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Characteristics of children of the Microcephaly Epidemic Research Group Pediatric Cohort who developed postnatal microcephaly

Regina Coeli Ferreira Ramos¹, Demócrito de Barros Miranda-Filho²,
 Celina Maria Turchi Martelli³, Thália Velho Barreto de Araújo⁴,
 Maria Angela Wanderley Rocha⁵, Vanessa van der Linden⁶,
 Maria Durce Costa Gomes de Carvalho², Laura Cunha Rodrigues⁷,
 Ulisses Ramos Montarroyos², Wayner Vieira de Souza³, Maria de Fátima Pessoa
 Militão de Albuquerque⁸, Elizabeth B. Brickley⁷ & Ricardo Arraes de Alencar Ximenes⁹✉

The number of studies published on postnatal microcephaly in children with Congenital Zika Syndrome is small, clinical presentations vary and aspects of the evolution of these children remain unclarified. The present case series examined clinical characteristics and assessed the growth velocity of the head circumference, weight and height Z-scores in 23 children who developed postnatal microcephaly during follow-up in the Microcephaly Epidemic Research Group Pediatric Cohort. To estimate the change in the head circumference, weight and height Z-scores over time and compare the mean difference between sexes, we used multilevel mixed-effects linear regressions with child-specific random effects. Among these children, 60.9% (n = 14/23) presented with craniofacial disproportion, 60.9% (n = 14/23) with strabismus, 47.8% (n = 11/23) with early onset seizures, 47.8% (n = 11/23) with dysphagia and 43.5% (n = 10/23) with arthrogryposis. Of the 82.7% (n = 19/23) children who underwent neuroimaging, 78.9% (n = 15/19) presented with alterations in the central nervous system. Monthly growth velocity, expressed in Z-scores, of the head circumference was -0.098 (95% CI -0.117 to -0.080), of weight was: -0.010 (95% CI -0.033 to 0.014) and of height was: -0.023 (95% CI -0.046 to 0.0001). Postnatal microcephaly occurred mainly in children who had already presented with signs of severe brain damage at birth; there was variability in weight and height development, with no set pattern.

Microcephaly is the most characteristic component of Congenital Zika Syndrome (CZS), likely due to the presence of craniofacial disproportion^{1–3}. Other clinical features may also be involved in CZS, such as ophthalmologic abnormalities, including retinal and macular changes, strabismus, or microphthalmia⁴, in addition to neurological and musculoskeletal changes in newborns, such as arthrogryposis^{5,6}. The most frequently observed abnormalities in the central nervous system (CNS) are intracranial calcifications, malformations of cortical development, a reduced volume of the cerebral white and gray matter, and ventriculomegaly^{5,6}. Although the most severe cases of CNS involvement are already well known, the phenotypic spectrum of CZS has not been fully defined and less severe cases, with minor repercussions on the CNS, have been described. There are reports in the literature of children with prenatal Zika virus (ZIKV) exposure who presented with late-onset microcephaly^{5,7–12}, thereby

¹Departamento de Infectologia Pediátrica, Hospital Universitário Oswaldo Cruz, Recife, Brazil. ²Pós-Graduação em Ciências da Saúde, Universidade de Pernambuco, Recife, Brazil. ³Instituto Aggeu Magalhães, Fiocruz, Recife, PE, Brazil. ⁴Programa de Pós-Graduação em Saúde Coletiva, Universidade Federal de Pernambuco, Recife, Brazil. ⁵Faculdade de Ciências Médicas, Universidade de Pernambuco, Recife, Brazil. ⁶Hospital Barão de Lucena, Recife, Brazil. ⁷Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK. ⁸Departamento de Saúde Coletiva, Instituto Aggeu Magalhães, Fiocruz, Recife, Brazil. ⁹Universidade Federal de Pernambuco and Universidade de Pernambuco, Recife, Brazil. ✉email: raaximenes@uol.com.br

justifying the need for clinical follow-up for early identification and intervention^{13,14}. However, the number of studies investigating postnatal microcephaly is small, clinical presentations vary and some aspects of the evolution of these children need to be better understood and characterized.

Although head circumference (HC) measurement is recommended for individual follow-up from 0 to 24 months, weight and height are accepted as the most important parameters in relation to the assessment of child growth¹⁵. Weight may be influenced by several factors while length is considered a more reliable indicator. Variation in length in the first year of life is largely influenced by perinatal factors (e.g., maternal age, alcohol use, prematurity), but after 12 months, determination is predominantly genetic. However, other factors like structural damage to the CNS of children, as it occurs in children with congenital Zika-related microcephaly, may affect their weight and height development through different mechanisms (e.g., altered feeding patterns, high rates of dysphagia, and endocrine disorders)^{16–18}.

The present study assessed the growth velocity of the HC, weight and height Z-scores among children born during the 2015–2017 microcephaly epidemic in Pernambuco, Brazil, who presented at birth with appropriate HC for gestational age (GA) and sex, according to the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) curves¹⁹ but later developed microcephaly.

Methods

This is a case series of children who developed postnatal Zika-related microcephaly and were followed-up as part of the Microcephaly Epidemic Research Group Pediatric Cohort (MERG-PC)²⁰.

For this study, we defined microcephaly at birth as a HC of at least 2 standard deviations (SD) below the mean for GA and sex, according to INTERGROWTH-21st curves¹⁹, and in the follow-up, according to the World Health Organization (WHO) Infant Growth Standards^{12,21}. The definition of CZS was based on the criteria of França et al.²²: confirmed cases were defined as those with laboratory evidence for ZIKV infection (maternal reverse transcription polymerase chain reaction [RT-PCR] or serology during pregnancy and/or newborn positive for ZIKV Immunoglobulin (Ig)M in the cerebrospinal fluid [CSF]), independently of other findings. Probable cases of CZS were classified based on neuroimaging, and negative laboratory results for ZIKV and for other congenital infections (cytomegalovirus, toxoplasmosis, syphilis, and human immunodeficiency virus [HIV]). Possible cases presented with characteristic neuroimaging findings for CZS (computed tomography (CT), magnetic resonance imaging (MRI) or transfontanelar ultrasound [TFUS]), no laboratory evidence of ZIKV infection and without results for one or more of the three infections (syphilis, toxoplasmosis, and cytomegalovirus)²². HC was measured with an inelastic measuring tape positioned over the occipital prominence and the arch of the eyebrow. With the child's head fixed, the tape was placed firmly around the frontal bone over the supraorbital sulcus and then wrapped around the head, at the same level on each side, over the maximal occipital prominence^{23,24}. Term births were defined as those occurring with 37 or more weeks of GA. Birth weight was assessed and classified as appropriate, small or large for GA and sex (AGA, SGA and LGA respectively), using the INTERGROWTH-21st standards^{19,25–28}. For prospective follow-up from birth up to 36 months of age, repeated HC, weight and length measurements were performed according to the routine protocol (20), in addition to brain imaging when indicated. Z-scores for HC, weight, length, and body mass index (BMI) were calculated using the WHO anthropometric calculator, the WHO Anthro 3.2.2²⁹. Microcephaly cases were classified as severe when the HC Z-score was ≤ -3 SD of the growth curves established according to sex and GA, and moderate when the HC Z-score was ≤ -2 and > -3 SD. Child's length was measured with a horizontal stadiometer. Weight was assessed on a calibrated precision digital platform scale. As children were unable to remain in an upright position without assistance, they were assessed in terms of the following weight difference: weight of adult assistant plus child weight minus adult assistant weight. The BMI was calculated by dividing weight in kilograms by squared height in meters and assessed against the WHO Child Growth Standards³⁰. Ophthalmologic assessment was conducted through study of the retina. All selected children presented a HC at birth that did not exceed 2SD below the mean for GA and sex, and therefore did not meet the definition of microcephaly at birth (at least 2SD below the mean, by the -Z score)²⁹.

Statistical analysis was performed using STATA SE 14.2 (College Station, TX, USA). Categorical variables were summarized in absolute numbers and percentages. Continuous variables were summarized as means and standard deviations. To estimate the change in HC (Z-score), weight (Z-score) and height (Z-score over time) we used multilevel mixed-effects linear regressions with child-specific random effects. To compare the mean Z-score difference between groups over time we used mixed effects random intercept regression.

The Research Ethics Committee of the Hospital Universitário Oswaldo Cruz approved the study on October 10, 2016 (Ethical Clearance Certificate—CAAE 52803316.8.0000.5192). The children's legal guardians signed an informed consent form to participate in the study. All research was conducted in accordance with the Declaration of Helsinki and Brazil's codes and regulations regarding research on human subjects.

Results

In the MERG-PC, 23 children who presented at birth with a HC $> 2SD$ (mean (SD) for HC Z-score = -1.09 (0.95)) later developed postnatal microcephaly (Table 1). These children were prospectively followed up during a median of 4 visits (P_{25} – P_{75} : 3 to 5, range: 2 to 8) with the pediatric infectious disease division. Of the 23 children with late-onset microcephaly, the HC at birth ranged between 32 and 33 cm, and 9 (39.2%) children were female. Seventeen (73.9%) of the children were born appropriate for gestational age (AGA), 2 (8.7%) were born small for gestational age (SGA), and 1 (4.3%) was born large for gestational age (LGA). Of the 20 with available information on gestational age at delivery, 100% were born at term (37–41 weeks of gestation). Positive results for ZIKV were obtained in 8 of the 11 (72.7%) children whose CSF was tested at birth by IgM Antibody Capture Enzyme Linked Immunosorbent Assay (MAC-ELISA).

Groups	Mean Z-score at birth (95% CI)	Mean monthly change in Z-score (95% CI)	p-value
Head circumference Z-score			
All	- 1.09 (- 1.50 to - 0.69)	- 0.098 (- 0.117 to - 0.080)	<0.001
Sex			
Female	- 1.45 (- 1.68 to - 1.21)	- 0.082 (- 0.104 to - 0.060)	<0.001
Male	- 0.87 (- 1.53 to - 0.21)	- 0.111 (- 0.139 to - 0.084)	<0.001
Comparison between sexes			
Female	Reference	Reference	-
Male	0.58 (- 0.24 to 1.40)	0.095 (- 1.028 to 1.217)	0.869
p-value	0.1590	-	-
Length z-score			
All	- 1.30 (- 1.78 to - 0.83)	- 0.023 (- 0.046 to 0.0001)	0.050
Sex			
Female	- 1.24 (- 2.23 to - 0.25)	- 0.032 (- 0.054 to - 0.010)	0.005
Male	- 1.34 (- 1.92 to - 0.76)	- 0.014 (- 0.050 to 0.023)	0.464
Comparison between sexes			
Female	Reference	Reference	-
Male	- 0.11 (- 1.19 to 0.98)	0.689 (- 0.510 to 1.887)	0.260
p-value	0.8365	-	-
Weight z-score			
All	- 0.65 (- 0.97 to - 0.33)	- 0.010 (- 0.033 to 0.014)	0.408
Sex			
Female	- 0.49 (- 1.15 to 0.17)	- 0.040 (- 0.067 to - 0.013)	0.004
Male	- 0.75 (- 1.14 to - 0.37)	0.016 (- 0.018 to 0.050)	0.361
Comparison between sexes			
Female	Reference	Reference	-
Male	- 0.26 (- 0.98 to 0.46)	0.509 (- 0.550 to 1.567)	0.346
p-value	0.4459	-	-

Table 1. Mean Z-score at birth and monthly change in head circumference, weight and length of children who developed postnatal microcephaly in the Microcephaly Epidemic Research Group Pediatric Cohort (MERG-PC), in Pernambuco, Brazil.

Of the 23 children with postnatal microcephaly, 15 (65.2%) presented with CNS abnormalities (i.e., ventriculomegaly, cerebral calcifications, cerebellar hypoplasia, trunk hypoplasia, cisterna magna alteration, cortical development disorder, and cortical atrophy) in at least one neuroimaging exam by TFUS, CT, and/or MRI (Table 2 and Supplementary Table 1). Four of the 23 children (17.4%) did not undergo imaging exams (i.e., due to lack of clinical indication), and 4 underwent imaging exams but presented with no abnormalities (one child underwent CT and MRI, two underwent CT and one underwent MRI and TFUS) (Supplementary Table 1). Of the 17 children who underwent CT, 12 (70.6%) presented with imaging abnormalities; of these, 12 (100%) presented with calcifications, 10 (83.3%) with ventriculomegaly and 2 (16.7%) with cortical atrophy. Ten children (43.5%) underwent brain MRIs, and 8 (80.0%) presented with ventriculomegaly. Of the 23 children in the study, 14 (60.9%) presented with craniofacial disproportion, 14 with strabismus, 11 (47.8%) with early onset seizures, 11 (47.8%) with dysphagia, and 10 with arthrogryposis (43.5%) (Table 1 and Supplementary Table 2). With regard to nutritional status at the latest assessment (median 23.3 months, P_{25} - P_{75} 18.8 to 27.8), the BMI was within the appropriate parameters for 91.3% of the children. Of the 20 children who underwent funduscopy and/or RetCam examinations, 8 (40.0%) presented with an abnormality, of which 6 (30.0%) presented with an abnormality in the fundus of the eye, 5 (25.0%) in the optic nerve, and 6 (30.0%) in the retina.

A monthly (i.e., per 30 days) decrease in the HC Z-score (- 0.098 (95% CI - 0.117 to - 0.080, $p < 0.001$)) was observed both when the children were assessed together and when the assessment was performed separately by sex (male: - 0.111 (- 0.139 to - 0.084); female: - 0.082 (- 0.104 to - 0.060)). The difference between sexes was not statistically significant, $p = 0.869$ (Table 2 and Fig. 1 (1st graph)). The monthly change in Z-scores for length and weight were, respectively, - 0.023 (95% CI - 0.046 to 0.0001, $p = 0.050$) and - 0.010 (95% CI - 0.033 to 0.014, $p = 0.408$) and the difference between sexes was not statistically significant (Table 2 and Fig. 1 (2nd and 3rd graphs)). Most children at the time of the final neurodevelopmental assessment were aged between 7 and 32 months (median, 18 months).

Eye abnormalities	Frequency among evaluated children	Frequency overall
Strabismus	14/20, 70.0%	14/23, 60.9%
Nystagmus	4/19, 21.1%	4/23, 17.4%
Microphthalmia	1/19, 5.3%	1/23, 4.3%
Motor and limb abnormalities		
Arthrogryposis distal	6/19, 31.6%	6/23, 26.1%
Arthrogryposis general	4/19, 21.1%	4/23, 17.4%
Club foot	10/20, 50.0%	10/23, 43.5%
Hip dysplasia	5/19, 26.3%	5/23, 21.7%
Other affected systems		
Gastroesophageal reflux	1/7, 14.3%	1/23, 4.3%
Dysmorphic features	20/23, 87.0%	20/23, 87.0%
Craniofacial disproportion	14/19, 73.7%	14/23, 60.9%
Hand contractures	13/19, 6.8%	13/23, 56.5%
Neurologic abnormalities		
Epileptic seizures	11/22, 50.0%	11/23, 47.8%
Brain imaging abnormalities		
Ventriculomegaly	12/19, 63.2%	12/23, 52.2%
Calcification	12/19, 63.2%	12/23, 52.2%
Cortical atrophy	9/19, 47.4%	9/23, 39.1%
Lissencephaly/pachygyria	3/19, 15.8%	3/23, 13.0%

Table 2. Clinical (ophthalmologic, neurologic, orthopedic) and brain imaging characteristics of children who developed postnatal microcephaly in the Microcephaly Epidemic Research Group Pediatric Cohort (MERG-PC), in Pernambuco, Brazil.

Discussion

This article has presented a case series of 23 children who presented with a normal Z-score for head circumference at birth and later developed microcephaly. Within this case series, most children presented with severe anatomical lesions in the CNS and almost 50% had ophthalmological abnormalities. The monthly growth velocity of the head circumference in these children, expressed as a Z-score, was -0.098 (95% CI -0.117 to -0.080).

In addition to the report of our case series, postnatal microcephaly related to congenital ZIKV infection has been described elsewhere^{22,28,31,32}, although studies were scarce and most refer to a smaller number of cases, ranging between 3 and 13 cases^{22,28,31,32}. Only Cavalcante et al.³³ described a number similar to ours, totaling 28 children. Although the mechanism(s) that leads to postnatal microcephaly are unclear, possible explanations proposed by van der Linden et al.²⁸ include the early intrauterine destruction of progenitor cells or other neural cells, the persistence of the inflammatory response or the persistence of the infection in the neural cells. Another factor that may influence the prenatal or postnatal development of microcephaly could be the location of the brain damage. Additional studies are still needed to further clarify this mechanism.

The measurement of HC from 0 to 24 months (i.e., the period with the greatest postnatal growth) is an important anthropometric indicator of brain growth^{34,35} and risks of neurological development deviations. By 12 months of age, the brain will have completed half of its postnatal growth and would be expected to reach 75% of the adult brain size in children without exposure to congenital infections^{34,36}. The assessment of head circumference growth using the Z-score enables standardized comparisons that account for age and sex. Published studies that reported postnatal microcephaly have not described the velocity of head circumference growth over time, making it difficult to compare to our results. The speed of decline observed in our case series was lower than that observed in children who already presented with microcephaly at birth, which has been reported as a monthly change in Z-score of -0.46 in the study by Silva et al.³². The difference is likely to be associated with the severity of neurological damage and/or different follow-up times in the two studies. Indeed, when the observation time of the children in our study was restricted to a period of 8 months, similar to Silva et al.³², we obtained a similar monthly growth velocity of -0.32 (95% CI -0.42 to -0.21). This follow-up time corresponds to the period in which HC growth is more accelerated in healthy children, which would make the difference more evident between the values observed in these children in relation to the standard for age and sex. Aguiar et al.³⁷ followed a group of 87 children with CZS, of whom 77% presented with microcephaly at birth, for three years, a period of follow-up similar to our study and also observed an impairment in the mean HC Z-score during the study period. As the reported HC Z-scores decreased from -2.75 ± 0.2 SD at birth to -5.2 ± 0.3 SD between 31 and 36 months, this suggests the children with CZS would have experienced a monthly growth velocity of approximately -0.07 , similar to that observed in the current study. However, this comparison needs to be interpreted with caution as the monthly growth velocity was estimated using only the extreme values, not taking into account variations throughout the observation period, and was based on a sample of children with CZS with and without microcephaly at birth. Further studies with larger sample sizes, such as the planned individual participant data meta-analyses of the Zika Brazilian Cohorts-Consortium³⁸ will be necessary to more accurately

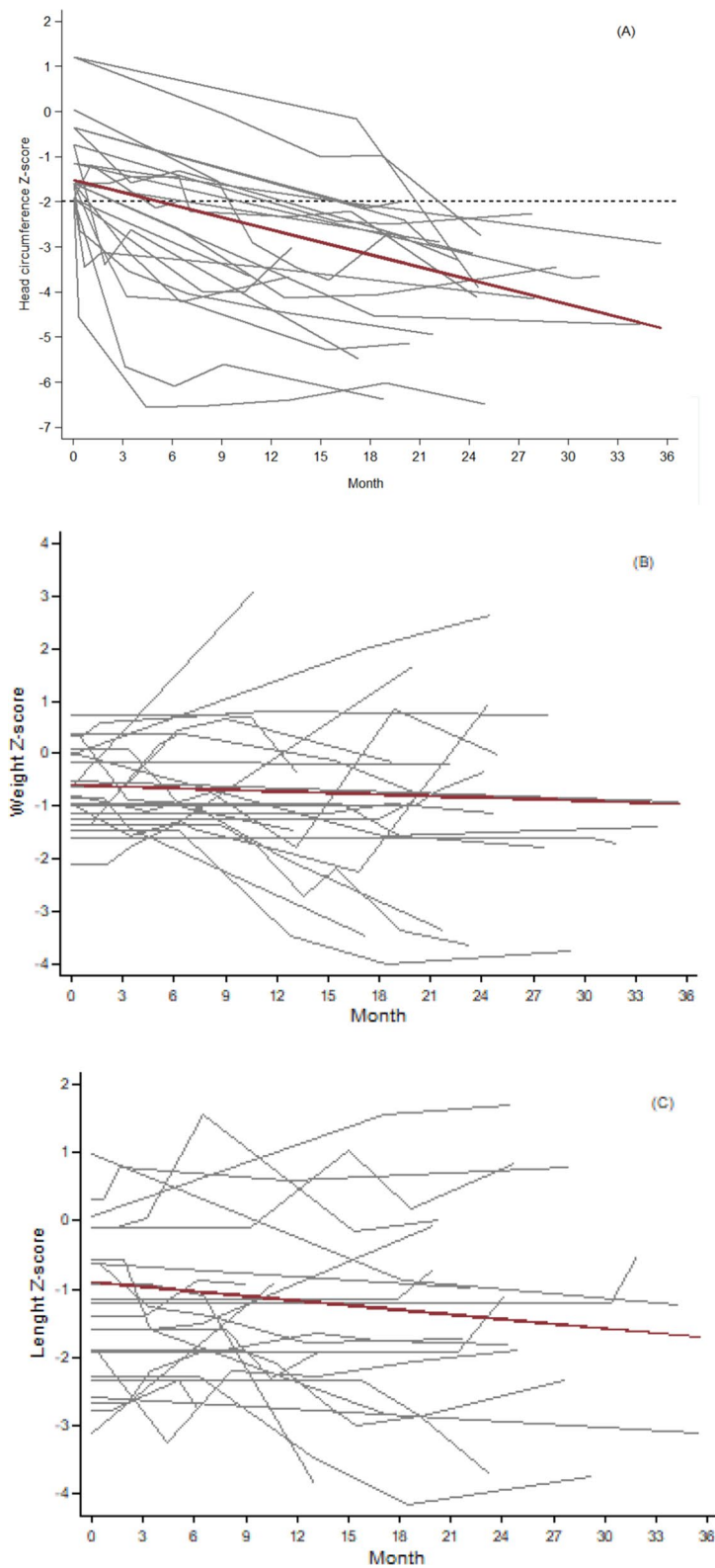


Figure 1. Monthly growth of head circumference (A), weight (B) and length (C) of children who developed postnatal microcephaly in the Pediatric Cohort of the Microcephaly Epidemic Research Group (MERG-PC), in Pernambuco, who developed postnatal microcephaly.

compare the findings across study sites. Although HC at birth and during development are associated with sex and is lower in female children^{35,39,40}, we observed no statistically significant differences between the sexes in terms of growth velocity of HC, suggesting that the mechanism underlying delayed microcephaly is similar in children of both sexes.

The main alterations observed in the neuroimaging exams of the children that made up our case series were reduced brain volume, ventriculomegaly, subcortical calcifications and cortical malformations, similar to that described in the study by Van der Linden et al.²⁸. Studies comparing characteristics of microcephaly at birth with postnatal microcephaly^{31,33} have reported differences in the frequency and/or type of structural changes. Aragão et al.³¹ observed cerebral calcifications in the cortex and subcortical white matter in both groups, although cerebral calcifications with another location were observed only in microcephaly at birth. On the other hand, polymicrogyria, possibly a less severe malformation of cortical development, was not detected in the microcephaly group at birth, but was observed in children who presented postnatal microcephaly or did not present with microcephaly. Cavalcante et al.³³ reported a higher frequency of ventriculomegaly, reduced brain parenchyma, malformation of cortical development and hypoplasia or malformation of the brainstem in children with microcephaly at birth than in the comparison group, which was composed of children without microcephaly at birth but the majority (87.5%) of whom developed postnatal microcephaly. The findings of these studies suggest a greater severity of structural changes in congenital microcephaly than in postnatal microcephaly.

In our study, in addition to structural changes in the central nervous system, a significant percentage of children with postnatal microcephaly also presented ophthalmological abnormalities, other malformations and arthrogryposis, configuring a picture of intense damage caused by ZIKV, similar to that described for cases of microcephaly at birth, and also referred to in the studies by Van der Linden et al.²⁸, Cavalcante et al.³³ and Aguiar et al.³⁷.

In our study, the monthly changes in weight and height, expressed in Z-scores were respectively -0.010 (95% CI -0.033 to 0.014) and -0.023 (95% CI -0.046 to 0.0001) per month, while in children with microcephaly in the study by Silva et al.³² these figures were, respectively -0.08 per month and -0.16 per month although the data of these authors refer only to the first 8 months of life. Since our results contain zero in the confidence intervals, the data may indicate individual variations in opposite directions over time or that there was no change in the growth rate. For girls as a group, there was a decrease in the Z-score over time, but also with individual variations during the follow-up period.

In summary, the brain damage that led to the development of postnatal microcephaly was not accompanied by a unique pattern of weight and height development. This variability will depend on a number of factors, such as the presence of dysphagia, described in approximately 80% of children with microcephaly¹⁷, or the presence of endocrine disorders¹⁸. Cavalcante et al.³³ reported a small decrease in the mean Z-score of weight for age and length for age, in the period from birth to 36 months, both in the group that presented microcephaly at birth and in that composed mainly of children who developed postnatal microcephaly. The study of Aguiar et al.³⁷ also showed a fluctuation in the mean Z-score for weight and length over time among the children with CZS born with and without microcephaly. To detect possible differences between the sexes and between the intensity of brain damage and the evolution of weight and height in children with ZIKV-related microcephaly, studies are needed with a larger sample size that may be achieved in meta-analyses with individual data.

The study presents advantages and limitations. This is one of the few studies that describes cases of postnatal microcephaly and estimate the growth velocity of head circumference, height, and weight during the first months of life. Although children were monitored regularly using standardized procedures and instruments, it remains possible that there was a misclassification bias due as the frequency and timing of measurements performed were not uniform for all children in the study.

Conclusion

Postnatal microcephaly, which occurs mainly in children who have already presented signs of severe brain damage at birth, is part of the broad spectrum of Congenital Zika Syndrome. This study provides evidence that children who experience postnatal microcephaly present with variability in their weight and height development, which do not manifest as single specific patterns. Although the possible mechanisms underlying the development of postnatal microcephaly still need to be better understood, our findings reinforce the need for strict monitoring of children with prenatal ZIKV exposure by the pediatrician and a multidisciplinary team over the first 1000 days.

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Author contributions

R.C.F.R., D.B.M-F, E.B.B, R.A.A.X. contributed to the conception and design of the work. U.R.M., C.M.T.M., T.V.B.A., M.A.W.R., V.v.d.L., M.D.C.G.C., L.C.R., W.V.S., M.F.P.M.A. contributed to the acquisition, analysis, or interpretation of data. R.C.F.R., D.B.M-F, E.B.B, R.A.A.X. have drafted the work. All authors revised the manuscript, approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, are appropriately investigated and resolved.

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Competing interests

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Additional information

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Correspondence and requests for materials should be addressed to R.A.A.X.

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