified a key role for IL-12 production in the development of protective responses[21]; and provided new perspectives on the causes of ocular disease by establishing that *T. gondii* parasites circulate in the blood of immunocompetent toxoplasmosis patients, regardless of whether they have retinal lesions or not.[22] Hence, circulating parasites in the blood of chronically infected people may exist as a source of *Toxoplasma* capable of causing retinal disease, rather than the classically held thought that it is attributable to cyst rupture in the retina. Changes in the immune signature between those with congenital and acquired toxoplasmosis have also been noted. Those with congenital disease have lower circulating levels of IL-2 and IFN-γ compared to the acquired group. Those patients who were asymptomatic demonstrated high levels of IL-12 and IFN-γ, while those with ocular lesions had high IL-1 and TNF-α.[23] Ocular toxoplasmosis patients do show evidence of retinal autoimmunity, but those responses are not an indication of more severe disease.[24] Another important observation was the finding that positive intraocular polymerase chain reaction for *Toxoplasma* is still possible despite an observed lack of active ocular lesions.[25] Finally, the first cross-sectional comparison performed between France and another South American country (Colombia) identified striking differences in vitreous

inflammation, vasculitis, and cytokine responses, consistent with South American strains causing more severe ocular toxoplasmosis by altering protective levels of IFN-γ and IL-17 in the aqueous humor of infected eyes.[26]

4. *Course of disease*. In the current articles, clinically apparent retinal lesions can first occur months or years after postnatal infections, as was known previously for congenital infections. Observations in Brazil also suggest that organisms reach the eye much earlier in many patients; individuals can have transient intraocular inflammatory reactions with transient retinal whitening that later develop into toxoplasmic retinochoroiditis lesions in the same area.[1,2,6] The same phenomenon has been seen in North American patients.[6]

5. *The concept of secondary prophylaxis to prevent recurrence*. Silveira and associates showed that long-term, intermittent treatment with TMP-SMX significantly reduces the risk of recurrent ocular toxoplasmosis.[11] Among only 3 controlled clinical trials of treatment for toxoplasmic retinochoroiditis identified in a Cochrane Library Review in 2002, the study by Silveira and associates was the only one to show treatment efficacy.[27] However, a more recent article confirms the usefulness of such treatment.[4] Secondary prophylaxis to prevent disease recurrence in high-risk patients is now the standard treatment throughout the world.

Future Considerations

The many contributions made by brazilian investigators have offered new public health perspectives by:

- Identifying other sources of infection. Studies in Brazil have added the important perspective that contaminated water, not just undercooked meat or unwashed vegetables, is an important source of infection.[28]
- Refinements of treatment. In addition to confirmation that long-term prophylaxis reduces recurrence risk, the study by Arantes and associates raises the possibility that early treatment of systemic infection may reduce the risk of ocular involvement.[1] specifically, they showed that 182 of 261 (69%) IgM-positive patients had symptoms of systemic disease. Of those with systemic disease, but without eye disease at baseline (105/182 or 58%), over the next 10 years, >60% develop eye disease (Figure 1) and >75% of these patients experience recurrent necrotizing retinochoroiditis (Figure 3), especially among older people who reactivate their disease earlier. This information is lacking in the United States, so it is unclear whether those individuals with systemic symptoms of disease (representing $\sim$ 10% of infections in the United States)[29] are those who are more likely to develop ocular disease. If what we know from Brazil is correct, this is the target population that should be studied to determine if they are more likely to develop eye disease and, therefore, may benefit from targeted prophylactic intervention.
- Insight from longitudinal studies. There is currently no better information regarding timed ophthalmic events during the months and years following initial systemic

infection; most studies of epidemic infections have dealt only with events at the onset of the outbreak, and in studies of endemic disease, the time of the original infection is rarely known. The studies reported by Arantes, which span more than 30 years, and Silveira, which follows a point-source outbreak, give us our first real glimpse of how disease progresses across time in both a highly endemic and an outbreak scenario.

We look forward to additional insights about ocular toxoplasmosis from teams working in Brazil.

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