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Neurodevelopmental outcomes in a cohort of children with congenital Zika syndrome at 12 and 24 months of age

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Abstract

Background: Early child development is a critical stage of life that influences social, educational and health outcomes worldwide. A few years after Zika epidemic, families of children born with congenital Zika syndrome (CZS) continue to face uncertainties when it comes to the development of their children. The present study sought to analyse the developmental trajectories of a subset of children born with CZS in the first 24 months of life.

Methods: Thirty-five children with CZS were assessed with the Bayley-III Scales at 12 and 24 months of age from November 2016 to December 2018 in a rehabilitation centre in Brazil. Inclusion criteria included children with established diagnosis of CZS. Exclusion criteria included the presence of arthrogryposis, prematurity, irregular follow-up, clinical complications or other causes of microcephaly. Children born with CZS who evolved with cerebral palsy (CP) were classified according to the Gross Motor Function Classification System (GMFCS) at 2 years of age.

Results: At 12 months of age mean composite scores on the Bayley cognitive, communication and motor scores were 57.71 (SD 7.11), 57.94 (SD 14.34) and 49.26 (7.20), respectively. At 24 months of age, composite scores were 57.43 (SD 7.11), 53.60 (SD 12.29) and 48.83 (7.76). In addition, 31 (88.57%) out of 34 children diagnosed with CP were classified as GMFCS levels IV and V.

Conclusion: Zika virus congenital infection is a risk factor for functional impairments across all developmental domains having a direct and substantial negative impact in early child development.

KEYWORDS

child development, cerebral palsy, developing countries, intra-uterine infection

1 | INTRODUCTION

Early child development is a critical stage of life that strongly influences social, educational and health outcomes worldwide (World Health Organization [WHO], [n.d.-a](#)). A few years after the peak of Zika epidemic, families of children born with congenital Zika syndrome (CZS) continue to face uncertainties when it comes to the health and development of their children (Bailey & Ventura, [2018](#)).

CZS is characterized by a constellation of symptoms observed in infants who have been exposed to the Zika virus (ZIKV) in utero. This may affect children's overall growth, global development and well-being (Marques et al., [2019](#)). Because of its neurotropism and related severe brain malformations, ZIKV was accountable as one of the leading causes of a new generation of children with neurological disorders (Wheeler, [2018](#)) in Brazil between 2015 and 2020. At that time, 3,577 confirmed cases out of 19,622 suspected cases of CZS

were reported to the Ministry of Health in Brazil (GovernodoBrasil, [n.d.](#)).

As they enter early childhood, developmental trajectories and outcomes become easier to predict, heightening health care providers the awareness of the long-term challenges. The severity of gross motor delays in children born with CZS has been recently documented (Marques et al., [2019](#)). However, the impact on cognitive and communication domains is not yet fully understood and may vary depending on the extent of microcephaly and additional sensory-motor complications frequently associated with CZS (Wheeler, [2018](#)).

Developmental assessments of infants can be complex and time-consuming; however, they constitute the foundation by which providers can create strategic care plans, which include comprehensive, multidisciplinary-based, care coordination-based and parental education-based approaches (Centers for Disease Control and Prevention [CDC], [n.d.-a](#)). The goal of this study was to describe neurodevelopmental trajectories at 12 and 24 months of age in a cohort of infants diagnosed with CZS without the clinical manifestation of arthrogryposis.

2 | METHODS

This study was conducted in a rehabilitation centre located in Rio de Janeiro, Brazil, where children born with suspected CZS were referred for multidisciplinary diagnostic assessments and integrated care plan.

From November 2015 to December 2016, children with suspected CZS were screened for CZS using the following criteria:

- born during the ZIKV epidemics (April 2015 to December 2016) (Pone et al., [2018](#)).
- mothers had symptoms compatible with ZIKV infection during pregnancy (mild and self-limiting symptoms that include mild fever, maculopapular rash, headache, conjunctivitis and myalgia) (Moore et al., [2017](#)).
- neuroimaging features characteristic of CZS (presence of brain calcifications at the cortical/subcortical brain white matter, cortical malformations, hypoplasia/hypogenesis of the corpus callosum, and myelination delay) (Aragao et al., [2016](#); Levine et al., [2017](#); Petribu et al., [2017](#)).
- negative laboratory tests for other etiologies (toxoplasmosis, cytomegalovirus [CMV], rubella, herpes simplex, syphilis, human immunodeficiency virus [HIV], dengue fever, chikungunya) (CDC, [n.d.-b](#)).

Magnetic resonance imaging (MRI) was performed at admission (mean age 4 months [1–11 months]) in spontaneous sleep states using a GE Signa HDXT with 3.0 or 1.5 Tesla resolution. Two radiologists described all neuroimaging exams in similar ways as previously related to ZIKV neuropathogenesis (Aragao et al., [2016](#); Levine et al., [2017](#); Petribu et al., [2017](#)). MRI findings are described in the Supporting Information.

The exclusion of other causes was made possible through the performance of serology tests for toxoplasmosis, CMV, rubella,

Key messages

- This article reports on a prospective assessment of the developmental trajectories of children born with congenital Zika syndrome (CZS).
- CZS is frequently a cause of global developmental delay.
- The gross motor skills of children born with CZS are significantly delayed in comparison with typically developing children.
- The results of the analysis regarding the communication domain of children born with CZS showed the lowest progression rate over time.
- CZS is highly associated with the diagnosis of cerebral palsy.

herpes simplex, syphilis, HIV, dengue fever and chikungunya. All 35 infants tested negative for all serology tests, except for 15 infants who presented IgG-positive for CMV; they were further submitted to a complementary evaluation with CMV urine screened via reverse transcription polymerase chain reaction (RT-PCR) before 6 months of age; the results came out as negative for all of them. The negative RT-PCR for CMV means that the positive IgG for CMV in this population likely reflected maternal antibody origin.

Exclusion criteria included the presence of arthrogryposis (a condition that limits the use of standardized developmental scales), prematurity (infants born <37 weeks of gestational age), irregular follow-up, clinical complications or any other cause of microcephaly and/or brain structural abnormalities (such as the ones resulting from hypoxic-ischemic injury, suspected genetic syndrome and congenital cytomegalovirus [CMV] syndrome).

Clinical assessment was initially undertaken by five developmental and behavioural paediatricians that were responsible for the definition of CZS diagnosis and for the participants' selection. Figure 1 illustrates the criteria used for participant selection.

During the follow-up of children with CZS at the rehabilitation centre where this study was performed, the motor, cognitive and communication domains were evaluated in the same sample of children by two physiotherapists and one clinical psychologist at 12 and 24 months using the Bayley-III Scales of Infant and Toddler Development (Bayley, [2006](#)) from November 2016 to December 2018. Special considerations such as, for example, level of background noise were essential to conduct meaningful developmental assessments and engagement in testing activities. Also, the examiners helped the participating children with proper body position and support to allow comfort, attention to task, movement control and communication. The Bayley-III Scales is a standardized instrument widely used worldwide to assess development in young children (Bayley, [2006](#)) in general. Bayley-III scales is culturally adapted to the Brazilian population and linguistically translated to Brazilian Portuguese (Madaschi et al., [2016](#)). The Bayley-III Scales has been shown to be a consistent

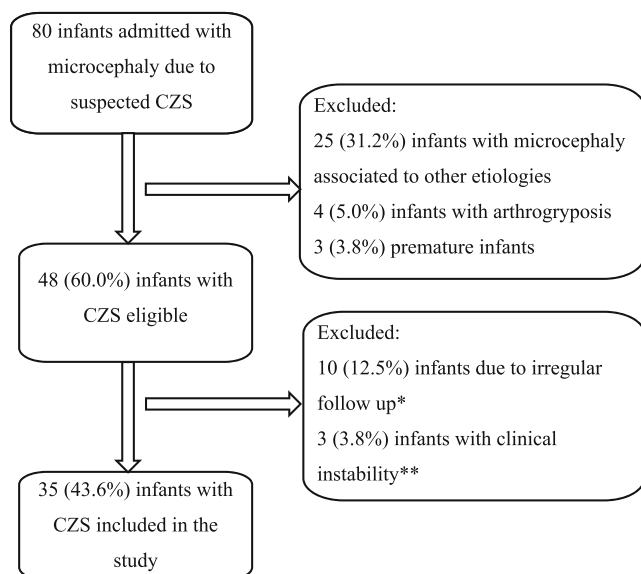


FIGURE 1 Flowchart representing the participant's selection. *Infants who attended the first clinical evaluation at 12 months but did not attend at 24 months of age for no specific reason; **Two infants with refractory epilepsy and one infant with chronic pulmonary disease were excluded due to recurrent hospitalization and consequently irregular follow-up.

test to be applied in special interest groups for clinical assessment and research purposes (Bayley, 2006).

The diagnosis of cerebral palsy (CP) was based on the presence of motor dysfunction (essential criterion) and at least one of the other two additional criteria (abnormal neuroimaging and/or clinical history indicating risk for CP) (Marques et al., 2019). The Gross Motor Function Classification System (GMFCS) comprises five levels of gross motor classification based on the child's motor functioning. GMFCS is used to classify severity of mobility, with a system classification based on the Gross Motor Function Measure (GMFM), a tool that is used to evaluate change that occurs over time in the gross motor function of children suspected of gross motor delays. This scale differentiates children with CP based on the child's current gross motor abilities, limitations in gross motor function and need for assistive technology and wheeled mobility. The classification emphasizes the level of functioning of the child's main postures such as sitting (trunk control) and gait within five different age ranges (<2 years, 2–4 years, 4–6 years, 6–12 years and 12–18 years). The classification system has five levels, being level I equivalent to minimal motor dysfunction and level V, equivalent to significant motor impairment (Palisano et al., 1997).

Statistical analysis was performed with statistical package SPSS 21.0™. Descriptive and inferential statistics were applied. For categorical variables, absolute and relative frequencies were used. For continuous variables, mean, range and standard deviation were utilized. For correlation analysis, the Pearson coefficient and for mean comparison, paired *t* test (with *P* value < 0.05) was utilized to determine significance amongst the results obtained by the Bayley-III Scales. For comparison between clinical features and the Bayley III results, independent *t* test was utilized for the analysis.

TABLE 1 Participants' clinical features

	(%) or median (range)
Gender	
Female	15/35 (42.9%)
Male	20/35 (57.1%)
Mother's age (years)	25.8 (14–40)
Region (Rio de Janeiro state)	
Capital	17 (48.6%)
Other regional cities	18 (51.4%)
Gestational age (weeks)	38.2 (37–41)
Birth weight (g)	2612 (1780–3855)
Mean head circumference at birth (cm)	
Female	29 (26–32)
Male	30 (26–36)
Z-score head circumference ^a	
<−3 SD	25/35 (71.4%)
<−2 SD	7/35 (20.0%)
<−1 SD	2/35 (5.7%)
1 SD	1 (2.9%)
Symptoms of ZIKV infection during pregnancy	
1st trimester	27/35 (77.0%)
2nd trimester	4/35 (11.5%)
3rd trimester	4/35 (11.5%)
Age at admission (months)	4 (1–11)
GMFCS	
I–III	3/35 (5.8%)
IV–V	31/35 (91.3%)
Developmental delay (no CP)	1/35 (2.9%)

Abbreviations: CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; ZIKV, Zika virus.

^aAccording to the WHO Child Growth Standards.

This study was approved by the SARAH network institutional review board, registered on a national digital platform (www.saude.gov.br/plataformabrasil) under Certificate of Presentation of Ethical Appreciation number 62342416.1.0000.0022. Prior informed consent was signed by the study subjects' parents or legal guardians.

3 | RESULTS

Thirty-five infants with CZS were included in this prospective cohort study. Twenty (57.1%) participants were male, and 15 (42.9%) were female. Mean head circumference at birth was 29 cm for females and 30 cm for males (three standard deviations [SDs] or more below the mean for their age and gender) (WHO, n.d.-b). Table 1 summarizes clinical and laboratory findings. MRI findings and analysis are described in the Supporting Information.

Thirty-five infants with CZS were evaluated for their motor, cognitive and communication development through the Bayley-III Scales at two points in time: at 12 and 24 months. Motor domain had a composite score mean at 12 months of 49.3 (SD 7.2) and at 24 months 48.8 (SD 7.7), representing three SDs below the mean in the Bayley-III Scales. The score remained almost the same, with no significant decrease over time ($P = 0.5$).

For the cognitive domain, the mean of composite scores at 12 months was 57.7 (SD 7.1) and at 24 months 57.4 (SD 7.1), representing two SD below the mean score in the Bayley-III Scales. The score remained almost the same, with no significant decrease over time ($P = 0.5$).

The communication domain showed a composite score at 12 months of 57.9 (SD 14.3) and at 24 months, 53.6 (SD 12.3), with a significant decrease over time ($P < 0.001$), representing a decrease from two to three SD below the mean score in the Bayley-III Scales. The Bayley III results, including the scaled score for each domain, are summarized on Table 2:

Figures 2 and 3 highlight the composite scores and scaled scores comparisons, respectively, between the two points in time (12 vs. 24 months) according to each developmental domain.

Notably, 34 of 35 children (97.1%) met clinical and neuroimaging criteria for the diagnosis of CP (Marques et al., 2019). The remaining patient presented with neurodevelopmental delays in the cognitive

TABLE 2 Bayley III results of 35 infants with CZS at 12 and 24 months of age. Most infants did not improve over time in all developmental domains. At 12 months, only four (11.4%) out of 35 infants, and at 24 months, only three (8.6%) out of 35, who underwent the Bayley-III testing reached scores above 85 for all three domains (1 SD below the mean [\pm SD] score of 100 ± 15 [scores range from 55 to 145, with lower scores indicating a greater degree of developmental delay]).

Bayley III scores	Mean	SD	S.E. Mean	Difference	P value (CI 95%)
Cognitive scaled score—12 months	1.54	1.42	0.24		
Cognitive scaled score—24 months	1.60	1.54	0.26	0.06	0.487
Expressive communication scaled score—12 months	2.86	2.48	0.42		
Expressive communication scaled score—24 months	1.94	2.00	0.34	−0.92	<0.001
Receptive communication scaled score—12 months	2.80	2.62	0.44		
Receptive communication scaled score—24 months	2.49	2.62	0.44	−0.31	0.270
Fine motor scaled score—12 months	1.60	1.50	0.25		
Fine motor scaled score—24 months	1.63	1.73	0.29	0.03	0.786
Gross motor scaled score—12 months	1.29	1.07	0.18		
Gross motor scaled score—24 months	1.23	0.97	0.16	−0.06	0.422
Cognitive composite score—12 months	57.71	7.11	1.20		
Cognitive composite score—24 months	57.43	7.11	1.20	−0.28	0.487
Communication composite score—12 months	57.94	14.34	2.42		
Communication composite score—24 months	53.60	12.29	2.08	−4.34	<0.001
Motor composite score—12 months	49.26	7.20	1.22		
Motor composite score—24 months	48.83	7.73	1.31	−0.43	0.505

Composite score per domain

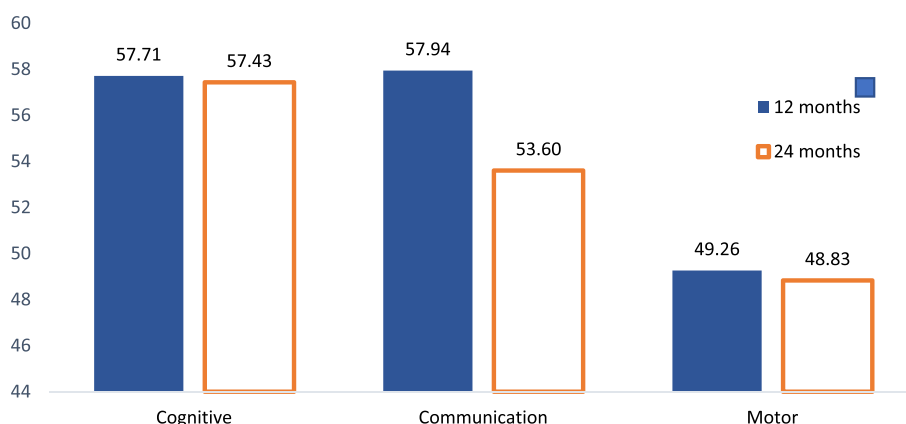


FIGURE 2 Bayley III composite scores at 12 and 24 months of age. The composite scores are classified as follows: average (90–110); below average (80–89); borderline (70–79) and extremely low for average (<70).

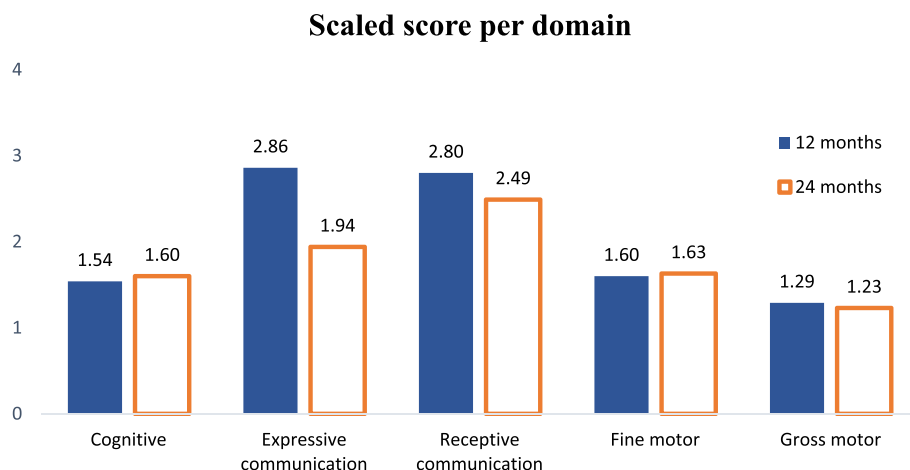


FIGURE 3 Bayley III scaled scores at 12 and 24 months of age. They are derived from the total raw scores on each of the subtests and are scaled to a metric with a range of 1 to 19, a mean of 10 and a standard deviation (SD) of 3. Scores of 7 and 13 are equivalent to 1 SD below and above the mean, respectively, and scaled scores of 4 and 16 are equivalent to 2 SDs from the mean.

and behavioural domains. At 2 years of chronological age, the GMFCS revealed that of those 34 infants secondarily diagnosed with CP, 27 (79.4%) were classified as level V; four (11.9%) classified as level IV; one (2.9%) level III, one (2.9%) level II and one (2.9%) as level I.

4 | DISCUSSION

In this study, we sought to evaluate childhood developmental domains in 35 children born with CZS using the Bayley-III Scales. Most infants scored below 70 standard score (SS) in all domains (cognitive, communication and motor) at 12 and 24 months of chronological age. That may indicate CZS can be frequently a cause of global developmental delay. Even in the small percentage of infants who progressed over time, deviation from typical developmental trajectories worsened compared with what would be expected for age. The high viral teratogenicity, which results in severe disruptive events in the embryonic period, is likely the main cause of these poor developmental outcomes.

Although all developmental domains were severely affected in this subset of children with CZS, gross motor skills had the lowest scores at 12 and 24 months. In agreement with previous studies reporting on the severity of gross motor skills involvement in infants with CZS (Alves et al., 2018; Carvalho et al., 2019; Einspieler et al., 2019; Marques et al., 2019; Oliveira Melo et al., 2016; Pessoa et al., 2018; Satterfield et al., 2017), only 10 (28.5%) infants from our study attained head balance, a finding that demonstrates an overall significant motor impairment established in the first years of life. Takahasi et al. (2021) reported in a prospective cohort the gross motor skills' evolution over time in children with CZS; almost all children had severe CP and were classified as having GMFCS level IV or V, approaching their maximal gross motor function capabilities in the third year of life. Carvalho et al. (2020) also described severe global impairment in infants with CZS at a 2-year follow-up. These findings are likely related to the widespread and complex nature of the brain damage that exceeds the neuroplasticity mechanisms by which a child's brain adapts to brain injury in early life (Marques et al., 2019).

Additionally, the fine motor domain was also severely affected in our cohort; 18 (51.4%) out of 35 infants decreased or remained at the same developmental stage in the two-point time evaluation. Like our findings, Alves et al. (2018) reported a 3.1-month equivalent for fine motor/adaptive skills in a case series study in infants with CZS at 18 months using the Denver Development Screening Test II.

The cognitive domain was also severely impaired, with a seemingly poor progression over time. As a direct relationship between small head size and intellectual disability is well-known (Dolk, 1991; Wilder-Smith et al., 2019), a guarded cognitive prognosis would be expected in the population analysed in our study. This discrepancy between the cognitive level seen in our sample and the expected cognitive level seen in typically developing peers agrees with a report published by França et al. (2016). The authors demonstrated that this population typically displays extremely low cognitive performance. Cognitive results should be interpreted carefully, as some cognitive tasks described in the Bayley-III Scales 'manual require that the child be capable to cooperate with motor coordination tasks. Severe motor incoordination is typically presented in children with CZS (Morgan et al., 2019).

Furthermore, when compared with the other domains, communication showed the lowest progression over time. Nielsen-Saines et al. (2019) described the neurodevelopment of a prospective cohort of infants exposed in utero to ZIKV, where language was the most affected domain. Assuming the scaled scores represent a child's performance relative to his/her same-age peers, when the expressive communication subtest is analysed longitudinally, the results indicate a significant numeric decrease, whereas the receptive communication subtest results remain essentially unchanged. Expressive language challenges generally stem from a combination of brain lesions that typically lead to a dysfunctional left frontal cortex and oral-motor impairments, including speech (Lopes Moreira et al., 2018). Because ZIKV is known to severely impair cortical development, these factors might be responsible for such high level of linguistic imbalance.

Indicators of ZIKV involvement in neurodevelopmental disorders have been already determined. These are prenatal screening, clinical syndromes and neuroradiological markers (Gullo et al., 2022).

However, they may present later during advanced stages of ZIKV-related pathology and clinical manifestations, or may be even absent, leading to delays in diagnostics. In that regard, a deeper understanding in factors influencing the natural history of maternal-placenta-fetal transmission and passage through the blood-brain barrier to the fetal brain could help improve prevention strategies.

Finally, genotype-phenotype correlations will likely increase the identification of protective and risk factors on the severity of the clinical neurological presentation of CZS. The same could be applicable to the prognostication of developmental trajectories (Gullo et al., 2022).

4.1 | Limitations

This study has some limitations. According to international protocols (CDC, n.d.-b), the most reliable way to confirm the presence of ZIKV in a biological tissue is the RT-PCR. Because these children were admitted after the window of time in which this test ideally should have been processed, the authors included only children whose mothers showed symptoms of ZIKV infection during pregnancy throughout the course of ZIKV epidemics. Additionally, all infants-recruited to participate in this study met neuroimaging criteria applicable to CZS (Aragao et al., 2016). To exclude different etiologies, serology tests and RT-PCR in the urine for CMV were performed. Also, the results showed in the Bayley Scales refer to a subset of children with CZS admitted to a rehabilitation centre and might have been somewhat underestimated. While the utilized measurements from the Bayley-III Scales were undertaken in a proper and adapted setting, technical scale-dependent administrative barriers that prevent significantly impaired children from fully cooperating with the applications of standardized tests may have impacted the results (Bayley, 2006; Madaschi et al., 2016).

5 | CONCLUSION

In conclusion, cognitive, motor and communication domains marginally progressed in a subset of children with CZS from the first to the second year of life. Gross motor skills were markedly delayed when compared with typically developing children of the same age-range. The communication domain showed the lowest progression in the 12-month comparison. Also, CZS was responsible for the coexistent diagnosis of CP in its most complex types of clinical presentation (GMFCS levels IV and V). In summary, CZS is a risk factor for significant functional impairments across all developmental domains directly affecting early child development.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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