





### Neuroimaging and motor development of twins with congenital microcephaly associated with Zika virus: a case report

### *Neuroimagem e desenvolvimento motor de gêmeas com microcefalia congênita por Zika virus: estudo de caso*

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#### ABSTRACT

**Objective:** We aimed to describe a case of congenital microcephaly caused by Zika virus infection in a monozygotic twin pregnancy. **Methods:** Transfontanelle ultrasonography and cranial computed tomography revealed different lesion patterns for both twins with congenital microcephaly caused by Zika virus infection. Motor development assessments were performed using the Alberta Infant Motor Scale and the Gross and Motor Function Measure before, during, and after physiotherapy. **Results:** The evaluations showed differences in motor acquisition between the twins. The values in the first case were much lower than those in the second case, which showed more motor delay. **Conclusion:** The present study showed that despite the twins being monozygotic, the effects of neurological lesions as revealed by neuroimaging were worse in the first case, and even with two weekly rehabilitation sessions, motor development over time was considerably worse in the twin in case 1 than in the other twin.

**Keywords:** Microcephaly, Zika Virus, Motor Skills Disorders, Neuroimaging, Rehabilitation

#### RESUMO

**Objetivo:** Descrever um caso de microcefalia congênita causada pela infecção do Zika vírus em uma gestação gemelar monozigótica. **Métodos:** A ultrassonografia transfontanelar e a tomografia computadorizada de crânio revelaram diferentes padrões de lesão para ambos gêmeos com microcefalia congênita causada pela infecção do Zika vírus. As avaliações do desenvolvimento motor foram realizadas por meio da Escala Motora Infantil de Alberta (EMIA) e da Medida de Função Motora Grossa antes, durante e após o tratamento fisioterapêutico. **Resultados:** As avaliações mostraram diferenças na aquisição motora entre os gêmeos. Os valores nas avaliações do primeiro caso foram menores do que os do segundo caso, que apresentou maior atraso motor. **Conclusão:** O presente estudo mostrou que apesar dos gêmeos serem monozigóticos, os efeitos das lesões neurológicas reveladas por exames de neuroimagem foram piores no primeiro caso, e mesmo com duas sessões semanais de reabilitação, o desenvolvimento motor ao longo do tempo foi consideravelmente pior no gêmeo do caso 1 quando comparado ao caso 2.

**Palavras-chaves:** Microcefalia, Zika Virus, Transtornos das Habilidades Motoras, Neuroimagem, Reabilitação

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## INTRODUCTION

In 2015, in Northeast Brazil, an outbreak of Zika virus (ZIKV) infection occurred, with an abrupt increase in the number of cases of children with microcephaly, suggesting an association between pregnancy and adverse outcomes in birth, most notably microcephaly and other serious brain anomalies due to ZIKV infection.<sup>1-4</sup> It is known that monozygotic twins are genetically identical and are simultaneously under the same maternal influence.<sup>5</sup> Usually, in the case of intrauterine infection, the infection can be transmitted to both twins through the placenta.<sup>5,6</sup> However, some studies on congenital infection in monozygotic twins have shown different outcomes despite the same maternal influence.<sup>5,6</sup>

Among the outcomes caused by the congenital syndrome associated with ZIKV, twins could present other clinical components and at different levels, besides microcephaly, such as alterations of the cerebral structure, muscular contractures, dysphagia, muscular hypertonia, irritability, the persistence of primitive reflexes, and, consequently, possible motor impairment.<sup>3,5,6</sup> Imaging tests may reveal calcifications, ventriculomegaly, decreased cortical gyration, and abnormalities in the white matter.<sup>1,7,8</sup>

Knowledge about the motor skills behavior of children with congenital Zika syndrome is still limited. It is extremely important to know the impact of this syndrome on the acquisition of motor skills and whether a physical therapy intervention program can improve motor development or minimize disabilities and morbidities associated with this condition.

This study will contribute to the description of the assessment and physical therapy treatment protocol for congenital microcephaly associated with ZIKV. This report aims to show neurological lesions by neuroimaging, as well as motor development, in monozygotic twins with congenital microcephaly associated with ZIKV. In addition, the present study aimed to present the physiotherapy treatment proposed for congenital microcephaly associated with ZIKV in monozygotic twins.

## CASE PRESENTATION

This study was approved by the institutional ethical review board, and the participants' parents provided written consent before data collection. The procedures used in this study were approved by the Human Research Ethics Committee (registration no. 2.540.537). The research was conducted according to the American Psychological Association's ethical standards.

The mother and father were 17 and 18 years old, respectively. They were residents of Sergipe State, in Brazil, an endemic region for ZIKV. The parents' education level was low, and their household income was 146 Reals (Brazilian currency).

During pregnancy, the mother consumed an alcoholic beverage once a week. She never smoked or used illicit drugs. She underwent eight prenatal visits without abnormalities and three fetal imaging tests. The infants were born at a gestational age of 37 weeks via cesarean section, without complications at childbirth.

At birth, the mother was informed that the two newborns had a clinical diagnosis of microcephaly. Neither the mother nor newborns required hospitalization. Maternal and twin serologies showed non-reactive IgM and IgG for rubella, CMV, toxoplasmosis, and syphilis.

**Case 1:** The first twin presented an Apgar score of 10 at the 1st and 5th minutes, with a birth length of 46 cm (with a mean z-score of -0.77), birth weight of 2362 grams (z-score of -1.2), and head circumference of 26 cm (z-score of -4.53). No other malformations were noticed.

Transfontanelle ultrasonography of the infant's brain was performed at 1 month and 24 days of age, which revealed a corpus callosum with reduced thickness, a scarcity of cerebral convolutions, reduced cerebral parenchyma, calcifications in the lentiform nuclei, sharp dilatations of the posterior horns and atria of the lateral ventricles, and mild dilatations of the body and anterior horns of the lateral ventricles, with a ventricular index of 0.44, and subependymal cysts at the level of the caudothalamic groove.

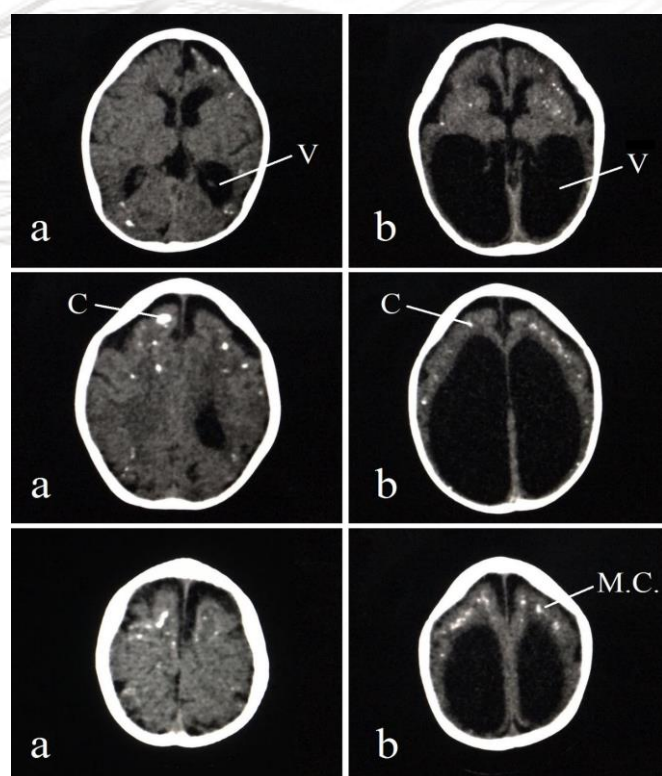
When the infant was 2 months old, the mother affirmed that the infant did not have a convulsive crisis and reported irritability that improved with the use of dimenhydrinate. At 6 months of age, the infant presented with myoclonic seizures twice a week, and treatment with phenobarbital was initiated.

Neurological examination revealed hypertonia in the lower and upper limbs, which increased progressively. Cranial computed tomography was performed when the infant was 10 months old, and microcephaly was still observed; parenchymal calcifications in both predominantly subcortical cerebral hemispheres, a normopositioned ventricular system, with markedly increased dimensions, with evident reduction in the thickness of the cortical mantle, notably in the parietal and occipital portions and hydrocephalus of supratentorial predominance (Figure 1).

**Case 2:** The second twin had an Apgar score of 10 at the 1st and 5th minutes, with a birth length of 45 cm (z-score of -1.37), birth weight of 2506 g (z-score of -0.8), and head circumference of 28.5 cm (z-score of -3.22). No other malformations were observed.

Transfontanelle ultrasonography was performed at 1 month and 24 days of age: the thickness of the corpus callosum was slightly reduced, the thickness of the cerebral parenchyma was slightly reduced with contours within the range of normality, subependymal cysts, and subcortical and periventricular punctate calcifications more evident to the right and ventricular system with normal dimensions. When the infant was 2 months old, the mother denied the occurrence of any convulsive crisis and irritability.

Neurological examination revealed movements of the four limbs, which were normotonic; however, the muscle tone progressively increased. Cranial computed tomography was performed when the infant was 10 months old, and microcephaly was observed, with parenchymal calcifications in both predominantly subcortical cerebral hemispheres and a normopositioned ventricular system, with increased dimensions, with a predominance of the right lateral ventricle (Figure 1).



a- Case 2; b- Case 1; V- ventricle; C- calcifications; M.C.- cortical mantle

**Figure 1.** Computed tomography of the skull, axial

When the infant was 5 months old, rehabilitation was started with physiotherapy. Motor development was evaluated using the Alberta Infant Motor Scale (AIMS) and Gross and Motor Function Measure (GMFM).

The AIMS assesses motor development from 0 to 18 months by observing postural alignment, antigravity movements, and weight support.<sup>9</sup> It consists of 58 items divided into subscales determined by the children's four postural positions: prone, supine, sitting, and standing. The total score ranges from 0 to 58 points.<sup>9</sup> The AIMS was applied at approximately 2 months (pre-treatment - 1<sup>st</sup> trimester), 5 months (2<sup>nd</sup> trimester), 8 months (3<sup>rd</sup> trimester), 11 months (4<sup>th</sup> trimester), 14 months (5<sup>th</sup> trimester), and age 18 months (post-treatment - 6<sup>th</sup> trimester).

The GMFM is an instrument with excellent reliability. It demonstrated the ability to evaluate meaningful changes in gross motor function in children with disabilities aged 5 months to 16 years. It is composed of tasks subdivided into five dimensions: (A) lying and rolling; (B) sitting; (C) crawling and kneeling; (D) standing; and (E) walking, running, and jumping.

Each task of the scale is to be performed by the child without help and scored on a scale of 0 to 3.<sup>10,11</sup> A value of 0 indicates that the child did not initiate the task, and 3 indicates that the child was able to complete the task.<sup>10,11</sup>

In the present study, the GMFM was applied after physiotherapy had started; however, the inclusion of this scale was important for follow-up, and it was applied at 8 months (3<sup>rd</sup> trimester), 11 months (4<sup>th</sup> trimester), 14 months (5<sup>th</sup> trimester), and age 18 months (post-treatment - 6<sup>th</sup> trimester). The protocol of physiotherapeutic intervention was based on the principles of the Neuroevolutionary Bobath Concept (Chart 1),

and the physiotherapy sessions occurred twice a week, with each session lasting approximately 1 hour for 13 months.

The exercises described in Chart 1 varied according to the infant's needs. It is noteworthy that, to make the session more playful, a therapeutic roller or Swiss ball, as well as visual, verbal, and auditory stimuli, was used. According to the mother's report, both infants received home stimulation daily and had similar routines.

## RESULTS

Based on the evaluation, the treatment aimed to improve neck and trunk control, postural transfers, and straightening reactions and promote manual activity (Chart 1).

Table 1 shows the results of the AIMS and GMFM assessments before, during, and after physiotherapy. As Table 1 shows, in the first (before treatment) and second (during treatment) trimesters, the twins had similar AIMS scores.

In the third trimester, when the first twin started to have myoclonus and the hypertonia in the lower and upper limbs worsened, the AIMS score in case 1 was lower than that in case 2, until after the treatment. In case 2, the AIMS and GMFM scores improved over time.

**Table 1.** Scores of the motor development assessments by Alberta Infant Motor Scale (AIMS) and Gross Motor Function Measure (GMFM) divided by trimesters

		Case 1	Case 2
<b>AIMS Score</b>	1 <sup>st</sup> Trimester <sup>a</sup>	7	6
	2 <sup>nd</sup> Trimester <sup>b</sup>	9	9
	3 <sup>rd</sup> Trimester <sup>b</sup>	9	11
	4 <sup>th</sup> Trimester <sup>b</sup>	8	18
	5 <sup>th</sup> Trimester <sup>b</sup>	5	21
	6 <sup>th</sup> Trimester <sup>c</sup>	6	26
<b>GMFM</b>	3 <sup>rd</sup> Trimester <sup>b</sup>	26	33
	4 <sup>th</sup> Trimester <sup>b</sup>	16	38
	5 <sup>th</sup> Trimester <sup>b</sup>	20	48
	6 <sup>th</sup> Trimester <sup>c</sup>	9	40




<sup>a</sup>Before Physiotherapy treatment; <sup>b</sup>During Physiotherapy treatment; <sup>c</sup>After Physiotherapy treatment

## DISCUSSION

This study aimed to present a case of congenital microcephaly with evidence of ZIKV infection in a monozygotic twin pregnancy, highlighting the neurological lesions identified by neuroimaging and motor development.

In this case report, although the two cases showed signs of acquired infection, the first case was more severely affected with respect to the cephalic perimeter, neuroimaging, and motor development. The alterations found in the imaging studies in this case report, such as diffuse calcifications, hydrocephalus, and a reduction of the cortical mantle, are similar to those found in other studies in which microcephaly is associated with ZIKV infection.<sup>1,3,8,12</sup>

**Chart 1.** Physiotherapy treatment description

PURPOSE	ACTIVITY	
<b>TRAINING 1 – 2<sup>nd</sup> TRIMESTER</b>		
<ol style="list-style-type: none"> <li>To maintain joint flexibility and mobility.</li> <li>To improve muscle recruitment.</li> <li>To promote manual activity.</li> <li>To improve the neck and trunk control.</li> <li>To acquire the postural transfers.</li> </ol>	<ol style="list-style-type: none"> <li>Mobilization and stretching by positioning in different postures.</li> <li>Sensory-motor stimulation and muscle strengthening.</li> <li>With a toy on the midline, the therapist encouraged the infant to reach it in the supine and side-lying positions.</li> <li>Lying prone on therapy ball/roll.</li> <li>From the supine/prone position, the therapist helped the infant to roll to the prone/supine position over both sides.</li> </ol>	
<b>TRAINING 2 – 3<sup>rd</sup> TRIMESTER</b>		
<ol style="list-style-type: none"> <li>To maintain joint flexibility and mobility.</li> <li>To improve muscle recruitment.</li> <li>To promote manual activity.</li> <li>To improve the neck and trunk control.</li> <li>To acquire the postural transfers.</li> </ol>	<ol style="list-style-type: none"> <li>Mobilization and stretching by positioning in different postures.</li> <li>Sensory-motor stimulation and muscle strengthening.</li> <li>With a toy on the midline, the therapist encouraged the infant to reach it in the supine, side-lying, and seated positions.</li> <li>Lying prone on therapy ball/roll and forward, backward, and sideways movements with infant sitting on a roll or parents/therapist's leg.</li> <li>From the supine position, the therapist helped the infant to sit.</li> </ol>	
<b>TRAINING 3 – 4<sup>th</sup> TRIMESTER</b>		
<ol style="list-style-type: none"> <li>To maintain joint flexibility and mobility.</li> <li>To improve muscle recruitment.</li> <li>To improve the neck and trunk control.</li> <li>To acquire the postural transfers.</li> <li>Straightening reactions.</li> </ol>	<ol style="list-style-type: none"> <li>Mobilization and stretching by positioning in an orthostatic posture.</li> <li>Sensory-motor stimulation and muscle strengthening</li> <li>Four-point kneeling with roll and forward, backward, and sideways movements with infant sitting on a roll or parents/therapist's leg.</li> <li>From the supine position, the therapist helped the infant to sit.</li> <li>Forward, backward, and sideways movements with infant sitting on a roll or parents/therapist's leg.</li> </ol>	
<b>TRAINING 4 – 5<sup>th</sup> TRIMESTER</b>		
<ol style="list-style-type: none"> <li>To maintain joint flexibility and mobility.</li> <li>To improve muscle recruitment.</li> <li>To improve the neck and trunk control.</li> <li>To acquire the postural transfers.</li> <li>To straighten reactions.</li> <li>To improve bone mineral density.</li> </ol>	<ol style="list-style-type: none"> <li>Mobilization and stretching by positioning in an orthostatic posture.</li> <li>Sensory-motor stimulation and muscle strengthening.</li> <li>Four-point kneeling with roll and forward, backward, and sideways movements with infant sitting on a roll or parents/therapist's leg.</li> <li>From the supine position, the therapist helped the infant to sit.</li> <li>Forward, backward, and sideways movements with the infant sitting on a roll or parents/therapist's leg.</li> <li>Standing posture.</li> </ol>	

Hazin et al.<sup>13</sup> evaluated computed tomography images of eight children with congenital microcephaly associated with ZIKV infection, identified calcifications at the level of the corticomedular junction in the frontal, parietal, and temporal lobes, and severe ventriculomegaly, severe cerebellar hypoplasia, supratentorial abnormal hypodensity, and decreased cortical gyrus in the basal ganglia.

Del Campo et al.<sup>3</sup> identified a combination of abnormalities in cranial computed tomography, including multiple calcifications, poor and abnormal swivel patterns, ventriculomegaly and prominent extra-axial spaces, and hypoplasia of the brainstem and cerebellum, suggesting prenatal infection consistent with ZIKV in 82 children. These findings suggest prenatal infection consistent with ZIKV infection. Furthermore, similar to our study, they found a decrease in gray and white matter volumes, with thinning or absence of the corpus callosum, and hypoplasia of the ventral pons, mainly seen in case 1.<sup>3</sup> Van der Linden et al.<sup>6</sup> which included two cases of twin pregnancies exposed to ZIKV

analyzed brain imaging using non-contrast computerized tomography, which revealed diffuse bilateral reductions of the cerebral parenchyma, ventriculomegaly, cortical underdevelopment, multiple calcifications predominantly in the basal ganglia and cortical/subcortical white matter regions, and hypoplasia of the brainstem and cerebellum. However, despite the same neuroimaging alterations, only one fetus was affected by microcephaly and brain damage.<sup>6</sup> This fact demonstrates the need for more studies regarding the pathophysiology of viral infection and the mechanisms involved in the natural protection against the virus, since, corroborating our study, despite being twins, the two children had different neuroimaging findings and different effects on motor development.<sup>6</sup>

Motor development was assessed using AIMS and GMFM, and the results demonstrated atypical motor development in the present study.<sup>13</sup>

The GMFM results in the first case showed a slight increase from the fourth to the fifth trimester, and, in the second case,

from the fifth to the sixth trimester, there was a reduction in the score.

The values in the first case were much lower than those in the second case, which showed worse motor delay. In the first case, the delay in motor development began to appear with a worsening AIMS score. This may be due to the greater sensitivity of AIMS in detecting delays in motor development from the second trimester.<sup>14</sup> Similarly, in a study by Marques et al.<sup>15</sup> 39 infants were evaluated using AIMS at the beginning of the second trimester, with a mean raw score of 9.74, which is equivalent to scores at 2–3 months.<sup>15</sup> The extent of damage to the central nervous system is directly associated with the worsening development, and it can also be related to the occurrence of seizures that occurred twice a week from the sixth month in case 1.<sup>15</sup>

In addition, corroborating our findings, Barbosa et al.<sup>16</sup> evaluated children with cerebral palsy using AIMS, and they observed that at the age of 6 months, 90% of the children scored below the cut-off level defined as <10%. In addition, at 9 and 12 months, the cut level was <5% and reached the mark of 90% of children.

Marques et al.<sup>15</sup> found that despite marginally progressing gross motor skills, children affected by congenital Zika syndrome still have severe motor delays and functional impairments. According to that study, the infants deviated from the norm to a greater extent at 18 months than they did at 6 or 12 months, corroborating the findings of the present study, which showed that despite a small increase in AIMS scores, motor development worsened over time, demonstrating that these infants are still at risk of gross motor delays.<sup>15</sup>

In another study evaluating early gross motor development in infants with ZIKV infection, using the GMFM, the authors found that even with the progress in scores among children and significant variability in the first 18 months of age, these children remained in the early stages of motor development and had no means of independent movement at 24 months.<sup>10</sup> The majority of children presented gross motor skills similar to those of children aged 4 months or younger.<sup>10</sup>

Although the present study was the first to describe a case of congenital microcephaly with evidence of ZIKV infection in a monozygotic twin pregnancy, it had some limitations, such as the inability to establish that physiotherapy was able to improve motor development in congenital microcephaly associated with ZIKV because of the small number of participants. However, a detailed description of the treatment can guide new studies. Furthermore, the description of this case report can help physiotherapy clinicians handle similar cases.

## CONCLUSION

The present study describes a physical therapy intervention for motor disorders caused by ZIKV, aiming to improve the motor development, functionality, and quality of life of infants with this condition. Since the present study is a report of two cases, further studies with larger samples are needed to evaluate the effectiveness of the intervention.

In addition, although the twins were monozygotic, the twin in case 1 had worse affections regarding neurological lesions by

neuroimaging and, even with rehabilitation, twice a week, the twin presented considerably worse motor development over time.

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