

ORIGINAL ARTICLE

Description of atypical pattern in twins with presumed congenital Zika and without microcephaly - Case Report



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Abstract

Introduction: Zika virus (ZIKV) infection was a public health emergency of Brazilian national interest until May 2017, due to the sudden increase in newborns with microcephaly and other neurological alterations during the epidemic started in Brazil in November 2015. The manifestations of Intrauterine infections by ZIKV are more severe when they occur in the first and second trimesters of gestation, especially in the first trimester. In this situation, early diagnosis of visual problems is essential for patients to progress in the neurological and motor fields, and there are complications such as refractive errors (myopia, astigmatism and hyperopia), strabismus and hypoaclotomy. The absence of microcephaly in infants exposed to the Zika virus is not indicative of changes in ophthalmology, and it is essential that the ophthalmologist perform the investigations that are relevant to the clinical case. Any and all eye lesions and their consequences are serious. The earlier the diagnosis, the sooner the child can undergo an intervention to enable vision.

Objective: To analyze atypical pattern in twins with presumed congenital Zika and without microcephaly.

Method: This is a case report, developed in the city of Serra Talhada, in the state of Pernambuco, Northeast Brazil.

Report: Case of twins whose mother was exposed to Zika virus in the second trimester of gestation (eleventh week). The children were born prematurely and without microcephaly. One of the twins had hydrocephalus requiring surgery. The same child was taken for ophthalmologic examination because of convergent strabismus; and hypocortical optic nerve and chorioretinal scar were found in the macular region in both eyes similar to the lesions described by Zika virus. A similar scenario, but with less visual impairment was identified in the second twin. Skull tomography demonstrated bilateral calcification foci in the cerebral hemispheres.

Conclusion: There was presence of convergent deviation and nystagmus to lateroversions. In the funduscopy, the optic nerve was pale and with cicatricial chorioretinal lesion with well delimited edges in the macular area of both eyes.

Keywords: pregnancy, Zika virus, ophthalmology, vision disorders.

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INTRODUCTION

The Zika virus infection (ZIKV) was a public health emergency of Brazilian national interest until May 2017, due to the sudden increase in newborns with microcephaly and other neurological changes during the epidemic that started in Brazil in November 2015. The manifestations of intrauterine infection by ZIKV are more severe when they occur in the first and second trimesters of gestation, especially in the first trimester.

The first case of ZIKV infection occurred in 1953 in Nigeria¹. After this first report, the virus circulated silently for more than 50 years in Africa and Asia, and few cases were described in isolation and without evidence of serious complications²⁻⁵.

It is known that the disease is transmitted by the *Aedes* mosquito, whose most important species in the transmission of recent outbreaks are *Aedes aegypti* and to a lesser extent *Aedes albopictus*^{4,7}. In Brazil, *Aedes aegypti* is endemic and is also a vector of other arboviruses such as dengue and chikungunya^{4,8,9}, which have clinical presentations similar to Zika, whose classic symptomatology is mild and self-limiting, usually with a maculopapular rash, low fever, arthritis or arthralgia, conjunctivitis, myalgia, headache and edema, being asymptomatic in most cases^{6,10,11}. Other forms of ZIKV transmission such as sexual¹²⁻¹⁵, blood transfusion¹⁶ and perinatal¹⁷ have also been described.

Initially documented in April 2015^{18,19}, the outbreak of Zika in Brazil reached pandemic proportions^{20,21}, spreading rapidly across the continent. It is postulated that this arbovirus was brought from the Pacific Islands during sports events in Brazil in 2014^{18,22}. An increase in the notification of cases of children born with microcephaly in the Northeast region²³ concomitant with the Zika outbreak caused a possible causal association between microcephaly and ZIKV infection during pregnancy²⁴, however, such a finding by the World Health Organization and by CDC (US Centers for Disease Control and Prevention) only occurred in April 2016^{25,26}. In compliance with the public health risk framework, in 2016 in Brazil, health surveillance measures were adopted based on laws published after the outbreak, in order to control dissemination of the transmitting mosquito and also to support the families of children with microcephaly²⁷.

The confirmation of vertical transmission of ZIKV joined forces in the characterization of a new entity: Congenital Zika syndrome. In this syndrome, ocular abnormalities, arthrogryposis and auditory deficits, as well as microcephaly and neurological abnormalities have been described^{8,28-30}. However, there have been few reports of changes in newborns whose mothers were exposed to ZIKV during pregnancy and who did not present microcephaly at birth³¹⁻³⁵, since it has been the criterion used for diagnosis and investigation of congenital Zika in most studies.

In addition, the early diagnosis of visual problems is essential for patients to progress in the neurological and motor fields, with complications such as refractive errors (myopia, astigmatism and hyperopia), strabismus and hypoactomy. The absence of microcephaly in infants

exposed to Zika virus is not indicative of changes in ophthalmology, and it is essential for the ophthalmologist to carry out the investigations pertinent to the clinical case. Any and all eye lesions and their attachments are serious. The earlier the diagnosis, the earlier the child can undergo an intervention to enable vision

Thus, this report describes the case of a twin pregnancy in which the mother was infected by ZIKV during pregnancy and the children were born with ophthalmological and neurological alterations, but without microcephaly.

CASE REPORT

Twenty-one dizygotic twins, a girl and a boy, were born in Serra Talhada, a city in the interior of the state of Pernambuco, Brazil, in June 2016. The 31-year-old female presented a rash with pruritus, low fever and edema in the fourth month of gestation, but was not subjected to further investigation at the time. She made prenatal care without any other changes in the five appointments registered on the pregnant woman's card. The patient underwent four obstetric ultrasonographies (USG) with no evidence of abnormalities as well as laboratory tests performed routinely in prenatal care (rubella, toxoplasmosis, VDRL and HIV). The mother denied using illicit drugs, alcohol and smoking. Delivery occurred vaginally at the 34th week of gestation, without complications. Data on the birth of children are given in table 1.

Table 1: Characterization of infants exposed to Zika virus in the city of Serra Talhada, PE, Northeast Brazil, 2018.

	Twin 1	Twin 2
HC (cm)	28	29
TP (cm)	27	27
AP (cm)	25	25
Weight (g)	1640	1675
Height (cm)	40	41
Apgar 1'	05	08
Apgar 5'	07	09

(HC: head circumference, TP: thoracic perimeter, AP: abdominal perimeter, 1': 1 minute, 5': 5 minutes)

The newborns were referred to the city of Recife for supportive therapy and weight gain in a neonatal intensive care unit.

Twin 1 (girl)

She was submitted, at three months of age, to endoscopic third ventriculostomy surgery with placement of ventriculoperitoneal shunt. Computerized axial tomography of the skull showed centers of calcification in the cerebral hemispheres bilaterally, more evident in the projection of the cauda-thalamic grooves and ventriculomegaly (Figure 1).

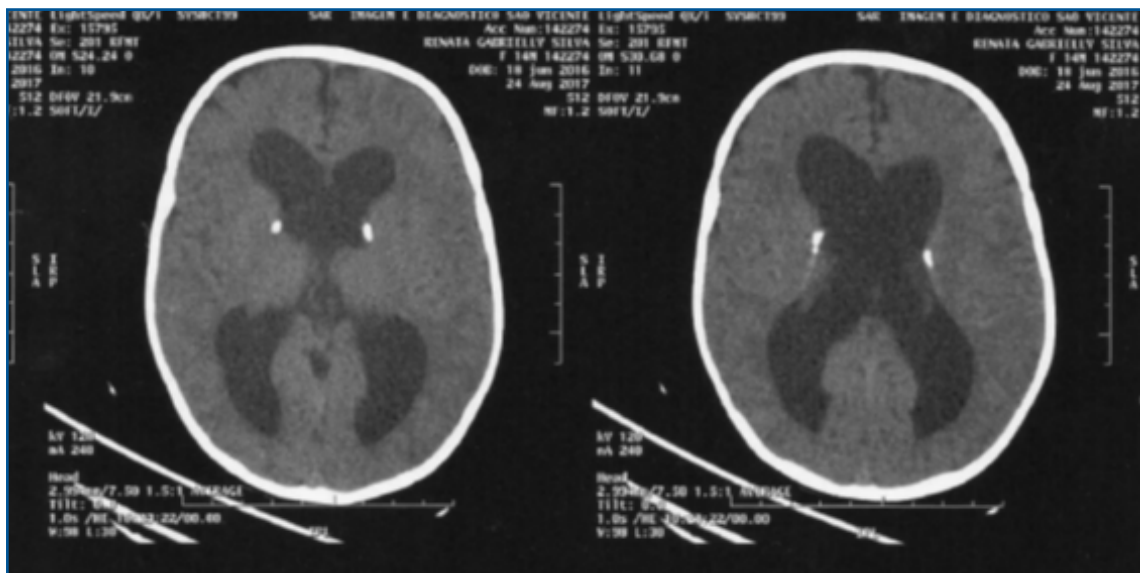


Figure 1: Axial computed tomography of the skull (Twin 1)

Twin 1 started suffering seizures. EEG examination (Figure 2), showed disorganization of the base rate with focal epileptiform activity, often in bilateral parietal projections occurring synchronously and independently; and having started phenobarbital for seizure control.

The child was brought by the mother at seven months for ophthalmological consultation under complaints of strabismus. Upon examination, convergent deviation and nystagmus were observed for lateroversions. In the fundoplication, the optic nerve (NO) was pale and

cicatricial chorioretinal lesion with well delimited edges in the macular area of both eyes was found, similar to lesions previously described in congenital Zika (Figure 3). Table 2 presents the data of the ophthalmologic examination. At 8 months, the neurological exam presented a head circumference of 41.5 cm, and open anterior fontanelle with 3 cm. She sat with support, smiled at the stimuli, followed with a vertical and horizontal gaze and chirped. The auditory evaluation was normal.

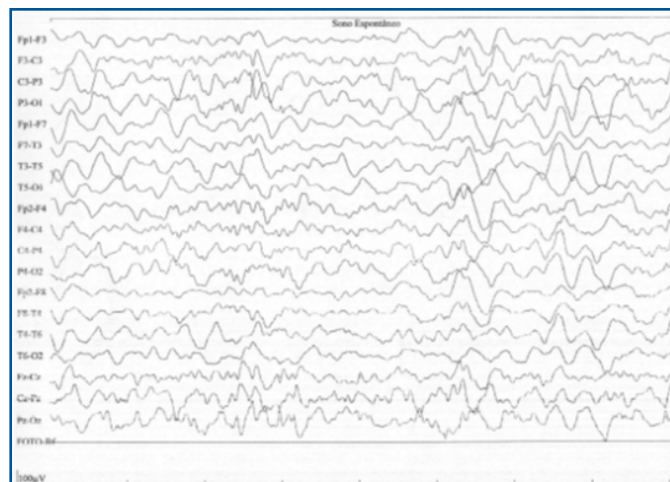


Figure 2: Electroencephalogram (Twin 1)

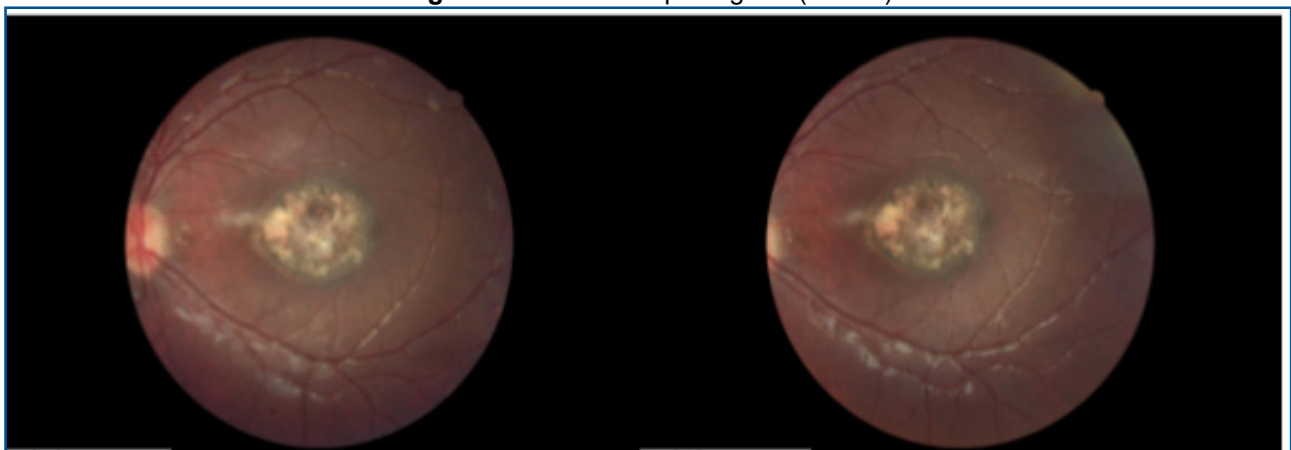


Figure 3: Fundoscopic examination (Twin 1)

Table 2: Data from the ophthalmological evaluation of the twins, born in the city of Serra Talhada, PE, northeastern Brazil, 2018.

	Twin 1	Twin 2
Visual acuity	2.4 cy/cm (Teller 38 cm)	4.8 cy/cm (Teller 55 cm)
Eye movements	Nystagmus	Normal
Strabismus	Esotropia (30 PD)	Absent
Ametropia	Hypermetropia	Hypermetropia
Biomicroscopy	Normal	Normal
Fundoscopy	Chorioretinal lesion in macular area and peripapillary atrophy	Chorioretinal lesion in peripheral area, normal macula

Twin 2 (male)

During the first six months, he was sent to childcare consultations without identifying phenotypic changes or delayed neuropsychomotor development. He underwent ophthalmologic examination at seven months after identification of fundus lesions in his sister. In funduscopy, mottled pigmentation was detected at the posterior pole and chorioretinal lesion already healed in both eyes (Figure 3). Table 2 presents data from the ophthalmological examination of both children. Neurological evaluation at eight months of age demonstrated normal neuropsychomotor development for the age. Auditory assessment was normal.

Screening tests for the most common causes of congenital infection (toxoplasmosis, cytomegalovirus, rubella, syphilis, herpes and HIV) and also dengue and chikungunya were negative for mother and children. IgG serology for Zika virus (ELISA) was positive in the mother, but negative in the infants.

DISCUSSION

Most of the current findings that direct medical care, as far as congenital Zika is concerned, are based on children with some degree of microcephaly. In this report, the possibility of individuals having visual and neurological problems is demonstrated; even in the absence of microcephaly, in an atypical setting of intrauterine exposure to Zika Virus (ZIKV). Few studies have described changes in these circumstances³¹⁻³⁵, but so far no reports have been found on twins.

Of the patients with microcephaly and infection presumed by ZIKV, 24 to 55% will present ocular alterations³⁶, however there is no way to estimate this appearance in children who did not develop microcephaly at birth. Zin *et al.*³⁴ found ophthalmological alterations in eight (13.1%) of the 61 newborns of pregnant women with ZIKV-positive serology and no central nervous system (CNS) abnormalities and 6.5% of those born with systemic abnormalities of the central nervous system (CNS), but without microcephaly.

Among the most common ophthalmologic findings described in association with congenital Zika³¹⁻⁴⁰, the scarred chorioretinal lesion in the macula and the posterior pole mottled pigmentation were identified in the twins of this case report, which triggered the investigation of the mother's exposure to the Zika virus. Reports of pallor of the optic nerve, convergent strabismus and

horizontal nystagmus were also found^{35,38} but the pattern of ocular findings differs from other classic congenital infections^{34,41,42}.

In agreement with the literature⁴³, the involvement of the twins described here is in different degrees. Even in the absence of microcephaly, the first twin presented neurological alterations compatible with congenital Zika spectrum^{36,44} ventriculomegaly, cerebral calcifications and epilepsy, but with an atypical phenotype of lower expression. Hydrocephalus and intra-cranial hypertension have also been identified in some cases as part of the clinical presentation of congenital infection by ZIKV⁴⁵, and in this report there is a clinical occurrence. In addition, Oliveira-Szejnfeld *et al.*⁴⁶ emphasize that in cerebral ventricle obstruction, the cephalic perimeter may be normal and even increased, making it difficult to diagnose Zika Syndrome, since it is characterized by the presence of microcephaly.

The complete spectrum of changes associated with congenital Zika is not known, as the atypical phenotype of the syndrome is still being elucidated. In this context, the discussion on the damage caused by congenital infection by Zika virus and its consequences raises a number of issues, including legal ones, such as abortion, in order to better assist the families involved or possibly involved, since measures that involve the population guarantee positive return on health issues. More studies in this sense are needed to support legislation and decisions that guide such controversial issues^{47,48}.

In addition, one of the main ways to assist in health issues, especially in cases of endemic diseases such as Zika is health promotion, especially in guiding the population to avoid measures that aid the development of the mosquito, expanding the traditional preventive model and ensuring a better quality of life for the population. Because health promotion is associated with a set of factors that constitute a humane and holistic care⁴⁹⁻⁵¹.

Recently, a genetic study⁵² demonstrated that the susceptibility to ZIKV infection in gestation has a genetic origin justifying the different expressions of the syndrome in each individual. However, this does not exclude that other mechanisms are involved in vertical transmission such as placental barrier, viral load distribution and virus tropism.

The gap between birth and the first medical evaluation to raise the diagnostic hypothesis of congenital Zika demonstrates the fragility of the surveillance

protocol⁵³ recommended by the Brazilian Ministry of Health, both in the failure to report cases of rash during pregnancy and in the fact of microcephaly being the starting point for research. This situation conveys a reality that does not fit with practice, where a larger universe of children has been affected and neglected, not being included in the statistics of the State.

Furthermore, considering that the majority of normal delivery NBs present (overlapping) horse sutures, it may occur that the head circumference is transiently below the cutoff parameter, it is recommended that the reference measure for microcephaly notification be performed only 24 hours after birth⁵³. Professionals should identify children who are deficient in neurological, psychological and motor development. It should also guide the mother or caretaker about the early stimulation measures and refer them to the specialized service when necessary⁵³.

It is essential for ophthalmological examination of the fundus of the eye to be performed in children exposed or suspected of exposure to the Zika Virus.

Thus, the study in question showed that other health problems can affect children whose mother was infected during pregnancy, evidencing the importance of quality care for individuals during the disease process. Finally, the study further adds information to the already described atypical phenotype of congenital Zika syndrome with the ophthalmologist having a relevant role

in the initial diagnosis. Also, that at the ophthalmological examination, it was observed that there was presence of convergent deviation and nystagmus to lateroversions. In the funduscopy, the optic nerve was pale and with cicatricial chorioretinal lesion with well delimited edges in the macular area of both eyes.

Infant follow-up is essential for detecting potential changes in ocular development and maintaining full potential for growth and development.

Author Contributions

A.C.Lucena had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design

A.C.Lucena, IMP Bezerra and LC Abreu.

Acquisition, analysis, or interpretation of data

A.C.Lucena, IMP Bezerra and LC Abreu.

Drafting of the manuscript

A.C.Lucena, IMP Bezerra and LC Abreu.

Critical revision of the manuscript for important intellectual content

A.C.Lucena, IMP Bezerra and LC Abreu.

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Resumo

Introdução: A infecção pelo Zika vírus (VZIK) foi emergência em saúde pública de interesse nacional brasileiro até maio de 2017, devido ao súbito aumento de nascidos com microcefalia e outras alterações neurológicas durante a epidemia iniciada no Brasil em novembro de 2015. As manifestações da infecção intrauterina pelo VZIK são mais graves quando ocorrem no primeiro e segundo trimestres de gestação, principalmente no primeiro trimestre. Nesta situação, o diagnóstico precoce dos problemas visuais é imprescindível para que os pacientes apresentem avanços nos campos neurológicos e até motores, sendo que há complicações como erros refrativos (miopia, astigmatismo e hipermetropia), estrabismo e hipoacomodação. A ausência de microcefalia em lactentes expostos ao Zika vírus não é indicativo de alterações ofatalmológicas, sendo imprescindível ao médico oftalmologista realizar as investigações pertinentes ao caso clínico. Toda e qualquer lesão ocular e em seus anexos são graves. Quanto mais precoce for o diagnóstico, mais cedo a criança pode ser submetida a uma intervenção para habilitação da visão.

Objetivo: Analisar padrão atípico de gemelares com Zika congênita presumida e sem microcefalia.

Método: Trata-se de um relato de caso, desenvolvido na cidade de Serra Talhada, interior do estado de Pernambuco, Nordeste Brasileiro.

Relato: Caso de gemelares cuja mãe foi exposta ao Zika vírus no segundo trimestre de gestação (décima primeira semana). As crianças nasceram prematuras e sem microcefalia. Um dos gemelares apresentou hidrocefalia com necessidade de intervenção cirúrgica. A mesma criança foi levada para exame oftalmológico por possuir estrabismo convergente e foi encontrado nervo óptico hipocorado e cicatriz coriorretiniana em região macular em ambos os olhos semelhantes às lesões descritas pelo Zika vírus. Quadro similar, mas com menor comprometimento visual foi identificado no segundo gemelar. A tomografia de crânio demonstrou focos de calcificação nos hemisférios cerebrais bilateralmente.

Conclusão: Houve presença de desvio convergente e nistagmo às lateroversões. Na fundoscopia, o nervo óptico apresentou-se hipocorado e com lesão coriorretiniana cicatricial com bordos bem delimitados em área macular de ambos os olhos.

Palavras-chave: gravidez, Zika Vírus, oftalmologia, transtornos de visão.

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