Zika virus and the eye

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Purpose of review
The aim of this study was to review the ocular findings related to the Zika virus (ZIKV) based on the main studies published to date, describe the patterns of the lesions and risk factors, and identify the public health implications and scientific importance of this emerging disease.

Recent findings
In most studies, the ZIKV seems related to congenital ocular lesions and most mothers reported mild symptoms during the first pregnancy trimester. Five fundus patterns were seen most often: macular chorioretinal atrophy, chorioretinal atrophy elsewhere, focal pigmentary changes in the macular region, optic nerve abnormalities and combined types. A few studies have suggested that the ZIKV might damage the anterior segment of these babies' eyes. Few reports have described the ocular complications seen in adults during the acute infection, including conjunctivitis, iridocyclitis and chorioretinitis.

Summary
Infants with congenital Zika syndrome might have vision-threatening fundus abnormalities. Although the full spectrum of ocular lesions caused by the ZIKV infection is not yet determined, a distinctive new disease has been observed. Recognition of these lesions by ophthalmologists can help ensure appropriate etiologic evaluation and clinical investigation to define the range of anomalies in an affected infant and determine essential follow-up and ongoing care.

Keywords
congenital Zika syndrome, ocular findings, Zika virus

INTRODUCTION

Ocular anomalies have been reported in infants with presumed and laboratory-confirmed prenatal Zika virus (ZIKV) infection [1▪▪,2▪▪,3,4▪,5]. Posterior findings have been the most prevalent, but some studies have reported that anterior segment and structural defects also might be related [2▪▪,4▪,5]. Larger series of 20 or more infants with presumed ZIKV-associated microcephaly have reported ocular findings in 34–55% of patients [2▪▪,6]. Some retinal lesions, including well defined chorioretinal atrophy and gross pigmentation, generally affecting the macular region, have been well described and seem to suggest ZIKV infection.

HISTORICAL ASPECTS OF ZIKA INFECTION

The ZIKV, an arbovirus that belongs to the Flaviviridae family and Flavivirus genus, is transmitted to humans by the Aedes mosquito species, that is *Aedes aegypti*, *Aedes albopictus* and *Aedes africanus* [7]. In the America, the main biologic vector is *A. aegypti,* the same vector that transmits dengue fever virus (DFV) and chikungunya virus. Sexual, perinatal and blood transfusion ZIKV modes of transmission have also been reported [8].

The virus was first identified in 1947 in the Zika forest near Kampala, Uganda, in a rhesus monkey (*Macaca mulatta*) [7]. Five years later, the virus was isolated in Africans for the first time [9]. The virus then migrated to Asia in the 1940s as a different strain from that in Africa [10]. In the past two decades, the Asian strain has been causing isolated outbreaks outside of Asia, resulting in a low number of cases on Yap Island in the Federated States of

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KEY POINTS

- Infants with CZS and microcephaly had approximately a 34–55% possibility of having severe ocular abnormalities; the posterior ocular findings observed more frequently were focal pigment mottling and chorioretinal atrophy with a predilection for the macular area and optic disc abnormalities, and congenital glaucoma is rare but can occur.
- In patients with macular impairment, OCT showed severe involvement of the neurosensory retina, including the internal and external layers, and choroid.
- Fundus abnormalities in infants with presumed ZIKV congenital infection were associated with smaller cephalic diameters at birth and with those infants whose mothers reported symptoms during the first trimester.
- This disease has the potential for rapid spread and heterogeneity manifestations.
- Regarding guidelines for disease prevention, vaccine development and control of *A. aegypti* are imperative; pregnant women should avoid endemic areas and/or use insect repellents; microcephalic newborns should be evaluated due to the marked changes in CZS and fundus lesions; sexual relations should be avoided or condoms used for 3–6 months after infection; multidisciplinary teams are needed for early cognitive and visual stimulation of newborns and additional studies with longer follow-up periods.

Micronesia and Easter Island in Chile and bigger outbreaks in French Polynesia during 2007, 2013 and 2014 [11].

ZIKA VIRUS OUTBREAK IN BRAZIL AND DEMOGRAPHY

The most recent and largest ZIKV outbreak in history started in May 2015 in northeastern Brazil and achieved pandemic proportions [7]. Between 0.4 and 1.3 million people have been estimated to be infected by ZIKV in Brazil in 2015 with fast spread worldwide [7].

CLINICAL ASPECTS OF ZIKA VIRUS INFECTION

Only 20% of patients with the ZIKV have reported mild symptoms (headache, maculopapular rash, arthralgia and/or conjunctivitis) lasting less than 1 week [12]. There is also evidence of viral neurotropism, which spares all bodily tissues except for nerve tissue. In Martinique, French Polynesia and many Brazilian states [13], the ZIKV infection has been associated with Guillain–Barré syndrome, an autoimmune disease that causes acute or subacute flaccid paralysis and even death and that has been associated previously with other flavivirus infections [14]. Conjunctivitis, uveitis and unilateral acute maculopathy have also been described in adults after an acute ZIKV infection [15–18].

CONGENITAL ZIKA SYNDROME

Until December 2015, the ZIKV was thought to cause microcephaly alone in newborns. However, ocular abnormalities, arthrogryposis and hearing deficits also have been described as part of a new syndrome, that is the congenital Zika syndrome (CZS) [19].

The Centers for Disease Control and Prevention reported that the distinctive features of the CZS are [19] microcephaly, including brain disruption sequence, partially collapsed skull, overlapping cranial sutures, prominent occipital bone, redundant scalp skin and neurologic impairment; brain abnormalities, including cerebral cortex thinning, abnormal gyral patterns, increased fluid spaces, subcortical calcifications, corpus callosum anomalies, reduced white matter and cerebellar vermis hypoplasia; ocular findings, such as macular scarring, focal pigmentary retinal mottling, structural anomalies (microphthalmia, iris coloboma, lens subluxation, cataract, glaucoma), chorioretinal atrophy and optic nerve hypoplasia or atrophy; and congenital contracture, including unilateral or bilateral clubfoot and arthrogryposis multiplex, such as pronounced early hypertonia or spasticity with extrapyramidal symptoms, motor disabilities, cognitive disabilities, hypotonia, irritability or excessive crying, tremors, swallowing dysfunction, visual impairment, hearing impairment and epilepsy.

The spectrum of the CZS has also been expanded to include children with severe brain abnormalities without microcephaly at birth [20,21]. van der Linden *et al.* [22] reported 13 infants with laboratory evidence of ZIKV infection and no microcephaly at birth who presented with ventriculomegaly and decreased brain volume, cortical malformations and subcortical calcifications.

CONGENITAL ZIKA SYNDROME AND OCULAR ABNORMALITIES

The first ocular lesions associated with presumed ZIKV congenital infections developed in Recife, Brazil, and the report described the ophthalmologic findings in three children with microcephaly born after the ZIKV outbreak in Brazil. One mother reported a rash and arthralgia during the first trimester of pregnancy. The mothers had no ocular

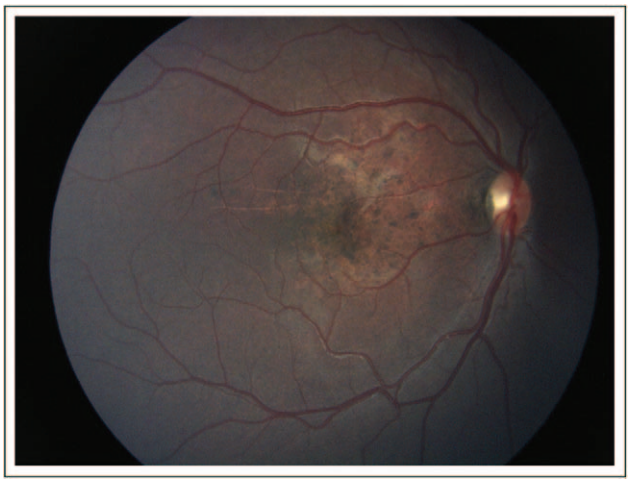

FIGURE 1. Right eye of an infant with CZS and focal piment mottling in the macular region.

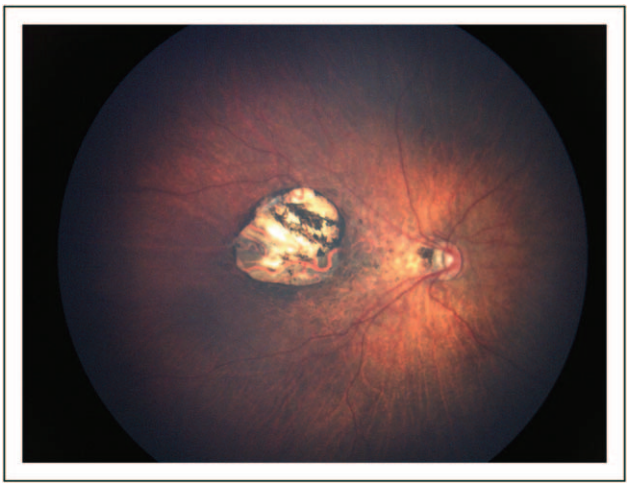

FIGURE 2. Right eye of an infant with CZS shows the three most common fundus findings: macular chorioretinal atrophy, hyperpigmented mottling and optic disc hypoplasia.

lesions, but the three infants had unilateral ocular findings involving the macula. Focal pigment mottling was observed in the macular region in all three children, (Fig. 1) and a well defined macular chorioretinal atrophy was detected in one infant [1▪▪].

In February 2016, the same group described the ocular abnormalities in 10 infants who had been diagnosed clinically with ZIKV-related microcephaly. Seven (70.0%) mothers reported symptoms during pregnancy (arthralgia, malaise and rash); of these, six (85.7%) mothers reported having symptoms during the first trimester. The mothers did not report ocular symptoms such as conjunctivitis during pregnancy, and their ocular examination did not show ophthalmologic abnormalities. Ocular findings included macular pigment mottling and/or chorioretinal atrophy in 15 (75.0%) eyes. Optic nerve abnormalities such as optic disc hypoplasia, pallor and/or increased cup-to-disc ratio were reported in nine (45.0%) eyes. All infants had normal anterior segment structures; one infant had horizontal nystagmus. No patient had inflammatory signs such as uveitis or vasculitis [3].

In addition to the studies in Recife, a study conducted at the same time in Salvador, Brazil, evaluated the ocular findings in infants with microcephaly associated with presumed intrauterine ZIKV infection. Twenty-three (79.3%) of 29 mothers reported suspected ZIKV infection signs and symptoms (rash, fever, arthralgia, headache, itch and malaise) during pregnancy, 18 (62.0%) in the first trimester, four in the second trimester and one in the third trimester. All mothers denied signs or symptoms of conjunctivitis and all had normal findings on ocular examination. Ophthalmologic abnormalities were present in 17 (29.3%) eyes of 10 children (34.5%), and bilateral findings were seen in seven of 10 patients presenting with ocular lesions. The most common lesions were focal retinal pigment mottling and chorioretinal atrophy in 11 (64.7%) of 17 eyes with abnormalities, followed by optic nerve abnormalities (optic disc hypoplasia and severe optic disc cupping) in eight (47.1%) eyes (Fig. 2). One infant had anterior segment findings, that is bilateral iris coloboma and lens subluxation, in one eye. No infants had vasculitis or active uveitis [2▪▪]. This study entitled 'Ocular Findings in Infants with Microcephaly Associated with Presumed Zika Virus Congenital Infection in Salvador, Brazil' was the first to measure the incidence of ocular findings in a population of microcephaly patients with presumed Zika infection during pregnancy.

In May 2016, to explore the risk factors associated with ophthalmic findings in neonates, Ventura *et al.* [6] used the IgM antibody-capture ELISA to test for ZIKV in the cerebrospinal fluid of infants with microcephaly born to infected mothers. All 24 tested infants had ZIKV infections, out of whom 63.6% had ophthalmic findings. Ocular involvement is observed more in babies with mothers reporting infective symptoms in the first trimester and a smaller cephalic diameter at birth. In parallel, de Paula Freitas *et al.* [2▪▪], in the case series cited previously involving 29 infants, most mothers (18 mothers) also experienced clinical signs and symptoms during the first trimester.

In a subsequent study, Miranda *et al.* [23] suggested the expansion of the spectrum of ocular findings in the CZS after describing retinal vascular changes in three patients with microcephaly and a

presumed Zika infection. All six eyes had pigmentary maculopathy ranging from mild to pronounced. In four eyes, well delineated macular chorioretinal atrophy with a hyperpigmented ring developed. Three eyes had vascular tortuosity and two eyes had pronounced early termination of the retinal vasculature on photographic evaluation. Two eyes had a washed-out peripheral retina with a hypolucent spot. One eye had scattered subretinal haemorrhages external to the macula. Finally, one eye had peripheral pigmentary changes and clustered atrophic lesions resembling grouped congenital albinotic spots (polar bear tracks).

In November 2016, de Paula Freitas *et al.* [4▪] also reported for the first time the case of a child with CZS and congenital glaucoma. The infant had severe microcephaly, bilateral lower extremity arthrogryposis, ventriculomegaly, diffuse parenchymal calcifications, dysgenesis of the corpus callosum and a simplified gyral pattern. A fundus examination showed chorioretinal atrophy and focal pigmented mottling bilaterally and optic nerve hypoplasia in the right eye. Serum obtained at birth was positive for anti-ZIKV immunoglobulin M antibodies and negative for anti-DFV virus immunoglobulin M antibodies and other congenital infections. Real-time reverse-transcriptase PCR testing of newborn blood did not detect ZIKV RNA. During an outpatient visit 95 days after birth, the right eye was enlarged with persistent tearing, irritability and severe photophobia. The horizontal corneal diameter in that eye was increased compared with the left eye (13 mm in the right eye vs. 10 mm in the left eye) and increased intraocular pressure (IOP) (30 mmHg in the right eye vs. 14 mmHg in the left eye). The right cornea was edematous with an unremarkable angle (Fig. 2). The left eye had posterior embryotoxon; gonioscopy showed a white membrane in the peripheral iris extending through the Schwalbe line. The angle was open without inflammation. The infant underwent a trabeculectomy of the right eye 114 days after birth, which resulted in normalization of the IOP (15 mmHg) and decreased corneal oedema, tearing and photophobia. Real-time reverse-transcriptase PCR did not detect ZIKV-specific RNA in the aqueous humour and vitreous obtained intraoperatively. In April 2017, Yepes *et al.* [5] reported five new patients with congenital glaucoma related to the CZS.

Subsequently, Ventura *et al.* [24] evaluated babies with a presumed diagnosis of CZS based on optical coherence tomography (OCT) to gain a better understanding of the retinal layers affected by the vertical transmission of the virus. Of the eight babies studied, seven tested positive for ZIKV IgM antibodies using the IgM antibody capture ELISA (MAC-ELISA) method to test the cerebrospinal fluid. Eleven (69%) of the 16 eyes of the eight infants had retinal alterations and OCT imaging was performed in nine (82%) of them. The main OCT findings in the affected eyes included discontinuation of the ellipsoid zone and hyperreflectivity underlying the retinal pigment epithelium in nine (100%) eyes, retinal thinning in eight (89%) eyes, choroidal thinning in seven (78%) eyes and colobomatous-like excavation involving the neurosensory retina, retinal pigment epithelium and choroid in four (44%) eyes [24] (Fig. 3).

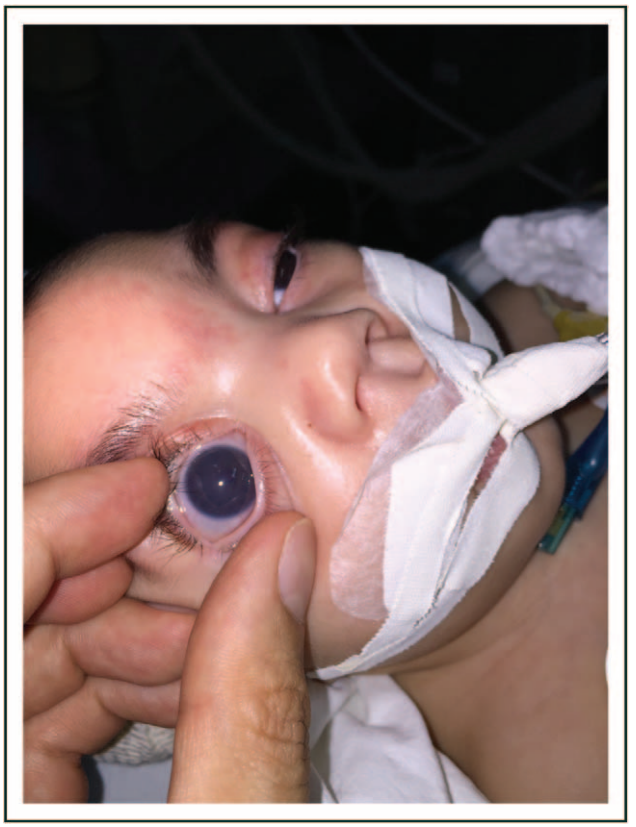

FIGURE 3. Severe corneal oedema (blue eye) associated with an enlarged right eye (buphthalmos) typically associated with congenital glaucoma in an infant presenting with the CZS.

The first report of a baby with a presumed diagnosis of the CZS who was born without microcephaly and presented with ocular findings defined a crucial hallmark in the history of the CZS [20]. Previously, only babies with microcephaly and suspicion of the CZS were evaluated further and underwent ocular screening. This criterion is now obsolete after Ventura *et al.* reported this case.

The spread of CZS cases to other regions of Brazil became evident when De Oliveira Dias *et al.* [25] reported for the first time development of the CZS in two infants born in São Paulo State, where almost

4000 cases of the ZIKV acute infection were reported from January to November 2016. Although outbreaks in the states of Rio de Janeiro and São Paulo in southeastern Brazil had been reported previously, no cases of ocular involvement outside northeastern Brazil had been published previously. Both infants showed IgG positivity for the ZIKV and negative serology for toxoplasmosis, herpes simplex virus (HSV), syphilis and HIV. IgG circulating antibodies were present for rubella and cytomegalovirus (CMV). The mothers' ocular examinations were normal. To date, those are the first published autochthonous cases of children with the CZS and ocular findings infected and born in southeastern Brazil, which confirms the spread of the infection throughout the country. The confirmation of the ZIKV infection was based on serology for the ZIKV. The fundus findings of both infants were similar to a lesion pattern already described [1▪▪,2▪▪,3,4▪,5].

It is important to emphasize that for all these studies, other congenital infections such as toxoplasmosis, rubella, CMV, HSV, syphilis, HIV were ruled out by serology.

CONCLUSION

All infants with CZS should be enrolled in multidisciplinary, early-intervention services provided by a team experienced in early childhood development, including visual impairment with additional disabilities or delays, and followed at regular intervals. The children should have scheduled ophthalmic evaluations every 3 months as part of continuing care and will undergo a formal evaluation at 1 year of age with standardized assessment of visual function. We propose performing ophthalmologic evaluations not only of newborns with clinical and/or laboratory evidence of ZIKV infection but also of apparently healthy children whose mothers presented with laboratory evidence of the ZIKV infection during pregnancy.

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Conflicts of interest

The authors have not received grant support or research funding for this paper. They declare that there are no competing interests.

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