First Autopsy of a Newborn with Congenital Zika Syndrome in Puerto Rico

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We report on the first autopsy performed on a neonate with congenital Zika syndrome in Puerto Rico. A term male was born to a mother with confirmed Zika virus infection; he had a prenatal diagnosis of microcephaly and multiple cerebral calcifications, among other anomalies, and a normal male karyotype (determined by amniocentesis). He required neonatal resuscitation at birth and died at 2 days of age. At autopsy, his head circumference was only 1.5 standard deviations below the mean, not fulfilling the criteria for microcephaly. He presented scissor legs, clenched and hyperflexed hands, and multiple contractures (arthrogryposis). The central nervous system findings were consistent with Zika encephalopathy: ventriculomegaly, lissencephaly, and severe encephalic degeneration with numerous dystrophic calcifications, among other findings. These anomalies were most likely secondary to congenital ZV infection. Although prenatally diagnosed with microcephaly, he did not fulfill the criteria after birth, which fact indicates the need for reassessment of the definition of microcephaly as it applies to patients exposed prenatally to the ZV. [*P R Health Sci J 2018;37(Special Issue):S81-S84*]

Key words: Microcephaly, Calcifications, Malformations, Contractures, Zika virus

The Zika virus (ZV) recently surged in a period spanning from 2015 to 2016, triggering outbreaks in Brazil as well as in other countries in North and South America and in the Caribbean, particularly in the US territory of Puerto Rico. Its effects on the fetus are of particular concern, as the virus in utero has been shown to be strongly neurotropic, targeting neural progenitor cells as well as neural cells at all stages of maturity (1).

Numerous cases of congenital Zika syndrome (CZS) have been reported in Brazil, with similar cases now emerging in Puerto Rico. This new syndrome involves a pattern of birth defects found in fetuses and infants exposed to the ZV in utero. These birth defects include, but are not limited to, microcephaly, decreased brain tissue and atrophy, abnormally formed or absent brain structures, hydrocephalus, congenital contractures, and ophthalmologic abnormalities (2). Specific differences have been described in the clinical manifestations seen in babies affected by the ZV versus the manifestations linked to other congenital infections (3). Calcifications within the gray matter–white matter junction (an unusual location for the calcifications that are seen in other congenital infections), for example, are particular to the ZV (4). Severe cortical malformations, ventriculomegaly, cerebellar hypoplasia, and abnormal hypodensity of the white matter are other distinctive characteristics (3).

For this reason Puerto Rico's Department of Health has focused on ZV prevention, especially during pregnancy. As of August 2017, there have been 3,923 pregnant women with laboratory confirmation of ZV infection in Puerto Rico. Of these, 1,927 (49%) were symptomatic and 1,996 (51%) were asymptomatic. Further, of the live births in Puerto Rico (from 2016 up till week 29 of 2017), 47 of the neonates were found to have the congenital syndrome associated with ZV infection (5). There has been a lack of autopsy cases of fetuses and/or newborns with the pattern of birth defects mentioned.

We present the findings of the first autopsy performed on a neonate born with CZS in Puerto Rico.

Case Report

A small-for-gestational-age neonate was born (delivered by cesarean section) at 39 weeks gestational age (wGA)

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to an 18-year-old mother (G1P0A0) with symptomatic, serologically confirmed (at 8 weeks, by RT-PCR) ZV infection; the mother was negative for dengue and chikungunya. Symptoms included rash and generalized arthralgia. The mother had a history of hypothyroidism treated with levothyroxine, was negative for HIV, hepatitis B, toxoplasmosis IGM and IGG, and cytomegalovirus IGM and IGG; VDRL was negative as well and she tested immune for rubella in her prenatal screening test. The patient had a normal alpha-fetoprotein level (her entire quad screen was negative). A prenatal sonographic evaluation at 30 weeks revealed a fetus with intrauterine growth restriction, microcephaly (>3 standard deviations below the mean), bilateral asymmetric ventriculomegaly, a decreased amount of cerebral parenchyma with a very thin cerebral cortex, and multiple cerebral calcifications in the cerebral cortex and periventricular areas. Other anomalies described included micrognathia, scissoring of the legs, and rocker bottom foot. Amniocentesis showed a normal male karyotype (46,XY). The mother was referred to the University District Hospital of Puerto Rico's high-risk clinics for her remaining prenatal care and childbirth.

At birth, the neonate required neonatal resuscitation and intubation. He presented micrognathia, multiple contractures of the joints (arthrogryposis), rocker bottom feet, clenched hands and scissor legs. He had a head circumference of 32.5cm, only 1.5 standard deviations below the mean, thus, not meeting the criteria for microcephaly. The head sonogram revealed severe asymmetric ventriculomegaly of the lateral ventricles (Figure 1) with associated compression and thinning of the cerebral cortex. The apparent absence of the septum pellucidum and corpus callosum was also revealed. Echocardiography disclosed a ventricular septal defect (VSD) and severe pulmonary hypertension. The patient remained critically ill and expired 2 days after his birth. A TORCH screen of the neonate was not performed nor were his ZV titers determined.

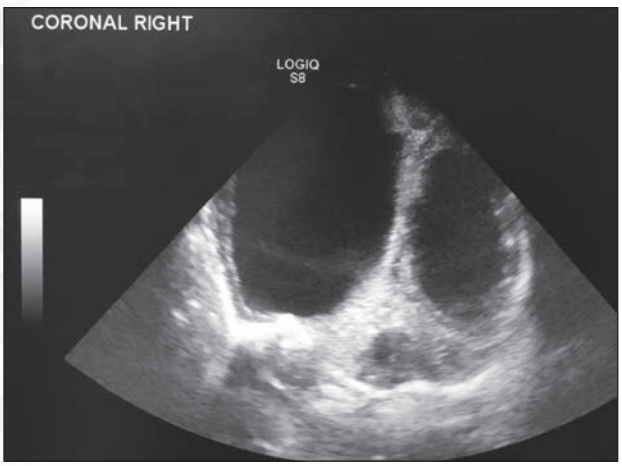

Figure 1. Head sonogram: right coronal view with evidence of severe dilatation of the lateral ventricles, more pronounced on the right.

The autopsy confirmed the multiple external anomalies previously mentioned (Figures 2 & 3). Body measurements and weights were below expected norms (Table 1). The heart presented a large perimembranous VSD, seen on echocardiography. On microscopy the lungs revealed acute pneumonia with hyaline membranes, focal hemorrhages, and hypertensive vascular changes. The brain weighed 150g after fixation, far below that expected (362g) for gestational age, and was grossly small and had a simplified gyral pattern. The infant's brain presented with a subarachnoid hemorrhage. On sectioning, the cerebrum disclosed poor differentiation between the gray and white matter. The ventricular system was markedly dilated, with ventricular lining granularities. Sections of the brainstem and cerebellum disclosed marked degeneration. On microscopy, there was severe encephalic degeneration with numerous dystrophic calcifications, subarachnoid, perivascular, and interstitial hemorrhages, microglial nodules, vascular proliferation, perivascular cuffing, and incomplete migration (Figure 4). These central

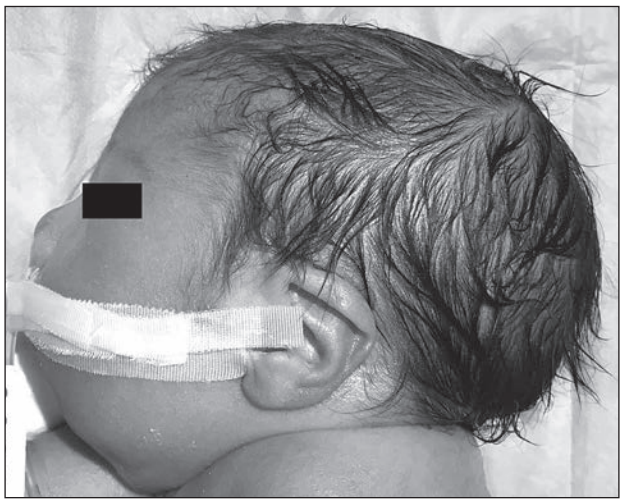

Figure 2. External anomalies of the head, including micrognathia and low set, posteriorly rotated ears.

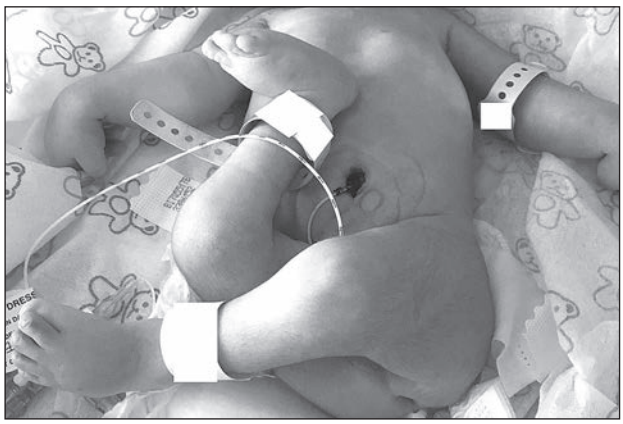

Figure 3. External anomalies of the extremities: rocker bottom feet, scissor legs, clenched and hyperflexed hands, and multiple contractures (arthrogryposis).

Table 1. Organ measurements and weights

	Observed (g ± cm)	Expected (g ± cm)
Body weight	2100	2789 ± 520
Crown to heel	45	46.7 ± 4.4
Crown to rump	30	34.3 ± 1.9
Toe to heel	7.5	7.5 ± 0.5
Liver	60	121.3 ± 39.2
Spleen	8	10.1 ± 3.5
Adrenal glands	3	7.4 ± 2.5
Thymus	14	9.4 ± 2.5
Kidneys	20	26.1 ± 4.9
Lungs	25	42.6 ± 14.9
Heart	9	19.1 ± 2.8
Brain	150	362

Expected measurements and weights from Women and Infants Hospital, Providence, RI, USA, for a 39-week gestational age, liveborn baby.

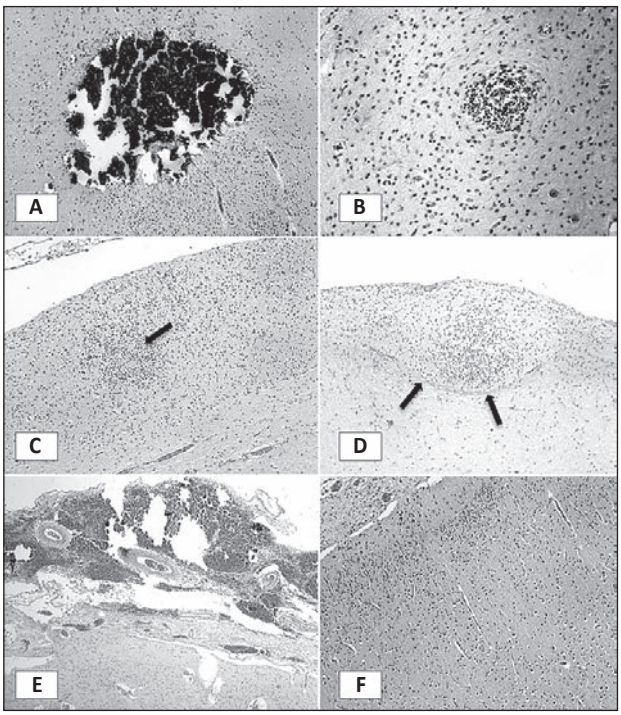

Figure 4. A: Dystrophic calcifications, 10x; B: Perivascular cuffing, 10x; C: Microglial nodule, 10x; D: subependymal nodules, 10x; E: Subarachnoid Hemorrhage, 4x; F: Incomplete neuronal migration.

nervous system findings are consistent with congenital Zika encephalopathy. A pathologic exam of the placenta revealed focal villous stromal edema and reactive amnion with pigment-laden macrophages.

Discussion

The numerous anomalies found in this neonate were most likely secondary to maternal ZV infection (at 8 wGA). The cerebral and physical abnormalities have been well described in recent research studies of CZS.

In Ceará, part of northeastern Brazil, Sousa et al. performed postmortem examinations of 7 neonates with CZS. As was the case with the mother of our patient, the mothers of these babies had contracted ZV infection during the first trimester of pregnancy, with 5 of them presenting symptoms of infection. Brain weight was decreased in all 7 neonates, with evidence also of ventriculomegaly, dystrophic calcification, and severe cortical neuronal depletion. Six of these neonates had arthrogryposis. One neonate did not have microcephaly but did have significant intracranial pathology, similar that of to our patient (6). The discrepancy between the prenatal finding of fetal microcephaly and the postnatal findings may be explained by the early development of hydrocephalus. Sousa's autopsy findings are in accordance with our autopsy findings and with the diagnosis of CZS.

Furthermore, Vasco et al., through brain imaging, disclosed the prevalence of a simplified gyral pattern, malformations of cortical development, abnormalities of the corpus callosum, decreased brain volume, ventriculomegaly, and hypoplasia of the cerebellum or brainstem in neonates affected by the ZV (7). Soares et al. also documented congenital brain abnormalities in ZV-infected fetuses, with a prevalence of ventriculomegaly, abnormalities of the corpus callosum, cortical migration abnormalities, and intracranial calcifications, most commonly at the gray–white matter junction (4). Many of these findings, such as the degeneration of the brainstem and cerebellum, incomplete migration, intracranial calcifications, ventriculomegaly, and severe encephalic degeneration, were noted in the autopsy presented herein.

After reviewing the recent literature and comparing what it describes with our autopsy findings, we believe the diagnosis of CZS is highly likely. This reinforces the importance of continued research on the effects of ZV on the fetus. Furthermore, although at birth he did not fulfill microcephaly criteria, prenatally he consistently had a head circumference more than 3 standard deviations below the mean. This illustrates the need to reassess the definition of microcephaly as it applies to patients prenatally exposed to the ZV.

Resumen

Presentamos la primera autopsia realizada a un recién nacido con síndrome congénito de Zika en Puerto Rico. El neonato nació a término de una madre con infección confirmada del virus de Zika, con diagnóstico prenatal de microcefalia y múltiples calcificaciones cerebrales entre otras anomalías y cariotipo masculino normal por amniocentesis. Requirió reanimación neonatal al nacer y falleció a los 2 días de vida. No llenó los criterios de microcefalia, con una circunferencia de cabeza de solo 1.5 desviaciones estándar por debajo de la media. La autopsia reveló anomalías externas incluyendo piernas en posición de tijera, manos hiperflexionadas y múltiples contracturas. Los hallazgos del sistema nervioso central fueron consistentes con la encefalopatía del Zika: ventriculomegalia, lisencefalia, y degeneración encefálica severa con calcificaciones

distróficas. Estas anomalías sugieren ser secundarias a la infección congénita por el virus del Zika. Aunque prenatalmente había evidencia de microcefalia, no presento la misma al nacer, lo cual exhorta una reevaluación de la definición de microcefalia en pacientes con sospecha de afectación por el virus prenatalmente.

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