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Screening Criteria for Ophthalmic Manifestations of Congenital Zika Virus Infection

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IMPORTANCE Current guidelines recommend screening eye examinations for infants with microcephaly or laboratory-confirmed Zika virus infection but not for all infants potentially exposed to Zika virus in utero.

OBJECTIVE To evaluate eye findings in a cohort of infants whose mothers had polymerase chain reaction–confirmed Zika virus infection during pregnancy.

DESIGN, SETTING, AND PARTICIPANTS In this descriptive case series performed from January 2 through October 30, 2016, infants were examined from birth to 1 year of age by a multidisciplinary medical team, including a pediatric ophthalmologist, from Fernandes Figueira Institute, a Ministry of Health referral center for high-risk pregnancies and infectious diseases in children in Rio de Janeiro, Brazil.

PARTICIPANTS Mother-infant pairs from Rio de Janeiro, Brazil, who presented with suspected Zika virus infection during pregnancy were referred to our institution and had serum, urine, amniotic fluid, or placenta samples tested by real-time polymerase chain reaction for Zika virus.

MAIN OUTCOMES AND MEASURES Description of eye findings, presence of microcephaly or other central nervous system abnormalities, and timing of infection in infants with confirmed Zika virus during pregnancy. Eye abnormalities were correlated with central nervous system findings, microcephaly, and the timing of maternal infection.

RESULTS Of the 112 with polymerase chain reaction–confirmed Zika virus infection in maternal specimens, 24 infants (21.4%) examined had eye abnormalities (median age at first eye examination, 31 days; range, 0-305 days). Ten infants (41.7%) with eye abnormalities did not have microcephaly, and 8 (33.3%) did not have any central nervous system findings. Fourteen infants with eye abnormalities (58.3%) were born to women infected in the first trimester, 8 (33.3%) in the second trimester, and 2 (8.3%) in the third trimester. Optic nerve and retinal abnormalities were the most frequent findings. Eye abnormalities were statistically associated with microcephaly (odds ratio [OR], 19.1; 95% CI, 6.0-61.0), other central nervous system abnormalities (OR, 4.3; 95% CI, 1.6-11.2), arthrogryposis (OR, 29.0; 95% CI, 3.3-255.8), and maternal trimester of infection (first trimester OR, 5.1; 95% CI, 1.9-13.2; second trimester OR, 0.5; 95% CI, 0.2-1.2; and third trimester OR, 0.3; 95% CI, 0.1-1.2).

CONCLUSIONS AND RELEVANCE Eye abnormalities may be the only initial finding in congenital Zika virus infection. All infants with potential maternal Zika virus exposure at any time during pregnancy should undergo screening eye examinations regardless of the presence or absence of central nervous system abnormalities.

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Supplemental content

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Zika virus is a flavivirus that can be spread by mosquito vectors, sexual contact, infected blood products, and perinatal transmission.[1] In May 2015, a large outbreak of Zika virus infection was detected in northeastern Brazil that yielded an exceedingly high number of microcephaly cases.[2] Thereafter, the epidemic rapidly spread to other countries in the Americas and Asia. In the United States, the first case of non-travel-related, locally transmitted Zika virus infection was reported in Florida in July 2016.[3]

Although identification of the full spectrum of congenital Zika virus infection features is still evolving, in its most severe form, congenital Zika virus infection may consist of (1) severe microcephaly with partially collapsed skull, (2) thin cerebral cortices with subcortical calcifications, (3) macular scarring and focal pigmentary retinal mottling, (4) arthrogryposis, and (5) marked early hypertonia and symptoms of extrapyramidal involvement.[4-6] It is evident that microcephaly is the most remarkable characteristic of this infection but is not an obligatory finding for the diagnosis of Zika virus congenital infection. Furthermore, infants who are seemingly asymptomatic at birth can later have abnormalities on brain imaging or subsequent neurologic examinations.[4]

Our group has recently reported the largest cohort to date of cases of maternal Zika virus infection during pregnancy confirmed by reverse transcription-polymerase chain reaction (RT-PCR) in Rio de Janeiro, Brazil.[4] After a report[7] of local Zika virus transmission in Rio de Janeiro in 2015, testing of pregnant women who presented with a rash at any week of gestation was initiated for a panel of arboviruses, including Zika virus, dengue, and chikungunya (by RT-PCR) as well as classic TORCH (*Toxoplasma gondii*, *Treponema pallidum*, varicella-zoster virus, Epstein-Barr virus, human immunodeficiency virus, rubella, cytomegalovirus, and herpes simplex). Of 126 infants born of symptomatic mothers who tested positive for Zika virus by RT-PCR, 42% presented with severe abnormal clinical examination findings, brain imaging findings, or both, including 4 infants with microcephaly.[4]

The primary objective of the present study was to report eye findings in infants born to women with Zika virus confirmed by RT-PCR during pregnancy who were referred to our institution. Secondary objectives included evaluating whether observable infant eye abnormalities were also associated with microcephaly, central nervous system findings, the timing of maternal infection, and arthrogryposis.

Key Points

Question Which infants exposed to Zika virus infection in pregnancy should undergo an eye examination?

Findings In this case series of a cohort of 112 infants born to mothers with polymerase chain reaction–confirmed Zika virus infection, 24 (21.4%) had eye abnormalities. Ten infants (41.7%) with abnormal eye examination findings did not have microcephaly, 8 (33.3%) did not have any central nervous system findings, and 2 (8.3%) had eye abnormalities despite maternal third trimester infection.

Meaning Eye abnormalities may be the only initial finding in congenital Zika virus infection, and all infants with potential Zika virus exposure should undergo screening eye examinations.

Methods

The study was performed at the Fernandes Figueira Institute (IFF), Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, which is a Ministry of Health referral center for high-risk pregnancies and infectious diseases in children. Pregnancies with confirmed Zika virus infection were referred to the IFF by the Acute-Febrile Illness Service of the Oswaldo Cruz Foundation, which is a reference site for arboviral infections in the region and currently runs a prospective cohort study of maternal Zika virus infection. In addition, other governmental and private institutions referred pregnant women with fetal abnormalities, including microcephaly identified by prenatal ultrasonography, who subsequently were found to have positive Zika virus RT-PCR results in amniotic fluid or placenta. The IFF and UCLA (University of California, Los Angeles) institutional review boards approved this study. Parents or guardians provided written informed consent. All data were deidentified.

Inclusion and Exclusion Criteria

All infants born to mothers with RT-PCR results positive for Zika virus during pregnancy were eligible for enrollment. The virus was identified in maternal blood, urine, amniotic fluid, and/or placental tissue samples.

Infants of mothers who did not have maternal specimens that were positive for Zika virus by RT-PCR were excluded from enrollment. Infants of mothers with other serologically proven prenatal infections whose mothers had an RT-PCR result negative for Zika virus were also excluded. Infants with genetic abnormalities, family history of microcephaly, and perinatal alcohol or illicit drug exposure whose mothers tested negative or had no Zika virus RT-PCR results were also excluded.

Study Procedures

Zika virus infection was identified after total RNA extraction performed with the TRIzol Reagent (Thermo Fisher Scientific) according to the manufacturer's instructions. We performed RT-PCR with the QuantiTect Probe RT-PCR kit (Qiagen) with the same primers and cycle times as described elsewhere.[4,8] If the mother had symptomatic Zika virus infection, the timing of maternal infection was defined as the week of gestation that coincided with symptom onset and a positive Zika virus RT-PCR result in maternal specimens. For mothers with a positive RT-PCR result for a placenta or amniotic fluid sample, the timing of infection was assumed to have occurred when the patient presented with symptoms of Zika virus infection during pregnancy. All women in our cohort had symptomatic Zika virus infection. Serologic testing for IgG antibodies to dengue (Abcam) and IgM antibodies to chikungunya (Euroimmum) was performed on serum specimens from mothers. Maternal serum samples were also tested by RT-PCR for dengue and chikungunya, parvovirus B19, cytomegalovirus (TaqMan; Applied Biosystem, Thermo Fisher Scientific),

and human immunodeficiency virus (RT HIV Viral Load, Abbott Laboratories). Screening tests for syphilis were performed with Venereal Disease Research Laboratory assays and confirmed by treponemal assays (Alere Determine Syphilis TP, Alere).

Detailed demographic, medical, and prenatal history information and clinical findings were documented by a pediatric infectious diseases specialist (M.V.d.S.P., S.M.P., or M.S.A.). Microcephaly was defined as a head circumference *z* score smaller than −2 (moderate) or −3 (severe) for gestational age and sex. Other central nervous system (CNS) abnormalities were identified by brain imaging (transfontanel ultrasonography, computed tomography, or magnetic resonance imaging). Eye examinations were performed from January 2 through October 30, 2016, and follow-up evaluations were scheduled every 3 months until 1 year of age. Eye abnormalities were documented with a wide-field digital imaging system (RetCam Shuttle, Clarity Medical Systems) after pupillary dilation.

Statistical Analysis

We evaluated potential associations between infant eye abnormalities and maternal trimester of infection, microcephaly, other CNS abnormalities, the timing of maternal infection, and arthrogryposis using the Fisher exact or Pearson χ^2 test. Two-sided $P \leq .05$ was considered to be statistically significant. Statistical analysis was performed using Stata statistical software (StataCorp).

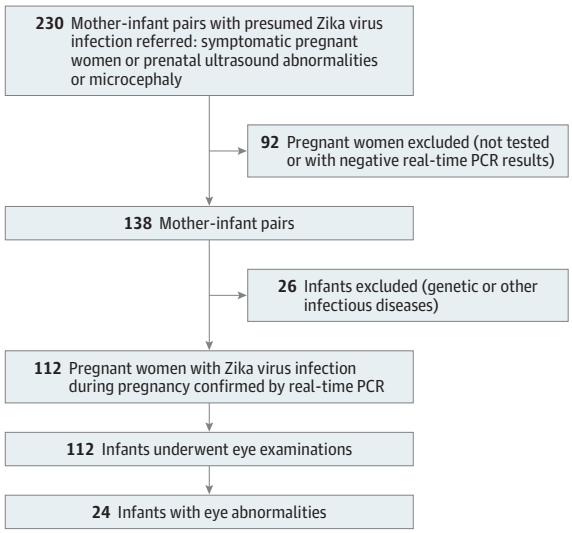
Results

Study Population

Two hundred thirty infants were referred to the IFF with prenatal microcephaly, with other stigmata of congenital Zika virus infection, or because they were born to mothers with Zika virus–positive results during pregnancy as of October 1, 2015. Ninety-two infants were excluded because of lack of a positive maternal Zika virus RT-PCR result. Twenty-six infants with genetic abnormalities or other infections were excluded from this analysis because Zika virus infection was ruled out. One hundred twelve infants underwent eye examinations (median age at first eye examination, 31 days; range, 0-305 days) and met the aforementioned inclusion criteria (96 mothers were positive in plasma, urine, or both and the remaining 16 in amniotic fluid or placental specimens) (**Figure 1**). Sixty-two of the 112 patients were from a prospective maternal cohort study, which has been previously characterized.[4] In addition, 42 of the 112 infants underwent RT-PCR testing for Zika virus in blood or urine samples, and 27 of 42 (64.3%) had positive results.

Among the 112 infants, 20 (17.9%) had microcephaly; 31 (27.7%) had other CNS abnormalities (ventriculomegaly, cerebral calcifications, posterior fossa abnormalities, pachygyria, and lissencephaly), which were not mutually exclusive; and 61 (54.5%) had no CNS findings. Thirty-two of 112 mothers (28.6%) had Zika virus infection in the first trimester of pregnancy, 55 (49.1%) in the second, and 25 (22.3%) in the third. Eye abnormalities were found in 14 of 20 infants (70.0%) with microcephaly, 2 of 31 (6.5%) with CNS abnormalities without microcephaly, and 8 of 61 (13.1%) without any CNS abnormality. Seven of 112 infants (6.3%) had arthrogryposis, eye abnormalities (optic nerve atrophy, chorioretinal atrophy, pigment mottling, and hemorrhage), microcephaly, and other CNS abnormalities.

Figure 1. Flowchart of Participant Recruitment



PCR indicates polymerase chain reaction.

Over time, 78 infants were examined once, 36 were examined twice, and 8 were examined 3 times in the eye clinic and by the neurology service staff. Twenty-seven infants underwent the first examination between the date of birth and the age of 7 days; of these, 10 (37.0%) had ocular abnormalities (optic nerve atrophy, focal pigment mottling, chorioretinal atrophy, and retinal hemorrhages). None had active exudative lesions.

Eye Abnormalities

Twenty-four of 112 infants (21.4%) presented with sight-threatening eye abnormalities; impaired optic nerve and/or retina were the most frequent findings (**Table 1**). Severe unilateral microphthalmia was present in 1 infant (4.2%), which prevented retina and optic nerve examination in the affected eye. Nineteen infants (79.2%) had optic nerve abnormalities (18 bilateral and 1 unilateral): 11 with bilateral optic nerve atrophy (pallor and increased cup), 7 with optic nerve hypoplasia (6 bilateral and 1 unilateral), and 1 with bilateral coloboma. The 4 infants with bilateral normal optic nerve presented with bilateral pigment mottling (1 infant) or retinal hemorrhages (3 infants). Fifteen infants presented with abnormal retinas: focal pigment mottling (only finding in 4 infants), chorioretinal atrophy (6 infants: 3 bilateral and 3 unilateral), hemorrhages (4 infants: 3 bilateral), and bilateral inferior coloboma (1 infant). The 7 infants with bilateral normal retinas had optic nerve atrophy (6 infants) and optic nerve hypoplasia (1 infant). Nystagmus was found in 6 of 24 infants (25.0%) with

Table 1. Clinical Summary of Patients With Eye Abnormalities

Patient No.	Maternal RT-PCR Sample Source	Trimester of Infection	Microcephaly	Arthrogryposis	Imaging Modality	Other CNS Abnormality
1	Blood	First	Yes	No	TFUS or CT	Intracranial calcification, increased fluid spaces, cerebellar anomalies
2	Blood	First	Yes	No	TFUS or CT	Intracranial calcification, increased fluid spaces, cerebellar anomalies, marked cortical thinning with abnormal gyral patterns
3	Blood	Second	Yes	No	TFUS or CT	Intracranial calcification, increased fluid spaces, marked cortical thinning with abnormal gyral patterns
4	Blood or placenta	First	Yes	No	TFUS or CT	Intracranial calcification, increased fluid spaces, cerebellar anomalies, marked cortical thinning with abnormal gyral patterns
5	Blood	Second	Yes	Yes	TFUS or CT	Intracranial calcification, increased fluid spaces. cerebellar anomalies, marked cortical thinning with abnormal gyral patterns
6	Blood	First	Yes	No	TFUS or CT	Intracranial calcification, increased fluid spaces, marked cortical thinning with abnormal gyral patterns
7	Placenta	First	Yes	Yes	CT	Intracranial calcification, increased fluid spaces, cerebellar anomalies, marked cortical thinning with abnormal gyral patterns
8	Placenta	First	Yes	Yes	TFUS or CT	Intracranial calcification, increased fluid spaces, marked cortical thinning with abnormal gyral patterns
9	Blood	First	Yes	No	TFUS or CT	Intracranial calcification, increased fluid spaces, marked cortical thinning with abnormal gyral patterns
10	Placenta	First	Yes	Yes	TFUS or CT	Intracranial calcification, increased fluid spaces, marked cortical thinning with abnormal gyral patterns
11	Blood	Third	No	No	TFUS	None
12	Blood or urine	Second	No	No	TFUS or CT	None
13	Blood or urine	Second	No	No	TFUS, CT, or MRI	None
14	Blood or placenta	First	Yes	Yes	TFUS or CT	Intracranial calcification, increased fluid spaces, cerebellar anomalies, marked cortical thinning with abnormal gyral patterns
15	Blood	Second	No	No	TFUS	None
16	Blood	First	Yes	No	TFUS or CT	Intracranial calcification, increased fluid spaces, marked cortical thinning with abnormal gyral patterns
17	Blood	Third	No	No	TFUS or CT	None
18	Blood	Second	Yes	Yes	CT	Intracranial calcification, increased fluid spaces
19	Blood	Second	No	No	TFUS or CT	None
20	Blood	First	No	No	TFUS or MRI	None
21	Amniotic fluid	First	No	Yes	TFUS or CT	Intracranial calcification, increased fluid spaces, cerebellar anomalies
22	Amniotic fluid	First	Yes	No	CT	Intracranial calcification, increased fluid spaces, cerebellar anomalies, marked cortical thinning with abnormal gyral patterns
23	Blood	Second	No	No	TFUS or CT	None
24	Blood	First	No	No	TFUS or CT	Intracranial calcification, increased fluid spaces, cerebellar anomalies

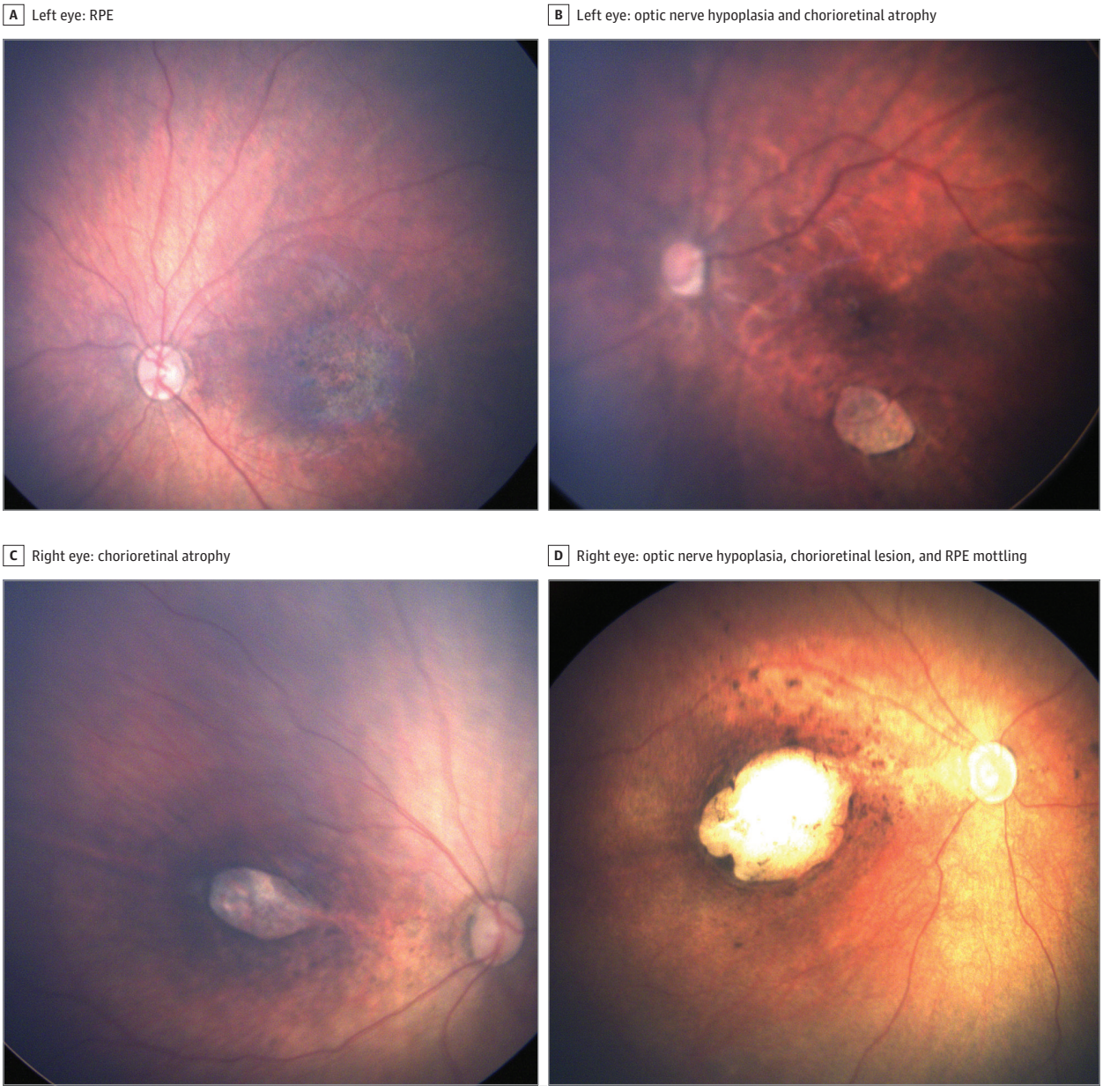
Abbreviations: CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; RT-PCR, reverse transcription–polymerase chain reaction; TFUS, transfontanel ultrasonography.

eye abnormalities (all with bilateral optic nerve atrophy or hypoplasia and chorioretinal atrophy) and other CNS abnormalities. Four of these patients had microcephaly. **Figure 2** depicts representative images of eye abnormalities.

Twelve of 24 infants (50.0%) returned for follow-up. Retinal hemorrhages identified in 4 infants earlier were not present during follow-up. Other previous findings remained unaltered in 8 infants (optic nerve atrophy, pigment mottling, and chorioretinal atrophy). None of the 24 infants had clinical signs of active anterior or posterior uveitis (Table 1).

Fourteen of 24 infants (58.3%) with eye abnormalities had microcephaly, 16 (66.7%) had other CNS findings, 7 (29.2%) had

Figure 2. Examples of Typical Retinal Lesions Seen in Congenital Zika Virus Infection From the Study Cohort



A, Retinal pigment epithelium (RPE) mottling of the macula in the left eye. B, Optic nerve hypoplasia and punched-out, extrafoveal chorioretinal atrophy in the left eye. C, Punched-out, foveal chorioretinal atrophy in the right eye. D, Optic nerve hypoplasia and excavated chorioretinal lesion with surrounding RPE mottling in the right eye.

arthrogryposis, and 8 (33.3%) had no CNS impairment. Fourteen infants (58.3%) had mothers infected in the first trimester, 8 (33.3%) in the second trimester, and 2 (8.3%) in the third trimester (**Table 2**). Among the third trimester infections, one infant had bilateral retinal hemorrhages and the other had extensive bilateral optic nerve and chorioretinal coloboma. Microcephaly or other CNS abnormalities were not present in both cases. Twenty-one infants (87.5%) had bilateral eye abnormalities, and the remaining 3 (12.5%) had unilateral findings (Figure 1). Associations were found between eye abnormalities and microcephaly (odds ratio [OR], 19.1; 95% CI, 6.0-61.0), other CNS abnormalities (OR, 4.3; 95% CI, 1.6-11.2), and earlier trimester infection in pregnancy (first trimester OR, 5.1; 95% CI, 1.9-13.2; second trimester OR, 0.5; 95% CI, 0.2-1.2; and third trimester OR, 0.3; 95% CI, 0.1-1.2), and arthrogryposis (OR, 29.0; 95% CI, 3.3-255.8).

Discussion

Our group sought to describe eye findings in infants born to mothers with RT-PCR–confirmed Zika virus infection in preg-

Table 2. Eye Examination Findings in Patients With Eye Abnormalities

Patient No.	Age at First Eye Examination, d	EOMs	Right Eye			Left Eye		
			Optic Nerve	Retina	Microphthalmia	Optic Nerve	Retina	Microphthalmia
1	210	Nystagmus	Hypoplasia	Chorioretinal atrophy, pigment mottling	No	Hypoplasia	Chorioretinal atrophy, pigment mottling	No
2	20	No	Pallor, increased optic cup	No	No	Pallor, increased optic cup	No	No
3	142	No	Pallor, increased optic cup	No	No	Pallor, increased optic cup	No	No
4	31	No	Hypoplasia	Diffuse pigment mottling	No	Hypoplasia	Pigment mottling,	No
5	49	Nystagmus	Hypoplasia	Pigment mottling, multiple chorioretinal atrophy	No	Hypoplasia	Pigment mottling	No
6	305	Nystagmus	Pallor	No	No	Pallor	No	No
7	113	No	No	No	No	No	Hemorrhage	No
8	7	No	Hypoplasia	Focal pigment mottling	No	Hypoplasia	Focal pigment mottling	No
9	103	Nystagmus	Pallor	Chorioretinal atrophy	No	Pallor, increased optic cup	No	No
10	4	No	Hypoplasia	Chorioretinal atrophy	No	Hypoplasia	Chorioretinal atrophy, pigment mottling	No
11	38	No	No	Hemorrhage	No	No	Hemorrhage	No
12	53	No	Pallor, Increased optic cup	No	No	Pallor, Increased optic cup	No	No
13	58	No	Pallor	No	No	Pallor	No	No
14	3	No	Pallor	Focal pigment mottling	No	Pallor	Focal pigment mottling	No
15	28	No	No	Focal pigment mottling	No	No	Focal pigment mottling	No
16	37	No	Pallor	Normal	No	Pallor	No	No
17	110	No	Coloboma	Inferior coloboma	No	Coloboma	Inferior coloboma	No
18	177	No	Pallor	Chorioretinal atrophy	No	Pallor	No	No
19	1	No	No	No	No	NA	NA	Yes
20	3	No	No	Hemorrhage	No	No	Hemorrhage	N
21	1	Nystagmus	Pallor	Hemorrhage	No	Pallor	Hemorrhage	No
22	1	No	Pallor, increased optic cup	Chorioretinal atrophy, pigment mottling	No	Pallor, increased optic cup	No	No
23	2	No	Hypoplasia	No	No	Hypoplasia	No	No
24	13	Nystagmus	Hypoplasia	Chorioretinal atrophy	No	Normal	Chorioretinal atrophy	No

Abbreviations: EOMs, extraocular muscles; NA, not applicable (extreme microphthalmia).

nancy. Thus, we evaluated a cohort of 112 infants from Rio de Janeiro in which 21.4% of infants were found to have abnormal eye findings. There was bias of ascertainment because some pregnant women with suspected Zika virus infection were referred for evaluation. Prior studies[9-16] detailing eye findings in congenital Zika virus infection did not have a strict case definition based on diagnostic RT-PCR results. Most cases previously describing eye abnormalities were from northeastern Brazil (eTable in the Supplement).

Other congenital infections, such as rubella, toxoplasmosis, cytomegalovirus, and herpes, can manifest as retinal pigmentary mottling, chorioretinal scars, optic nerve atrophy, and microphthalmia. In rubella infection, the pigment mottling is usually diffuse compared with the focal pigment mottling seen in Zika virus infection. Optic nerve hypoplasia is believed to occur secondary to failure of development of ganglion cells of the retina and is seldom seen in rubella, toxoplasmosis, herpes, and cytomegalovirus congenital infections. Infants with congenital toxoplasmosis can present with active exudative chorioretinal lesions or a regressed scar, usually macular or peripapillary. However, chorioretinal lesions found in infants with Zika virus congenital infection were atrophic and colobamatous-like and could be found in the macula or retinal periphery (Figure 2).[9-12] The most characteristic optic nerve

abnormalities were atrophy (pallor and increased optic cup) and hypoplasia, which can occur separately or in combination with retinal pigment mottling and chorioretinal atrophy, as previously described.[9-12] Chorioretinal atrophy is usually associated with pigment mottling and can occur without optic nerve abnormalities.

Nearly half of the infants (41.7%) with confirmed congenital Zika virus infection had eye abnormalities as the first evident manifestation of Zika virus disease. All but 8 infants also had CNS abnormalities on neuroimaging. It appears that isolated eye pathologic findings with no CNS findings on imaging can still occur in third trimester Zika virus infection, as seen in our cohort. In general, infections in the third trimester of pregnancy are believed to be relatively nonteratogenic to the infant because organogenesis is largely complete.[17] However, the retina and other eye structures are still developing after birth. We would not expect, however, for a third trimester infection to cause optic nerve coloboma, as seen in one of our cases, because closure of the optic fissure typically occurs by 7 weeks of gestational age. This finding could be explained by earlier trimester infection with persistence of viremia until the third trimester. However, the coloboma may have been unrelated to Zika virus infection.[18,19] Ventura and colleagues[12] found that ocular involvement in presumed Zika virus congenital infection was more often seen in infants whose mothers reported symptoms during the first trimester of pregnancy. Our study confirmed this finding.

Of interest, progression of eye findings did not seem to occur among the 12 infants who returned for follow-up. Ophthalmic lesions seemed to reflect disruption of development or scarring rather than ongoing active and progressive infection.

Current Brazilian Ministry of Health guidelines recommend screening eye examinations for infants born in areas endemic for Zika virus only in the presence of microcephaly.[20] Our findings indicate that eye abnormalities are not restricted to infants with microcephaly, which is in line with other studies.[13,21] Furthermore, we found that eye abnormalities were not limited to infants with CNS abnormalities, which is an important finding. Current Centers for Disease Control and Prevention guidelines recommend eye screening only in pregnancies with laboratory evidence of congenital Zika virus infection.[22] Such tests might not be widely available, which jeopardizes identification of eye pathologic findings.

Therefore, microcephaly, presence of other CNS manifestations, and laboratory evidence of congenital Zika virus infection are inadequate inclusion criteria for screening eye abnormalities. If the presence of CNS abnormalities were used as screening criteria for eye examination in our population, 3 infants with abnormal eye examination findings would have been missed. Universal screening is the only way to capture all eye findings associated with congenital Zika virus infection, but this is not always possible given the limited availability of ophthalmologists. Digital retinal imaging with remote image interpretation (teleretinal imaging) is an emerging health care technology that has been used to screen retinopathy of prematurity and diabetic retinopathy and could be extended to patients in areas endemic for Zika virus.[23-25]

When eye abnormalities were first reported in cases of presumed Zika virus infection with microcephaly,[9-11] it was unclear whether eye abnormalities were secondary to the presence of microcephaly or attributable to Zika virus infection.[26-28] Our study putatively solves this issue by reporting that 10 of 24 eye abnormalities (41.7%) occurred in the absence of microcephaly in RT-PCR–confirmed cases of Zika virus infection. Thus, it seems that Zika virus can be deemed to be directly related to eye pathologic findings.

Limitations

Our study is limited by a referral bias for microcephaly and other stigmata of congenital Zika virus infection. Although we enrolled 62 patients from our prospective maternal cohort study, the present analysis also included patients referred to the IFF for investigation of potential Zika virus congenital infection. Because our institution is a tertiary care center, our data cannot be extrapolated to provide information about the risk of eye abnormalities, microcephaly, or CNS disease in the general population in areas where Zika virus is endemic. However, our data are unique because we describe pathognomonic eye lesions associated with congenital Zika virus infection in the largest cohort of infants born to mothers infected with RT-PCR–proven Zika virus to date.

Another major limitation of our study is the lack of a control group. We cannot affirm with absolute certainty that all eye findings were attributable to Zika virus infection. In particular, 3 of 24 infants (12.5%) had findings of retinal hemorrhage only. It is possible that these findings were related to birth trauma rather than Zika virus infection.

Conclusions

Eye abnormalities may be the only initial finding in congenital Zika virus infection. All infants with potential Zika virus exposure should undergo screening eye examinations regardless of CNS abnormalities, timing of maternal infection during pregnancy, or laboratory confirmation.

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