SURVEY OF OPHTHALMOLOGY VOLUME 53 • NUMBER 2 • MARCH–APRIL 2008

MAJOR REVIEW

# Eye Manifestations of Intrauterine Infections and Their Impact on Childhood Blindness

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**Abstract.** Intrauterine infections are important causes of childhood blindness in both developed and developing countries. Chorioretinal scars are the most characteristic eye manifestation of a congenital or prenatal infection. The various ocular manifestations of congenital infections, summarized by the mnemonic TORCH, and recent additions to the "other" category (lymphocytic choriomeningitis virus and West Nile virus) are discussed. (**Surv Ophthalmol 53**:95–111, 2008. © 2008 Elsevier Inc. All rights reserved.)

**Key words.** congenital • cytomegalovirus • eye • herpes • lymphocytic choriomeningitis • rubella • systemic • toxoplasmosis • West Nile virus

## I. Introduction

The most common congenital intrauterine infections can be summarized by the mnemonic TORCH: *Toxoplasma gondii*, others, rubella, cytomegalovirus, and herpes simplex virus. "Others" includes treponema pallidum, varicella–zoster virus, Epstein–Barr virus, human immunodeficiency virus, lymphocytic choriomeningitis virus, and West Nile virus. These are a potential cause of preventable childhood blindness in all parts of the world.

These agents produce a relatively mild illness in the mother, compared to the impact in the developing fetus. More virulent agents result in a spontaneous abortion or stillbirth, although the named agents, if contracted early in the first trimester, may result in abortion or stillbirth as well. They are transmitted transplacentally, and have a direct toxic effect (inflammation and necrosis). Additionally, in the first trimester, when the fetus has immature, developing organs, there may be a teratogenic effect. If the fetus is unable to eliminate the organism, this may lead to chronic infection and, in some cases immune tolerance, and the diagnosis can be made by elevated levels of IgM and IgA antibodies.

In humans IgG is actively transported across the placenta. IgM is not. This placental transfer onsets at the 24th week of gestation and increases exponentially during the second half of pregnancy. The baby receives from the mother, pre-natally, IgG and post-natally (from colostrum and breast milk), mostly s IgA (secretory IgA) and small amounts of IgG and IgM (short half life of one to two days).[13,51,90] After birth, the child's own production of IgM starts almost immediately, but the production of IgG does not start for almost 6 months. Therefore, in the first 6 months of life, elevated levels of IgG were mostly likely from transplacental transfer from the mother. Elevated levels of IgM antibodies in the mother support the congenital nature of the infection.

## II. Toxoplasma Gondii

### A. AGENT AND EPIDEMIOLOGY

*Toxoplasma gondii* derives from the Greek, *toxon* meaning bow (the shape of the proliferative form),





0039-6257/08/$–see front matter
doi:10.1016/j.survophthal.2007.12.003

and *gondii*, for a rodent (*Ctenodactylus gundi*) indigenous to North Africa from which the organism was first isolated.[82] *Toxoplasma gondii* is an obligate intracellular parasite, which probably evolved from a unicellular alga because it has an organelle similar to a chloroplast. It has a life cycle that has three forms, an oocyst (found in the gut of cats), a tissue cyst, and an active, or proliferative form. Three different strains have been reported (type I, II, and III), with variable virulences. Congenital disease in humans is associated mostly with type I and II whereas type III is found mainly in other animals.[75] The source to humans includes cat feces, in which the oocyst may be infective for up to 1 year in warm, moist soil, and raw meat, in which the tissue cysts are viable. Other risk factors include eating raw vegetables outside the home, contact with soil, poor hand hygiene, and drinking water from a contaminated reservoir.[53]

In the United States, the prevalence in humans varies with age; in children under 5 years of age, the antibodies are found in less than 5% of the population, whereas in adults over 80 years of age, they are present in 60%. Seventy percent of the obstetric population has negative antibodies, and is at risk for transmission to the fetus.[58] The reported prevalence of congenital toxoplasmosis is in the range of 1–10 per 10,000 live births, depending on the population.[75] The risk of passage to the fetus and the severity of the infection are affected by the gestational age at the time of maternal infection. Transmission to the fetus is 25% in the first trimester, 75% in the third trimester, and over 90% in the last few weeks of pregnancy. The severity of the fetal infection is inversely related to gestational age, with the earlier infections being the most severe.[30,92] Transmission has also been reported from organ transplantation from a seropositive donor to a seronegative recipient.[75]

## B. DIAGNOSIS

The diagnosis of *Toxoplasma gondii* infection is made by multiple methods, including ELISA for IgM and IgA. It is important to test undiluted samples, because the serum levels may be very low in eye disease and samples are needed for both the patient and the mother.The work-up includes a CBC, with differential and platelet levels, and a CT scan looking for hydrocephalus and intracranial calcifications, especially in the periventricular regions.

## C. SYSTEMIC MANIFESTATIONS

The systemic manifestations are the classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications. Ninety percent of neonates are asymptomatic; however, they can show a continuous clinical spectrum including abnormal cerebrospinal fluid, anemia, petechiae due to thrombocytopenia, deafness, seizures, intracranial calcifications, jaundice, fever, hepatosplenomegaly, hydrocephalus, microcephalus, mental and growth retardation, spasticity and palsies, lymphadenopathy, maculopapular rash, vomiting, and diarrhea.[53,61,75,104] In premature infants toxoplasmosis manifests in the form of CNS and ocular disease in the first three months of life while in full-term infants, a milder disease develops with hepatosplenomegaly and lymphadenopathy in the first two months. Of course, full-term infants may be severely affected, but the overall spectrum is worse in premature infants, in which 80% develop some learning or visual disabilities later in life.[76]

## D. EYE MANIFESTATIONS

Eighty-five percent of patients with subclinical congenital infections are reported to develop chorioretinitis.[104] The eye manifestations of congenital toxoplasmosis found in a large study are summarized in Table 1.[70]

### 1. Anterior Segment

Microcornea was seen in 19% of patients and cataracts in 10%.[71] It should be noted that these were never isolated findings and that they were always seen in association with posterior segment disease.

TABLE 1

*Ophthalmologic Manifestations of Congenital Toxoplasmosis (n = 94)*

| Diagnosis off Patients Checked | Percentage of Patients with Findings |
|---|---|
| Chorioretinal scars | 79 (74) * |
| Macular** | 58 |
| Juxtapapillary** | 52 |
| Peripheral** | 64 |
| Strabismus | 33 (31) |
| Nystagmus | 27 (25) |
| Optic atrophy | 20 (19) |
| Microcornea | 19 (18) |
| Microphthalmos | 13 (12) |
| Retinitis (active) | 11 (10) |
| Cataract | 10 (9) |
| Retinal detachment | 10 (9) |
| Vitritis (active) | 5 (5) |
| Phthisis | 4 (4) |

Table based on data from McAuley et al.[68]

*Number in parentheses is the total number of patients with findings.

**Percentage of patients with chorioretinal scars.