Motor function in children with congenital Zika syndrome

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ABBREVIATIONS

CZS	Congenital Zika syndrome
PCR	Polymerase chain reaction
ZIKV	Zika virus

AIM To evaluate gross motor function and associated factors in children with congenital Zika syndrome (CZS).
METHOD Fifty-nine children (30 males, 29 females) with CZS at a mean (SD) age of 14.7 (3.9), months (range 5–29mo) were evaluated using the Gross Motor Function Measure (GMFM) and classified according to the Gross Motor Function Classification System (GMFCS). Neurological damage was evaluated by neuroimaging. The mothers' sociodemographic characteristics and general data on the children were obtained from interviews with the mothers and from the children's medical records. Correlational and multiple regression analyses were performed to identify factors associated with these children's motor function.
RESULTS In 81% of the children, motor function impairment was severe, classified as GMFCS level V. The overall GMFM score ranged from 5 to 210 (median 18; interquartile range 11), with only four children receiving scores in the D and E dimensions. The factors found to affect motor function were the presence of severe malformations of cortical development and small head circumference at birth.
INTERPRETATION Although motor impairment may be mild in some children, it is generally severe. Severe malformations of cortical development and small head circumference at birth were factors associated with poorer motor function, reflecting the greater severity of brain damage.

Zika virus (ZIKV) is a flavivirus transmitted by the Aedes aegypti mosquito. The alarming increase in the incidence of congenital microcephaly after an epidemic of ZIKV infection initially recorded in north-eastern Brazil in 2015 led to a hypothesis that these two events were associated.[1]

In 2016, the hypothesis of an association between ZIKV, fetal microcephaly, and brain abnormalities gained strong support from the first evaluation performed using imaging and laboratory tests from two pregnant women infected with ZIKV.[2] Later, two studies conducted in Brazil – a cohort study carried out in the state of Rio de Janeiro[3] and a case–control study conducted in the state of Pernambuco[4] – confirmed the association of ZIKV infection, microcephaly, and brain damage in fetuses and infants. Those studies established the etiological base of congenital Zika syndrome (CZS), which affects children whose mothers were infected with ZIKV during pregnancy.

In physio-pathological terms, the neuroimaging findings of fetal impairment are principally associated with the central nervous system and include reduced brain volume, malformations of cortical development, ventriculomegaly, calcifications in the basal ganglia, dysgenesis of the corpus callosum, and hypoplasia of infratentorial structures (cerebellum, cerebellar vermis, pons, brainstem).[5,6] Of the radiological findings associated with ZIKV infections during pregnancy, so far the presence of calcifications at the gray–white matter junction have only been described in brains affected by ZIKV.[7]

From a clinical perspective, the most important of the neurological abnormalities seen in children with CZS include severe spastic hypertonia with hyperreflexia, irritability, hyperexcitability, excessive crying, and swallowing disorders, as well as impaired auditory and visual responses.[8,9] Convulsive seizures in the neonatal period may also be present, with the occurrence of epileptic seizures being more evident from 3 months of age onwards and epileptic spasms being the most common type.[8]

Although the clinical characteristics of these children at birth have already been described, little information is available on motor function and further studies on this subject are required. Describing the motor function of children with CZS using validated instruments is relevant in understanding the true impact of the intrauterine infection and may help in the design of effective rehabilitation programmes aimed at minimizing motor difficulties.

Hence, this study aimed to evaluate the gross motor function of children with CZS and its associated factors.

METHOD

A cross-sectional observational study was conducted using data collected between February and June 2017 at a support centre for children with microcephaly associated with the Instituto de Pesquisa Professor Joaquim Amorim Neto in the city of Campina Grande, Paraíba, Brazil. The institute's internal review board approved the study protocol (reference C.A.A.E.52888616.4.0000.5693). All the mothers/guardians of children who fulfilled the eligibility criteria were invited to participate in the study and were included after signing an informed consent form.

Participants

The inclusion criteria consisted of a diagnosis of CZS confirmed by reverse transcription polymerase chain reaction (PCR) or a presumed diagnosis based on obstetric ultrasound, transfontanellar ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) performed in the first months of life. The child had to be aged 5 months or older at the time of inclusion.

Children with calcifications in the gray–white matter junction and any degree of delayed cortical development (ranging from mildly simplified gyral pattern to abnormalities such as lissencephaly, pachygyria, or malformations of cortical development) were presumed to have CZS (Figs. S1 and S2, online supporting information). Children in whom no neuroimaging abnormalities were found were excluded.[5,7]

Mothers who were still pregnant when they first attended the clinic were submitted to fetal neurosonography, performed by a maternal–fetal medicine specialist. If neurological damage was found, amniocentesis was offered to investigate for the presence of the ZIKV by reverse transcription PCR in amniotic fluid samples. The pregnant females were monitored until delivery, with blood samples from the umbilical cord and fragments from the placenta being collected. In the case of females who arrived at the clinic after their child was born, blood and urine samples were collected from the child for reverse transcription PCR and CT and/or MRI were performed. The final sample consisted of all the children receiving care at the Instituto de Pesquisa Professor Joaquim Amorim Neto specialist centre whose mothers authorized their participation in the study and attended the evaluation appointment.

Measures

The children were initially classified according to the Gross Motor Function Classification System (GMFCS).[10] This five-level system, widely used for children with cerebral palsy, defines a child's independence and functionality level according to their age.[10–14] In addition, the Gross Motor Function Measure (GMFM), originally developed to evaluate gross motor function in children with cerebral palsy, was used to evaluate motor function. The GMFM can be used in children at least 5 months old.[15,16] It is a scale of 88 gross motor tasks subdivided into five dimensions: (A) Lying and Rolling (17 items); (B) Sitting (20 items); (C) Crawling and Kneeling (four items); (D) Standing (13 items); and (E) Walking, Running, and Jumping (24 items). Each task is to be performed by the child without the parents' or therapist's help, and is scored on a scale of 0 to 3, with 0 indicating that the child did not initiate the task and 3 that the child was able to complete the task.[15,16]

What this paper adds

- Motor impairment is severe in most children with congenital Zika syndrome (CZS).
- Motor skills are adequate or close to adequate for age in 7% of children with CZS.
- Severe malformations of cortical development are associated with poor motor control.
- Small head circumference at birth is also associated with poor motor control.

The fetal neurosonography, MRI, and CT scans were evaluated by specialists in fetal medicine and neuroradiologists. The following malformations of cortical development were considered severe: lissencephaly, pachygyria, agyria, and disorganized gyral development; a simplified gyral pattern was considered mild. Neurosonography was performed using a WS80 Elite System (Samsung, Seoul, South Korea), MRI using a 1.5 Tesla scanner (Espree; Siemens Medical Solutions, Erlangen, Germany), and CT using a 16-section scanner (Siemens Healthcare, Erlangen, Germany).

The mothers' sociodemographic data (age, marital status, schooling, employment status, per capita family income, place of residence, number of living children) and data on the symptoms of ZIKV during pregnancy were collected. Birth data were obtained from the children's health cards (gestational age, weight, brain circumference, first- and fifth-minute Apgar scores). The child's age at evaluation was calculated from their date of birth, and data on anticonvulsant use were collected from the medical records.

Procedures

All children were evaluated in a private, specially adapted environment at Instituto de Pesquisa Professor Joaquim Amorim Neto. Four specially trained physiotherapists performed the evaluations, which lasted from 45 to 60 minutes. For the purposes of this study, only spontaneous motor behaviour was taken into consideration, with only verbal encouragement or the use of toys being allowed when necessary (Video S1, online supporting information).

Statistical analysis

The Gross Motor Ability Estimator software package was used to calculate the overall GMFM score and the scores for each domain. The Stata software program, version 12.0 (StataCorp, College Station, TX, USA), and MedCalc, version 17.9.7 (MedCalc Software, Ostend, Belgium), were

Table I: Gross Motor Function Measure (GMFM) score according to dimension and classification level

GMFM evaluation	Score			Percentage score		
	Range	Median	IQR	Range	Median	IQR
Dimension						
(A) Lying and Rolling (max score=51)	4–51	13	5	7.8–100	25.5	9.8
(B) Sitting (max score=60)	0–60	6	7	0–100	10	11.7
(C) Crawling and Kneeling (max score=42)	0–42	0	0	0–100	0	0
(D) Standing (max score=39)	0–30	0	0	0–76.9	0	0
(E) Walking, Running, and Jumping (max score=72)	0–30	0	0	0–41.7	0	0
Overall score (max score=264)	5–210	18	11	2–82.9	6.5	4.2
GMFCS level						
I (*n*=1)	–	210	–	–	82.9	–
II (*n*=3)	98–167	146		36.9–66	57	
III (*n*=0)	–	–	–	–	–	–
IV (*n*=7)	19–71	42	43	7.2–26.9	15.7	15.7
V (*n*=48)	5–30	16	9.5	2–11.2	5.9	3.28

IQR, interquartile range; GMFCS, Gross Motor Function Classification System.

used for the statistical analysis. First, the variables were coded as 1 (yes) or 0 (no). Second, frequency distribution was calculated for the categorical variables and measures of central tendency and dispersion for all the variables. A Kruskal–Wallis test was run comparing children with confirmed and presumed diagnosis. This test showed no between-group differences for any GMFM outcome measures, and because of that the data from both groups were collapsed into one group in the subsequent analysis. After that, Pearson's linear correlation coefficient was calculated to evaluate the association between independent or predictive variables and the dependent variable (overall GMFM score). Then, a linear regression analysis was carried out to calculate the coefficients for key clinical and epidemiological risk factors: per capita income, schooling, symptoms of maternal infection, gestational age at delivery, birthweight, head circumference at birth, severe malformations of cortical development, and number of anticonvulsants. For all tests, a 5% level of significance was adopted.

RESULTS

Fifty-nine children with confirmed (*n*=27) or presumed (*n*=32) CZS participated in the study (Fig. S3, online supporting information). Maternal age was 17 to 38 years (mean 26y 3mo). Around 41% of the mothers had no steady partner. Most had little schooling, with 97% having elementary education or less, and 81% were not in paid employment. Mean per capita income was around $76. Most of the mothers were multiparous and around 59% had delivered by Caesarean section. Most (68%) had experienced ZIKV symptoms during the first trimester of pregnancy; however, 15% reported having been asymptomatic (Table SI, online supporting information).

Thirty children were males and 29 females. Overall, 20% were born preterm. Mean birthweight was 2732g. Mean head circumference at birth was 29cm for females and 30.2cm for males. Median Apgar scores were 8 and 9 at the first and fifth minutes respectively. At the time of motor evaluation, the children were 5 to 29 months of age (mean 14.7mo [SD 3.9]). Around 76% used an anticonvulsant, with the number of anticonvulsants used ranging from 0 to 7. Calcifications at the gray–white matter junction were found in all cases (Table SI).

Only four children could be scored for the tasks in the Walking, Running, and Jumping dimension (E) of the GMFM. Conversely, all the children were scored in the Lying and Rolling dimension (A), scoring a median of 13 points, with an interquartile range of 5 points. The median overall score was 18 points (interquartile range 11 points). Table I shows the overall score and scores per dimension with their respective percentage scores. One child (2%) was classified in GMFCS level I, three (5%) in GMFCS level II, seven (12%) in GMFCS level IV, and 48 (81%) in GMFCS level V.

A positive correlation was found between the overall GMFM score and head circumference (R=0.344; p=0.008), whereas negative correlations were found between the overall GMFM score and the number of anticonvulsants used (R=–0.323; p<0.014), and the presence of a severe

Table II: Correlation analysis between predictive factors and Gross Motor Function Measure (GMFM) score

Characteristic/overall GMFM score	*R*
Maternal age (y)	–0.143
Per capita income (USD)	0.099
Schooling (y)	0.102
Has a stable partner (yes/no)	0.155
Parity (number of deliveries)	–0.205
Symptoms of maternal infection (yes/no)	0.102
Gestational age at delivery (mo)	0.129
Vaginal delivery (yes/no)	0.009
Birthweight (g)	0.115
Male infant (cm)	0.093
Head circumference at birth (cm)	0.344
Age at the time of evaluation (mo)	0.037
Severe malformations of cortical development (yes/no)	–0.461
Number of anticonvulsants	–0.323

malformation of cortical development (R=–0.461; p<0.001; Table II).

The presence of a severe malformation of cortical development, head circumference at birth, and per capita income were the only factors that remained associated with the overall GMFM score after multiple linear regression analysis. Specifically, there was a negative correlation between the presence of a severe malformation of cortical development and gross motor function (t=5.910; p<0.001) and a positive correlation between head circumference at birth and gross motor function (t=2.316; p=0.024) and per capita income and gross motor function (t=2.207; p=0.031; Table III).

DISCUSSION

Characterizing the motor function of children with CZS and analysing the effect of associated factors may be particularly important when designing therapeutic interventions aimed at improving motor function, ultimately minimizing functional motor limitations, and improving these children's quality of life. In general, motor function impairment was severe (GMFCS level V) in most cases, which was reflected in the children's inability to execute most of the tasks proposed in the GMFM scale. Furthermore, the presence of severe malformations of cortical development, head circumference at birth, and per capita income were factors found to be associated with gross motor function.

Most of the mothers were young, multiparous, poorly educated, and unemployed. All these factors may interfere negatively with the children's development in early infancy (1–48mo).[17–19] The only sociodemographic factor associated with gross motor function was per capita income. A study carried out in Pernambuco concluded that the risk of microcephaly was greater in populations with lower social status;[20] however, no study related low income to greater motor impairment. This association can be related to living in adverse socio-economic and health conditions, with greater virus exposure, larger viral loads, more severe neurological damage, and maternal immunological conditions. Nevertheless, considering the homogeneity of the sociodemographic characteristics in the study sample, future studies involving a greater number of children should be conducted to confirm this hypothesis.

Most of the children (n=32) were diagnosed with presumed CZS based on imaging examinations performed in the first month of life. Currently, only reverse transcription PCR performed while symptoms are present can confirm a diagnosis of Zika infection.[21,22] Most of the children in this sample (54%) tested negative at PCR performed at birth in the samples investigated (blood, urine, cerebrospinal fluid). This may be because the infection occurred in the first trimester of pregnancy and was over before birth, with some children being born without any sign of the virus, making detection by PCR impossible.

Although serological testing for ZIKV is used in research protocols, false-positive results may occur as a result of cross-reaction with the dengue virus, which is highly prevalent in this region.[21] Conversely, radiological exams, including obstetric ultrasound, transfontanellar ultrasound, CT, and MRI describe signs that, when present, are typical of Zika infection. The presence of calcifications at the gray–white matter junction has so far only been described in children with CZS. This pattern is different from the calcifications caused by cytomegalovirus, which are periventricular, and those caused by toxoplasmosis, which are scattered throughout the brain parenchyma.[5,7,23] The presence of calcification in this region is the result of the death of neurons during neuronal migration, as ZIKV acts on the germinal matrix, affecting neuronal proliferation and migration.[24] This was found in all the children in the present sample, both in those with a presumed diagnosis and in those whose diagnosis was confirmed. As the techniques used for serological diagnostic testing advance, the description of findings in cases of CZS may change as new radiological and clinical findings are added.

The course of this disease is not yet fully understood and in view of the severe brain damage already reported in the literature,[2,23,24] it is important to understand these children's motor development more fully. Evaluating their gross motor development would represent a starting point. The present results show that 81% of the children were classified in GMFCS level V; this level indicates more severe motor impairment and poorer functional capacity, with the children being more dependent in performing motor tasks.[10]

Table III: Linear regression analysis

Independent variables	Coefficient	SEM	T	p
Per capita income (USD)	8.4572	3.8312	2.2075	0.031
Schooling (number of years)	6.3899	6.1849	1.0332	0.306
Symptoms of maternal infection (yes/no)	7.3667	4.9971	1.4742	0.146
Gestational age at delivery (mo)	–23.6629	35.3371	–0.6696	0.506
Birthweight (g)	2.7923	9.5124	0.2935	0.770
Head circumference at birth (cm)	–60.4512	26.1056	–2.3156	0.024
Severe malformations of cortical development (yes/no)	28.1875	4.7695	5.9100	<0.001
Number of anticonvulsants	16.7954	2.9589	5.6762	<0.001

Key risk factors for Gross Motor Function Measure (GMFM) score. SEM, standard error of the mean.

The median overall GMFM score was 18 points (interquartile range 11 points). Considering each dimension in the GMFM, the lowest score was for dimension (E) (Walking, Running, and Jumping), with scores that ranged from 0 to 30 points, showing that this was the dimension in which the children had the greatest difficulty in assuming positions and performing movements. The fact that not all the children managed to perform the items listed in this dimension explains the huge variation found. These results agree with previous studies showing the association between GMFCS levels and the overall GMFM score in children with cerebral palsy,[25,26] in which children in higher GMFCS levels had poorer results in the GMFM.

Although most of the children had severe motor impairment (GMFCS level V) and a low overall GMFM score, four were classified in GMFCS level I or II, with overall GMFM scores ranging from 98 to 210 points. This variation in motor development is probably due to differences in the severity of the neurological damage caused by the virus, with damage being more severe in some children, as characterized by a much smaller head circumference and severe malformations of cortical development.[23,24] A positive association was found between head circumference and motor development evaluated according to the GMFM and a negative association with the presence of severe malformations of cortical development. In other words, when head circumference is larger and cortical malformations less severe, motor development is better. This variation in the degree of motor development is also seen in other congenital infections such as cytomegalovirus and is equally associated with the severity of the brain injury,[27,28] with head circumference representing an important predictor of neurocognitive development.

Although not maintained in the final analytical model, the number of anticonvulsants also had an effect on motor function in the children investigated here, with those using more drugs scoring fewer points in the GMFM. Convulsions are common in children with CZS from 3 months of age onwards,[8] making anticonvulsants necessary in view of the severity of neurological damage and the increased risk of death in cases of epilepsy. Conversely, the four children with better motor development (GMFCS levels I and II) were not using anticonvulsants, suggesting mild neurological impairment. The effects of the neurological damage and the use of anticonvulsants on the motor function of children with CZS appear to be cumulative and limiting, as anticonvulsants may reduce motor response or have a negative effect on the process of motor learning. Furthermore, the need for anticonvulsants may also be indicative of greater neurological impairment.

One unexpected observation was that the period on which symptoms of infection was described was not maintained in the final analytical model, as speculated by Soares-Marangoni et al.[29] This finding can be associated with the number of children whose mothers described the symptoms of infection in the third trimester of pregnancy, and with other facts, not analysed in this study, such as maternal immunity and viral charge. Therefore, this finding should be interpreted with caution and explored in future studies.

So far, only two studies have published data on the motor performance of children with CZS. One described the psychomotor status of four children and reported atypical motor behaviour with alterations in muscle tone and spontaneous motricity.[30] The other described the motor function of two children with CZS evaluated at 4 and 12 months of age using the Alberta Infant Motor Scale and the General Movements Assessment.[29] In both evaluations, one of the children was found to have severe motor impairment, rendering scoring according to the Alberta Infant Motor Scale impossible. The other child had mild motor impairment, with motor performance compatible with age. Considering the few participants in those studies and the clinical and physiopathological diversity of CZS, these results cannot be generalized.

Despite the importance of the present findings, some limitations must be mentioned. First, the study was performed in only one Brazilian state, in a sample population with similar sociodemographic variables, making it difficult to determine whether the lack of any association between motor function and certain sociodemographic factors is, indeed, a limitation of the study, the relatively small sample size, or a factor inherent to all the mothers affected whose exposure to the ZIKV may have been greater as a result of their poor socio-economic conditions. Second, only some of the factors that could be associated with the motor impairment of children with CZS were investigated, whereas analysis of other factors such as additional radiological characteristics and maternal viral load during pregnancy could provide important information. Third, other factors such as visual and auditory problems that could affect motor development were not investigated, as many children remain under evaluation. Finally, the children were not compared with neurologically typical children or with children with neurological disabilities resulting from other congenital infections.

Nevertheless, this represents the first step towards understanding motor function in children with CZS using a validated scale. Monitoring these children is crucial to improve understanding of the real impact of ZIKV on motor development and on their abilities. This information will be important when defining the interventions needed to minimize motor sequelae and functional limitations in these children.

CONCLUSION

These results highlight the severe motor impairment presented by most children with CZS, although in some cases motor impairment was mild. Furthermore, factors such as the presence of severe malformations of cortical development and head circumference at birth were found to be associated with motor impairment and should be taken

into consideration in future studies. Much remains to be investigated regarding the development of children with CZS; however, these results may serve as a basis for more in-depth evaluations and protocols of intervention aimed at this population.

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Children with congenital Zika syndrome

Figure S2: Calcifications at the gray–white matter junction at fetal neurosonography and computed tomography after birth

Figure S3: Flowchart depicting participant recruitment

Video S1: Representation motor function evaluation by GMFM

Table SI: Demographic characteristics of the mothers, the children, and the pregnancy

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