

# Neurodevelopmental delay in normocephalic children with in utero exposure to Zika virus

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## ABSTRACT

Neurodevelopment in 29 normocephalic children with in utero exposure to Zika virus (ZIKV) was evaluated by the Bayley Scales of Infant and Toddler Development-Third Edition. Ten (35%) infants presented neurodevelopment delay. Language, cognitive and motor delays were identified in 9 (31%), 4 (14%) and 1 (3%) infants, respectively. Children exposed to ZIKV in utero must undergo careful evaluations for the early detection of any neurodevelopment delays in order to implement prompt intervention.

## INTRODUCTION

Congenital Zika infection (CZI) was identified as a devastating consequence of Zika virus (ZIKV) infection during pregnancy.<sup>1</sup> The clinical presentation of CZI is variable, including microcephaly, sensorineural hearing loss, visual impairment and arthrogryposis.<sup>2</sup> Moreover, a broad clinical spectrum of outcomes, including minor disorders, have also been identified.<sup>3</sup> Furthermore, late-onset microcephaly was reported in infants with confirmed CZI and normocephaly at birth<sup>4</sup>

## METHODS

The present study aimed to investigate the neurodevelopment of non-microcephalic infants with intrauterine exposure to ZIKV who were born in Salvador, located in north-eastern Brazil, in an effort to contribute to the understanding of the broad spectrum of manifestations associated with this congenital infection.

Normocephalic infants were recruited from a previous CZI hospital surveillance programme,<sup>5</sup> if their serological testing or a quantitative PCR assay (RT-qPCR) for ZIKV was positive. Six (20%) of the newborns had ZIKV positivity by RT-qPCR and the others by serology. All their mothers had anti-ZIKV IgG positivity at the time of delivery. All infants were born during the 2016 ZIKV outbreak,

and all mothers reported ZIKV infection symptoms during pregnancy. Newborns were considered normocephalic if head circumference (HC) at birth measured within 2 SD for gestational age and sex, according to the INTERGROWTH-21 standards.<sup>6</sup>

Development was assessed using the Bayley Scales of Infant and Toddler Development-Third Edition (BSID-III), which was previously validated for the Brazilian population.<sup>7</sup> An adjustment to the age at the time of testing was made to evaluate infants with prematurity. According to the BSID-III, deviations in an individual's composite score from the normative mean (100±15) are used to classify neurodevelopment as normal: within 1 SD of the mean (≥85); mild: -1 to -2 SD (≥70 and <85); moderate: -2 to -3 SD (≥55 and <70); or severe: more than 3 SD below the standard mean scores (<55).

Complementary evaluations included retinal mapping, refraction evaluation and the assessment of brainstem auditory evoked response. No neuroimaging was performed.

## PATIENT AND PUBLIC INVOLVEMENT

The present study did not include patient or public involvement.

## RESULTS

Thirty-one infants were enrolled and 29 infants were evaluated, as two were excluded due to hydrocephalus or genetic disorders. Of the total evaluated, 16 (55%) were male with a mean age of 18.2±3.8 months. All maternal and newborn sociodemographic data are presented in [table 1](#).

Developmental assessment showed that 10 (34%) of the infants exhibited a delay in at least one of the BSID-III scale domains. Language delay was identified in 9 (31%)



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**Table 1** Sociodemographic and clinical data of 29 children evaluated by the BSID-III, Salvador, Brazil

	n (%)
<b>Mothers</b>	
Mother's age (years)*	25±6.4
<b>Maternal schooling</b>	
Elementary	8 (27.6)
Secondary	20 (69.0)
University	1 (3.4)
<b>Marital status</b>	
Married	8 (27.6)
Single	21 (72.4)
<b>Household income (minimum monthly wage)</b>	
<1	13 (44.8)
1–3	14 (48.3)
>3	2 (6.9)
<b>Infants</b>	
Gestational age at birth* (weeks)	38.4±2.1
Prematurity	5 (17.2)
Birth weight (g)*	3060±573.5
Head circumference at birth (cm)*	33.5±1.8
Mean age at time of BSID evaluation (months)*	18.2±3.8
Male gender	16 (55.2)

\*Mean±SD; minimum monthly wage=\$R954 (US\$~240). BSID-III, Bayley Scales of Infant and Toddler Development-Third Edition.

infants, cognitive delay in 4 (14%) and motor delay in 1 (3%) child (table 2).

Regarding the nine infants who exhibited language impairment, one presented a severe delay, one had moderate delay and seven were classified as having mild delay. When analysing their respective scaled scores, 2 (22%) infants demonstrated an expressive ability below average.

Audiological evaluations were performed in 16 (55%) infants, who showed normal auditory conduction, including five of the infants with language delay.

Ophthalmological evaluations were performed in 23 (79%) infants, with no abnormalities identified. All HC were found to be within the normal range in accordance with age and gender.

## DISCUSSION

In this study, 10 (34%) normocephalic infants presented some type of neurodevelopmental delay. These findings corroborate results reported by a prospective cohort study in Rio de Janeiro that evaluated children by neuroimaging and the BSID-III, in which neurodevelopment delays were observed in the cognitive, language and motor function domains.<sup>8</sup> Language function was found to be the most impaired domain among the children evaluated. Verbal abilities are known to be more sensitive to myelination in typical children, and children with language delays are reported to be at greater risk for below-average academic, social and emotional development, thereby compromising quality of life.<sup>9</sup>

This study suffers from some limitations, as the present design prevented us from establishing any causal relationships between exposure to ZIKV and developmental delay.

In conclusion, our evaluations identified abnormalities in neurodevelopmental outcome, especially language functioning, which should be confirmed by larger scale studies involving prospective cohorts and long-term follow-up. The systematic assessment of these children, through standardised tools, is crucial for the early detection of abnormal development, as well as to provide intervention to achieve best outcomes and prevent disabilities.

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**Contributors** ICdS, AXA and LCJA contributed to study design, writing of the manuscript and data analysis. AVF, JCdO, JVO, BLdA and IAA contributed to the enrolment of participants in the study, reviewed the medical records and clinical evaluations.

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**Table 2** Neurodevelopmental evaluations of 29 children with intrauterine exposure to ZIKV using the Bayley Scales of Infant and Toddler Development-Third Edition (BSID-III), Salvador, Bahia, 2018

Categorisation of developmental delay, n (%)						
BSID-III domain	Mean score (SD)	Range	Severe (score <55) –3 SD	Moderate (score 55–69) –2 SD/–3 SD	Mild (score 70–84) –1 SD/–2 SD	None (score ≥85) 1 SD
Cognitive	102.2±16.9	70–145	0	0	4 (13.8%)	25 (86.6%)
Language	93.8±18.5	47–135	1 (3.4%)	1 (3.4%)	7 (24.1%)	20 (69.1%)
Motor	103.5±12.0	79–127	0	0	1 (3.4%)	28 (96.6%)

BSID-III, Bayley Scales of Infant and Toddler Development-Third Edition; ZIKV, Zika virus.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethical approval** This study was approved by the Institutional Review Board of the Oswaldo Cruz Foundation (IGM-FIOCRUZ) (protocol number 1.935.854/2016).

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