

Original Article

Gross Motor Function and Musculoskeletal Deformities in Children With Congenital Zika Virus Syndrome

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Abstract

Objectives: The objective of the present study was to assess gross motor function and describe musculoskeletal deformities in patients diagnosed with Congenital Zika syndrome (CZS). **Methods:** This is a cross-sectional study, carried out at the Association for Assistance of Disabled Children (AACD) in Pernambuco, Brazil, between June 2017 and April 2023. Medical records and assessments were carried out to describe musculoskeletal deformities and measure gross motor function, using the GMFM-88. **Results:** The study included 37 patients between 1 and 2 years old, 56.8% infected during the first trimester of pregnancy. The patients' mean GMFM value was 5.63 and standard deviation was 6.37. A moderate correlation was observed between head circumference at birth and the patients' current gross motor function (Pearson coefficient = 0.594) ($p < 0.001$). We also observed 19 types of deformities, which were more prevalent in the lower limbs. **Conclusion:** CZS brings significant impairments to motor function and the musculoskeletal system. In this context, measuring head circumference at birth can serve as a predictor of impaired gross motor function in these children.

Keywords: Congenital Abnormalities, Congenital Zika Syndrome, Neuromuscular Manifestations, Motor Skills Disorders, Zika Virus Infection

Introduction

The Zika Virus (ZIKV) is a member of the *Flaviviridae* family, genus *Flavivirus*. It was first isolated in April 1947 from the blood of Rhesus monkeys in the Zika forest, which is how it got its name¹. In May 2015, the first cases of ZIKV infection were reported in Brazil². During this period, the state of Pernambuco was the epicenter of the epidemic, with the highest number of reported cases between 2015 and 2016³.

The potential for perinatal transmission of ZIKV was initially documented in 2014⁴. Subsequently, multiple congenital abnormalities associated with ZIKV infection were observed, defining the condition known as Congenital Zika Virus Syndrome (CZS)⁵. The main characteristic of CZS is the presence of microcephaly at birth. However, this is just one aspect of the neurological damage to the central nervous system and an important diagnostic element, although it is not present in all cases and may only manifest as the patient develops⁶. Neurological changes in patients with CZS lead to alterations in cognitive and motor development, impairments in visual and auditory functions⁷, arthrogyposis, dysphagia, and abnormal neurological findings such as spasticity, hyperreflexia, tremors, and seizures⁸.

Non-progressive lesions occurring in the fetal or infantile central nervous system generally result in a group of permanent disorders. The development and posture of affected patients are characterized by sensorimotor

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alterations, which, in turn, affect the acquisition of typical motor skills and developmental milestones⁹. Motor skill development primarily occurs through sensorimotor experiences in the child's early years, spanning from zero to 3 years. This period is considered critical for the maturation of the central nervous system and neural plasticity, as it is more susceptible to changes caused by the external environment¹⁰.

As a means of assessing motor development, the Gross Motor Function Measure (GMFM-88) is used. It is a standardized and validated test designed to measure changes in gross motor function, originally in children with cerebral palsy. It consists of 88 items grouped into five different dimensions of gross motor function: lying and rolling, sitting, crawling and kneeling, standing, walking, running, and jumping. Each item is scored on a four-point scale based on the child's ability to perform the task. The scores are then converted into percentages of the expected performance for each dimension, and the final GMFM-88 score is the average of these percentages¹¹.

Numerous articles have been published since 2015 with the aim of describing the clinical characteristics of CZS. Due to the wide spectrum of CZS, ranging from asymptomatic cases to severe forms with microcephaly diagnosed at birth, there are still many unanswered questions. A complete evaluation of the neurological picture requires central nervous system maturation, necessitating follow-up and detailed assessment over time for a comprehensive description of the symptomatic form of this condition, predominantly diagnosed in the first year of life. Thus, the objective of this study was to assess gross motor function and describe musculoskeletal deformities in patients diagnosed with CZS.

Methods

This is a cross-sectional study conducted at the Association for Assistance of Disabled Children (AACD) in Pernambuco, Brazil. The study was carried out between June 2017 and March 2022, involving the assessment of children and the review of medical records spanning from 2015 to 2016.

In this study, the sample size was obtained by convenience, including individuals under care at the institution with confirmed CZS diagnosis (through IgM antibody positivity in serum or cerebrospinal fluid or by the presence of viral genetic material confirmed via real-time RT-PCR) or probable diagnosis (based on clinical and radiological characteristics of CZS, where specific investigation for CZS in the first month of life was not feasible, ruling out other causes of congenital infection such as Cytomegalovirus, Toxoplasmosis, HIV, and Rubella). Patients with incomplete medical records or diagnosed with other congenital infections mentioned above were excluded.

All patients were under the care of the Orthopedics and Neurology departments following the institution's protocol. Diagnosis of deformities was made based on clinical assessment and imaging studies as deemed necessary by the Orthopedics team. Data regarding

Gender, Age, Mode of Delivery, Maternal History of Multiple Pregnancies, Maternal History of Miscarriage, Gestational Trimester of ZIKV Infection, Head Circumference at Birth, Gestational Age at Birth, and Maternal Gestational Age at ZIKV Infection were extracted from medical records. Gross motor function was assessed using the Gross Motor Function Measure (GMFM-88) conducted by a trained professional within the institution.

Data were managed using Microsoft Excel® 2019 software. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) - version 21, which described categorical variables in terms of absolute and relative frequencies. For quantitative variables, mean and standard deviation were calculated. To compare the current GMFM of patients infected in the first trimester of gestation with those infected in subsequent trimesters, the Mann-Whitney U test was utilized. Fisher's exact test was employed to compare the presence of orthopedic malformations between patients infected in the first trimester and others. Additionally, GraphPad Prism - version 8 was utilized to conduct linear regressions aiming to correlate the current GMFM of patients with head circumference at birth and maternal gestational age at ZVS infection. For all analyses, a significance level of 95% was considered.

Results

Thirty-seven patients were included in the study, diagnosed with CZS and followed up at AACD in Pernambuco, Brazil, from August 2015 to December 2016. Demographic and personal and maternal antecedents were described in terms of absolute and relative frequency in Table 1.

The mean GMFM value of all patients in the study was 5.63, and the standard deviation was 6.37. Patients infected in the first trimester had a mean GMFM and a standard deviation of 6.99 and 8.11, respectively, while the mean and standard deviation of the others were 3.84 and 1.94, respectively. When analyzing these variables, it was observed that there was no statistically significant difference between the GMFM of these two groups ($p = 0.820$)

When analyzing the relationship through linear regression between the gestational age of maternal Zika Virus infection and the individuals gross motor function, no statistically significant correlation was found. The Regression showed a Pearson coefficient ($r = -0.205$) ($p\text{-value} = 0.223$), indicating an inversely proportional trend, but with a negligible correlation. The scatter plot of these values is represented in Figure 1, where the X-axis represents the gestational age at which the maternal infection occurred, the Y-axis represents the patient's current GMFM value, and the solid line represents the dispersion trend line, defined by the equation $Y = -0.19X + 8.08$, with the dotted lines representing the 95% confidence interval.

In the linear regression evaluating the head circumference (HC) at birth and the current gross motor function of the individuals, The Regression also showed a Pearson coefficient

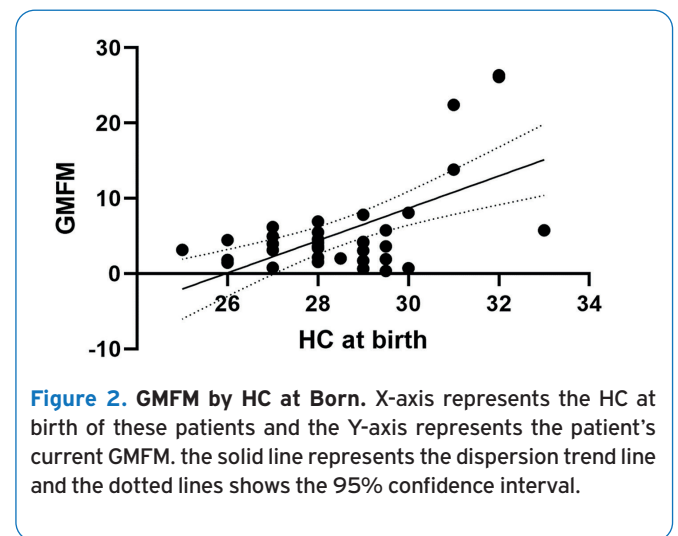
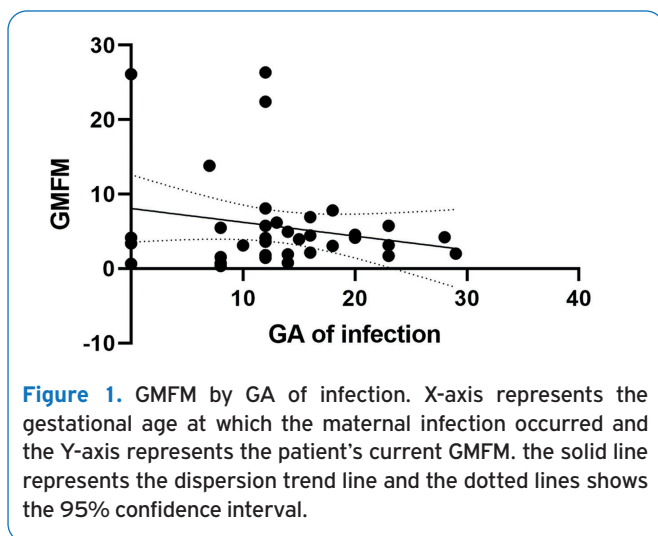
Table 1. Demographic data.

Variable	N	% of 37
Sex		
Female	20	54,1
Male	17	45,9
Age		
1 year	1	2,7
2 years	36	97,3
Mode of delivery		
Vaginal birth	21	56,8
Cesarean	16	43,2
Maternal history of multiple pregnancy		
Yes	1	2,7
No	36	97,3
Maternal history of miscarriage		
Yes	7	18,9
No	30	81,1
Gestational trimester of Zika Virus infection		
1 st Trimester	21	56,8
2 nd Trimester	13	35,1
3 th Trimester	3	8,1
Head circumference at birth (Mean+/- SD)	28,66 (1,76)	
Gestation duration (Mean+/- SD)	38,15 (1,60)	
Gestational age of infection (Mean+/- SD)	13,22 (7,06)	

Legend: SD = Standard Deviation.

Table 2. Orthopedic deformities found and association with infections in the 1st trimester and HC at birth.

Deformity	N	% of 37	1 st Tri P-value	Birth HC P-value
Adduction contracture of the thumb	7	18,92	0,658	0,925
Flat feet	7	18,92	0,333	0,227
Limitation of hip abduction	6	16,22	0,528	0,560
Developmental dysplasia of the hip	6	16,22	0,472	0,054
Flexion deformity of the wrist	5	13,51	0,266	0,064
Plantigrade foot	4	10,81	0,206	0,869
Hip dislocation	3	8,11	0,604	0,855
Valgus knee	3	8,11	0,396	0,616
Varus knee	3	8,11	0,171	0,472
Congenital clubfoot	3	8,11	0,604	0,507
Metatarsus adductus	2	5,41	0,685	0,631
Lower Limb Length Discrepancy	2	5,41	0,315	0,396
Elbow stiffness	1	2,70	-	-
Scoliosis	1	2,70	-	-
Adduction and internal rotation contracture of the hips	1	2,70	-	-
Tibia vara	1	2,70	-	-
Femoral dysplasia	1	2,70	-	-
Equinovalgus foot	1	2,70	-	-
Campodactyly	1	2,70	-	-



(r) = 0.594, (p -value < 0.001) indicating a proportional tendency to increase between the head circumference at birth and the GMFM of the patients, under a moderate correlation. The scatter plot of these values is represented in Figure 2, where the X-axis represents the HC at birth of these patients and the Y-axis represents the patient's current GMFM value, the solid line represents the dispersion trend line, defined by the equation $Y = 2.15X - 55.72$, with the dotted lines showing the 95% confidence interval.

In the orthopedic evaluation, 19 types of deformities were observed, which are presented in Table 2, either in isolation or in conjunction with another type of deformity, as well as bilaterally or on just one side of the individual. These deformities were more prevalent in the lower limbs and when analyzing the distribution of these conditions between the groups infected in the 1st trimester of pregnancy and in the others, it was not possible to observe a statistically significant difference between these groups, with p -values between 0.171 and 0.685. The evaluation between those with and those without each of the deformities also showed no statistically significant differences regarding the Head Circumference value at birth, with p -values between 0.054 and 0.925.

Discussion

Observing the demographic data, it is possible to draw some inferences about the Zika Virus and the study sample. The first is considering that all patients included in the study are between 1 and 2 years old, reflecting the 2015 outbreak that occurred in the state of Pernambuco. Thus, At the end of 2017, when the data was collected, there will be a higher prevalence of these cases in the population between 1 and 2 years of age.

It is also noteworthy that most cases result from infection during the first trimester of pregnancy, followed by the second and third trimesters, respectively, with an average gestational age of infection of 13.22 weeks. This reflects the fact that pregnant women in the first trimester are considered a population at risk for the development of CZS, as it is the fetal formation phase, in the second trimester, there is a risk of malformation triggered by the virus, but to a lesser extent, and from the third trimester onwards, the risks are reduced, as the fetus is already formed¹².

When analyzing the impairment of gross motor function, a very serious impairment is evident, as a consequence of the pathophysiology of the disease itself. The Zika virus crosses the placental barrier and predominantly affects neural progenitor cells, leading to apoptosis and cell death. This leads to a disruptive process of normal brain growth and failure of neuronal organization and migration mechanism¹³⁻¹⁵. The characteristic pathophysiological abnormalities result in severe disturbance of cortical development, calcifications, cortical and subcortical atrophies, cerebellar malformations, brain stem and spinal cord¹⁶. These injuries cause a group of permanent

disorders, including those related to development and posture characterized by sensorimotor changes, which in turn affect the acquisition of motor skills.

This impairment of motor function is also evident in other works in the literature. However, studies on the topic, in general, rely on the GMFCS criteria, which simplify the analysis of motor function and classify it into 5 types: level I indicates unrestricted movement; level II indicates limited walking in an external environment; and level III is assigned to those requiring support for mobility. At level IV, there is a need for assistive technology equipment for mobility, and at level V, the child has severe movement restrictions, even with more advanced technologies. When comparing these works with the present study, it is apparent that the literature and the present work converge regarding the serious impairment of motor function caused by the syndrome¹⁷⁻²².

When analyzing the orthopedic deformities found in these patients, it is clear that these manifestations are diverse, occurring mainly in the lower limbs, as already reported in the literature²³. This reveals that there are more factors than the infection itself that can influence how neuromuscular manifestations cause orthopedic deformities. When trying to analyze the correlation between the presence of these deformities and the trimester of pregnancy in which the infection occurred, no statistically significant correlation was noted. This can be explained by the low number of appearances of each of the deformities, given the heterogeneous distribution of these malformations.

This study has limitations, such as a small sample and the lack of a control group, which may affect the reproducibility and generalization of results, especially orthopedic results. To ensure reproducibility, future research should consider larger and more diverse samples, as well as apply consistent data collection methods, as this study did. This will contribute to strengthening the knowledge base on congenital Zika virus syndrome.

It is important that transdisciplinary studies with these children continue to be published, even after the end of the epidemic, as they can provide important information about how to deal with future epidemics. As children grow, new discoveries can be made. The present study, even with the relatively small sample, offers a good opportunity to better understand the development of the disease after a few years

Conclusion

Congenital Zika virus syndrome causes significant impairments to children's gross motor function and the musculoskeletal system, and can present itself as a wide range of orthopedic changes and deformities. Measurement of head circumference at birth can serve as a predictor of impaired motor functionality in these children, assisting in therapeutic planning and future care for these patients.

Ethics approval

This study was approved by the institutional ethics committee of the AACD (CAAE: 68400017.9.0000.0085).

Consent to participate

Written informed consent was obtained from the parents or legal guardian for the participation of each child

Authors' Contributions

Conceptualization, AUS, VVL and ELRF; methodology, AUS, AGSM, MBVA and ELRF validation, AGSM, APMMB, SGCL and VVL; formal analysis, AGSM, APMMB and FOZ; investigation, AUS, APMMB, MMBA, RMH and SGCL; resources, FOZ and ELRF; data curation, AGSM and MMBA; writing—original draft preparation, AUS and RMH; writing—review and editing, AUS, APMMB, MBVA, MMBA, RMH and SGCL; visualization, FOZ and ELRF; supervision, AUS, MBVA and ELRF; project administration, VVL. All authors made substantial contributions to conception and design and have read and agreed to the published version of the manuscript. All authors read and approved the final manuscript.

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