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Atypical Bilateral Multifocal Congenital Toxoplasmosis Retinochoroiditis: Case Report With Literature Review

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Abstract

Background. Toxoplasmosis gondii is ubiquitously present on earth and infection, including congenital infection, is common. Neurological, developmental, and ocular effects can be devastating in the congenital toxoplasmosis population. At present, there is no standard, nation-wide neonatal screening for this disease in the United States. *Case Presentation*. A 17-month-old Caucasian female presented to our institution by way of referral for macular scarring. She was diagnosed with intrauterine growth retardation and born with low birth weight and microcephaly at an outside institution, but no systemic workup was conducted at that time. On ocular examination, she was found to have nystagmus and extensive multifocal chorioretinal pigmented scars involving the macula and peripheral retina in both eyes with fibrous vitreous strands extending between scars in the right eye. Toxoplasmosis immunoglobulin G was found to be highly positive. Magnetic resonance imaging of the brain showed supratentorial intracranial calcifications. *Conclusions*. Our patient presented with severe chorioretinal lesions, microcephaly, and nystagmus with a positive immunoglobulin G toxoplasmosis titer. She did not receive any evaluation, including TORCH infectious panel workup, on being born with low birth weight and microcephaly. There are currently no national programs in place for toxoplasmosis to be included in routine neonatal screening, despite the grave sequelae of congenital infection or that studies in other countries have shown cost-effectiveness in early screening and treatment.

Keywords

congenital toxoplasmosis, retinochoroiditis, nystagmus, screening

Introduction

Congenital toxoplasmosis (CT) is caused by a transmission of the protozoan parasite *Toxoplasma gondii* via vertical transmission during pregnancy. Clinical manifestations are wide ranging, from subclinical and asymptomatic to intracranial calcifications, seizures, developmental delay, and chorioretinal lesions with potential visual loss, or even fetal demise. Prenatal or newborn infection can only be detected by serum immunoglobulin testing in utero or on newborn screening, which is routinely performed in Europe but not in the United States at present. Maternal infection is by far most common in the third trimester; however, the potential for more severe infectious sequelae to fetus occur with first or second trimester infection. It is well established that congenital *Toxoplasma* infection can lead to chorioretinal scarring in the macula, among other ocular and neurological abnormalities.[1] We present a case of a toddler with intrauterine growth retardation and microcephaly with delayed ophthalmic examination, who presented with severe bilateral macular and peripheral retinal scarring and vitreous stranding connecting chorioretinal lesions. A written informed consent was taken from the parents prior to submission.

Case Presentation

We report the case of a 17-month-old female toddler who presented to the University of Florida pediatric ophthalmology clinic by way of second opinion for macular scars and poor vision. The patient was born at an outside facility at 37 weeks gestation via uncomplicated vaginal delivery at 4 pounds and 7 ounces. Prenatal course was significant for chlamydia infection in mother in the first trimester, which was successfully treated with unknown antibiotics. Intrauterine growth retardation (IUGR) was noted on prenatal ultrasound. Despite IUGR at birth, no systemic or genetic workup was initiated during stay at outside hospital. The mother first noted abnormal eye movements around 3 months of age, at which time she also began to notice the

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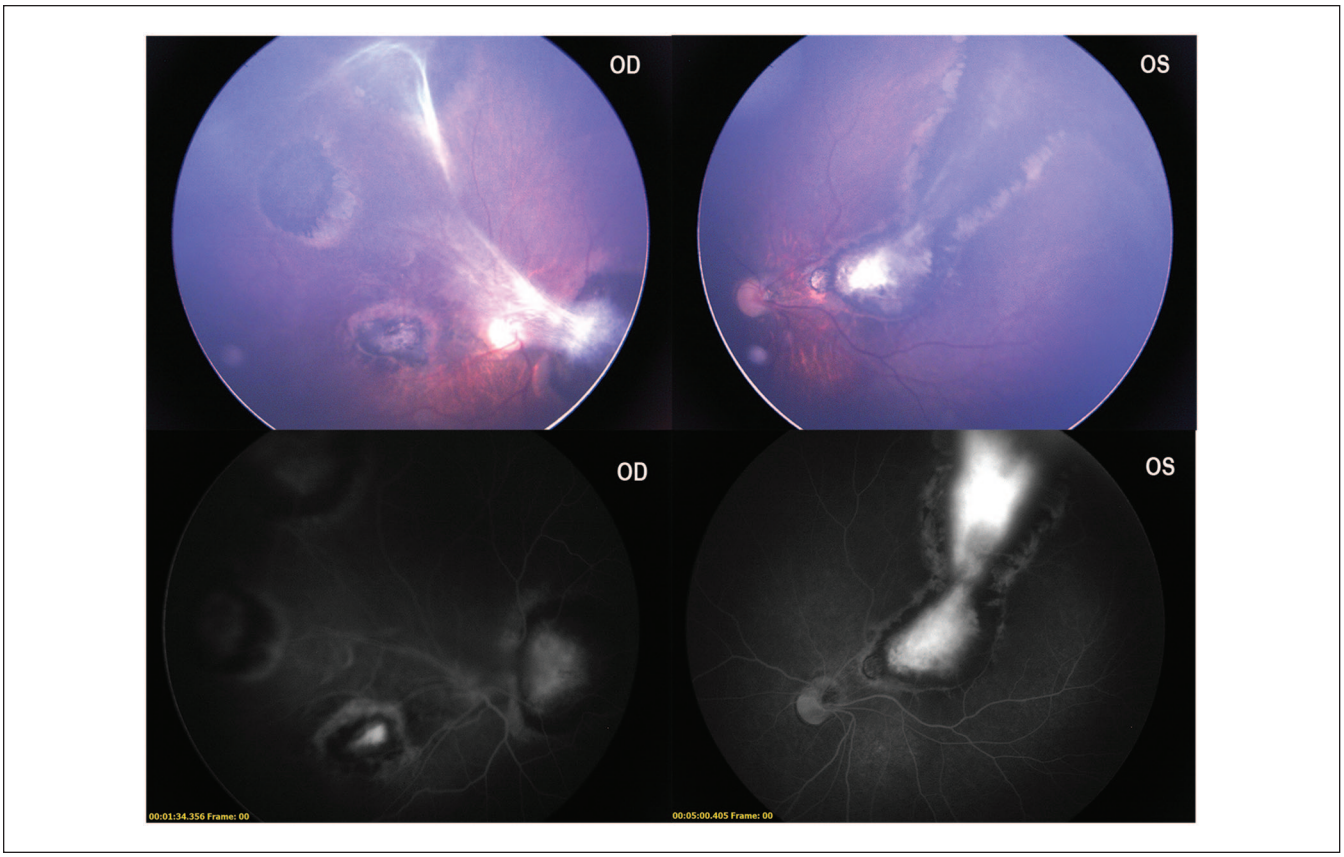

Figure 1. Top upper left—Color fundus photo of the right eye exhibiting extensive multifocal chorioretinal pigmented scars involving the macula and peripheral retina with fibrous vitreous strands. Upper right—Color fundus photo of left eye showing an extensive large macular scar extending between the arcades to the periphery. Bottom—Fluorescein angiography photos of the right and left eyes depicting hyperfluorescent staining centrally with hypofluorescent borders with no indication of active disease.

child did not respond well to visual stimuli. Mother reports being assured that these findings were normal, which contributed to delayed presentation to an ophthalmologist. The mother also noted a few seizure-like episodes with generalized limb jerking. Family was eventually referred to retinal specialist in their area and were reportedly informed that the patient had retina scarring and no intervention would be helpful at this stage. Family presented to our pediatric ophthalmology clinic at the University of Florida-Gainesville for a second opinion. The child was examined under anesthesia and found to have borderline microcornea (horizontal corneal diameter 10 mm), myopic astigmatism, with extensive multifocal chorioretinal pigmented scars involving the macula and peripheral retina with fibrous vitreous strands that spread between lesions in the right eye and an extensive large macular scar extending between the arcades to the periphery in the left eye (Figure 1, top). The scars appeared congenital in nature with no signs of activity seen clinically and on fluorescein angiography (Figure 1, bottom) and thus our top differential diagnoses included Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections (TORCH) and congenital hamartoma of the retinal pigment epithelium. TORCH studies returned negative with the exception of *Toxoplasma* IgG (immunoglobulin G) positivity >400.0 IU/mL (range: 7.1 IU/mL or less—not detected; 7.2-8.7 IU/mL—indeterminate; 8.8 IU/mL or greater—detected). On further discussion, mother admitted exposure to outside cats, but denied changing litter boxes and did not believe she consumed raw meat during pregnancy. The patient was referred to pediatric genetics, neurology, and infectious disease services. Neurology examination revealed jerk nystagmus, an increased right Achilles tendon reflex, and microcephaly (<1% head circumference). Other etiologies considered were other intrauterine infections: cytomegalovirus (CMV), rubella, Zika virus, as well as lymphocytic choriomeningitis, though exposure history did not align with the latter 2 entities. No further laboratory testing initiated by these services for various infectious etiologies yielded any positive results. Magnetic resonance imaging of the brain showed scattered supratentorial white matter calcifications and electroencephalogram revealed no seizure-like activity during monitoring (Figure 2). The patient is yet to undergo other ancillary testing and services as well,

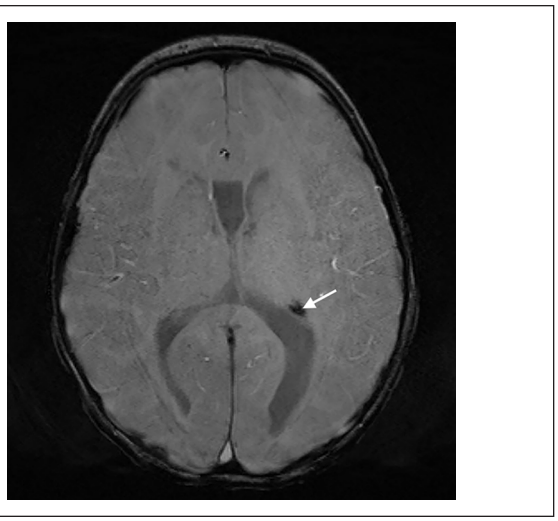

Figure 2. Brain magnetic resonance imaging susceptibility weighted sequence displaying a calcification (white arrow) in the parenchyma adjacent to the left posterior horn of the lateral ventricle.

including audiology testing, repeat serial IgG *Toxoplasma* titers on patient, serum testing and fundus examination on mother and siblings, as well as low vision therapy for the patient. There are socioeconomic and access to care issues that are contributory to the uncompleted studies and therapy in this patient's case. The decision was made not to treat the *Toxoplasma* infection, given it was not active at the time of evaluation. Recommendation from other services was for ophthalmology to monitor and initiate traditional triple therapy if reactivation should occur.

Discussion

Disease History, Transmission, and Areas of Prevalence

Toxoplasma gondii is a globally ubiquitous, obligate intracellular parasite that is believed to have infected approximately one third of the human population. The disease is spread primarily through exposure to oocysts present in contaminated water, food, or soil or by ingestion of cysts in infected meat. It can also be spread transplacentally by infected mothers. There are 3 stages of the parasite: tachyzoite, bradyzoite, and sporozoite. Tachyzoites cause the active infectious form in human tissues, while bradyzoites are the dormant cyst stage awaiting reactivation should the host become immunocompromised. Sporozoites exist within oocysts and are the form in which the parasite is spread through the environment, primarily by feline hosts. *Toxoplasma* infection prevalence is highest in tropical or humid environments and lowest in arid or cold environments. Population estimates show that 1.1 million people are newly infected in the United States each year with 21 000 new cases of retinochoroiditis (RC), 4800 of which are symptomatic.[1,2]

Disease in General, Presentation, Geography, Trends, and Strains

Most individuals infected with toxoplasmosis are immunocompetent, and if symptoms are experienced, they are usually mild arthralgias, lymphadenopathy, fever, or headache. The infection can result in more severe sequelae; however, if it is transmitted transplacentally to a growing fetus, with effects ranging from no apparent pathology to intracranial lesions, seizures, and RC, even to fetal demise. *Toxoplasma* infections occur throughout the world, but there are numerous different strains of the parasite with varying virulence. There are 3 main clonal lineages (labeled Types 1-3), with Type 2 predominantly in Europe, Types 1 and 3 in South America, and all 3 types present in North America. There are also atypical strains present in the Americas thought to have a higher level of virulence resulting in worse clinical manifestations, even in immunocompetent infected hosts.[1,3,4]

Pathophysiology of Disease

Once the host intestinal epithelial cells are infected, *T gondii* spreads hematogenously with ability to cross vascular barriers and utilize host dendritic cells and macrophages to infect target organs. Once the parasite has invaded intracellularly, *T gondii* is particularly adept at balanced control of intracellular signaling between immune modulators and pro-inflammatory cytokines resulting in a remarkable prevention of typical immune pathology implicit in parasitic invasion. The degree to which *T gondii* infection causes pathology in the infected host is believed to be heavily influenced by the virulence of the parasitic strain and/or the immune status of the host. Given the appearance of clinical manifestations even in immunocompetent patients in virulent strains, such as Type 2 and atypical genotypes, some authors postulate that the extent to which pathology develops in these individuals is heavily reliant on the strain. This may be in contrast to immunocompromised patients, in which host immune response may more heavily influence clinical manifestation and any given strain can cause clinically apparent disease. Some authors have noted that ocular toxoplasmosis in AIDS patients is far more severe and can present with an atypical, more fulminant course when compared with infection of immunocompromised individual, even with the same parasitic strain.[2]

Vertical Transmission

It is well-established that toxoplasmosis is one of the several maternal infections that can be transmitted through the placenta to the fetus and cause prenatal infection, sometimes

with grave consequences. Around 50% of infected pregnant women have no identifiable exposure or risk factors for acquiring the disease.[1] Vertical transmission rates are estimated to be less than 10% in the first trimester with typically much more severe CT manifestations compared with a transmission rate of greater than 60% in the third trimester with typically less severe disease in child.[5] Other factors that seem to increase risk of mother-to-child transmission are acute maternal infection during pregnancy, maternal immunocompromise, increased strain virulence, increased parasitic load, and lack of antepartum treatment.[1] In Europe, where prenatal and neonatal screening is mandatory, several centers have studied the benefits of early diagnosis and treatment of toxoplasmosis infection for the health of the child. Several studies found an association with treatment timing relative to maternal seroconversion, with onset of treatment less than or equal to 3 weeks after known seroconversion decreasing the risk of mother-to-child transmission when compared with the onset of treatment at >8 weeks after seroconversion.[1,6,7] With regard to the efficacy of treatment on pathological sequelae, the European Multicentre Study of Congenital Toxoplasmosis (EMSCOT) found a reduction in neurological disease such as intracranial lesions, but no reduction in ocular disease risk if prenatal treatment is performed.[5] There were some ocular sequelae risk factors identified, particularly with regard to risk of developing RC. One study found that prematurity, non-ocular CT lesions present at baseline, and confirmed CT diagnosis in early maternal infection were all risk factors for the development of RC.[8]

Ophthalmic Features

The most commonly diagnosed ophthalmic finding in toxoplasmosis infection is RC, but numerous other ocular manifestations are reported in the literature. Strabismus, vitreous opacities, micophthalmia, cataracts, retinal detachment, vitreomacular traction, retinal neuroepithelial necrotic granulomas, optic nerve atrophy, iridocyclitis, nystagmus, glaucoma, choroidal neovascularization, phthisis, choroidal colobomas, enophthalmia, and ptosis have all been listed in various reports.[1,9-14] These associated ocular pathologies appeared at later than RC and were exclusively seen in eyes with macular scarring.[10] Our patient's presentation was unusual due to the extent of the macular lesions spreading continuously into the periphery and the vitreous adhesions between RC plaques, which has seldom been documented in other publications.[13] It is crucial that ophthalmologists be aware of the broad spectrum of ocular manifestations of toxoplasmosis and be able to identify individuals at risk who need to be evaluated and monitored. Olariu and colleagues[9] identified significantly higher toxoplasmosis IgA levels in individuals with ocular findings, perhaps yielding a future screening tool to indicate higher suspicion of ocular involvement. Numerous studies have shown that patient frequently experience RC recurrence from months to years later, with some presenting as late as 12 years from initial diagnosis. Many investigators concluded that long-term ophthalmology follow-up would be prudent given late presentation of disease, recurrences, and need for initiation of treatment for systemic or ocular disease.[1,3,8,10,15,16]

Ophthalmic Imaging

Standard diagnosis of *Toxoplasma* chorioretinitis is through serum testing and fundus examination by an ophthalmologist. Advanced retinal imaging is not typically used, but has been shown to reveal a significant amount of useful information with regard to the state of the retina in infected individuals that cannot be otherwise obtained through clinical examination. Fluorescein angiography has been utilized in previous studies to show choroidal neovascularization, macular edema, vascular inflammation, vessel occlusions and shunting, as well as potential involvement of the optic nerve. Indocyanine green angiography and now optical coherence tomography (OCT) angiography (OCTA) are capable of showing the extent of choroidal involvement and damage. Recent studies of OCTA showed that both retinal and choroidal vascular obliteration persist well after toxoplasmosis-associated lesions have healed. There is hope that with the further advancement and availability of OCTA that diagnostic and prognostic value may be found in cases of toxoplasmosis RC.[17,18]

Similarity to Other Congenital Infections

The clinical presentation of congenital toxoplasmosis can show numerous similarities to other congenital infections, including rubella, Zika virus, CMV, and others. Microcephaly, choroidal colobomas, optic nerve atrophy, glaucoma, strabismus, and nystagmus can be seen in both CT and Zika virus infection. Intracranial calcifications and hearing loss can be seen in CT, rubella, and CMV infection. However, in CMV, the intracranial califications are typically periventricular and patients presents more frequently with hypotonia, lethargy, and nonspecific retinitis. In congenital rubella, babies more commonly present with "blueberry muffin" rash, "salt and pepper" retinopathy, and cardiovascular defects. Retinal lesions typically present differently between Zika and CT, with the former displaying a circumscribed macular atrophy with retinal pigment epithelial mottling, and the latter displaying sometimes extensive chorioretinal scarring in posterior pole and periphery.[1,19,20] Toxocariasis infection was also considered; however, fundus features were not characteristic and the infection is not typically congenital as was thought to be the case in this patient given the IUGR, microcephaly, and nystagmus-like movements by 3 months of age. In addition, serological testing, if available, can be very helpful in differentiating these congenital infections. Of note, toxoplasmosis IgG was highly positive in our patient (>400 IU/mL,

normal range <8.8 IU/mL) and presence of this IgG positivity at greater than 1 year of age is considered diagnostic of congenital toxoplasmosis.[21]

Utility of Screening, Europe Versus the United States

In Europe, mandatory prenatal and antenatal screening has been in place in many countries for decades. Numerous cohort studies have been performed with regard to the presentation of CT and the effect of early treatment on infected babies. These patients have been followed from birth up to 22 years in some cases with regular monitoring of serum toxoplamosis IgG and IgM, as well as routine ophthalmological follow-up. Chorioretinal scarring has been shown to develop in between 12% and 30% of those with CT. Significant visual loss, especially bilateral vision loss, has been rare in these cohorts.[3-8,10,15,16] Prenatal and antenatal treatment with various antibacterial agents have not shown any effect on the development of retinal lesions, though it has shown to reduce risk of intracranial lesions.[5,7,16] Incidence and severity of retinal scarring, intracranial calcifications, and developmental delay have been shown to be significantly higher in one US study.[9] The authors noted, however, that the severity of clinical manifestations in this cohort could be skewed given only patients with clinically diagnosed CT or high suspicion of it had serum drawn and sent to their laboratory for analysis. Additionally, multiple investigators attribute these geographical differences to a lack of prenatal/antenatal screening in the United States, a more virulent strain of toxoplasmosis in North and South America, and the higher incidence of abortion for neurological abnormalities in Europe, or a combination thereof. The only screening program in the United States is the New England Newborn Screening Program, which began routinely screening for toxoplasmosis in 1986. Nearly all cases of CT diagnosed through neonatal screening were found in patients without overt symptoms or signs of the disease, but around 40% of those babies were found to have clinical evidence of the disease under closer subsequent examination.[22] In addition to these findings, many studies have found that babies without signs of clinical disease at birth can have disease manifest months to years later. No cost-benefit analysis of neonatal screening in this cohort in Massachusetts and New Hampshire have been published, but studies in Europe and Canada have performed such analyses. Sahai and Onyett[23] studied prenatal screening in Canada and reported that at incidence rates even below the current estimates in Canada at the time, the cost of screening prenatally was easily justified when compared with the cost of long-term medical, social, and educational services for the patients and their families of those affected. European studies have concluded with a similar notion.[24] One US study from 2000 to 2011 found 789 cases of death secondary to toxoplasmosis, resulting in an estimated $815 million cumulative productivity loss.[1] More studies are needed to investigate the utility and cost-effectiveness of incorporating toxoplasmosis into neonatal screening panels in the United States.

Conclusion

Toxoplasma gondii infection is widespread worldwide and a high percentage of pregnant women are at risk for infection and possible subsequent vertical transmission to their babies. CT can result in a wide array of ocular and neurological manifestations that can be devastating to patients and their families. Ophthalmologists and other pediatric providers should be aware of these varied presentations and the potential for delayed onset of clinical manifestation necessitating long-term follow-up. Routine prenatal and neonatal screening is not performed in the majority of the United States, but studies done in Canada and Europe have shown this might be cost-effective when compared with cost of caring for affected patients. More studies are needed to examine cost-effectiveness of incorporating toxoplasmosis into routine neonatal screening.

Author Contributions

Gavin Reed conceived the case presentation design, carried out the literature review, and drafted the case presentation, discussion, and the abstract.
Swati Agarwal-Sinha operated the RetCam and took fundus photographs, edited photographs, and the body of the manuscript. Both authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Ethics Approval

No ethics approval was needed for the case.

Informed Consent

Written informed consent was obtained from the patient's legal guardian(s) for publication of this case report and any accompanying images.

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