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Overlapping Spectrum of Retinochoroidal Scarring in Congenital Zika Virus and Toxoplasmosis Infections

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Abstract

BACKGROUND AND OBJECTIVE: Antenatal Zika virus (ZIKV) or toxoplasmosis infections may present with isolated eye abnormalities with absence of other apparent birth defects. The purpose of this article is to discuss the overlapping spectrum of clinical presentation and retinochoroidal scarring in congenital ZIKV and toxoplasmosis infections.

PATIENTS AND METHODS: Prenatal ultrasound abnormalities seen from antenatal ZIKV and toxoplasmosis infections overlap and may include intracranial calcifications, microcephaly, and intrauterine growth restriction. The clinical spectrum of both infections in less severely affected infants and children may include nonspecific neurological impairment such as developmental delay and seizures.

RESULTS: Inherent limitations in serological testing pose additional barriers in establishing a diagnosis. Retinal pigment epithelium (RPE) mottling in ZIKV infection can occur in isolation or adjacent to retinochoroidal atrophy. In contrast, RPE mottling outside of the borders of retinochoroidal atrophy is not typically seen in toxoplasmosis. To date, post-natal reactivation of congenital eye lesions as seen in toxoplasmosis have not been reported with ZIKV infection.

CONCLUSIONS: As children infected with congenital ZIKV grow older, subclinical eye abnormalities may be indistinguishable from toxoplasmosis. Brazil has had high prevalence of both diseases with long-term information available on toxoplasmosis only. Surveillance guidelines for asymptomatic eye abnormalities will likely evolve.

INTRODUCTION

During the Brazilian epidemic of 2015 to 2016, Zika virus (ZIKV) became recognized as a new congenital “TORCH” infection, joining toxoplasmosis, syphilis, rubella, cytomegalovirus, and herpes simplex virus as infections that have the potential to cause severe birth defects when acquired in utero.¹ Although congenital ZIKV infection may present with a wide spectrum of findings, its most devastating form (also known as congenital Zika syndrome) is readily identifiable and includes (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices with sub-cortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) arthrogryposis; and (5) marked early hypertonia and symptoms of extra-pyramidal involvement.²

In contrast to ZIKV infection, toxoplasmosis is a well-studied and longstanding parasitic infection caused by the intracellular protozoan *Toxoplasma gondii*.^{3–5} Toxoplasmosis is one of the most common human infections found throughout the world and in adults is mostly asymptomatic.⁶ However, primary toxoplasmosis infection during pregnancy can cause severe and disabling birth defects in the developing fetus.⁷ Congenital toxoplasmosis is a leading cause of visual impairment in Brazilian children.^{8–11}

The clinical spectrum of both congenital ZIKV and toxoplasmosis infections in less severely affected infants and children may include nonspecific neurological impairment, such as developmental delay and seizures (Table 1). As children infected during the ZIKV epidemic grow older, subclinical eye abnormalities may be indistinguishable from toxoplasmosis. The purpose of this article is to discuss the overlapping spectrum of congenital ZIKV and toxoplasmosis infections, with an emphasis on retinochoroidal scarring.

Maternal Presentation and Diagnostic Testing

Only about 20% of adults infected with either ZIKV or toxoplasmosis are symptomatic. Therefore, when presented with a child who has findings compatible with an in utero infection, lack of maternal symptoms during pregnancy does not rule out the possibility of either infection.

Prenatal ultrasound findings indicative of toxoplasmosis are nonspecific and include intracranial calcification, microcephaly, hydrocephalus, ascites, hepatosplenomegaly, or severe intrauterine growth restriction.¹² Prenatal ultrasound findings reported with ZIKV include microcephaly, lissencephaly, agenesis of corpus callosum, intracranial calcification, cerebellar atrophy, ventriculomegaly, microphthalmia, hydrocephalus, intrauterine growth restriction, and arthrogryposis.¹³ ZIKV infection may be distinguishable from other “TORCH” infections by its emphasis on neurologic abnormalities with relative sparing of other organ systems.¹⁴ In addition, although toxoplasmosis and ZIKV both have the potential to cause severe fetal brain destruction, findings such as severe microcephaly with partial skull collapse, thin cerebral cortex with calcifications, brain calcifications at the gray and white matter junction, dysgenesis of corpus callosum, congenital contractures (arthrogryposis and severe early hypertonia), and macular scarring with focal pigmentary retinal mottling are more classically seen in ZIKV infection.^{2,14}

Diagnosis of ZIKV infection during pregnancy includes a positive ZIKV polymerase chain reaction (PCR) test from maternal blood, urine, or amniotic fluid. Limitations of PCR testing is that the technology is not readily available in many regions of the world and may only be positive during the acute phase of infection, typically lasting 2 weeks. ZIKV serological testing (ie, ZIKV immunoglobulin M (IgM) and IgG via antibody capture enzyme-linked immunosorbent assay) may be uninterpretable because they cross-react with other endemic mosquito-borne flaviviruses like dengue virus.¹⁵ Plaque reduction neutralization testing (PRNT) may help distinguish between ZIKV positive antibodies and other flaviviruses, but PRNT is costly, labor-intensive, and therefore not readily available. Other “TORCH” infections such as syphilis, rubella, cytomegalovirus, herpes simplex virus, and HIV can usually be excluded with antibody or PCR testing.

Diagnosis of toxoplasmosis infection during pregnancy includes maternal seroconversion of toxoplasmosis IgG, elevated IgM, and PCR amniocentesis for infants with a prenatal ultrasound abnormality consistent with in utero infection. Recently, IgG avidity testing has allowed better indication of the timing of toxoplasmosis infection.¹⁶ Serological confirmation in an infant includes positive IgM, persistently elevated IgG past 1 year of life, and/or rising IgG during the first year of life. Because toxoplasma serological testing may be prone to false-positives, testing should be sent to a reference laboratory.¹⁷ During episodes of ocular reactivation in adults, PCR testing of ocular fluid can be considered to confirm the diagnosis but does not distinguish congenital from acquired disease.¹⁸ The rate of positive PCR results from a vitreous sample of clinically suspicious immune competent patient has yielded positive results in 50% of cases¹⁹ and sensitivity of newer tests may be even higher.

Clinical Presentation in Children

With or without maternal symptoms during pregnancy, ZIKV and toxoplasmosis infections can lead to severe effects on the developing fetus.^{20,21} The most characteristic finding of ZIKV infection is microcephaly with a partially collapsed skull and, in a series of microcephalic infants examined during the ZIKV epidemic in northeast Brazil, 10 of 29 (34.5%) had eye findings, which included optic nerve pallor, atrophy, hypoplasia, retinochoroidal scarring, and retinal pigment epithelium (RPE) mottling.²² Another series in northeast Brazil reported eye abnormalities in 22 of 40 (55%) microcephalic infants.²³ In our series from Rio de Janeiro in southeast Brazil, we reported on infants with PCR confirmation of infection and found 24 of 112 (21%) infants had similar eye abnormalities as reported in northeast Brazil, and half of those with eye findings had retinochoroidal scarring and/or RPE mottling.²⁴ These percentages do not reflect the prevalence of ZIKV eye abnormalities in the population, as there was referral bias in all case series.

The RPE mottling associated with ZIKV is typically located in the macula and has a speckled appearance (Figure 1A). Superficial or deep retinochoroidal scarring is also commonly associated with RPE mottling outside of atrophic areas (Figures 1B and 1C). In extreme cases, large areas of retino-choroidal atrophy can occur (Figure 1D). Of note, eight of 24 (33%) infants in the Rio de Janeiro series had eye findings without microcephaly or other central nervous system abnormalities. To our knowledge, no active retinochoroidal lesions from reactivation of congenital ZIKV infection have been reported to date.

Retinochoroidal lesions in congenital toxoplasmosis seen after birth are most typically located in the macula, bilateral, and can be active or healed. There can be an outer ring of RPE atrophy and lesions can be extra-macular (Figure 2A). Toxoplasmosis can also classically manifest as a larger retinochoroidal lesion with pigment within the affected area in a “wagon-wheel” configuration. There is usually not RPE mottling seen outside of areas of chorioretinal atrophy, as seen in ZIKV.

In a series of 44 serologically confirmed infants with congenital toxoplasmosis syndrome in Brazil, more than half were found to have active retinochoroiditis.²⁵ During periods of activity, toxoplasmosis retinochoroiditis is described as a single, focal “head light in fog” with vitritis and active white retinitis (Figure 2B). Lesions can be contiguous with prior areas or arrive de novo as satellite lesions. Nonspecific associated uveitis findings during periods of activity include macular edema, retinal vasculitis, optic nerve swelling, anterior segment inflammation, and elevated intraocular pressure.

In infants and children, the differential diagnosis of active retinitis due to toxoplasmosis includes cytomegalovirus, herpes virus, and disseminated retinoblastoma.²⁶ Of note, active inflammation has not been noted with congenital ZIKV virus yet but children born during the Brazilian ZIKV epidemic are only 3 to 4 years old, and most do not routinely have follow-up eye examinations.

In both congenital ZIKV and toxoplasmosis infections, less-common ophthalmic birth defects such as strabismus, micro-ophthalmia, and cataract have also been described.^{25,27} When a child presents with any of these less typical eye abnormalities and no or nonspecific systemic associations (ie, intracranial calcifications, seizures, developmental delay), the diagnosis can also remain unclear.

Pathogenesis of Eye Lesions

The placenta, brain, and eye are the main immune-privileged sites in the body, which may contribute to the pathogenesis of congenital infections in these organs. The pathogenesis of eye lesions due to toxoplasmosis appears to be host and parasite strain dependent, as there is much variability in who manifests signs of infection and who remains asymptomatic.²⁸ Necrotizing retinochoroiditis involving the inner layers of the retina is the characteristic eye lesion during active infection. The retina is the primary site for the multiplying parasites, while the choroid and the sclera may be the sites of contiguous inflammation.^{29–31}

There is some evidence to show that specific genetic polymorphisms of *ABCA4*-encoding genes or cytokines may predispose to eye lesions due to toxoplasmosis.^{32,33} It appears that the parasite enters target organs using dendritic cells and macrophages as “Trojan horses.” Once in the host cell, toxoplasmosis can suppress some host defense mechanisms.^{34,35} Tissue cysts form as early as 7 days after infection and remain for the lifespan of the host. The encysted toxoplasma organism can reactivate to cause posterior uveitis, particularly during times of immuno-suppression.

Less is known about the mechanism of eye injury in congenital ZIKV infection. It appears that the Asian lineage of ZIKV is more neurotropic and have a higher viral burden than the

original African lineage both in the brain and eye.³⁶ Optical coherence tomography findings in infants showed retinochoroidal scarring and lesions similar to cobalamin C deficiency leading to the hypothesis that this vitamin could be involved in the pathogenesis of eye lesions due to ZIKV infection.³⁷ Animal models, which have been developed to study ZIKV infection, include mice, guinea pig, and nonhuman primates.³⁸

Mouse models of congenital ZIKV infection have shown the virus affects Müller's cells and RPE cells in immature animals only with adult mice being less susceptible to ocular infection.³⁹ A neonatal mouse model showed that ZIKV was primarily located in optic nerve, retinal ganglion cells, and inner nuclear layer cells and associated with thinning of the outer plexiform layer. During active infection, the eyes demonstrated increased expression of tumor necrosis factor, interferon-gamma, granzyme B, and perforin.⁴⁰

DISCUSSION

The clinical spectrum of neurological abnormalities and retinochoroidal scarring from congenital ZIKV and toxoplasmosis infections overlap and may be difficult to distinguish without other respective pathognomonic systemic findings. Interpretation of laboratory testing is challenging including both false negatives and positives but can help rule out other congenital infections. Brazil has had a long history of clinical expertise caring for mothers and children with toxoplasmosis and a still evolving history of those with ZIKV infection. Surveillance guidelines for asymptomatic eye abnormalities will likely evolve.

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Figure 1.

Spectrum of retinal lesions associated with Zika virus (ZIKV) infection. All mother-infant pairs tested polymerase chain reaction-positive for ZIKV and negative for toxoplasmosis immunoglobulin G (IgG)/IgM. (A) Retinal pigment epithelium (RPE) mottling in the macula. (B) RPE mottling with superficial atrophy in the macula. (C) Deep chorioretinal atrophy with RPE hyperpigmentation outside of the lesion. (D) RPE mottling and large areas of chorioretinal atrophy.

Figure 2.
Typical retinochoroidal lesions seen in toxoplasmosis. (A) Extra-macular lesion with pigmented and fibrotic retinochoroidal scar. (B) Active lesion with vitritis causing “fog in headlight” appearance.

TABLE 1

Comparison of Toxoplasmosis and Zika Virus Infections

Organism	Mode of Transmission	Congenital Ophthalmic Abnormalities	Congenital Systemic Abnormalities
<i>Toxoplasma gondii</i>	Ingestion of contaminated water, cat feces, raw meat, vertical, blood borne	Retinochoroiditis, optic neuritis/pallor, cataracts, microphthalmia, microcornea, nystagmus	Hydrocephalus, microcephaly, intracranial calcification, hearing loss, rash
Zika virus	Mosquitoes, sexual, vertical, blood borne	RPE mottling, retinochoroiditis, optic neuritis/pallor, optic nerve hypoplasia cataracts, microphthalmia, microcornea, nystagmus	Microcephaly with partially collapsed skull, intracranial calcification, ventriculomegaly, arthrogryposis, hypotonia, hearing loss

RPE = retinal pigment epithelium