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Original article

Clinical and neurodevelopmental features in children with cerebral palsy and probable congenital Zika

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Abstract

Objective: To describe the neurological and neurodevelopmental features at 1 year of age in children with cerebral palsy (CP) related to probable congenital Zika (CZ), followed in a referral neurorehabilitation hospital.

Methods: Data on 82 children with CP associated with probable CZ, who consecutively attended the neurodevelopmental and neurological assessment around one year of age, were collected. For neurodevelopmental evaluation, Bayley-III Scales of Infant and Toddler Development was used. Descriptive statistical analysis was performed.

Results: The children were admitted into the rehabilitation program at a young age (mean age: 4.8 months, SD 3.1), followed beyond the first year of life (mean age of follow up: 13.2 months, SD 2.1), born to young mothers (mean age: 28.1 years, SD 5.9), in their first pregnancy (62.2%). The majority had severe congenital microcephaly (62.0%), spastic CP (96.3%), epilepsy (63.4%), absent expected postural reactions (93.2%), abnormal persistence of primitive reflexes (94.7%), and severe neuroimaging abnormalities, predominantly calcifications (97.6%). Extremely low performances on cognitive (95.1%), language (97.6%) and motor (97.6%) developmental composite scores were observed. There was a correlation between the cognitive score with the birth head circumference (HC) ($r = 0.3$, $p = 0.01$) and with the follow up HC ($r = 0.4$, $p < 0.01$), as well as between the follow up HC with the motor score ($r = 0.2$, $p = 0.03$).

Conclusion: Congenital Zika may be associated with a severe form of CP, mainly bilateral spastic, with a severe global neurodevelopmental impairment and early signs of a poor prognosis for independent walking. Head circumference may be a prognostic marker among those children. These results may help establish goals for the rehabilitation program and identify priority health services.

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Keywords: Zika virus; Cerebral palsy; Neurodevelopment

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1. Introduction

Zika virus (ZIKV) is an RNA virus of the *Flaviviridae* family. The primary transmission of the disease is by mosquitos, usually *Aedes* species [1]. The virus was first isolated in 1947 in sentinel rhesus monkeys, in the Zika Forest of Uganda [2]. In 2015, after an outbreak in Brazil, an increased incidence of microcephaly was observed, mainly in northeast states [3]. Subsequently, a causal relationship between ZIKV and microcephaly was recognized [4]. From November 2015 to April 2018, 15.874 children with suspected developmental disturbances presumably related to ZIKV or other congenital infections were identified in Brazil, 59.8% in northeast states. Salvador, capital of Bahia state, is the most populous city in this region and the one with the largest absolute number of confirmed cases [5].

Studies have shown that ZIKV is able to efficiently infect human cortical neural progenitor cells, resulting in reduced growth and dysregulation [6]. Robust evidence has now been published indicating that ZIKV can be vertically transmitted [7 8] and is associated with brain damage in the fetus, resulting in the congenital ZIKV syndrome (CZS) [9]. Previous reports indicated that cerebral palsy (CP) is part of the CZS spectrum [10]. Cerebral palsy is defined as a group of permanent disorders of movement and posture, related to a non-progressive injury in the developing fetal or child brain [11]. The diagnosis relies on clinical signs and data indicate that it can be performed as early as around 12 months of age [12].

Describing the clinical features and the developmental outcome of the affected children will help individualize the rehabilitation program and identify their main needs, regarding assistance services. However, since CZS has been recently recognized, few studies have described the CP features and the neurodevelopmental outcomes, so far. The aim of this study was to describe the neurological and neurodevelopmental profile in infants with CP associated with probable congenital Zika, followed in a referral rehabilitation hospital.

2. Methods

2.1. Study design, participants and setting:

This was a prospective study performed at a neurorehabilitation hospital in Northeastern Brazil, which is a reference service for children with CP. The study subjects were children with CP associated with probable congenital Zika infection, who consecutively attended neurodevelopmental evaluation around 1 year of age.

Because of the difficulties with laboratory confirmation of the infection and as the participants were admitted for rehabilitation beyond neonatal period, serological or molecular evidence of Zika congenital infection was not possible in all the cases. Therefore, we considered the following criteria used by França *et al* [13] to define highly probable cases of CZS: neuroimaging studies suggestive of congenital infection (brain calcifications, ventricular enlargement or both), and negative laboratory results for toxoplasmosis, cytomegalovirus, syphilis and rubella.

Children who met the following criteria were eligible for enrollment: 1) Born to mothers whose pregnancies occurred during ZIKV outbreak in Brazil, with the date of birth after July 1 st 2015; 2) Admitted for neurorehabilitation program from November 1 st 2015 to 31st December 2016; 3) Had the aforementioned criteria for a highly probable case of CZS; 4) Mother had history of a rash illness during pregnancy, to further strengthen the relationship with a potential ZIKV infection. The exclusion criteria were: to have any suspected or confirmed associated genetic syndrome; and the absence of motor abnormalities on neurologic examination suggestive of CP. The study was approved by the Ethical Committee of the hospital and all parents signed a written informed consent form.

2.2. Variables and procedures

The children were initially evaluated by a team of experienced developmental pediatricians. Laboratory and neuroimaging investigation were performed as indicated by the Brazilian Minister of Health and the hospital's clinical protocol. The demographic and clinical features, as well as the exam results, were collected by analysis of the electronic medical records, at admission, using a standard form.

Regarding the period of the microcephaly diagnosis, it was categorized in prenatal (during pregnancy) and postnatal (after delivery), according to the moment when the mother was told by a physician about this finding. The moment of the mother's symptoms during pregnancy was defined to be the first trimester if before 12 weeks of pregnancy, the second if between 13 and 27 weeks, and the third if after 28 weeks. Neonatal complication was considered present if there was any history of seizures, jaundice, respiratory distress, metabolic abnormality, feeding difficulties or other health problems during the first 28 days of life. Congenital microcephaly was defined as a birth head circumference (HC) below −2DP for age and sex, and severe congenital microcephaly as below −3DP, according to the INTERGROWTH 21st [14]. Prematurity was defined as a gestational age below 37 weeks of pregnancy. Intrauterine growth restriction (IUGR) was present if the birth weight was below −2DP for age, sex and gestational age [14]. Low birth weight was considered if the birth weight was below 2.5 kg. Epilepsy was considered if there was any history of recurrent unprovoked seizures.

Serological tests (IgM and IgG) to rule out toxoplasmosis, rubella and cytomegalovirus were performed using an Enzyme Linked Fluorescent Assay (ELFA) method; Venereal Disease Research Laboratory test (VDRL) was used for screening of syphilis; and serology for ZIKV was performed using a commercial ELISA (enzyme-linked immuno-sorbent assay) kit (Euroimmun, Lubeck, Germany). If the child or the mother had performed a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for ZIKV prior to admission, the result was collected if well documented in the medical record, as this technique is not available at the study setting.

Cranial computed tomography scan (CT) was performed through volumetric acquisition by multislice technique, without contrast, and brain magnetic resonance imaging (MRI) included techniques spin-echo (SE), fast-spin-echo (FSE) and gradient-echo, sequences weighted in T1, T2, FLAIR and SWI, in multiplanar acquisitions (GE Signa HDxt 1.5 Tesla). In accordance with the hospital's protocol, neuroimaging was performed during spontaneous sleep, without sedation. First, the child was submitted to an MRI attempt and, if it was unsuccessful, the CT was performed. Neuroimaging descriptions were done by experienced neuroradiologists, who were blinded to the clinical outcomes and collected from the electronic medical records. Videoelectroencephalogram (VEEG) (Nihon-Kohden, model LS-125) trace was registered by a fitting helmet designed for microcephaly, containing ten electrodes, according to international system 10–20, with 20 min duration. It was considered abnormal if any type of epileptiform activity or abnormal background activity were present. Brainstem auditory evoked potential (Natus® Neurology, Nicolet™ EDX-Viking V20.1) was performed with monoaural stimuli applied (rarefaction click), with contralateral masking, intensity of 90 dB and frequency of 10,1Hz. Waves I, III and V were obtained, with absolute and between peak latencies evaluated. V-waved audiometry was performed with the same technique, an intensity of 70, 60, 50, and 35 dB, frequency of 10,3Hz. The results were considered abnormal if wave V was not replicable above 35 dB hearing level. Visual evoked potential was performed with the same equipment; monocular stimuli were applied, using a FLASH pattern and P100 response evaluated. The results were considered abnormal if replicable P100 responses were not detected in either eye. All the neurophysiological exams were performed according to the hospital's clinical protocol, with the children awake or during spontaneous sleep. The results were analyzed by a neurophysiologist blinded to the clinical and neuroimaging findings and extracted from the medical records.

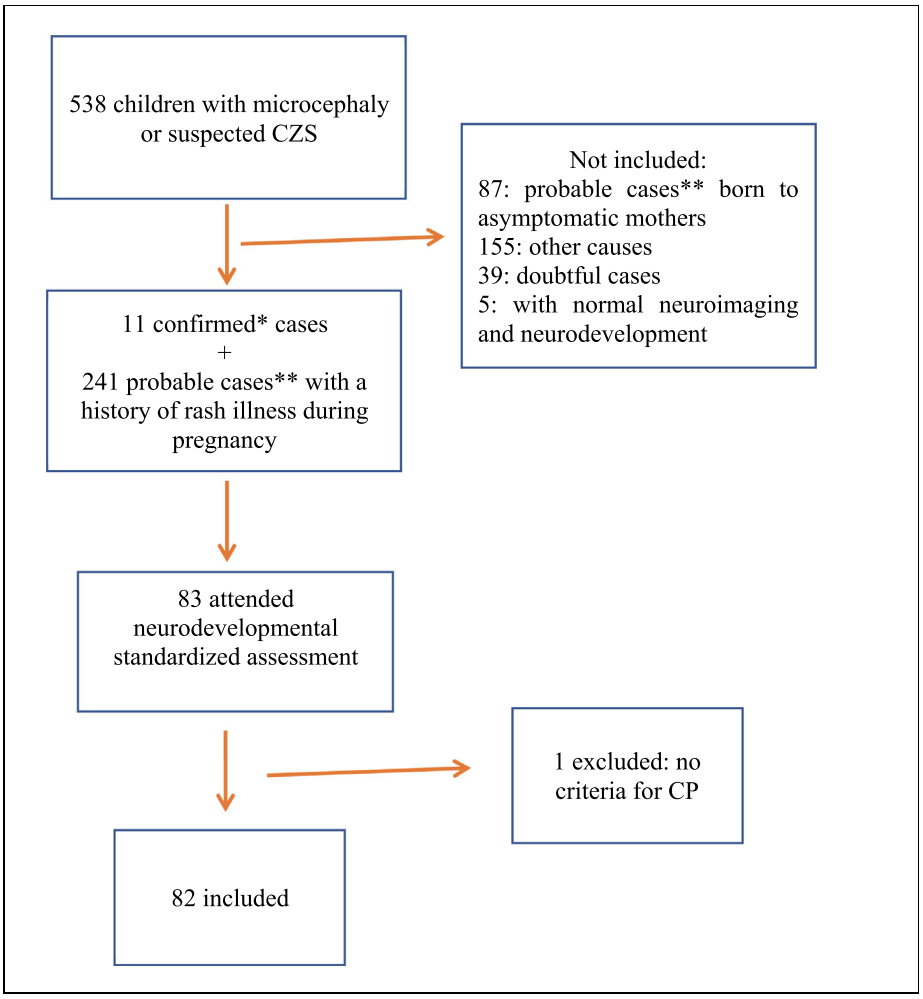
The follow up evaluation was performed around 1 year of age by the same pediatrician, the main author. Cerebral palsy diagnosis was established on a clinical basis, at that time, according to the Definition and Classification of Cerebral Palsy, April 2006 [11]. The subjects had a neurologic examination, with focus on muscle tone evaluation, primitive reflexes (Moro, asymmetrical tonic neck reflex and palmar grasp), postural reactions (Placing and Parachute), HC measurement (classified according to the World Health Organization charts), as well as motor severity assessment using the Gross Motor Function Classification System (GMFCS) for children under 2 years of age [15]. Developmental performance was assessed by the Bayley-III Scales of Infant and Toddler Development Test (BSID III), a gold standard tool for developmental evaluation of children from 1 to 42 months of age, adapted and translated in Brazil [16], and we considered the final composite scores of the cognitive, language and motor domains.

Statistical analysis was performed with statistical package SPSS 22.0™. For categorical variables, absolute and relative frequencies were used. For continuous variables, we used mean and standard deviation. Spearman correlation coefficient was used to evaluate the relationship between continuous variables. A $p < 0.05$ was considered significant.

3. Results

Since the beginning of the ZIKV outbreak in Brazil, 538 children with microcephaly or suspected CZS entered a neurorehabilitation program at the study setting, a tertiary rehabilitation hospital for children with brain and spinal cord injuries, in Northeastern Brazil [17]. As shown in Fig. 1, 83 out of the 252 eligible children consecutively attended neurodevelopmental assessment, from November 2016 to May 2017, and were included. One child was excluded because did not meet CP diagnostic definition. Tables 1 and 2 show the main clinical, demographic and neuroradiological features of the final sample of 82 children.

Fifty-one (62.2%) children were born from a first pregnancy. Sixty-six mothers (80.5%) had symptoms during the first trimester and 16 (19.5%) during the second trimester. None had symptoms during the third trimester. Only 22 (26.8%) children had neonatal complications (further details provided in Supplementary Table 1) and 6 required intensive care in the first days of life. The mean time for hospital discharge was 8.5 (SD 9.6) days. During the first year of life, 77 had a VEEG, with a mean age of 5.8 (SD 2.7) months; 43 (55.8%) had abnormalities: focal epileptogenic activity in 37 (48.1%), abnormal background activity in 28 (36.4%), generalized epileptogenic activity in 8 (10.4%), and hypsarrhythmia in 8 (10.4%). Five (6.5%) children had electroclinical seizures. Sixty-nine (84.1%) patients underwent CT at a mean age of 4.5 (SD 3.9) months and 17 (20.7%) children had MRI



CZS, congenital Zika syndrome; CP, cerebral palsy.

* Those with a positive immunoglobulin M or reverse-transcriptase-polymerase-chain reaction assay in samples from the mother or the child. All of them were born to symptomatic mothers.

** Children with neuroimaging findings suggestive of CZS and without serological evidence of other congenital infections (toxoplasmosis, rubella, syphilis and cytomegalovirus).

Fig. 1. Flowchart showing the study population and sample.

at a mean age of 4.6 (SD 4.2) months. The main neuroradiological findings were brain calcifications (97.6%), ventriculomegaly (90.2%) and abnormal gyral pattern (81.7%). Two children developed progressive worsening of hydrocephalus during the first year of life and, after neurosurgical evaluation, one of them had a ventriculoperitoneal shunt placed. Seventy-three infants had an evoked visual potential, with abnormalities present in 5 (6.8%); and 74 had a brainstem auditory evoked potential, with abnormalities seen in 10 (13.5%).

Of the evaluated children, 6 (7.3%) had a positive IgM for ZIKV on the child's blood, 1 (1.2%) had a positive RT-PCR on the child's blood and 1 (1.2%) a positive RT-PCR on the mother's blood during pregnancy. Forty (48.8%) children had a positive or inconclusive IgG for ZIKV on blood and 34 (41.5%) had negative IgG and IgM. No major differences regarding clinical, epidemiological and neuroradiological features were seen between the children with and without laboratory evidence of previous contact with ZIKV (details provided in Supplementary Tables 2 and 3). The mean age at serology

Table 1
Clinical and demographic characteristics of infants with cerebral palsy and probable congenital Zika, followed at the rehabilitation hospital, 2017.

Characteristic	No. or Mean (% or SD)
Female sex	43/82 (52.4)
Age at admission, months	4.8 (3.1)
Mother's age, years	28.1 (5.9)
Microcephaly diagnosis	
Prenatal	58/82 (70.7)
Postnatal	24/82 (29.3)
Cesarian delivery	45/80 (56.3)
Five minute Apgar score 7–10	61/63 (96.8)
Neonatal complications	22/82 (26.8)
Arthrogryposis	8/82 (9.8)
Gestational age, weeks	38.5 (1.5)
Prematurity	6/82 (7.3)
IUGR	16/82 (19.5)
Low birth weight	27/82 (32.9)
Microcephaly	70/79 (88.6)
Severe microcephaly	49/79 (62.0)
Birth HC, cm[*]	29.2 (1.9)
Birth HC, SD[*]	−3.2 (1.1)

SD, standard deviation; IUGR, Intrauterine growth restriction; HC, head circumference.
[*] Head circumference at birth was missing for 3 children

Table 2
Neuroradiological features in infants with cerebral palsy and probable congenital Zika, followed at the rehabilitation hospital, 2017.

Feature	No. (%)
Brain calcifications	80 (97.6)
Subcortical	54 (65.9)
Basal ganglia	41 (50.0)
Cortico-subcortical junction	31 (37.8)
Periventricular	23 (28.0)
Cortical	19 (23.2)
Thalamus	17 (20.7)
Brainstem	7 (8.5)
Corpus callosum	2 (2.4)
Cerebellum	1 (1.2)
Ventriculomegaly	74 (90.2)
Abnormal gyral pattern	67 (81.7)
Brain atrophy	62 (75.6)
Corpus callosum anomaly	54 (65.9)
Posterior fossa abnormalities[†]	21 (25.6)
Brainstem hypoplasia	15 (18.3)

[†] Cerebellum hypoplasia and/or megacisterna magna.

performance was of 3.9 (SD 2.0) months among the 48 children with any laboratory evidence of previous contact with ZIKV, as compared with the mean age of 7.3 (SD 3.2) months in the group without evidence.

The mean age of the follow-up evaluation was of 13.2 (SD 2.1) months. The data about the neurological and neurodevelopmental outcome are described in Table 3. Epilepsy was present in 52 (63.4%) children and spastic CP was predominant, with hypertonia observed in 79 (96.3%). On neurodevelopmental evaluation with BSID III, the majority showed extremely low performances on

Table 3
Neurological and neurodevelopmental evaluation in infants with cerebral palsy and probable congenital Zika, followed at the rehabilitation hospital, 2017.

Characteristic	No. (%)
Cognitive score[†]	
Extremely low	78/82 (95.1)
Borderline	2/82 (2.4)
Low average	2/82 (2.4)
Language score[†]	
Extremely low	80/82 (97.6)
Low average	2/82 (2.4)
Motor score[†]	
Extremely low	80/82 (97.6)
Borderline	2/82 (2.4)
Muscular tone abnormalities[‡]	
Generalized hypertonia	41/80 (51.2)
Upper extremities predominant hypertonia	33/80 (41.2)
Lower extremities predominant hypertonia	1/80 (1.3)
Unilateral hypertonia	4/80 (5.0)
Hypotonia	1/80 (1.3)
Abnormal persistence of primitive reflexes	70/74 (94.6)
Presence of expected postural reactions	5/73 (6.8)
HC categories[*]	
<−3SD	72/80 (90.0)
−2 to −3SD	6/80 (7.5)
−2 to −1SD	2/80 (2.5)
GMFCS classification	
I	1/82 (1.2)
II	3/82(3.7)
III	7/82 (8.5)
IV	38/82 (46.3)
V	33/82 (40.2)

HC, head circumference; SD, standard deviation; GMFCS, gross motor classification system.
[†] Bayley Scales composite scores: 69 and below = extremely low; 70–79 = borderline; 80–89 = low average; 90–109 = average; 110–119 = high average; 120–129 = superior; 130 and above = very superior.
[*] According to World Health Organization charts for age and sex.
[‡] One child had involuntary movements and muscle tone evaluation was missing for 1 child.

cognitive (95.1%), language (97.6%) and motor (97.6%) domains (details provided in Supplementary Table 4).

We found a correlation between the cognitive composite score with the birth HC ($r = 0.3$, $p = 0.01$) and with the follow up HC ($r = 0.4$, $p < 0.01$). The follow up HC was also correlated with the motor composite score ($r = 0.2$, $p = 0.03$). We found a negative correlation between the number of days for hospital discharge after birth and birth HC ($r = -0.5$, $p < 0.01$). Details are provided in Supplementary Table 5.

4. Discussion

This study presents a large group of children with CP associated with probable congenital Zika prospectively followed up. We showed that CP associated with CZS is mainly bilateral spastic, with early signs of a poor motor prognosis, as well as a severe language and cognitive

impairment. The pyramidal signs may be more prominent at the upper extremities in some cases. Epilepsy with focal discharges on electroencephalogram is a common condition among those children. Also, we found a correlation between birth HC and follow up HC with some of the developmental scores, suggesting that HC may be a marker of a worse neurodevelopmental outcome.

We observed a clinical-epidemiological profile of children admitted into a rehabilitation program at a young age, followed beyond the first year of life, born to young mothers, in their first pregnancy. The mothers presented with symptoms mainly during the first trimester of pregnancy and microcephaly was diagnosed during prenatal period for the majority. Prematurity, IUGR, low birth weight and neonatal complications were not common, although the mean time for hospital discharge was prolonged, suggesting that it may have been delayed because of the diagnostic work-up. Most children showed congenital microcephaly and severe microcephaly, but notably, there were 9 (11.4%) children with HC within the normal range at birth, which, in agreement with recent reports [13 18], demonstrates that congenital microcephaly is not an obligatory finding in CZS. It is also remarkable that at the time of follow up, only 2 children were not microcephalic, which further reinforces that some children may develop postnatal microcephaly.

The main clinical and demographic features are in line with previous publications, as the young mean age of the mothers [19] and the preponderance of the rash during the first trimester [20]. The patient as the first child was predominant in our series, similarly to a study in Recife [19], but it was not observed in the cohort of symptomatic pregnant women in the French territories, where only 24.0% were primigravidas [21]. Del Campo et al, among 83 participants from ten Brazilian states found a higher frequency of prematurity (22.5%) and children without microcephaly (24.6%) than we observed [22]. Arthrogryposis was present in a slight less extent than described by previous series, that showed a range from 10.0% [22] to 27.3% [23].

Laboratorial evidence of the congenital Zika virus infection (i.e., positive IgM or RT-PCR) was seen in only 8 (9.7%) children and serological evidence of previous contact with ZIKV was noted in 48.8%, meaning that the majority (58.5%) had some laboratory evidence, even though the serological test has been reported to have a low sensitivity [24]. Also, there have been a few descriptions showing individuals with no seroconversion after the acute phase of a ZIKV infection [25] and the case of a typical CZS child with a positive RT-PCR in amniotic fluid, but whose postnatal RT-PCR and IgM were negative [26]. In a previous study in US, only 4% of the 843 evaluated children with CZS had a positive IgM or molecular test [27].

Most subjects had VEEG abnormalities during the first year of life, predominantly focal discharges, and 63.4% presented epilepsy on follow-up. Other studies observed epilepsy to a lesser extent: 50% in a study from northeastern Brazil with a 4.4 months follow up [28] and 58% in a series of 19 cases at 22 months [29]. Abnormal auditory evoked potential (13.5%) was noted in a smaller frequency than previously reported (22.8%), in a study which further confirmed sensorineural hearing loss in 5 of their cases (7.0%) [30]. A study from Rio de Janeiro with 19 children noted auditory evoked abnormalities in only one case [31]. In our series, 6.8% had abnormal visual evoked potentials. To the best of our knowledge, visual evoked potential abnormalities were not previously reported in a larger sample, except for 2 of 3 children evaluated during postnatal period in a cohort from Colombia [20].

On neuroimaging evaluation, the most common features were brain calcifications (mainly subcortical), ventriculomegaly and abnormal gyral pattern suggestive of neuronal migration disorder. The main locations of the calcifications are in accordance with observed in other studies [22 32]. Two children in our series developed symptomatic hydrocephalus, one of them requiring a shunt placement, raising concern about careful HC measurement during follow up. Shunt placement was required in 40.5% of 37 subjects in a follow-up study with CZS patients from Pernambuco [33].

On follow-up evaluation, the majority had bilateral spastic CP, with absent expected postural reactions and abnormal persistence of primitive reflexes, signs of a poor prognosis for future independent walking ability [34]. The vast majority had all three neurodevelopmental domains classified as extremely low. The more severe GMFCS level (IV-V) was also predominant. This severe clinical presentation is probably due to the high prevalence of an extensive brain damage observed in neuroimaging in this series, as well as the predominance of severe microcephaly among the studied children, which further emphasizes the early negative impact of ZIKV on fetal brain development. Pyramidal or extrapyramidal signs are also described in previous CZS studies, in up to 75% of the cases [22]. A case series of 19 children with microcephaly and laboratory evidence of congenital ZIKV infection, evaluated at a median age of 22 months, showed that the majority had severe motor impairment (78.9%) and 14 had criteria for CP [29]. We found a positive correlation between birth HC and HC at follow up with some developmental scores, suggesting that HC may be an important prognostic marker. A previous study with 57 children with postnatal microcephaly of other causes found that the developmental score and HC were also correlated [35].

4.1. Limitations

This study has four main limitations. First is the selection of the subjects, who were enrolled in a referral

rehabilitation hospital. Therefore, the majority had severe brain and developmental impairment, so the generalizability of our findings may not be extrapolated to the full spectrum of CZS. Cerebral palsy is probably the most severe form of this spectrum. Second is the difficulty with laboratory confirmation of congenital ZIKV infection and the use of a serological method to rule out cytomegalovirus infection, since molecular evaluation was not available at the study setting. Also, as the subjects were enrolled after the newborn period, serological or molecular confirmation of a congenital ZIKV infection were not possible in all the cases. However, all the subjects were born during Brazil's ZIKV outbreak, in one of the most affected areas, and all the mothers had clinical symptoms consistent with ZIKV infection during pregnancy. Further, other common congenital infections were ruled out. Third is for the observational design of the study, subject to risk of confounders, such as recall bias. Fourth is the early diagnosis of CP and the relative short duration of follow up. Although CP diagnosis is usually established after 2 years of age, a study from Denmark showed that the median diagnostic age of CP was 11 months and the diagnosis was earlier in children with more severe disabilities [12]. As the causal connection between ZIKV and neurological abnormalities has only been known for about three years, further follow up of this cohort is warranted to gain a better understanding of this condition.

5. Conclusion

This study demonstrates that congenital ZIKV infection may be associated with a severe form of CP, mainly bilateral spastic, with a severe neurodevelopmental impairment at 1 year of age, signs of a poor motor prognosis and frequently associated with epilepsy. Also, HC is probably a prognostic marker of a poorer developmental outcome at this age. These results may help establish goals on the rehabilitation program in this population, identify priority health services needed and set basis for future prognostic studies.

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Appendix A. Supplementary data

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