

# The visual system in infants with microcephaly related to presumed congenital Zika syndrome



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<b>PURPOSE</b>	To describe and analyze ocular features in infants with microcephaly due to presumed congenital Zika syndrome.
<b>METHODS</b>	Ophthalmologic evaluation, including indirect ophthalmoscopy and eye fundus imaging, visual acuity testing with Teller Acuity Cards, and strabismus assessment were performed in infants with microcephaly at a nongovernmental organization clinic for visually disabled children.
<b>RESULTS</b>	A total of 70 infants with microcephaly were referred to the clinic. Of these, 25 (mean age, 3 months; 14 males) had ophthalmologic changes: 18 (26%) had intraocular abnormalities, including macular chorioretinal atrophy, mottled retinal pigment epithelium and optic nerve pallor; 7 patients (10%) had strabismus or nystagmus without intraocular abnormalities. Visual acuity was below normal range in all 11 infants tested.
<b>CONCLUSIONS</b>	Ophthalmologic abnormalities occurred in 36% of the patients. Macular circumscribed chorioretinal atrophy, focal mottled retinal pigment epithelium, optic nerve pallor, early-onset strabismus, nystagmus and low visual acuity were common ophthalmologic features in infants with microcephaly due to presumed congenital Zika syndrome. (J AAPOS 2017;21:300-304)

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The Zika virus (ZIKV) is a single-stranded RNA virus of the *Flaviviridae* family and genus *flavivirus*. It is transmitted by the mosquito *Aedes Aegypti*. In 2015 the ZIKV infection was confirmed in Brazil, in patients who were suspected to have dengue fever but had negative serology for the dengue virus.<sup>1</sup> Recent studies documented a 20-fold increased incidence of newborns with microcephaly within a period of a few months. The newborns had severe central nervous system malformations, arthrogryposis, seizures and ophthalmic abnormalities. Maternal history of ZIKV infection during pregnancy was reported.<sup>2-6</sup>

Epidemiological studies of congenital Zika syndrome (CZS) are necessary to understand environmental factors and population genetic characteristics that might be associated with the disease—a first step in the development of specific serological tests and effective prevention strate-

gies and vaccines. The objective of this study was to describe ophthalmological features and to analyze functional visual results in infants with microcephaly due to presumed CZS.

## Subjects and Methods

A clinical study was conducted at CAVIVER, a nongovernmental organization clinic and referral center dedicated to visually disabled children, at the city of Fortaleza, Brazil. All patients with microcephaly due to presumed CZS were evaluated by a medical team composed of ophthalmologists, neurologists, geneticists, and pediatricians from January to May 2016. This study was approved by the Albert Sabin Pediatric Hospital Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from the families for the collection, use and publication of clinical photographs and use of the data of the infants for scientific purposes.

The inclusion criteria included patients with head circumference (HC) at birth >2 standard deviations below the mean for gestational age and sex according to the Fetal International and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) for fetal and newborn growth and the World Health Organization Child growth standards for infants ([www.who.int/childgrowth/en/](http://www.who.int/childgrowth/en/)).<sup>7</sup>

Gestational data from the mothers included questions regarding the symptoms and signs of ZIKV infection during

See accompanying editorial on p. 259.

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Table 1. Demographic ophthalmological features in patients with microcephaly

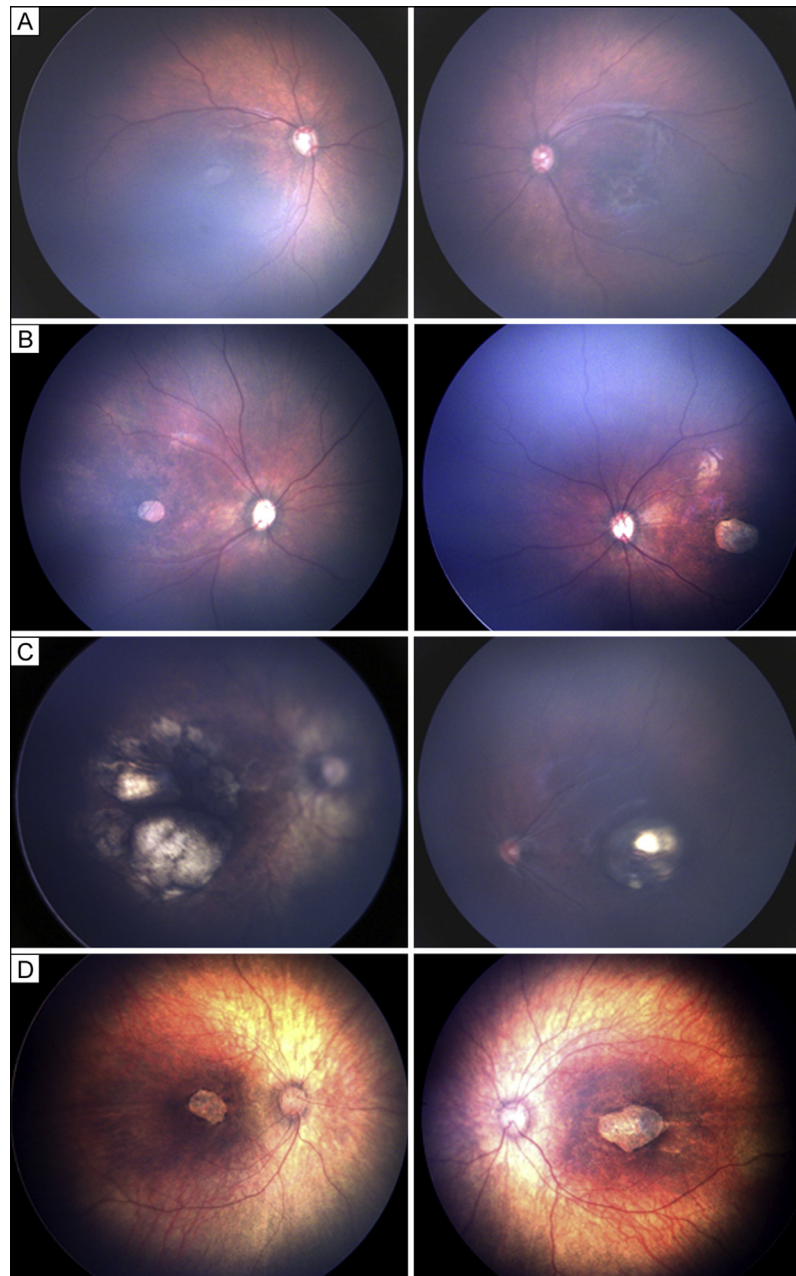
Case	Birthday	Age, months	BW, g	HC at birth, cm	GA of ZIKA infection symptoms, trimester	Ophthalmological features	VA <sup>a</sup>	Age-matched normal VA <sup>a</sup>
1	11/27/15	6	3,140	31.8	2	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments	—	
2	11/30/15	6	3,530	31.7	1	Strabismus	—	
3	01/06/16	4	2,910	29	1	Bilateral optic nerve pallor, focal mottled retinal pigments, strabismus	—	
4	01/06/16	4	3,350	27	1	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments	—	
5	11/10/15	1	2,990	31.9	2	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments, nystagmus	No response	20/260
6	01/23/16	4	3,205	29.5	No symptoms	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments	No response	20/145
7	03/19/16	1	2,425	29	No symptoms	Macular chorioretinal atrophy LE, focal mottled retinal pigments	—	
8	12/09/15	5	2,760	27.5	1	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments	—	
9	12/03/15	5	1,935	25	No symptoms	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments, strabismus	RE 20/2700 LE 20/2700	20/85
10	03/28/16	2	2,395	27	2	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments, optic nerve pallor RE	—	
11	08/05/15	8	2,900	31.9	1	Macular chorioretinal atrophy LE, focal mottled retinal pigments, bilateral optic nerve pallor	RE 20/360 LE 20/1400	20/70
12	01/25/16	4	2,976	30.5	No symptoms	Strabismus	RE 20/270 LE 20/360	20/145
13	10/30/15	2	1,495	25.2	2	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments, bilateral optic nerve pallor, nystagmus	No response	20/260
14	12/23/15	1	2,630	28	1	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments, bilateral optic nerve pallor, nystagmus	—	
15	02/03/16	3	3,305	30	No symptoms	Macular chorioretinal atrophy LE, focal mottled retinal pigments	—	
16	01/11/16	4	3,120	30	No symptoms	Strabismus	RE 20/360 LE 20/360	20/145
17	10/25/15	6	2,625	29	1	Strabismus	—	
18	11/27/15	5	2,750	30	1	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments	—	
19	03/21/16	1	2,160	27.5	1	Bilateral optic nerve pallor, focal mottled retinal pigments, strabismus	RE 20/360 LE 20/360	20/260
20	04/15/16	1	2,445	27	1	Bilateral macular chorioretinal atrophy, focal mottled retinal pigments, optic nerve pallor LE	RE 20/670 LE 20/670	20/260
21	09/25/15	3	2,835	30	1	Nystagmus	—	
22	01/28/16	3	2,930	29	1	Optic nerve pallor LE, focal mottled retinal pigments, strabismus	—	
23	01/29/16	3	3,015	31	1	Bilateral macular chorioretinal atrophy focal mottled retinal pigments, bilateral optic nerve pallor, nystagmus	RE 20/1400 LE 20/1400	20/195
24	10/01/15	7	1,550	27	1	Strabismus	—	
25	02/07/16	3	2,490	30	1	Strabismus	RE 20/270 LE 20/1340	20/195

BW, birth weight; GA, gestational age; HC, head circumference; LE, left eye; RE, right eye; VA, visual acuity.

<sup>a</sup>Teller Acuity Cards.

pregnancy, such as fever, exanthematic cutaneous rashes, itching or redness of the eyes, conjunctivitis, myalgia, or arthralgia.

All infants underwent serologic testing for toxoplasmosis, cytomegalovirus, rubella, and syphilis in order to rule out other infectious causes of microcephaly. No specific serological testing or



**FIG 1.** The right and left eyes of patients with congenital Zika syndrome and structurally affected eyes. A, Patient 6 (4 months old) with bilateral mottled retinal pigment epithelium and macular chorioretinal atrophy. B, Patient 10 (2 months old) with bilateral macular chorioretinal atrophy, with 1 disk diameter on the right and 2 disk diameters on the left, mottled retinal pigment epithelium, and optic disk pallor in the right eye. C, Patient 14 (1 month old) with right eye optic nerve pallor and macular chorioretinal atrophy (10 disk diameters of extension) and left eye macular chorioretinal atrophy (5 disk diameters). There is bilateral mottled retinal pigment epithelium. D, Patient 20 (1 month old) with right eye macular chorioretinal atrophy (1 optic disk diameter) and left eye macular chorioretinal atrophy (2 optic disk diameters) and optic disk pallor. There is mottled retinal pigment epithelium and attenuated blood vessels in both eyes.

reverse transcriptase polymerase chain reaction (RT-PCR) for ZIKV was available. The geneticist assessed the parents and family for consanguinity and performed a physical examination of the infants for syndromal forms of microcephaly. Patients with probable genetic or syndromal forms of microcephaly were excluded.

Ophthalmological evaluation included the following: assessment of visual acuity, anterior segment evaluation, motility

evaluation, and binocular indirect ophthalmoscopy performed with mydriasis (tropicamide 1%). The patients who were diagnosed with retinal changes were examined under anesthesia to measure intraocular pressure (Perkins handheld applanation tonometer; Clement Clarke International Limited, Essex, England) and to obtain wide-angle fundus digital images using the RetCam (RetCam Imaging System, Shuttle; Clarity Medical

Systems, Pleasanton, CA) for documentation and detailed study and mapping of retinal lesions.

Visual acuity was evaluated using Teller Acuity Cards (Teller Acuity Cards II Stereo Optical Company, INC., Chicago, IL) at 38 cm and paired according to the age-matched reference table.<sup>8,9</sup>

## Results

A total of 70 infants with microcephaly were included; of these, 25 (36%) had ocular abnormalities on examination (Table 1). Of the 25 children, 14 (56%) were male, and mean age (with standard deviation) was  $3.7 \pm 1.99$  months (range, 1–8 months). Fifteen mothers (60%) reported symptoms associated with ZIKV infection in the first trimester of pregnancy, 4 (15%) reported symptoms in the second trimester, and 6 (24%) were asymptomatic. The average HC at birth was 29 cm (range, 24–31.9 cm). All infants showed craniofacial disproportion.

Anterior segment analysis was normal in all patients. None had cornea, iris, or lens abnormalities. Intraocular pressure measurements were obtained in 18 children, who underwent examination under anesthesia. The mean pressure was  $11 \pm 2$  mm Hg (range, 8–14 mm Hg).

Of the 70 patients, 18 (26%) were diagnosed with intraocular abnormalities. A total of 33 eyes were structurally affected (Figure 1). Macular chorioretinal atrophy was observed in 27 eyes of 15 infants (60% of the patients with ocular abnormalities), and wide-angle digital imaging was obtained. Chorioretinal atrophic lesions were whitish, flat, circumscribed, resembling choroidal coloboma (colobomatous-like lesions), unique or multiple, varying in size from about 1 to 10 disk diameters. No retinal detachments, vitreous changes, or inflammatory signs or cells were observed in any affected eye. Mottled retinal pigment epithelium changes were observed in the posterior pole in 18 patients (72%). Optic nerve pallor was observed in 10 children (bilateral in 7 and unilateral in 3).

Strabismus was observed in 10 infants (14%), with a mean age of 4 months, esotropia in 9 infants and exotropia in 1 infant. Nystagmus was observed in 6 patients. Six cases of strabismus and 1 case of nystagmus were detected in children without intraocular abnormalities.

Visual acuity was tested in 11 infants (eFigure 1) using Teller Acuity Cards. Three infants had no intraocular abnormalities. Visual acuity range varied from light perception to 20/270 (logMAR = 1.13). The average visual acuity in these patients was 20/670 (1.52 logMAR). All patients showed visual acuity results below the normal range for age-matched controls (Table 1).<sup>9</sup> Visual acuity was not obtained in all patients because of neurological conditions. During the visual acuity assessment, some babies showed excess irritability or seizures; others showed lack of alertness due to systemic medication.

## Discussion

The 5 major signs that differentiate CZS from other congenital infections are as follows: (1) severe microcephaly with craniofacial disproportion, narrow and laterally depressed frontal bone and occipital prominence with abnormal skull morphology; (2) central nervous system malformation and thin cerebral cortex with subcortical calcifications; (3) macular scarring with chorioretinal areas of atrophy and mottled retinal pigment epithelial changes; (4) congenital contractures or arthrogryposis; and (5) early hypertonia and extrapyramidal involvement.<sup>10</sup> All systemic and ocular characteristics of CZS do not necessarily occur in the same patient.<sup>11</sup> A study of 13 babies diagnosed with CZS on the basis of laboratory evidence in the absence of microcephaly at birth detected macular chorioretinal atrophy in 3 infants.<sup>12</sup> The ophthalmic features with unique anatomical characteristics may help to identify CZS in patients born without microcephaly.

In our study, 25 of 70 infants (36%) with microcephaly due to presumed CZS showed ocular anomalies, including 18 patients with intraocular lesions (26%) and 7 (10%) with altered ocular motility. The circumscribed chorioretinal atrophy and optic nerve abnormalities observed in our patients were similar to those reported previously.<sup>5,6,13,14</sup>

The macular chorioretinal atrophy observed in CZS differs from toxoplasmosis scars, because there is an absence of intraocular inflammatory signs or chorioretinitis, and there are no dark pigmentation surrounding the atrophic circular area. The retinal involvement seen in Aicardi syndrome is somewhat similar to the colobomatous-like atrophic lesions in infants with CZS; however, patients with Aicardi syndrome have corpus callosum agenesis or dysgenesis, optic nerve anomalies, and chorioretinal lacunae typically surrounding the optic nerve.<sup>15</sup>

Ventura and colleagues<sup>16</sup> evaluated the affected retinal layers of 8 affected eyes of infants with CZS using optical coherence tomography (OCT), which showed substantial neurosensory retinal thinning with discontinuation of the ellipsoid zone, choroidal thinning, and hyperreflectivity underlying areas of presumed atrophic retinal pigment epithelium. Colobomatous-like excavation involving the neurosensory retina, retinal pigment epithelium, and choroid was found in 4 eyes (44%), causing severe damage to the retina.

Circumscribed macular atrophy seems to be unique and should be considered as pathognomonic to CZS, although the pathogenesis of these lesions is yet unknown. Ophthalmological screening should be performed in newborns with presumed CZS within 30 days of life to detect ocular abnormalities when neuroimaging or laboratory tests are not obtained.

Ventura and colleagues<sup>14</sup> found that first trimester maternal infection and smaller head circumference were statistically correlated with abnormal ocular findings and may be considered a risk factor for CZS. In our patients, 15 mothers had symptoms associated with ZIKV infection



in the first trimester of pregnancy, and 6 were asymptomatic. These data reveal the importance of fetal morphological ultrasound for prenatal diagnosis of CZS and of ophthalmological screening of infants in the endemic areas.

Optic nerve anomalies such as hypoplasia, atrophy, or pallor are a common ocular feature in CZS.<sup>5,6</sup> Optic nerve pallor occurred in 14% of the cases in this study.

Strabismus occurred in 10 infants, at a mean age of 4 months. Seven patients (10%) without intraocular abnormalities had strabismus (6 cases) or nystagmus (1 case). These findings were not previously reported. Those signs are associated with neurological visual deficits due to brain damage or cerebral visual impairment. Pediatricians, orthoptists, healthcare personnel and ophthalmologists should be aware of early onset strabismus occurrence in otherwise healthy infants born in high-risk areas for ZIKV infection. This rate of strabismus may increase, as patients get older.

It is not always possible to test visual acuity in infants with CZS because of neurological problems. Visual acuity was obtained in 11 patients in this study. All infants tested showed functional vision deficits, with visual acuity below normal for age-matched children. Three infants had no intraocular abnormalities, and their low vision was related to cerebral visual impairment (Table 1).<sup>9</sup>

Ophthalmological screening guidelines and follow-up of the children with CZS is mandatory and follows the SOPLA/SBOP (Latin American Pediatric Ophthalmology Society and Brazilian Pediatric Ophthalmology Society) recommendation letter (eSupplement 1, available at [jaapos.org](http://jaapos.org)).<sup>17</sup> Detection and isolation of ZIKV from conjunctiva swab samples has been reported,<sup>18,19</sup> and medical and healthcare personnel should take the necessary precautions during ophthalmological examination to avoid the risk of tear-born contamination.

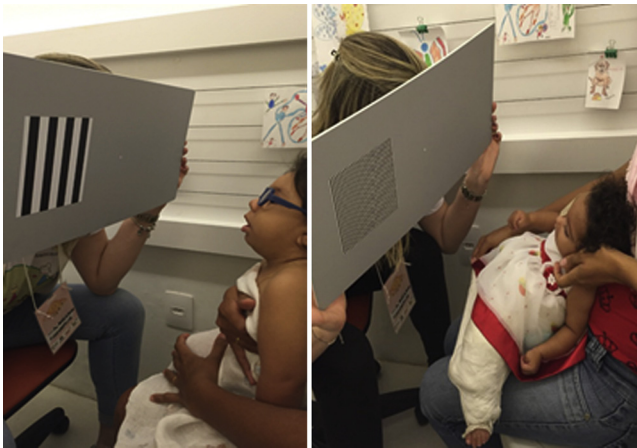
Our study was limited by the lack of laboratory evidence with specific serological testing to confirm ZIKV. Longer ophthalmologic follow-up with retinal imaging records and visual development assessment are needed for further understanding of the CZS ocular involvement and consequences for visual performance.

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**eFIG 1.** Visual acuity evaluation with Teller Acuity Cards test in children with congenital Zika syndrome.