Association of Zika Virus Exposure in Utero with Ocular Phenotypes in a Group of Newborns in Puerto Rico

Leticia Gely-Rojas MD*; Raúl Pérez MD†; Lourdes García-Fragoso MD‡; Inés García-García, MD‡

Objective: After the outbreak in January 2016, researchers in Brazil reported the first cases of ophthalmic abnormalities in infants with microcephaly and presumed Zika virus (ZIKV) intrauterine infection. Screening for ocular lesions in all newborns exposed to ZIKV prenatally has been emphasized because of a chorioretinal macular scar found in a number normocephalic patient exposed to ZIKV.

Methods: A retrospective review of the medical records of infants born to mothers found to be ZIKV-positive during their pregnancies (January 2016–July 2017) was performed. We included all newborns and infants admitted to the NICU and/or receiving ambulatory care at the high-risk clinics at the University Pediatric Hospital, San Juan, Puerto Rico. The creation of this database was approved by the IRB of the University of Puerto Rico, Medical Sciences Campus.

Results: Records from 234 newborns born to Zika-positive mothers were identified. The ophthalmic evaluations of 95 patients were available. Sixty-three of them had normal findings (66%). Twelve of the 95 patients had microcephaly (12.6% of the cohort). Of the microcephalic group, half had normal ophthalmological findings. Of the normocephalic group (83/95), almost 31% had ocular findings: a small optic nerve in 3%, a double-ring sign in 10%, macular stippling in 8%, mottling in 4%, an oval optic nerve in 2%, a tilted nerve in 1%, and blunted foveal reflex in 1%.

Conclusion: We report herein ZIKV-associated ophthalmologic findings, similar to those published, in 34% of the infants with suspected/confirmed ZIKV fetal exposure. These data underline the importance of ocular examination in patients with suspected congenital Zika but without other findings on physical exam. [*P R Health Sci J 2018;37(Special Issue):S77-S80*]

Key words: Macular stippling, Double-ring sign, Microcephaly, Normocephalic

After the outbreak in January 2016, researchers in Brazil reported the first cases of ophthalmic abnormalities in infants with microcephaly and presumed Zika virus (ZIKV) intrauterine infection. Ventura et al. published findings of macular pigment mottling and foveal reflex loss detected unilaterally in 3 cases, with 1 showing well-delineated macular atrophy (1). Ventura and her team later reported on 10 microcephalic children with similar presentations of chorioretinal atrophy and optic nerve alteration (2), while in their February 2016 article, de Paula Freitas et al. reported on a group of 10 (out of 29) infants from Salvador, Bahia, and Brazil, all of whom were suffering from ZIKV-related microcephaly. The ocular lesions observed by the latter team included focal pigment clumping, chorioretinal atrophy, optic nerve changes, bilateral iris coloboma, and lens subluxation (3). Further, Miranda et al.'s August 2016 study observed vascular changes and hemorrhagic retinopathy in 3 microcephalic infants (boys), all evidencing maculopathy (4); beings how the 3 boys were all microcephalic, it was conjectured that microcephaly might be a causative agent in (or barring that, a risk factor for) the development of this kind of ophthalmic abnormality (1,3,5). In June 2016, Ventura et al. emphasized the importance of screening all newborns exposed to ZIKV prenatally for ocular lesions because of the previous detection of chorioretinal scarring in the macular regions of patients exposed to ZIKV but without microcephaly (6).

The Zika virus infection was first identified in Puerto Rico in December 2015, and the outbreak that occurred prompted health care workers and investigators to attempt to

*Neonatal-Perinatal Medicine Resident, Neonatology Section, Department of Pediatrics, University of Puerto Rico Medical Sciences Campus, San Juan, PR; †Professor, Department of Ophthalmology, University of Puerto Rico Medical Sciences Campus, San Juan, PR; ‡Professor, Neonatology Section, Department of Pediatrics, University of Puerto Rico Medical Sciences Campus, San Juan, PR

The author/s has/have no conflict/s of interest to disclose.

Address correspondence to: Inés García-García MD, UPR School of Medicine, Department of Pediatrics, Neonatology Section, PO Box 365067, San Juan, PR 00936-5067. Email: ines.garcia@upr.edu

characterize the clinical manifestations and laboratory findings of intrauterine-exposed fetuses and develop guidelines for their management. From January 2016 to July 2017, there have been 3,887 pregnant women with ZIKV-positive tests in Puerto Rico, with 49% (1,917) of them being symptomatic and 51% (1,970) being asymptomatic (7). Of the babies resulting from these pregnancies, 44 have been reported to have congenital anomalies, with or without microcephaly (7). As do the cerebral and cerebellar cortices, the neural retina develops into a layered array of different neuronal types. The formation of this highly structured tissue is one of the most intensely studied issues of developmental neurobiology (8). The extent of ocular involvement in this population is not well understood, which argues for the continued examination of its members.

Methods

A retrospective review of the medical records of infants born to mothers found to have ZIKV during their pregnancies (January 2016 to July 2017) was performed. Mothers with RT-PCR-positive or IgM-positive serum were consider to be Zika positive. We included all newborns and infants admitted to the Neonatal Intensive Care Unit and/or receiving ambulatory care at the high-risk clinics at the University Pediatric Hospital, San Juan, Puerto Rico. Patients with urine that was positive for cytomegalovirus (CMV) or who were TORCH IgM positive were excluded. We collected demographic and clinical data, including symptoms and laboratory findings during the first 10 days of life. The creation of this database was approved by the Institutional Review Board (IRB) of the University of Puerto Rico, Medical Sciences Campus.

Results

A total of 234 newborns from mothers who were ZIKV positive during their pregnancies were identified. The average gestational age was 38 weeks (range: 29 to 41 weeks), weight, 3.05 kg (range: 1.2 kg to 4.2 kg), and head circumference, 32.8 cm (range: 27 cm to 38 cm). No female or male predominance was seen in the newborns. A total of 95 medical records (40 percent of the infants with intrauterine ZIKV exposure) with included ophthalmologic evaluations (Diagram 1) were identified, of which 66% had normal findings. Abnormal findings were seen in 32 of the patients evaluated, which findings included double ring sign (Figure 1) in 8% of the patients, macular stippling in 8%, intraretinal hemorrhage in 6%, small optic nerve (Figure 1) in 5%, distal peripheral perivascular hemorrhage in 2%, and mottling (Figure 2) in 3%. Other findings noted were vertically oval optic nerve (2%) (Figure 3), grayish pigments (1%), tilted nerve (1%), stage 1 retinopathy (2%), and blunted foveal reflex (1%) (Figure 4).

Of the 95 patients who underwent an ophthalmological evaluation, 12 had microcephaly. Of these, half had abnormal ophthalmological findings (described in Table 1). Of the normocephalic group (83/95), almost 31% had the ocular findings described in Table 1. In 1 individual of the 8% who presented with macular clumps/stippling, the clumps were within an oval fuzzy perimacular lesion. The lesion regressed within 6 weeks, leaving no visible retinal pigment epithelial changes.

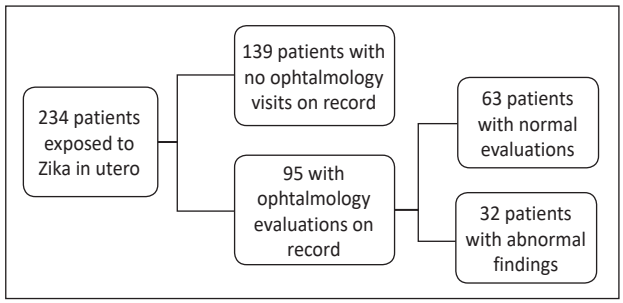

Diagram 1.

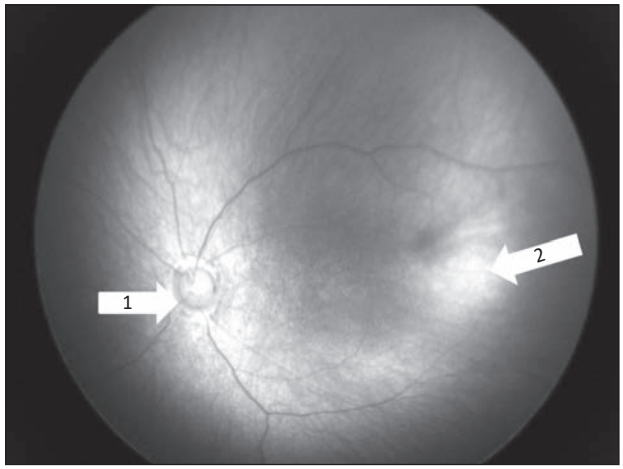

Figure 1. Left eye. Arrow 1 is pointing at a small optic nerve head with a "double ring" sign. Arrow 2 is pointing at a washed out retinal area within the temporal arcades.

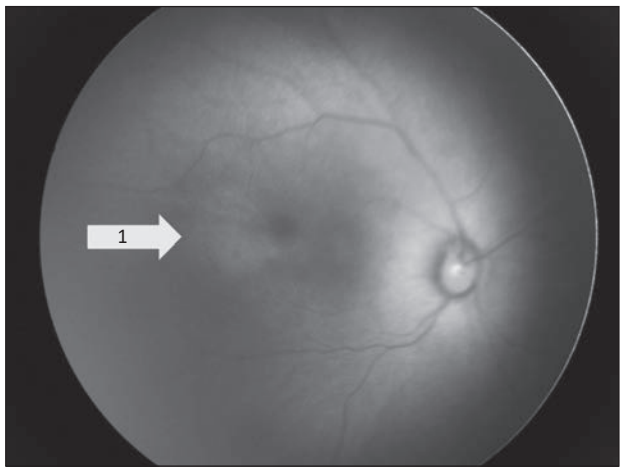

Figure 2. Right eye. Arrow 1. Irregular light washed out area (mottling) of the retina, lying within the macular area and the superior temporal, extending to where a fovea with foveal reflex is expected to develop.

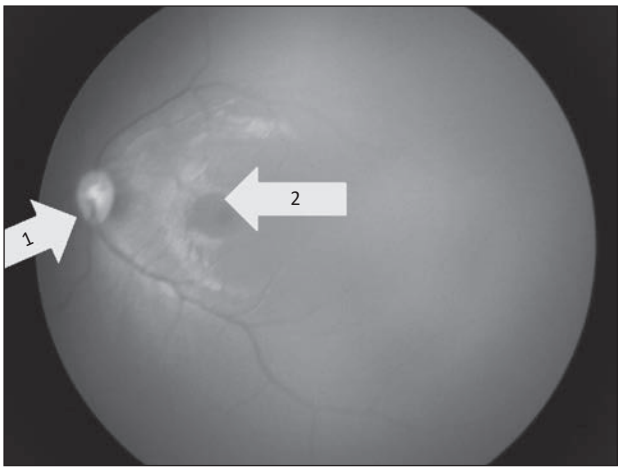

Figure 3. Left eye. Wide-angle image: vertically oval cupped, optic nerve head with unusual vascular architecture (arrow 1). Perifoveal reflex seen (arrow 2).

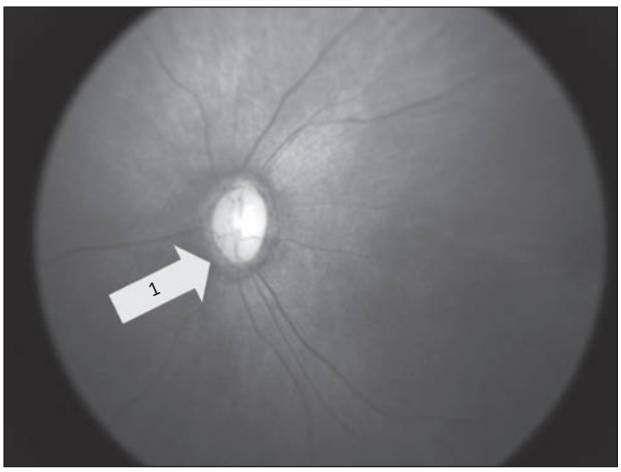

Figure 4. Left eye. Magnified image: Arrow 1 is pointing at a vertically oval cupped optic nerve head with unusual vascular architecture and a pigmented double ring. Perifoveal reflex not seen.

Table 1.

Ocular finding	Microcephalic (N = 12)	Normocephalic (N = 83)
Double Ring Sign	0% (0)	11% (9)
Small Optic Nerve	25% (3)	4% (3)
Macular Stippling	8% (1)	8% (7)
Mottling	0% (0)	4% (3)
Retinopathy of Prematurity Stage 1, Zone III	17% (2)	0% (0)
Oval Optic Nerve	0% (0)	2% (2)
Tilted Nerve	0% (0)	1% (1)
Blunted Foveal Reflex	0% (0)	1% (1)

Discussion

As of today, we still do not have a clear explanation of how ZIKV exposure affects the fetus or a clear understanding of the extent of the congenital Zika syndrome (CZS) spectrum. Currently, multiple studies have described the neurological and ocular findings seen in children in Brazil with CZS. To our knowledge there are no reports of ocular findings in children in Puerto Rico exposed prenatally to ZIKV. After reviewing the collected records, we described the most significant findings in newborns born from ZIKV-positive (during pregnancy) mothers in Puerto Rico. These findings should help other investigators compare what has been found in other countries and have a better idea of what the CZS spectrum entails.

We have seen major neurological findings in some of the exposed newborns, especially in those exposed early in pregnancy. We focused on newborns that had been exposed to ZIKA in utero and found that many of them had worrisome ophthalmological findings, though they were free of microcephaly and other signs. It is concerning that a number of infants are not being evaluated promptly because of the general lack of clinical manifestations; the dearth of effective and prompt evaluation may lead to detrimental effects in the visual development of the aforesaid infants.

Viral type, genetic susceptibility, and environmental factors could explain the absence of gross macular lesions in this group of patients (9, 10). The association of the particular signs of or of a cluster of signs of ZIKV exposure should help in the detection of subtler lifelong retinal involvement (11). The most frequently affected retinal structures or tissues seem to be those of the optic nerve head or papilla, the macular area, and the choroidal vessels (as revealed by the attendant loss of pigment).

One of the limitations of our study is that the sample was obtained from 1 care center in a tertiary institution, which may not represent the general population of pregnant mothers in Puerto Rico who are positive for ZIKV. Furthermore, only 40% of the patients who had been exposed to ZIKV had ophthalmologic evaluations available for review. Another limitation of our study is that our sample population included premature babies. No historical controls are available for this population at this time, which itself highlights the need for further research in this area. The main strength of our study is that we screened both normocephalic and microcephalic patients exposed to ZIKV in utero and obtained important results in terms of the normocephalic population that was studied. As previously emphasized by Ventura in June 2016, ocular findings might be underdiagnosed if microcephaly continues to be an inclusion criterion in the screening of this group of infants (6). She also pointed out findings in a case report of a patient without microcephaly but with a circular hypopigmented lesion superior to the optic nerve on the fundus of the left eye (12). As previously described, around 40% of our patients had ophthalmological findings. Of the patients without microcephaly, 31% had ocular findings, most commonly double-ring sign and macular stippling.

In conclusion, we report here the ophthalmologic findings of 95 infants with ZIKV intrauterine exposure, of which around 40% had abnormal ocular exams. The patients had normal anterior segment structures and important macular and optic nerve abnormalities.

This data underlines the importance of ocular examinations for patients with suspected congenital Zika but without other findings. Because of the unknown sequelae of congenital Zika, it is of public health importance to designate funds for this evaluation and for the future follow-up of these patients.

Resumen

Objetivo: Después de la epidemia del 2016, los investigadores en Brasil reportaron los primeros casos de anomalías oftalmológicas en infantes con microcefalia e infección intrauterina por el virus de Zika. El cernimiento de lesiones oculares ha sido enfatizado para todos los recién nacidos expuestos a Zika prenatalmente ya que se encontraron lesiones en el área macular corioretinal en pacientes normo-cefálicos. Métodos: Se llevó a cabo una revisión retrospectiva de expedientes médicos de la estadía hospitalaria de los infantes nacidos de madres Zika positivo durante su embarazo de enero 2016 a julio 2017 que recibieron servicios en las clínicas de alto riesgo del Hospital Pediátrico Universitario en San Juan, Puerto Rico. La creación de esta base de datos fue aprobada por la Junta de Revisión Institucional, de la Universidad de Puerto Rico, Recinto de Ciencias Médicas. Resultados: Se identificaron 234 infantes. Evaluaciones oftalmológicas estuvieron disponibles en 95 pacientes. Sesenta y tres de ellos tenían hallazgos normales (66%). Doce pacientes (13%) tenían microcefalia (12/95). De estos, la mitad tenía hallazgos oftalmológicos normales. Los hallazgos oftalmológicos en los pacientes normo-cefálicos (N = 83) incluyeron: nervio óptico pequeño en 3%, signo de doble anillo en 10%, macula punteada en 8%, apariencia moteada en 4%, nervio óptico ovalado en 2%, nervio inclinado en 1% y reflejo foveal suavizado en 1%. Conclusión: Nosotros reportamos hallazgos oftalmológicos asociados con el virus de Zika similares a los antes publicados en 34% de los infantes con sospecha o confirmación de exposición a Zika fetal que tuvieron evaluación oftalmológica. Esta data reitera la importancia del examen oftalmológico en los pacientes con sospecha de exposición a Zika intrauterino sin ningún otro hallazgo físico.

References

1. Ventura CV, Maia M, Bravo-Filho V, Góis AL, Belfort R Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. Lancet 2016;387:228.
2. Ventura CV, Maia M, Ventura BV, Linden VV, Araújo EB, Ramos RC, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. Arq Bras Oftalmol 2016;79:1–3.
3. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, Sacramento GA, Ko AI, Maia M, Belfort R Jr. Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil. JAMA Ophthalmol 2016;134:529–535.
4. Parke DW, Almeida DR, Albini TA, Ventura CV, Berrocal AM, Mittra RA. Serologically Confirmed Zika-Related Unilateral Acute Maculopathy in an Adult. Ophthalmology 2016;123:2432–2433.
5. Ventura CV, Maia M, Travassos SB, Martins TT, Patriota F, Nunes ME, et al. Risk Factors Associated With the Ophthalmoscopic Findings Identified in Infants With Presumed Zika Virus Congenital Infection. JAMA Ophthalmol 2016;134:912–918.
6. Ventura CV, Maia M, Dias N, Ventura LO, Belfort R Jr. Zika: neurological and ocular findings in infant without microcephaly. Lancet 2016;387:2502.
7. Departamento de Salud de Puerto Rico. Informe Semanal de Enfermedades Arbovirales (ArboV) Departamento de Salud de Puerto Rico, Semana 27 (2 al 8 de julio de 2017). Available at: Url: http://www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Informes%20Arbovirales/Reporte%20ArboV%20semana%2027-2017.pdf. Accessed July 20, 2017.
8. Gilbert SF. Development of the Vertebrate Eye. In: Developmental Biology. 6th ed. Sunderland, MA: Sinauer Associates; 2000:359. Available at: Url: http://www.ncbi.nlm.nih.gov/books/NBK10024/. Accessed July 21,2017.
9. Spiess K, Gonzalez I. Accidental Finding of Retinal Pigment Epithelium Abnormality. Ophthalmol Retina 2017;1:256.
10. Santos A, Traboulsi EI. Congenital Abnormalities of the Retinal Pigment Epithelium. In: Marmor MF, Wolfenberger TJ, eds. The Retinal Pigment Epithelium. New York, NY: Oxford University Press, 1998:307–318.
11. Ashina H, Li XQ, Olsen EM, Skovgaard AM, Larsen M, Munch IC. Association of Maternal Smoking During Pregnancy and Birth Weight With Retinal Nerve Fiber Layer Thickness in Children Aged 11 or 12 Years: The Copenhagen Child Cohort 2000 Eye Study. JAMA Ophthalmol 2017;135:331–337.
12. Ventura CV, Fernandez MP, Gonzalez IA, Rivera-Hernandez DM, Lopez-Alberola R, Peinado M, et al. First travel-associated congenital Zika Syndrome in the US: Ocular and neurological findings in the absence of microcephaly. Ophthalmic Surg Lasers Imaging Retina 2016;47:952–955.