# Cases Series of Congenital Zika Syndrome with Arthrogryposis

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<tr>
<td>Complete List of Authors:</td>
<td>van der Linden, Vanessa; Association for Assistance of Disabled Children (AACD), Filho, Epitacio; Association for Assistance of Disabled Children (AACD), in Recife Lins, Otavio; Federal University of Pernambuco (UFPE), Recife, Brazil van der Linden, Ana; Prof. Fernando Figueira Integral Medicine Institute (IMIP) de Fatima Vasco Aragao, Maria; Centro Diagnostico Multimagem, Brainer-Lima, Alessandra; PROCAPE- University of Pernambuco Cruz, Danielle; Prof. Fernando Figueira Integral Medicine Institute (IMIP), Recife, Brazil Rocha, Maria Angela Wanderley Rocha; Oswaldo Cruz University Hospital (HUOC), Recife, Brazil Gomes de Carvalho, Maria Durce; Oswaldo Cruz University Hospital (HUOC) da Silva, Paula; Oswaldo Cruz University Hospital (HUOC) Amaral, Fernando; Barão de Lucena Hospital, Recife, Brazil Gomes, Joelma; Barão de Lucena Hospital, Recife, Brazil Medeiros, Igor; Hospital Infantil Jorge de Medeiros Coeli, Regina; Oswaldo Cruz University Hospital (HUOC)</td>
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<td>Keywords:</td>
<td>Zika virus; microcephaly; arthrogryposis; congenital infection</td>
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</table>
Figure 1: Observe the images of joint deformities. (A) Contracture in flexion of the knee; (B) hiperrecurvato knee - dislocation; (C) clubfeet; (D) deformities of chirodactyls - observe camptodactyly of 2, 3 and 4 fingers; (E) joint contractures in the lower and upper limbs without involvement of the trunk.

50x43mm (300 x 300 DPI)
Figure 3: Magnetic resonance imaging of the spinal cord and the brain of a baby who has arthrogryposis. Sagittal T2 weighed Fast Imaging Employing Steady-state Acquisition (FIESTA) (A) shows an apparently reduced spinal cord thickness (short arrows) and mega cisterna magna (long arrow). On the axial reconstruction of T2 weighed FIESTA (B), we can observe reduction of the medullary cone ventral roots (long arrows) compared with dorsal roots (short arrows). Sagittal T2 weighed imaging (C) shows hypogenesis of the corpus callosum (long white arrow), enlarged cisterna magna (long black arrow), enlarged IV ventricle (short black arrow) and pons hypoplasia (short white arrow). Axial T2 weighed imaging (D) shows pachygyria in the frontal lobes (black arrows) and severe ventriculomegaly, mainly at the posterior part of the lateral ventricles. Axial susceptibility weighed imaging (E and F) shows some hypointense small dystrophic calcifications (white arrows) in the junction between cortical and subcortical white matter (E) and in the midbrain (F).
Figure 4: Intraoperative aspect of the adductor longus muscle hip of a study of patients with irreducible dislocation of the hips before surgery. Observe the color characteristic changes of fibrofatty infiltration like in the initial phase of the neuropathies.

160x153mm (300 x 300 DPI)
Figure 2: Images of the hips (A, B, C) and knees (D). (A) MRI - observe bilateral dislocation of the hips, epiphyseal core (small arrow) and dysplastic acetabulum (large arrow); (B) Computed tomography 3D where show bilateral dislocation of the hips; (C) X-ray AP in the hips where is observed radiographic parameters compatible with dislocation of the hips: breaking the arc Shenton, epiphysis hypoplastic proximal femoral, acetabular index of 35° and proximal localization of the proximal femoral epiphysis right and left located on the side and bottom quadrant Ombredane; (D) X-ray shows knee subluxation (arrows).
What is already known of this topic

Until 2015 there was no report of human association of congenital infection by viruses and arthrogryposis. After microcephaly outbreak in Brazil associated with the Zika virus just a work described this association, however without a deepening of the possible causes and characterization of deformities. Here were publish a series of cases of Congenital Zika Syndrome and arthrogryposis with extensive imaging, neurological and ortopedic investigations.

What this study adds

This is the first time a congenital infection syndrome presents – albeit in a minority of cases- with arthrogrypotic joints. The clinical findings, electromyographic and image, remove primary joints causes and suggest a neurogenic origin of arthrogryposis associated with Zika virus congenital infection. In addition, the authors suggest that the pathophysiology of this condition may be related to the tropism of the virus by the upper and lower motor neurons or embryonic vascular change affecting these two segments.

ABSTRACT

OBJECTIVE

The objective of this study is to describe the clinical, radiological and electromyographic features in a series of seven patients with arthrogryposis associated with congenital infection presumably by ZIKV.

DESIGN

Retrospective study with a case series.

SETTING

Association for Assistance of Disabled Children (AACD), Pernambuco state, Brazil

PARTICIPANTS

Seven children diagnosed with congenital infection presumably caused by ZIKV during the Brazilian microcephaly epidemic with arthrogryposis.

INTERVENTIONS

Investigation cause of arthrogryposis in patients diagnosed with Congenital Zika Syndrome with neurologic and orthopedic evaluation and additional exams: X-ray, brain imaging with computerized tomography scan without contrast or magnetic resonance imaging without contrast, high definition ultrasonography of the joints and nerve conduction studies and needle electromyography.

MAIN OUTCOME MEASURES

The main clinical, radiological and electromyography findings of children diagnosed with presumed congenital infection by ZIKV associated with arthrogryposis are described and try to establish a likely correlation between the clinical and primary neurological abnormalities found in patients.

RESULTS

All 7 patients presented brain images characteristics of congenital infection and arthrogryposis, 3 of the 7 patients tested for IgM for ZIKV in the CSF were positive. Seven patients were evaluated; six of them
(85.7%) had joint deformities arthrogryposis both in the upper and lower limbs and a patient (14.3%) had joint contractures of the lower limbs. Radiographs of the hips showed bilateral dislocation in seven cases, subluxation of the knee associated with genu valgus in three (42.85%), bilateral in (28.57%) two patients associated with valgus. All patients underwent a high definition ultrasonography of the joints and there were no evidence of joint abnormalities. Needle electromyography (monopolar) showed moderate signs of remodeling of the motor unities and a reduced recruitment pattern. Five patients underwent CT-Scan and MRI and two patients only CT-Scan. All presented malformation of cortical development, calcifications predominantly in the cortex and subcortical white matter (especially in the transition between the cortex and white matter), volumetric reduction in brain, ventriculomegaly and volumetric reduction of the brainstem and cerebellum. Four patients underwent spinal MRI that showed cord thinning, especially in the thoracic region, with ventral predominance, reducing the ventral roots.

CONCLUSION

Congenital Zika Syndrome should be added to the differential diagnosis of congenital infections and arthrogryposis. The rare and unusual arthrogrypotic joints did not result from abnormalities of the joints themselves and are likely to be of neurogenic origin, with chronic involvement of central and peripheral motor neurons, leading to intrauterine fixed postures and consequently deformities. Based on our neurophysiological observations and the literature finding, we suggest two possible mechanisms, tropism for the neurons, with involvement of peripheral motor neurons and central motor neurons or related with vascular disorders.

Cases Series of Congenital Zika Syndrome with Arthrogryposis.

Vanessa van der Linden,1,2 MD, MSc; Epitacio Leite Rolim Filho,1,3 MD, PhD; Otavio Gomes Lins,3 MD, PhD; Ana van der Linden,4 MD; Maria de Fátima Viana Vasco Aragão,3,5,6 MD, PhD; Alessandra Mertens Brainer-Lima,5,7 MD, MSc; Danielle Di Cavalcanti Sousa Cruz,4 MD; Maria Angela Wanderley Rocha,8 MD, MSc; Paula Sobral da Silva,8 MD, MSc; Maria Durce Costa Gomes de Carvalho,8 MD, MSc; Fernando José do Amaral,2 MD, MSc; Joelma Arruda Gomes,2 MD, MSc; Igor Colaço Ribeiro de Medeiros,9 MD; Regina Coeli Ramos,8 MD, MSc.

1. Association for Assistance of Disabled Children (AACD), in Recife, Brazil.
2. Barão de Lucena Hospital, Recife, Brazil.
3. Federal University of Pernambuco (UFPE), Recife, Brazil.
4. Prof. Fernando Figueira Integral Medicine Institute (IMIP), Recife, Brazil.
5. Centro Diagnóstico Multimagem, Recife, Brazil
6. Mauricio de Nassau University, Recife, Brazil
7. University of Pernambuco (UPE), Recife, Brazil
8. Oswaldo Cruz University Hospital (HUOC), Recife, Brazil.
9. Hospital Infantil Jorge de Medeiros Recife, Brazil.
Keywords: Zika virus; microcephaly; arthrogryposis; congenital infection

Correspondence to: Vanessa van der Linden, Association for Assistance of Disabled Children (AACD), Avenida Advogado José Paulo Cavalcante, 155, Ilha de Joana Bezerra, Recife, Brazil, CEP 50080-810, vanessavdlinden@hotmail.com, +55 81 34194000, +55 81 999617134

Introduction

The Zika virus (ZIKV) is a RNA virus in the family Flaviviridae, genus Flavivirus. ZIKV carries the name of a forest close to Kampala in Uganda, where it was first identified in Rhesus monkeys in 1947. In 1952 it was isolated in humans in Africa for the first time. Until 2007 the ZIKV was known to cause sporadic infections in Africa and Asia, characterized by a dengue-like syndrome, including fever, headache, arthralgia, myalgia, maculopapular rash and conjunctivitis. In 2007 occurred an epidemic in Micronesia and in 2013 in French Polynesia. The first report of ZIKV outside Asia and Africa occurred in 2014 and in Brazil the first case was reported in May 2015.

By 2015 it had not been reported in the literature, ZIKV associated with fetal malformation. In October 2015, the government of the State of Pernambuco in Brazil reported an increase in cases of microcephaly with changes in brain imaging suggestive of congenital infection and later in November 2015 the Minister of Health from Brazil, based on epidemiological characteristics and laboratory and pathological findings, established the relationship between the increased occurrence of microcephaly and infection ZIKV by detecting genome ZIKV in blood and tissues of a baby in Ceara state.

Epidemiological data suggested that microcephaly cases in Brazil might be associated with the introduction of ZIKV. Calvet et al (2016) detected ZIKV genome and anti-Zika-virus IgM in amniotic fluid of pregnant women with microcephalic fetuses. Mlakar et al (2016), in a case of a fetal autopsy, described the complete genome of ZIKV recovered from the fetal brain.

A Congenital Zika Syndrome has as a main characteristic the brain impairment, with microcephalus, however it is still little known about this entity and its clinical spectrum that includes newborns with normal head circumference. Schuler-Faccini et al (2016) described the association between arthrogryposis and microcephaly in newborns presumed to have been infected by congenital ZIKV. The term arthrogryposis is used in various diseases that have similar characteristics, specifically reduced fetal movements, congenital joint contracture of two or more joints and varying degrees of muscle weakness and shortening presented in the newborn. Thus, arthrogryposis may be considered more as a symptom rather than a specific disease, which may be associated to different disorders. However there are no reports in literature about congenital infection in humans associated with arthrogryposis. Since the beginning of this new epidemic, presumably related to ZIKV, the scientific community has sought to better understand this new disease.
The objective of this study is to describe the clinical, radiological and electromyographic features in a series of seven patients with arthrogryposis associated with congenital infection presumably by ZIKV and try to establish a likely correlation between the clinical and primary neurological abnormalities found in patients.

Samples and Methods

We conducted a descriptive, retrospective study by reviewing the medical records of patients with congenital infection diagnosis presumably by ZIKV associated with arthrogryposis, registered at the Rehabilitation Centre of Association for Assistance of Disabled Children of Pernambuco (AACD PE) between January and March 2016. Two patients were treated by the team of AACD in the intensive care unit of other hospitals. The AACD Pernambuco is a reference rehabilitation center in the state of Pernambuco and since January 2016 follow up patients with Congenital Zika Syndrome. All investigations described were conducted as part of a clinical protocol; no investigations were conducted for research reasons, therefore neither ethical approval nor informed consent was not necessary (other than for the photographs of patients presented in this paper). All authors had full access to the data and had responsibility for submission of the manuscript.

It was included patients diagnosed with Congenital Zika Syndrome who had arthrogryposis. The diagnosis of Congenital Zika Syndrome was based on brain imaging findings, whose main characteristic is malformations of cortical development, calcifications predominantly in cortex and subcortical white matter and ventriculomegaly. Cerebral spinal fluid (CSF) samples of XX patients were tested by IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) for ZIKV following CDC protocol, as described by Martin et al (2000). Microcephaly is an important signal, however it is not present in all cases of Congenital Zika Syndrome, not being a factor of exclusion the normal head circumference for gestational age and sex. Microcephaly was defined as head circumference less than two standard deviations (SD) below the average for gestational age and sex and severe microcephaly when the head circumference was below 3 SD average for age and sex, according to The Fetal International and Newborn Growth Consortium for the 21st Century (Intergrowth-21st). It was evaluated birth weight and classified as appropriate, small or large for gestational age and sex, by the curve of Intergrowth-21st.

Arthrogryposis was defined as contractures of at least two joints into at least two different corporal segments.

We excluded patients with other known causes of congenital infection. The main causes of congenital infection that occur with cerebral calcifications and microcephaly were identified by performing paired serological test (mother / child) for cytomegalovirus, toxoplasmosis, rubella, syphilis and HIV. Molecular biology was held for cytomegalovirus. Brain imaging examinations, computerized tomography and magnetic resonance imaging were also used to confirm the diagnosis and remove other causes of microcephaly.

All patients went through neurologic and orthopedic evaluation with clinical examination and additional exams: X-ray, brain imaging with computerized tomography scan (CT-scan) without contrast...
or magnetic resonance imaging (MRI) without contrast, high definition ultrasonography of the joints (with specific attention to cartilage, synovia, pericapsular structures and muscular tissue around joints, looking for joint abnormalities), and nerve conduction studies and needle electromyography (to study neurogenic causes). Four patients underwent spine MRI. According to microcephaly protocol of the State of Pernambuco, six out of seven patients underwent ophthalmologic examination with fundus and 6 out of 7 patients underwent hearing assessment with hearing screening, by otoacoustic emissions or brainstem evoked potentials.

One of the patients underwent orthopedic surgery for deformity correction of the feet and hips. It was carried out assessment of range of motion under anesthesia and macroscopic evaluation of the muscles.

Results

In March 2016, the AACD Recife was follow 104 patients investigating congenital infection presumably by ZIKV. Seven Patients met the inclusion criteria, two females (29%). 2 of the 7 patients tested for IgM for ZIKV in the CSF were positive. Table 1 summarizes the characteristic of the cases.

Dates of birth ranged from October to November 2015. All of them were born in the State of Pernambuco, Brazil. All patients were born at term. In 4/7 patients (57%) described maternal history of rash in between the second and fourth gestational month. The head circumference was normal in 1/7 (14%) patients, in 2/7 (29%) patients was below average of 2 standard deviations for gestational age and gender and 4/7 (57%) patients was below 3 standard deviations of the average for gestational age and sex. 3/7 (43%) patients were appropriate for gestational age and 4/7 (57%) small for gestational age. In 6 out of 7 (85.7%) patients studied was evidenced craniofacial disproportion; 3 out of 7 (42%) patients had at birth redundant skin on the scalp. Dysphasia was evidenced in 6/7 (86%) patients, 2 of these underwent gastrostomy and tracheostomy. All male patients (5/7) had cryptorchidism, one case of unilateral and four bilateral.

Seven patients were evaluated; six of them (85.7%) had joint deformities arthrogryposis both in the upper and lower limbs and a patient (14.3%) had joint contractures of the lower limbs. Lower limb deformities were observed as follow: congenital clubfoot arthrogryposis was presented in six of them (85.7%), three out of this six bilateral patients (42.85%); knee flexion contracture was observed in five patients (71.4%) , three of them (42.85%) bilateral patients and two patients unilateral(28.57%); hyperextension associated with subluxation of the knee were identified in three (42.85%) patients, two of these (28.57%) was bilateral; the seven patients had contractures of hip flexion, adduction and external rotation associated with irreducible bilateral dislocation (not reducible to clinical maneuver of borlow). They were not identified in the seven patients fixed deformities of the spine in the sagittal and coronal plane. The chest had a barrel aspect in four (57.14%) patients. In the upper limbs the following deformities were identified: camptodactyly in six (85.7%) patients, five out of this (71.4%) bilateral; flexion deformations of the 2nd, 3rd, 4th and 5th chirodactyls was observed in all patients. Thumb adduct were present in five of them (71.4%) and abduct in two (28.57%) patients, bilateral simian crease in one (14.28%) patient; deformities in hyperextension of the elbow in four (57.14%) patients and flexion contracture in two
patients bilaterally; and decreased range of motion of the shoulder with contracture in adduction and internal rotation in two (28.57%) patients. Figure 1 show the clinical pictures of patients with arthrogryposis.

It was not observed any deformities or limitation of motion of the cervical spine in the seven patients studied.

Other findings were: ligamentous laxity in one patient (14.28%); skin hemangioma in four patients (57.14%), located one frontal, three occipital and one on the left parathoracic region.

Radiographs of the hips showed bilateral dislocation in seven cases, subluxation of the knee associated with genu valgus in three (42.85%), bilateral in (28.57%) two patients associated with valgus. A simple x-rays of the bones of the appendicular skeleton and spine showed no dysplastic changes and were not identified in these deformities tests along its sagittal and coronal axes in all patients; dysplastic changes were identified in the dislocated hips, related to dysplastic acetabular (all acetabular index above 30 degrees). Table 2 shows the main deformities more often found in the study patients and Figure 2 shows some radiologic aspects.

All patients underwent a high definition ultrasonography of the joints with specific attention to cartilage, synovia, pericapsular structures and muscular tissue around joints and there were no evidence of joint abnormalities.

Nerve conduction studies and needle electromyography was performed all 8 neonates. Nerves studied were Median and Ulnar (sensory and motor conduction studies), Tibial and Fibular (motor conduction studies) and Medial Plantar (sensory conduction studies). Muscles studied were Biceps Brachii (BB), Extensor Digitorum Communis (EDC), Tibialis Anterior (TA) and Medial Gastrocnemius (MG), Not all of these nerves and muscles were studied in all babies. The procedure is technically challenging due to the presence of anatomical abnormalities and to the characteristic irritability of babies. Table 3 summarizes the results of electromyography.

The obtained sensory nerve action potentials (SNAP) of all babies had normal amplitudes and conduction velocities for the age. In one case we could not obtain the SNAP of the medial plantar nerve, possibly for technical reasons. Compound motor action potentials (CMAP) could be obtained in all babies, most with moderately low amplitudes and normal distal motor latencies and conduction velocities.

Needle electromyography (monopolar) showed moderate signs of remodeling of the motor units (polyphasic motor unit potentials (MUP) with elevated amplitude and duration) and a reduced recruitment pattern. In babies with severe weakness of carpal and finger extension and/or ankle dorsiflexion the activation of motor units seemed to be reduced as well.

Five patients underwent CT-Scan and MRI and two patients only CT-Scan. All presented malformation of cortical development, calcifications predominantly in the cortex and subcortical white matter (especially in the transition between the cortex and white matter), volumetric reduction in brain, ventriculomegaly and volumetric reduction of the brainstem and cerebellum.
Four patients underwent spinal MRI that showed cord thinning, especially in the thoracic region, with ventral predominance, reducing the ventral roots. Figure 3 shows typical images of the brain and spine.

The assessment of range of motion of a patient under anesthesia showed that there was muscle shortening and not just spasticity. The findings of intraoperative macroscopic evaluation of the hip adductors muscles were consistent with fibro-fatty degeneration (Figure 4).

In addition to the 6 patients who underwent fundus, five showed alterations in at least one eye and six who underwent hearing screening, four were normal, one had unilateral abnormalities and other bilateral, however it was not the objective of this work to deepen these assessments.

Discussion

The seven patients described showed changes in brain imaging exams, with calcifications predominantly in cortex and subcortical white matter (especially in the transition between the cortex and white matter), with abnormalities of cortical development and brainstem and cerebellar atrophy. Tests for evaluation of arthrogryposis were consistent with neurogenic pattern with findings of EMG and spine MRI suggesting involvement of lower motor neuron. Microcephaly and craniofacial disproportion have been frequent but not in all cases.

Microcephaly is a condition where a baby has a head that is smaller when compared with other babies of the same sex and age. Microcephaly is a clinical sign and not a disease. Increased rates of congenital microcephaly have been reported in the context of the ZIKV outbreak in Brazil, beginning in late 2015. Genetic or environmental in utero brain damage can result in congenital microcephaly at birth and infectious causes are well known: rubella, cytomegalovirus and toxoplasmosis. Before 2015, there were no evidence for congenital infectious presumed to be caused by ZIKV.

This pathology goes beyond the microcephaly, with other symptoms such as visual, hearing impairment, and unusual signs and symptoms of other congenital infections, such as arthrogryposis. It is therefore more most patients had microcephaly, however one patient had regular head circumference, showing appropriate the use of the term Congenital Zika Syndrome. The visual changes in Congenital Zika Syndrome have been described by Ventura et al, 2016.

The presence of disorder of cortical development suggests that the injury occurred up to 5 months of pregnancy. Russell et al (1984) previously reported three infants with a recognizable pattern of defects consisting of severe microcephaly, overlapping sutures, prominence of the occipital bone, and scalp rugae. This condition appears to be produced by partial brain destruction during the second or third trimester, diminution in intracranial hydrostatic pressure, and subsequent collapse of the fetal skull. Several different causes for this condition have been suggested including partial disruption of the blood supply to the brain and viral prenatal infection. This finding is similar to our patients. Dysphagia was a common symptom, probably related to the severity of brain imaging changes, including the presence of brainstem and cerebellar atrophy.

Arthrogryposis is derived from the Greek words arthro (joint) and gryposis (crooked). The term arthrogryposis is often used as shorthand to describe multiple congenital contractures that affect two
or more different areas of the body. Arthrogryposis is not a specific diagnosis, but rather a clinical finding, and it is a characteristic of more than 300 different disorders. Arthrogryposis can be divided into subgroups, as a way of generating a differential diagnosis which includes neurological diseases (brain, spine, or peripheral nerve), connective tissue defects (diastrophic dysplasia), muscle abnormalities (muscular dystrophies or mitochondrial abnormalities), space limitations within the uterus (oligohydramnios, fibroids, uterine malformations, or multiple pregnancy), intrauterine or fetal vascular compromise (impaired normal development of nerves, or anterior horn cell death), and maternal diseases (diabetes mellitus, multiple sclerosis, myasthenia gravis, infection, drugs, or trauma).

Neurologic abnormalities seem to be one of the most common causes of arthrogryposis (approximately 70–80% of cases). Developmental abnormalities affecting the forebrain (e.g., hydranencephaly, microcephaly, or forebrain neuronal migration disorders), whether due to primarily genetic factors or as a consequence of fetal central nervous system infection, are sometimes associated with arthrogryposis. In most such cases, joint contractures are probably due to diminished cortico-spinal tract activation of spinal cord motor neurons or sometimes the underlying disease also directly injures spinal cord motor neurons, contributing to fetal hypomotility.

By 2015 there was no report of congenital infections associated with arthrogryposis in humans. Schuler-Faccini et al (2016) described the association between arthrogryposis and microcephaly in newborns presumed to have been infected by congenital ZIKV. The Arkabane virus, arboviruses of the Simbu group of the family Bunyaviridae, may cause abortions, stillbirths, premature births, and deformed or anomalous bovine, caprine, and ovine fetuses or neonates, including brain malformations and arthrogriposis. There is no evidence that humans can be infected by Akabane virus.

The rare and unusual arthrogrypotic joints did not result from abnormalities of the joints themselves and are likely to be of neurogenic origin, with chronic involvement of central and peripheral motor neurons, leading to intrauterine fixed postures and consequently deformities. Electromyography findings suggest chronic involvement of peripheral motor neurons. In severely weak muscles the activation of the motor units was severely reduced suggesting reduced central drive and involvement of central motor neurons. The pattern of peripheral denervation seems to correspond to the pattern of central involvement, what could suggest a component of trans-synaptic degeneration. The spine MRI show thinning of the spinal cord, most severe in the thoracic region, affecting the ventral cord preferentially, corroborates to the findings of electromyography. An intraoperative macroscopic evaluation under anesthesia is also consistent with electromyography and image findings.

It is interesting that cortical development abnormalities and arthrogryposis are found together also in syndromes resulting from in utero misoprostol exposure and in The Syndrome of Perisylvian Polymicrogyria. Mlakar et al, describe an autopsy and neuropathological findings, and indicate a possible location of the virus in neurons.

Multiple hypotheses have been proposed to explain the presence of congenital joint contractures in some patients with abnormalities of brain development; these include an in utero vascular insult affecting both central and peripheral nervous systems, a common developmental mechanism of altered migration in both the brain and spinal cord, and a direct central effect of the brain malformation on fetal joint contractures.
Based on our neurophysiological observations and the literature finding, we suggest two possible mechanisms, tropism for the neurons, with involvement of peripheral motor neurons and central motor neurons or related with vascular disorders.

Congenital Zika Syndrome should be added to the differential diagnosis of congenital infections and arthrogryposis. Further research is needed to study the neurological abnormalities behind arthrogryposis with a larger number of cases, including histopathology of deceased cases or stillbirths. As we do not know the evolution of congenital Zika infection as its potential implications, it is important an orthopedic followup of these children, even those who had the first orthopedic evaluation considered as standard, because they could develop musculoskeletal deformities secondary to neurological impairment, central and/or peripheral, as it occurs in patients with cerebral palsy and other chronic encephalopathies.

Contributors: All authors contributed to the clinical assessment in their own speciality, to the conception and design or analysis and interpretation of the data and to the draft of final version.

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Competing interests: All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: All investigations described were conducted as part of a clinical protocol approved by the Brazilian government and analyzed retrospectively; no investigations were conducted for research reasons and, therefore, neither ethical approval nor informed consent was necessary.

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Legends of tables and figures:

Table 1: Summarizes the characteristic of the cases.

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<tr>
<th>Patient</th>
<th>Sex</th>
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<th>HC**</th>
<th>Microcephalus</th>
<th>Craniofacial disproportion</th>
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**Tabla 2:** Deformities more often found in the study patients.

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<tr>
<th>Joint Deformities</th>
<th>Number of Patients</th>
<th>TOTAL 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilateral (n)</td>
<td>Bilateral (n)</td>
</tr>
<tr>
<td>clubfoot</td>
<td>3 50%</td>
<td>3 50%</td>
</tr>
<tr>
<td>Dislocation or subdislocation of the knee</td>
<td>1 33.33%</td>
<td>2 66.67%</td>
</tr>
<tr>
<td>Contracture in flexion of the knees</td>
<td>2 40%</td>
<td>3 60%</td>
</tr>
<tr>
<td>Dislocation of the hips</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Contracture in flexion of the wrist and fingers</td>
<td>1 16,66%</td>
<td>5 83,34%</td>
</tr>
<tr>
<td>Camptodactyly (hands)</td>
<td>1 16,66%</td>
<td>5 83,34%</td>
</tr>
<tr>
<td>thumb adducted</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flexion contracture elbow</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Extension contracture elbow</td>
<td>2 50%</td>
<td>2 50%</td>
</tr>
<tr>
<td>Contracture in adduction and internal rotation of the shoulders</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(1) Percentage of deformities considering the total of 7 patients.
Table 3: Electromyography findings

<table>
<thead>
<tr>
<th>Initials</th>
<th>Sensory nerve action potentials</th>
<th>Compound motor action potentials</th>
<th>Motor unit action potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>r/l Med, r Uln, r mPl: normal</td>
<td>L Med, r Uln: Low amplitude</td>
<td>r/l EDC, r/l TA: neurogenic</td>
</tr>
<tr>
<td>2</td>
<td>r Med, r mPl: normal</td>
<td>r Tib, r/l Fib: low amplitude</td>
<td>r EDC, r/l TA: neurogenic</td>
</tr>
<tr>
<td>3</td>
<td>L Uln, r mPl: normal</td>
<td>l Uln, r Tib: low amplitude</td>
<td>l EDC, l TA: neurogenic</td>
</tr>
<tr>
<td>4</td>
<td>l mPl: normal</td>
<td>r/l Tib, r/l Fib: low amplitudes</td>
<td>r/l EDC, TA: neurogenic</td>
</tr>
<tr>
<td>5</td>
<td>r Med, r mPl: normal</td>
<td>L Tib: normal; r/l Fib: low amplitude</td>
<td>r/l EDC, r/l TA: neurogenic</td>
</tr>
<tr>
<td>6</td>
<td>r/l Med, r Uln: normal</td>
<td>l Med, r Uln: normal</td>
<td>r BB, r/l EDC, r/l TA: normal</td>
</tr>
<tr>
<td>7</td>
<td>r/l Med, r/l Uln, r/l mPl: normal</td>
<td>l Med/Tib, r Uln/Fib: low amplitude</td>
<td>r/l EDC, r/l TA, l MG: neurogenic</td>
</tr>
</tbody>
</table>

Legends of figures:

**Figure 1:** Observe the images of joint deformities. (A) contracture in flexion of the knee; (B) hiperrecurvato knee - dislocation; (C) clubfeet; (D) deformities of chirodactyls - observe camptodactyly of 2, 3 and 4 fingers; (E) joint contractures in the lower and upper limbs without involvement of the trunk.
Figure 2: Images of the hips (A, B, C) and knees (D). (A) MRI - observe bilateral dislocation of the hips, epiphyseal core (small arrow) and dysplastic acetabulum (large arrow); (B) Computed tomography 3D where show bilateral dislocation of the hips; (C) Radiographs AP in the hips where is observed radiographic parameters compatible with dislocation of the hips: breaking the arc Shenton, epiphysis hypoplastic proximal femoral, acetabular index of 35° and proximal localization of the proximal femoral epiphysis right and left located on the side and bottom quadrant Ombredane; (D) X-ray shows knee subluxation (arrows).

Figure 3: Magnetic resonance imaging of the spinal cord and the brain of a baby who has arthrogryposis. Sagittal T2 weighed Fast Imaging Employing Steady-state Acquisition (FIESTA) (A) shows an apparently reduced spinal cord thickness (short arrows) and mega cisterna magna (long arrow). On the axial reconstruction of T2 weighed FIESTA (B), we can observe reduction of the medullary cone ventral roots (long arrows) compared with dorsal roots (short arrows). Sagittal T2 weighed imaging (C) shows hypogenesis of the corpus callosum (long white arrow), enlarged cisterna magna (long black arrow), enlarged IV ventricle (short black arrow) and pons hypoplasia (short white arrow). Axial T2 weighed imaging (D) shows pachygyria in the frontal lobes (black arrows) and severe ventriculomegaly, mainly at the posterior part of the lateral ventricles. Axial susceptibility weighed imaging (E and F) shows some hypointense small dystrophic calcifications (white arrows) in the junction between cortical and subcortical white matter (E) and in the midbrain (F).

Figure 4: Intraoperative aspect of the adductor longus muscle hip of a study of patients with irreducible dislocation of the hips before surgery. Observe the color characteristic changes of fibrofatty infiltration like in the initial phase of the neuropathies.