

## Analysis of neuropsychomotor development in children with congenital zika syndrome: cross-sectional study

## Análise do desenvolvimento neuropsicomotor em crianças com síndrome pós-zika vírus: um estudo transversal

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**RESUMO | INTRODUÇÃO:** No Brasil, a epidemia ocasionada pelo Zika Vírus gerou aumento de casos de microcefalia, caracterizando que mulheres infectadas durante o período gestacional transmitiram o vírus ao feto. As consequências da infecção pelo vírus são caracterizadas como síndrome pós Zika, evidenciadas através da microcefalia associada, ou não, às alterações visuais, auditivas e osteomioarticulares, podendo ser reversíveis ou permanentes. **OBJETIVO:** Detectar atrasos no desenvolvimento neuropsicomotor em crianças acometidas no período pré-natal pelo Zika Vírus através da infecção materna. **MATERIAIS E MÉTODOS:** Estudo observacional, de corte transversal e análise descritiva, com crianças que foram infectadas pelo Zika Vírus através da genitora durante período gestacional, pertencentes à Associação de Pais de Anjos da Bahia, sendo os participantes submetidos à avaliação com o teste de Denver II e seus responsáveis entrevistados por meio de um questionário semiestruturado. Estudo aprovado sob CAAE: 64655616.2.0000.5032. **RESULTADOS:** Foram avaliadas 8 crianças, 5(62,5%) do sexo feminino, com uma média de idade de 1,8±0,11 anos e perímetro cefálico de 29,5±1,5 centímetros. Houve predomínio de diagnóstico de Zika das gestantes no primeiro trimestre (37,5%). Das comorbidades associadas 7 (87,5%) alteração osteomioarticular, 5(62,5%) história prévia de convulsão. Disfunções: 5(62,5%) comprometimento visual e 1(12,5%) déficit auditivo. Dos aspectos avaliados pelo Denver II, o mais afetado foi o motor grosseiro. **CONCLUSÃO:** É possível constatar que crianças com síndrome pós-Zika apresentam atrasos no desenvolvimento neuropsicomotor.

**PALAVRAS-CHAVE:** Zika vírus. Síndrome pós-zika. Desenvolvimento infantil.

**ABSTRACT | INTRODUCTION:** In Brazil, an epidemic caused by Zika Virus generated an increase in cases of microcephaly in live births, characterizing that women infected during the period of gestation transmitted the virus to the fetus. The consequences of virus infection are characterized as congenital Zika syndrome and can be evidenced through microcephaly associated with or not, to visual, auditory and osteomioarticular, may be reversible or permanent. **OBJECTIVE:** To detect delays in neuropsychomotor development in children affected in the prenatal period by Zika Virus through maternal infection. **MATERIALS AND METHODS:** Observational study, cross-sectional with descriptive analysis in children diagnosed with Zika Virus belonging to the Associação de Pais de Anjos da Bahia, the participants were submitted to the Denver II test and their responsible interviews through a semi-structured questionnaire. Study approved, CAAE: 64655616.2.0000.5032. **RESULTS:** Eight children were evaluated, 5 (62.5%) female, with a mean age of 1.8 ± 0.11 years and cephalic perimeter of 29.5±1.5 centimeters. There was a predominance of Zika's diagnosis of pregnant women in the first trimester (37.5%). Of the associated comorbidities, all children had microcephaly, 7(87.5%) osteomioarticular alterations, 5(62.5%) had previous convulsion. Disorders: 5(62.5%) impairment visual and 1(12.5%) had a hearing loss. Of the aspects evaluated by the Denver II, the most affected was the gross motor. **CONCLUSION:** It is possible to verify that children with congenital Zika syndrome present delays in neuropsychomotor development.

**KEYWORDS:** Zika vírus. Congenital Zika syndrome. Child development.

## Introduction

The Zika Virus (ZIKV), genus *Flavivirus* belong to the family *Flaviviridae*, was discovered in 1947 in the blood of monkey feverish in the Uganda and subsequently was detected in the mosquito *Aedes Aegypti*, in the 1960s, in the Malaysia. In Brazil, the first case of Zika virus associated with the mosquito was registered in May 2015 in the Northeast region, beginning of an epidemiological outbreak<sup>1</sup>. With the epidemic in the country, was verified increase of cases of microcephaly in live births, your relation with Zika Virus was confirmed been in May 2015, through specific laboratory test, demonstrated the amniotic fluid analysis of microcephalic fetuses from pregnant women found ZIKV infection<sup>1,2</sup>. They were confirmed 2,653 cases of microcephaly because of congenital infections by April 2017<sup>3</sup>.

However, the consequences of ZIKV go beyond of the microcephaly, being confirmed correlation with alterations morphological of the central nervous system, intracranial calcifications, craniofacial dysmorphia, ophthalmic, auditory and osteomioarticular alteration, difficulties in the development of language and deglutition and behavioral disorders, characterizing the congenital syndrome of the Zika Virus<sup>4-7</sup>.

These disorders influence in the neuropsychomotor development (NPMD), defined as progress in the reach of skills and development physical, cognitive, neurological maturation, social adaptation, behavioral and language, being accentuated when linked to the risks factors presents in the pre, peri and postnatal period carrying alterations reversible or permanent<sup>8</sup>.

One of resources that allow to track the delay of the NPMD is the test of Denver II. In 2007, the test was adapted for the Brazilian population through of one study done by Drachler, due the population characteristics are distinct from the country of origin<sup>9</sup>.

The objective of the study was to detect delays in neuropsychomotor development in children affected by the Zika Virus in the prenatal period through maternal infection.

## Methods

This was an observational, cross-sectional study with descriptive analysis, children from the Association of Angels from Bahia (APAB), who were infected by ZIKV through the gestational period, were diagnosed through laboratory tests, clinical or physical. Children whose caregivers were not living daily were excluded. The sample was non-probabilistic, of the convenience type.

The data were collected after signature of the Informed Consent Form, through of semi-structured interview, prepared by authoress, with the responsible for the children, with personal and gestational information, about the child's birth and e current child's history, and the application of the Denver Development Screening Test II (DDST-II) in children.

The Denver II test allowed to appraise personal-social, fine motor adaptive, language and gross motor through the observation of the child during the activities and, sometimes, with information reported by responsible. The data were classified according to the child's age and interpreted as: normal, when the child execute the task according to her age; suspected, in the moment in that to failure or to refuse execute activities performed by 75% to 90% of children with similar age; delay, when refuse or non-execute task that is already executed by contemporaries<sup>10</sup>.

A pilot study was realized for the calibration of the research instruments in May 2017, and after, from June to October 2017, data were collected with the eligible participants of the research, keeping the collection instruments unaltered after preliminary study. Both executed in a private institution, in Salvador-Ba, in reserved place with the parents, child to be evaluated and the researcher.

The numerical dependent variable was the result of the Denver II. The numerical independent variables are age, birth weight, gestational age and cranial circumference and the categorical independent variables are prenatal, gestational

drug use, gestational complications, interference during and after childbirth, current treatments and children comorbidities. The categorical variables were presented in absolute and relative frequency, and the numerical variable, on mean and standard deviation. The data were inserted into the software Microsoft Excel 2007 and analyzed using software SPSS (Statistical Package for the Social Sciences) for Windows (version 22).

The ethical aspects were respected, following the Resolution n° 466/12 of National Health Council and submitted the Research Ethics Committee SUPRIMIDO.

## Results

Eight children were evaluated, majority female (62.5%), with an mean age of  $1.8 \pm 0.11$  years presenting mean cephalic perimeter of  $29.5 \pm 1.5$  centimeters and borned with a mean weight of  $2.876 \pm 0.58$  grams. The drug treatment and physical therapy were the most used, both corresponded the 5 children in the sample (62.5%). Of the comorbidities associated with the base pathology : 5 with history of convulsion (62.5%), 7 (87.5%) osteomioarticular alterations; dysfunctions: 5 (62.5%) visual impairment and 1 (12.5%) hearing deficit, Table 1.

**Table 1.** Clinical characteristics of children with congenital zika syndrome belong to Associação de Pais de Anjos da Bahia.

	<i>f</i>	<i>f<sub>i</sub></i> (%)	<b>M ± SD</b>
<b>Sex</b>			
Female	5	(62,5)	
Male	3	(37,5)	
<b>Age<sub>(years)</sub></b>			1,8 ± 0,11
<b>Cranial circumference<sub>(cm)</sub></b>			29,5 ± 1,5
<b>Birth weight<sub>(g)</sub></b>			2,876 ± 0,58
<b>Current treatments</b>			
Medicated	5	(62,5)	
Physiotherapy	5	(62,5)	
Swimming	4	(50)	
Speech Therapy	3	(37,5)	
Occupational Therapy	2	(25)	
Hydrotherapy	1	(12,5)	
<b>Associated comorbidities</b>			
Microcephaly	8	(100)	
Osteomioarticular	7	(87,5)	
Visual	5	(62,5)	
History of seizure	5	(62,5)	
Auditory	1	(12,5)	

Legend: *f* – absolute frequency; *f<sub>i</sub>* – relative frequency; M- mean; SD- standard deviation; cm- centimeters; g-grams.

About the gestational aspects, shown in the table 2, the mean gestational age was  $39.6 \pm 1.9$  weeks, all the mothers performed complete prenatal care, only one reported drug use during pregnancy representing 12.5% in sample and had a predominance of the diagnosis of zika virus in pregnant women in the first trimester, characterizing 37.5% of the population. According the complications, none mothers reported any interurrences during the gestational period or childbirth.

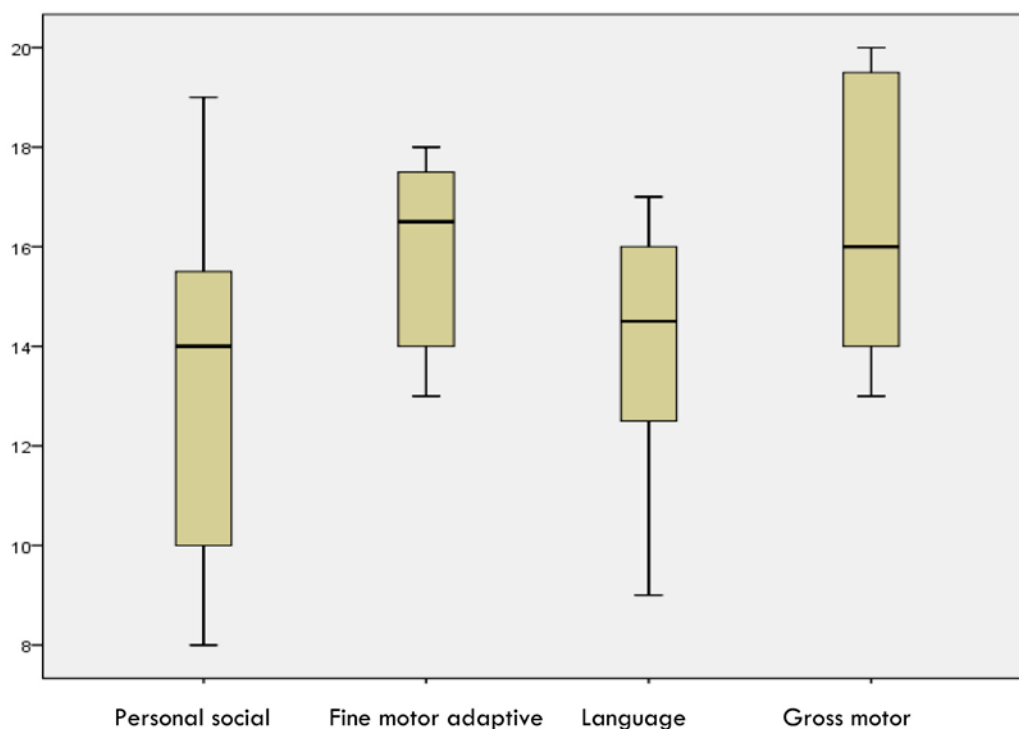
**Table 2.** Characteristics of the gestational aspects of genitoras with children congenital zika syndrome belong to Associação de Pais de Anjos da Bahia.

	<i>f</i>	<i>f<sub>i</sub></i> (%)	<b>MD ± DP</b>
<b>Gestacional Age</b> (weeks)			39,6 ± 1,9
<b>Prenatal</b>			
Complete	8	(100)	
<b>Drugs used during pregnancy</b>			
Yes	1	(12,5)	
No	7	(87,5)	
<b>Gestacional period of contagion by Zika Virus</b>			
1° trimester	3	(37,5)	
2° trimester	2	(25)	
3° trimester	1	(12,5)	
Not reported /asymptomatic	2	(25)	
<b>Gestational complications</b>			
No	8	(100)	
<b>Intercurrences during/after childbirth</b>			
No	8	(100)	

Legend: *f* – absolute frequency; *f<sub>i</sub>* – relative frequency ; M- mean; SD- standard deviation

The figure 1, shown the repercussion in the neuropsychomotor development, in which children were classified with delay in the aspects reported through of the Denver II test. On the personal-social aspect presented median of 14 months, with variation between 8 to 19 months with interquartile range (IQR) of 4.25 months. According to the language domain, there was median of 14.5 months with amplexness from 9 to 17 and interquartile range of 2.75, reflected in months. The elements of the test, fine adaptive motor and gross motor obtained median of 16.5 months changing from 14 to 18 com IQR from 3.25 to 16.5 months with amplexness from 13 to 19.25 months presenting IQR of 4.75 months, respectively. After analysis it was noticed that scope that showed preponderance in the delay of development was the gross motor aspect, followed of the adaptative fine motor, having less expressive impact in the language and personal-social aspect.

**Figure 1.** Repercussions in the neuropsychomotor development of children exposed to the Zika Virus during gestational period through the Denver scale II.



## Discussion

Based on the data presented, children with congenital zika syndrome have delayed neuropsychomotor development, as well impairments that characterize the syndrome, these possibly impact on quality of life and functional dependence.

According to the Brazilian Society of Pediatrics, specific conditions are related high risk for impairment in the development of children, including prematurity, perinatal asphyxia, neurological disorders, small for gestational age and/or low birth weight (LBW), reduction cephalic perimeter and congenital infections<sup>11</sup>.

Ventura et al.<sup>12</sup> describe the prevalence of female sex (60%), according to the current study with 62% of the sample. In contrast, Petribu et al.<sup>13</sup> present most of the male sample (59%) and Vargas et al.<sup>14</sup> present homogeneous data from the population. Thus, it was not possible to observe a sex pattern in Zika virus infected children, although the male embryos were more prone to congenital malformations due to the chromosomal genetic difference caused by the recessive gene<sup>15</sup>.

Flor et al.<sup>16</sup> describe the mean age in  $8.9 \pm 2.13$  months, different of the data of the research presented with  $1.8 \pm 0.11$  years. However, the ages tend to be similar in the children with Zika Virus syndrome, because period of epidemic in Brazil, in 2015<sup>2</sup> and the advertisement of the end of national emergency by the Ministério da Saúde<sup>3</sup>, with a 95% decline in registered, in 2017, characterizing the mean age of the children evaluated in the present study. This decay is related to the campaigns for the eradication of the *Aedes Aegypti* mosquito carried out by the Federal Government with the help of the population through preventive measures<sup>3</sup>.

The result on birth weight was described by Alvino et al.<sup>17</sup> expressed in  $2.371 \pm 508$  grams (g), characterizing as low birth weight through of standards adopted by the World Health Organization (WHO) classifying the neonate weighing  $<2.500\text{g}$  differing from the current study, framing the sample with insufficient birth weight, which corresponds to values from 2.500 to 2.999g<sup>18</sup>. However, information from the study by Linden et al.<sup>19</sup> differs that proposed, in which the children presented adequate weight at birth. LBW is an important aspect of child morbidity and mortality with a direct influence on the development process<sup>11</sup>.

The cephalic perimeter is a predictor of the severity of microcephaly, based on WHO recommendations, the standardization carried by the Ministry of Health of Brazil for cases of microcephaly, in which boys will have measure equal or lower than 31.9 centimeters and the girl equal or lower than 31.5 centimeters, being ideal the measurement after the first 24 hours or until the first week of birth<sup>20</sup>. Cut point was also established, classifying severe microcephaly with answer lower than -3 standard deviations<sup>20</sup>. Thus, Abreu et al.<sup>11</sup> and Vargas et al.<sup>14</sup> showed results that corroborate with the present study, with average cephalic perimeter (cm) from  $27.8 \pm 2.2$  and  $29$  (23-33), respectively.

Considering that microcephaly is only one of the complications of the Zika Virus syndrome, others impairments associated with malformations cephalic are evidenced. Among them, alterations osteomioarticular in neonates, with arthrogryposis being the most frequent<sup>17</sup>, having as characteristics muscular hypertonia and joint stiffness in limbs, seen in the children of this study. The ophthalmologic alterations were described by Freitas et al.<sup>5</sup>, with 10 of 29 children (34,5%) ocular abnormalities and Leal et al.<sup>6</sup> (2016) reported hearing deficit being confirmed in 7 of 70 children (10%) with similarity with the results of the present study.

One of the items evaluated as a risk factor is the period of infection by ZIKV, the first three months of gestational are more susceptible to infection, because it corresponds to the germinative and embryonic stage that represent the conception phase and implantation and beginning of the development of the fetus with the formation of internal structures, respectively<sup>15</sup>. Others authors describe prevalence during the first gestational trimester with 88.89%<sup>11</sup> and 86.36%<sup>16</sup> of the sample.

Authors report that the women participating in the study performed prenatal care, being that 9 (50%) had 6 or more visits, differing of the current study<sup>11</sup>. Prenatal care is primary factor for the identification of gestational risk factors and fetal pathologies, as microcephaly. Although the clinical condition of the fetus is not modified, the gestational follow provides the pregnant woman and her family knowledge about possible complications and limitations to the child allowing the search for appropriate treatments<sup>21</sup>.

With the use of the Denver II scale, Flor et al.<sup>16</sup> showed equivalent results, 22 (100%) infants had delays in NPMD in the evaluated items. In the coarse motor domains was represented superior impact ( $7.50 \pm 15.35$ ) and personal-social ( $7.12 \pm 12.68$ ), in the present study greater delays was found in the gross motor, followed by the fine motor adaptive. Thus, there may be a negative repercussion in the execution of transfers and greater functional dependence and, in the future, in the school period, when manual dexterity are required to perform activities<sup>16,22</sup>.

It is assumed that difference of the data found is related to the mean of age, considering that present study has children around the age of 2 years, being more susceptible to the influence of the external environment with greater possibility of personal interaction<sup>23</sup>.

Brunoni et al.<sup>24</sup> emphasizes the importance of the follow by multiprofessional in the knowledge of the consequences of the Zika Virus infection, and suggesting interventions mainly in the first three years of life due to the development of the central nervous system that may be potentiated in this period with approaches that foster neurological maturation for the child development<sup>21</sup>.

The study allows characterization of the population contributing to the elaboration of more targeted therapeutic plans that allow the prevention and reduction of physical and functional limitations. Nevertheless, appraisalment of development is necessary with a more comprehensive sample to increase knowledge about the consequences of this syndrome and its impacts on children affected.

## Conclusion

The children infected by Zika Virus in the prenatal period presented delayed neuropsychomotor development, with lower performance in the gross motor, followed of the fine motor adaptive. However, the language and personal-social elements presented less expressive results.



The alterations in child development due the congenital syndrome of Zika Virus have been linked comorbidities characteristics of the base pathology, including microcephaly, history of convulsion and visual, hearing and osteomiarticular impairment.

### Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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