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Cerebral Palsy in Children With Congenital Zika Syndrome: A 2-Year Neurodevelopmental Follow-up

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Abstract

Objective: To describe the 2-year neurodevelopmental outcome in children with cerebral palsy associated with congenital Zika (CZ) and explore variables associated with a more severe presentation. **Methods:** Data on 69 children with cerebral palsy associated with CZ, followed in a neurorehabilitation hospital, who consecutively attended the neurodevelopmental assessment at 2 years of age, were collected. Bayley III Scales of Infant and Toddler Development, Hammersmith Infant Neurological Examination, and Gross Motor Function Classification System were used for the outcome evaluation. Descriptive and inferential statistical analysis were performed. **Results:** The median age at follow-up was of 24.0 (23-32) months. Only 3 (4.3%) children were not microcephalic. The majority presented with bilateral (94.2%), spastic (100.0%), Gross Motor Function Classification System grade IV or V (92.8%) cerebral palsy, epilepsy (73.1%), extremely low performances on cognitive (94.2%), language (95.7%), and motor (95.7%) Bayley-III Scales of Infant and Toddler Development Test scores. The median Hammersmith Infant Neurological Examination score was of 21.0 (range 9-75). There was a correlation between birth head circumference with the cognitive ($r = 0.3$, $P < .01$), language ($r = 0.3$, $P < .01$), and motor ($r = 0.3$, $P < .01$) Bayley-III Scales of Infant and Toddler Development Test scores, as well as with the Hammersmith Infant Neurological Examination score ($r = 0.2$, $P < .03$). An association was observed between an inferior median Hammersmith Infant Neurological Examination score with congenital microcephaly ($P = .04$), arthrogryposis ($P = .02$), and epilepsy in the first year ($P < .01$). **Conclusion:** Cerebral palsy related to CZ presents with a severe global impairment at a 2-year follow-up. Birth head circumference, arthrogryposis, and early epilepsy are associated with a worse outcome and may be considered as prognostic markers. These findings are important for the neurorehabilitation planning, parents' guiding, and future prognostic studies.

Keywords

Zika virus, congenital Zika, cerebral palsy, neurodevelopment

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The congenital Zika syndrome was described in 2016[1] after an outbreak of Zika virus infection that spread throughout the Americas,[2] followed by a microcephaly epidemic.[3] Brazil was the most affected country, especially in the Northeast.[4] In the last US report about the follow-up of children with confirmed or possible exposure to Zika virus during pregnancy, the largest cohort ever reported, 9% of the 1450 cases had at least 1 neurodevelopmental abnormality.[5] It seems clear now that congenital Zika syndrome is a spectrum, with confirmed cases that will be asymptomatic,[6] children with subtle abnormalities,[7] and the ones who will evolve with neurodevelopmental delays or even cerebral palsy.[8,9] Cerebral palsy is an umbrella term that refers to a nonprogressive lesion of the developing brain of any cause, leading to a permanent motor disorder.[10] It has been reported as a possible outcome in the most severe extreme of the congenital Zika syndrome spectrum.[11]

SARAH Salvador Hospital is a tertiary neurorehabilitation service located at Salvador, one of the most affected northeastern states, in Brazil, by the microcephaly outbreak. At the beginning of the epidemics in late 2015, more than 500

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children with suspected microcephaly related to Zika virus started a rehabilitation program.[12] We have published the results of the 1-year follow-up of a sample of these children,[13] but we did not expand a more detailed prognostic analysis then, considering the early age of the children.

The additional follow-up of these children is relevant because it will allow a better understanding of the long-term prognosis. The majority of the studies have described the congenital Zika syndrome profile in children below the age of 2 years, which has been reported as the ideal age for functional prognosis establishment.[14] Such description will improve the rehabilitation planning, help to guide the parents, and identify possible early factors related to a worse outcome. We aimed to evaluate the neurodevelopmental 2-year-outcome in children with cerebral palsy associated with congenital Zika syndrome and explore possible early clinical prognostic variables.

Methods

Study Design, Participants, and Setting

This is the second-year follow-up report of a prospective cohort study performed at a referral neurorehabilitation hospital in northeastern Brazil. The participants were children with cerebral palsy related to congenital Zika infection, who consecutively attended neurodevelopmental evaluation at 1 and 2 years of age.

Children enrolled had all of the following criteria: (1) were born after July 1, 2015 (ie, during the Zika virus outbreak); (2) had neuroimaging features characteristic of congenital Zika syndrome (brain calcifications, ventricular enlargement, or malformation of cortical development); (3) had negative laboratory results for toxoplasmosis, cytomegalovirus, syphilis, and rubella; and (4) their mothers had a rash illness during pregnancy, suggestive of a Zika virus infection.

Children who had an associated genetic syndrome, who did not present a clinical diagnosis of cerebral palsy, or who did not attend the 2-year developmental evaluation were excluded.

Variables and Procedures

On admission, all the children were evaluated and followed by a neurorehabilitation team. The workup was guided by the Brazilian Minister of Health and the hospital's protocol. The clinical variables and examination results were extracted from the electronic medical records and used to fill a standard form.

Congenital microcephaly was considered present if the birth head circumference was below –2 standard deviations (SDs) for age and sex, and severe congenital microcephaly if below –3 SD, according to the INTERGROWTH-21st.[15] Prematurity was present if the birth gestational age was below 37 weeks of pregnancy. Epilepsy was defined as the presence of recurrent unprovoked seizures. Serologic tests (immunoglobulin M [IgM] and G [IgG]) were performed to investigate toxoplasmosis, rubella, and cytomegalovirus (enzyme-linked fluorescence assay method), and the Venereal Disease Research Laboratory test was performed for screening of syphilis. For Zika virus serology, a commercial enzyme-linked immunosorbent assay kit (Euroimmun, Lubeck, Germany) was used. If available, the child's or the mother's reverse transcription polymerase chain reaction for Zika virus results, performed outside the study setting, were collected from the records.

For the brain computed tomography (CT) scans, we performed a volumetric acquisition by multislice technique, without contrast; for brain magnetic resonance imaging (MRI), we used the techniques spin-echo, fast-spin-echo, and gradient-echo, sequences weighted in T1 and T2, fluid-attenuated inversion recovery and susceptibility-weighted imaging, in multiplanar acquisitions (GE Signa HDxt 1.5 Tesla). Those examinations were done during spontaneous sleep, without sedation, in accordance with the setting's protocol. Neuroimaging analysis were performed by experienced neuroradiologists, blinded to the outcomes, and extracted from the electronic medical records. For video-electroencephalogram (Nihon-Kohden, model LS-125) trace, a helmet for microcephaly was used, with 10 electrodes, in accordance with the international system 10-20, and 20 minutes' duration. We considered abnormal if there was any type of epileptiform activity or abnormal background activity. During the examinations, the child was awake or spontaneously sleeping. Two neurophysiologists, blinded to the outcomes, analyzed the results and they were collected from the medical records.

The outcome evaluation was done at 2 years of age by the same pediatrician, the main author (ALC). Cerebral palsy diagnosis was performed in accordance with the Definition and Classification of Cerebral Palsy, April 2006.[10] The head circumference was measured and categorized according to the World Health Organization (WHO) charts, and the children were classified in accordance with the Gross Motor Function Classification System.[14]

A full neurologic examination, using the Hammersmith Infant Neurological Examination, was performed. The Hammersmith Infant Neurological Examination is a standardized neurologic examination for infants between 2 and 24 months of age, considered the criterion standard for prediction of the cerebral palsy diagnosis and prognosis. Scores lower than 40 are predictors of nonambulant cerebral palsy. It is a scoreable examination comprising 26 items divided into 5 domains, including cranial nerve function, posture, movement quality and quantity, muscle tone, reflexes, and reactions. Each item is scored individually, ranging from the minimum of 0 (if not observed) to the maximum of 3 (fully observed). The overall global score is calculated as the sum of all the items (range: 0-78). Higher scores indicate better neurologic performances.[16,17]

Developmental performance was evaluated by the Bayley-III Scales of Infant and Toddler Development Test (BSIDIII), adapted and translated in Brazil.[18] The final composite cognitive, language, and motor Bayley-III Scales of Infant and Toddler Development Test scores and the Hammersmith Infant Neurological Examination optimality global scores were considered as outcome measures.

For statistical analysis, we used the statistical package SPSS 22.0. Absolute and relative frequencies were used for categorical variables; mean, median, range, and standard deviation (SD) were used for the continuous ones. For correlation analysis, we used the Spearman correlation coefficient; and for mean comparisons, we used the Mann-Whitney U test. A $P < .05$ was considered significant.

Results

We started to follow this cohort of children with cerebral palsy related to congenital Zika at the beginning of the microcephaly outbreak in Brazil. Of the 252 eligible children, 82 were evaluated at 12 months of age[13] and, of these, 69 attended the neurodevelopmental evaluation at 24 months of age and were

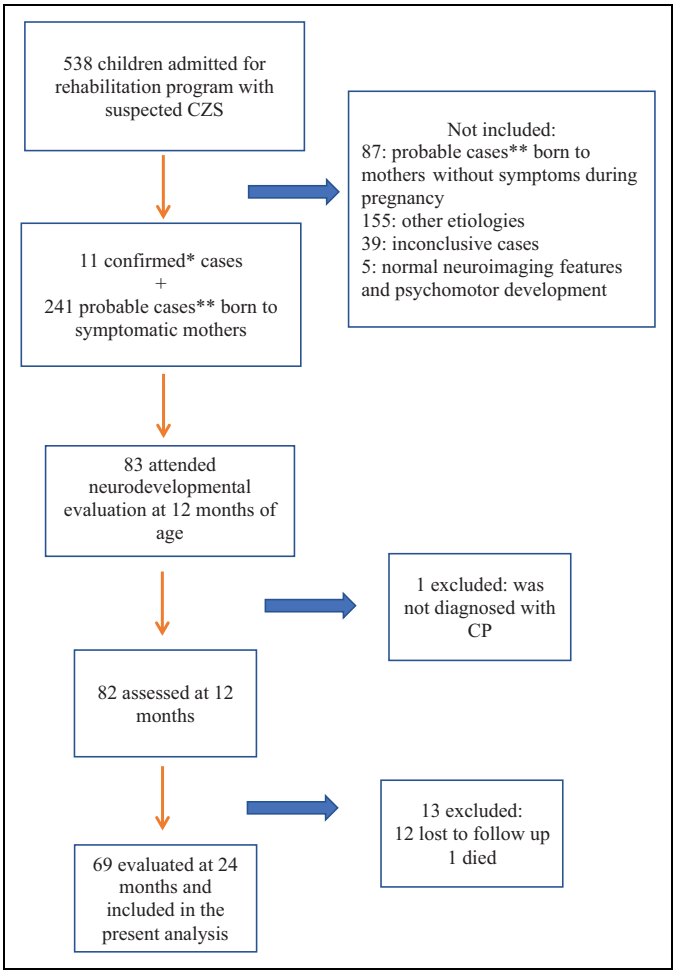

Figure 1. Flowchart showing the study population and sample. *Those with a positive immunoglobulin M or reverse transcriptase-polymerase chain reaction assay in the mother or the child. All of them were born to symptomatic mothers. **Children with neuroimaging findings suggestive of CZS and without serologic evidence of other congenital infections (toxoplasmosis, rubella, syphilis, and cytomegalovirus). CP, cerebral palsy; CZS, congenital Zika syndrome.

Table 1. Clinical and Neurodevelopmental Characteristics of Infants With Cerebral Palsy Related to Congenital Zika at 2-Year Follow-up, Brazil, 2018.

Feature	n (%) or median (range)
Female sex	36/69 (52.2)
Mother's age, y	29.0 (17-40)
Gestational age, wk	39.0 (34-42)
Prematurity	6/69 (8.7)
Congenital microcephaly	60/67 (89.6)
Severe congenital microcephaly	44/67 (65.7)
Birth HC, cm[a]	29.0 (25.0-33.0)
Birth HC, SD[a,b]	–3.2 (–5.3 to 0.0)
Birth weight, kg	2.7 (1.3-3.9)
Epilepsy at first year	44/69 (63.8)
VEEG abnormality at first year	35/65 (53.8)
Cognitive score[c]	
Extremely low	65 (94.2)
Low average	2 (2.9)
Average	2 (2.9)
Language score[c]	
Extremely low	66 (95.7)
Borderline	3 (4.3)
Motor score[c]	
Extremely low	66 (95.7)
Borderline	2 (2.9)
Low average	1 (1.4)
CP topography	
Bilateral	65/69 (94.2)
Unilateral	4/69 (5.8)
GMFCS level	
I-III	5/69 (7.2)
IV-V	64/69 (92.8)

Abbreviations: CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; HC, head circumference; SD, standard deviation; VEEG, video-electroencephalogram.
[a]Head circumference at birth was missing for 2 children
[b]Standard deviation according to INTERGROWTH-21st.
[c]According to Bayley Scales composite scores.

included in the present analysis. Twelve children were lost to follow-up and 1 child died. The study population flowchart is shown in Figure 1. Table 1 shows the main clinical and neurodevelopmental features of these children. The neuroradiologic profile of the sample is seen in Supplementary Table S1 and the mean scores on Bayley-III Scales of Infant and Toddler Development Test are provided in Supplementary Table S2.

The majority of the mothers had symptoms during the first trimester of pregnancy (56/81.2%). Arthrogryposis was observed in 4 of 69 children (5.8%). The median age at follow-up evaluation was of 24.0 (range 23-32) months. Only 3 children (4.3%) were not microcephalic then and 61 (88.4%) had a head circumference below 3 SD for age and sex, according to the WHO charts. The median head circumference was 40.5 cm (range 35.0-45.5), whereas at this age the normal would be 47.2 cm for girls and 48.3 cm for boys, according to the WHO charts. At the time of follow-up, epilepsy was present in 49 out of 67 children (73.1%), and abnormal persistence of primitive reflexes and absence of expected postural reactions were seen in 62 children (89.9%). Spasticity was predominant in all the children. Sixty-three children (91.3%) had quadriplegic cerebral palsy, 4 children (5.8%) had hemiplegic cerebral palsy, and 2 (2.9%) diplegic cerebral palsy. The median overall Hammersmith Infant Neurological Examination score was 21.0 (range 9-75). Among the quadriplegic children, the median Hammersmith Infant Neurological Examination score was 19.0 (range 9-43), and among the non-quadriplegic infants, the median Hammersmith Infant Neurological Examination score was 69.5 (range 63-75).

Forty-two children (60.9%) had laboratorial evidence of previous contact with Zika virus: 6 (8.7%) had a positive IgM for Zika virus on the child's blood; 1 (1.5%) had a positive reverse transcription polymerase chain reaction on the child's blood; 35 (50.7%) had a positive or inconclusive IgG on the child's blood; and 27 (39.1%) had both negative IgG and IgM. When comparing the clinical and neuroradiologic characteristics

Table 2. Correlation Analysis Between Early Clinical Features and Neurodevelopmental Outcome of Infants With Cerebral Palsy Related to Congenital Zika at 2-Year Follow-up, Brazil, 2018.[a]

Feature	HINE	CCS	LCS	MCS
Mother's age	0.0 (.95)	0.0 (.82)	–0.1 (.25)	0.0 (.93)
Gestational age	0.0 (.97)	0.2 (.13)	0.2 (.08)	0.2 (.11)
Birth weight	0.0 (.85)	0.1 (.48)	0.1 (.50)	0.1 (.50)
TD	–0.2 (.10)	–0.2 (.09)	–0.2 (.19)	–0.2 (.12)
Birth HC	0.3 (<.01)	0.3 (<.01)	0.3 (<.01)	0.3 (<.01)
Follow-up HC	0.3 (<.01)	0.3 (<.01)	0.5 (<.01)	0.3 (<.01)

Abbreviations: CCS, cognitive composite score of Bayley Scales; HC, head circumference; HINE, Hammersmith Infant Neurological Examination; LCS, language composite score of Bayley Scales; MCS, motor composite score of Bayley Scales; TD, time for discharge.
[a]Values within parentheses are *P* values.

Table 3. Median HINE Scores Comparisons in Infants with Cerebral Palsy Related to Congenital Zika at 2-Year Follow-up, Brazil, 2018.

Features	HINE score	*P* value
Gender		.62
Female	22.5	
Male	20.0	
Trimester of symptoms		.75
First	20.5	
Second	23.0	
Congenital microcephaly		.04
Yes	20.0	
No	29.0	
Severe congenital microcephaly		.02
Yes	18.0	
No	23.0	
Prematurity		.46
Yes	23.0	
No	20.0	
Arthrogryposis		.02
Yes	14.5	
No	22.0	
Epilepsy at first year		<.01
Yes	18.0	
No	34.0	
VEEG abnormality at first year		<.01
Yes	18.0	
No	26.0	

Abbreviations: HINE, Hammersmith Infant Neurological Examination; VEEG, video-electroencephalogram.

of children with and without laboratorial evidence, we did not notice important differences (details provided in Supplementary Tables S3 and S4). The median age of serology performance was of 5.0 months (range 1-13).

Table 2 shows the correlation analysis between early clinical variables and the outcome scores, and evidence that there were significant correlations between the birth head circumference and the neurodevelopmental scores, as well as between the follow-up head circumference and the neurodevelopmental scores. Table 3 describes the comparisons between median Hammersmith Infant Neurological Examination scores at 24 months of age according to the presence of early clinical features in the first year of life. The data show that children with congenital microcephaly, arthrogryposis, epilepsy, and with video-EEG abnormalities during the first year of life had significantly lower median Hammersmith Infant Neurological Examination scores.

Discussion

Here we described the 2-year follow-up of a cohort of children with cerebral palsy related to congenital Zika, evaluated at a referral rehabilitation center, in northeastern Brazil. The majority evolved with a severe functional presentation of cerebral palsy, maintaining the extremely low performances in language and cognitive domains, as observed in the first 12 months of life.[13] Epilepsy was even more common than in the first year. Head circumference at birth, congenital microcephaly, as well as the presence of arthrogryposis and epilepsy in the first year of life were associated with a worse neurologic outcome.

As the children entered the third year of life, the vast majority had microcephaly and bilateral spastic cerebral palsy, with a severely impaired gross motor development, as observed by Gross Motor Function Classification System classification and mean motor Bayley-III Scales of Infant and Toddler Development Test scores. Also, extremely low scores in language and cognitive evaluation were also predominant.

A few studies have described the neurodevelopmental outcome so far using Bayley-III Scales of Infant and Toddler Development Test[6,19,20] and other scales, such as the Alberta Infant Motor Scale,[19,21] the Test of Infant Motor Performance,[22] Denver II,[23] and Gross Motor Function Measure.[9,24] These studies have demonstrated a similar pattern of severe developmental impairment in motor, cognitive, and language domains, but all with a shorter time of follow-up and with a smaller sample of microcephalic children than we reported here.

Regarding motor aspects, a previous study of 34 children with microcephaly related to congenital Zika showed a severe disability in 64.7% at a median age of 21 months, using Gross Motor Function Measure 88. In that series, almost 90.0% had a severe impairment in muscle tone functions and lack of voluntary muscles control.[24] Marques et al reported Bayley-III Scales of Infant and Toddler Development Test motor scores in 25 children followed in a similar setting, during an 18-month follow-up. The authors described, also using the Alberta Infant Motor Scale, that the gross motor development marginally improved, but with a worse deviation from normal as time passed.[19]

The median Hammersmith Infant Neurological Examination score of our sample was of 21.0, which is highly predictive of cerebral palsy.[25] In the only study that used this same instrument, Satterfield et al[8] demonstrated that the majority had a Hammersmith Infant Neurological Examination score <40. Melo et al[9] reported that among 59 confirmed or presumed congenital Zika syndrome cases, at a mean age of 14.7 months,

81% were classified as Gross Motor Function Classification System level V, which was also far more common in our series.

In the Northeast Region, Brazil, a study[23] reported that the most affected domain was language, using Denver II test, but the study had a small sample and a mean age below 24 months. Ferreira et al[24] showed that 88.3% had severe or complete impairment in intellectual functions and all had language delay. In combination with our findings, those data suggest that the neurologic impairment caused by Zika virus is global, equally affecting motor, language, and cognitive domains in most cases.

Even fewer studies have described the associations between early variables and the neurodevelopmental outcome. We had already described, at the 1-year follow-up report of the present cohort,[13] that there was a correlation between head circumference and the Bayley-III Scales of Infant and Toddler Development Test scores, suggesting that this feature may be a prognostic marker. Here we expanded the explored variables and added that, in addition to the birth head circumference and the presence of congenital microcephaly, the presence of arthrogryposis, epilepsy, and video-EEG abnormalities during the first year of life are associated with a more severe presentation. Lopes et al,[6] in a cohort of confirmed cases in Rio de Janeiro, found an association between normal neuroimaging and higher Bayley-III Scales of Infant and Toddler Development Test scores. Also, another study reported the association between severe malformation of cortical development and head circumference with a worse gross motor function, evaluated with Gross Motor Function Measure.[9]

Limitations

We acknowledge that this study had 2 main limitations. First, the subjects were enrolled in a tertiary hospital for children with cerebral palsy and, therefore, may represent the most severe extreme of the congenital Zika syndrome spectrum. Second, laboratory confirmation of congenital Zika syndrome with reverse transcription polymerase chain reaction or IgM was not possible for the majority, because of the challenges of the molecular and serologic diagnosis, as well as the study's setting peculiarities. On the other hand, all the cases had typical neuroradiologic and clinical presentation, were born to symptomatic mothers, during the Zika virus outbreak, in one of the most affected regions in Brazil, and had other common congenital infections ruled out.

Conclusion

The present study demonstrated that on a 2-year follow-up, cerebral palsy related to congenital Zika evolve with a severe motor, cognitive, and language impairment, which corroborates the 1-year follow-up findings. Head circumference at birth, arthrogryposis, and epilepsy in the first year of life were associated with a worse outcome and may be considered as prognostic markers. These findings are important for the neurorehabilitation program planning, parents' guiding, and future prognostic studies.

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Author Contributions

ALC conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, reviewed and revised the manuscript. PV participated in the design of the study, reviewed and revised the manuscript. TT collected data, reviewed and revised the manuscript. IB drafted the initial manuscript, reviewed and revised the manuscript. CB and RL participated in the design of the study, reviewed and revised the manuscript.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

Ethical Approval

The study was approved by the SARAH network's institutional Research Ethics Committee (no. 58977816.6.0000.0022), and all parents signed a written informed consent form.

References

1. Moore CA, Staples JE, Dobyns WB, et al. Characterizing the pattern of anomalies in congenital zika syndrome for pediatric clinicians. *JAMA Pediatr*. 2017;171(3):288-295.
2. Pan American Health Organization, Organization PAHOWH. Neurological syndrome, congenital anomalies, and zika virus infection. *Epidemiological Update*. https://www.paho.org/hq/dmdocuments/2016/2016-jan-17-cha-epi-update-zika-virus.pdf. Published 2016. Accessed July 22, 2017.
3. Brazil. Minister of Health. Health Surveillance Secretary. Integrated monitoring of growth and developmental abnormalities related to Zika virus infection and other infectious causes, until Epidemiological Week 48 of 2017 [in Portuguese]. *Epidemiol Bull*. 2018;49(3):1-10. http://portalarquivos2.saude.gov.br/images/pdf/2018/janeiro/30/2018-002.pdf. Accessed Jule 12, 2018.
4. World Health Organization. Zika virus, microcephaly, Guillain-Barré Syndrome, 10 march 2017 (situation report). Brasilia, DF. http://apps.who.int/iris/bitstream/10665/254619/1/WHO-ZIKV-SUR-17.1-eng.pdf. Published 2017. Accessed April 18, 2019.
5. Rice ME, Galang RR, Roth NM, et al. Vital signs: Zika-associated birth defects and neurodevelopmental abnormalities possibly

associated with congenital Zika virus infection—U.S. territories and freely associated states, 2018. *Morb Mortal Wkly Rep*. 2018; 67(31):858-867.
6. Lopes Moreira M, Nielsen-Saines K, Brasil P, et al. Neurodevelopment in infants exposed to Zika virus in utero. *N Engl J Med*. 2018;379(24):2377-2379.
7. Carvalho AL de, Brites C, Taguchi TB, Pinho SF, Campos G, Lucena R. Congenital Zika virus infection with normal neurodevelopmental outcome, Brazil. *Emerg Infect Dis*. 2018;24(11): 2128-2130.
8. Satterfield-Nash A, Kotzky K, Allen J, Bertolli J, Moore CA, Pereira IO. Health and development at age 19-24 months of 19 children who were born with microcephaly and laboratory evidence of congenital Zika virus infection during the 2015 Zika virus outbreak—Brazil, 2017. *MMWR Morb Mortal Wkly Rep*. 2017;66(49):1347-1351.
9. Melo A, Gama GL, da Silva Júnior RA, et al. Motor function in children with congenital Zika syndrome [published online ahead of print April 4, 2019]. *Dev Med Child Neurol*. doi:10.1111/dmcn. 14227.
10. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol*. 2007;109:8-14.
11. Pessoa A, Van Der Linden V, Yeargin-Allsopp M, Carvalho MDCG, Ribeiro EM, Van Naarden Braun K. Motor abnormalities and epilepsy in infants and children with evidence of congenital Zika virus infection. *Pediatrics*. 2018;141(suppl 2):S167-S179.
12. Carvalho AL De, Brandi IV, Sarmento M, Brites C, Lucena R. Difficulties with laboratory confirmation of congenital Zika virus infection in a tertiary hospital in Northeastern Brazil. *Clin Microbiol Infect*. 2019;25(4):524-525.
13. Carvalho A, Brites C, Mochida G, et al. Clinical and neurodevelopmental features in children with cerebral palsy and probable congenital Zika. *Brain Dev*. 2019;41(7):587-594.
14. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4):214-223.
15. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet*. 2014;384:857-868.
16. Romeo DM, Ricci D, Brogna C, Mercuri E. Use of the Hammersmith Infant Neurological Examination in infants with cerebral palsy: a critical review of the literature. *Dev Med Child Neurol*. 2016;58(3):240-245.
17. Romeo DM, Cioni M, Scoto M, Mazzone L, Palermo F, Romeo MG. Neuromotor development in infants with cerebral palsy investigated by the Hammersmith Infant Neurological Examination during the first year of age. *Eur J Paediatr Neurol*. 2008;12: 24-31.
18. Madaschi V, Mecca TP, Macedo EC, Silvestre Paula C. Bayley-III Scales of infant and toddler development: transcultural adaptation and psychometric properties. *Paid (Ribeirão Preto)*. 2016; 26(64):189-197.
19. Marques FJP, Teixeira MCS, Barra RR, et al. Children born with congenital Zika syndrome display atypical gross motor development and a higher risk for cerebral palsy. *J Child Neurol*. 2018; 34(2):81-85.
20. Einspieler C, Utsch F, Brasil P, Aizawa CYP, Peyton C, Hasue RH. Association of infants exposed to prenatal Zika virus infection with their clinical, neurologic, and developmental status evaluated via the general movement assessment tool. *JAMA Netw Open*. 2019;2(1):e187235.
21. Soares-Marangoni D, Tedesco N, Nascimento A, Almeida P, Santos Pereira C. General movements and motor outcomes in two infants exposed to Zika virus: brief report. *Dev Neurorehabil*. 2018;16:1-4.
22. Botelho A, Neri L, da Silva M, et al. Presumed congenital infection by Zika virus: findings on psychomotor development—a case report. *Rev Bras Saúde Matern Infant*. 2016;16(1):S39-S44.
23. Alves LV, Paredes CE, Silva GC, Mello JG, Alves JG. Neurodevelopment of 24 children born in Brazil with congenital Zika syndrome in 2015: a case series study. *BMJ Open*. 2018;8(7): e021304.
24. Ferreira H, Schiariti V, Regalado I, et al. Functioning and disability profile of children with microcephaly associated with congenital Zika virus infection application of the ICF brief core set for cerebral palsy in children with microcephaly associated with congenital Zika virus infection in Braz. *Int J Environ Res Public Health*. 2018;15(6):pii: E1107.
25. Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. *JAMA Pediatr*. 2017;171(9):897-907.