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ARTICLE

Clinical characteristics of children with congenital Zika syndrome: a case series

Características clínicas de crianças com síndrome do zika congênita: uma série de casos

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ABSTRACT

Background: The congenital Zika syndrome involves structural brain changes, including ventriculomegaly, thin cerebral cortices, abnormal gyral pattern, cortical malformations, hypoplasia of the corpus callosum, myelination delay, subcortical diffuse calcifications, brainstem hypoplasia, and microcephaly in newborns. **Objective:** This study aimed to describe the clinical characteristics of children with congenital Zika syndrome; to compare the outcomes of infants infected in the first (1T, n=20) and second trimesters of pregnancy (2T, n=11); to investigate correlations between birth weight, birth and follow-up head circumference, birth gestational age, and gross motor scores. **Methods:** Participants were evaluated with Alberta Infant Motor Scale (AIMS) and part A of the Gross Motor Function Measure (GMFM-A). ANOVA compared head circumference, birth gestational age, birth weight, and gross motor performance of 1T and 2T. **Results:** The correlations were investigated by Pearson correlation coefficients. ANOVA showed differences in birth and follow-up head circumferences. Head circumference was smaller in 1T, compared to 2T. Motor performance was classified as below the fifth percentile in AIMS in all children and 1T showed lower scores in prone, sitting, and total AIMS score, compared to 2T. Children ranged from 8 to 78% on GMFM-A and there was a poorer motor performance of 1T. Nineteen children showed hypertonia, six showed normal tone and six showed hypotonia. Birth head circumference was correlated with AIMS prone postural control. Follow-up head circumference was correlated to prone, supine and total AIMS scores. Smaller head circumference at birth and follow-up denoted poorer postural control. **Discussion:** Children with congenital Zika syndrome showed microcephaly at birth and follow-up. Smaller head circumferences and poorer motor outcomes were observed in 1T. Infants showed poor visual and motor outcomes. Moderate positive correlations between birth and follow-up head circumference and gross motor function were found.

Keywords: Zika Virus; Microcephaly; Child.

RESUMO

Introdução: A síndrome congênita do zika envolve alterações estruturais do cérebro, incluindo ventriculomegalia, córtices finos do cérebro, padrão giral anormal, malformações corticais, hipoplasia do corpo caloso, atraso de mielinização, calcificações difusas subcorticais, hipoplasia do tronco cerebral e microcefalia em recém-nascidos. **Objetivo:** Este estudo teve como objetivo descrever as características clínicas de crianças com síndrome congênita do zika; comparar os resultados de bebês infectados no primeiro (1T, n=20) e no segundo trimestres da gravidez (2T, n=11); investigar correlações entre peso ao nascer, perímetro cefálico ao nascer e acompanhamento, idade

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gestacional ao nascer e escores motores brutos. Método: Os participantes foram avaliados com a Escala Motora Infantil de Alberta (Alberta Infant Motor Scale – AIMS) e a parte A da Medida da Função Motora Grossa (Gross Motor Function Measure – GMFM-A). A ANOVA comparou a circunferência da cabeça, a idade gestacional ao nascer, o peso ao nascer e o desempenho motor bruto de 1T e 2T. As correlações foram investigadas pelos coeficientes de correlação de Pearson. A ANOVA mostrou diferenças no perímetro cefálico ao nascimento e acompanhamento. A circunferência da cabeça foi menor no 1T, em comparação ao 2T. Resultados: O desempenho motor foi classificado como abaixo do quinto percentil na AIMS para todas as crianças e o 1T apresentou escores mais baixos na posição de bruços, sentado e no escore total da AIMS, em comparação ao 2T. As crianças variaram de 8 a 78% no GMFM-A e houve um desempenho motor pior de 1T. Dezenove crianças apresentaram hipertonia, seis apresentaram tônus normal e seis apresentaram hipotonia. A circunferência da cabeça no nascimento foi correlacionada com o controle postural em posição de bruços à AIMS. Discussão: O perímetro cefálico de acompanhamento foi correlacionado aos escores AIMS em posição de bruços, em supino e no escore total. Menor perímetro cefálico ao nascimento e acompanhamento indicaram pior controle postural. Crianças com síndrome congênita do zika apresentaram microcefalia ao nascimento e acompanhamento. Circunferências da cabeça menores e piores resultados motores foram observados no 1T. Os bebês apresentaram maus resultados visuais e motores. Foram encontradas correlações moderadas positivas entre o nascimento e a circunferência da cabeça de acompanhamento, e a função motora grossa.

Palavras-chave: Zika vírus; Microcefalia; Criança.

Zika virus is a flavivirus transmitted by the Aedes aegypti mosquito[1,2,3]. Infection can be asymptomatic or may cause mild skin rash[1,2,3]. Zika virus infection during pregnancy was associated with brain and musculoskeletal abnormalities in newborns[4,5,6,7]. The congenital Zika syndrome involves structural brain changes, including ventriculomegaly, thin cerebral cortices, abnormal gyral pattern, cortical malformations, hypoplasia of the corpus callosum, myelination delay, subcortical diffuse calcifications, brainstem hypoplasia, and microcephaly[8,9,10,11,12,13] in newborns.

The gestational age in which the exposure to the virus occurs can influence clinical outcomes. First- and second-trimester infections have the highest risk of developing central nervous system anomalies, compared to third-trimester infections. Although there is not a consensus in literature, some studies reported that infants infected in the first trimester (more specifically 14 to 17 weeks of gestational age) presented poorer neurological outcomes than the ones exposed in the second trimester[12,13,14,15]. A case series described 10 infants with microcephaly, who were born during the Zika virus infection outbreak of 2015[6]. The authors reported that seven mothers had dengue-fever-like symptoms (malaise, rash, and arthralgia) during pregnancy. Six from these 10 children were infected in the first trimester of pregnancy[6]. Another study included 183 cases of congenital Zika syndrome with microcephaly. The authors reported that 77% of the women had the skin rash in the first trimester, 18% in the second trimester, and only 5% in the third trimester of pregnancy[14].

The brain, ocular, hearing, and musculoskeletal abnormalities in newborns who contracted Zika virus in utero lead to impaired motor performance[4,5,6,7,16]. Macular scarring and focal pigmentary retinal mottling were described as pathological signs in congenital Zika syndrome[16,17]. Sensory (visual and auditory) impairments make postural acquisitions even more challenging. The musculoskeletal contractures are usually accompanied by marked early hypertonia or hypotonia and extrapyramidal movements[17]. A diagnosis often assigned to children born with congenital Zika syndrome is cerebral palsy[16]. These severe symptoms limit the social participation of children and families[18].

In a recent study, a weak correlation between motor performance and the head circumference at assessment was found[7]. However, the trimester of pregnancy in which the infection occurred was not considered for data stratification, nor for the correlation analysis[7]. Besides, the authors used only a general motor score and did not provide detailed information about posture control and acquisition in children with congenital Zika syndrome.

In the present study, we describe the clinical characteristics of 31 children aged 6 to 18 months, with congenital Zika syndrome. Children were admitted in two rehabilitation centers of two cities (Arcoverde and Recife) of the state of Pernambuco, in the northeast of Brazil. We aimed to (1) describe the head circumference measure, birth gestational age, birth weight, gross motor performance, visual and auditory outcomes, and muscle tone of children with congenital Zika syndrome; (2) compare the clinical outcomes of infants infected in the first trimester (1T) and in the second trimester (2T) of pregnancy; and (3) investigate possible correlations between birth weight, head circumference measures at birth and on assessment day, gestational age at birth, age at assessment, and gross motor performance.

METHODS

This cross-sectional, prospective, and descriptive study was approved by the Ethics Committee for Analysis of Research Projects of the University of São Paulo, School of Arts, Sciences and Humanities, (CAAE: 65822017.3.0000.5390). Parents or caregivers gave written informed consent prior to participating. Children were evaluated by three physiotherapists, who had at least two years of neuropediatric practice. Children were evaluated in two rehabilitation centers in the cities of Arcoverde and Recife in Pernambuco, Brazil.

Sample

We recruited 65 children with congenital Zika syndrome of two rehabilitation centers: Salud Serviços de Reabilitação Clinic (Recife) and Mens Sana Clinic (Arcoverde), both in Pernambuco state, in the northeast region of Brazil. Thirty-four children were excluded: 20 because of unconfirmed diagnosis, and 14 because of missing information about head circumference and/or motor scales and/or gestational age in which the Zika infection occurred.

The inclusion criteria were having congenital Zika syndrome diagnosis based on clinical history and serology tests (positive IgG test for Zika virus and positive postnatal IgM test for Zika virus infection). The exclusion criteria were having other infections during pregnancy, such as toxoplasmosis, rubella, herpes, or cytomegalovirus (n=2). Thirty-one children (18 girls and 13 boys, aged 6 to 18 months) with congenital Zika syndrome participated in this study. The mean birth weight was 2739 g (SD 431g), and the mean gestational age was 38.5 weeks (SD 3.7). All children were receiving physical therapy, occupational therapy, speech therapy and families were receiving psychological and social support.

Assessment

Head circumference measures at birth and at assessment (cm), gestational age at birth (weeks), age at assessment (months), sex, muscle tone (increased, decreased, or normal), and visual and hearing impairments (present or absent) were also collected. Microcephaly was defined as a head-circumference z score of less than two standard deviations[5]. Birth head circumference was collected from the "Caderneta de Saúde do Recém-Nascido" (Newborn Health Booklet), which is given to all children at birth. This booklet is filled by health professionals who follow the child.

Participants were evaluated with Alberta Infant Motor Scale (AIMS, prone, supine, sitting, standing, total score and corresponding percentile) [19-23]. The AIMS is a standardized, reliable, and easy-to-use clinical assessment tool for the evaluation of infant gross motor development from birth until the acquisition of independent walking[19,20]. AIMS is a norm-referenced measure of the gross motor development of high-risk infants[21,22]. The scale comprises 58 items, which assess the control and integrity of the antigravity muscles during observation of infant motor skills in prone (21 postures), supine (9 postures), sitting (12 postures), and standing (16 postures)[21,23]. Each posture attained is scored as 1 and the total score is obtained by the sum of all scores. AIMS has been recognized as a useful tool to assess gross motor maturation during infancy, to trace motor delay, and to identify infants who may benefit from early intervention[21]. Supine, prone, sitting, standing scores and the total score were registered, as well as the corresponding percentile ranks[23].

The Gross Motor Function Measure (GMFM, dimensions A: lying/rolling)[24,25] was used. GMFM is a clinical tool designed to evaluate the change in gross motor function in children with disabilities[24]. It consists of 88 items that evaluate lying and rolling up to walking, running, and jumping skills. There is a four-point scoring system for each item. In the present study, only dimension A (lying and rolling, GMFM A) was used[24]. When the task is fully accomplished, children are scored as 3. When the task is not even started, score 0 is given. Scores 2 and 1 denote that the child performs the task with partial range of motion or maintains the posture for less time than expected[24,24].

Auditory and visual tests were made by checking behavioral responses to a female voice and eye to eye and objects tracking (classified as present or absent)[26,27]. Muscle tone was evaluated by gentle passive stretching of upper and lower limbs and. Children, whose upper and/or limbs showed increased resistance to passive stretching, were classified as having hypertonia. Decreased resistance to passive stretching was described as hypotonia[7].

Statistical analysis

The software package used was *Statistica*. Alpha was determined as <0.050 for all analyses. Analysis of variance compared head circumference measure at birth, head circumference measure at assessment, birth gestational age, birth weight, age, and gross motor performance of infants infected on the first and second gestational trimesters (1T and 2T groups). Whenever necessary, Tukey tests were used in *post hoc* analyses.

Sex, muscle tone, visual and hearing performance of children infected on the first and second gestational trimesters (1T and 2T groups) were compared by chi-square tests.

The correlations between birth weight, head circumference measures at birth and at assessment, birth gestational age, age at assessment, and gross motor (AIMS and GMFM A) scores were investigated by Pearson correlation coefficients. Coefficients above 0.70 were considered as strong correlations and between 0.40 and 0.70 were considered as moderate correlations.

RESULTS

Twenty women were infected by Zika virus in the first trimester and 11 in the second trimester of pregnancy. There were relatively more females in the 2T group than in the 1T group, according to chi-square test (p=0.047). As this is a case series, such difference was not corrected. There was no significant difference in birth weight of 1T and 2T groups (2674.7 and 2856.8 g, respectively; $F_{1,29}$=1.28; eta-squared=0.042; p=0.267, f 1).

Most children presented with microcephaly at assessment. Two girls had head circumference measures between the mean (*z=0*) and the minimum acceptable (z=-1.9) standard deviation (Table 1 and Figure 1). One-way ANOVA showed significant differences in head circumference at birth ($F_{1,29}$=8.54; eta-squared=0.227; p=0.007), and head circumference at assessment ($F_{1,29}$=12.51; eta-squared=0.301;

Table 1. Sample characterization.

TP	Sex	BW (g)	BHC (cm)	HC (cm)	GA (weeks)	Age (months)	Prone (AIMS)	Supine (AIMS)	Sitting (AIMS)	Standing (AIMS)	Total (AIMS)	AIMS (%)	GMFM A	Muscle tone	Visual impairment	Hearing impairment
	F	2620	28	37	38	12	3	4	3	2	12	Below 5th	12	Increased	N	N
	M	2100	27	38	34	13	6	5	4	3	18	Below 5th	12	Normal	Y	N
	M	3100	32	39	40	14	3	2	3	2	10	Below 5th	16	Increased	Y	N
	M	2200	26	33	36	9	2	2	2	1	7	Below 5th	12	Increased	Y	N
	M	2700	27	31	39	6	4	2	4	1	10	Below 5th	32	Normal	N	N
	F	2960	30	41	35	14	4	5	2	2	13	Below 5th	13	Increased	Y	N
	M	2770	29	35	41	10	3	4	2	2	11	Below 5th	14	Increased	N	N
	M	2615	28	38	41	15	4	3	3	2	12	Below 5th	9	Increased	Y	N
	F	2165	26	35	37	11	3	5	3	3	13	Below 5th	12	Increased	N	N
1st trimester	M	2100	29	38	36	14	2	2	3	1	8	Below 5th	4	Increased	Y	N
	F	2100	29	32	38	11	5	3	2	3	12	Below 5th	12	Increased	Y	N
	M	2965	29	38	37	11	5	4	3	2	14	Below 5th	12	Increased	Y	Y
	F	2165	29	37	36	13	4	5	4	1	14	Below 5th	21	Increased	N	N
	F	2660	29	37	37	11	3	2	1	1	7	Below 5th	15	Decreased	Y	N
	M	3595	32	42	40	14	5	5	2	3	15	Below 5th	23	Decreased	N	N
	F	2640	29	35	37	11	5	5	4	3	17	Below 5th	12	Normal	Y	N
	F	2895	31	39	40	12	4	3	4	3	14	Below 5th	8	Increased	Y	N
	M	3890	30	39	38	13	6	5	2	2	15	Below 5th	18	Increased	N	N
	F	2600	29	38	40	10	2	3	2	2	9	Below 5th	7	Increased	Y	N
1st trimester	M	2655	31	39	39	11	2	2	2	2	8	Below 5th	5	Increased	N	N
Mean	-	2856.8	31.4	41.3	39.3	13.5	5.6	4.6	3.8	2.3	16.6	-	20.5	-	-	-
SD	-	2674.8	29.0	37.1	38.0	11.8	3.8	3.6	2.8	2.1	12.0	-	13.0	-	-	-
	F	3200	31	44	39	15	7	6	4	4	21	Below 5th	24	Normal	Y	N
	F	2600	29	38	40	10	4	4	3	2	13	Below 5th	9	Increased	Y	Y
	F	2505	30	40	40	11	7	5	6	2	20	Below 5th	37	Decreased	N	N
	M	2535	29	39	40	13	2	3	3	2	10	Below 5th	28	Decreased	Y	N
	F	3100	30	41	40	16	4	2	3	3	12	Below 5th	27	Decreased	N	N
2nd trimester	M	2500	28	40	40	17	2	3	1	1	8	Below 5th	16	Increased	N	N
	F	2680	30	37	39	12	5	3	5	1	15	Below 5th	28	Increased	N	N
	F	3230	37	51	36	12	10	8	4	2	24	Below 5th	12	Normal	Y	N
	F	3100	33	42	39	13	9	7	7	3	26	Below 5th	40	Decreased	N	N
	F	3000	35	40	40	18	2	3	2	1	9	Below 5th	15	Increased	N	N
	F	2975	33	42	39	11	10	7	4	4	25	Below 5th	12	Normal	Y	N
Mean	-	2856.8	31.4	41.3	39.3	13.5	5.6	4.6	3.8	2.3	16.6	-	20.5	-	-	-
SD	-	293.5	2.8	3.8	1.2	2.7	3.1	2.1	1.7	1.1	6.8	-	7.9	-	-	-
p-value	0.047	0.267	0.007	0.001	0.056	0.060	0.024	0.079	0.030	0.511	0.013	-	0.005	0.407	0.436	0.657

TP: trimester of pregnancy; BW: birth weight; BHC: birth head circumference; HC: birth circumference; GA: gestational age; M: male, F: female, below 5th: score below the fifth percentile of Alberta Infant Motor Scale (AIMS); Y: yes; N: no. P-value: results of analyses of variance (parametric data) and chi-square tests (non-parametric data).

p=0.001). Head circumference was smaller in 1T, compared to 2T group (Table 1).

There were no differences between 1T and 2T groups in gestational age at birth (38 and 39 weeks, respectively; p=0.056), nor in age at assessment (12 and 13 months, respectively, $F_{1,29}$=3.95; eta-squared=0.119; p=0.060, Table 1). All children were classified as having motor performance below the fifth percentile in AIMS (Table 1 and Figure 2). One-way ANOVA showed significant differences between 1T and 2T groups in prone ($F_{1,29}$=5.62; eta-squared=0.162; p=0.024), sitting ($F_{1,29}$=5.17; eta-squared=0.151; p=0.030), and total AIMS score ($F_{1,29}$=6.96; eta-squared=0.193; p=0.013, Table 1). In these items, 1T showed significant lower scores than 2T group. No significant differences were found in supine ($F_{1,29}$=3.31; eta-squared=0.102; p=0.079), and standing postures ($F_{1,29}$=0.441; eta-squared=0.014; p=0.511, Table 1).

Children ranged from 8 to 78% on lying and rolling (GMFM A). One-way ANOVA showed significant differences in GMFM A ($F_{1,29}$=9.91; eta-squared=0.237; p=0.005). There was a poorer performance of 1T, compared to 2T group (Table 1). GMFM A detailed scores are presented in Table 2. Chi-square tests showed that the group 1T showed lower scores than the group 2T in head control in supine and prone positions and hip and knee flexion in supine position.

Nineteen children showed increased muscle tone (hypertonia), six showed normal tone and six showed decreased muscle tone (hypotonia). Chi-square tests compared the number of children with normal and abnormal muscle tone in 1T and 2T groups and found no significant difference (p=0.407). There were no differences in the number of children with visual impairment and hearing impairments in 1T and 2T (p=0.436 and 0.657, respectively, Table 1).

Table 3 shows Pearson correlation coefficients. Birth head circumference was correlated with AIMS prone postural control (r=0.404; p=0.027). Smaller head circumference denoted poorer prone postural control. Head circumference at assessment was correlated to prone (r=0.426; p=0.019), supine (r=0.522; p=0.003), and total score of AIMS (r=0.431; p=0.017). Smaller head circumference at follow-up denoted poorer postural control acquisition (Table 3).

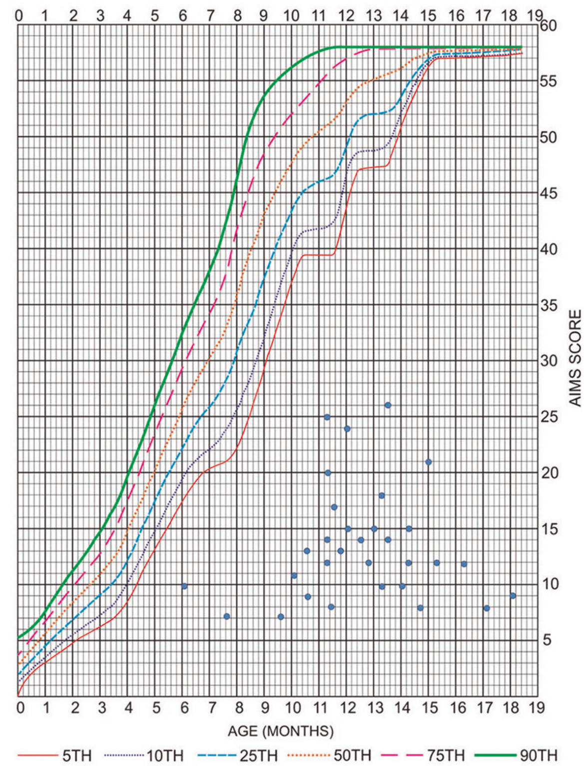

Figure 2. Alberta Infant Motor Scale scores and age (months) on assessment day.

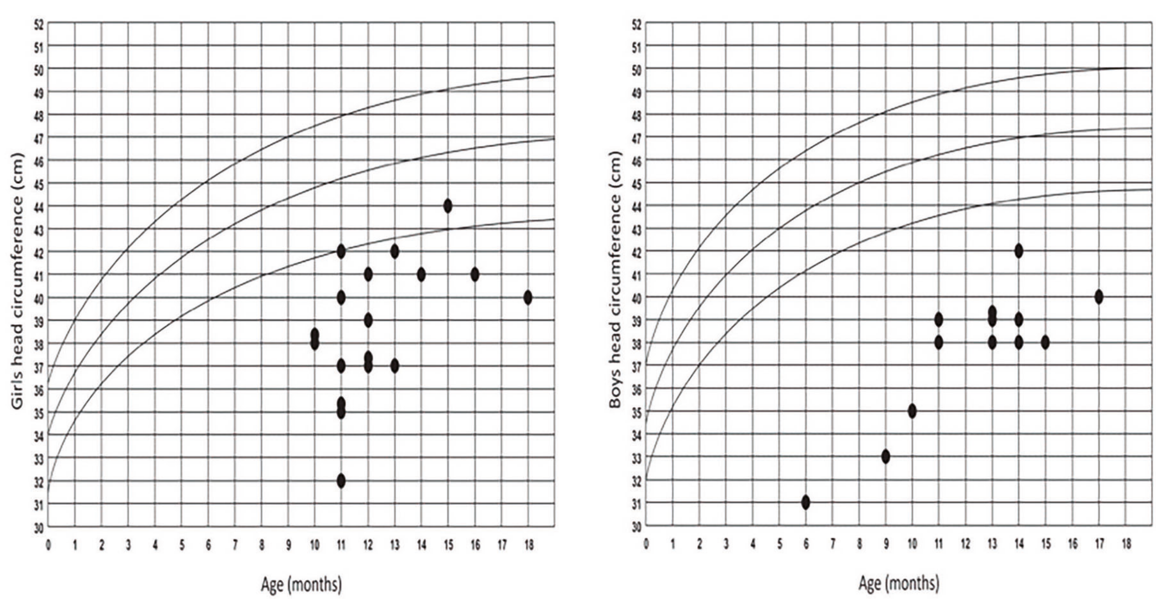

Figure 1. Head circumference measures on assessment day. Plotted curves represent mean and upper and lower standard deviations of head circumference measures (cm) by age (months).

Table 2. Number and percentage of children affected in the first and second trimesters of pregnancy in each item of lying and rolling dimension of GMFM (GMFM A).

GMFM A	Lying and rolling score	trimester	3	2	1	0	preserved	altered	total	chi-square
Item	A: LYING AND ROLLING		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n	p-value
1	SUPINE, head in midline: turns head with extremities symmetrical	1T	15 (75)	3 (15)	2 (10)	0 (0)	15 (75)	5 (25)	20	0.283
		2T	10 (91)	1 (9)	0 (0)	0 (0)	10 (91)	1 (9)	11	
2	SUPINE: brings hands to midline, fingers one with the other	1st	1 (5)	4 (20)	6 (30)	9 (45)	1 (5)	19 (95)	20	0.127
		2nd	4 (36)	5 (45)	0 (0)	2 (18)	4 (36)	7 (64)	11	
3	SUPINE: lifts head 45º	1st	4 (20)	13 (65)	3 (15)	0 (0)	4 (20)	16 (80)	20	0.049
		2nd	6 (55)	4 (36)	0 (0)	1 (9)	6 (55)	5 (45)	11	
4	SUPINE: flexes RIGHT hip & knee through full range	1st	0 (0)	17 (85)	3 (15)	0 (0)	0 (0)	20 (100)	20	0.001
		2nd	5 (45)	6 (55)	0 (0)	0 (0)	5 (45)	6 (55)	11	
5	SUPINE: flexes LEFT hip & knee through full range	1st	1 (5)	15 (75)	2 (10)	2 (10)	1 (5)	19 (95)	20	0.001
		2nd	8 (73)	3 (27)	0 (0)	0 (0)	8 (73)	3 (27)	11	
6	SUPINE: reaches out with RIGHT arm, hand crosses midline toward the toy	1st	0 (0)	5 (25)	6 (30)	9 (45)	0 (0)	20 (100)	20	0.171
		2nd	1 (9)	5 (45)	3 (27)	2 (18)	1 (9)	10 (91)	11	
7	SUPINE: reaches out with LEFT arm, hand crosses midline toward the toy	1st	0 (0)	3 (15)	2 (10)	15 (75)	0 (0)	20 (100)	20	0.171
		2nd	1 (9)	6 (55)	2 (18)	2 (18)	1 (9)	10 (91)	11	
8	SUPINE: rolls to prone over RIGHT side	1st	0 (0)	0 (0)	4 (20)	16 (80)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	0 (0)	9 (82)	2 (18)	0 (0)	11 (100)	11	
9	SUPINE: rolls to prone over LEFT side	1st	0 (0)	0 (0)	4 (20)	16 (80)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	0 (0)	8 (73)	3 (27)	0 (0)	11 (100)	11	
10	PRONE: lifts head upright	1st	2 (10)	8 (40)	1 (5)	9 (45)	2 (10)	18 (90)	20	0.002
		2nd	7 (64)	2 (18)	0 (0)	2 (18)	7 (64)	4 (46)	11	
11	PRONE ON FOREARMS: lifts head upright, elbows extended, chest raised	1st	0 (0)	4 (20)	7 (35)	9 (45)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	7 (64)	2 (18)	2 (18)	0 (0)	11 (100)	11	
12	PRONE ON FOREARMS: weight on RIGHT forearm, fully extends opposite arm forward	1st	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	0 (0)	5 (45)	6 (55)	0 (0)	11 (100)	11	
13	PRONE ON FOREARMS: weight on LEFT forearm, fully extends opposite arm forward	1st	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	0 (0)	5 (45)	6 (55)	0 (0)	11 (100)	11	
14	PRONE: rolls to supine over RIGHT side	1st	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	0 (0)	0 (0)	11 (100)	0 (0)	11 (100)	11	
15	PRONE: rolls to supine over LEFT side	1st	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	0 (0)	0 (0)	11 (100)	0 (0)	11 (100)	11	
16	PRONE: pivots to RIGHT 90º using extremities	1st	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	0 (0)	0 (0)	11 (100)	0 (0)	11 (100)	11	
17	PRONE: pivots to LEFT 90º using extremities	1st	0 (0)	0 (0)	0 (0)	20 (100)	0 (0)	20 (100)	20	NA
		2nd	0 (0)	0 (0)	0 (0)	11 (100)	0 (0)	11 (100)	11	

GMFM scores: 3 is given when the task is fully accomplished and 0 is given when the task is not even initiated; NA: The posture was not fully acquired by none of the 31 children included in this case series.

Table 3. Correlations between clinical characteristics and Alberta Infant Motor Scale (AIMS) scores.

	R and P coefficients	Prone (AIMS)	Supine (AIMS)	Sitting (AIMS)	Standing (AIMS)	Total score (AIMS)	Lying and rolling (GMFM A)
Birth weight	R	0.351	0.287	-0.080	0.252	0.291	0.174
	P	0.057	0.124	0.674	0.180	0.118	0.359
Birth head circumference	R	**0.404**	0.357	0.048	0.160	0.357	-0.149
	P	**0.027**	0.053	0.802	0.399	0.053	0.432
Head circumference at assessment	R	**0.426**	**0.522**	-0.002	0.269	**0.431**	-0.230
	P	**0.019**	**0.003**	0.993	0.151	**0.017**	0.222
Gestational age at birth	R	-0.323	-0.395	-0.166	0.049	-0.308	0.106
	P	0.082	0.031	0.379	0.799	0.098	0.579
Age at assessment	R	-0.234	-0.079	-0.313	0.015	-0.168	-0.166
	P	0.213	0.680	0.093	0.938	0.376	0.380

AIMS: Alberta Infant Motor Scale; GMFM A: Part A of gross motor function measure (Lying and rolling). Pearson correlation coefficients were corrected by trimester of pregnancy (first or second). Coefficients between 0.40 and 0.70 were considered as moderate and are presented in bold.

DISCUSSION

The present study describes the clinical characteristics (head circumference, birth gestational age, birth weight, gross motor performance, visual and auditory outcomes, and muscle tone) of a case series of 31 children aged 6 to 18 months, with congenital Zika syndrome, in two rehabilitation centers of two cities (Arcoverde and Recife) of the state of Pernambuco, in the northeast of Brazil.

The present study shows new findings in relation to congenital Zika syndrome, as we have included children with significant smaller head circumferences than previous studies[5,27,28,29]. All participants presented microcephaly (head circumference below 33 cm) at birth, but two children had normal head circumference at the follow-up assessment[5]. A study in Rio de Janeiro (2016) included 117 children whose mothers had been infected. The authors reported that 49 children had neurological impairments (42%), but only four had microcephaly[5]. Opposite, in the study by Alves et al., head circumference of 24 children born with congenital Zika syndrome remained below the third percentile[30]. Therefore, it is possible that only the most severe cases were included in the present study (children with confirmed congenital Zika syndrome and infected in the first or second trimesters of pregnancy), as well as in the study by Alves et al[30]. Other endemic cases of congenital Zika syndrome may have not been detected or may have not reached the rehabilitation centers due to the lack of information, and/or social exclusion (e.g. involving mobility, health assistance, locomotion and transportation).

The infection did not affect birth gestational age and birth weight in the 31 cases included in the present study. A recent study reported a mean gestational age of 38 weeks in 24 children born with congenital Zika syndrome, which was the same obtained in the present study[27]. Another recent study described 5 cases of children with microcephaly and congenital Zika syndrome, after investigating 104 possible cases. These five children were born between 34 and 41 weeks of gestational age and weighed between 1940 and 3400 g[28]. In the present study the gestational age varied from 34 to 41 weeks and the birth weight varied from 2100 to 3890 g.

Although there were no differences between muscle tone and sensory deficits of 1T and 2T groups, a high number of participants showed muscle tone (n=25), and visual (n=17) impairments. Cerebral calcifications, cerebral atrophy, ventricular enlargement, parenchymal brain hemorrhages, and hypoplasia of cerebral structures were seen in previous studies[5] and correlated to upper neuron deficits, e.g. hypertonia, clonus, hyperreflexia, abnormal movements, spasticity, and contractures in children with congenital Zika syndrome[7]. Muscle tone was increased in 23 of 24 children in a case series that also evaluated children in Pernambuco, Brazil[30]. A variety of other findings, including visual and hearing deficits, seizure activity, dysphagia, and feeding difficulties were also reported[5].

The first-trimester infection was associated with smaller head circumference at birth and at assessment follow-up. Our results are consistent with previous studies that reported that disproportionate microcephaly was seen in infants infected in the first trimester of pregnancy[5,29]. The most common timing of infection, as determined by maternal symptoms, seems to be the late first and early second trimester[17]. However, no definitive association between the timing of infection and the severity of the phenotype had been documented so far.

The first-trimester infection was associated with poorer motor outcomes: lower prone, sitting, and total AIMS motor scores and lower lying and rolling (GMFM A) score. In a recent study, Carvalho et al. reported extremely low performances on motor (97.6%) scores of Bayley-III Scales of Infant and Toddler Development[7]. Alves et al. followed 24 Brazilian children (also from Pernambuco) with congenital Zika syndrome. Children were evaluated by Denver Developmental Screening

Test II and for an average chronological age of 19.9 months, gross motor performance was correspondent to 2.7 months[30]. The present study complements these data because we found that the group 1T showed lower scores than the group 2T in tasks involving head control in supine and prone positions and hip and knee flexion in supine position. Therefore, although both groups showed few motor acquisitions, the postural control of 1T was poorer than the postural control of 2T. To our knowledge, this is the first study that provided detailed information about specific postural control and acquisition in children with congenital Zika syndrome.

Correlations between head circumference at birth and at follow-up assessment and gross motor function were found. The size of birth head circumference was correlated to prone postural control in AIMS (r=0.40). The size of head circumference at follow-up assessment was correlated to prone, supine and total score of AIMS (r=0.43, 0.52 and 0.43, respectively). Carvalho et al. found a weak correlation between the motor performance, detected by Bayley-III Scales of Infant and Toddler Development, and the birth head circumference at follow-up assessment (r=0.20)[7]. Such difference may be explained due to the inclusion of more severe cases in the present study and due to the use of a scale that emphasizes antigravity postural axial control (AIMS), which seems to be critically affected in the most severe cases of microcephaly.

Infants with motor dysfunction must be identified early so that appropriate interventions can be implemented[31]. Movement and motor coordination are critical components of development[32], and motor assessment plays an important role in clinical and research settings for identification, classification, and diagnosis of motor dysfunction, as well as in evaluating the effectiveness of interventions[31]. As limitations of the present study, we must mention that children were not evaluated at the same age at follow-up, but between 6 and 18 months. Visual, auditory, muscle tone assessment was based on clinical observation, but not detailed, nor quantified by specific scales. Many women may have not been tested during the skin rash, or may not have had the skin rash, and these women did not meet the inclusion criteria of the present study. Besides, only children with microcephaly were included and other children may have been born with congenital Zika syndrome and normal head circumference.

CONCLUSION

Children with congenital Zika syndrome presented microcephaly at birth and at follow-up assessment. Children infected in the first trimester showed lower head circumference measures than children infected during the second trimester of pregnancy.

Infants infected in the first trimester showed poorer motor outcomes than infants infected in the second trimester of pregnancy. Infants showed poor sensory (mainly visual impairments) and motor outcomes (impaired muscle tone and antigravity postural control). Moderate positive correlations between head circumference at birth and at follow-up assessment and gross motor function were found.

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