Congenital Zika Syndrome in Puerto Rico, Beyond Microcephaly, A Multiorgan Approach

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Objective: Zika virus (ZIKV) infection was identified in Puerto Rico on December 2015, and the outbreak encouraged us to characterize clinical manifestations and laboratory findings of intrauterine exposed infants.

Methods: Retrospective medical record review of infants born to mothers with confirmed ZIKV infection during pregnancy was performed from January 2016-June 2017. We included patients admitted to UPH Neonatal Intensive Care Unit or referred for follow-up at UPH High Risk Clinics. The database was approved by the University of Puerto Rico, Medical Sciences Campus, IRB.

Results: 191 infants born to ZIKV positive mothers during pregnancy were identified. Normal head sonogram was found in 93% of the normo-cephalic infants. Ocular findings were reported in 50% of the patients with microcephaly and 31% of the normo-cephalics. Fifteen newborns (7.8%) presented with microcephaly, of which 73% showed calcifications in head sonogram, and had severe anomalies on brain MRI. Auditory brainstem response test was performed on all newborns, 80% were within normal limits.

Conclusion: Among the group of infants born to mothers with Zika positive test 4% had microcephaly. Of concern to us is the fact that 31% of normo-cephalic infants had ocular manifestations and 7% of them had findings on head sonogram. While microcephaly is the severest form of Congenital Zika Syndrome, ocular manifestations might characterize the spectrum of disease. These findings reiterate the importance of detailed neonatal evaluations of exposed infants. [*P R Health Sci J 2018;37(Special Issue):S73-S76*]

Key words: Lissencephaly, Calcifications, Double-ring sign, Macular stippling

Zika virus (ZIKV) is a mosquito-transmitted flavivirus primarily transmitted by Aedes aegypti mosquitoes (1, 2). Ae. Aegypti mosquito is found throughout much of the Region of the Americas, Caribbean, and including parts of the United States, and also transmit dengue and chikungunya viruses (3).

Vertical transmission of ZIKV infection can occur through intrauterine transmission resulting in a congenital infection and through intrapartum transmission from a viremic mother to her newborn (4, 5). Due to reports in Brazil, the association of ZIKV with microcephaly led the World Health Organization to declare a public health emergency in the beginning of 2016 (6).

ZIKV infection was first identified in Puerto Rico on December 2015, and the outbreak encouraged us to characterize clinical manifestations and laboratory findings of intrauterine exposed fetuses and develop guidelines for their management. As of June 2, 2017, there are 3,703 pregnant women with a ZIKV positive test in Puerto Rico since 2016 with 51% (1,902) of them being symptomatic and 49% (1,801) asymptomatic (7).

A Congenital Zika Syndrome (CZS) has been defined with five distinctive features that focus on brain development abnormalities (including microcephaly and brain calcifications), cranial morphology anomalies, retinal manifestations, defects on extremities including congenital contractures and hypertonia, and neurological sequelae and neurological prognosis (8).

Because of the increased number of exposed infants, prompt and coordinated responses were needed to characterize clinical manifestations and laboratory findings and to develop appropriate care guidelines for intrauterine exposed fetuses admitted to the neonatal intensive care unit (NICU) following

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the recommendations of the Centers for Disease Control and Prevention (CDC). The purpose of this study is to characterize neonates born to ZIKV positive mothers in Puerto Rico and provide information for the development of adequate protocols to follow up these patients.

Methods

A retrospective medical record review was performed from infants born to mothers with a ZIKV positive test during pregnancy from January 2016 to June 2017. Mothers with RT-PCR positive or IgM positive in serum where consider as Zika positive. We included patients admitted to University Pediatric Hospital (UPH) Neonatal Intensive Care Unit and/or referred for follow-up to the UPH High Risk Clinics. The UPH at San Juan, Puerto Rico, is a level IV Neonatal Intensive Care Unit (NICU), which provides medical care to high-risk neonates island-wide. Data collected included demographic information and clinical data, including neonatal symptoms and laboratory results during the first 10 days of life, if available. Also radiographic data such as head sonograms, head computer tomographic (CT) image scan or brain magnetic resonance image were collected. Microcephaly was defined as head circumference below the 3rd percentile for gestational age and sex. Auditory brainstem response (ABR) results and ophthalmology evaluations by direct visualization or RetCam results were collected as well. Descriptive statistical analysis was performed using Excel, Microsoft Office 2013. This database was approved by the University of Puerto Rico, Medical Sciences Campus, Institutional Review Board.

Results

During the 18 months period, we identified 191 infants with potential intrauterine ZIKV exposure. Most newborns were born by vaginal delivery (63%). The mean gestational age was 38 weeks (range 29-41 weeks), of which 9% (N 17) were born with less than 34 weeks. The mean birth weight 3.05 kg (range 1.2 kg to 4.2 kg). The mean head circumference was 32.7cm (range 27 cm to 38 cm). One infant with no physical findings of intrauterine infection, developed a spontaneous pneumothorax at day 2 of life.

Ophthalmologic evaluation was available in 86 patients (45%) at time of record review. Of the normo-cephalic group (74/86), thirty-one percent had ocular findings (Table 1). Normal head sonogram was found in 93% of the normo-cephalic patients (Table 2). No CT scan or brain MRI available at the time of review for the normo-cephalic group with findings in head sonogram.

Fifteen newborns presented with microcephaly. All newborns with microcephaly required admission to the NICU for further evaluations and management. The mothers of newborns with microcephaly had a ZIKV test positive during the first trimester in 80% of the cases, the other 20% had a positive test in the second trimester. The mean gestational age was 39 weeks (range 37 weeks to 41 weeks). The mean birth weight was 2.84 kg (range 2 kg to 4 kg) and the mean head circumference 29 cm (range 27cm to 31 cm). C-section delivery was required in 20%, most of them due to previous C-section Basic metabolic panel and CBC performed upon admission were reported within normal limits. All newborns had negative laboratory results for other perinatal infections associated with congenital anomalies such as; Toxoplasmosis, Syphilis, Rubella, and Herpes. Only one newborn tested positive for Cytomegalovirus IgG, prenatally acquired infection. One newborn (7%) had an initial neonatal screen test suggestive of hypothyroidism but two repeated samples were normal. Half of the microcephalic newborns had pertinent ocular findings (Table 1).

Table 1. Ocular findings

Ocular finding	Microcephalic percentage (N)	Normocephalic percentage (N)
Double Ring Sign	0% (0)	11% (9)
Optic Nerve Anomalies*	25% (3)	7% (6)
Retinal anomalies**	25%(3)	12%(10)
Blunted Foveal Reflex	0% (0)	1% (1)

*Optic nerve: small, oval or tilted, **Retina: mottling, macular stippling, retinopathy

Head sonogram showed presence of calcifications in 73% of the microcephalic group, 20% of the calcifications found on basal ganglia, 13% of the calcifications on choroid plexus, and other calcification areas varied from frontal, subcortical, temporal, and periventricular areas. Brain MRI was done in 13/15 patients with microcephaly showing 33% prevalence of dysgenesis of corpus callosum and one patient (6.6%) had dysgenesis of the brainstem. It is also relevant to mention that 54% of them presented with lissencephaly. Only one infant presented with seizures prior to discharge and only one required gastrostomy placement due to inadequate sucking. ABR test was performed in all newborns and 80% of them were within normal limits.

Table 2. Normo-cephalic group head sonogram findings.

Head sonogram finding	Percentage (N)
Normal	93% (178)
Arachnoid cyst	3% (5)
Mineralizing Vasculopathy	1.1% (2)
Dysgenesis of Corpus Callosum	0.6% (1)
Frontal Echogenic Focus	0.6% (1)
Increase Echogenicity on left cerebellar hemisphere	0.6% (1)

Discussion

We have described findings compatible with the CZS among 4% of the infants born to mothers with confirmed ZIKV infection in our cohort. These infants demonstrated significant CNS abnormalities and related structures. At time of evaluation

none showed contractures but close monitoring is needed due to high risk of developing them as per the definition of CZS states. In addition, one third (31%) of the normo-cephalic infants born to ZIKV positive mothers, had ocular manifestations. While microcephaly is the severest form of CZS, ocular manifestations might characterize the spectrum of disease.

A multidisciplinary approach is needed in the evaluation of patients with possible congenital Zika syndrome due to the unknown full spectrum of the condition. The Centers for Disease Control and the American Academy of Pediatrics have established protocols for the follow-up of infants with intrauterine exposure to ZIKV. Infants born to mothers with laboratory evidence of ZIKV infection should receive a comprehensive physical examination, including precise measurement of head (occipitofrontal) circumference, length and weight, assessment of gestational age, and examination for neurologic abnormalities and dysmorphic features. For all infants with abnormal findings suggestive of CZS, an extensive evaluation is recommended. This evaluation should include a complete blood count, metabolic panel, liver function tests, a comprehensive examination by an ophthalmologist, ABR testing, and advanced neuroimaging. Infants with abnormal brain development can develop hypothalamic dysfunction and pituitary insufficiency, reason why thyroid screening is recommended (9).

An ophthalmologist evaluation is indicated during the first month of life on all suspected congenital ZIKV cases, due to possible ocular manifestations of the syndrome. Moshfeghi DM,et al. published an article describing the ophthalmologic findings in these infants (10). They described multiple anomalies including pigmentary retinopathy affecting the macula, vascular tortuosity in the fundus, well-delineated ovoid lesions with temporal pointed tails in the fovea, washed-out or mottled retina with faint hypolucent spots, among others (10). In our experience we found normo-cephalic patients with double ring-sign, hyper-pigmented halo around optic nerve, small optic nerve, macula stippling and pigmentation, and peripapillary aggregate molting. Most of these findings could represent risk for visual impairment in the future which prompt the need to closely follow up these patients. No longitudinal studies are available referring to the effects on visual acuity changes. Also there are no historical controls in our population to compare with uninfected patients, which gives a window for future research. This emphasizes the importance of ocular examination of patients with suspected congenital Zika without other clinical findings.

Like the cerebral and cerebellar cortices, the neural retina develops into a layered array of different neuronal types (11). It has been hypothesized that Zika Virus affects the development of these areas. The impact of congenital Zika infection in the development of the visual and the auditory systems is still uncertain and need further research in the field. Vision screening and eye examination are vital for the detection of conditions that distort or suppress the normal visual image, which may lead to inadequate school performance or, at worst, blindness in children. The tracking and management of these intrauterine Zika exposed infants must be integrated with the pediatric care to ensure ophthalmology evaluation to possibly reduce the incidence of loss of vision.

The extent of the neurological deficits due to CZS is not well understood. Many brain structural anomalies have been seen with CZS (9). As reported on the literature, we found on brain studies multiple intracranial calcifications, dysgenesis of corpus callosum and brainstem, and lissencephaly. These findings reiterate the importance of an adequate follow-up of this patient due to the high-risk of developing seizures, infantile spams and severe neurodevelopmental delay. We emphasize the importance of tracking and management of these intrauterine Zika exposed infants, and the integration of primary pediatric care with a multidisciplinary team.

Resumen

Objetivo: La infección por el virus de Zika fue identificado en Puerto Rico en 2015. Debido a la epidemia caracterizamos las manifestaciones clínicas y hallazgos en laboratorios en infantes expuestos intrauterinamente. Métodos: Se llevó a cabo una revisión retrospectiva de expedientes médicos de los infantes nacidos de madres confirmadas con infección con Zika durante el embarazo entre enero 2016 a junio 2017. Se incluyeron pacientes admitidos a la unidad de cuidado intensivo neonatal y/o referidos para seguimiento a las clínicas ambulatorias de alto riesgo en el Hospital Pediátrico Universitario. La creación de esta basa de datos fue aprobada por la Junta de Revisión Institucional. Resultados: Se identificaron 191 infantes. Sonogramas de cabeza demostraron hallazgos normales en 93% de los infantes normo-cefálicos. Se encontraron hallazgos oculares en 50% de los infantes con microcefalia y en 31% de los normo-cefálicos. Microcefalia fue evidente en 15 infantes, 73% presentaron calcificaciones cerebrales y anomalías cerebrales severas. La audiometría por potenciales evocados se encontró normal en el 80%. Conclusión: Entre el grupo de infantes nacidos de madre Zika positivo el 4% presentaron con microcefalia. Es de preocupación que el 31% de los infantes normo-cefálicos presentó con manifestaciones oculares y el 7% con hallazgos en sonograma de cabeza. Aunque la microcefalia es la forma más severa de Zika congénito, las manifestaciones oculares pueden representar el espectro de la enfermedad. Estos hallazgos reiteran la importancia de una evaluación detallada a todo infante expuesto.

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