

# CONGENITAL OCULAR TOXOPLASMOSES

Dwight D. Perry, MD, and John C. Merritt, MD  
Chapel Hill, North Carolina

**Congenital ocular toxoplasmosis is a significant cause of blindness. Retinochoroiditis is the most common finding, but other ocular manifestations include microphthalmus, nystagmus, strabismus, and ptosis. The serologic tests and lymphocyte stimulation test are the most useful aids in making the diagnosis. Pyrimethamine, sulfonamides, and corticosteroids are useful to treat active lesions. Primary care physicians, obstetricians, and ophthalmologists may help to prevent transmission of the disease and its serious ocular sequelae.**

Congenital toxoplasmosis was first identified in 1939 when Wolf et al<sup>1</sup> established toxoplasmosis as the cause of a meningoencephalitis and retinochoroiditis. Later these investigators verified the transmissibility of the disease.<sup>2</sup> Evidence has accrued and investigators have proposed theories about the prevalence, manifestations, diagnostic techniques, and therapeutics of toxoplasmosis. This paper reviews these developments, with emphasis on the congenital ocular sequelae.

## BIOLOGY

Toxoplasmosis, caused by the obligate intracellular protozoan *Toxoplasma gondii*, occurs in

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From the Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina. Requests for reprints should be addressed to Dr. John C. Merritt, Department of Ophthalmology, University of North Carolina, 617 Clinical Sciences Bldg. 229H, Chapel Hill, NC 27514.

many mammals and birds. The organism has three infective forms: oocyst, free trophozoite, and tissue cyst. The oocyst is ovoid, measures approximately 9 by 14  $\mu\text{m}$ , and contains two separate sporocysts.<sup>3</sup> In the alimentary tract of the cat, the definitive host of *T gondii*, the organism undergoes a sexual cycle leading to the production of oocysts that are passed in the feces. The oocysts are presumed to be swallowed by (1) children sucking their fingers, (2) persons who eat after contact with soil or cat litter without first washing their hands, and (3) persons who eat unwashed vegetables.<sup>4,5</sup> Also, flies and cockroaches are believed to contaminate human food with viable oocysts for up to 48 hours after contact with cat feces.<sup>6,7</sup>

Trophozoites appear as elongated teardrops and measure approximately 4 to 7  $\mu\text{m}$  by 2 to 4  $\mu\text{m}$ . Cysts consist of toxoplasma aggregates containing large glycogen granules. The encysted organism, surrounded by a limiting structure that is partially produced by the parasite, remains viable for the life of the host.<sup>8,9</sup> Raw or inadequately cooked meat that contains toxoplasma cysts and trophozoites is a frequent source of infection. It is believed the organism may be transmitted through handling of infected meat with failure to wash hands afterwards.<sup>10,11</sup>

## EPIDEMIOLOGY

Toxoplasmosis, a world-wide disease, is more prevalent in temperate and tropical climates than in cold climates.<sup>12</sup> Prevalence data concerning

toxoplasmosis have shown wide variations, ranging from 5 to 95 percent among young adults living in different parts of the world.<sup>13</sup> These variations may be related to factors such as differences in meat-eating habits, degree of exposure to infectious feces of cats, and temperatures that influence the survival of the oocyst once outside the cat. The serologic prevalence of toxoplasmosis, which increases with age, is approximately 30 percent in the US adult population.

In an extensive survey it was found that approximately 70 to 80 percent of females enter reproductive age without evidence of seroimmunity. The incidence of primary infection in pregnant women was approximately 1.25 percent per year.<sup>14</sup> The overall rate of transmission to the fetus from a primary maternal infection has been found to be approximately 40 percent, depending upon the gestational age at the time of infection.<sup>13,15</sup> First trimester maternal infection appears to result in a 17 percent rate of fetal infection, whereas the risk increases to 25 percent and 65 percent for the second and third trimesters, respectively.<sup>16</sup> The observed incidence of congenital toxoplasmosis in a prospective study was 1.1 per 1000 live births. Therefore, of the 3.3 million live births per year in the US, approximately 3300 infants are likely to be infected congenitally with *Toxoplasma*.<sup>17</sup>

Although acquired toxoplasmosis is most often asymptomatic, congenital infection more commonly presents with significant manifestations. Congenital infection occurs only as a result of maternal infection acquired during a current pregnancy.<sup>15,17</sup> There have been case descriptions of congenital toxoplasmosis in siblings;<sup>18,19</sup> however, no prospective study has shown a case of congenital toxoplasmosis that developed in the absence of maternal infection during the current pregnancy. Desmonts and Couvreur determined that the risk of severe clinical disease in infants resulted from maternal infection acquired during the second through sixth months of gestation. Acquisition later in pregnancy usually resulted in a subclinical infection.<sup>15</sup>

Perkins studied 150 cases of uveitis and found that 21 percent were due to toxoplasmosis.<sup>20</sup> In a separate study, toxoplasmosis was seen to cause 19 percent of all chorioretinal scars suspected of having an infectious etiology.<sup>21</sup> Surveying schools for the blind, Fair found 26 of 46 (56 percent) students with visual impairment that was believed to

have resulted from congenital chorioretinitis.<sup>22</sup> Only congenital cataract was a more frequent cause of school admission than chorioretinitis. Toxoplasmic retinochoroiditis, therefore, is a significant world-wide public health problem.

## CLINICAL MANIFESTATIONS

Approximately 20 to 30 percent of infants born with congenital toxoplasmosis manifest severe disease.<sup>23,24</sup> Another 10 percent are born with ocular involvement, but without clinical evidence of disease of other organ systems.<sup>24</sup> The remaining 60 to 70 percent are asymptomatic at birth.<sup>23</sup> However, a substantial proportion of asymptomatic infants develop delayed adverse sequelae of the congenital infection months to years later.<sup>25,26</sup>

Congenital toxoplasmosis is known to produce a variety of disease processes. Central nervous system involvement may cause cerebral calcification, hydrocephaly or microcephaly, and psychomotor retardation. Commonly, nonspecific findings of lymphadenopathy, hepatosplenomegaly, rash, and anemia are present. However, retinochoroiditis is the most common finding in congenital toxoplasmosis, occurring in about 80 percent of cases.<sup>27</sup> Retinochoroiditis may be asymptomatic, or may cause various symptoms including blindness.<sup>27</sup> Though reintochoroiditis is common in congenital toxoplasmosis, it is rarely recognized in acquired systemic toxoplasmosis.<sup>28</sup> It is believed that most cases diagnosed as acquired toxoplasmosis are actually recurrences of congenital infection.<sup>29</sup>

Retinochoroidal lesions caused by toxoplasmosis are characterized histologically by granulomatous inflammation and necrosis of the retina and choroid.<sup>30,31</sup> The necrotic retina contains the *Toxoplasma*. The lack of organisms in the choroid suggests that the infection is principally retinal, with secondary choroidal involvement. The lesion contains epithelioid cells, lymphocytes, plasma cells, and varying numbers of polymorphonuclear leukocytes and eosinophiles. There is also outgrowth of granulation tissue into the vitreous, which corresponds to raised masses seen ophthalmoscopically. The vast majority of ocular lesions involve the posterior pole, particularly the macular region.<sup>22</sup> Although there have been many cases describing peripherally located lesions, it is

believed that peripheral lesions are more common in blacks than in whites. In a study of immigrants to Great Britain from West Africa and the West Indies, Chesterson and Perkins reported that peripherally situated lesions were found in 25.9 percent of blacks and 3.8 percent of whites studied.<sup>32</sup>

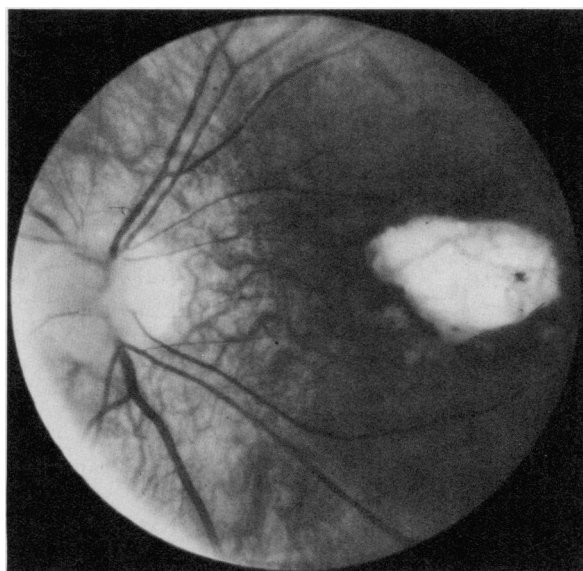
Fundusoscopic findings of acute retinochoroidal lesions reveal yellowish-white patches sometimes accompanied by a small hemorrhage, an overlying exudate, and vitreous opacities (Figure 1). Small satellite lesions may surround the principal foci.<sup>33,34</sup> As the lesions become chronic, pigment becomes visible at the margins.<sup>33</sup> The lesions usually heal within a few weeks to several months. The healed lesion is characterized by a whitish-gray appearance with distinct but irregular borders (Figure 2). The pigment at the margins becomes more prominent and usually extends to the center of the lesion. Peripapillary lesions are present in approximately 20 percent of toxoplasmosis cases with retinal involvement. Small peripapillary lesions can produce extensive visual field defects resulting from destruction of the nerve fiber layer.<sup>35</sup>

Nystagmus and strabismus are frequent symptoms of congenital toxoplasmosis. These symptoms may occur because of poor fixation due to decreased central acuity from macular lesions or loss of visual function from central nervous system involvement.<sup>33</sup> Ptosis associated with exotropia may occur due to oculomotor nerve palsy.<sup>36</sup> Other ocular complications include anterior uveitis, which is secondary to posterior disease,<sup>37</sup> microphthalmus, and remnant of the hyaloid system.<sup>38</sup>

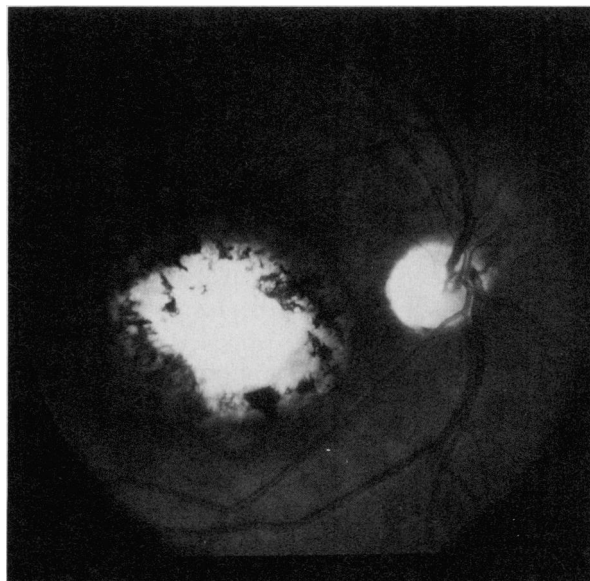
## LABORATORY MANIFESTATIONS

Laboratory tests that have been used to diagnose a toxoplasmosis infection include (1) histologic examination, (2) isolation of the parasite, (3) skin test, (4) serodiagnosis, and (5) demonstration in vitro of antigen-specific lymphocyte recognition. Histologic examination is only helpful retrospectively, since it is possible to examine the histologic appearance of the granulomatous lesions containing the toxoplasma only after enucleation of the eye.

The organism may be isolated from digested placental tissue. It then may be injected intraperi-



**Figure 1. Focal hypopigmented lesion in the posterior pole typical of acute to subacute stages of inflammation**



**Figure 2. Chronic macular lesion with area of central atrophy surrounded by zone of hyperpigmentation**

toneally into laboratory mice whose lack of prior infection has been established.<sup>15</sup> However, this test has utility only when the newborn is suspected of having congenital toxoplasmosis and the pla-

centa is preserved for diagnostic purpose. Also, this method is not routinely available clinically.

The skin test demonstrates hypersensitivity as a result of cell-mediated immunity, similar to the tuberculin skin test. However, the reaction requires several months to develop, and an unacceptably large number of false-negative results have been observed in one investigation.<sup>8</sup>

Serologic tests used for the diagnosis of toxoplasmosis include (1) the Sabin-Feldman dye test (DT), (2) the conventional indirect fluorescent antibody test, (3) the IgM-fluorescent antibody test (IgM-IFA), (4) the complement fixation test, and (5) the indirect hemagglutination test. The DT and IgM-IFA tests are the most useful in diagnosing congenital toxoplasmosis.

The DT is unsurpassed in sensitivity and specificity. Therefore it has become the reference serologic procedure.<sup>8</sup> It is performed by mixing the patient's serum with a suspension of living toxoplasma organisms, human serum accessory factor, and methylene blue dye.<sup>17</sup> The organisms fail to stain with methylene blue dye in the presence of IgG antibodies. The titer refers to the highest dilution at which 50 percent of the extracellular toxoplasma lose their affinity for the dye.<sup>39</sup> In patients with only retinochoroiditis, the DT titer is frequently low. In one case cited, the DT titer was positive only in undiluted serum and many toxoplasma were identified in the eye at autopsy.<sup>40</sup> Therefore, a positive test at any titer is significant when associated with a patient who has a fundus lesion compatible with toxoplasmosis. In most infections, IgM antibodies appear earlier and disappear sooner than IgG antibodies. Also, IgM antibodies do not normally cross the placenta. Therefore, the IgM-IFA test may establish the diagnosis sooner than the dye test.<sup>41</sup> A major disadvantage is its lack of sensitivity—the IgM-IFA test has been negative in a significant number of infected children.<sup>42</sup>

The lymphocyte stimulation test (LST) is the newest aid for the diagnosis of toxoplasmosis. Since lymphocyte transformation reflects a specific immune response in the newborn, the test measures the blastogenic response of lymphocytes incubated with *Toxoplasma* antigen. The LST has been found to be more sensitive than the IgM-IFA test in infants older than three months;<sup>43</sup> however, further investigation is needed to define better the sensitivity and specificity of this technique.

## TREATMENT

Conventional anti-*Toxoplasma* drugs are active only against the proliferative trophozoites and have no effect on tissue cysts.<sup>44</sup> Because of the progressive nature of the disease and its tendency toward delayed damage, some authors recommend treatment regardless of symptoms or type of lesion.<sup>15,24,26</sup> Others, however, believe treatment should be instituted only under specified conditions,<sup>35,37,45</sup> which include the presence of (1) active macular lesions, (2) active lesions within the papillomacular bundle, (3) lesions threatening or involving the optic nerve, or (4) lesions causing massive vitreous reaction sufficient to cause subsequent retinal detachment.

The preferred therapy is a combination of sulfonamides (sulfadiazine in particular) and pyrimethamine (Daraprim) which acts synergistically to block the conversion of para-aminobenzoic acid to folic acid.<sup>46</sup> The mammalian host can utilize preformed folic acid whereas the toxoplasma cannot.<sup>47</sup> The recommended dosage for pyrimethamine consists of a single loading dose of 1 mg/kg and a maintenance dose of 0.5 mg/kg/d; for sulfadiazine the dosage is 100 to 150 mg/kg/d in four divided doses. The disadvantage of therapy is that pyrimethamine inhibits human folate metabolism and thereby produces leukopenia and thrombocytopenia. For this reason, the drug is administered for no more than four consecutive weeks, with a two- to three-week interval between treatments. Folic acid, 5 to 10 mg intramuscularly three to four times per week during therapy, reduces the frequency of complications without interfering with the efficacy of the drug.

Corticosteroids should be used for active vision-threatening lesions. Prednisone, 1 to 2 mg/kg/d, should be given in conjunction with sulfadiazine and pyrimethamine. Therapy should be continued until healing is established, as evidenced by a well demarcated and pigmented lesion. However, sulfadiazine and pyrimethamine may be discontinued only after the corticosteroids are tapered.<sup>37,46</sup>

Immunocompromised patients and others that cannot tolerate sulfadiazine and pyrimethamine have benefited from other drugs. Spiramycin is a macrolide antibiotic that is unavailable in the United States, but has been used widely in Europe. It is less toxic, but is much less effective

than the preferred treatments of retinochoroiditis.<sup>45</sup> Some evidence supports treatment with clindamycin to resolve active toxoplasmic retinochoroiditis.<sup>48,49</sup> Clindamycin develops a high ocular tissue concentration and is believed to be effective in the chronically infected cyst containing retinochoroidal lesions.<sup>49,50</sup> Although it carried a significant risk of pseudomembranous colitis in adults, there is not a high risk of this complication in children.

## PREVENTION

Obstetricians can make a significant contribution to the prevention of toxoplasmosis. Pregnant women should be instructed to (1) wash hands thoroughly after handling raw meat, (2) eat only well-cooked meat, (3) wear gloves while handling material potentially infected with cat feces (eg, cat litter boxes, soil, sand), (4) wash hands after handling materials infected with cat feces, and (5) disinfect cat litter boxes with boiling water. In those women identified as "high risk" (eg, due to cat exposure or raw meat infestation during pregnancy), serial toxoplasma antibody titers can be drawn to detect acute subclinical infection.

The primary care physician can also make a significant contribution. The presence of nonspecific signs and symptoms at birth should prompt a careful funduscopic examination. Establishing the diagnosis in the early neonatal period may prevent irreparable damage or further ocular tissue destruction.

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## TOXOPLASMOSIS

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