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Letter to the Editor

Congenital Zika syndrome: is the heart part of its spectrum?

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To the editor

Zika virus (ZIKV) is an emerging flavivirus responsible for a significant outbreak of disease in the Americas. The disease usually presents in adults as a self-limiting rash/febrile syndrome. Current data support an association between ZIKV infection and adverse perinatal outcomes known as the congenital Zika syndrome (CZS) [1]. The full phenotypic spectrum of this syndrome remains to be elucidated. Angelidou *et al.* reported a case of complex congenital heart disease (CHD) in one infant with CZS, generating the hypothesis of heart disease associated with intrauterine exposure to ZIKV [2]. Two recent studies in Brazil reported an increased proportion (13.5%) of non-severe congenital heart defects in infants with CZS [3] and a 10.8% prevalence of major cardiac defects in infants with antenatal exposure to ZIKV, contrasting with the <5% CHD rate observed in the control age group [4].

Herein, we evaluated a series of 18 children with CZS for CHD. Transthoracic echocardiograms with standard paediatric views [9] were performed between February and August 2018 using a Philips HD11 XE. We included infants meeting the WHO case definition of probable case of congenital syndrome associated with Zika virus, which is 'a live newborn who meets the criteria for a suspected case of congenital syndrome associated with Zika virus AND who has intracranial morphological alterations detected by any imaging method, and not explained by other known causes; OR whose mother had rash during pregnancy'. These children were followed up at a neuro-paediatric centre. Microcephaly was defined as the presence of a head circumference below −2 standard deviations for gestational age and sex, measured at 24 h postpartum. Probable CZS included the presence of maternal rash and at least one or more symptoms suggestive of acute ZIKV infection during pregnancy and negative serology for TORCH (toxoplasmosis, syphilis, rubella, cytomegalovirus, herpes simplex virus), hepatitis B and C, and HIV. All infants were born between 2015 and 2017 in the state of Rio de Janeiro. The study was approved by the Institutional Review Board. Data collection was done according to the WHO standardized clinical–epidemiological questionnaire aimed at exploring maternal–infant outcomes in women exposed to ZIKV during pregnancy [5].

All 18 mothers had a rash during pregnancy, accompanied by one or more of the following: conjunctivitis (61%), pruritus (55%), arthralgia (55%) and fever (44%). Twelve mothers were ill in the first trimester of pregnancy, and six in the second. There was no family history of known genetic abnormalities or previous infants with congenital malformations. Characteristics of the 18 mothers who had infants with probable CZS are summarized in Table 1. The mean age of the children at the time of cardiac evaluation was 21.5 (±8.2) months. Males predominated (11/18, 61%). The mean gestational age was 37 weeks (±1.96) and 33% were preterm. All children had microcephaly, spasticity and neurodevelopmental delay. Epilepsy was present in 15 of the 18 cases (83%), and microphthalmy was common. Four of 18 had swallowing impairment and were fed by gastrostomy. We found two cases (2/18, 11%) of echocardiographic abnormalities. One had complex CHD consistent with anomalous drainage of the pulmonary veins, total atrioventricular septal defect, and a persistent ductus arteriosus. This same child had a cardiac axis shift to the right and paroxysmal supraventricular

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Table 1
Features of the 18 mothers and children with probable congenital Zika syndrome evaluated for heart disease in Rio de Janeiro, Brazil (2015–2017)

Features	$n = 18$
Children data:	
Median age at birth (weeks)	37 ± 1.96
Age at ECHO (months), mean ± SD	21.5 ± 8.2
Median head circumference (cm)	31.61 ± 0.91
Microcephaly *n* (%)	18 (100%)
Epilepsy *n* (%)	15 (83%)
Spasticity *n* (%)	18 (100%)
Maternal demographics:	
Age (years) at interview, mean ± SD	29.33 ± 5.83
Occupation *n* (%)	
Employed *n* (%)	6 (33.3)
Unemployed *n* (%)	2 (11.1)
Student *n* (%)	3 (16.7)
Other *n* (%)	7 (38.9)
Socioeconomic status proxies:	
Household income	
<1 minimum wage *n* (%)	5 (27.8)
1–2 minimum wages *n* (%)	9 (50)
>2 minimum wages *n* (%)	4 (22.2)
Housing with:	
Sanitation facilities *n* (%)	16 (88.9)
Electricity *n* (%)	18 (100)
Radio *n* (%)	12 (66.7)
Television *n* (%)	14 (77.8)
Refrigerator *n* (%)	17 (94.4)
Mobile telephone *n* (%)	17 (94.4)
Bank account holder *n* (%)	17 (94.4)
Lifestyle data during pregnancy:	
Alcohol use *n* (%)	2 (11.1)
Smoking *n* (%)	1 (5.6)
Recreational drugs	0
Travel aboard	0
Environmental exposure during pregnancy:	
Type of residence during pregnancy:	
House *n* (%)	14 (77.8)
Apartment *n* (%)	4 (22.2)
Location of residence:	
Urban/suburban *n* (%)	17 (94.4)
Rural *n* (%)	1 (5.6)
Presence of neighbours with ZIKV infection during the time of pregnancy *n* (%)	9 (50)

SD, standard deviation; ZIKV, zika virus, ECHO, echocardiogram.

tachycardia episodes on ECG. At the time of the initial evaluation, the infant—a 2-month old female who had a head circumference of 30 cm at birth—presented with dyspnoea, irritability, and central cyanosis. Delivery had occurred without complications at 38 weeks' gestation. The mother reported a history of fever and rash in the second trimester of pregnancy. The infant had a brain computed tomography (CT) scan with evidence of cortical and subcortical calcifications highly suggestive of CZS related to intrauterine exposure to ZIKV. Cardiac surgery was necessary and resulted in complete remission of the cardiovascular symptoms.

The other child was a boy aged 2 years and 4 months at the ECG examination; head circumference was 33 cm at birth and delivery occurred at 37 weeks' gestation. Echocardiography signs of increased right atrial and ventricular dilation, denoting overload of the right cavities, were observed. The child's mother reported skin rash and conjunctivitis during the second trimester of pregnancy. The child also had brain CT findings of cerebral calcification suggestive of CZS. Both mothers denied smoking or the use of alcohol or illicit drugs during or before pregnancy.

Our report supports previous data linking CZS with cardiovascular involvement [2,3], suggesting ZIKV's tissue tropism beyond the central nervous system. Although we had a small sample size, we evaluated infants and children with probable CZS for heart defects through clinical and imaging assessments and we used a standardized clinical–epidemiological WHO questionnaire to explore maternal–infant outcomes in women exposed to ZIKV during pregnancy. These data suggest an urgent need for further studies to elucidate the mechanism and breadth of cardiac involvement associated with the spectrum of ZIKV infection.

Transparency declaration

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