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Expanded Spectrum of Congenital Ocular Findings in Microcephaly with Presumed Zika Infection

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Purpose: To describe the ocular findings of 3 cases of suspected congenital Zika viral infection with microcephaly and maculopathy.

Design: Retrospective, consecutive case series.

Participants: Three male infants born in northern Brazil whose mothers demonstrated a viral syndrome during the first trimester and who subsequently were born with microcephaly.

Methods: Observational report of macular findings.

Main Outcome Measures: Continued observation.

Results: Three male infants were born with microcephaly to mothers who had a viral syndrome during the first trimester of gestation in an area that subsequently has demonstrated epidemic Zika infection, a flavivirus related to Dengue. Ocular examination was performed. All 6 eyes demonstrated a pigmentary maculopathy ranging from mild to pronounced. In 4 eyes, well-delineated macular chorioretinal atrophy with a hyperpigmented ring developed. Three eyes demonstrated vascular tortuosity and 2 eyes demonstrated a pronounced early termination of the retinal vasculature on photographic evaluation. Two eyes demonstrated a washed out peripheral retina with a hypolucent spot. One eye had scattered subretinal hemorrhages external to the macula. Finally, 1 eye demonstrated peripheral pigmentary changes and clustered atrophic lesions resembling grouped congenital albinotic spots (polar bear tracks).

Conclusions: Zika virus has been linked to microcephaly in children of mothers with a viral syndrome during the first trimester of pregnancy. Ocular findings previously described a pigmentary retinopathy and atrophy that now can be expanded to include torpedo maculopathy, vascular changes, and hemorrhagic retinopathy. Ophthalmologic screening guidelines need to be defined to determine which children would benefit from newborn screening in affected regions. *Ophthalmology 2016;■:1–7 © 2016 by the American Academy of Ophthalmology.*

The southern region of the Americas, Brazil in particular, has experienced an outbreak of Zika viral infection transmitted by the *Aedes* species of mosquito. Originally identified in Uganda in 1947,[1] Zika is a flavivirus related to Dengue and yellow fevers. In the past year, it has been associated with an outbreak of microcephaly and Guillain-Barré syndrome in Brazil. Three cases of maculopathy along with microcephaly were recently reported in children with suspected congenital Zika infection.[2] The authors followed up with a larger case series of 10 patients with microcephaly who were noted to have 17 affected eyes, with findings including focal pigment mottling, chorioretinal atrophy, optic nerve abnormalities, iris coloboma, and lens subluxation.[3] We report herein 3 cases of chorioretinal maculopathy and expanded pigmentary and hemorrhagic retinopathy in children with microcephaly and suspected congenital Zika infection.

Methods

Three consecutive cases of congenital microcephaly with chorioretinal atrophy and pigmentary maculopathy are described in infants of mothers who had viral syndrome findings of fever, rash, and asthenia consistent with Dengue fever in an endemic area during the first trimester of pregnancy. The infants underwent a full ophthalmologic examination with wide-angle fundus photography (RetCam Shuttle; Clarity Medical Systems, Pleasanton, CA) as part of microcephaly evaluation. The institutional review board (Stanford University, Palo Alto, CA) ruled that approval was not needed for this study.

Results

Patient 1

A male infant with microcephaly (head circumference, 28 cm; Fig 1A) was born after 39 weeks of gestation (birth weight, 2750 g) in November 2015. The mother was in Pernambuco (Northeastern Brazil) during pregnancy, where she was diagnosed with Dengue fever, without serologic testing. The antenatal test results were negative for human immunodeficiency virus (HIV) and Venereal Disease Research Laboratory (VDRL) test.

Cranial computed tomography demonstrated lissencephaly, diffuse parenchymal calcifications, and ventriculomegaly. Fundus examination demonstrated focal chorioretinal atrophy in the periphery of both eyes as well as 2 well-delineated chorioretinal atrophic

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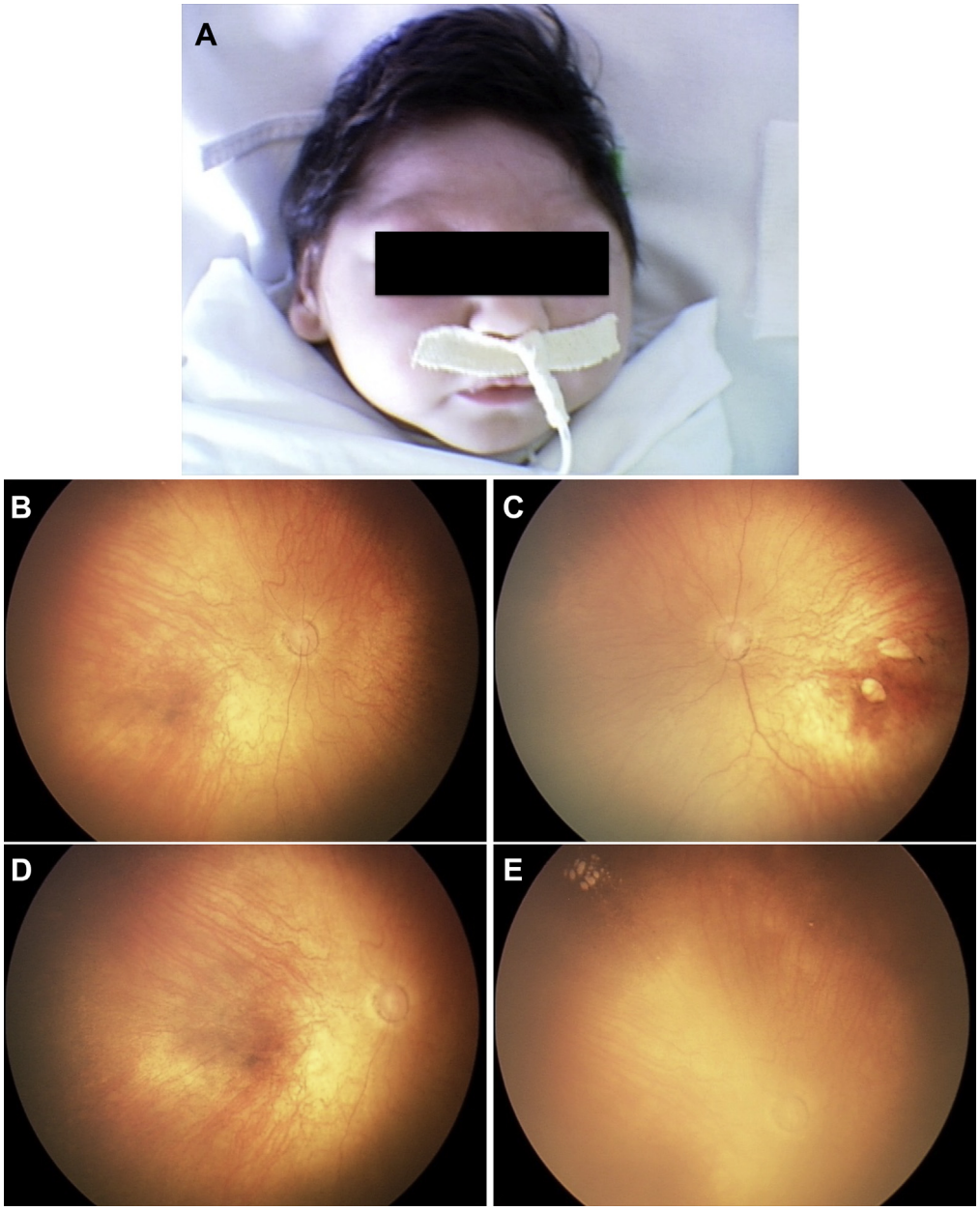

Figure 1. **A**, Characteristic features of microcephaly. **B**, **C**, Fundus photographs showing bilateral mild pigmentary retinopathy affecting the macula of each eye: (**B**) vascular tortuosity in the right fundus and (**C**) 2 well-delineated ovoid lesions with temporal pointed tails in the fovea and just superior in the left eye. **D**, Fundus photograph of the right eye demonstrating early termination of the retinal vessels. **E**, Fundus photograph of the left eye demonstrating polar bear tracks in the superonasal area. **F**, Fundus photograph showing vaso-obliteration of the retinal vasculature temporally in the right eye (left of the dotted line) with the underlying choroid clearly visible. **F**, **G**, **H**, **I**, Fundus photographs of both the right and left eyes showing a washed-out or mottled retina with faint hypolucent spots that resemble peau d'orange in the peripheral retina (arrows).

lesions with temporal pointed tails, 1 ovoid lesion in the fovea, and a more torpedo-shaped lesion just in the superotemporal region in the left eye. Both eyes had mild spicular hyperpigmentation scattered throughout the macula (Fig 1B, C). The temporal retinal vasculature appeared to be absent, with extensive vascular tortuosity in the right eye (Fig 1B [left of the dotted line], D, F). There were grouped congenital albinotic spots in the superonasal region of the left eye (Fig 1E), as well as vascular tortuosity (Fig 1C, E). There was a washed-out appearance of the peripheral retina in the inferior and nasal regions in the right eye and in the temporal region in the left eye, with faint hypolucent spots (Fig 1F–I, arrows).

Patient 2

A male infant with microcephaly (head circumference, 26 cm; Fig 2A) was born prematurely after 34 weeks of gestation (birth weight, 1495 g) in November 2015. The mother was in Pernambuco during the 13th week of pregnancy, where she had a viral illness with fever, rash, and asthenia, requiring hospitalization for 4 days. The antenatal test results were negative for VDRL, HIV, toxoplasmosis, and cytomegalovirus immunoglobulin M antibody. The cytomegalovirus immunoglobulin G antibody concentration was 204.8 IU/ml.

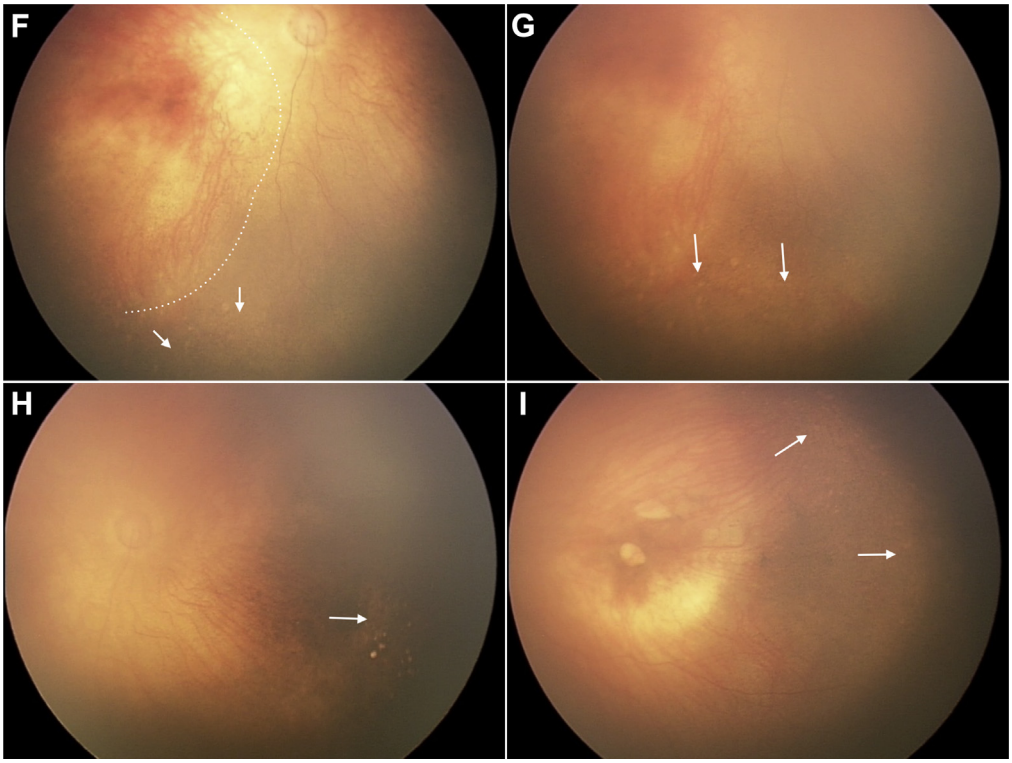

Figure 1. (*continued*).

Cranial computed tomography demonstrated lissencephaly. Fundus examination demonstrated a well-delineated ovoid lesion pointing at the fovea, with a frayed tail pointed anteriorly in the right eye (Fig 2B), bilateral clustered hyperpigmented spots in a paramacular location, vascular tortuosity, and subretinal hemorrhages external to the arcades in the left eye (Fig 2C). In the periphery, there was abnormal termination of the vessels superiorly in the left eye (Fig 2D, E, long arrows), with a focal vascular dilation (Fig 2E, short arrow).

Patient 3

A male infant with microcephaly (head circumference, 26 cm; Fig 3A) was born after 37 weeks of gestation (birth weight, 1185 g) in December 2015. The mother was in Ceará (Northeastern Brazil) during the first trimester of pregnancy, where she was diagnosed with Dengue fever, based on the finding of fever. The antenatal test results were negative for VDRL, HIV, toxoplasmosis, and cytomegalovirus immunoglobulin M antibody.

Cranial computed tomography demonstrated lissencephaly. Dilated fundus examination demonstrated clustered areas of hyperpigmentation scattered throughout the macula. Both eyes demonstrated focal, well-delineated macular lesions of chorioretinal atrophy measuring 1 disc area in the right eye (Fig 3B), with a bilobed appearance, and measuring 2 disc areas pointing to the fovea temporally in the macula, with a rounded anterior temporal border (Fig 3C) and a faded point aimed temporally (Fig 3D).

Discussion

Zika virus is a flavivirus transmitted by the mosquito species *Aedes aegypti* and *Aedes albopictus*, which are also vectors of Dengue fever and chikungunya.[1] Infection causes a self-limited Dengue-like illness characterized by exanthema, low-grade fever, conjunctivitis, and arthralgia, although it may be asymptomatic in some cases. Increased rates of Guillain-Barré syndrome have been observed during outbreaks.[4] The detection of the Zika viral infection genome by reverse-transcriptase polymerase chain reaction analysis in the amniotic fluid of 2 women whose fetuses were diagnosed with microcephaly and in the blood of a newborn with microcephaly and other abnormalities led the European Centre for Disease Prevention and Control to suspect an association between the increased prevalence of microcephaly in Brazil and intrauterine Zika infection.[5] After an outbreak of Zika virus in French Polynesia in 2014 and 2015, a significant increase in the prevalence of brain lesions, fetal cerebral malformations, and brainstem dysfunction abnormalities in fetuses and newborns was reported.[6] This supports the notion of an association between microcephaly (and related central nervous system abnormalities) and maternal Zika viral infection in the first or second trimester of gestation.[6] In January 2016, a pigmentary maculopathy was described in the macula of 3 infants with both microcephaly and mothers with presumptive Zika viral infection during the first trimester in endemic areas of Brazil.[2] One of these cases was noted to have focal chorioretinal atrophy involving the macula.[2] Subsequently, the same group reported a larger case series of 10 patients with microcephaly who were noted to have 17 affected eyes, with findings including focal pigment mottling, chorioretinal atrophy, optic nerve abnormalities, iris coloboma, and lens subluxation.[2] In neither case series was microcephaly

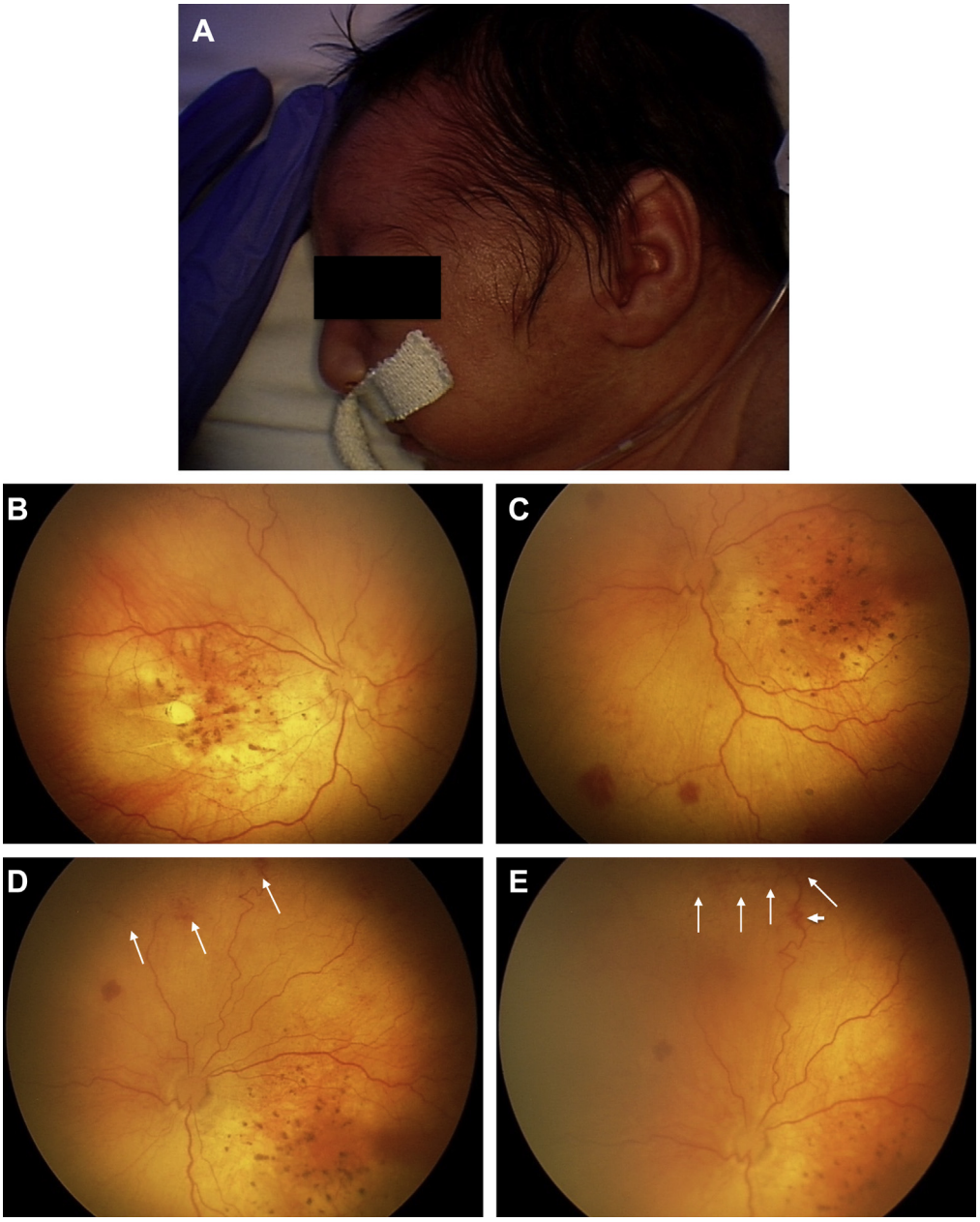

Figure 2. **A**, Characteristic features of microcephaly. **B**, **C**, Fundus photographs showing bilateral clustered bone-spicule pigmentary clumping in a paramacular location, (**B**) a well-delineated ovoid lesion pointing at the fovea, with a frayed tail pointed anteriorly in the right eye, and (**C**) bilateral vascular tortuosity (worse in the left eye) with subretinal blot hemorrhages inferiorly and superiorly in the left eye. **D**, **E**, Fundus photographs showing abnormal termination of the vasculature in the left eye (long arrows), with (**E**) focal vascular dilation (short arrow).

alone considered as a potential causative agent in the development of the ocular findings.[2,3]

Microcephaly is defined as an occipitofrontal head circumference of 32 cm or less at birth, or 2 standard deviations less than average for the age and gender.[7] Other signs and symptoms may be present, such as seizures, spastic quadriplegia, dysphagia, and delayed cognitive and motor development.[7] Several conditions can cause microcephaly, including genetic syndromes; metabolic disorders; hypoxic-ischemic insult; vascular changes; exposure to drugs, alcohol, and chemical substances during pregnancy; severe gestational malnutrition; and infections in the antenatal, perinatal, and postnatal periods.[7,8] According to the Live Birth Information System (sistema de informações de nascidos vivos [SINASC]) (national information system on live births), 1248 cases of microcephaly were reported in Brazil in 2015 (through the end of November), corresponding to a prevalence of 99.7 cases per 100 000 live births.[6] In 2000 and 2010, the prevalence was 5.5 and 5.7 cases per 100 000 live births, respectively, representing a 20-fold increase in 5 years,[6] which is unlikely to represent a new genetic predisposition. Microcephaly has been associated

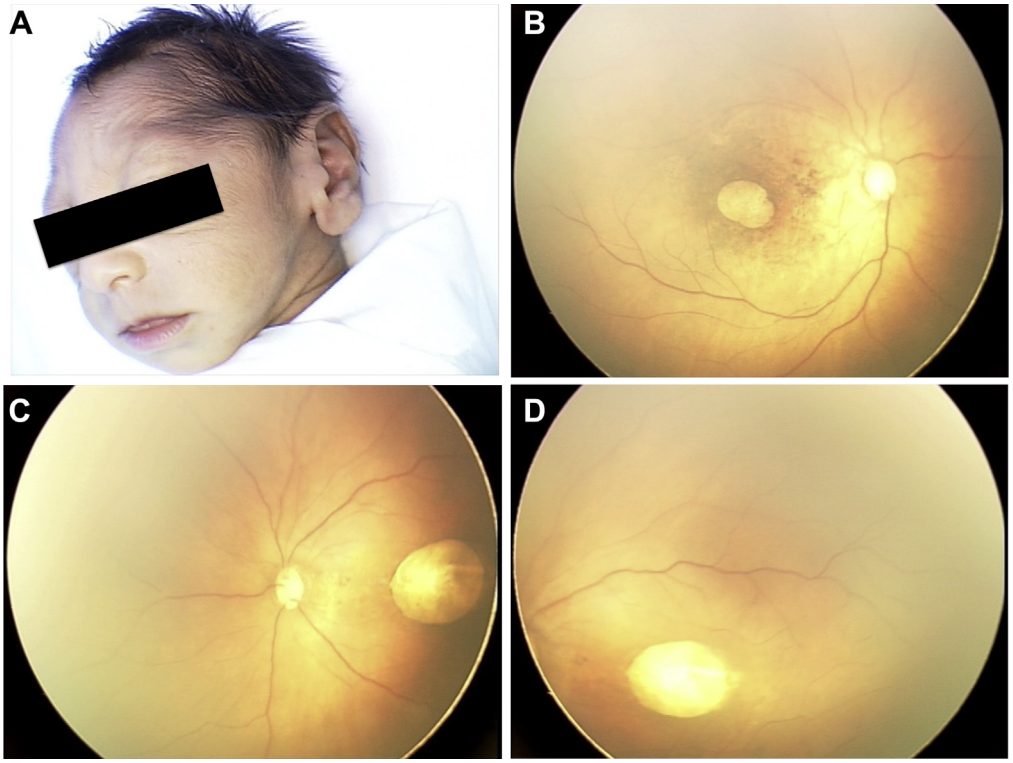

Figure 3. **A**, Characteristic features of microcephaly. **B**, **C**, **D**, Fundus photographs showing bilateral clustered bone-spicule pigmentary deposits in a paramacular location, with (**B**) bilobed, well-delineated, punched-out chorioretinal atrophy with a hyperpigmented rim and an ovoid punched-out chorioretinal lesion with a sharp point directed toward the fovea, with a faint tail emanating from a rounded edge directed temporally, (**C**) enclosed by a hyperpigmented rim and (**D**) a faded point aimed temporally.

independently with the following: chorioretinal atrophy,[8,9] a retinitis pigmentosa clinical picture with spicules and pale nerve,[10] diffuse lacunar chorioretinopathy,[10] optic atrophy,[10–12] optic hypoplasia,[13] optic nerve coloboma,[10,11] nystagmus,[10,11,13] cataracts,[10,11,13] retinal dysplasia,[10] micro-ophthalmia,[10,11,13] microcornea,[9,11] falciform folds,[10] esotropia,[9] hyperopia,[9] persistent fetal vasculature,[13] retinal pigmentary changes,[9–12] chorioretinal degeneration and atrophy,[9–13] and vascular attenuation.[11] Importantly, absence of the retinal vasculature has been described in association with microcephaly, lymphedema, and chorioretinal dysplasia, as well as optic nerve aplasia.[13] The retinal vasculature was absent temporally in patient 1 (Fig 1F).

The current case series reports 4 eyes with chorioretinal atrophy involving the macula, 3 of which resemble torpedo maculopathy (right and left eyes of patient 2 and the left eye of patient 3).[14,15] Shields et al[15] summarized the various presentations that occur, including the appearance of a frayed tail pointed anteriorly, as well as hyperpigmentation on the temporal margin similar to that seen in Figure 2B, right eye. In Figure 3B, we see a classic torpedo lesion with a sharp point directed toward the fovea and a rounded temporal edge. In patient 1, we saw multiple well-delineated lesions in the macula (Fig 1C). The differential in this patient includes torpedo maculopathy, congenital hypertrophy of the retinal pigment epithelium, Gardner's syndrome, as well as viral damage.[16] More uncommonly, multiple lesions have been reported with the enhanced S-cone syndrome and are similar in appearance to torpedo lesions, resembling the superotemporal lesion in Figure 1C.[17] The foveal lesions in Figures 1C and 3B are more similar in appearance to that described by Ventura et al[2] in 1 infant with a suspected congenital Zika infection. Bilateral lesions have been described previously on 1 occasion,[18] similar to those found in patient 2. Torpedo maculopathy has never been reported as part of the microcephaly spectrum, and the lacunar chorioretinal dysplasia in sporadic and hereditary microcephaly tends to be more diffuse and less delineated.[9–13]

Dengue fever is the most common mosquito-borne viral disease worldwide.[19] Ocular complications are rare but have been reported at a growing frequency over the past decade.[20] On fundus examination, findings may be discreet, such as mild hemorrhage in the macular region associated with increased vascular permeability.[20] However, visual acuity may be reduced significantly (usually 1 week after the onset of fever) because of immune-mediated maculopathy.[21] On optical coherence tomography, 3 patterns may be observed: diffuse retinal thickening, cystoid macular edema, and photoreceptor layer abnormalities.[20] Up to 10% of hospitalized patients with Dengue fever will demonstrate maculopathy.[22] The fact that the Dengue and Zika viruses belong to the same genus suggests the latter is capable of inducing ocular changes as well. In patient 2, we noted mild hemorrhagic retinopathy similar to what can be seen in Dengue fever

(Fig 2C–E). In the 3 patients described in this report, retinal changes were atypical and unlike those observed for other congenital infections, such as toxoplasmosis, rubella, herpes, cytomegalovirus, syphilis, and HIV. In addition, the 3 patients had similar obstetric antecedents (Dengue-like illness acquired in the same gestational period and in the same endemic region).

Both patients 1 and 2 demonstrated abnormal vascular development (Fig 1D, F, left of the dotted line, and Fig 2D, E, long arrows), and patient 2 also demonstrated vascular tortuosity (Fig 2E, short arrow). This is most likely related to presumptive Zika infection in patient 1 because of term birth. In patient 2, a theoretic argument could be made for concurrent retinopathy of prematurity (ROP). This was a postterm infant (34 weeks), although birth weight was 1495 g and there was significant concurrent illness, a risk factor for development of ROP[23]; vascular tortuosity also was present in both eyes. Nevertheless, ROP did not develop in either eye, leaving whether or not concurrent of ROP exists open for debate, particularly because both abnormal termination and absence of the vasculature developed in patient 1, as well as vascular tortuosity in 1 eye in the absence of prematurity and ROP.

To summarize, congenital sporadic and heritable microcephaly is associated with a pigmentary retinopathy resembling retinitis pigmentosa and also can be associated with more diffuse lacunar chorioretinal dysplasia and even the absence of the retina vasculature. Additionally, the most common mosquito-borne flavivirus, Dengue, is associated with maculopathy in up to 10% of hospitalized patients. Brazil has experienced an epidemic outbreak of Zika virus, a flavivirus related to Dengue virus that has been linked to a dramatic increase in the incidence of congenital microcephaly in infants of women with Dengue-like symptoms during the first trimester of pregnancy. Clinical examination of the infants' eyes demonstrated a spectrum of pigmentary retinopathy, chorioretinal atrophy, torpedo and torpedo-like maculopathy, vascular absence, and hemorrhagic retinopathy. Microcephaly has not been reported as a complication of Dengue infection; however, in the absence of definitive isolation of Zika viral infection in the affected patients, it is not possible to exclude Dengue from the differential diagnosis in these infants. It seems likely that maternal infection with Zika virus induces a spectrum of microcephaly-associated chorioretinal disease. On November 17, 2015, the Brazilian Ministry of Health issued a note about the management of patients with suspected Zika viral infection.[23] The note included a description of frequently observed changes in the central nervous system: microcalcifications, hypoplasia of the cerebellar vernix, and (less commonly) lissencephaly, compatible with fetal ultrasound scan findings during gestation.[24] The note also recommended examining the fundus of the eye as a routine procedure.[24]

This report expands on the previously reported pigmentary retinopathy and isolated chorioretinal atrophy in children with microcephaly and presumed congenital Zika viral infection[2] to include pigmentary and hemorrhagic retinopathy in conjunction with vascular tortuosity, vascular absence, and early abnormal vascular termination in infants with microcephaly and with mothers with prodromal Dengue-like symptoms in the first trimester, as well as a torpedo maculopathy. Infection with Zika virus during pregnancy can cause a condition potentially leading to brain and skull abnormalities and atypical retinal lesions. It remains unknown whether Zika viral infection causes a direct effect with ophthalmologic findings or an indirect effect after induction of microcephaly. In support of the link between Zika infection and microcephaly, Zika viral infection recently was demonstrated to infect human neural progenitor cells,[25] and it has been isolated in fetal brain tissue in 2 infants with microcephaly who died and whose mothers had fever and rash in the first trimester.[26,27] Until further notice, health professionals in regions endemic for Zika infection are advised to submit all newborns with microcephaly to retinal examination. The procedure can contribute significantly to our understanding of the condition. Furthermore, there is no reason to suspect that the retinopathy is isolated to infants after infection, and any infants with suspected infection and ocular symptoms should undergo ophthalmologic evaluation. We encourage all infants with microcephaly born to infected mothers or in endemic regions to undergo an ophthalmologic evaluation shortly after birth to identify potentially treatable disease.

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Abbreviations and Acronyms:
HIV = human immunodeficiency virus; **ROP** = retinopathy of prematurity; **VDRL** = Venereal Disease Research Laboratory.

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