First Locally Acquired Congenital Zika Syndrome Case in the United States: Neonatal Clinical Manifestations

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ABSTRACT: In the spring of 2017, a full-term infant with microcephaly was delivered in South Florida. During first trimester, the mother presented with fever, nausea, and vomiting. She reported no foreign travel for herself or her partner. The infant's neurologic, ophthalmologic, neuroradiologic, and audiologic findings were highly suggestive of congenital Zika syndrome (CZS), confirmed by IgM antibodies and plaque reduction neutralization test. New observations, including peripheral temporal retinal avascularity and peripapillary retinal nerve fiber layer thinning, are presented from this first known case of non-travel-associated CZS in the United States.

[*Ophthalmic Surg Lasers Imaging Retina.* **2018;49:e93-e98.**]

INTRODUCTION

Congenital Zika syndrome (CZS) is characterized by a broad spectrum of neurological defects, ophthalmological findings, skeletal malformations, and hearing deficits.[1] According to the Pan American Health Organization, as of November 16, 2017, 27 countries and territories in the Americas have reported confirmed CZS cases, including the United States.[2]

Through November 2017, 98 liveborn infants with Zika-associated birth defects were identified in the continental United States.[3] Nevertheless, there is a lack of data describing the mode of virus transmission (travel-associated, local mosquito-borne transmission, or sexual transmission). Until now, the only case of CZS reported in the United States has been travel-associated, and the first was from Miami, Florida.[4] Herein, we report the first locally transmitted case of CZS in the United States and contribute new

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Originally submitted November 27, 2017. Revision received November 27, 2017. Accepted for publication February 27, 2018.

This work was supported by the Florida Department of Health Biomedical Research Program, Zika Research Initiative Awards 7ZK08 (Bandstra), 7ZK14 (Saigal), 7ZK20 (Younis), and 7ZK26 (Gonzalez).

The authors report no relevant financial disclosures.

Drs. Ventura and Bandstra contributed equally to this manuscript.

* The authors would like to thank the University of Miami Pediatric Zika Research Consortium Investigators, the names of whom are listed at the end of this study. Special thanks to the participating mothers and their infants. They are also grateful for the contributions of the collaborators and staff at the Florida and Miami-Dade County Departments of Health (Danielle Stanek, DVM; Lea A. Heberlein-Larson, BS, MPH; Lillian Rivera, RN, MSN, PhD; Reynald Jean, MD, MPH, MSN, AGPCNP-BC; and Marie Ketty Etienne, RN, MPH), the Centers for Disease Prevention and Control, the Bascom Palmer Eye Institute, the Batchelor Children's Research Institute, the Florida Early Steps Program, the Mailman Center for Child Development, the Jackson Health Systems, and the Healthy Start Coalition of Miami-Dade County.

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doi: 10.3928/23258160-20180907-14

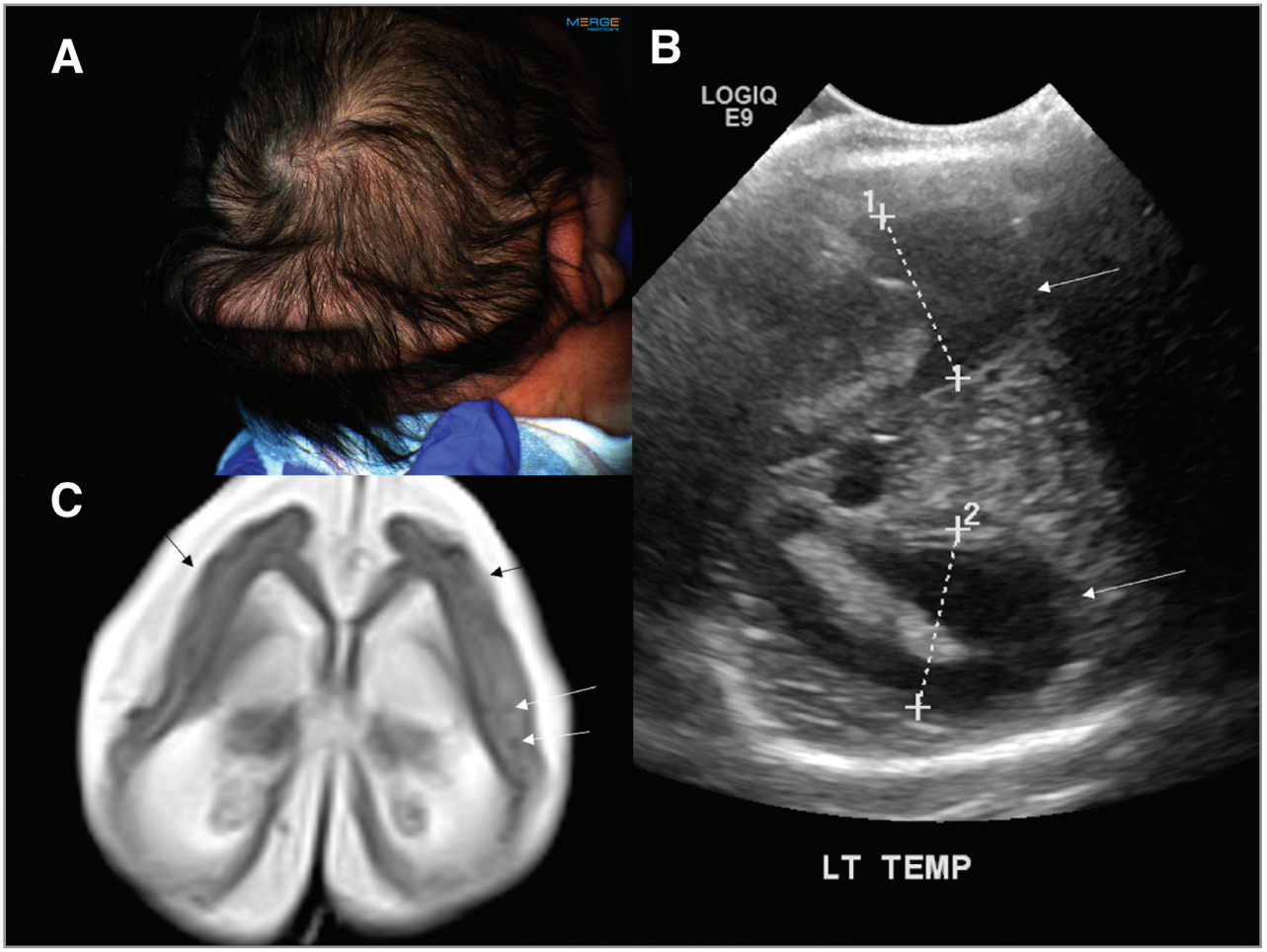

Figure 1. Clinical features of full-term infant with congenital Zika syndrome. (A) Posterior view of excessive scalp folds. (B) Cranial ultrasound using a mastoid window demonstrating moderate ventriculomegaly (white arrows). (C) Axial T2-weighted magnetic resonance imaging of the brain demonstrating marked prominence of the extra axial spaces and ventriculomegaly consistent with severe atrophy of the brain and a simplified gyral pattern (short black arrows). Punctate hypointensities consistent with calcifications are also seen in the periventricular white matter (long white arrows).

ocular findings to the previously identified clinical spectrum of CZS.

CASE REPORT

A 1-day-old female infant born to a 22-year-old African-American mother at 39 weeks gestational age (GA) via cesarean section in Miami was referred for ophthalmologic consultation with a high suspicion of CZS.

During the first trimester, the mother presented to the emergency department with a history of fever, nausea, and vomiting. Ultrasonography confirmed an intrauterine pregnancy at 8 weeks GA. She reported no foreign travel for herself and her partner and denied prenatal alcohol, tobacco, and drug use or having any other symptoms such as arthralgia, myalgia, rash, and / or conjunctivitis during pregnancy. Fetal ultrasonography at 22 weeks GA was normal. Follow-up ultrasound at 37 weeks GA disclosed an estimated fetal weight of 2,063 grams, less than tenth percentile; head circumference and biparietal diameter less than third percentile; and bilateral ventriculomegaly, suspected absence of the corpus callosum, and frontal lobe flattening.

Physical examination at birth revealed severe microcephaly with partially collapsed skull [head circumference: 27.5 cm (< first percentile); birth weight: 2,410 grams (third percentile); birth length: 45 cm (third percentile) (Figure 1A). The only other anomaly was bilateral postaxial polydactyly type 2B (familial). There was no other family history of congenital anomalies, developmental delay, or hearing loss.

The newborn was admitted to the neonatal intensive care unit for microcephaly evaluation. Toxoplasmosis, rubella, cytomegalovirus, HIV, and syphilis were ruled out. Real-time transcription polymerase chain reaction assays (Trioplex real-time polymerase chain reaction [RT-PCR] assay) for Zika, dengue, and chikungunya viruses were negative in maternal serum and urine, and infant serum, urine, and cerebrospinal fluid (CSF).

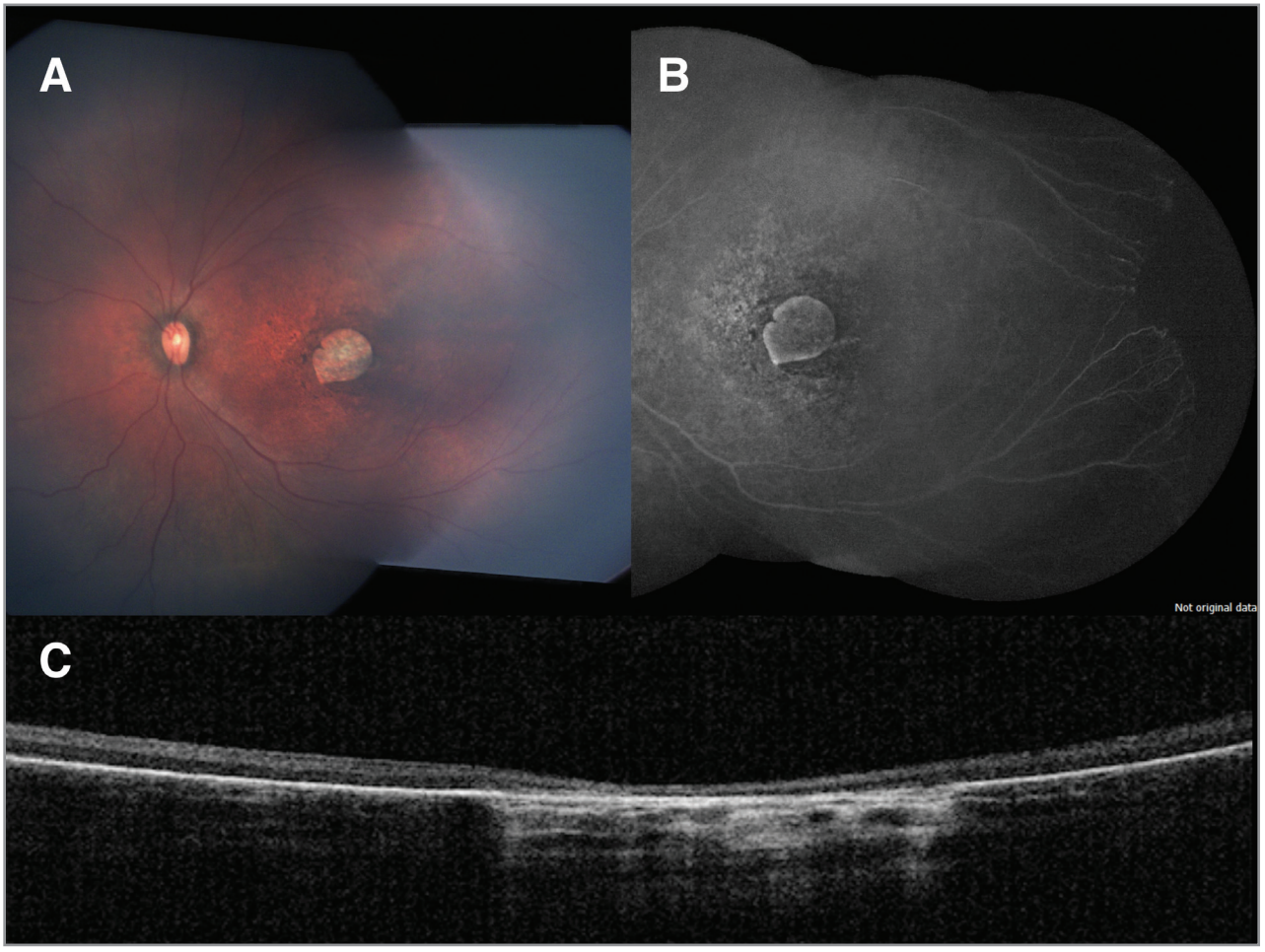

Figure 2. Ophthalmological findings in a full-term infant with congenital Zika syndrome. (A) Fundus montage of the left eye (OS) demonstrating increased optic nerve cupping, focal pigmentary changes, and well-defined chorioretinal atrophy within the macular region. (B) Fluorescein angiography montage of the OS showing a window defect in the macular region and peripheral avascularity of the temporal retina. (C) Macular optical coherence tomography of the right eye revealing retinal and choroidal thinning with discontinuation of the ellipsoid zone.

However, immunoglobulin M (IgM) testing for Zika antibodies (Centers for Disease Control and Prevention [CDC] Zika IgM ELISA assay [MAC-ELISA]) was positive in maternal and infant sera and infant CSF. Serum plaque reduction neutralization test was positive for Zika in maternal and infant sera. Placental tissue was positive for Zika virus-NS5 gene RT-PCR.

Cranial ultrasonography with a poor acoustic window showed moderate ventriculomegaly (Figure 1B). Brain magnetic resonance imaging demonstrated severe brain abnormalities (Figure 1C).

Comprehensive ophthalmic examination revealed normal anterior segment structures and pupil reaction to light with no afferent pupillary defect bilaterally. Funduscopy showed bilateral increased cup-to-disc ratio, pigment mottling, and sharply demarcated chorioretinal atrophy within the macular regions (Figure 2A). Axial lengths were approximately 16.5 mm in the right eye and 16.8 mm in the left. Fluorescein angiography disclosed a window defect in the macular region and peripheral avascularity of the temporal retina bilaterally (Figure 2B). Using spectral-domain optical coherence tomography (SD-OCT) (iVue; Optovue, Fremont, CA), average retinal nerve fiber layer (RNFL) thickness was 63 µm on the right and 59 µm on the left. Macular OCT images showed neurosensory retinal thinning with discontinuation of the ellipsoid zone, choroidal thinning, and hyperreflectivity underlying the retinal pigment epithelium (Figure 2C).

Comprehensive audiology examination showed possible mild hearing loss in the mid-frequency region bilaterally (Table).

The infant was discharged on postnatal day 11 and was scheduled for ambulatory care and multidisciplinary subspecialty follow-up.

DISCUSSION

The CDC characterizes CZS by five rare or unique features: severe microcephaly with partially col-

TABLE

Auditory Brainstem Response Results

Right Ear Threshold (db nHL)		Left Ear Threshold (db nHL)	
Click	70, 50, 30, 25, 20	Click	70, 50, 45, 40, 35, 30
1,000 Hz	50, 40, 35, 30	1,000 Hz	50, 45, 40
4,000 Hz	40, 35, 30, 25	4,000 Hz	60, 40, 35, 20, 25, 20

Note: Minimum response for wave V is in bold type. Correction factors have not been applied.

The first row lists the intensities evaluated for click stimuli. The bolded value at 20 dB signifies the lowest intensity of click stimuli at which repeatable waveforms could be obtained. The lowest intensity for click stimuli was 20 dB for the right ear and 30 dB for the left ear. 1,000 Hz and 4,000 Hz tone bursts were also used to obtain some frequency-specific information. The 4,000 Hz tone burst was in good agreement with the click results with minimum levels of waveform replication at 30 dB for the right ear and 20 dB for the left ear. However, the 1,000 Hz tone burst results suggested mild mid-frequency hearing loss with thresholds recorded at 40 dB for the right ear and 45 dB for the left ear.

By virtue of the neurophysiological mechanism by which a response can be recorded, audiologists generally consider 30 dB or less as the indicator of normal hearing sensitivity for the stimulus. Minimum response levels of 40 dB to 45 dB are sufficiently outside of the normal range to suggest mild bilateral hearing loss in the mid-frequencies.

lapsed skull; thin cerebral cortices with subcortical calcifications; macular scarring and focal pigmentary retinal mottling; congenital contractures; and marked early hypertonia and symptoms of extrapyramidal involvement.[1] The neuroimaging findings of CZS detected in the present case such as severe microcephaly, subcortical calcifications, ventriculomegaly, and marked thinning of the corpus callosum reflecting severe central nervous system (CNS) damage have been reported previously.[1,5]

The observed chorioretinal scar and focal pigmentary changes as seen in the current case were first reported in 2016 by Ventura et al. in Brazilian infants and corroborated in cases from other South American countries.[6-10] In this CZS case, macular OCT showed evidence of severe retinal and choroidal destruction similar to previous reports.[10,11] Importantly, this is the first study of CZS to report results of RNFL thickness analysis quantifying diffuse bilateral RNFL thinning in the peripapillary region. According to Vajzovic et al., term babies have a RNFL thickness of approximately 170 µm at the parafoveal region.[12] Taking into consideration that the RNFL measurement was performed in a different region, the current infant's RNFL can still be considered significantly thin (63 µm right and 59 µm left). In addition, diffuse RNFL thinning has been similarly observed in patients with hereditary optic neuropathies such as Leber's hereditary optic neuropathy and dominant optic atrophy.[13,14] Therefore, we postulate that the observed RNFL thinning may correlate with the severe CNS and visual system damage caused by infection with Zika virus (ZIKV).[1,15]

Another interesting ocular finding identified was the bilateral peripheral retinal avascularity, which can be key to understanding the pathophysiology of the ocular manifestations in CZS. Mladinich et al. recently demonstrated that ZIKV infects persistently the primary human brain microvascular endothelial cells to serve as cellular reservoirs for ZIKV replication and enable viral spread across the blood-brain barrier into neuronal compartments.[16] They hypothesized that the endothelial cells from other sites may also favor ZIKV to cross testicular, placental, and retinal tissues in affected patients. Clinically, these retinal vascular findings serve as an alert to possible progression such as neovascularization, traction, and/or complex retinal detachment as seen in retinopathy of prematurity, incontinentia pigmenti, and familial exudative vitreoretinopathy.[17-19] Thus, close follow-up with comprehensive ophthalmological examination of the peripheral retina is vital.

The demonstrated early hearing sensitivity loss in the mid-frequencies on auditory brainstem response test raises concern for late-onset hearing loss requiring follow-up.[20]

To our knowledge, this is the first case of non-travel-associated, locally transmitted congenital Zika infection in the continental United States. The identification of this sentinel CZS case should heighten national and global awareness of ZIKV's reach. The current case emphasizes the importance of early Zika screening of pregnant women and their partners and multidisciplinary assessments and interventions for affected infants. This report also substantiates the urgent need for more effective mosquito-vector control measures and innovative vaccine and drug research to prevent and treat this potentially devastating infection.

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