

Association of arthrogryposis in neonates with microcephaly due to Zika virus - a case serie

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Abstract

Introduction: in 2015 an increasing number of congenital microcephaly cases were associated to maternal infection due to Zika virus. Some of these patients presented other alterations and arthrogryposis was the most frequently found. Arthrogryposis is defined as congenital joint contractures involving at least two different areas of the body.

Description: arthrogryposis was found in 18 patients with congenital microcephaly due to Zika virus. 67% of the cases were vaginal deliveries. 50% of resuscitation performed in the delivery room was necessary. The mean birth weight was 2.371g, gestational age was 39 weeks and the head circumference was 28.3cm, 15 (83%) of these patients presented severe microcephaly. All the neonates resulted in concomitant hip joints and some also had knees, ankles and wrists affected. Nine neonates (50%) presented an early respiratory distress and four (22%) died due to respiratory failure.

Discussion: the neurological result found in patients with Congenital Zika Syndrome seems to be associated to the maternal infection period. During the early stages of embryogenesis, in addition to microcephaly, could be related to the peripheral motor nerves leading to fetal akinesia, joint stiffness and arthrogryposis. These neonates tend to present greater morbimortality with the worst prognosis.

Key words *Microcephaly, Arthrogryposis, Zika virus*

Introduction

From the second half of 2015, there was a growing number of cases of congenital microcephaly in Brazil, especially in the Northeast region. Pernambuco is the state with the highest number of cases.¹ Although, there is no consensus regarding the definition of microcephaly, it was taken in consideration the head circumference with less than two or more deviations in relation to the mean of the population's gender and gestational age.² The etiologies that may determine this alteration varies: genetic syndromes, structural abnormalities structure of the brain, craniosynostosis, hypoxic-ischemic insults, teratogenic and infectious agents.³ However, by assessing epidemiological and laboratorial cases identified during this period, an association could be maternal infection due to Zika virus during the pregnancy.⁴

Zika virus belongs to the *Flavivirus* genre in the *Flaviridae* family and is transmitted primarily through the mosquito, *Aedes aegypti*. In pregnant women it causes a self-limiting disease, which the main symptoms are maculo papular rash, feverish sensation and arthralgia, however it can also be asymptomatic.⁵ The effects on the fetus seem to be more severe when the infection occurs in the first trimester of the pregnancy. The concept involved causes a congenital Zika syndrome, a disease that is not completely clear, but its main manifestation is severe malformation of the central nervous system (CNS), characterized by microcephaly.⁶

The published articles and ongoing studies have identified that these newborns are, most of them, at term and with alterations in the neurological exam which varies from hypertonia and irritability to difficult control of seizures. Despite presenting a severe malformation in the CNS, most do not need resuscitation in the delivery room. The findings on neuro imaging seen on the computerized tomography of the skull are characteristics of: ventriculomegaly, intracranial calcifications, hypoplasia of the structures of the posterior cranial fossa, cortical atrophy and even more severe cases of lissencephaly.⁷

However, there is a group of patients besides microcephaly, which has other associated malformation, the most frequent one is arthrogryposis. This is defined as congenital joint contractures involving at least two different areas of the body, and it usually is not progressive. There is a limitation of the passive and active movements with the presence of the structural abnormalities and/or functions of the articular capsule and ligaments. The main joints affected are knees, hips, ankles and wrists.⁸

The pathological mechanism for this alteration is related to the absence of active fetal movements (akinesia), usually around the 8th week of pregnancy, but for at least three weeks, fetal akinesia is already able to cause alterations in the articular system resulting in fibrosis of periarticular structures. A direct injury to the peripheral nerve motor also seems to contribute to the framework. The determined cause for the decrease of fetus' mobility is uncertain, although it may be resulted to neurogenic factors such as myogenetics, diseases of connective tissue and articulations, maternal myasthenia gravis, maternal diabetes, anatomic abnormalities of the uterus, amniotic band, nutritional and vascular disorders and among others.⁹

The neurogenic are the main factors and include disorders of the CNS such as abnormalities of neuronal migration, pyramidal disorders and olivocerebellar point, in addition to diseases of the neuron alpha motor of the previous spinal column. Zika virus has intrinsic characteristic of neurotropism, as proven in studies on fetal autopsy with viral isolation by *polymerase chain reaction* (PCR) in the tissues of the brain. The involvement of the Cerebral Nervous System in these children suggests that the insult occurred in the initial phase of embryogenesis.¹⁰

It is important to understand that all aspects related to Congenital Zika Syndrome should provide patients and family members an appropriate follow-up. This type of alteration in joints requires a management of a multidisciplinary team involving a pediatrician, orthopedist, physical therapist, occupational therapist and others. The treatment includes the use of orthosis, surgeries and rehabilitation. Therefore, it is necessary to analyze the presence of arthrogryposis on researched children, the clinical severity and the impact on the prognosis.

Description

During the period of October 2015 to April 2016, 89 newborns with congenital microcephaly associated to Zika virus were evaluated in the neonatology unit at Instituto de Medicina Integral Prof. Fernando Figueira (IMIP). Of the 89 newborns, 18 of them (20%) had arthrogryposis, which the clinical aspect and laboratorial tests will be described. IMIP is a tertiary hospital, where neonatal unit consists of mother and child rooming, kangaroo mother care rooming, unit for intermediate care and intensive care unit (ICU).

The mothers' average age was 24 years; 17 of them (94%) reported some symptoms of the exanth-

matic disease during pregnancy, taken in consideration the presence of fever, rash and arthralgia; twelve (71%) presented the symptoms in the first quarter of the pregnancy, three (17%) in the 2nd and two (12%) in the 3rd; the diagnosis of microcephaly was performed during the fetal ultrasound examination in 16 (89%) patients.

12 (67%) cases were born by vaginal delivery, 18 neonates were born at term, the mean gestational age of 39.2 weeks (± 1.39), 11 (61%) were females, the average weight at birth of 2.371g (± 508 g) and 15 (83%) were classified as small for the gestational age. The severe microcephaly was considered when the head circumference was less than 3 or more than the standard deviations, in which was present in 15 cases (83%).

Nine neonates (50% of the cases) were observed and needed some resuscitation maneuver in the delivery room. The median of the Apgar score in the first minute was 7 (6-9, inter-quartile interval) and in the fifth, 9 (8-9, inter-quartile interval).

In the physical examination, the hip involvement in all the patients was observed associating alterations in the knees, ankles and wrists. Figure 1 represents one of the newborns evaluated in this study was observed and found arthrogryposis in the upper and lower limbs. These neonates expressed the most severe framework, including higher rates of respiratory distress, the necessity to be admitted to the neonatal ICU and have a longer hospital stay. There were a total of four deaths (22%), the other 14 (78%) patients progressed favorably and were discharged with an oral diet and subsequently forwarded to a specific multidisciplinary follow-up.

As for imaging examinations, 14 (78%) performed a computerized tomography (CT) of the skull and in all of them found alterations as: calcifications (100%); ventriculomegaly (100%); ridge alterations (85.7%) and posterior fossa hypoplasia (78.6%). Due to the clinical severity, only four patients performed transfontanelar ultrasound with similar alterations to those seen in the CT's.

Table 1 describes 18 cases evaluated in the study, in relation to clinical characteristics and findings in the CT's.

This research was approved by the Ethics Committee Research in Humans at IMIP, under the

number of CAE 52537516.3.0000.5201 and approved on March 9th, 2016.

Discussion

In newborns with congenital microcephaly associated to Zika virus stood out in a group that also presented joint alterations compatible to arthrogryposis. Before the neurotropism of the virus and the alterations in the neuro imaging that are evidences of the involvement in the initial phase of the development of the brain in these children, this seems to be the pathogenic mechanism for the manifestation of the joint involvement.¹⁰

The first quarter was the period of which most of the pregnant women reported having the disease. For this reason, the fetus' mobility would be jeopardized by a longer period of time. Either way, the medical literature describes that even a three week period could cause progression to the fibrosis of the fetus, justifying, therefore, the triggering of the arthrogryposis even in the four cases that the mothers reported the symptoms later in the pregnancy.⁹

In neonates at term, the considering rate for the need of neonatal resuscitation was around 10%. In the group of patients with microcephaly, this rate was higher reaching 22%. The association to microcephaly with arthrogryposis, this value became even higher, reaching half of the patients. The finding may be justified by the great neurological compromised impairment of these individuals, corroborated by severe microcephaly, whose severity caused an inclusive reduction of fetus mobility intrauterine. Also, all patients with microcephaly that progressed to death presented joint contracture.

Despite the knowledge is still incipient on the issue, it is possible to observe the importance of the neurological compromised impairment in patients with the Congenital Zika Syndrome. The identification of the factors as arthrogryposis is added to morbidity and worsens the prognosis of these children and is essential for the clinical management to be well planned. The participation of multidisciplinary team early in this scenario gives the patient a better and appropriate adaptation, in addition a better support and clarification to the family.

Figure 1

Neonate diagnosed with congenital microcephaly associated to Zika virus with arthrogryposis. Instituto de Medicina Integral Prof. Fernando Figueira, 2016.



Table 1

Clinical characteristics and findings of neuro imaging on neonates diagnosed with congenital microcephaly associated to Zika virus with arthrogryposis. Instituto de Medicina Integral Prof. Fernando Figueira, 2016.

Patient (Number)	Type of birth	Gender	Gestational age	Birth weight	Z-score of HC	Apgar 1	Apgar 5	Changes in computerized tomography of the skull			
								Calcification	Ventriculomegaly	Posterior fossa hypoplasti	Ridge Alterations
1	V	M	37	1630	22	-	-	Y	Y	N	Y
2	V	M	39	2356	28	9	10	Y	Y	Y	Y
3	C	F	40	2025	26	6	9	-	-	-	-
4	C	M	40	2975	25	8	9	Y	Y	N	N
5	V	M	39	2110	28.5	9	9	Y	Y	N	Y
6	C	M	40	2175	28	7	8	Y	Y	Y	Y
7	C	F	37	3005	29	9	10	Y	Y	Y	Y
8	V	F	37	1475	25	5	7	Y	Y	Y	Y
9	V	F	40	2320	29.5	7	8	Y	Y	Y	N
10	C	F	38	2165	25	7	8	Y	Y	Y	Y
11	V	F	42	2395	26.5	1	1	-	-	-	-
12	V	M	38	2610	26	9	10	Y	Y	Y	Y
13	V	F	39	3195	26	8	9	Y	Y	Y	Y
14	V	F	40	1715	28	6	8	Y	Y	Y	Y
15	V	F	39	2565	31	7	7	-	-	-	-
16	C	F	41	2075	28	5	8	-	-	-	-
17	V	M	40	2770	29.5	10	10	Y	Y	Y	Y
18	V	F	40	3110	28.5	9	9	Y	Y	Y	Y

V= vaginal; C= cesarean section; F= female; M= male; HC=head circumference; Y= Yes; N= No.

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Received on July 5, 2016

Final version presented on September 13, 2016

Approved on September 27, 2016