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Decline in head circumference growth and associated factors in congenital Zika syndrome

Declínio no crescimento do perímetro cefálico e fatores associados à síndrome congênita associada à infecção pelo vírus Zika

Disminución del crecimiento del perímetro cefálico y factores asociados en el síndrome congénito del Zika

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Abstract

Little is known about the evolution of head circumference (HC) in children with congenital Zika syndrome (CZS). This study aims to evaluate HC growth in children with CZS in the first three years of life and identify associated factors. HC data obtained at birth and in neuropediatric consultations from 74 children with CZS were collected from the Child's Health Handbook, parents' reports, and medical records. Predictors of HC z-score were investigated using different mixed-effects models; Akaike's information criterion was used for model selection. The HC z-score decreased from -2.7 ± 1.6 at birth to -5.5 ± 2.2 at 3 months of age, remaining relatively stable thereafter. In the selected adjusted model, the presence of severe brain parenchymal atrophy and maternal symptoms of infection in the first trimester of pregnancy were associated with a more pronounced reduction in the HC z-score in the first three years of life. The decrease of HC z-score in CZS children over the first three months demonstrated a reduced potential for growth and development of the central nervous system of these children. The prognosis of head growth in the first 3 years of life is worse when maternal infection occurs in the first gestational trimester and in children who have severe brain parenchymal atrophy.

Zika Virus; Anthropometry; Cephalometry; Growth; Statistical Models

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Introduction

Congenital Zika virus infection has been shown to be more aggressive than other congenital infectious diseases, with the potential to induce fetal brain disruption [1,2,3], almost equivalent to anencephaly [4]. Several characteristics distinguish congenital Zika virus syndrome (CZS) from other congenital infections, including a thin cerebral cortex with subcortical calcifications and severe microcephaly with a partially collapsed skull [5].

The total volume of grey and white matter in the baby's brain correlates with the head circumference (HC) measure [6,7]. Therefore, measuring the HC routinely is an accessible way to assess brain growth in children and an important marker of neurological disorders [8]. Children with CZS present a significant HC reduction at birth, with a mean HC z-score of -2.3 to -3.61 [9,10,11]. The deficit in HC appears to increase as the child grows [11,12], at least until the end of the first or second year of life; the mean z-score for a sample of 65 children with CZS was -5.43 [10].

Even when compared to other populations with neurological disorders, the HC in children with CZS is severely compromised. On average, children with moderate to severe cerebral palsy have a standardized HC measurement at birth for sex and gestational age (z-score) of -0.4; this measure tends to decrease and reach 2.0 at the end of the first year of life [13]. In CZS, there is evidence of viral replication after the child's birth [5], which could lead to a reduced rate of brain growth that is reflected in the HC measurement.

The factors that influence HC in the first years of life for children with CZS are poorly studied. Children exposed to Zika virus (ZIKV) in the first trimester of pregnancy tend to have lower HC values compared to those exposed in the second trimester [14]. The relationship between neuroimaging findings and HC evolution is unknown.

Little is known about the evolution of HC in children after the second year of life or in continuous follow-ups. This study aims to evaluate the HC growth of children with CZS in the first 3 years of life and to identify associated factors.

Methods

Study design

This is an ambispective cohort study of children with probable or confirmed CZS who were followed from March 2016 to August 2019 at the Reference Center on Neurodevelopment, Assistance, and Rehabilitation of Children (NINAR) and at the NINAR Support House, both linked to the State Health Department of the State of Maranhão, Brazil. Exposure data were retrospectively collected, and the outcome measure (head circumference) was prospectively collected.

Participants

The cohort inclusion criterion included clinical and/or laboratorial evidence of CZS [15,16]: (1) positive result in the plate reduction neutralization test (PRNT) for ZIKV (40 children); (2) evidence of ZIKV infection on rapid chromatographic immunoassay for qualitative detection of IgM antibodies (three children); or (3) negative results for other congenital infections (toxoplasmosis, cytomegalovirus, syphilis) and brain CT scans with changes suggestive of CZS (calcifications, brain parenchymal atrophy, ventriculomegaly, malformation of cortical development, malformation/hypoplasia of cerebellum, brainstem malformation/hypoplasia and corpus callosum agenesis/dysgenesis) (67 children).

In this study, two children with an associated diagnosis of Dandy-Walker syndrome and hydrocephalus at birth, three children having only one HC measurement, and 31 children with incomplete data on the studied variables were excluded, leaving a final sample of 74 children.

Data collection procedures

CZS children and their families are regularly invited to stay for one week in the NINAR Support House in order to attend routine medical appointments and participate in a circuit of multidisciplinary activities. The mothers and guardians were invited to participate in the study during inpatient care at the NINAR Support House.

Data on pregnancy, childbirth, socioeconomic, and demographics of the family were collected during interviews with the mothers and guardians. The mothers were asked about presence of symptoms compatible with ZIKV infection during pregnancy. Data on the child's growth and development were taken from the child's health handbook (weight, length, head circumference, gestational age), medical reports on childbirth, and the NINAR and NINAR Support House medical records. The child's HC measurement was preferably collected from the consultation records of the neuropediatrician who treated the children and participated in the study, with a maximum of one record per month being considered. Due to disparities in the initial age at follow-up, follow-up period, and intervals between appointments, the number of HC measurements from each child ranged from 1 to 19.

Mothers and guardians were asked to bring the computed tomography scans of the child's head. These scans and those in the child's medical records at NINAR and at the NINAR Support House were evaluated by two experienced radiologists.

The collected data were entered into REDCap software version 6.17.1 (https://redcapbrasil.com.br/) by research fellows, and it was systematically reviewed by specialists in the various fields.

Variables

The HC was measured in centimeters and later standardized according to age and sex (z-score). The International Standards for Size at Birth program (INTERGROWTH-21st Network, version 1.0.6257.25111; https://intergrowth21.tghn.org/) was used to calculate the HC z-score at birth. For measurements of HC after birth, the z-score was obtained using the World Health Organization's Anthro program version 3.2.2 (http://www.who.int/childgrowth/software/en/).

Microcephaly was defined as HC z-score < -2 and ≥ -3 and severe microcephaly as HC z-score < -3.

Maternal symptoms during pregnancy were fever, skin rash, pruritus, arthralgia, and myalgia; in the presence of one or more symptoms, the mother was considered to be symptomatic for ZIKV infection. The answer choices were "yes", "no", and "don't know". Symptoms were classified according to the gestational trimester in which they occurred: first trimester or second/third trimester of pregnancy.

Two criteria for injury severity were defined from the imaging scans. The first was related to the degree of brain parenchymal atrophy (none; mild to moderate; severe) and the second criterion considered the location of brain alterations. In all scans evaluated, supratentorial lesions (affecting the brain) were observed. Children with isolated supratentorial lesions were differentiated from those who, in addition to supratentorial lesions, also presented infratentorial lesions (affecting the brainstem and/or the cerebellum), which could denote a more severe impairment of the central nervous system.

Statistical analysis

The mean and standard deviation of the numerical variables were calculated in the descriptive analysis of the data. Absolute frequencies and percentages of categorical variables were described.

Five mixed-effects models were adjusted to describe HC z-score trajectory, with degree of brain parenchymal atrophy, location of lesions in the brain, and gestational trimester in which the mother had symptoms compatible with ZIKV infection as explanatory variables:

(a) Model 1: mixed-effects linear regression model [17], which presents both fixed factors that are shared by all individuals, and random factors that are specific to each one, in addition to experimental error. This model assumes that each individual has its own average trajectory, and a subset of the regression parameters are taken as random. The model is represented by:

$$y_{ij} = X'_{ij}\,\beta + Z'_{ij}\,\varsigma_i + \varepsilon_{ij}$$

With $i = 1,\ldots m$ and $j = 1,\ldots n_i$

In which y_{ij} is the answer of the ith child on the ith occasion, X'_{ij} is the p-dimensional vector of covariates associated with fixed effects β, Z'_{ij} is the q-dimensional vector of covariates associated with random effects ς_i, and ε_{ij} is the random error.

(b) Model 2: mixed segmented model [18], assuming data y_{ij}, with $j = 1,\ldots n_i$ for individual $i = 1,\ldots n$, represented by the equation:

$$y_{ij} = \beta_{0i} + \beta_{1i}\,t_{ij} + \delta_i\,(t_{ij} - \psi_i)\,\varepsilon_{ij}$$

In which each parameter is given by the sum of fixed (Greek letters) and random (italic letters) components, $\delta_i = \delta + d_i$. The fixed term may depend on additional covariates; variations for the intercept, slope, and changepoint parameters were evaluated in the following models.

(c) Model 3: mixed segmented model with independent random effects on each model parameter, that is, the covariance matrix is diagonal.

(d) Model 4: mixed segmented model with diagonal block covariance matrix, in which the second block assumes correlated random effects.

(e) Model 5: mixed segmented model with block diagonal covariance matrix, in which both blocks assume correlated random effects.

The models were compared using the Akaike information criterion (AIC) and the model with the lowest AIC value was selected as the best fitted model.

The 95% confidence intervals (95%CI) of the independent variables of the best fitted model were evaluated to identify those with a significant association with the variable of interest (the HC z-score).

Data were analyzed using the statistical programs R (http://www.r-project.org) and Stata version 14.0 (https://www.stata.com).

Ethical aspects

The research meets the criteria of *Resolution n. 466/2012* of the Brazilian National Health Council. It is part of the project *Congenital Zika Virus Syndrome, Seroprevalence and Spatial and Temporal Analysis of Zika and Chikungunya Viruses in Maranhão*, approved by the Ethics Research Committee of the University Hospital of the Federal University of Maranhão (CEP/UFMA), Certificate of Presentation of Ethical Appreciation (CAAE n. 65897317.1.0000.5086). Mothers and guardians who agreed to participate in the study signed an Informed Consent Form.

Results

Most children were born at full term (83.8%) and were male (59.5%). High proportion of children with microcephaly had the condition observed at birth (58.1%). Most mothers reported the presence of symptoms compatible with ZIKV infection during pregnancy in the first trimester of pregnancy (68.9%; Table 1).

In the imaging scans, 74.3% of the children had isolated supratentorial lesions, and 45.9% were diagnosed with severe brain parenchymal atrophy (Table 1).

The number of HC measurements obtained from medical records for each child ranged from 1 to 19. At birth, four children did not have the HC measurement recorded. Including the birth measurements, 667 records of the sample were analyzed, which is an average of nine measurements for each child. Children were followed up to a mean age of 32.2 months (standard deviation – SD = 8.5) and 18 children were followed up after 36 months of age (minimum 11 months; maximum 39 months).

After birth, 91.9% of the 74 children were considered microcephalic, with all HC z-score measures < -2 (63 children) or all but one measure < -2 (four children). One child began to show values of HC z-score < 2 after five months of age and was also considered microcephalic. In one child, it was not

Table 1

Clinical characteristics of children with congenital syndrome associated with Zika virus infection (n = 74). State of Maranhão, Brazil, 2015-2019.

Characteristic	n (%)	Mean (SD)
Sex		
Female	30 (40.5)	
Male	44 (59.5)	
Gestational age		
Preterm	10 (13.5)	
Full term	62 (83.8)	
Post-term	2 (2.7)	
Birthweight (n = 73)		2.845g (502)
Length at birth (n = 58)		45.9cm (3.4)
Head circumference at birth (n = 70)		30.0cm (2.4)
Head circumference z-score at birth		2.8 (1.6)
> 2	27 (36.5)	
< 2 and > 3	11 (14.9)	
< 3	32 (43.2)	
Not recorded	4 (5.4)	
Maternal infection symptoms		
First gestational trimester	51 (68.9)	
Second or third gestational trimester	23 (31.1)	
Brain parenchymal atrophy		
None	11 (14.9)	
Mild to moderate	29 (39.2)	
Severe	34 (45.9)	
Location of brain lesions		
Supratentorial only	55 (74.3)	
Supratentorial and infratentorial	19 (25.7)	

SD: standard deviation.

possible to define the HC classification since their z-score values ranged between 1.3 and 2.3 without any apparent pattern.

Different patterns of the individual HC z-score curves were observed for each child, with a non-linear trend (Figure 1a).

When analyzed together, the sample showed a significant reduction in the HC z-score in the first 3 months of life. At birth, mean HC z-score was 2.7 ± 1.6 and at 3 months, the mean dropped to 5.5 ± 2.2. At 6 and 12 months of age, the mean HC z-score remained unchanged (5.5 ± 2.2 at 6 months; 5.5 ± 2.4 at 12 months). At 24 months, the mean HC z-score was 6.7 ± 1.9. Only three children were evaluated at exactly 36 months of age, with a mean HC z-score of 3.8 ± 1.8 (Figure 1b).

Among the models studied, Model 3, which fitted a mixed segment model with independent random effects for each parameter of the model, presented the best fit and the lowest AIC value (Table 2).

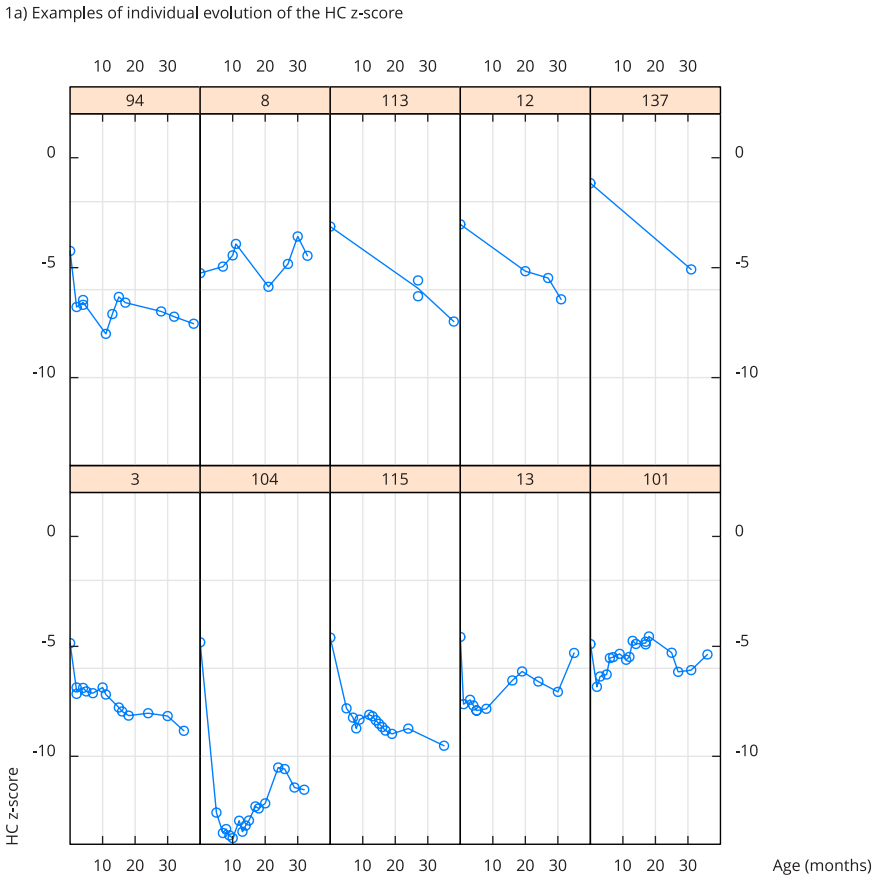
According to this model, the presence of severe brain parenchymal atrophy was associated with a reduction in the HC z-score in the first 3 years of life (Table 3; Figure 1c).

Children whose mothers had infectious symptoms in the first trimester of pregnancy also had a reduced HC z-score during the study period (Table 3; Figure 1d).

There was no difference in the evolution of the z-score when comparing children with isolated supratentorial lesions and children with both supratentorial and infratentorial lesions (Table 3).

Figure 1

Standardized measurements for age and sex (z-score) of head circumference (HC) of children with congenital syndrome associated with Zika virus infection. Maranhão State, Brazil, 2015-2019.



(continues)

Discussion

In our study, the HC z-score in children with CZS showed a tendency for a sharp drop in in the first 3 months of life, remaining relatively stable thereafter. Furthermore, severe brain parenchymal atrophy and the presence of infectious symptoms in the first trimester of pregnancy were associated with a reduction in the HC z-score in the first 3 years of life.

Previous studies have shown similar findings, with a drop in HC z-score up to the second year of life [10,11,12]. The HC z-score was much lower than expected for children with severe cerebral palsy. At 12 months of age, children with CZS had a mean z-score of 5.5, with some children reaching 12.9, whereas children with moderate to severe cerebral palsy present a mean z-score of 2.0. At 24 months, the mean HC z-score (6.7) was lower than that reported in a previous study for age-matched children with CZS (5.43) [10].

The decrease in the HC z-score was reflected in the significant increase in the rate of children with microcephaly observed after birth, which rose from 58.1% to 91.9%. The proportion of children with microcephaly at birth was within the wide range of 37.9% to 88.6%, as reported in the literature [2,11,19]. This variation seems to be due to the different inclusion criteria in the various studies. The expressive

Figure 1 (continued)

1b) Mean and standard deviation of the HC z-score by age (n = 74)

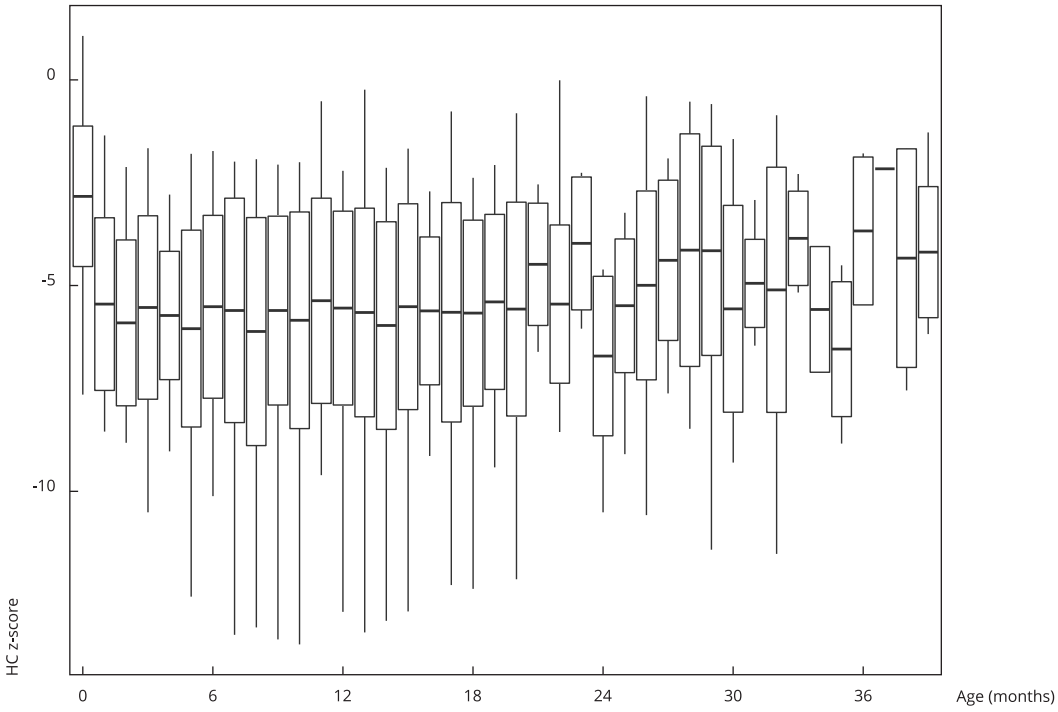


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Table 2

Akaike information criterion (AIC) values for adjusted models of head circumference z-score of children with congenital syndrome associated with Zika virus infection. São Luís, Maranhão State, Brazil, 2015-2019.

Model	AIC
1	2,198.688
2	1,978.995
3	1,909.630
4	2,093.519
5	2,172.849

rate of microcephaly after birth has been reported previously: a cross-sectional study conducted by Satterfield-Nash et al. [20] showed that 15 out of 19 children had a diagnosis of severe microcephaly between 18 and 24 months of age.

Even children with CZS born with an HC considered normal evolved to postnatal microcephaly, as already indicated in previous studies [21,22]. This reinforces the need to investigate and monitor HC growth and to include children in programs to stimulate the development of any children with suspected CZS, even if they are not diagnosed with microcephaly at birth.

Table 3

Adjusted analysis of factors associated with the head circumference z-score of children with congenital syndrome associated with Zika virus infection. São Luís, Maranhão State, Brazil, 2015-2019.

Characteristic	Coefficient	95%CI
Maternal infection symptoms		
Second or third gestational trimester	-	-
First gestational trimeste	0.9	1.6; 0.1
Brain parenchymal atrophy		
None	-	-
Mild to moderate	0.8	1.8; 0.2
Severe	2.6	3.6; 1.5
Location of brain lesions		
Supratentorial lesions only	-	-
Supratentorial and infratentorial	0.2	1.0; 0.7

95%CI: 95% confidence interval.

Figure 1 (continued)

1c) Mean and standard deviation of the HC z-score according to the degree of brain parenchyma atrophy

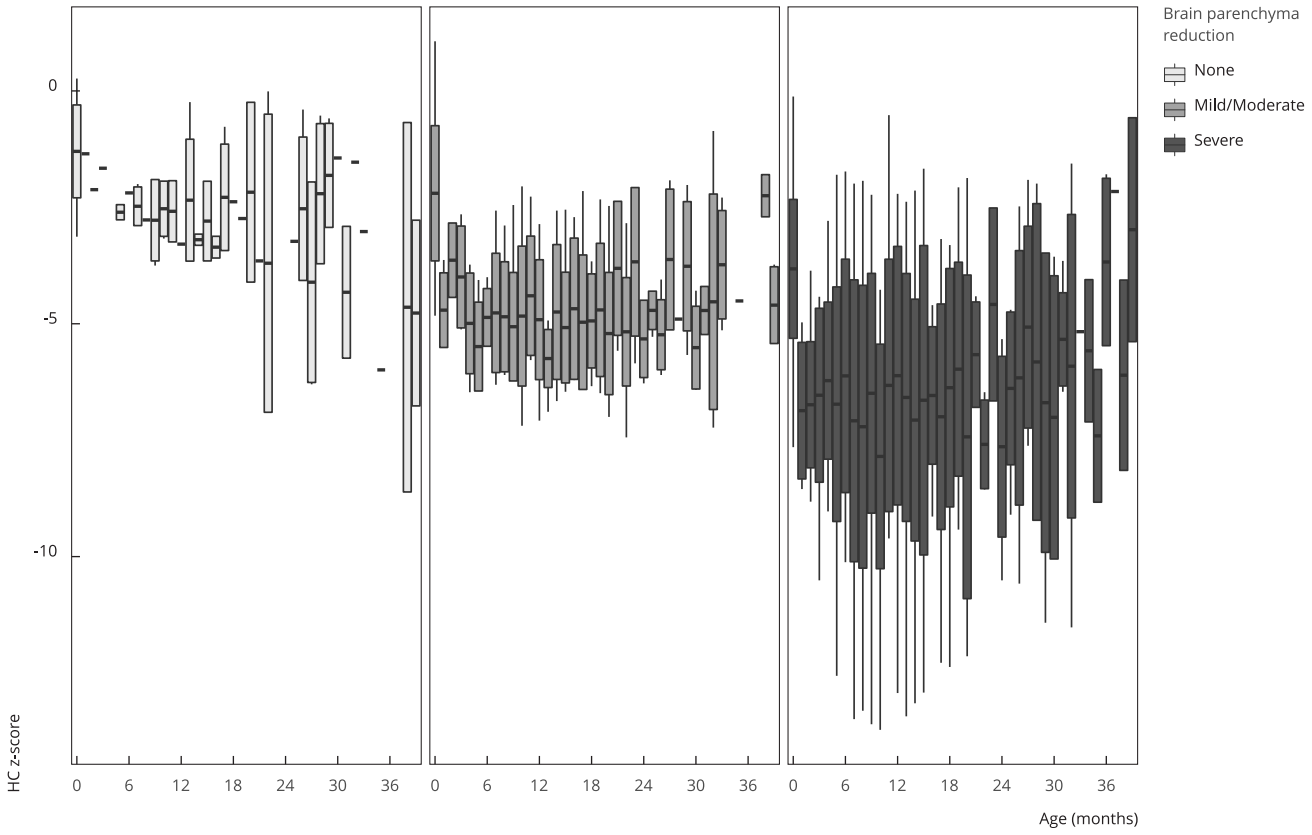

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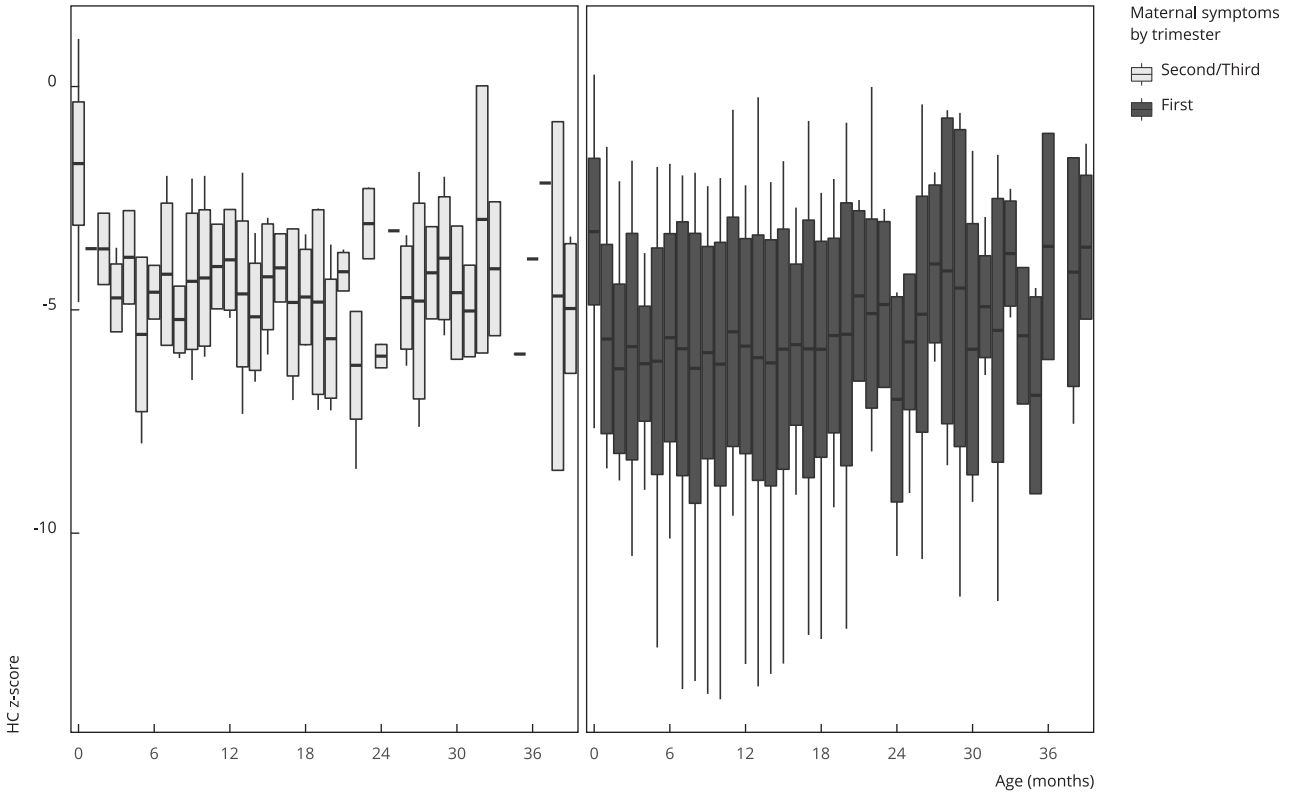
Figure 1 (continued)

1d) Mean and standard deviation of the HC z-score according to the presence of maternal symptoms of infection during pregnancy



Notes: Figure 1c: line inside box is the mean head circumference z-score, upper and lower box boundaries are mean +/- standard deviation, with the bars representing minimum and maximum values. The measurements vary in the groups classified according to the degree of atrophy of the brain parenchyma at the different ages. When few or no measures are available, or when there is little variability, gaps are seen in the graph.
Figure 1d: line inside box is the mean head circumference z-score, upper and lower box boundaries are mean +/- standard deviation, with the bars representing minimum and maximum values. The measurements vary in the groups classified according to the presence of maternal symptoms of infection during pregnancy at the different ages. When few or no measures are available, or when there is little variability, gaps are seen in the graph.

The identification of severe brain parenchymal atrophy as a factor associated with a reduction in the HC z-score highlights the importance of complementing the physical examination with the evaluation of neuroimaging scans to determine the prognosis of head growth in children with CZS.

A previous study had already indicated that ZIKV infection in early pregnancy would be associated with a more serious condition in the child [14], with the need to emphasize the orientation of preventive measures against ZIKV infection in pregnant women, especially during this period.

The presence of infratentorial lesions in association with supratentorial alterations could represent an earlier and more aggressive involvement of the central nervous system, which could lead to a lower potential for head growth. However, our study did not find evidence to support this hypothesis.

The continuous deceleration of head growth found in this study seems to reflect a severe involvement of the central nervous system by congenital ZIKV infection and a reduced capacity for growth and neurological development in these children. In typically developing children, an increase of 1cm in HC per month is expected in the first year of life, and at the end of this period the brain completes half of its postnatal growth and already corresponds to 75% of adult size [23]. In children with CZS,

growth is much lower than expected and therefore a marked drop in the z-score occurs in the first months of life.

The lack of improvement in the HC z-score (catch-up) shown by children with CZS is an indication of poor prognosis. Children with microcephaly of other etiologies that do not present catch-up of the HC measure are at greater risk of presenting learning deficits and cerebral palsy [8].

Although part of the sample does not have laboratory confirmation of ZIKV infection, studies have shown that the syndromic diagnosis of CZS, based on clinical and imaging characteristics, is valid and recommended [15,24,25] since laboratory tests currently available have limitations in identifying congenital infection after the child is born, including a high rate of false negatives [15,16].

A possible limitation for the study was that the development of hydrocephalus, a complication that has been observed in some children with CZS [26] and that interferes with the HC measurement, was not investigated. The non-inclusion of this analysis is due to the performance of neuroimaging scans, which would allow the diagnosis of hydrocephalus, not being undertaken in a systematic way in this population. Children who were born with hydrocephalus or presented an evolution that suggested the presence of hydrocephalus were excluded from the sample to avoid any interference from this variable in the results.

A limitation of the study is that the more severe cases of CZS are more likely to be diagnosed and referred to health services and thus would have been included in the study, resulting in sample selection bias. Another limitation is the lack of control on the influence of socioeconomic indicators. Previous study showed that lower educational level, low household income [27], and environmental factors, including malnutrition and toxins [28], are associated with more severe cases of prenatal exposure do ZIKV.

A strong point for our study is the larger sample size (74 children) and greater number of HC observations (667 records of the standardized HC value) in comparison to previous studies, in addition to the longer period of follow-up of children [9,10,11,14,29]. Longitudinal studies provide more accurate data on the impact of congenital Zika virus infection on the head circumference, in view of the possibility of errors in this measurement at birth [30].

Furthermore, the use of adjusted mixed segmented models is another strength of the study. This analysis allowed us to identify factors associated with the evolution of head circumference, despite the variability in the number of assessments and the age at which head circumference measurements were taken.

Conclusion

The decrease of HC z-score of CZS children in the first 3 months demonstrates that the HC increased more slowly than expected, reflecting the reduced potential for growth and development of the central nervous system of these children. The prognosis of head growth in the first 3 years of life is worse when maternal infection occurred in the first gestational trimester and in children who had severe brain parenchymal atrophy.

Contributors

E. H. M. Takahasi paticipated on the design, analysis, and interpretation of data, article writing, final approval of the version to be published. M. T. S. S. B. Alves and M. R. C. Ribeiro contributed on the conception and interpretation of data, relevant critical review of intellectual content, final approval of the version to be published. A. M. Santos and M. A. G. Campos contributed on the analysis and interpretation of data, relevant critical review of intellectual content, final approval of the version to be published. V. M. F. Simões and D. B. Miranda-Filho contributed on the interpretation of data, relevant critical review of intellectual content and final approval of the version to be published. G. A. Amaral participated on the design and interpretation of data, relevant critical review of intellectual content and final approval of the version to be published. P. S. Sousa collaborated on the project design, interpretation of data, relevant critical review of intellectual content and final approval of the version to be published. A. A. M. Silva participated on the project design, analysis and interpretation of data, relevant critical review of intellectual content and final approval of the version to be published. All authors are responsible for all aspects of the study, ensuring the accuracy and completeness of any of its parts.

Additional informations

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Resumo

Pouco se sabe sobre a evolução do perímetro cefálico (PC) em crianças com síndrome congênita associada à infecção pelo vírus Zika (SCZ) em acompanhamentos contínuos. Este estudo buscou avaliar o crescimento do PC em crianças com SCZ nos primeiros três anos de suas vidas e identificar os fatores associados a ele. Os dados do PC ao nascimento e obtidos em consultas neuropediátricas de 74 crianças com SCZ foram coletados no Cartão da Criança, nos laudos paternos e em seus prontuários. Os preditores de escore-z para PC foram investigados utilizando-se diferentes modelos de efeitos mistos. O critério de informação de Akaike foi utilizado para selecionar os modelos usados. O escore-z de PC diminuiu de -2,7 ± 1,6 ao nascimento para -5,5 ± 2,2 aos 3 meses de idade, mas permaneceu relativamente estável desde então. No modelo ajustado selecionado, a presença de atrofia parênquimal cerebral grave e sintomas maternos de infecção no primeiro trimestre de sua gravidez estiveram associados a uma redução mais acentuada no escore-z de PC nos primeiros três anos de vida dos participantes. A diminuição do escore-z de PC em crianças com SCZ nos primeiros 3 meses de sua vida monstra o potencial reduzido de crescimento e desenvolvimento do sistema nervoso central dessas crianças. O prognóstico de crescimento do perímetro cefálico nos primeiros 3 anos de vida é pior quando a infecção materna ocorreu no primeiro trimestre gestacional e em crianças que tiveram atrofia parênquimal grave.

Zika Virus; Antropometria; Cefalometria; Crescimento; Modelos Estatísticos

Resumen

Se conoce poco sobre la evolución del perímetro cefálico (PC) en niños con síndrome de Zika congénito (SZC) en los seguimientos continuos. El objetivo del estudio fue evaluar el crecimiento del PC en niños con SZC en los primeros 3 años de vida e identificar los factores asociados. Se recogieron datos del PC al nacimiento y obtenidos en las consultas de neuropediatría de 74 niños con SZC a partir de la Tarjeta del Niño, los informes de los padres y los registros médicos. Se investigaron los predictores de la puntuación Z del PC mediante diferentes modelos de efectos mixtos; se utilizó el criterio de información de Akaike para la selección del modelo. La puntuación Z del PC disminuyó de -2,7 ± 1,6 al nacer a -5,5 ± 2,2 a los 3 meses de edad, pero a partir de entonces se mantuvo relativamente estable. En el modelo ajustado seleccionado, la presencia de atrofia grave del parénquima cerebral y los síntomas maternos de infección en el primer trimestre del embarazo se asociaron con una reducción más pronunciada de la puntuación Z del PC en los primeros 3 años de vida. La disminución de la puntuación Z del PC en los niños con SZC durante los primeros 3 meses demuestra el menor potencial de crecimiento y desarrollo del sistema nervioso central de estos niños. El pronóstico del crecimiento de la cabeza en los primeros 3 años de vida es peor cuando la infección materna se produjo en el primer trimestre gestacional y en los niños que tenían una atrofia grave del parénquima cerebral.

Virus Zika; Antropometría; Cefalometría; Crecimiento; Modelos Estadísticos

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