Orthopedic abnormalities in patients presenting with Congenital Zika syndrome: an analysis of 157 patients

Anormalidades ortopédicas em pacientes com síndrome Congênita do Zika: análise de 157 pacientes

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ABSTRACT

Purpose: The study aimed to describe the characteristics of orthopedic examination in patients with microcephaly associated with congenital infection by the Zika virus, the epidemiological profile, the characteristics of orthopedic disorders, and their relationship to pregnancy. Methodology: We reviewed 157 medical records of infants with microcephaly treated at AACD/PE. All the patients had positive serology for Zika virus infection, and those with positive serology for another condition or incomplete records data were excluded. Physical exam findings were divided into primary and secondary orthopedics abnormalities and were analyzed by the prevalence. Hypothesis testing for proportions was utilized to verify possible associations between the time of infection (before or after the first trimester) and the presence or absence of musculoskeletal abnormalities present at birth. Results: After reviewing patient data, we found a prevalence of abnormal orthopedic findings in 66.88%. The lower limbs were the most commonly affected area. We also found an abnormally high incidence of arthrogryposis and developmental hip dysplasia, which was the most prevalent one. Most patients presented with more than one deformity. We also found that the association between the time of infection at an early gestational age and the presence of orthopedic deformities was statistically significant. Conclusion: The present research described the main orthopedic alterations found in the physical exam of newborns with microcephaly associated with congenital infection by the Zika Virus, giving special attention to alterations in the lower limbs, and in line with other congenital infections, the gestational period that has the greatest potential to cause changes in the normal development of the child is the first trimester.

Keywords: microcephaly, Zika virus, orthopedic disorders, congenital infections.
RESUMO
Objetivo: O estudo teve como objetivo descrever as características do exame ortopédico em pacientes com microcefalia associada à infecção congênita pelo vírus Zika, o perfil epidemiológico, as características dos distúrbios ortopédicos e sua relação com a gravidez.
Metodologia: Foram revisados 157 prontuários de lactentes com microcefalia atendidos na AACD/PE. Todos os pacientes apresentaram sorologia positiva para infecção pelo vírus Zika, sendo excluídos aqueles com sorologia positiva para outra afecção ou dados incompletos nos prontuários. Os achados do exame físico foram divididos em anomalias ortopédicas primárias e secundárias e analisados pela prevalência. Testes de hipóteses de proporções foram utilizados para verificar possíveis associações entre o momento da infecção (antes ou depois do primeiro trimestre) e a presença ou ausência de anomalias musculoesqueléticas presentes ao nascimento.
Resultados: Após análise dos dados dos pacientes, encontramos uma prevalência de achados ortopédicos anormais em 66,88%. Os membros inferiores foram a área mais acometida. Também encontramos uma incidência anormalmente alta de artrogripose e displasia do desenvolvimento do quadril, que foi a mais prevalente. A maioria dos pacientes apresentava mais de uma deformidade. Verificamos também que a associação entre o tempo de infecção em idade gestacional precoce e a presença de deformidades ortopédicas foi estaticisticamente significativa. Conclusão: A presente pesquisa descreveu as principais alterações ortopédicas encontradas no exame físico de recém-nascidos com microcefalia associada à infecção congênita pelo Zika Vírus, dando especial atenção às alterações nos membros inferiores, e em consonância com outras infecções congênitas, o período gestacional que tem maior potencial para causar alterações no desenvolvimento normal da criança é o primeiro trimestre.

Palavras-chave: microcefalia, vírus Zika, doenças ortopédicas, infecções congênitas.

1 INTRODUCTION

Despite passing mostly unnoticed by international medical authorities since its isolation in a Ugandan monkey in 1947 [1], the zika virus rose quickly to infamy in 2015 due to its association with the sudden epidemics of microcephaly first detected in Brazil [2,3]. In May 2016, in a special report to the new england journal of medicine, The Center for Disease Control officially recognized the causality relationship between congenital zika virus infection and microcephaly [4].

In contrast to other congenital infections such as Rubella and Cytomegalovirus [5], clinical aspects found in congenital zika syndrome (CZS) have been shown mainly to reflect prenatal neurological damage due to death and abnormal development of neural cells [6,7]. The underlying mechanism for this specific vulnerability of fetal brain cells is yet to be fully explained, however, there is in vitro evidence that ZIKV sequesters MS1 protein which is highly important for neural development [8].

However, the literature on orthopedic disorders secondary to SCZ is limited and lacking in information, which contrasts with the findings of current practice in the care of these patients. This disparity motivated the research team to review institutional records.
This detailed Zika virus orthopedic manifestation document facilitates effective communication between healthcare team members, providing an objective and reliable record on which to base clinical decisions and adjust treatment strategies in a personalized way. Ultimately, the documents on the orthopedics manifestations of patients with congenital Zika virus syndrome promote continuous improvement in care, the generation of scientific evidence, and the advancement of knowledge about this complex condition, seeking to provide a better quality of life and well-being of the patients.

The present study describes and quantifies the prevalence of orthopedic abnormalities in 157 patients with (CZS) and verifies possible association between the time of maternal infection and the presence of orthopedic deformities.

2 MATERIALS AND METHODS

A cross-sectional retrospective study was carried out between January and October of 2022 by reviewing medical records from patients being treated between 2016 and 2021 at the Association of Assistance to the Disabled Child (AACD), a Brazilian reference center for neuromuscular disorders.

Following Ministry of Health protocols, every child with suspected microcephaly (head circumference two standard deviations below the curve for age and sex) [8] was referred to a pediatric infectious disease center and a rehabilitation center. The following clinical tests and exams were conducted based on clinical practice procedures.

Every child underwent neurologic and orthopedic evaluation by qualified physicians, which would order, when deemed necessary by physical examination, imaging exams: radiography, non-contrast brain tomography (CT), or non-contrast brain magnetic resonance imaging (MRI), high-definition joints ultrasonography (focusing mainly on cartilage, synovia, pericapsular structures, and muscular tissue around joints), nerve conduction studies, and needle electromyography.

As to rule out infection by Cytomegalovirus (CMV), toxoplasmosis, rubella, HIV, and syphilis, the main etiologies of microcephaly associated with intracranial calcifications [10], we performed paired serology for IgM and IgG from samples of both patient and mother. If CMV IgG were present at both laboratory tests, we would utilize urine polymerase chain reaction [11]. Imaging studies were also utilized to rule out differential diagnoses and confirm (CZS).
The exclusion criteria were: lack of orthopedic evaluation, no spinal or appendicular skeleton radiograph, or no large joints ultrasonography. Positive serology for any other congenital infection. Incomplete medical records.

Data was collected using a standard form which was then organized and stored using Microsoft Excel for iOS. The following variables were collected: Sex, birth method, gestation period, gestational age when the mother was struck by exanthematic illness, occipitofrontal circumference both at time of birth and latest, family history of malformations, number of siblings, previous abortion history, ultrasonographic and radiographic imaging abnormalities, and physical exam findings. Physical examination abnormalities were classified as primary abnormalities (arthrogryposis, clubfoot) and secondary orthopedic deformities (muscle contracture, spastic hip, among others).

Through the utilization of the Statistical Analysis System program, Hypothesis testing for proportions was utilized to verify possible associations between the time of infection (before or after the first trimester) and the presence or absence of musculoskeletal abnormalities present at birth. The significance level was set at 5%.

The Research Project was approved by the Brazilian national ethics committee under the registration number 54590016.0.0000.0085.

3 RESULTS

A total of 157 with positive serology for zika virus patients were selected, yielding 250 musculoskeletal abnormalities. Forty-six (18.4%) were primary orthopedic congenital alterations, in this case, normally presented patients diagnosed with arthrogryposis, the rest presenting with musculoskeletal abnormalities commonly associated with spasticity-increasing pathologies, such as cerebral palsy. The most frequent congenital deformities observed in those patients are the congenital teratological dislocation of the hips followed by clubfoot deformity, camptodactyly, and knee subluxation or dislocation. The latter abnormalities are normally found in patients affected by arthrogryposis, coexisting in the same patient. In contrast, isolated deformities such as clubfoot, evolutionary hip dysplasia, and other isolated congenital deformities seemed not to have a greater incidence if compared to the population in general. Appendicular and axial skeletal X-ray images of patients showed no long bone or spinal dysplasia. The site with the highest prevalence of abnormality is the hip (29.94%) (Figure 1). There was a specially high rate of limitation of hip abduction, probably secondary to increased spasticity, a hallmark of congenital zika syndrome [12]. Hemimelia, transverse limb deformities, defects of duplication, and other bone dysostoses were not found. (Tables 1 and 2)
Table 1: Secondary orthopedic deformities found in CZS patients

<table>
<thead>
<tr>
<th>Secondary Orthopedic Deformity</th>
<th>N</th>
<th>% of 157</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLEXION DEFORMITY OF THE WRIST</td>
<td>10</td>
<td>6.37%</td>
</tr>
<tr>
<td>ADDUCT POLLEX</td>
<td>13</td>
<td>8.28%</td>
</tr>
<tr>
<td>FLEXION DEFORMITY OF FINGERS</td>
<td>4</td>
<td>2.55%</td>
</tr>
<tr>
<td>BILATERAL GENU VALGUM</td>
<td>7</td>
<td>4.46%</td>
</tr>
<tr>
<td>UNILATERAL GENU VARUM</td>
<td>2</td>
<td>1.27%</td>
</tr>
<tr>
<td>BILATERAL GENU VARUM</td>
<td>4</td>
<td>2.55%</td>
</tr>
<tr>
<td>POLENGAR EMPALMADO</td>
<td>4</td>
<td>2.55%</td>
</tr>
<tr>
<td>FLAT FOOT+FLEXIBLE VALGUS</td>
<td>15</td>
<td>9.55%</td>
</tr>
<tr>
<td>PES PLANUS</td>
<td>7</td>
<td>4.46%</td>
</tr>
<tr>
<td>KNEE DIPLOE</td>
<td>10</td>
<td>6.37%</td>
</tr>
<tr>
<td>POLLEX ADDUCTUS</td>
<td>3</td>
<td>1.91%</td>
</tr>
<tr>
<td>TIBIA VARA</td>
<td>2</td>
<td>1.27%</td>
</tr>
<tr>
<td>DYSMETRIA</td>
<td>7</td>
<td>4.46%</td>
</tr>
<tr>
<td>REDUCTIBLE PES EQUINUS</td>
<td>3</td>
<td>1.91%</td>
</tr>
<tr>
<td>ELBOW DIPLOE</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>ELBOW (FLEXION LIMITATION)</td>
<td>2</td>
<td>1.27%</td>
</tr>
<tr>
<td>ADDUCTION EXTERNAL ROTATION</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>SHOULDER DEFORMITY</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>PES EQUINUS VALGUS</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>METATARSUS ADDUCTUS</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>KNEE FLEXION DEFORMITY</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>PES VALGUS</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>PÉ EQUINUS ADDUCTUS</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>PÉ EQUINUS VARUS</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>IRREDUCTIBLE PES EQUINUS CAVUS VARUS ADDUCTUS</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>SUPINE PES EQUINUS ADDUCTUS</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>IRREDUCTIBLE PES EQUINUS</td>
<td>1</td>
<td>0.64%</td>
</tr>
<tr>
<td>MUSCLE CONTRACTURE</td>
<td>28</td>
<td>17.83%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>105</td>
<td>66.88%</td>
</tr>
</tbody>
</table>

Source: From Authors, 2023.

Table 2: Primary orthopedic deformities found in CZS patients

<table>
<thead>
<tr>
<th>Primary Orthopedic Deformity</th>
<th>N</th>
<th>% of 157</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNILATERAL HIP DISLOCATION</td>
<td>6</td>
<td>3.82%</td>
</tr>
<tr>
<td>BILATERAL HIP DISLOCATION</td>
<td>8</td>
<td>5.10%</td>
</tr>
<tr>
<td>PES ADDUCTOVARUS</td>
<td>4</td>
<td>2.55%</td>
</tr>
<tr>
<td>HIP Dysplasia</td>
<td>32</td>
<td>20.38%</td>
</tr>
<tr>
<td>PES EQUINOS ADDUCTOVARUS</td>
<td>2</td>
<td>1.27%</td>
</tr>
</tbody>
</table>

Source: From Authors, 2023.
FLAT FOOT+CALCANEUS VALGUS 1 0.64%
KNEE SUBLUXATION 1 0.64%
BILATERAL FEMORAL NECK DYSPLASIA 1 0.64%
CLUBFOOT 4 2.55%
ROCKER FEET 1 0.64%
ELBOW PRONOSUPINATION RESTRICTION 1 0.64%
CAMPTODACTYLIA 4 2.55%
FINGER HYPOPLASIA 1 0.64%
TOE HYPOPLASIA 1 0.64%
TOTAL 67 42.68%

Source: From Authors, 2023.

In total, there were 250 musculoskeletal abnormalities: 44 (17.6%) in the upper limbs, 150 (60%) in the lower limbs, and 56 (22.4%) in the trunk and abdomen. (Figure 2)

We also found that the association between the time of infection at an early gestational age and the presence of orthopedic deformities was statistically significant (p=0.008635). (Table 3)

<table>
<thead>
<tr>
<th>Time of mother infection</th>
<th>Prevalence of abnormalities (1:100)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>2nd trimester</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>3rd trimester</td>
<td>5%</td>
<td>p=0.008635*</td>
</tr>
</tbody>
</table>

*Hypothesis testing for proportions
Source: From Authors, 2023.
4 DISCUSSION

This present work’s sole focus is on orthopedic deformities other than arthrogryposis\(^1\). The orthopedic findings in CZS patients seem to mirror those of classical arthrogryposis and cerebral palsy, suggesting a bimodal distribution in the incidence of deformities, firstly at the womb, due to fetal hypomotility syndrome, followed thereafter by deformities appearing after birth, due to increased spasticity and muscle tone, mimicking cerebral palsy. Orthopedic deformities are just one of the various pathologic findings in congenital zika syndrome [13,14].

However, this early incidence of deformities contrasts markedly with the natural history of cerebral palsy, pointing to a more severe involvement in CZS, in line with the knowledge base of the medical literature about the pathophysiology of this disease, which affects both the central nervous system as the peripheral.

Due to the limitations of a cross-sectional study, we could not establish a temporal relationship between CZS and the incidence of orthopedic deformities and between CZS and timing of the incidence of orthopedic deformity. Studies following up on this population will be needed to comprehend the pathogenesis of limb deformities in zika patients fully.

The study findings, when compared with the existing literature, assert the need for a multidisciplinary approach in caring for CZS patients, aiming for the same goals, such as the prevention of pain, fixed deformities, and optimizing opportunities for self-care and communication. The feasibility of such goals will be determined with future studies focusing on the long-term neurological outcomes of CZS patients, which are still underway. Regarding gestational age during infection and incidence of congenital disabilities are similar to those in the previous works [15].

5 CONCLUSION

The present research described the main orthopedic alterations found in the physical exam of newborns with microcephaly associated with congenital infection by the Zika Virus, giving special attention to alterations in the lower limbs. In line with other congenital infections, the gestational period that has the greatest potential to cause changes in the normal development of the child is the first trimester, so the congenital infection caused by the Zika Virus must include the differential diagnosis of perinatal congenital infections and the follow-up should be carried out by a multidisciplinary team.
REFERENCES


