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ORIGINAL ARTICLE

A Novel Radiologic Finding to Predict Ophthalmic Abnormalities in Children With Congenital Zika Syndrome

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Background. The Zika virus (ZIKV) epidemic had devastating consequences in Brazil. We investigated whether a radiologic finding (ie, infratentorial abnormalities) was associated with sight-threatening defects in children born with congenital Zika syndrome (CZS). We also investigated whether ophthalmic abnormalities correlated with head circumference (HC) and gestational age of infection.

Methods. Cross-sectional evaluation based upon a previous cohort from March 2016 to December 2018, in Paraíba, Brazil. The study population was comprised of children born to mothers with laboratory-confirmed ZIKV infection during pregnancy (ZIKV reverse transcriptase polymerase chain reaction [RT-PCR]+) and children born with clinical and radiologic features of CZS.

Results. A total of 75 infants had complete data. All 75 had brain calcifications. Microcephaly was present in 53 (71%) of them. Infratentorial abnormalities were present in 17 infants (22.7%). Ophthalmic abnormalities were seen in 16 of the 17 children (94%) with infratentorial abnormalities, while 28% of children without infratentorial abnormalities had ophthalmic findings (odds ratio [OR]: 42.0; 95% confidence interval [CI]: 5.1-342.9). Similar associations were observed when macular chorioretinal atrophy and optic nerve abnormalities were analyzed individually (OR: 23.7; 95% CI: 6.0-93.3 and OR: 11.5; 95% CI: 3.3-40.0, respectively). Infratentorial abnormalities were more frequently associated with ophthalmic abnormalities (94%) than microcephaly (43.4%) ($P < .001$). Mean HC was statistically different between groups with and without ophthalmic abnormalities ($P = .01$). A statistically significant difference in gestational age between both groups was not noted ($P = .12$).

Conclusions. In children with CZS, the presence of infratentorial abnormalities is a significant predictor of ophthalmic abnormalities. All neonates whose mothers had ZIKV exposure during pregnancy should have an ophthalmologic examination.

Key words. congenital Zika syndrome; epidemic; ocular findings; Zika virus.

In early 2015, Latin America, especially Brazil, was afflicted by an epidemic of neonatal microcephaly due to an emerging infectious pathogen later identified as Zika virus (ZIKV), an arbovirus transmitted by *Aedes* mosquitoes. The epidemic first started in northeastern Brazil and then spread along the coast to the southeastern region of the country. The first cases in Brazil were detected in the states of Bahia, Pernambuco, and Paraiba [1–6].

Congenital Zika syndrome (CZS), which was first identified during the Brazilian epidemic, is a spectrum of clinical findings observed in infants who were exposed to ZIKV in utero [7]. It has a variable presentation, severity, and prognosis, which is dependent on several factors: the gestational age in which the infection occurred, head circumference (HC) at birth, and the presence of central nervous system (CNS) manifestations [8]. CZS, in its most severe form, has 5 features that are rarely seen with other congenital infections: (1) severe microcephaly with partially collapsed skull, (2) thin cerebral cortices with subcortical calcifications, (3) macular scarring and focal pigmentary retinal mottling, (4) congenital contractures, and (5) marked early hypertonia and symptoms of extrapyramidal involvement [9]. Additionally, within the spectrum of ZIKV disease, there are infants who are asymptomatic at birth but can develop clinical repercussions later in infancy.

Obtaining laboratory diagnosis of ZIKV during pregnancy and/or during infancy is challenging in endemic areas. A more accessible radiologic diagnosis with prenatal ultrasound performed by skilled radiologists has been a valuable tool in the recognition of at-risk cases [10]. Although the radiologic finding of in utero microcephaly is the hallmark of Zika, in our experience, the presence of infratentorial abnormalities (severe cerebellum/vermis cerebelli defects associated with hypoplasia or absent segmentation of the brainstem) seems to be a more

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significant predictor of disease severity [10, 11]. The association between microcephaly and ophthalmologic abnormalities has been described in recent literature [12–14]; however, these abnormalities can be present with or without concurrent microcephaly or other CNS defects [12, 15]. Early identification of severe cases is critical for appropriate counseling of caregivers and prompt initiation of rehabilitation for improved long-term outcomes especially neurodevelopment, which can lead to better motor and cognitive functions [16, 17]. A radiologic finding to predict ophthalmologic abnormalities has yet to be elucidated in the literature. The aim of this study was to evaluate the association between radiologic findings, specifically infratentorial abnormalities, and ophthalmic abnormalities to provide additional means of early recognition and intervention. A secondary aim was to investigate previously described associations with ophthalmologic abnormalities such as HC and gestational age of infection [12, 13].

METHODS

Study Population and Study Setting

A total of 102 infants were eligible for evaluation. These children came from 2 distinct sources: (1) 24 infants from a prospective cohort comprised by mother-infant pairs with positive RT-PCR for ZIKV infection during pregnancy in follow-up at the Instituto de Pesquisa Professor Joaquim Amorim Neto (IPESQ), a nonprofit organization located in Campina Grande, State of Paraíba, Brazil, and (2) 78 infants referred to the same institution during maternal gestation or after birth because of radiologic abnormalities resembling ZIKV. Infants were enrolled between March 2016 and December 2018.

Newborn infants were evaluated according to a standard assessment protocol that included history and physical examination, pediatric wellness, ophthalmologic examination, and neurological assessment. The evaluations were repeated every 3 months or earlier if necessary. Imaging studies such as cerebral ultrasonography (US), computerized tomography (CT), and/or magnetic resonance imaging (MRI) were included in the evaluation. Infants referred to IPESQ were seen within the first week of life. All cases had at least 1 CT and potentially 1 MRI examination performed for a better evaluation. The vast majority of infants had transfontanelle US performed since it was the first imaging screening tool readily available. CT scans were performed when US was abnormal. When possible, MR imaging was also performed although this required referral to an outside facility. The first imaging studies were performed in the newborn period. Examiners were not aware of radiologic findings.

Inclusion Criteria

Two inclusion criteria were used for the definition of congenital Zika infection: (1) laboratory based-diagnosis: positive RT-PCR for ZIKV in the newborns and/or their mothers during pregnancy and (2) neuroimaging based-diagnosis: presence of calcifications in the gray-white matter junction [10, 18] (Figure 1) associated with any degree of delayed cortical development ranging from mildly simplified gyral patterns to abnormalities such as lissencephaly, pachygyria, or malformations of cortical development, visualized by CT and/or MRI in additional to transfontanelle or prenatal ultrasound. All infants had either CT or MRI performed; transfontanelle or prenatal US was performed first as the first screening diagnostic imaging tool due to its availability. Generally, MRIs were performed to further delineate CT findings.

The subcortical calcification (gray-white matter junction) is highly suggestive of congenital ZIKV infection and has not been observed in other Toxoplasmosis, Rubella, Cytomegalovirus and Herpes (TORCH) conditions. Brain calcification was categorized by its location as subcortical area, basal ganglia, or cerebellum.

Pregnant women had US performed with Samsung WS80 Elite, and infants were evaluated with MRI 1.5-T Espree unit (Siemens Healthcare) and cranial CT with a 16-section CT scanner (Siemens Healthcare) and/or MRI 1.5-T Espree unit (Siemens Healthcare). Radiologic findings were interpreted by an experienced team of radiologists specialized in neuroimaging; this included 2 pediatric neuroradiologists with expertise in fetal and neonatal radiology and 1 obstetrician with expertise in obstetric/fetal MRI.

Exclusion Criteria

Twenty-seven children were excluded from the analysis due to missing information (ie, either radiologic or ophthalmologic results). Of note, 9 of these children did not have ophthalmological information available because of early death (Figure 2).

Radiologic Classification

The main radiologic criterion used to differentiate the 2 groups was the occurrence of infratentorial abnormality, which was defined as the presence of severe hypoplasia or dysmorphic cerebellum and vermis cerebelli associated with severe hypoplasia or absent segmentation of the brainstem (Figure 3).

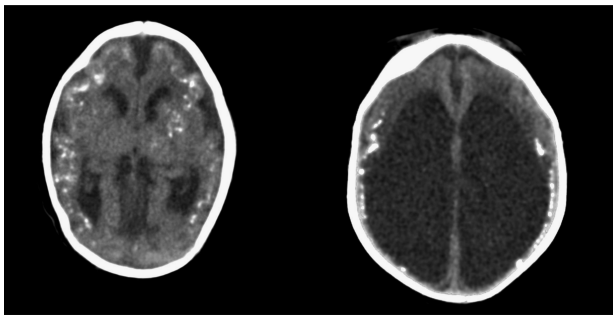

Figure 1. Calcifications in the gray-white matter junction.

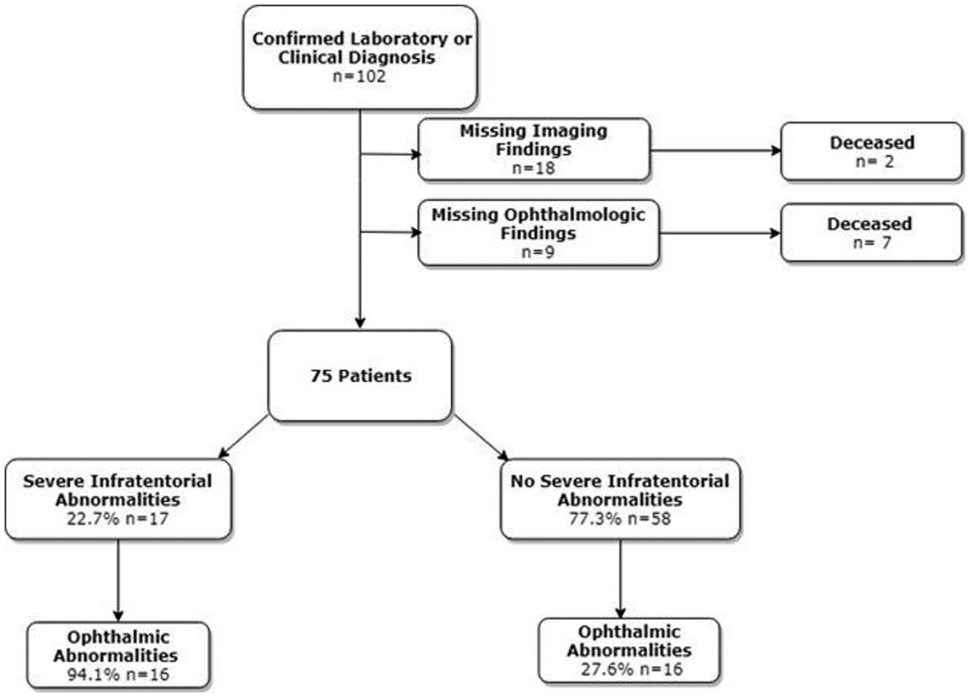

Figure 2. Patient flowchart.

Definition of Microcephaly and Classification

Microcephaly was defined according to head circumference (HC) taking into account prematurity by using *z*-scores from Intergrowth-21st [19]: "Mild Microcephaly" with HC below 2 standard deviations (SD) and "Severe Microcephaly" with HC below 3 SD for gestational age and sex. This measurement reflects brain size and brain development in primary microcephaly [20].

Definition of Ophthalmic Abnormality

Infants were considered to have an abnormal ophthalmologic exam if they had macular chorioretinal atrophy and/or optic nerve alterations such as atrophy, hypoplasia, or coloboma in at least 1 eye. Both abnormalities are recognized causes of vision impairment (Figure 4).

Ophthalmologic Examination

Comprehensive examinations were performed as soon as possible after delivery and every 3 months thereafter until 1 year of age; after that, a complete eye examination was performed every 6 months if no other abnormality requiring closer follow-up was noted. A comprehensive eye examination consisted of the assessment of binocular vision acuity (*Teller Acuity* Cards II), ocular alignment and motility, biomicroscopy, pupillary reflex, cycloplegic refraction, and indirect ophthalmoscopy to evaluate eye fundus. Children with any major fundus eye abnormalities were evaluated by Retinography (CF-1 Digital Mydriatic Retinal Cameras Canon, USA).

Other Potential Factors Associated with Ophthalmic Abnormalities.

Other variables collected for possible confounder adjustment in the statistical analysis included mother's gestational age at infection, presence and severity of microcephaly, and mother's socioeconomic status.

Institutional Review Board and Informed Consent

The study was approved by the Institutional Review Board (IRB) for Local Research UEPB/PRPG – Universidade Estadual da Paraíba/Pró Reitoria de Pós-Graduação and by the UCLA – University of California Los Angeles IRB. All mothers or caretakers of children who fulfilled enrollment criteria were invited to participate in the study and provided written informed consent for study participation. Data were de-identified.

Statistical Analysis

Descriptive and exploratory statistics were described as means (±SD), medians (interquartile range [IQR]), and frequency distributions. The main outcome of interest was the presence of ophthalmic abnormality as a dichotomous variable (normal/abnormal), and the main predictor of interest was the presence or absence of infratentorial abnormality. Fisher's exact test was used for small sample analysis and Pearson's chi-squared test (χ^2) for categorical data. Logistic regression was used to assess the relationship between the dependent binary outcome variable and other independent variables. A 2-sided P-value $\leq .05$ was considered statistically significant. Statistical analysis was performed using SAS statistical software (9.4 SAS Institute Inc., Cary, NC, USA).

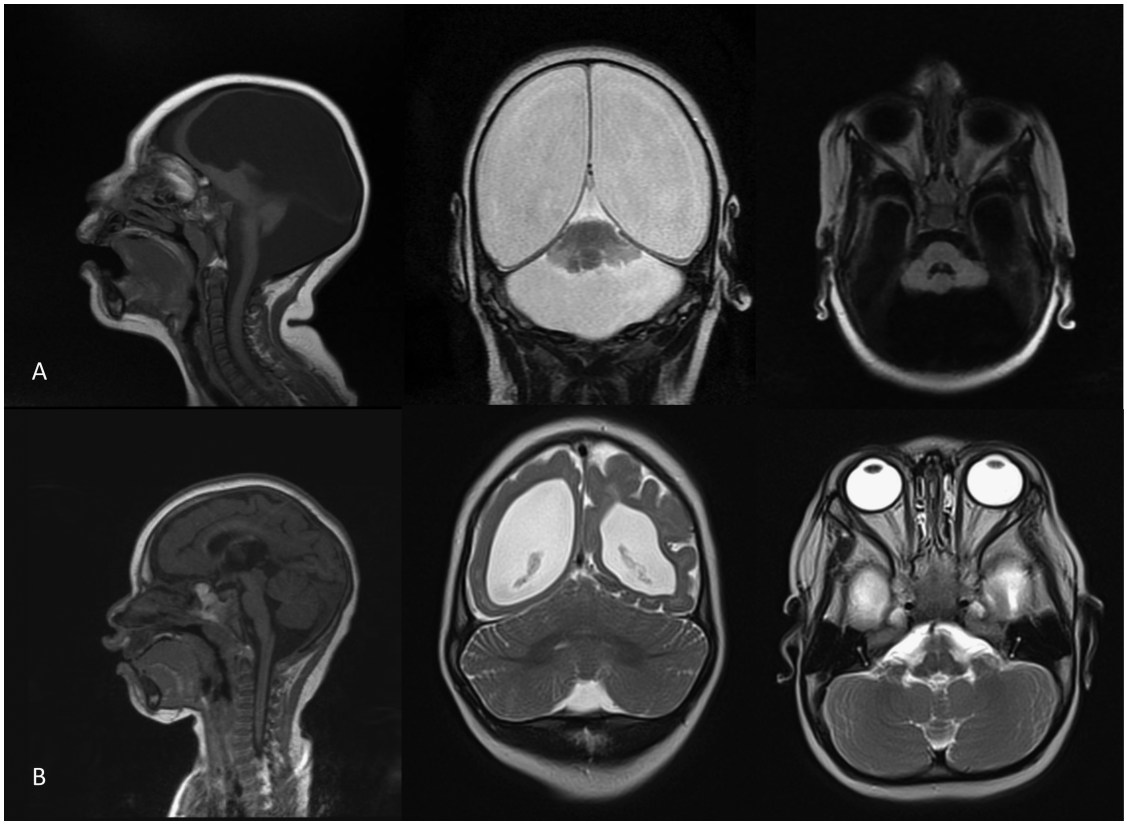

Figure 3. Magnetic resonance imaging of 2 children with congenital Zika syndrome (from left to right sagittal, coronal, and transversal views). (A) Severe infratentorial abnormality (severe hypoplasia of cerebellum, vermis cerebelli, and brainstem). (B) Absence of severe infratentorial abnormality.

RESULTS

A total of 102 infants whose mothers were exposed to ZIKV during pregnancy were referred to IPESQ from March 2016 to December 2018 and were eligible for study participation (Figure 2). Sixteen (21.3%) infants were identified because of a positive maternal ZIKV RT-PR during pregnancy, and 59 (78.7%) were referred because of clinical suspicion of ZIKV infection due to a radiologic abnormality. Twenty-seven infants were excluded from this analysis because of missing data. Table 1 presents descriptive summary statistics.

The mean home income per capita was approximately 85 USD per month. The mean maternal age was 27 years (SD ± 6.7). More than 90% of mothers presented with a cutaneous rash at a mean gestational age of 13 weeks (SD ± 7.2). Almost half of the infants were male (49.3%).

Among 17 infants with infratentorial abnormalities, 16 (94.1%) had ophthalmic abnormalities, whereas in 58 patients without infratentorial abnormalities, 16 (27.6%) had ophthalmic abnormalities (odds ratio [OR]: 42.0; 95% confidence interval [CI]: 5.1-342.9, $P < .001$) (Table 2). The

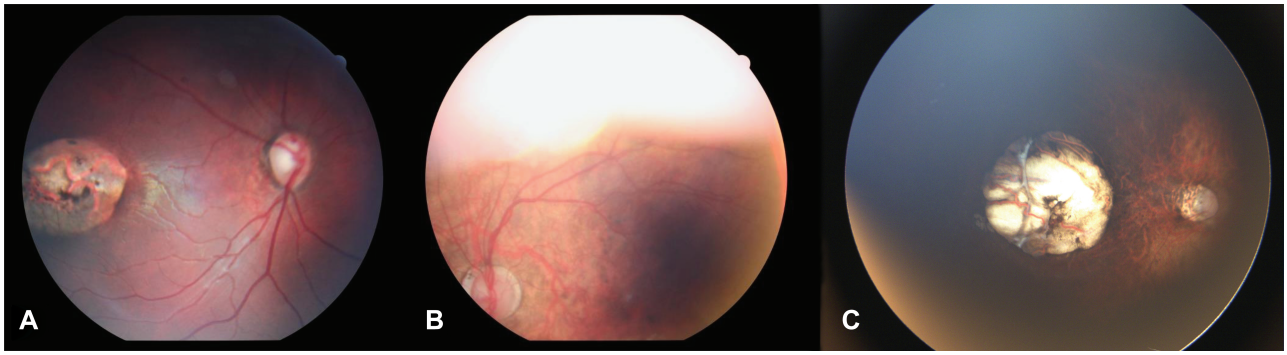

Figure 4. Chorioretinal macular atrophy, abnormal optic disk with coloboma and pallor and pigment mottling.

infratentorial abnormalities noted were severe hypoplastic or dysmorphic cerebellum and vermis cerebelli as well as severe hypoplasia or absent segmentation of the brainstem. Similar associations were observed when the 2 types of ophthalmic abnormalities were analyzed individually. Patients with infratentorial abnormalities were almost 24 times more likely to have chorioretinal atrophy in the macular area when compared with those without infratentorial abnormalities (OR: 23.7; 95% CI: 6.0-93.3; $P < .001$). Similarly, infants with infratentorial abnormalities were also very likely to have optic nerve abnormalities (OR: 11.5; 95% CI: 3.3-40.0; $P < .001$) (Table 2). Follow-up evaluations of sight-threatening lesions did not show any change over time. Infratentorial abnormalities were more frequently associated with ophthalmic abnormalities (94%) than microcephaly (43.4%), $P < .001$.

The group of children with ophthalmic abnormalities (N = 32) had a mean HC of 29.1 cm (SD ± 2.4 [IQR: 23-35]). By comparison, the group without ophthalmic abnormalities (N = 43) had a mean HC measurement of 30.3 cm (SD ±1.5 [IQR: 27-34]). There was a statistically significant difference in HC between the 2 groups ($P = .016$). For every centimeter decrease in HC, there was a 1.4 increase in the likelihood of ophthalmic abnormalities being present (OR: 1.4; 95% CI: 1.065-1.784, $P = .015$). Eighty-five percent of our infants were term infants; HC was plotted according to Intergrowth 21st, which takes into account prematurity [19].

The group of children with ophthalmic abnormalities for whom information on maternal gestational age of infection was available (N = 30) had a mean gestational age at infection of 11.5 weeks (SD ± 5.5 [IQR: 6-28]). The group without ophthalmic abnormalities (N = 39) had a mean gestational age at infection of 14.1 weeks (SD ± 8.2 [IQR: 6-34]). A statistically significant difference in gestational age between both groups was not noted ($P = .12$). A comparison of ophthalmic outcomes between first trimester infections and combined second and third trimester infections did not yield statistically significant results (OR: 2.8; 95% CI: 0.9-8.3). For every weekly increase in gestational age, there was a trend toward a decrease in the risk of ophthalmic abnormalities (OR: 0.95; 95% CI: 0.9-1.0); however, this finding was not statistically significant.

DISCUSSION

The presence of infratentorial abnormalities was strongly associated with ophthalmologic findings in our study. These findings are unlikely due to bias or confounding. To the best of our knowledge, this is the first report of a radiologic finding predicting ophthalmic abnormalities in children with CZS. It is important to point out, however, that the absence of infratentorial abnormalities was not necessarily associated with a normal ophthalmologic outcome. Of the 32 infants who had ophthalmic abnormality, 50% did not have the radiologic predictor (Table 1).

Table 1. Descriptive Summary Statistics

			With Ophthalmic Abnormality N = 32			Without Ophthalmic Abnormality N = 43		
Characteristics	Total n	Total %	n	%	Mean ± SD	n	%	Mean ± SD
Diagnosis								
Laboratory	35	46.7	21	60	—	14	40	—
Clinical	40	50.3	11	27.5	—	29	72.5	—
Infratentorial abnormality								
Yes	17	22.3	16	94	—	1	5.9	—
No	58	77.7	16	28	—	42	72.4	—
Microcephaly								
Yes	53	70.7	23	43.4	29.1 ± 2.4	30	56.6	30.3 ± 1.5
No	22	29.3	9	40.1		13	59.1	
Trimester of maternal infection								
First	47	68.1	24	51.1	11.5 ± 5.5	23	48.9	14.1 ± 8.2
Second	19	27.5	6	31.6		13	68.4	
Third	3	4.4	0	0		3	100	
Calcification pattern								
1	24	32	5	20.8	—	19	79.2	—
2	48	64	24	50	—	24	50	—
3	3	4	3	100	—	0	0	—
Birthweight								
Adequate	68	90.7	29	42.6	2651 ± 484.8	39	90.7	2857 ± 457.9
Small for gestational age	5	6.7	2	40		3	7.0	
Big for gestational age	2	2.6	1	50		1	2.3	

Means of head circumference in cm, trimester of maternal infection in weeks, and birthweight in grams. Calcification pattern 1: subcortical; 2: subcortical and basal ganglia; 3: subcortical, basal ganglia, and cerebellum.

Table 2. Evaluation of Variables Potentially Associated With Ophthalmic Abnormalities, (n = 75)

	Total		Crude Odds Ratio (cOR)		Adjusted Odds Ratio (aOR)[a]		
Characteristic	n	%	cOR 95% CI	*P*-value	aOR 95% CI	*P*-value	*t*-test[b]
Infratentorial abnormalities	17	100					
With ophthalmic abnormalities	16	94.1	42.0 5.1-342.9	<.001	37.2 4.4-14.4	.003	—
Chorioretinal atrophy	13	76.5	23.7 6.0-93.3	<.001	—	—	—
Optic nerve abnormality	12	70.6	11.5 3.3-40.0	<.001	—	—	—
Without ophthalmic abnormalities	1	5.9	1.0	—	1.0	—	—
Microcephaly (head circumference)	53	100					
With ophthalmic abnormalities	23	43.4	1.4 1.1-1.8	.015	0.8 0.2-2.8	.72	0.016
Without ophthalmic abnormalities	30	56.6	1.0	—	1.0	—	—
Gestational age	69	100					
With ophthalmic abnormalities	30	43.5	2.8 0.9-8.3	.068	2.5 0.7-9.3	.17	0.12
Without ophthalmic abnormalities	39	56.5	1.0	—	1.0	—	—

[a]aOR values were generated by the simultaneous entry of covariates in a logistic regression model, adjusting for gestational age and presence of microcephaly.
[b]Comparing results with and without ophthalmic abnormality.

Although several ophthalmologic abnormalities have been described in patients with antenatal ZIKV exposure including cataracts, calcifications, microphthalmia, remnants of a pupillary membrane, and glaucoma, the most prevalent and sight-threatening findings are observed in the retina and optic nerve, which are the ophthalmic abnormalities studied in this analysis [12, 13, 21, 22]. ZIKV is recognized for its neurotropism and ability to injure neural progenitor cells; this contributes to its devastating impact in the brain and other neurosensory organs such as the eye [23]. In addition to its pathophysiologic effects, there is in vivo evidence that ZIKV leads to depletion of ganglion cells, borderline inner nuclear layer thinning, and also less prominent photoreceptor loss, which can be attributed to foveal maldevelopment and central chorioretinal atrophy [24].

The sensitivity of the radiologic predictor was 50%, which implies that half of the neonates with ophthalmic abnormalities would not be identified if infratentorial abnormality was used as a radiologic screening test. On the other hand, the specificity of the radiologic predictor was 97.7%. The main public health advantage of identifying infratentorial abnormalities during a prenatal ultrasound would be the possibility of predicting low vision outcomes in utero, which would allow infants to enter early rehabilitation programs soon after birth in order to curtail repercussions of visual impairment. In resource-limited settings, access to CT or MRI is generally not available. It would be important to maximize the existing infrastructure in settings such as our own (which have now become endemic for ZIKV infection) by adequately training medical neuro-ultrasonographers in the imaging of posterior fossa structures.

Prenatal US has been shown to have a sensitivity of 48.9% in predicting adverse neonatal outcomes in a study that evaluated mothers with ZIKV exposure during pregnancy [25]. There are still no data available to demonstrate whether any specific ultrasonographic prenatal feature may be associated with ophthalmic abnormalities. ZIKV infection is a relatively new disease where most affected individuals do not have any symptoms. For this reason, the majority of cases were diagnosed after delivery.

In our patient sample, the prevalence of ophthalmic abnormalities (42.7%) was higher when compared with other ZIKV infection ophthalmologic studies. Other cohorts reported frequencies of approximately 18.6% (Yepez et al [26]), 21.4% (Zin et al [12]), and 24.1% (Freitas et al [14]) (Table 3). We evaluated a heavily symptomatic group of children that were referred to our institution because of the presence of fetal abnormalities detected during prenatal care; this comprised 79% of the children in our study. Consequently, patients with varied radiologic abnormalities were overrepresented in our population, which allowed the analysis of an association with ophthalmic abnormalities. All our patients had radiologic abnormalities including cerebral calcifications, ventriculomegaly, infratentorial abnormalities, pachygyria, or lissencephaly, whereas in the other studies, those findings were not as prevalent (Zin et al [12] [27.7%]). The study with the most similar patient population with the greatest geographic proximity

to our site was conducted in Pernambuco [13] and reported a high prevalence of radiologic abnormalities (96.7%) and comparable ophthalmologic abnormalities (46.3%) (Table 3).

Previous studies have suggested an association between the presence of lower HC and ophthalmologic findings [12, 13]; this association was also noted in our study when we compared the means of HC between children with and without ophthalmic abnormalities. Most of the patients in our sample had microcephaly (70.7%), whereas, in a Rio de Janeiro eye study, the prevalence was 17.9% [12]. The prevalence of microcephaly was 100% in other studies from northeastern Brazil [13, 14], Venezuela, and Colombia [26]. Although this association seems to be true, we hypothesize that there might not be a linear relationship between HC and ophthalmic abnormalities or potentially such an association could be present except for the most severe cases. We noted that most of the children who died early did not have microcephaly (66.7%). A potential explanation is that a compensatory ventriculomegaly may develop with the intention to balance the lack of brain tissue. Thus, children may have a near-normal or normal HC in this setting. It is likely that ZIKV infection without microcephaly is under notified. Therefore, instead of the HC measurement, other brain measurements should be considered as an alternative to HC for a more reliable correlation with CNS abnormalities and ophthalmic abnormalities. Although there is definitely an association, microcephaly is not always predictive of ophthalmologic abnormalities. It is also important to highlight that microcephaly is the "tip of the iceberg" type situation, ranging in prevalence between 3% and 5% in prospective cohorts of ZIKV-exposed children [27, 28]. As our institution was located in the epicenter of the Zika epidemic in Brazil, the ZIKV attack rate was exceedingly high with a very high number of cases of microcephaly reported. We anticipate that for every microcephalic child with CZS in our setting, there were likely 20 ZIKV-exposed normocephalic children who may not have been diagnosed with this exposure.

Contrary to other studies [12–14], we did not see an association between first trimester infections and ophthalmic abnormalities. This is likely due to the fact that our patients were mainly infected in the first trimester and the comparator number in the other trimesters was low. Given the very high number of eye abnormalities in our patients, we can infer that infection in the first trimester was likely to result in newborns with ophthalmic abnormalities.

Visual impairment might not be the only consequence of viral pathogenesis in the retinal structures. Brain damage by ZIKV also has the potential to cause detrimental consequences to visual acuity. Further studies determining which brain abnormalities correlate with low vision are essential in order to address this issue.

The major strength of our study is that we were able to demonstrate a strong association between a radiologic risk factor (infratentorial abnormalities) and ophthalmic abnormalities. The sample size was adequate for our main objective as it included one of the largest groups of children reported to date with a variety of radiologic abnormalities and significant disease severity with and without microcephaly. The findings have important public health repercussions since the radiologic parameter allows parents/caretakers to anticipate an abnormal ophthalmologic outcome in advance, thus avoiding delays in diagnosis and enabling prompt initiation of rehabilitation efforts. Early identification of an ophthalmologic pathology is particularly important for infants because vision significantly affects global development; visual stimuli are an important tool to infant physical development [29]. Vision encourages the baby to move and touch and also allows the recognition

Table 3. Population Characteristics and Ophthalmic Abnormalities Reported in Different ZIKV Studies

	Total	MC	Radiologic Abnormalities[a]	Presence of Ophthalmic Abnormality (Sight-Threatening Lesions)					
				Total	Macular Atrophy	Optic Nerve	With MC	Without MC	Without CNS Abnormality
Ipesq, Paraiba	75	53 (70.7%)	75 (100%)	32 (42.7%)	20 (62.5%)	22 (68.7%)	23 (71.9%)	9 (28.1%)	0 (0%)
Zin, Rio	112	20 (17.9%)	31 (27.7%)	24 (21.4%)	7 (29.2%)	19 (79.2%)	14 (58.3%)	10 (41.7%)	8 (33.3%)
Ventura, Pernambuco	40	40 (100%)	29/30 (96.7%)*	22 (46.3%)	7 (31.8%)	5 (22.7%)	22 (100%)	0	**
Yepez, Colombia/ Venezuela	43	43 (100%)	**	8 or less?	3 (7%)	5 (12%)	8 at least	0	**
Freitas, Bahia	29	29 (100%)	**	7 (24.1%)	3***	4	7	0	**

Abbreviations: CNS, central nervous system; CT, computerized tomography; MC, Microcephaly; ZIKV, Zika virus.
[a]At least one present: ventriculomegaly, calcifications, posterior fossa abnormality, pachygyria, or lissencephaly.
*30 had CT results, and 29 had calcifications.
**Not mentioned.
***Eyes.

of familiar faces, which is important for the infant's emotional and cognitive development. Early recognition of the problem allows an early referral to a multidisciplinary group, avoiding the typical delay in care. This care involves physical therapists, psychologists, ophthalmology technicians, and ophthalmologists. Orientation and mobility training can be initiated, and it involves teaching the child how to use residual vision to perform daily activities independently without harming themselves. The implementation of overplus eyeglasses has also been shown in our setting to improve tracking and visual function in children with microcephaly.

One of our study limitations was that we had a very limited number of children who were mildly symptomatic or asymptomatic, so we could not make inferences regarding the absence of radiologic findings and the absence of ophthalmologic abnormalities. There were no cases of isolated infratentorial brain abnormalities with eye findings. In addition, all of our patients had supratentorial abnormalities; all had subcortical calcifications. We also did not have laboratory confirmation of ZIKV infection in most of the pregnant women. Given that all our children were born in the epicenter/ground zero of the ZIKV epidemic in Brazil and fulfilled the criteria for CZS, we are confident of their ZIKV exposure status. Because of our entry criteria, pregnant women with asymptomatic ZIKV infection were not included. Our population had extensive radiologic abnormalities, which underscores the inclusion of more severe cases than other studies. This can be considered a study limitation, but because our main purpose was to evaluate predictors of ophthalmologic abnormalities in microcephalic children, a large number of affected children were necessary for the analyses.

In conclusion, the presence of infratentorial abnormalities is a significant predictor of ophthalmic abnormalities if identified during prenatal US. All neonates of mother with possible ZIKV exposure at any time during pregnancy should have a complete ophthalmologic evaluation.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. They also have no financial relationships relevant to this article to disclose. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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