Original Article

Neuropsychomotor development of children with congenital Zika virus infection

Desenvolvimento neuropsicomotor de crianças expostas à infecção congênita pelo Zika vírus

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ABSTRACT | INTRODUCTION: The proof of the association of microcephaly in Brazil with congenital Zika virus infection leads to the need for studies on the impact on children's development resulting from the involvement of the central nervous system (CNS). **OBJECTIVE:** To evaluate the neuropsychomotor development (NPMD) of children exposed to congenital Zika virus infection and its association with prenatal, neonatal, and postnatal characteristics and diagnoses of the mother/child. **METHODS:** Cross-sectional study with children aged zero to three years, born between 2015 and 2018, classified with congenital Zika virus infection. In the collection of clinical and socio-demographic characteristics, a semi-structured questionnaire was used, and the Denver II Screening Test was used to assess the DNPM. In the association, Fisher's exact test was used (p<0.05). **RESULTS:** Thirty children were evaluated; 46.67% had DNPM alterations, the greatest ones were in the language (46.67%) and fine motor skills (43.33%). 23.33% were older than 24 months, an age-associated with changes in DNPM (p<0.012). Infection predominated between 4 and 12 weeks of gestation and was associated with DNPM delays (p<0.002). 46.67% of children had microcephaly and 40% cerebral calcifications, both associated with DNPM delays (p<0.001). On physical examination, 36.7% had changes in posture and persistence of primitive reflexes, 40% hyperirritability, 33.33% dysphagia, and joint deformities, all with an important association with changes in DNPM (p<0.001). **CONCLUSIONS:** Children exposed to congenital Zika infection had developmental delays. It is noteworthy that the earlier the infection in pregnancy, the greater the involvement of the central nervous system of children.

KEYWORDS: Gestation. Zika virus. Neurodevelopmental Disorders.

RESUMO | INTRODUÇÃO: A comprovação da associação de microcefalia no Brasil com a infecção congênita pelo Zika vírus, leva a necessidade de estudos sobre a repercussão no desenvolvimento das crianças decorrentes do comprometimento do sistema nervoso central (SNC). **OBJETIVO:** Avaliar o desenvolvimento neuropsicomotor (DNPM) de crianças expostas à infecção congênita pelo Zika vírus e sua associação com características e diagnósticos pré natais, neonatais e pós natais da mãe/criança. **MÉTODOS:** Estudo transversal com crianças de zero a três anos, nascidas entre 2015 e 2018, classificadas com infecção congênita pelo Zika vírus. Na coleta das características clínicas e sócio demográficas, utilizou-se um questionário semiestruturado e na avaliação do DNPM o Teste de Triagem de Denver II. Na associação, utilizou-se o teste exato de Fisher (p<0,05). **RESULTADOS:** Avaliou-se 30 crianças, 46,67% apresentavam alterações do DNPM, os maiores foram na linguagem (46,67%) e motricidade fina (43,33%). 23,33% tinham mais que 24 meses, idade que se associou a alterações do DNPM (p<0,012). A infecção predominou entre 4 e 12 semanas de gestação e obteve associação com os atrasos do DNPM (p<0,002). 46,67% das crianças apresentaram microcefalia e 40% calcificações cerebrais, ambos com associação a atrasos no DNPM (p<0,001). Em exame físico 36,7% apresentaram alterações de postura e persistência de reflexos primitivos, 40% hiperirritabilidade, 33,33% disfagia e deformidades articulares, todas com associação importante com as alterações no DNPM (p<0,001). **CONCLUSÕES:** Crianças expostas à infecção congênita pelo Zika vírus apresentaram atrasos no DNPM e quanto mais precoce a infecção na gravidez, maior o envolvimento do sistema nervoso central.

PALAVRAS-CHAVE: Gestação. Zika vírus. Transtornos do Neurodesenvolvimento.

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Introduction

Neuropsychomotor development (NPMD) is a multidimensional and integral process, having the effect of making the child able to respond to their needs and those of the environment; physical growth, acquisitions related to cognition, language, motor skills, sensory function, socio-emotional, behavioral development and neurological maturation, which occurs mainly in early childhood, between 29 days and 2 years old and is considered the best phase for stimulating development.[1-4]

Good performance in this stage results from the interaction between intrinsic and extrinsic factors for the child. Among the intrinsic factors are the care and biological risks, which are considered prenatal, neonatal, and postnatal events and infections. Extrinsic factors include the risks related to environmental, social, and cultural conditions found in the child. When these factors act negatively on neurological maturation, they increase damage in NPMD, and they are then considered risk factors for child development.[3-6]

Among the intrinsic risk factors, congenital infections that alter the proper functioning of the CNS stand out, such as neurogenesis, dendritic and axonal growth, synapse, and myelinization. In this context, Zika virus, flavivirus of the family Flaviviridae, discovered on the African continent on April 20, 1947, is a highly teratogenic infectious pathogen (ability to produce congenital malformations) and neurotropic (predilection for neurons).[1,5,7,8]

In 2015, the Zika virus was associated with severe congenital infection with direct consequences for the CNS, the characteristic diseases such as severe microcephaly, thin cerebral cortex, subcortical calcifications, macular scar, and focal pigmentation of the retina gave rise to Congenital Zika Syndrome.[9] Since then, it has been initially considered by the Ministry of Health (MoH) and sequentially by the World Health Organization (WHO) as an international public health emergency.[10]

In the newly known Congenital Zika Syndrome, several clinical signs that compromise NPMD have been associated concomitantly with CNS damage, such as hypertonia, early-onset contractures, the persistence of primitive reflexes, consequences for vision and hearing, seizures, hyperexcitability, dysphagia, lower than expected intrauterine growth, low birth weight, among others. The results of the studies also include a slowdown in the growth of the postnatal head circumference.[8,9,11]

It is known to date that the delay in NPMD in children will depend on the degree of CNS injury and in which period of gestational age occurred to Zika virus infection; there are reports that the earlier the infection during pregnancy, the greater the number of brain changes.[8] The literature also mentions that the more anticipated the measures of diagnosis and intervention occur in these children, the smaller the impacts on their development and future life.[10]

The severity of congenital Zika virus infection and its repercussions in childhood have been demonstrated to the world for the first time in Brazil. The involvements for the CNS and NPMD reached great proportions, as well as the difficulty in early diagnosis and insertion of children affected in the appropriate treatments, revealing the worldwide lack of information on the subject. This scenario demonstrates a real need for studies on the NPMD of these children and analyses on the repercussion that congenital infection will cause to their development.[2,5,11]

To address this important knowledge gap, this study aimed to evaluate the NPMD, between the ages of 0 to 3 years old, the most important stage of child development, of children born to mothers with a confirmed or probable diagnosis of Zika virus in the prenatal period and to associate it with the prenatal, neonatal and postnatal characteristics and diagnoses of the mother/child.

Methods

All ethical aspects of research with human beings were respected with the respective approval of the Ethics and Research Committee on Human Beings. Likely, those responsible for the children signed the Free and Informed Consent Form (TCLE).

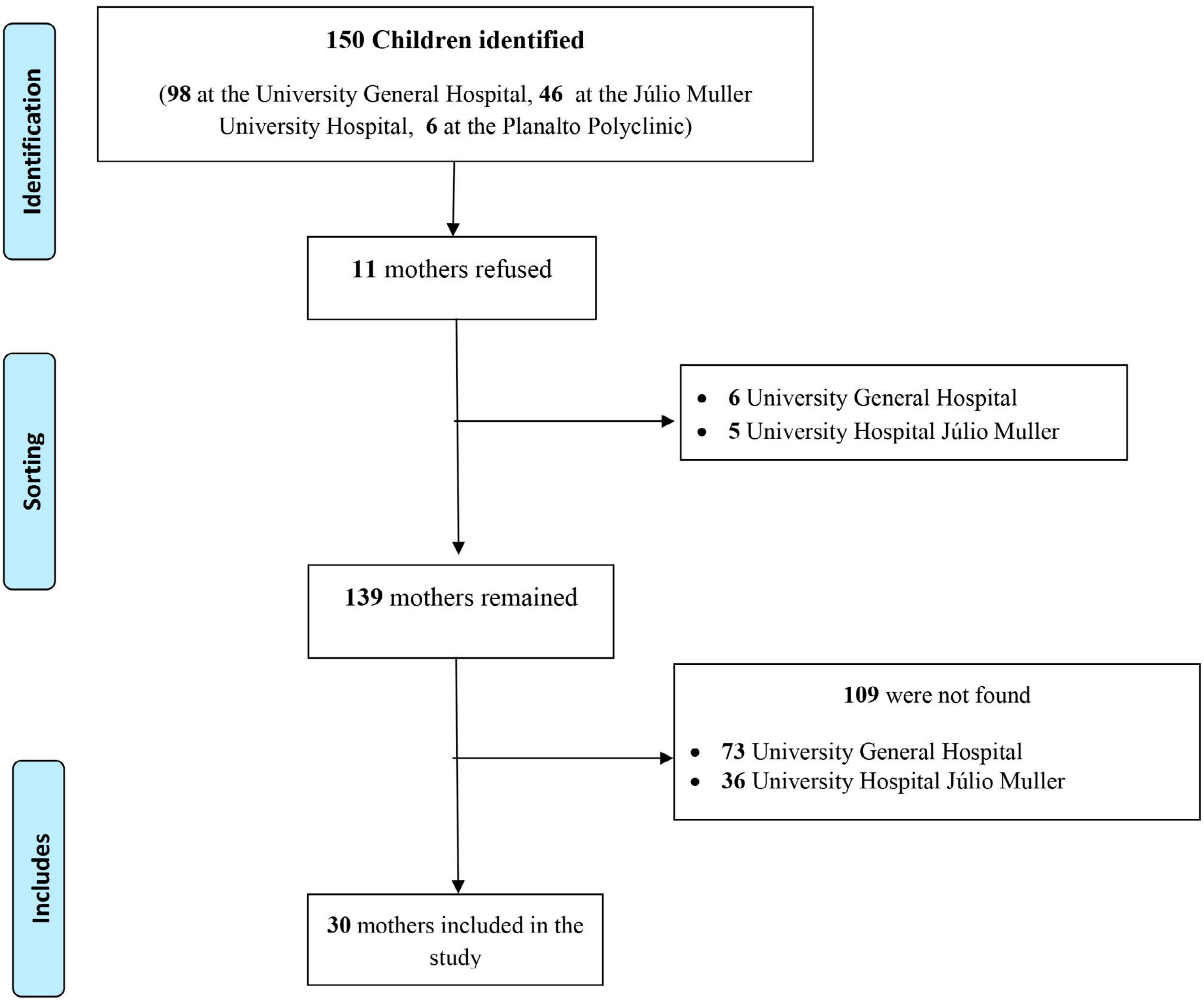
This is a cross-sectional study with children between zero and three years old, born from 2015 to 2018, reported as confirmed and/or probable congenital Zika virus infection cases. The evaluation services were chosen because they are part of the care network of pregnant women with suspected Zika virus infection.

Together, the clinical and epidemiological recommendations of the Ministry of Health (MoH)2 were used to detect confirmed and/or probable cases of infection without laboratory diagnosis. Infants with microcephaly and/or head circumference < -2 standard deviations for age/gender of genetic etiology and mothers exposed to substances with teratogenic potential during pregnancy were excluded.[1]

The sample was of convenience, where we tried to place all the children from the health services who could participate in the evaluations. The survey was conducted from May to September 2018 through all medical records of health services (hospital infection control committee sector) that were part of the research, and that indicated contact with Zika virus during pregnancy, totaled 150 children identified.

Then, the parents' phone number was collected, contact was contacted to clarify the research, inviting them to it; after the acceptance, the appointment was made to fill out the TCLE and evaluation of the children. Of the invitations made by telephone, 11 mothers refused even with a proposal for evaluation at home, 109 were not found because of incorrect filling out of telephone contacts and addresses in medical records. Therefore, in the end, the population consisted of 30 children, as detailed in the flowchart (Figure 1).

Figure 1. Case selection flowchart



The evaluations were conducted until October 2018. Data collection was performed in a reserved place, lasting 50 to 60 minutes, directed through a semi-structured script, composed of personal, gestational information, delivery, and current history of the child, the information collected from all phases (prenatal, neonatal, and postnatal) was made in a single meeting with parents, through detailed anamnesis, the exams they brought and the children's health booklet. The evaluation of neuropsychomotor development was performed by the application of the Denver II Sorting Test (DIIST) performed by the physiotherapist and master-student author of the research, according to the original instruction manual of Frankenburg and Doods[15], adapted in Brazil by Souza et al.[16] that allows evaluating the four fields of development: social personnel, fine-adaptive motor, language, and thick motor. The detailed description of the application of DIIST can be verified in previous publications.[15,16]

According to the DIIST, the results of the NPMD were considered: normal, when the children did not present any delay or only caution in all tests performed in the four sectors; equally, it suspects only a delay or two or more cautions and abnormals, those with two or more delays. For statistical analysis purposes, suspicious and abnormal classifications were regrouped as altered and normal classifications categorized as adequate. Thus, the dependent variable was the altered or adequate performance in the DIIST.

The independent variables of the study were: characteristics related to mother and child, socioeconomic conditions, and prenatal, neonatal, and postnatal diagnoses. Regarding the characteristics related to the mother and socioeconomic conditions, the following were evaluated: age by age group, family income, mother's schooling, gestational age of diagnosis of Zika virus infection, fever, and rash during pregnancy.

Variables related to the child's characteristics include gender, age in months, classification of the newborn (term, preterm, late/moderate preterm), professional follow-up for the NPMD. Birth weight/current, the current length of birth/height, head circumference of birth/current, all following the WHO classification that, when necessary, considers Z-score for age and sex: 'very low,' children with standard deviations < -3; 'low,' standard deviation between -3 and -2; 'adequate,' with standard deviation > -2.[15,16]

The independent variables related to prenatal, neonatal, and postnatal diagnoses were microcephaly (Z-score for age and sex); brain calcifications on imaging; Altered Brainstem Evoked Response Audiometry (BERA), posture changes, the persistence of primitive reflexes (RTCA and RTCS), hyperexcitability/hyperirritability, dysphagia, joint deformities of limbs and hypertonia. All variables were obtained through records of the medical records of the services, documents (imaging tests, laboratory reports, and child health booklet), and interviews with parents or guardians.

Initially, to assist the analyses, the continuous variables were grouped into categorical. After that, the variables were tabulated, calculating the frequencies that were part of the body of the tables, that is, the simple absolute frequency and simple relative frequency.

Next, a bivariate analysis was performed in which the choice of the test was due to the sample size. Fischer's exact test is accurate for all sample sizes and was used to study the association between the independent categorical variables (related to the mother, socioeconomic conditions, prenatal, neonatal, and postnatal diagnoses) and the categorical dependent variable (Denver II Screening Test).

The Microsoft Excel Software, version 2010, was used for database construction and analysis, the STATA statistical package version 12. Considering significance level of 5% (p-value < 0.05).

Results

Of the 30 children exposed to the Zika virus during pregnancy, 46.67% presented alterations of any order in TTDD II. Concerning the development fields, 36.67% presented alterations in the personal social sector, 43.33% in the thin engine, 46.67% in language, and 40% in the large motor sector.

In CNS diagnoses, 14 of the 30 children evaluated (46.67%) had lower head circumference for gestational age during prenatal care (12th to 20th week). Of these same children, 12 (40%) were born with microcephaly and two with adequate head circumference, but after the 1st month of life, all 14 (46.67%) had head circumference below adequate and evolved in fact with microcephaly, thus suggesting late microcephaly in two children. Brain calcifications were present in 12 of the 30 children (40%) during prenatal care, which persisted at birth and after the first month of life. It is observed that the 40% of children who presented brain calcifications also had microcephaly, but not every child who had microcephaly (46.67%) also demonstrated brain calcifications (Table 1).

In the clinical examination of BERA, 14 of the 30 children (46.67%) presented alterations at birth. Of these children, 12 (41.38%) presented BERA alterations after the first month of life. On physical examination, 11 children (36.7%) presented changes in posture and persistence of primitive reflexes at birth and after the 1st month of life; 12 (40%) presented hyperexcitability/hyperirritability at birth and after the 1st month of life; 10 (33,33%) presented dysphagia and deformity at birth and after the 1st month of life; 11 (36,67%) hypertonia at birth and after the 1st month of life (Table 1).

Table 1. Frequency distribution of variables related to prenatal, neonatal and postnatal diagnoses of children exposed to Zika virus during pregnancy

Variables	During prenatal care		At birth and in the 1st month of life		After 1st month of life	
	n	%	n	%	N	%
Microcephaly	14	46.67	12	40.00	14	46.67
Brain Calcifications	12	40.00	12	40.00	12	40.00
Bera[b] changed	NA[a]	NA[a]	14	46.67	12	41.38
Posture changes	NA[a]	NA[a]	11	36.67	11	36.67
Persistence of Primitive Reflexes	NA[a]	NA[a]	11	36.67	11	36.67
Hyperexcitability	NA[a]	NA[a]	12	40.00	12	40.00
Hyperirritability	NA[a]	NA[a]	12	40.00	12	40.00
Dysphagia	NA[a]	NA[a]	10	33.33	10	33.33
Joint Deformity	NA[a]	NA[a]	10	33.33	10	33.33
Hypertonia	NA[a]	NA[a]	11	36.67	11	36.67

[a] Does not apply.
[b] *Brainstem Evoked Response Audiometry.*

In the association of microcephaly with developmental changes, after the 1st month of life, 12 of the 14 children with microcephaly (85.71%) had altered performance in the DIIST with a statistically significant association between both (p<0.001). The 12 (100%) children identified with brain calcifications had developmental changes and significant statistical association with DIIST (p<0.001). (Table 2).

In the changes in the clinical examination of the BERA, after the 1st month of life, 11 of the 12 children identified (91.67%) development difficulties with a statistically significant association with DIIST (p<0.001). All children (100%) who presented alterations in physical examinations (postural alterations, persistence of primitive reflexes, hyperexcitability/hyperirritability, dysphagia, joint deformities and hypertonia) demonstrated difficulties in development, at birth and remaining after the 1st month of life, with a statistically significant association with DIIST (p<0.001) (Table 2).

Table 2. Association between Denver II Sorting Test and prenatal, neonatal and postnatal diagnoses of children exposed to Zika virus during pregnancy

Variables	Performance changed in Denver II test								
	During prenatal care			At birth and in the 1st month of life			After the 1st month of life		
	n	%	p-value	n	%	p-value	n	%	p-value
Microcephaly									
Yes	12	85.71	*0.001	11	91.67	*0.001	12	85.71	*0.001
No	2	14.28		1	0.08		2	14.28	
Brain calcifications									
Yes	12	100	*0.001	12	100	*0.001	12	100	*0.001
No	0	0.00		0	0.00		0	0.00	
Examination of BERA[b]									
Yes	NA[a]	NA[a]	NA[a]	11	78.57	0.003	11	91.67	*0.001
No	NA[a]	NA[a]		3	21.42		1	0.08	
Postural changes									
Yes	NA[a]	NA[a]	NA[a]	11	100.00	*0.001	11	100.00	*0.001
No	NA[a]	NA[a]		0	0.00		0	0.00	
Persistence of primitive reflexes									
Yes	NA[a]	NA[a]	NA[a]	11	100.00	*0,001	11	100.00	*0.001
No	NA[a]	NA[a]		0	0.00		0.00	0	
Hyperexcitability									
Yes	NA[a]	NA[a]	NA[a]	12	100.00	*0.001	12	100.00	*0.001
No	NA[a]	NA[a]		0	0.00		0.00	0	
Hyperirritability									
Yes	NA[a]	NA[a]	NA[a]	12	100.00	*0.001	12	100.00	*0.001
No	NA[a]	NA[a]		0	0.00		0.00	0	
Dysphagia									
Yes	NA[a]	NA[a]	NA[a]	10	100.00	*0.001	10	100.00	*0.001
No	NA[a]	NA[a]		0	0.00		0.00	0	
Joint deformities									
Yes	NA[a]	NA[a]	NA[a]	10	100.00	*0.001	10	100.00	*0.001
No	NA[a]	NA[a]		0	0.00		0	0.00	
Hypertonia									
Yes	NA[a]	NA[a]	NA[a]	11	100.00	*0.001	11	100.00	*0.001
No	NA[a]	NA[a]		0	0.00		0	0.00	

[a] Does not apply. [b] *Brainstem Evoked Response Audiometry.* * Fischer exact test (*p-valor<0.05*)

In the sociodemographic characteristics, 56.67% were between 20 and 29 years old, 26.67% were between 30 and 35 years old, and 16.67% were 35 years or older, and in the latter group the highest number of children (60%) with change in DIIST, however, there was no significant association. In the monthly family income, 53.33% of the mothers reported less than R$ 1,300 and 46.67% between R$ 1,300 and R$ 6,000. It is observed that 62.50% of the children with alteration were in the income group lower than R$ 1,300. (Table 3).

Concerning the mother's schooling, 60% were between 0 and 8 years and 40% 9 years or more, in absolute numbers. The two groups also had children with alterations in the NPMD. Among the children's ages, 40% were less than 12 months old, 36.67% between 12 and 24 months, and 23.33% had 24 months or more, with the highest percentage of children (85.71%) with development alteration he was 24 months or more months old, which demonstrated a statistically significant association (p<0.012) with altered performance in the DIIST (Table 3).

Table 3. Association between the Denver II Test and the mother's sociodemographic characteristics and of children exposed to Zika during pregnancy, Cuiabá - MT, 2018

Variables	General		Performance changed in the test Denver II		p-value
	n	%	n	%	
Mother's age group					
20 - 29	17	56.67	9	52.94	
30 - 35	8	26.67	2	25.00	
35 or more	5	16.67	3	60.00	0.421
Family income (real)					
Less than 1300	16	53.33	10	62.50	0.067
1300 to 6000	14	46.67	4	28.57	
Mother's schooling (years)					
0 - 8	18	60.00	7	38.89	0.457
9 or more	12	40.00	7	58.33	
Child's age (months)					
Less than 12	12	40.00	2	16.67	
Between 12 and 24	11	36.67	6	54.55	
24 or more	7	23.33	6	85.71	*0.012
Child gender					
Male	19	63.33	10	52.63	0.466
Female	11	36.67	4	36.36	

* accurate Fischer test (*p-valor<0.05*)

The diagnosis of Zika virus infection predominated between 4 and 12 weeks of gestation (63.33%), and the most significant proportion (68.42%) of the children with developmental alteration was in this group, obtaining a statistically significant association between early contamination in pregnancy and altered performance in the DIIST (p<0.002). Furthermore, it is observed that 12 (40%) children with a very low head circumference at birth and 14 (46.67%) with low head circumference and very low current presented the most developmental alterations with significant association with DIIST (p<0.001), which corroborates the findings of microcephaly presented. Interestingly, the children who had the most developmental delays (92.31%) were those who performed professional follow-up to stimulate the NPMD with a statistically significant association with DIIST (p<0.001) (Table 4).

Table 4. Association between Denver II sorting test and characteristics related to mother and children exposed to Zika virus during pregnancy

Variables	general		Performance changed in Denver II test		p-value
	n	%	n	%	
Gestational age of diagnosis of Zika virus infection (weeks)					
4 - 12	19	63.33	13	68.42	*0.002
13 - 38	11	36.67	1	9.09	
Fever during pregnancy					
Yes	25	83.33	10	40.00	0.157
No	5	16.67	4	80.00	
History of exanthema in pregnancy during **pregnancy**					
Yes	27	90.00	11	40.74	0.090
No	3	10.00	3	100.00	
Classification of the newborn					
Term	25	83.33	12	48.00	1.000
Preterm	4	13.33	2	50.00	
Moderate preterm	1	3.33	0	0.00	
Birth weight (grams)					
1500 - 2499	5	16.67	2	40.00	1.000
2500 or more	25	83.33	12	48.00	
Current weight (Z score for age/gender)					
Adequate	21	70.00	8	38.10	
Low	7	23.33	4	57.14	0.237
Too low	2	6.67	2	100.00	
Length of birth (Z score for age/sex)					
Adequate	20	66.67	9	45.00	
Low	1	3.33	1	100.00	0.840
Too low	9	30.00	4	44.44	
Current height (Z score)					
Adequate	22	73.33	10	45.45	
Low	7	23.33	3	42.86	0.830
Too low	1	3.33	1	100.00	
Head circumference of birth (Z score)					
Adequate	18	60.00	3	16.67	
Too low	12	40.00	11	91.67	*0.001
Current head circumference (Z score)					
Adequate	16	53.33	2	12.5	
Low	9	30.00	9	100.00	*0.001
Too low	5	16.67	5	100.00	
Performs professional monitoring for NPMD					
Yes	13	43.33	12	92.31	*0.001
No	17	56.67	2	11.76	

* accurate Fischer test (*p-valor<0.05*)

Discussion

Neuropsychomotor development has a close and complex relationship with several intrinsic and extrinsic factors. Hierarchical models for the study of their determinants and interrelationships facilitate this understanding.[7]

From the epidemiological point of view, the analytical model of Mosley and Chen's social determinants of health (2003) and the risk factors pointed out by the Ministry of Health stipulate three levels of factors that interrelate and alter the outcome of the cases: proximal (act directly on the outcome), intermediate and distal. From this model, exposure to the Zika virus during pregnancy can be considered.[3,6]

Among the proximal and intermediate determinants, with direct action to the CNS, are maternal factors such as congenital Zika virus infection, gestational age of exposure, clinical signs such as fever and rash; children's factors such as professional stimulus to NPMD, age of the child-related to the onset of symptoms, clinical/physical characteristics and prenatal, neonatal and postnatal diagnoses thereof. Among the dystalium determinants are socioeconomic status and low family income.[3,4]

The present study showed that the highest percentage of mothers was young, with low schooling and family income, who reported the infection even at the beginning of pregnancy, and in the last two characteristics, their children had the greatest developmental delays according to the DIIST.[17-19]

Regarding these distal determinants, Freitas et al.[17] corroborate the findings of this study because they describe that the sociodemographic profile of mothers who had congenital Zika virus infection is composed mostly of young women with low schooling and low income. Maternal education and monthly family income affect the burden and quality of the stimuli offered, health care, and education, and these conditions are related to the NPMD of children. In the present study, there was no significant association between TTDD II and these variables, which may have contributed to this result is the homogeneity of the sample regarding the social characteristics described.[6,12]

Regarding proximal determinants, characteristics of the mother, the results found showed that almost all reported probable clinical signs of infection, such as fever and rash. Similar results were observed in other studies on congenital Zika virus infection.[18] Concomitantly with reports of rash and fever, most mothers presented the infection at the beginning of pregnancy, being this predictor of different prevalence in the severity of sequelae of the child.[19]

Several authors have already demonstrated that the more anticipated the congenital infection at gestational age, especially in the 1st and beginning of the 2nd trimesters, an essential phase for the formation of neurons and synapses, the more severe the involvement on the CNS, and may evolve to Congenital Zika Syndrome, with higher probabilities of brain anomalies and sequelae that compromise the NNPM of these children.[7,19-22] These findings reinforce our analyses, in which associations were found between exposure to congenital infection early in pregnancy and delays in NNPM.

Children 24 months of age or older had higher developmental delays with a significant association with DIIST. A first reflection is that as the child grows, their neuropsychomotor repertoires are refining themselves, making them more need to explore the world and consequently, require more resources, access to adequate materials, greater personal stimulation; all these aspects depend on good social and economic levels, which, as described, are concentrated in a minority of the sample.[15,16]

The second hypothesis is since children aged between two and three years evaluated were born in the initial period of the outbreak in Brazil (2015/2016), concomitant with the period of little knowledge about the disease/disease and the potential for morbidity in children, hindering diagnostic measures and early referral to appropriate treatments, reflecting the delay of NPMD.[2,7,23] It is worth noting that more than half of the children evaluated received professional follow-up for development, but still, they presented the most alterations in the NPMD, denoting that they may have been slow to have access to early stimulation services.[5]

In the United States, a cohort of children born to mothers with confirmed or probable Zika virus infection during pregnancy demonstrated that early identification and intervention of adverse events in neurological development were determinant to improve cognitive, social, and behavioral functioning. Therefore, it is recommended that the most critical moment to intervene is during the first three years, proposing standardized multi-professional evaluation at birth and each consultation.[23]

In Brazil, early care is recommended for children affected by congenital Zika virus infection and performed by a multidisciplinary team, especially pediatricians, neurologists, physiotherapists, occupational therapists, and speech therapists.[4,13] This information corroborates the current study, in which possibly the lack of early stimulation was a decisive factor in the prognosis of major changes.

In proximal determinants with direct action to the CNS, when it is the clinical sign of microcephaly, the literature reports that children exposed to Zika virus infection during pregnancy may develop it. Microcephaly is characterized by a lower head circumference than expected for age and sex. According to the World Health Organization, it is a malformation of complex and multifactorial etiology involving genetic and environmental factors, identified through the head circumference measurement. It can be classified according to the time of its onset in congenital. That is, it is already present at birth or postnatal microcephaly when normal growth failure of the head circumference occurs after birth.[1,2]

The occurrence of this malformation does not necessarily mean that motor or cognitive changes occur because the measurement of the head circumference may not reflect an abnormally small brain with reduction of neurons; may occur in children with normal microcephaly, when it is of the family origin or without etiology, as well as to offer the appropriate stimulus during early childhood, favoring neurological maturation and neuroplasticity.[1,13]These reports corroborate our findings in which two children with microcephaly did not present motor complications and major brain involvements.

However, other studies explain that 90% of cases of microcephaly cases are accompanied by alterations[1,13] and that children with microcephaly due to Zika virus infection may present important neurological impairments that hinder the progress of NPMD, associating with motor and cognitive changes that vary according to the degree and extent of brain involvement, in addition to hearing, visual, physical and intellectual deficits.[7,22]

Flor et al.[1,11] evaluated the development of infants with congenital Zika virus and microcephaly infection and found severe impairments, such as difficulties in rolling, crawling, and dissociating scapular pelvic girdle, restricting the main normal patterns of movements for proper development. Confirming our findings, there was a significant association between microcephaly and delays in NPMD in 85.71% of children.

Among the brain abnormalities, as well as in this study, other findings in Brazil identified that children with confirmation of infection had alterations on imaging, such as brain calcifications and delay of the postnatal head circumference with microcephaly in the 5th month of life.[8]

The postnatal development of microcephaly in children with congenital Zika virus infection has been previously reported; Van der Linden et al. described 13 babies with infection at varying gestation times. Several findings were found, such as dysphagia, epilepsy, irritability, degrees of hypertonia, and hemiparesis. Microcephaly was not evidenced at birth, but all children evolved with postnatal microcephaly.[8]

These reports corroborate the data of this study, in which two children evolved with microcephaly after the first month of life, providing evidence that among babies with prenatal exposure to Zika virus, the absence of microcephaly at birth does not exclude congenital infection or regression of brain growth late, because brain growth continues after birth, until the first three years of the individual's life, in addition to supporting the recommendations that such children require early medical follow-up even without motor symptoms or microcephaly at birth.[8,14,21]

Regarding the evaluation of NPMD in children with congenital Zika virus infection and alteration in neuroimaging, Moreira et al.[24] pointed out that children with normal brain imaging were 20% less likely to delay development when compared to those with abnormal brain imaging. The information described reinforces this study, as significant associations were observed between developmental delays and neuroradiological alterations.

Among the disorders in the locomotor system, there was a high prevalence in children affected by congenital Zika virus infection, and when associated with development changes, they became unanimous. Of the alterations of the NPMD of any order, the most prevalent were delays in language and motor aspects. Other studies have shown that delays in the development of this population mainly affect language and motricity.[7,17,21]

These children may be born with inadequate posture resulting from joint and member deformities, such as congenital toes, hip dislocation, arthrogryposis, and may maintain reflexes that should normally disappear as growth (RTCA and RTCS). These are symptoms of neurological impairments with signs of extrapyramidal involvement, which hinder the learning of new skills with consequences to NPMD.[9]

Another study showed that these children have in common hyperreflexia and hypertonia, atypical development, and deficit in manual function, reporting that after birth in the first trimester of life, it is already possible to identify signs of severe brain lesions from these abnormalities present in muscle tone and persistence of primitive reflexes, corroborating our analyses, in which an association was found between hypertonia/persistence of primitive reflexes and developmental changes since the 1st month of life.[20]

It is also evident in the literature, a clinical sign referring to phonoarticulatory aspects, being more prevalent the incoordination in the suction function with consequent evolution to dysphagia, also demonstrated in a greater number of children evaluated, with an important association with developmental disorders. This characteristic is justified by injury in several structures that make connections with the center of swallowing, such as the cerebellum, base nuclei, thalamus, and cortical, subcortical region, regions also associated with aspects of coordination, balance, fine motricity, and learning.[14,20]

This study presented as a limitation the poor completion of the records and medical records of the patients, the vast majority with telephone numbers, cell phones and addresses were incorrect or incomplete, making contact impossible, which also compromised the sample number. Due to the identification of several inadequate fillings, it is suspected that the classifications of mothers in relation to Zika virus contagion in pregnancy are not completely correct, so to try to reduce probable identification error, detailed anamnesis was performed with the mother, also using the clinical and epidemiological recommendations of the MS[11] and seeking when necessary tests to prove the infection. In addition, it should be considered that the children included in the study were not evaluated for autism spectrum disorders.

Final notes

Children with congenital Zika virus infection have significant delays in NPMD, especially language and fine motricity, associated with CNS changes, and the more CNS changes, the greater the developmental impairments. Additionally, it was identified that the earlier the infection occurs during pregnancy, the greater the CNS concomitant involvements with The NPMD, and these manifestations become more complex when considering the temporal relationship of the age group and circulation of the etiological agent and early access to professional follow-up for the NPMD.

It is also observed that the absence of microcephaly at birth does not rule out infection during pregnancy and other impairments that may occur by it, as well as that microcephaly, can occur late in these children.

We emphasize the importance of public policies that provide children with earlier access to appropriate treatments in the SUS, with periodic evaluations, the intervention of a multidisciplinary team, aiming to optimize their acquisitions as much as possible and minimizing the impacts of sequelae, facilitating the better evolution of development and quality of life, as well as psychological monitoring and guidance to parents.

Authors' contributions

Lopes AKKLS, Takano OA, and Terças-Trettel ACP participated in the conception, design, search, and statistical analysis of the research data, interpretation of the results, and writing of the scientific article. Andrade ACS participated in the data analysis and interpretation of the results. Nascimento VF and Silva JI participated in the writing of the scientific article.

Conflicts of interest

No financial, legal, or political conflict involving third parties (government, companies and private foundations, etc.) has been declared for any aspect of the work submitted (including, but not limited to grants and financing, participation in the advisory board, study design, manuscript preparation, statistical analysis, etc.).

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