Outbreak of Acquired Ocular Toxoplasmosis Involving 248 Patients

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Objective: To describe the demographic profile and clinical and laboratory findings of 248 patients with acquired retinitis caused by systemic infection with toxoplasmosis in a presumed outbreak of the disease.

Design: Retrospective observational case series.

Results: Most patients (209) were residents of one city in Southern India. A total of 35 patients had a prodrome of fever, and 242 patients had unilateral retinitis without associated old retinochoroidal scars. All had laboratory evidence of acquired systemic infection with Toxoplasma gondii, and all favorably responded to anti-toxoplasma therapy. Toxoplasma IgM and IgG antibodies were detected, suggesting recently acquired systemic disease. Complications seen were macular scars in 50 eyes (25.1%); epiretinal membranes, 23 eyes (11.5%); cataract, 5 eyes (2.5%); posterior vitreous detachment, 12 eyes (6%); and retinal detachment, 12 eyes (6%). One recurrence has been seen. The suspected source of infection is municipal drinking water.

Conclusion: Large numbers of residents of any age in a population are at risk of acquiring ocular disease during an outbreak of toxoplasmosis, which can go unnoticed, and can cause significant ocular morbidity.


TOXOPLASMA GONDII IS A COCCIDIAN PARASITE OF WORLDWIDE DISTRIBUTION THAT INFECTS A WIDE RANGE OF BIRDS AND ANIMALS BUT DOES NOT APPEAR TO CAUSE DISEASE IN THEM. THEIR NORMAL HOSTS ARE CATS AND OTHER MEMBERS OF THE FAMILY FELIDAE.1 IT CAN CAUSE SEVERE LIFE-THREATENING OR DESTRUCTIVE CEREBRAL AND OCULAR DISEASE IN NEWBORNS, AND IT IS AN IMPORTANT CAUSE OF OCULAR DISEASE IN BOTH IMMUNOCOMPETENT AND IMMUNOSUPPRESSED INDIVIDUALS.2

Most cases of retinitis have been thought to be congenital in origin, with periodic activations. Ocular disease in patients with acquired T gondii infection is believed to be uncommon.3,4 However, several studies suggest that postnatally acquired disease causes retinitis that might be more prevalent than previously thought.5–9 More recently, in a well-documented outbreak of acquired T gondii infection in the Greater Victoria area of British Columbia, Canada, 20 cases of serologically proven acquired toxoplasmosis retinitis have been reported.10

METHODS

This study is a retrospective observational case series. Cases were studied at the time of presentation. A case was defined as an individual with evidence of retinal involvement—newly acquired, active retinitis lesions—without evidence of previous retinochoroidal scarring, and with serologic findings consistent with acquired toxoplasmosis, ie, laboratory findings positive for toxoplasma IgM and IgG. Detailed medical histories were collected that included age, residence, food habits, pets at home, and recent systemic illness. A full ophthalmic examination including refraction, tonometry, slit-lamp assessment, and dilated fundus examination was performed. Serum testing to detect toxoplasma IgM (n=198) and IgG (n=209) antibody levels were performed with commercially available enzyme-linked immunosorbent assay (ELISA) kits, which provided quantitative and semiquantitative results. Fundus photography was recorded in almost all cases; fundus fluorescein angiography was done for documentation or when viewing of the fundus was obstructed by vitreous inflammation. Patients were treated with systemic antibiotics and corticosteroids. Patients were seen at days 1 and 3, after 2 weeks, and then at monthly intervals.

RESULTS

In 2003 at Aravind Eye Hospital in Coimbatore, Tamil Nadu, India, a total of 35 cases of ocular toxoplasmosis were seen. In 2004, only 12 cases of ocular toxoplas-
mosis were seen in the first half of the year. These patients had a characteristic retinitis adjacent to an old scar or showed presence of a scar in the other eye, with serologic evidence suggestive of recurrent ocular toxoplasmosis (IgG positive only). In August 2004, we saw a marked rise in the number of cases of active retinitis without evidence of chorioretinal scars, with serological evidence compatible with that of acquired acute toxoplasmosis (IgM positive). The striking aspect in this case series was the sheer number of patients who reported to our hospital: 28 in September, 56 in October, 51 in November, 43 in December 2004, and then 24 in January, 15 in February, 8 in March, 10 in April, 12 in May, and 1 to 2 cases per month until July 2005 (Figure 1 and Figure 2). Demographic data showed that most patients were residents of the city of Coimbatore and its suburbs, in Tamil Nadu, South India. A total of 248 patients were seen from August 2004 to July 2005.

From 2004 to 2005, 248 patients (254 eyes) presented with clinical and/or serological evidence of acquired T gondii retinitis. Patients aged between 12 and 73 years (Figure 3) were seen, with male preponderance (64.7%). One patient had tested positive for human immunodeficiency virus, and 1 was pregnant. Most (209 patients; 84.27%) were residents of the city of Coimbatore and its suburbs in Tamil Nadu, India; 237 patients (95.56%) used municipal drinking water for drinking/consumption purposes. Most patients (242; 97.58%) were not vegetarian (chicken and lamb were the most common meats consumed), and only 5 patients (2%) had household pets (cat). A prodrome of fever was seen in 35 patients (14.11%), with onset ranging from 7 to 180 days preceding the ocular symptoms.

Ophthalmic symptoms consisting of defective vision in 240 patients (96.77%) and floaters in 71 patients (28.62%) were present, with onset 1 to 210 days (mean, 24.2 days) before the first hospital visit. Right and left eyes were almost equally affected (123 right and 131 left). Six patients (2.41%) had bilateral involvement. Anterior chamber inflammation was seen in 174 eyes (68.50%), and 3 of those had granulomatous keratic precipitates. Intraocular pressure was measured by applanation tonometry in 199 eyes, and was elevated in 18 eyes (9%; range, 22-44 mm Hg).

Unifocal retinitis was seen in 230 eyes (90.55%). The location of retinitis was categorized in zones as described by Holland et al.11 In 171 eyes (67.32%), it was located in zone I (3000 µm from the fovea or 1500 µm from the optic nerve head margin); in 75 eyes (29.52%), zone II (from zone 1 to anterior borders of the vortex veins); and in 8 eyes (3.14%), zone III (anterior from zone 2 to the ora serrata). All lesions were active, raised, yellowish patches with irregular ill-defined borders (Figure 4). Lesions in zones I and II were predominantly 1 to 2 disc diameter (DD) in size, and lesions in zone III were larger. Vitritis was seen in 228 eyes (89.76%). All lesions healed with scar formation with early retinal pigment atrophy and later pigment clumping. Multifocal retinitis was seen in 24 eyes (9.44%). Vasculitis was a feature in 89 eyes (35.03%), involving arterioles in most patients. Focal plaque-like yellow deposits on branches of the arteriolar tree known as Kyrieleis-type periarteritis were seen in 42 eyes (47.19% of those with vasculitis). The periarteritis was seen in vessels that were coursing through the retinitis, both proximal and distal to the lesion, and also in vessels that were adjacent to the lesion (Figure 5). Disc edema due to peripapillary retinitis was seen in 17 eyes.
(6.69%) (Figure 6), and 3 of those patients had associated hard exudates in the macula, suggesting neuroretinitislike presentation. One patient who presented with severe panuveitis and was diagnosed with endogenous endophthalmitis had a core vitrectomy during which active retinitis was detected. Fundus fluorescein angiography typically showed blockage of fluorescence in early phases and staining of the lesion and leakage of the dye in the later phases.

All 198 patients had IgM antibodies against *T. gondii* in their serum samples as well as high levels of toxoplasma IgG antibodies. Levels of IgG against *T. gondii* were 200 IU/mL or higher in 90.18% and higher than 500 IU/mL in 50.4% of cases. Serology was repeated for only 10 patients 2 to 3 months following their first visit and demonstrated a fall in IgG titers in all 10 patients (Table). Most patients were treated with a combination of 160 mg of trimethoprim and 800 mg of sulphamethoxazole (Bactrim DS, Roche, Basel, Switzerland) twice daily for a minimum of 5 weeks. Patients with vision-threatening retinitis (in zone 1) were also treated with 40 mg of oral prednisolone daily, 2 days after beginning therapy with Bactrim DS, for the first week, which was then tapered by 10 mg every week for a maximum of 5 weeks. One pregnant woman was treated with 3 million U of oral spiramycin 3 times per day, and one patient who developed dry mouth and dry throat after using Bactrim DS was treated with 300 mg of clindamycin orally 3 times per day. One patient received 500 mg of azithromycin orally once per day.

Most patients were followed up (194; 78.22%), while 54 patients (21.77%), of whom 1 patient had bilateral ocular disease, were lost to follow-up. Improvement in visual acuity of at least 1 Snellen line was seen in 141 eyes (70.8%); in 46 eyes (23.1%), visual acuity remained the same, while 11 eyes (5.52%) worsened.

Complications seen were scars in zone 1, with resultant decrease in visual acuity occurring in 30 eyes (25.1%), epiretinal membrane in 23 eyes (11.5%), cataract in 5 eyes (2.5%), juxtapapillary and juxtapfoveal lesions causing retinal folds in the macula in 3 eyes (1.50%) (Figure 7), posterior vitreous detachment in 12 eyes (6%), retinal detachment in 6 eyes (3%), persistent vitritis in 3 eyes (1.5%), and branch retinal vein occlusion in 1 eye (0.5%). One recurrence was seen in a 46-year-old woman 13 months after initial presentation; the recurrent retinitis was 2 DD away and nasal to the first healed scar. Both lesions were 2 DD inferior to the optic disc (Figure 5).

**COMMENT**

Retinochoroidal lesions can occur in acquired toxoplasmosis, either sporadically or in the context of an epidemic of acute toxoplasmosis. Whether toxoplasmic chorioretinitis is congenital or postnatally acquired is difficult to determine. The diagnosis of acute systemic toxoplasmosis is usually based on clinical features combined with an increase of specific IgG antibodies in the blood during a 3-week period. The presence of IgM antibodies is also a sign of recently acquired infection. If chorioretinitis develops subsequently, it is presumed to be acquired. We have described ocular involvement due to toxoplasmosis in 248 patients who had active retinochoroiditis and with no preexisting scars in either eye. Only
1 patient was immunodeficient (positive for human immunodeficiency virus); all other patients were immune competent.

The clinical presentation of our patients differs from those of patients with toxoplasmic chorioretinitis that occurs as a late sequela of infection that occurs in utero. Congenital disease tends to be bilateral, while acute acquired toxoplasmosis tends to be unilateral, single, and variable in size. Those with recrudescent congenital disease are relatively young, and have bilateral disease, old scars, and involvement of the macula. Acute acquired systemic toxoplasmosis in 80% to 90% of adults and children is an asymptomatic, self-limiting disease that goes unnoticed. Not all patients with postnatally acquired toxoplasmosis will develop ocular disease, as evidenced by a study from a Pacific island in which 90% of the adult population had been infected with *T gondii*; no adult had ocular toxoplasmosis. Those affected with visual symptoms later may visit the ophthalmologist weeks to months after the systemic illness. Most of our patients (n=242; 97.58%) had unilateral disease, while only 6 (2.42%) had bilateral disease. Most patients presented with solitary, discrete, active focus of retinochoroiditis with no preexisting scars, consistent with acquired ocular toxoplasmosis. The mean age of 40.47 years in our patients is higher than those with recurrent congenital disease in whom toxoplasmic retinochoroiditis occurs more frequently in the second and third decades of life. However, the mean age of our patients is lower than that reported in 2 other case series of acquired ocular toxoplasmosis reported by Remington and Montoya (mean, 50.2 years) and by Burnett et al (mean, 54 years). In our series only 35 patients (14.1%) had a prodrome of fever preceding their ocular symptoms. Our patients visited the hospital an average of 37 days after a prodrome (fever). In the case series by Burnett et al, 8 of 20 patients had systemic symptoms and signs consistent with acute *T gondii* infection that preceded the onset of ocular symptoms by a mean of 6 weeks.

Antibodies to IgM develop within 1 to 2 weeks after infection and persist for up to 1 year at low titers. They have repeatedly been found months or even years later, especially in pregnant women and patients with acquired toxoplasmosis. The capture ELISA technique used to detect IgM antibodies has a high specificity and does not give false-positive results in the presence of high *T gondii* IgG levels, antinuclear antibodies, or rheumatoid factor. In our series, serum was positive for *T gondii* IgM antibodies in all 198 cases for whom the tests were done. We have repeatedly shown a demonstrable fall in IgG titers in 10 patients on follow-up, suggesting a recent previous acute phase of the systemic disease.

Response to treatment in all of our patients has been excellent, though patients with large retinitis needed pro-

### Table. Repeated Serologic Testing in 10 Patients

<table>
<thead>
<tr>
<th>Patient No./Age, y</th>
<th>IgM</th>
<th>IgG</th>
<th>Repeated IgM</th>
<th>Repeated IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>74/54</td>
<td>10.5</td>
<td>669</td>
<td>2.3</td>
<td>305.9</td>
</tr>
<tr>
<td>173/27</td>
<td>6.5</td>
<td>251.5</td>
<td>2.6</td>
<td>117.9</td>
</tr>
<tr>
<td>185/60</td>
<td>Positive</td>
<td>231.7</td>
<td>1.6</td>
<td>136.8</td>
</tr>
<tr>
<td>196/16</td>
<td>6.1</td>
<td>744.8</td>
<td>Negative</td>
<td>0.1</td>
</tr>
<tr>
<td>197/61</td>
<td>1.5</td>
<td>775.2</td>
<td>3.4</td>
<td>213.6</td>
</tr>
<tr>
<td>198/28</td>
<td>Positive</td>
<td>735</td>
<td>1.4</td>
<td>377.1</td>
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<tr>
<td>200/34</td>
<td>Positive</td>
<td>560.4</td>
<td>3.6</td>
<td>208.1</td>
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<tr>
<td>201/35</td>
<td>Positive</td>
<td>426.2</td>
<td>3.4</td>
<td>64.9</td>
</tr>
<tr>
<td>202/31</td>
<td>9.8</td>
<td>565</td>
<td>1.6</td>
<td>76.2</td>
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<tr>
<td>221/45</td>
<td>4</td>
<td>788</td>
<td>0.6</td>
<td>113.3</td>
</tr>
</tbody>
</table>

*Repeated enzyme-linked immunosorbent assay (ELISA) shows a fall in IgG titers in all 10 patients.*
longed antimicrobial treatment beyond the 5 weeks of routine therapy. Visual acuity worsened from baseline values in only 11 eyes (5.52%). Except for 1 patient who experienced dry mouth and throat, there were no complications seen with Bactrim DS therapy.20

Recent estimates show the city’s population at 1.5 million, predominantly Hindu, with a sizeable Muslim and Christian population.

A noticeable feature was that 209 patients (84.27%) were residents of a city and its suburbs, implying the source of infection to be common to everyone infected. Unfortunately, we have not been able to pinpoint the source of infection, as we have not seen similar cases of retinitis after the latter half of 2005. Documented modes of transmission in acquired toxoplasmosis are exposure to oocysts shed by cats in their feces, consumption of inadequately cooked infected meat, particularly pork or lamb, leukocyte transmission, and possibly, consumption of raw milk.2-21 Other well-documented modes of transmission are aeroalization of oocysts and oocysts in municipal drinking water.6,22 Most of our patients used municipal drinking water for drinking/consumption purposes, indicating municipal drinking water as the most probable source of infection. Small rivers and streams from the hills in the west and north of Coimbatore city contribute to its large reservoirs, the source of its municipal drinking water.

The fact that those affected with visual symptoms came to the hospital in high numbers (as opposed to earlier statistics) between the months of September 2004 and July 2005, 14.1% with a history of prodromal symptoms (in only 11 eyes (5.52%). Except for 1 patient who experienced dry mouth and throat, there were no complications seen with Bactrim DS therapy.20

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REFERENCES

COMMENTS AND OPINIONS

Pitfall of Nonfasting Venous Blood Samples

I read with interest the article by Jeganathan and colleagues. Participants are overdiagnosed with lipid disorders and diabetes mellitus. First, the authors use nonfasting venous blood to evaluate the lipid profile. Nonfasting blood can be used to measure total cholesterol and high-density lipoprotein cholesterol levels, while triglyceride and low-density lipoprotein cholesterol levels require a 9- to 12-hour fasting state. Second, the authors defined persons with diabetes as those with only casual glucose levels of 200 mg/dL or higher but fail to recognize symptoms of hyperglycemia (polyuria, polydipsia, and unexplained weight loss), which are mandatory, as described in the standard diagnostic criteria of diabetes in the Table.3

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Table. Criteria for the Diagnosis of Diabetes Mellitus4,5

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Symptoms of hyperglycemia plus a casual blood glucose level ≥200 mg/dL (11.1 mmol/L)</td>
</tr>
<tr>
<td>Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L)</td>
</tr>
<tr>
<td>2-Hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test</td>
</tr>
</tbody>
</table>

In the absence of unequivocal hyperglycemia these criteria should be confirmed by repeat testing on a different day.


Correction

Error in Figure Legends: In the Clinical Sciences article titled “Outbreak of Acquired Ocular Toxoplasmosis Involving 248 Patients” by Balasundaram et al, published in the January 2010 issue of the Archives (2010; 128[1]:28-32), the legends for Figures 5, 6, and 7 were incorrectly matched to the images. The legend that appears under Figure 5 actually applies to Figure 7; the legend under Figure 6, to Figure 5; and the legend under Figure 7, to Figure 6.