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ORIGINAL RESEARCH

Hip Dysplasia in Congenital Zika Syndrome: A 5 Year Follow-Up

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Abstract

Background: Children with Congenital Zika Syndrome (CZS) usually have severe neurological impairment with extrapyramidal involvement mainly spastic quadriplegia, so we believe they would have the same spasticity-related abnormalities, such as high prevalence of hip subluxation, as children with other aetiologies of cerebral palsy (CP). The aim of this study was to investigate hip status and describe the radiographic measures, Reimer's migration percentage (MP) and acetabular index (AI) in infants diagnosed with CZS.

Methods: 29 infants with CZS's medical records and pelvis' radiography were analysed. 22 patients had consecutive exams taken for comparison. The sample was divided into two groups, in the first group, X-rays were obtained from children aged 24 months or younger, in the second group, X-rays were obtained from the same children aged more than 24 months, a second measure.

Results: The mean MP was 24.7% and AI was 27.4° for the right hip, 21.4% and 27.4° for the left hip in the first group. The mean MP was 53.2% and AI was 27.4° for the right hip, 53.9% and 26.8° for the left hip, in the second measure. MP was statically different for the first and second measures ($p = 0.001$), AI was not statically different ($p > 0.44$).

Conclusion: AI was abnormal in children 2-years-old and younger, there was a high femoral head migration and hip subluxation in children older than 2 years, the changes were bilateral and symmetrical; thus hip surveillance should be used for the follow-up of patients with CZV.

Keywords

Congenital Zika syndrome, Hip dysplasia, Radiographic evaluation

Abbreviations

CZS: Congenital Zika Syndrome; CP: Cerebral Palsy; MP: Reimer's Migration Percentage; AI: Acetabular Index; GMFCS: Gross Motor Function Classification System

Introduction

Congenital Zika syndrome (CZS) exhibits various clinical features that are a direct consequence of severe intracranial volume loss and neurological damage. Severe microcephaly with partially collapsed skull; thin cerebral cortices with subcortical calcifications; macular scarring and focal pigmentary retinal mottling; congenital contractures, marked early hypertonia and symptoms of extrapyramidal involvement are remarkable components of this syndrome [1].

Investigations state that children with extrapyramidal involvement in cerebral palsy (CP), mainly with spastic quadriplegia, have a high prevalence of hip subluxation. Children with spasticity affecting all four limbs and those who cannot walk are most at risk. The occurrence of painful hip dislocation is directly related to the severity of neurological involvement and the child's ambulatory status [2]. Many studies reported that children with CZS presented a higher incidence of hip dislocation and hip dysplasia [3-5]. Authors have noted that hips may begin to displace as early as 18 months of age; therefore, it is advisable that the hips should be examined radiologically

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at 18 months of age in all children with bilateral cerebral palsy and at 6-to-12-monthly intervals thereafter [6].

Radiographic surveillance of the hip is used to monitor the hip status in children with CP using standardized supine anteroposterior (AP) radiographs of the pelvis to include both hip joints. Radiographic measures are the basis of hip surveillance, Reimer's migration percentage (MP) is the most widely accepted and reproducible measurement for hip displacement and the acetabular index (AI) is a measure to evaluate the extent of the acetabular dysplasia [7].

Noticing that children with CZS usually have severe neurological impairment with extrapyramidal involvement mainly spastic quadriplegia, we believe they would have the same spasticity-related abnormalities, such as high prevalence of hip subluxation, as children with other aetiologies of cerebral palsy (CP). For this reason, we requested pelvic radiographs at an early age for all these children as it is advised in monitoring hip surveillance for children with CP, particularly GMFCS III and above.

The purpose of this study was to describe accurately the radiographic measures MP and AI in infants diagnosed with CZS and suggest the prevalence of hip dislocation, subluxation and migration in this sample.

Methods

A retrospective study based on data and pelvis radiological studies from all infants with CZV treated at the paediatric neurology outpatient clinic of the Clinical Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil. The study was approved by the Research Ethics Committee/UPE (CAAE 56522216.0.0000.5440), including parents' consent and it was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsink) for experiments involving humans.

A standard form was used to collect clinical and complementary investigation information, including pelvis radiographies. All information was obtained as part of the clinical protocol or as the result of clinical indication.

A total of 29 medical records of infants with CZS were analysed. Pelvis' radiography and medical records assessment were performed in 22 patients that had earlier radiography in order to make a comparison with the new X-ray to compare MP and AI.

Inclusion criteria

Individuals with either a confirmed or a presumed diagnosis of the disease and with congenital microcephaly. The diagnosis of CZS was based on negative investigations for other congenital infections and other causes of microcephaly, together with neuroimaging characteristics, such as the presence of malformations of cortical development and calcification of the cortical-subcortical junction. When possible, Zika virus was confirmed based on a positive result for either IgM antibodies or Reverse Transcription Polymerase Chain Reaction (RT-PCR), from cerebrospinal fluid or serum.

Exclusion criteria

Patients without parents´ consent, patients with positive investigations for other congenital infections and other causes of microcephaly.

Classifications and measurements

Functional levels were classified by neurologists according to the expanded and revised version of the Gross Motor Function Classification System (GMFCS) [8].

Standardized supine anteroposterior (AP) X-rays of the pelvis to include both hip joints were taken in supine position, the pelvis as symmetrical as possible, hips in neutral abduction/adduction. The Hilgenreiner's line was drawn through the superior aspect of the open triradiate cartilage and Perkin's lines through the lateral acetabular margin and perpendicular to Hilgenreiner's line. The MP was calculated as the percentage of ossified femoral head that lies lateral to Perkin's line. The acetabular index (AI) measures the extent of the acetabular dysplasia. AI was the angle in degrees between the slope of the acetabular roof and Hilgenreiner's line [9]. All measurements were recorded by the same orthopaedist. The same hospital's computer software for storing patient radiographic records was used to measure and calculate different angles and distances to minimize measurement errors.

Statistical analyses

The numerical continuous data were analyzed using SPSS 11.0 software calculating the mean, median, quartiles, standard deviation and range. The differences between means were calculated for MP and AI for paired samples with Wilcooxon non-parametric test, the Confidence Interval (CI) 95% of the difference before and after was presented.

Results

In total, 29 children with CZS, born from 11/30/2015 to 11/11/2016, were reported to database. For appreciation, the descriptive values for clinical characteristics are in Table 1.

Radiographic assessment of the hip

Pelvis' radiography of 22 patients aged 2-years-old or less was assessed (1st measure), another radiograph was obtained from the same children but they were older than 24 months (2nd measure). For children aged 24 months or younger, the mean MP was 24.7% and AI was 27.4° to the right hip, 21.4% and 27.4° the left hip.

Table 1: Clinical characteristics.

Patient demographic	Class/grade	N	%
Sex	Male	13	45
	Female	16	55
CP subtype			
	Spastic quadriparetic	27	93
	Spastic hemiparetic	2	7
GMFCS			
	II	2	6
	III	1	3
	IV	17	60
	V	9	31
Clinical features			
	Microcephaly	28	96
	Microcephaly and arthrogryposis	1	4
Total	29	29	100

System CP: Cerebral Palsy; GMFCS: Gross Motor Functional

Table 2: Study radiographs, statistics for MP (%).

Measure	Hip	N	Min.	Interquartile range	Median	Mean	SD	Max.	Mean CI 95%
1st	Left	22	0	28	21	21.36	4.12	84	12.79-29.94
	Right	22	0	13	24.5	24.73	2.84	46	18.82-30.64
2nd	Left	22	23	61	37.5	53.95	6.28	100	40.88-67.03
	Right	22	25	48	40	53.18	5.96	100	40.79-65.68

1st measure: X-rays obtained in children aged 24 months or younger; 2st measure: same children, X-rays taken older than 24 months, MP: Migration Percentage; CI: Confidence Interval

Table 3: Study radiographs, statistics for AI (degrees).

Measure	Hip	N	Min.	Interquartile range	Median	Mean	SD	Max.	Mean CI 95%
1st	Left	22	20	8	28	27.4	1.01	36	25.34-29.56
	Right	22	20	8	29	27.82	0.99	35	25.74-29.89
2nd	Left	22	16	4	26.5	26.86	0.95	35	24.88-28.84
	Right	22	19	16	27	27.45	0.98	35	25.41-29.50

1st measure: X-rays obtained in children aged 24 months or younger; 2nd measure: Children older than 24 months; AI: Acetabular Index; CI: Confidence Interval

Table 4: Median of the differences between measures evaluated in the 1st X-ray and in the 2nd X-ray. Wilcoxon test to paired sample.

X-rays measures	Hip	Sig.	The null hypothesis can be rejected (p-value 0.05)
Migration Percentage (%)	Left	0.001	Yes
	Right	0.001	Yes
Acetabular Index (angle)	Left	0.441	No
	Right	0.628	No

The significance level is 0.05.

When they were older than 24 months, the mean MP was 53.2% and AI was 27.4º to the right hip, 53.9% to and 26.8° the left hip. For appreciation, the comparative values are in Table 2 and Table 3.

MP was statically different for the first and second measures, no significant differences in AI were found between measures, CI 95%. For appreciation, the comparative values are in Table 4.

Discussion

In this study, we analyzed the prevalence of hip dysplasia, hip migration and subluxation/luxation in

children with CZS at all functional levels. Based on our findings, hip abnormal acetabular index was present in early ages and hip subluxation was highly prevalent in children older than 2 years. This supports the notion that the frequency hip migration increases rapidly during early childhood in this population.

CZS is characterized by microcephaly and cerebral malformations. This disease is also associated with many signs and symptoms, such as visual and auditory alterations and other features that are uncommon in congenital infections, such as arthrogryposis [10].

For this report, microcephaly was defined as head circumference (HC) (also known as occipitofrontal circumference) more than 2 SD below the mean for gestational age and sex, according to the Fetal International and New Born Growth Consortium for the 21st Century (INTERGROWTH-21st) for fetal and new born growth and the World Health Organization Child Growth Standards for infants). All infants had microcephaly.

Although a frequently observed clinical sign was arthrogryposis, reported in many articles [4,11-17], in this sample, only one child was born with arthrogryposis.

Hip displacement in cerebral palsy (CP) is highest between the ages of two and five years in children with severe limitation of gross motor function, and occurs predominantly in children with the spastic or dyskinetic subtypes [18]. In this study, 90% of the children with CZV were classified as GMFCS IV and V and they were quadripatetic, confirming the severity of motor impairment in CZS.

The most widely accepted and reproducible measurement for hip displacement is Reimer's migration percentage (MP). MPs of 4 per cent correspond to the upper limit for the »optimal« hips in children above the age of 4 years [19]. Nevertheless, in this study, children 2-years-old and below had abnormal hips (mean MP 21-24%) and all children above the age of 2 years, had at least one hip subluxation (mean MP 53%). We must consider a standard error of ± 10% for the MP based on an estimate of the errors accordingly to Reimer [20].

The acetabular index (AI) has long been utilized as one of the key radiographic parameters in the evaluation of acetabular morphology in DDH. It is considered useful both in research as an outcome measure and also clinically to monitor and guide treatment, such as to determine the need for surgical intervention. In normal newborns, the acetabular index averages 27.5 degrees, at six months 23.5 degrees and at two years, 20 degrees [19]. In our sample, measures obtained for AI was 27° in children younger than 2 years, which did not change with child's growth. This can be considered a signal that the hips had some degree of dysplasia at an early age and higher risk for dislocation. Indeed, femoral head migration, defined as the difference between two instantaneous MPs determined at two different times, was noticed in this study.

Hip displacement in CP has already been demonstrated to contribute to high rates of pain and impaired health-related quality of life in no ambulant children with CP. The condition originally studied was spastic cerebral palsy, but it was found that the principles demonstrated corresponded fully, to what is known, in the case of other, diseases, therefore radiographic surveillance of the hip is very important to monitor the hip status in children with CP.

The children with CZS of this study were assisted by a multidisciplinary team with the physical therapy and occupational therapy. They also underwent periodic application of botulinum toxin and were assisted by the paediatric orthopaedics group.

This study has limitation, more statistical inferences could not be performed considering the small and homogenous sample, but we can suggest that hip surveillance is an important tool to be used for the follow-up of patients with CZV.

Conclusion

Despite the small sample, we observed that our patients presented a high hip subluxation incidence that is usually presented in children with severe neurological impairment. Femoral heads' migration and high incidence of hip subluxation was also observed in this 5-years follow-up. Children 2-years-old and younger had abnormal AI, which did not change with the child's growth and and all children older than 2 years had at least one hip subluxation. Thus, this study contributed to suggest a pattern of hip involvement in CZS patients with microcephaly.

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Author Contributions

Dr. Caldas and Dr. Magalhães conceived the study and were involved in study design, acquisition of data, analysis of data and manuscript preparation; Dr. De Lucca was involved in the interpretation of data and revision of the manuscript. All authors read and approved the final version of the paper.

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