EARLY CHILD DEVELOPMENT AND CARE
https://doi.org/10.1080/03004430.2022.2080203

Routledge
Taylor & Francis Group

Growth in children with congenital Zika syndrome: a 4-years longitudinal cohort study

Jousilene de Sales Tavares [a], Gabriela Lopes Gama [a,b], Hannah Cavalcante Guedes Pinheiro [a], Girlene Souza de Azevedo [a], Mariana Balbino da Silva [a], Chanazy Ayalla de Castro Meira[a], Adriana Suely Oliveira Melo [a,b] and Melania Maria Ramos Amorim [a]

[a]Professor Joaquim Amorim Neto Research Institute, Campina Grande, Paraíba, Brazil; [b]UNIFACISA University Center, Campina Grande, Paraíba, Brazil

ABSTRACT

To describe and analyze the changes in anthropometric parameters in children with congenital Zika syndrome (CZS) from birth to four years of age. This prospective study evaluated 117 children diagnosed with CZS. Anthropometric indices evaluated annually were classified with respect to presence of microcephaly and adequacy of weight-for-age, length/height for-age and body mass index-for-age (BMI-for-age). At birth, 69.6% of the children had microcephaly, 90.2% had adequate weight and 72.1% had adequate length. The following year, an increase occurred in the proportion of children with microcephaly, with a reduction of those with adequate weight. In the second year, the proportion of children with microcephaly increased again, while those with adequate BMI decreased. In the third to fourth years of life, a reduction was found in the proportion of children with adequate height. Anthropometric indices are affected in children with CZS over the first four years of life and appear to be potentiated over time.

ARTICLE HISTORY
Received 7 March 2022
Accepted 15 May 2022

KEYWORDS
Zika virus infection; child development; microcephaly; disability evaluation

Introduction

Congenital Zika syndrome (CZS) is characterized by clinical signs related to the fetal brain damage that results from Zika virus infection during pregnancy, particularly following primary maternal infection during the first trimester of pregnancy (A. S. Melo et al., 2016; Oliveira Melo et al., 2016). From a radiological point of view, this syndrome is characterized by the presence of diffuse calcifications, principally in the subcortical areas and the basal nuclei, a reduction in brain volume that results in hydrocephalus ex vacuo, delayed cortical development (agyria and pachygyria), hypoplasia of the brainstem and/or cerebellum, dysgenesis of the corpus callosum, delayed myelination and microcephaly (Chimelli et al., 2017; Chimelli et al., 2018; Sarno et al., 2017). These brain alterations can result in a wide spectrum of neurological signs such as changes in muscle tonus, persistence of primitive reflexes, irritability, epileptic seizures and clonus (Chimelli et al., 2017; Saad et al., 2018).

In addition to the brain damage in this population, restricted growth has been described in fetuses, newborn infants(Dos Santos, Soares, de Abranches, da Costa, Gomes-Junior, et al., 2019; Moura da Silva et al., 2016; Prata-Barbosa, Martins, Guastavino, & Cunha, 2019) and in children of up to two years of age (Dos Santos, Soares, de Abranches, da Costa, Moreira, et al., 2019; Franca

CONTACT Gabriela Lopes Gama gabilopes_@hotmail.com Instituto de Pesquisa Professor Joaquim Amorim Neto (IPESQ), Campina Grande, Rua Salvino de Oliveira Neto, 87, Paraíba 58402-040, Brazil UNIFACISA University Center, Campina Grande, Paraíba, Brazil

et al., 2018; Moura da Silva et al., 2016; Prata-Barbosa et al., 2019). In general, the weight and length/height of children with CZS tend to be below that of their peers who were not exposed to the virus during pregnancy, (Franca et al., 2018; Soares et al., 2019) with one study suggesting an association between the neurological damage and restricted growth in children with CZS (Prata-Barbosa et al., 2019).

Bearing in mind the consequences of Zika virus infection, awareness of its short- and long-term effects on child development are crucial in understanding the natural history of CZS and its effect on child development. In addition, developing such a knowledge base is relevant to implementing management and interventions aimed at supporting individuals with this diagnosis. Therefore, the objective of the present study was to describe and analyze the changes in anthropometric parameters (weight, length/height and head circumference) in children with CZS monitored from birth to four years of age.

Material and methods

This prospective cohort study evaluated children receiving care at a support center for children with microcephaly affiliated to the Instituto Paraibano de Pesquisa Professor Joaquim Amorim Neto (IPESQ) in the city of Campina Grande, Paraiba, Brazil. This institute has been providing care for pregnant women and children infected with Zika virus since 2015. The study was approved by the ethics committee of Alcides Carneiro university hospital. Prior to undergoing any evaluation, the children's mothers or guardians signed an informed consent form.

Sample

The sample was obtained from children who were receiving care at IPESQ. The inclusion criteria were: (1) Have under five years of age, (2) Have CZS diagnosis confirmed by laboratory exams (RT–PCR) or imaging tests such as computed tomography and/or magnetic resonance performed in the first months of life and (3) have anthropometric measurements registered at the institute and/or were available from a child chart. For some children the exposure to Zika virus was confirmed during pregnancy through laboratory tests on their mothers, however, diagnosis was confirmed just after birth.

CZS was defined by the spectrum of symptoms observed in infants exposed to ZIKV in utero whose mothers had a non-negative test for ZIKV infection associated with clinical and/or imaging tests factors. Considered clinical factors were severe microcephaly with the skull partially collapsed, decreased brain tissue related to brain damage, damage to the back of the eyes, and joints with limited range of motion (Center for Diseasse Control and Prevention, 2019, 2021; Wheeler, 2018). On the other hand, considered imaging factors were calcification at junction between cortical and subcortical white matter (most common); basal ganglia ana periventricular, ventriculomegaly, enlarged cisterna magna, abnormalities of the corpus callosum, delayed myelination, cerebellar and brainstem hypoplasia(de Fatima Vasco Aragao et al., 2016).

Children with microcephaly and/or brain damage of other causes including infection by other infectious agents such as syphilis, toxoplasmosis, rubella and cytomegalovirus infection confirmed by laboratory tests, children without a confirmed diagnosis of CZS and children whose anthropometric indices had not been recorded at any time over the first four years of their life were excluded from the study.

Evaluation procedures and data collection

First, data were registered with respect to the mother (age, schooling, per capita income, marital status and parity), the pregnancy (whether symptoms of Zika virus infection had occurred, and if yes, at which gestational age), delivery (mode of delivery, 1st and 5th minute Apgar scores,

birthweight, birth length and head circumference) and children (sex, underwent surgery, gastrostomy until four years of age, presence of arthrogryposis and breast in first six months of life).

Data on the children's development were obtained from the annual registration of the anthropometric variables *weight*, *length/height* and *head circumference* from birth to the fourth year of life. Pediatric scales (Welmy, Santa Bárbara d'Oeste, São Paulo, Brazil) were used to determine the children's weight and a portable stadiometer and a measuring tape were used to measure height to the nearest centimeter. Head circumference was measured using a non-elastic tape measure.

Using the absolute values of the anthropometric variables at birth, z-scores were calculated from the reference values proposed in the Intergrowth-21st, (Brasil, 2005; INTERGROWTH-21st, n.d.) taking gestational age at birth and the sex of the child into consideration. In the subsequent evaluations, the z-scores for head circumference, length/height, weight and body mass index (BMI) (weight/height^2) were calculated using the World Health Organization Anthro® software program, version 3.2.2 (WHO, 2011).

Based on the z-score values obtained, the children's weight and length/height were classified as follows: much below expected (z-score > −3), below expected (z-score between −2 and −3), adequate (z-score between 2 and −2) and above expected (z-score > 2) (Brasil, 2018). According to head circumference measurements, the children were classified as: not having microcephaly (z-score > −2), having mild microcephaly (z-score of −2 to −3) or having severe microcephaly (z-score > −3) (WHO, 2016). In addition, when the z-score was > 2, the child was classified as having macrocephaly.

Finally, the children's motor function was classified according to the Gross Motor Function Classification System (GMFCS). This scale was initially proposed to classify the mobility and functionality of children with cerebral palsy, with classifications ranging from level I, reflecting minimal limitations, to level V, which corresponds to severe limitations (Palisano, Rosenbaum, Bartlett, & Livingston, 2007). All variables were measured by health professional of IPESQ, as physical therapists, nurses and biomedical professionals, whose have experience in caring for children with SCZ and in handling the assessment instruments used in this study.

Statistical analysis

First, the characteristics of the sample were described by calculating means and standard deviations for the continuous variables such as gestational age at birth and per capita family income at the initial evaluation, while absolute and relative frequencies were calculated for the categorical variables such as sex and prematurity.

To analyze the anthropometric variables, the absolute and relative frequency of the children with and without microcephaly were determined, as well as that of the children with adequate weight-for-age, length/height-for-age and BMI-for-age throughout the follow-up period. Chi-square tests were used to compare the proportion of children with respect to the classification of their anthropometric measurements over their first four years of life. Spearman's rank correlation (Spearman's rho) was used to evaluate the effect of the presence of microcephaly at birth and of the classification of motor function (GMFCS level) on the anthropometric variables analyzed.

Finally, repeated measures analysis of variance (ANOVA) was performed to evaluate the changes in the absolute values of the anthropometric variables. Medcalc, version 19.0.7 (MedCalc Software bvba, Ostend, Belgium) was used to perform the entire statistical analysis, with significance set at 5%.

Results

Over the four years in which this study was conducted, 117 children registered at the support center for children with microcephaly were evaluated. Of these, 57.3% ($n = 67$) were boys; 54.3% ($n = 63$) had been delivered vaginally; 12.1% ($n = 14$) were premature; and 4.3% ($n = 5$) had arthrogryposis at birth. Mean gestational age at birth was 38.3 ± 1.92 weeks. When the children began to be monitored at the support center, the mean age of their mothers was 26.7 ± 6.6 years; mean per capita

income was 71.6 ± 52.17 dollars; 85.5% (n = 100) lived in an urban area; 35.9% (*n* = 42) of the mothers were in a stable union; and 11.2% (*n* = 13) had university education. Table 1 describes the general characteristics of the children who participated in this study and their mothers.

Birth data were available for 112 children (95.7%). Over the follow-up period, data were available for 94 children at one year (80.3%), for 100 children at two years (85.4%), 107 children at three years (91.4%) and for 86 children at four years (73.5%). Only 68 children (58.1%) attended all the annual evaluations and had complete anthropometric indices with no missing data. For the other children, they had either missed at least one of the annual evaluations or data referring to their birth were missing. In addition, over the follow-up period, seven deaths were registered (5.9%), one in the first year, two in the third year and four in the fourth year of life. Figure 1 shows the flowchart describing the evaluation of the children over the study period.

Table 1. Demographic characteristics of the participating mothers and children.

Characteristics	*n* (%)	Mean ± SD	Range
Maternal and pregnancy-related characteristics			
Age, years		26.7 ± 6.6	14–46
Education level			
No schooling	1 (0.9)		
Some elementary school	40 (34.5)		
Completed elementary school	62 (53.4)		
Some university	13 (11.2)		
In a stable marital union or married	79 (67.5)		
Parity			
Primipara	53 (45.7)		
Multipara	64 (54.3)		
Per capita income ($)		71.6 ± 52.17	0–303.5
Symptoms of infection			
In the 1st trimester of pregnancy	75 (72.8)		
In the 2nd trimester of pregnancy	23 (22.3)		
In the 3rd trimester of pregnancy	4 (3.9)		
No symptoms	14 (12.1)		
Duration of symptoms of infection (days)		4.1 ± 2.7	0–15
Characteristics of the children			
Gestational age at birth		38.3 ± 1.9	30–42
Prematurity			
Yes	14 (12.1)		
No	102 (87.9)		
Sex			
Male	67 (57.3)		
Female	50 (42.7)		
Apgar score			
1st minute		8.3 ± 0.9	4–9
5th minute		9.1 ± 0.8	4–10
Arthrogryposis			
Yes	5 (4.3)		
No	110 (95.7)		
Underwent surgery, excluding gastrostomy			
Yes	18 (15.4)		
No	99 (84.6)		
Gastrostomy			
Yes	9 (7.7)		
No	100 (92.3)		
Age at gastrostomy (years)		2.71 ± 0.82	1–4
Breastfeeding in first days of life			
Yes	98 (84.5)		
No	18 (15.5)		
Exclusive breastfeeding (days)		142.17 ± 112.85	
GMFCS level			
Levels I, II, III or IV	9 (7.7)		
Level V	108 (92.3)		

GMFCS: The Gross Motor Function Classification System.

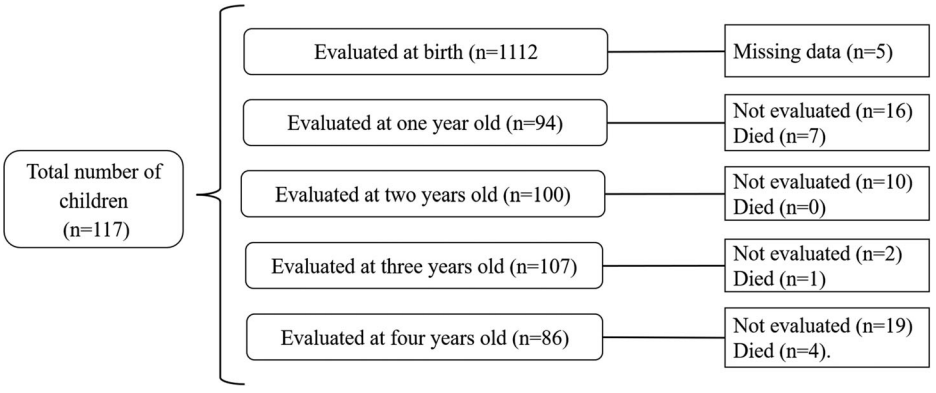

Figure 1. Flowchart of the evaluation conducted with the children.

At birth, 69.6% of the children evaluated had microcephaly. Of these, 66.7% had severe microcephaly, 89.4% had adequate birthweight and 71.4% had adequate birth length. One year later, the proportion of children with microcephaly was found to have increased ($p = 0.002$), as did the proportion with severe microcephaly ($p = 0.0004$). At that time, the proportion of children with adequate weight decreased ($p = 0.0002$), while no statistically significant difference was found in the proportion of children with adequate length.

When the first and second years of life were compared, the only findings were an increase in the overall proportion of children with microcephaly ($p = 0.013$) and a reduction in the proportion of children with adequate BMI ($p = 0.01$). There were no statistically significant differences in any of the other anthropometric indices. In the following years, no difference was found in the proportion of children with microcephaly, severe microcephaly or adequate weight compared to the preceding year. Nevertheless, significant differences were found between the proportion of children with adequate height in the third (57%) and fourth (43%) years of life ($p = 0.04$). Table 2 shows the changes in the anthropometric parameters according to the proportion of children classified in each category.

The presence of microcephaly at birth was associated with birth length ($p = 0{,}0003$), birthweight ($p = 0.0006$) and BMI in the second year of life ($p = 0.04$). In this respect, children with microcephaly had lower z-score values for all these associated parameters. An association was found between motor impairment and head circumference at all the evaluations (at birth, $p = 0.001$, 1 year, $p < 0.0001$, 2 years, $p < 0.0001$, 3 years, $p < 0.0001$ and 4 years, $p = 0.0001$), length/height at all the evaluations after birth year of life (1 year, $p = 0.008$, 2 years, $p = 0.03$, 3 years, $p = 0.01$ and 4 years, $p = 0.01$), weight in the second and third years of life (2 years, $p = 0.01$, 3 years, $p = 0.01$) and BMI in the third year of life ($p = 0.04$). Children with GMFCS level V had lower z-score values for all the associated parameters, except the BMI in the third year of life (Table 3).

Finally, changes in the absolute values of the anthropometric indices were evaluated exclusively in the group of children who had attended all the annual evaluations and for whom no data were missing. A progressive increase was found in the absolute values of length/height ($p < 0.001$), weight ($p < 0.001$), head circumference ($p < 0.001$) and BMI ($p < 0.001$) over the first four years of life. Figure 2 shows the changes in the anthropometric indices of the 68 children who attended all the evaluations.

Discussion

Evaluation of the weight, head circumference, length/height and BMI of the children with CZS over their first four years of life emphasizes the effects of fetal Zika virus infection, even following birth. More specifically, a progressive increase was shown in the proportion of children with microcephaly

Table 2. Anthropometric parameters of the children in this study sample.

	At birth ($n = 112$)	1 year ($n = 94$)	2 years ($n = 100$)	3 years ($n = 107$)	4 years ($n = 86$)
Z-score HC					
Median	−2.61	−4.93	−5.37	−5.35	−5.53
Range	−4.8–0.9	−9.4–6.3	−9.02–0.2	−8.7–0.3	−8.7–0.1
Microcephaly					
n (%)	78 (69.6)	82 (89.1)	98 (98)	102 (95.3)	80 (95.2)
p-value*		0.002#	0.013#	0.29	1.0
Severe microcephaly					
n (%)	52 (66.7)	75 (91.5)	88 (89.8)	94 (92.2)	73 (91.2)
p-value*		0.0004#	0.71	0.57	0.82
Z-score weight					
Median	−0.61	−0.94	−1.67	−1.8	−1.45
Range	−2.9–2.6	−6.1–3.9	−5.0–4.1	−5.6–3.1	−5.2–1.8
Adequate weight					
n (%)	101 (89.4)	61 (64.2)	54 (54)	58 (54.2)	51 (60)
p-value*		0.0002#	0.27	0.98	0.54
Z-score Length/Height					
Median	−1.32	−0.96	−1.13	−1.61	−2.11
Range	−4.5–1.8	−6.1–2.9	−5.3–1.3	−5.1–0.5	−5.5–1.9
Adequate length/height					
n (%)	80 (71.4)	65 (69.1)	71 (71)	61 (57)	37 (43)
p-value*		0.81	0.81	0.98	0.04#
Z-score BMI					
Median		−0.59	−1.48	−0.78	−0.12
Range		−4.48–4.6	−4.440–4.93	−4.81–6.16	−4.16–4.67
Adequate BMI					
n (%)		69 (73.4)	52 (52)	72 (67.3)	61 (70.9)
p-value*			0.01#	0.08	0.65

HC: Head circumference. *Comparison with the proportion in the previous evaluation; #Statistically significant difference.

Table 3. Association between anthropometric parameters and microcephaly at birth and GMFCS V.

	Microcephaly at birth ($n = 78$)			GMFCS level V ($n = 108$)		
Anthropometric parameter	Rho	95%CI	*p*-value	Rho	95%CI	*p*-value
At birth						
Z-score weight	0.32	0.14–0.48	0.0006	0.002	−0.18–0.18	0.97
Z-score length	0.33	0.16–0.49	0.0003	−0.02	−0.21–0.16	0.79
Z-score HC	0.79	0.72–0.85	<0.0001	0.31	0.13–0.46	0.001
1 year						
Z-score weight	0.11	−0.09–0.32	0.28	0.19	−0.01–0.38	0.06
Z-score length	0.13	−0.07–0.33	0.21	0.27	0.07–0.45	0.008
Z-score HC	0.47	0.29–0.62	<0.0001	0.44	0.25–0.59	<0.0001
Z-score BMI	0.05	−0.16–0.25	0.65	0.021	−0.18–0.22	0.84
2 years						
Z-score weight	0.19	−0.006–0.38	0.06	0.25	0.057–0.43	0.01
Z-score length	0.11	−0.09–0.29	0.31	0.21	0.01–0.39	0.03
Z-score HC	0.42	0.24–0.57	<0.0001	0.42	0.25–0.57	<0.0001
Z-score BMI	0.21	0.009–0.39	0.04	0.12	−0.07–0.31	0.24
3 years						
Z-score weight	0.03	−0.16–0.23	0.73	0.24	0.049–0.41	0.01
Z-score height	0.17	−0.02–0.35	0.09	0.24	0.05–0.41	0.01
Z-score HC	0.47	0.31–0.61	<0.0001	0.41	0.24–0.56	<0.0001
Z-score BMI	−0.05	−0.25–0.14	0.58	0.19	0.004–0.37	0.04
4 years						
Z-score weight	−0.02	−0.23–0.19	0.87	0.193	−0.01–0.38	0.07
Z-score height	0.19	−0.02–0.39	0.08	0.27	0.06–0.46	0.01
Z-score HC	0.42	0.23–0.58	0.0001	0.401	0.21–0.5	0.0001
Z-score BMI	−0.15	−0.36–0.06	0.15	0.12	−0.09–0.32	0.27

GMFCS: The Gross Motor Function Classification System; HC: head circumference.

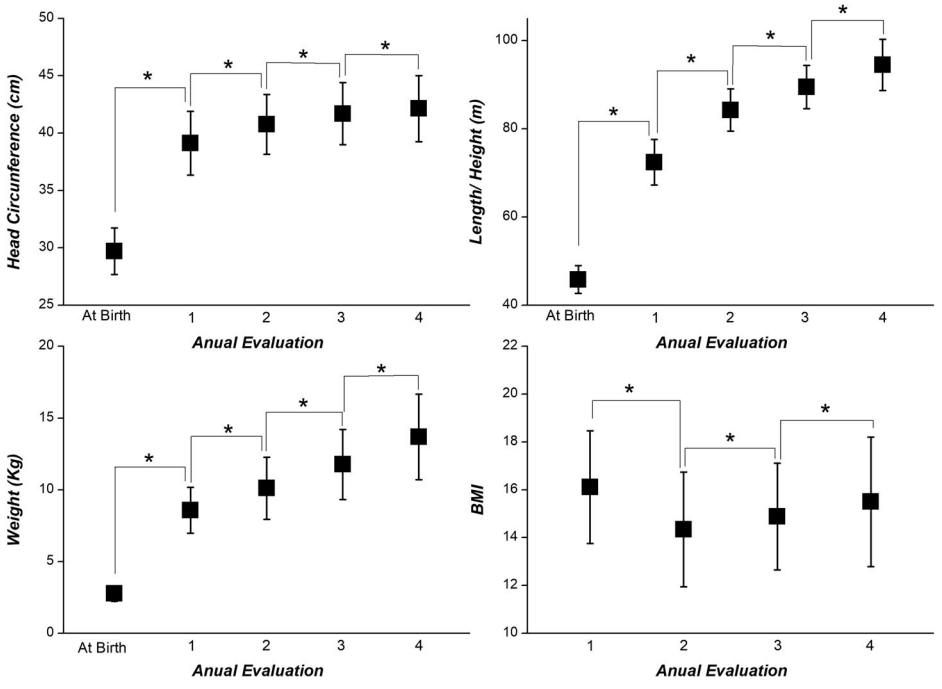

Figure 2. Changes in the anthropometric indices of the 68 children who attended all the evaluations. NOTE: BMI = Body mass index * Statistically significant difference, $p < 0.05$.

up to the second year of life and a reduction in the proportion of children with adequate weight in the first year of life, adequate BMI in the second year of life and adequate height in the third year of life. Furthermore, an association was found between the presence of microcephaly at birth and the anthropometric parameters, with children with microcephaly at birth having lower birthweight and birth length, as well as lower BMI in the second year of life. In addition, children with GMFCS level V had shorter length/height after the first year of life, lower weight in the second and third years of life and lower BMI in the second year of life.

The majority of the children in the present study were born with adequate weight and length, as also found in the studies conducted by Del Campo et al. (2017) and Dos Santos, Soares, de Abranches, da Costa, Gomes-Junior, et al. (2019) Nevertheless, a significant reduction was found in the proportion of children with adequate weight and height in the first and fourth years of life, respectively. This finding could have been influenced by clinical and environmental factors experienced by the children in their first years of life.

The clinical factors that could affect anthropometric indices include the occurrence of gastrointestinal reflux and dysphagia, which have been reported to be common in children with CZS (Leal et al., 2017) and that can lead not only to nutritional consequences but may also result in microaspiration events and recurrent pneumonia (Aragao et al., 2019). Furthermore, the inability of the central nervous system of children with neurological damage such as CZS to coordinate suction, swallowing and breathing during feeding can have a negative effect on the nutritional support required for adequate child development (Penagini et al., 2015; Sullivan et al., 2000).

Another point that has to be taken into consideration refers to the harmful effects of motor and sensorial impairment on feeding, which have also been described in children with CZS (Lowe et al., 2018; Saad et al., 2018). In fact, motor and sensorial impairment can generate a disagreeable sensation during feeding depending on the texture and consistency of the food offered. In addition, it is common for children with CZS to show signs of tiredness and exhaustion when feeding, a fact that could be related to the motor and energy demands required during the generally

prolonged periods of feeding. These factors may render feeding ineffective and may represent a source of stress for the children and their caregivers.

Environmental factors such as the unfavorable socioeconomic conditions described by the children's mothers in the present study, as also documented in other previous reports, (Lowe et al., 2018; Quintana-Domeque, Carvalho, & de Oliveira, 2018; Souza et al., 2018) could have affected child development. Indeed, low education level of mothers and unfavorable socioeconomic conditions can deny the child the right to adequate nutritional intake and learning opportunities in an enriched environment, with a consequent negative effect on child development. Conversely, adequately nourished children with adequate care and learning opportunities are known to have greater chances of maximizing their growth and development (Black et al., 2017). Unfortunately, this is not the situation for the majority of the mothers of children with CZS, whose characteristics, according to Freitas et al. (Sindrome congenita do virus Zika: perfil sociodemografico das maes./ 2019) were living in northeastern Brazil, being generally poor, and having little schooling and fragile insertion in the job market.

Two aspects of the present findings are particularly noteworthy: the significant increase in the proportion of children with microcephaly over the first two years of life and the reduction in the proportion of children with adequate height only from the third year of life onwards.

Firstly, concerning microcephaly, the first two years of life is a period of intense neurogenesis and synaptogenesis, essential for the maturation of the nervous system (Ismail, Fatemi, & Johnston, 2017). Del Campo et al. (2017) previously identified a reduction in head circumference growth when evaluating children with CZS in the first months of life, reporting an association between head circumference and birthweight and birth length and an increase in the proportion of cases of microcephaly over the follow-up period. In addition, Dos Santos, Soares, de Abranches, da Costa, Moreira, et al. (2019) reported a reduction in head circumference, length and weight in 65 children with CZS evaluated at birth, 12 and 23 months. Therefore, in agreement with these previous studies, the data described here show that children with CZS can develop microcephaly over the first years of life, which could be related to viral replication and to the deceleration of neural growth caused by the virus even after birth (van der Linden et al., 2016; Wheeler et al., 2018). Significant changes in head circumference, however, only appear to occur up to the second year of life. From then onwards, other anthropometric parameters such as BMI and height appear to be those most affected. This may serve as a warning call with respect to the need to evaluate children whose mothers had a history of exanthematous diseases during pregnancy, whether or not microcephaly was present at birth, and suggests that the effects of fetal Zika virus infections may continue even after birth.

The second point that merits attention is the reduction in the proportion of children with adequate height only from the third year of life onwards. These finding complements those reported by Carvalho-Sauer et al. (2020) who evaluated children with CZS up to 12 months of life and suggested an increasing risk of delays in length/height growth. In the present study, the period in which an increase was found in the proportion of children with less than adequate height coincides with the period in which, during typical development, an increase is seen in the motor repertoire through the child exploring the surrounding environment after learning to walk (Hadders-Algra, 2018). Hence, the fact that restricted growth in children with CZS was detected only after the third year of life reinforces how relevant learning opportunities are for child growth and development (Black et al., 2017). Furthermore, other factors such as atrophy from disuse and endocrine factors could be related to growth restrictions in children with neurological impairments (Andrew & Sullivan, 2010). The association between the level of motor impairment and the z-score for length/height found in the children in the present study further reinforces this hypothesis.

The severe motor impairment (GMFCS level V) was associated with the z-score for head circumference since birth and with the children's weight in the second and third years of life. The association between head circumference and GMFCS level V of motor impairment confirms our previous findings by Melo et al. (2020) according to whom the motor function of children with CZS aged between 5 and 29 months was associated with head circumference and delays in cortical

development (A. Melo et al., 2020). On the other hand, lower weight in children with greater motor impairment could be related to greater neurological impairment and other clinical factors. Herrera-Anaya, Angarita-Fonseca, Herrera-Galindo, Martinez-Marin, and Rodriguez-Bayona (2016) reported a reduction in weight, BMI and height as GMFCS level increased in children with cerebral palsy. Those authors also listed other possible clinical factors, including an increase in muscle tone, (Herrera-Anaya et al., 2016; Tavares et al., 2021) muscle spasms and involuntary movements, all of which have also been described in children with CZS (Leal et al., 2017; Saad et al., 2018; Tavares et al., 2021).

Finally, a finding that cannot be overlooked is the small number of children who underwent gastrostomy, despite the progressive impairment of anthropometric variables and the intrinsic relationship between nutritional support and adequate child development. This observation raises two important points of our sample related to cultural and economic factors. First, in our region this surgery is expensive and many families cannot afford to pay for it. In addition, even in the face of evaluation and surgery indication by health professionals, some mothers do not allow their children to undergo gastrostomy, once believe that this type of procedure will put their child's life at risk.

The strongpoint of the present study is the number of children evaluated. Nevertheless, any generalizations of these findings need to take certain factors into consideration. First, all the children evaluated were, at some point, monitored at a specialist institute providing multidisciplinary care for children with CZS, which may have minimized the frequent lack of access to healthcare and its negative effects on the children's growth and development. Secondly, not all the children were submitted to all the evaluations, a fact that could be explained principally by the mothers' difficulty in consistently attending the support center in which the study was conducted, mainly due to lack of transportation. Besides of that, data of some children were not available, such as information about childbirth as weight, length and CP at birth or even mothers did not remember the date of some events occurrence prior to child's follow-up by IPESQ, such as the child's age at gastrostomy. Thirdly, only inferences and suggestions were made on the possible causes of growth restrictions, including socioeconomic conditions, the child's level of sensory and motor impairment, calorie intake and neurological impairment, since the pertinent variables were not systematically evaluated.

Therefore, future studies should analyze correlations between anthropometric parameters and other important variables related to feeding, oropharyngeal function and long-term clinical conditions of children, as well as, the repercussion of gastrostomy in these children growth. That will help clarify the natural history of this pathology and serve as a research base for the implementation of multidisciplinary approaches when providing healthcare to this population.

Impaired anthropometric indices in children with CZS can be potentiated over time, even in children without microcephaly at birth. The present findings represent one more step towards understanding the natural history of CZS and the need to monitor the growth of these children, as well as the need to implement interventions aimed at encouraging their growth, development and functionality over the short and long-term.

Acknowledgements

Authors would like to thank the entire research department at IPESQ, as well as the children and their mothers or guardians for having participated in this study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study received support from the Coordination for the Improvement of Higher Education Personnel (CAPES)/Ministry of Education (MEC) (grant number 443372/2016-0), Technological Development (CNPq) (grant number 440619/

2016-5). This study was also supported by the Department of Science and Technology, Secretariat of Science, Technology and Strategic Supplies, Ministry of Health.

Notes on contributors

Joseline de Sales Tavares is a Physical education professional (2005) and PhD in Maternal and Child Health (2015). Currently is a researcher and coordinator of the research institute Professor Joaquim Amorim Neto in Campina Grande, Paraiba Brazil, where she has been developing research on congenital Zika virus syndrome since 2005. Has experience in Epidemiology and Public Health, working mainly on the following topics: determinants of fetal growth, low birth weight, infant growth velocity, weight gain during pregnancy, physical exercise and pregnancy.

Gabriela Lopes Gama graduated physical therapist (2009) and PhD in health sciences (2017). Professor at the UNIFACISA University Center and Researcher at Professor Joaquim Amorim Neto Research Institute, both in in Campina Grande, Paraiba Brazil. Ai the latter institutions she has been researching about children with congenital Zika Syndrome since 2017. Have experience in rehabilitation of children with neurological disease mainly on the following topics: gross motor function, gait and rehabilitation approaches.

Hannah Cavalcante Guedes Pinheiro Nurse graduated (2016). Currently works as a nurse and researcher assistant at Professor Joaquim Amorim Neto Research Institute, in Campina Grande, Paraiba Brazil, where she provides assistance and develops studies related with Congenital Zika Syndrome.

Girlene Souza de Azevedo Graduated in Biomedicine (2019). She is currently a clinical analyst at Elpidio de Almeida Institute and at the Professor Joaquim Amorim Neto Research Institute, both in Campina Grande, Paraiba Brazil. At latter institution, she is also an assistant researcher and has been developing studies about Zika virus since 2009.

Mariana Balbino da Silva Undergraduate student in biomedicine. She is a research assistant at Instituto de Pesquisa Professor Joaquim Amorim Neto, located in the city of Campina Grande Paraiba Brazil, where has been developing studies about congenital Zika Syndrome.

Chanazy Ayalla de Castro Meira Graduated in Occupational Therapy (2014), completed the multi professional residency in hospital with an emphasis on child and adolescent health (2018). She has experience in child development. Autism Spectrum Disorder and childhood neurological and syndromes. Currently works as an occupational therapist and researcher assistant at Professor Joaquim Amorim Neto Research Institute (IPESQ), in Campina Grande, Paraiba Brazil, where provides assistance and develops studies related to Congenital Zika Syndrome since 2018.

Adriana Suely Oliveira Melo Graduated in Medicine (1994), has a medical residency in Gynecology and Obstetrics (1996) and PhD in Maternal and Child Health (2012) She is currently Professor at Federal University of Campina Grande, researcher at the UNIFACISA university center, as well as researcher and president of the Professor Joaquim Amorim Neto Research institute, all institutions located in Campina Grande, Paraiba Brazil. In 2016, published the description of the ultrasound findings of congenital Zika syndrome for the first time in the world. She has experience in fetal medicine, epidemiology and public health, working mainly on the following topics: determinants of fetal growth, low birth weight and macrosomia at birth, fetal and maternal visceral adiposity, weight gain during pregnancy, physical exercise and pregnancy, infectious diseases and pregnancy, with an emphasis on Zika virus and congenital Zika infection and arboviruses.

Melania Maria Ramos Amorim Graduated in Medicine (1989), completed medical residency in Gynecology and Obstetrics (1992) and doctorate in Tocogynecology (1998). She is currently an associate professor at Federal University of Campina Grande and at graduate professor at the Professor Fernando Figueira Integral Medicine Institute, Member of the American College of Obstetricians and Gynecologists (ACOG), USA and Global Doctors for Choice, founder and Director of the Feminist Network of Gynecologists and Obstetricians (Brazil) as well as Senior Researcher at Research Institute Professor Joaquim Amorim Neto. She works in the area of Women's and Children's Health, with emphasis on lines of research: Evidence-Based Medicine, Humanization of Childbirth and Birth, Hypertension and Pregnancy, High-Risk Pregnancy, Fetal Medicine, Maternal Mortality, Abortion, Intensive Care in Obstetrics, Translational Research, and Gynecologic Surgery. Participated in the group that produced the Brazilian Guidelines for Assistance to Normal Childbirth and Cesarean Section. She was part of the Guideline Development Group (GDG) for the World Health Organization's recommendations on intrapartum care for a positive birth experience.

ORCID

Jousilene de Sales Tavares http://orcid.org/0000-0002-4040-9164
Gabriela Lopes Gama http://orcid.org/0000-0002-7352-6711
Hannah Cavalcante Guedes Pinheiro http://orcid.org/0000-0003-0212-7569
Girlene Souza de Azevedo http://orcid.org/0000-0001-8287-1245
Mariana Balbino da Silva http://orcid.org/0000-0001-5333-3536

Adriana Suely Oliveira Melo http://orcid.org/0000-0002-8575-544X
Melania Maria Ramos Amorim http://orcid.org/0000-0003-1047-2514

References

Andrew, M. J., & Sullivan, P. B. (2010). Growth in cerebral palsy. *Nutrition in Clinical Practice*, *25*(4), 357–361. doi:10.1177/0884533610374061

Aragao, M. F. V. V., van der Linden, V., Petribu, N. C., Valenca, M. M., Parizel, P. M., & de Mello, R. J. V. (2019). Congenital Zika syndrome: The main cause of death and correspondence between brain CT and postmortem histological section findings from the same individuals. *Topics in Magnetic Resonance Imaging*, *28*(1), 29–33. doi:10.1097/RMR.0000000000000194

Black, M. M., Walker, S. P., Fernald, L. C. H., Andersen, C. T., DiGirolamo, A. M., Lu, C., … Lancet Early Childhood Development Series Steering, C. (2017). Early childhood development coming of age: Science through the life course. *Lancet*, *389*(10064), 77–90. doi:10.1016/S0140-6736(16)31389-7

Brasil, M. d. S. (2005). *Pré-natal e puerpério: Atenção qualificada e humanizada – manual técnico/Ministério da Saúde*. Brasília – DF, Brazil: Ministério da saúde.

Brasil, M. d. S. (2018). Boletim Epidemiológico. Monitoramento integrado de alterações no crescimento e desenvolvimento relacionadas à infecção pelo vírus Zika e outras etiologias infecciosas, até a Semana Epidemiológica 30 de 2018. [Brazil, Ministry of Health. Integrated monitoring of growth and developmental changes related to Zika virus infection and other infectious etiologies by Epidemiological Week 30 of 2018.] Brazil, Ministry of Health. Retrieved 8 August, from http://portalarquivos2.saude.gov.br/images/pdf/2018/setembro/11/2018-047.pdf

Carvalho-Sauer, R. C. O., Costa, M., Paixao, E. S., de Jesus Silva, N., Barreto, F. R., & Teixeira, M. G. (2020). Cross-sectional study of the anthropometric characteristics of children with congenital Zika syndrome up to 12 months of life. *BMC Pediatrics*, *20*(1), 479. doi:10.1186/s12887-020-02365-6

Center for Diseasse Control and Prevention, C. (2019). *Understanding Zika virus test results*. Retrieved January 2018, from https://www.cdc.gov/zika/hc-providers/testing-for-zika-virus.html?CDC_AA_refVal = https%3A%2F%2Fwww.cdc.gov%2Fzika%2Fhc-providers%2Ftestresults.html

Center for Diseasse Control and Prevention, C. (2021). *Congenital Zika syndrome & other birth defect*. https://www.cdc.gov/pregnancy/zika/testing-follow-up/zika-syndrome-birth-defects.html

Chimelli, L., Melo, A. S. O., Avvad-Portari, E., Wiley, C. A., Camacho, A. H. S., Lopes, V. S., … Tanuri, A. (2017). The spectrum of neuropathological changes associated with congenital Zika virus infection. *Acta Neuropathologica*, *133*(6), 983–999. doi:10.1007/s00401-017-1699-5

Chimelli, L., Moura Pone, S., Avvad-Portari, E., Vasconcelos, F. M., Araujo Zin, Z., Prado Cunha, A., … da Silva Pone, M. V. (2018). Persistence of Zika virus after birth: Clinical, virological, neuroimaging, and neuropathological documentation in a 5-month infant with congenital Zika syndrome. *Journal of Neuropathology and Experimental Neurology*, *77*(3), 193–198. doi:10.1093/jnen/nlx116

de Fatima Vasco Aragao, M., van der Linden, V., Brainer-Lima, A. M., Coeli, R. R., Rocha, M. A., Sobral da Silva, P., … Valenca, M. M. (2016). Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: Retrospective case series study. *BMJ*, *353*, i1901. doi:10.1136/bmj.i1901

Del Campo, M., Feitosa, I. M., Ribeiro, E. M., Horovitz, D. D., Pessoa, A. L., Franca, G. V., … Zika Embryopathy Task Force-Brazilian Society of Medical Genetics, Z.-S. (2017). The phenotypic spectrum of congenital Zika syndrome. *American Journal of Medical Genetics*, *173*(4), 841–857. doi:10.1002/ajmg.a.38170

Dos Santos, S. F. M., Soares, F. V. M., de Abranches, A. D., da Costa, A. C. C., Gomes-Junior, S., Fonseca, V. M., & & Moreira, M. E. L. (2019). Nutritional profile of newborns with microcephaly and factors associated with worse outcomes. *Clinics*, *74*, e798. doi:10.6061/clinics/2019/e798

Dos Santos, S. F. M., Soares, F. V. M., de Abranches, A. D., da Costa, A. C. C., Moreira, M. E. L., & de Matos Fonseca, V. (2019). Infants with microcephaly due to ZIKA virus exposure: Nutritional status and food practices. *Nutrition Journal*, *18*(1), 4. doi:10.1186/s12937-019-0429-3

Franca, T. L. B., Medeiros, W. R., Souza, N. L., Longo, E., Pereira, S. A., Franca, T. B. O., & Sousa, K. G. (2018). Growth and development of children with microcephaly associated with congenital Zika Virus syndrome in Brazil. *International Journal of Environmental Research and Public Health*, *15*, 9. doi:10.3390/ijerph15091990

Freitas, P. S. S., Soares, G. B., Mocelin, H. J. S., Lacerda, L. C. X., do Prado, T. N., Sales, C. M. M., … Maciel, E. L. N. (2019). Congenital Zika syndrome: Sociodemographic profile of mothersSindrome congenito por el virus del Zika: Perfil sociodemografico de las madres. *Open Access Revista Panamericana de Salud Pública*, *43*, e24. doi:10.26633/RPSP.2019.24

Hadders-Algra, M. (2018). Early human motor development: From variation to the ability to vary and adapt. *Neuroscience and Biobehavioral Reviews*, *90*, 411–427. doi:10.1016/j.neubiorev.2018.05.009

Herrera-Anaya, E., Angarita-Fonseca, A., Herrera-Galindo, V. M., Martinez-Marin, R. D., & Rodriguez-Bayona, C. N. (2016). Association between gross motor function and nutritional status in children with cerebral palsy: A cross-sectional study from Colombia. *Developmental Medicine and Child Neurology*, *58*(9), 936–941. doi:10.1111/dmcn.13108

INTERGROWTH-21st. (n.d.). *Standards/references*. http://intergrowth21.ndog.ox.ac.uk/

Ismail, F. Y., Fatemi, A., & Johnston, M. V. (2017). Cerebral plasticity: Windows of opportunity in the developing brain. *European Journal of Paediatric Neurology*, *21*(1), 23–48. doi:10.1016/j.ejpn.2016.07.007

Leal, M. C., Van der Linden, V., Bezerra, T. P., de Valois, L., Borges, A. C. G., Antunes, M. M. C., … Ximenes, C. R. (2017). Characteristics of dysphagia in Infants with microcephaly caused by congenital Zika virus infection, Brazil, 2015. *Articles from Emerging Infectious Diseases*, *23*(8), 1253–1259. doi:10.3201/eid2308.170354

Lowe, R., Barcellos, C., Brasil, P., Cruz, O. G., Honorio, N. A., Kuper, H., & Carvalho, M. S. (2018). The Zika virus epidemic in Brazil: From discovery to future implications. *International Journal of Environmental Research and Public Health*, *15*, 1. doi:10.3390/ijerph15010096

Melo, A., Gama, G. L., Da Silva Junior, R. A., De Assuncao, P. L., Tavares, J. S., Da Silva, M. B., … De Amorim, M. M. R. (2020). Motor function in children with congenital Zika syndrome. *Developmental Medicine and Child Neurology*, *62*(2), 221–226. doi:10.1111/dmcn.14227

Melo, A. S., Aguiar, R. S., Amorim, M. M., Arruda, M. B., Melo, F. O., Ribeiro, S. T., … Tanuri, A. (2016). Congenital Zika Virus Infection: beyond neonatal microcephaly. *JAMA Neurology*, *73*(12), 1407–1416. doi:10.1001/jamaneurol.2016.3720

Moura da Silva, A. A., Ganz, J. S., Sousa,, P. D., Doriqui, M. J., Ribeiro, M. R., Branco, M. D., … Soares de Britto, E. A. M. T. (2016). Early growth and neurologic outcomes of infants with probable congenital Zika virus syndrome. *Articles from Emerging Infectious Diseases*, *22*(11), 1953–1956. doi:10.3201/eid2211.160956

Oliveira Melo, A. S., Malinger, G., Ximenes, R., Szejnfeld, P. O., Alves Sampaio, S., & Bispo de Filippis, A. M. (2016). Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: Tip of the iceberg? *Ultrasound in Obstetrics and Gynecology*, *47*(1), 6–7. doi:10.1002/uog.15831

Palisano, R., Rosenbaum, P., Bartlett, D., & Livingston, M. (2007). *GMFCS – E & R Gross Motor Function Classification System Expanded and Revised*. Retrieved July from, https://www.canchild.ca/system/tenon/assets/attachments/000/000/058/original/GMFCS-ER_English.pdf

Penagini, F., Mameli, C., Fabiano, V., Brunetti, D., Dilillo, D., & Zuccotti, G. V. (2015). Dietary intakes and nutritional issues in neurologically impaired children. *Nutrients*, *7*(11), 9400–9415. doi:10.3390/nu7115469

Prata-Barbosa, A., Martins, M. M., Guastavino, A. B., & Cunha, A. (2019). Effects of Zika infection on growth. *Jormal de Pediatria*, *95*(Suppl 1), 30–41. doi:10.1016/j.jped.2018.10.016

Quintana-Domeque, C., Carvalho, J. R., & de Oliveira, V. H. (2018). Zika virus incidence, preventive and reproductive behaviors: Correlates from new survey data. *Economics and Human Biology*, *30*, 14–23. doi:10.1016/j.ehb.2018.04.003

Saad, T., PennaeCosta, A. A., de Goes, F. V., de Freitas, M., de Almeida, J. V., de Santa Ignez, L. J., … Antunes Kramberger, L. A. (2018). Neurological manifestations of congenital Zika virus infection. *Child's Nervous System*, *34*(1), 73–78. doi:10.1007/s00381-017-3634-4

Sarno, M., Aquino, M., Pimentel, K., Cabral, R., Costa, G., Bastos, F., & Brites, C. (2017). Progressive lesions of central nervous system in microcephalic fetuses with suspected congenital Zika virus syndrome. *Ultrasound in Obstetrics and Gynecology*, *50*(6), 717–722. doi:10.1002/uog.17303

Soares, F., Abranches, A. D., Villela, L., Lara, S., Araujo, D., Nehab, S., … Moreira, M. E. (2019). Zika virus infection in pregnancy and infant growth, body composition in the first three months of life: A cohort study. *Scientific Reports*, *9*(1), 19198. doi:10.1038/s41598-019-55598-6

Souza, W. V., Albuquerque, M., Vazquez, E., Bezerra, L. C. A., Mendes, A., Lyra, T. M., … Martelli, C. M. T. (2018). Microcephaly epidemic related to the Zika virus and living conditions in Recife, Northeast Brazil. *BMC Public Health*, *18*(1), 130. doi:10.1186/s12889-018-5039-z

Sullivan, P. B., Lambert, B., Rose, M., Ford-Adams, M., Johnson, A., & Griffiths, P. (2000). Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford feeding study. *Developmental Medicine and Child Neurology*, *42*(10), 674–680. doi:10.1017/s0012162200001249

Tavares, J. S., Gama, G. L., Dias Borges, M. C., de Sousa Santos, A. C., Tavares, J. S., Amorim, M. M. R., & Melo, A. (2021). Classification of congenital Zika syndrome: Muscle tone, motor type, body segments affected, and gross motor function. *Developmental Neurorehabilitation*, 1–7. doi:10.1080/17518423.2020.1866706

van der Linden, V., Pessoa, A., Dobyns, W., Barkovich, A. J., Junior, H. V., Filho, E. L., … Moore, C. A. (2016). Description of 13 Infants born during October 2015-January 2016 with congenital Zika virus infection without microcephaly at birth - Brazil. *Morbidity and Mortality Weekly Report*, *65*(47), 1343–1348. doi:10.15585/mmwr.mm6547e2

Wheeler, A. C. (2018). Development of infants with congenital Zika syndrome: What do we know and what can we expect? *Pediatrics*, *141*(Suppl 2), S154–S160. doi:10.1542/peds.2017-2038D

Wheeler, A. C., Ventura, C. V., Ridenour, T., Toth, D., Nobrega, L. L., Silva de Souza Dantas, L. C., … Ventura, L. O. (2018). Skills attained by infants with congenital Zika syndrome: Pilot data from Brazil. *PloS One*, *13*(7), e0201495. doi:10.1371/journal.pone.0201495

WHO. (2011). *Anthro for personal computers, version 3.2.2, 2011: Software for assessing growth and development of the world's children*. WHO https://www.who.int/toolkits/child-growth-standards/software

WHO. (2016). *Screening, assessment and management of neonates and infants with complications associated with Zika virus exposure in utero*. Retrieved June, from https://apps.who.int/iris/bitstream/handle/10665/204475/WHO_ZIKV_MOC_16.3_eng.pdf;jsessionid = C870DD37A09252368149E2B2A221D889?sequence = 1