Oral and maxillofacial conditions, dietary aspects, and nutritional status of children with congenital Zika syndrome

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Objective. The aim of this study was to investigate oral and maxillofacial outcomes in children with congenital Zika syndrome (CZS) and the presence of nonnutritive sucking habits, functional habits, and features related to breastfeeding and nutrition of these children.

Study Design. We conducted a cross-sectional study with 45 children with CZS and 50 healthy controls in Sergipe state, Brazil, from February 2018 to June 2018. Demographic and clinical data, including breastfeeding and feeding data, were obtained for each child. Additionally, oral and maxillofacial evaluation was performed.

Results. Low weight (prevalence rate [PR] 8.33; 95% confidence interval [CI] 2.02−34.45), nonexclusive breastfeeding up to 6 months (PR 1.56; 95% CI 1.18−2.08); mouth breathing (PR 3.46; 95% CI 1.83−6.52); difficulty in swallowing (PR 6.00; 95% CI 2.53−14.25); and excessive salivation (PR 4.81; 95% CI 2.18−10.62) were more frequent in children with CZS. Children with CZS were more likely to have abnormal insertion of the upper labial frenulum (PR 7.04; 95% CI 2.23−22.20); ogival palate (PR 3.70; 95% CI 1.63−8.40), dental enamel defects (PR 2.22; 95% CI 1.05−4.69); and delayed dental eruption (PR 8.89; 95% CI 1.16−68.32) compared with healthy children.

Conclusions. Children with CZS had a higher frequency of problems related to breastfeeding, low weight, and oral and maxillofacial abnormalities compared with healthy children. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:71−77)

Zika virus (ZIKV) is an arbovirus of the Flaviviridae family and typically inhabits tropical and subtropical areas, mainly in Africa and Asia.[1] In 2013−2014, a ZIKV epidemic was recorded in French Polynesia,[2] and it rapidly spread across the Pacific nations and South America.[3] The first autochthonous case of ZIKV transmission in Brazil was recorded in May 2015, followed by an unexpected increase in the number of neonates born with microcephaly, especially in the Northeast region.[4-6]

Studies have shown strong evidence for an association between congenital ZIKV infection and microcephaly,[7-9] which is defined by the measurement of occipital−frontal circumference that is at least 2 standard deviations (SDs) below the mean for age and gender or less than the third percentile for age and gender.[10] Congenital microcephaly is the most striking manifestation of a set of signs and symptoms present in children born to mothers infected by ZIKV during pregnancy. Recently, the spectrum of anomalies that is both consistent and unique in fetuses and infants with presumed or laboratory-confirmed ZIKV infection has been called *congenital Zika syndrome* (CZS) and includes severe microcephaly, thin cerebral cortices with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures, marked early hypertonia, and symptoms of extrapyramidal involvement.[11]

Most studies available on CZS reported on neurodevelopmental,[12-15] auditory,[16,17] and visual[18,19] outcomes, with less attention paid to the oral and maxillofacial outcomes. A limited number of case series have found that children with CZS can present with delayed dental eruption,[20] enamel defects,[21] mouth breathing,[22] and dysph-

Statement of Clinical Relevance

Zika virus infection during pregnancy is associated to feeding disorders, deleterious oral functional habits, and oral and maxillofacial abnormalities. These findings support the need for long-term multiprofessional treatment of children with congenital Zika syndrome.

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gia.[23] Recognition of the CZS phenotype may ensure appropriate and timely evaluation and follow-up of the affected infants.[11] This study aimed to describe the oral and maxillofacial outcomes in children with CZS and investigate the presence of nonnutritive sucking habits, functional habits, and features related to breastfeeding and nutrition of these children.

MATERIALS AND METHODS

Study design and setting

This was a cross-sectional study conducted in 3 rehabilitation centers of the Brazilian Unified Health System (SUS) in Sergipe, Northeast Brazil. Sergipe is one of the poorest states in Brazil with a Human Development Index of 0.665 and has a population of approximately 2 million. During the ZIKV epidemic in Brazil, 138 cases of CZS were diagnosed in Sergipe, which had one of the highest CZS incidence rates, with 24 cases for every 10,000 live births.[24]

Participants

We included 45 children who had been diagnosed with CZS and were receiving periodic monitoring and treatment in 3 rehabilitation centers of the SUS in Sergipe between February 2018 and June 2018. Children with CZS presented head circumferences that were at least 2 SDs below the mean for the age and gender, as well as typical alterations indicating congenital infection, including intracranial calcifications, cerebral ventricles dilation or changes in the posterior fossa, and other clinical signs revealed by diagnostic imaging methods or ZIKV identification in laboratory tests. The control group included 50 healthy children selected from the study base population by using convenience nonrandom sampling. We tried to match the groups in terms of mother and infant characteristics. Participants were well balanced with regard to study arms and characteristics.

Data sources

Data were collected through a face-to-face interview with the mothers in the health care centers; the participants answered structured questions on demographic and socioeconomic conditions (age, marital status, educational level, and family income) and the general health characteristics of the children, including gender and age. The standardized interviews were performed in a nonjudgmental atmosphere by well-trained interviewers to reduce interviewer bias. Examiners were calibrated in a pilot study to ensure the accuracy of diagnosis and to standardize the procedures. A substantial interexaminer reliability was found (kappa agreement value >0.9).

Physical examinations of the children were conducted in a place with adequate lighting and with the presence of the mothers. Anthropometric measurements were obtained by 2 trained nurses. Weight in kilograms was measured by using a pediatric weighing scale set to 0. The children were weighed without shoes, and the weight of the clothing was not deducted. Height was measured by using an anthropometer, with the children in the supine position, with hips and knees extended. Head circumference was measured by using a nondistensible tape measure positioned over the occipital bone and the eyebrow arch. The anthropometric measurements were analyzed by using the World Health Organization (WHO) Anthro Software (version 2.0.4).

Oral and maxillofacial evaluations were performed by 2 dental surgeons while the children remained in their mother's lap. The examinations were carried out by visual observation, with the examiners using personal protective equipment, and displacement of the oral structures with the aid of a wooden spatula. The extraoral examination was performed by comparing the 2 hemifaces to detect any differences in size and shape. The intraoral examination included evaluation of the shape and integrity of the gingival tissue, insertion of the lingual and labial frenulum, palate shape and depth, buccal mucosa, tooth integrity, and eruption sequence.

The same criteria were adopted by the examiners during the observations, thus reducing the risk of reaching different conclusions.

Outcomes and measures

The outcomes of interest included were as follows:

1. *nonnutritive sucking habits, functional habits, and excessive salivation:* nonnutritive sucking habits (NNSH) included pacifier and finger sucking, and functional habits included mouth breathing and difficulty swallowing of solid, semisolid, or liquid foods. Mouth breathing was recorded from direct observation of the patient and parent reports, as previously described in the literature about patients with developmental disabilities.[25,26] Difficulty swallowing was assessed on the basis of the subjective perceptions of mothers regarding their children's behavior. Dysphagia was defined subjectively as the sensation of a delay in the transit of a liquid or solid bolus during the oropharyngeal or esophageal stages of swallowing.[27] The severity of drooling was recorded by the mothers using the Drooling Rating Scale (DRS), which consists of a subjective report of saliva production using a 5-point scale (1 = never drools; 5 = drools profusely). Excessive salivation was considered to be present if the mothers reported moderate (wet lips and chin) to profuse (wet clothing, hands, tray, and objects) drooling.[28]
2. *Breastfeeding, diet, and nutritional status:* The aspects related to breastfeeding and diet were recorded according to WHO's *Guiding Principles*

for Complementary Feeding of the Breastfed Child.[29] We collected information about breastfeeding after birth, exclusive breastfeeding until age 6 months, and use of supplements (iron, vitamins, and minerals), enteral nutrition (gastrostomy or jejunostomy), and the daily intake of ultraprocessed food, including carbonated soft drinks, chocolate, yogurt and other dairy beverages, biscuits, cakes, instant noodles, and bread. Nutritional status was assessed by measuring the body mass index (BMI), which is defined as weight divided by height squared (kg/m^2), according to age and gender, as recommended by the WHO. A z-score 2 or less SDs was used as the low-weight cutoff point.[30,31]

3. *Disorders of tooth development and eruption, presence of dental caries, and oral and maxillofacial conditions:* Disorders of dental development included enamel defects and tooth size and shape anomalies (concrescence, fusion, and gemination; macrodontia and microdontia). Enamel defects were evaluated according to the Developmental Defects of Enamel (DDE) Index,[32] which classifies the defects in terms of hypomineralization (qualitative defect of enamel characterized by changes in translucency) or hypoplasia (quantitative defect with reduction of the enamel thickness). Detection of carious lesions in the primary teeth was made through visual inspection. We evaluated the initial (first visual change in enamel); moderate (either localized enamel breakdown or an underlying dark shadow from dentin); and extensive stages of caries (distinct cavitation exposing visible dentine).[33] Oral and maxillofacial anomalies included the presence of microcephaly,[10] hypoplasia of the middle third of the face (characterized by flattening of the facial profile as a result of lack of forward development of the nose and maxilla); ankyloglossia (short, tight, lingual frenulum); and papillary insertion of the upper labial and ogival palate (high-arched palate).

To evaluate tooth eruption disorders, children were grouped into categories according to their age and on the basis of the developmental chronology of the human dentition: 0 to 6 months (edentulous); 7to 12 months (eruption of incisors); 13 to 24 months (eruption of the first primary molar); and older than 24 months of age (eruption of second primary molars).[34]

Statistical analysis

We used χ^2 and Mann-Whitney U tests for between-groups comparisons with significance level set at 0.05. The magnitude of the association between CZS and the outcomes of interest was expressed as the prevalence ratio (PR) and their 95% confidence intervals (95% CI), which were calculated by Poisson regression method with robust variance estimates.[35,36] Analyses were performed with R software (version 3.2.3; http://r-project.org/).

Ethical considerations

The study was approved by the Ethics Committee of the Federal University of Sergipe and was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the parents or guardians of children before the procedures.

RESULTS

Maternal and infant sociodemographic characteristics, as well as the cephalic perimeters, weights, and heights of children, are presented in Table I. Most mothers were younger than 30 years of age; were either married or in a stable relationship; had only primary education; and worked in up to 3 minimum-wage per month (~US $250). All children were younger than 24 months of age at the time of assessment, and most of them were females. Between-group differences were observed in the cephalic perimeter ($P < .001$) and weight ($P < .001$).

Table I. Characteristics of mothers and children with congenital Zika syndrome

Variable	*CZS (N = 45)*	*Controls (N = 50)*	*P value*
	n (%)	*n (%)*	
Mothers' characteristics			
Age in years, median (IQR)	24.0 (21.0, 31.0)	25.5 (22.0, 31.3)	.876
Marital status			
Married/ wedded	40 (88.9)	40 (80.0)	.366
Not married	5 (11.1)	10 (20.0)	
Schooling			
Primary education	22 (48.9)	17 (34.0)	.267
High school	14 (31.1)	17 (34.0)	
Undergraduate	9 (20.0)	16 (32.0)	
Family income	27 (60.0)	5 (10.0)	
0−3 minimum-wage	43 (95.6)	44 (88.0)	.273
>3 minimum-wage	2 (4.4)	6 (12.0)	
Children characteristics			
Age in months, median (IQR)	17.0 (16.0, 18.0)	17.0 (12.3, 20.0)	.340
Gender			
Female	24 (53.3)	30 (60.0)	.654
Male	21 (46.7)	20 (40.0)	
Head circumference, median (IQR)	38.8 (37.0, 40.6)	48.0 (47.0, 49.0)	<.001
Weight (kg), median (IQR)	8.4 (7.8, 10.0)	10.6 (10.0, 12.0)	<.001
Length (cm), median (IQR)	77.0 (72.3, 80.3)	78.0 (72.0, 83.0)	.899

CZS, congenital Zika syndrome; *IQR,* interquartile range.

Table II. Nonnutritive sucking habits, functional habits, and report of excessive salivation in children with congenital Zika syndrome

Variable	CZS	Control	PR	95% CI
	n (%)	n (%)		
Pacifier use	24 (53.3)	19 (38.0)	1.40	0.90−2.20
Finger sucking	2 (4.44)	4 (8.0)	0.55	0.11−2.89
Mouth breathing	28 (62.2)	9 (18.0)	3.46	1.83−6.52
Difficulty swallowing	27 (60.0)	5 (10.0)	6.00	2.53−14.25
Excessive salivation	26 (57.8)	6 (12.0)	4.81	2.18−10.62

CI, confidence interval; *CZS,* congenital Zika syndrome; *PR,* prevalence ratio.

Presence of mouth breathing (PR 3.46; 95% CI 1.83−6.52); difficulty in swallowing (PR 6.00; 95% CI 2.53−14.25); and excessive salivation (PR 4.81; 95% CI 2.18−10.62) were more common in children with CZS than in healthy children (Table II). With regard to breastfeeding and dietary aspects, nonexclusive breastfeeding until age 6 months (PR 1.56; 95% CI 1.18−2.08); use of iron supplementation (PR 1.82; 95% CI 1.29−2.57); vitamins and minerals (PR 1.42; 95% CI 1.02−1.99); and ultraprocessed food intake (PR 1.28; 95% CI 1.01−1.62) were also more common among children with CZS. In 7 children with CZS (15.6%) enteral nutrition through gastrostomy or jejunostomy was used. Higher prevalence of low weight defined as z-score 2 SDs or less (PR 8.33; 95% CI 2.02−34.45) was also observed among children with CZS (Table III).

Microcephaly and hypoplasia of the middle third of the face were observed only in children with CZS. Higher frequency of abnormal insertion of the upper labial frenulum (PR 7.04; 95% CI 2.23−22.20); ogival palate (PR 3.70; 95% CI 1.63−8.40); enamel defects (PR 2.22; 95% CI 1.05−4.69); and eruption delay (PR 8.89; 95% CI 1.16−68.32) was found among children with CZS compared with the control group (Table IV). In both groups, neither the presence of natal or neonatal teeth nor changes in the shape of dental structures were observed. No carious lesions were identified in any of the evaluated patients.

Table III. Breastfeeding and eating aspects of children with congenital Zika syndrome

Variable	CZS	Control	PR	95% CI
	n (%)	n (%)		
Not breastfed at birth	5 (11.1)	3 (6.0)	1.85	0.47−7.31
Nonexclusive breastfeeding up to age 6 months	38 (84.4)	27 (54.0)	1.56	1.18−2.08
Iron supplementation	36 (80.0)	22 (44.4)	1.82	1.29−2.57
Vitamin and mineral supplementation	32 (71.1)	25 (50.0)	1.42	1.02−1.99
Gastrostomy or jejunostomy	7 (15.6)	0 (0)	–	–
Intake of ultraprocessed foods	38 (84.4)	33 (66.0)	1.28	1.01−1.62
Low weight (z-score ≤2 SD)	15 (33.3)	2 (4.0)	8.33	2.02−34.45

CI, confidence interval; *CZS,* congenital Zika syndrome; *PR,* prevalence ratio; *SD,* standard deviation.

Table IV. Developmental and eruption disorders of teeth, presence of dental caries and oral and maxillofacial anomalies in children with congenital Zika syndrome

Variable	CZS	Control	PR	CI 95%
	n (%)	n (%)		
Microcephaly	45 (100.0)	0 (0)	–	–
Hypoplasia of the middle third of the face	8 (17.8)	0 (0)	–	–
Short lingual frenulum	1 (2.2)	3 (6.0)	0.37	0.04−3.43
Abnormal insertion of the upper labial frenulum	19 (42.2)	3 (6.0)	7.04	2.23−22.20
Ogival palate	20 (44.4)	6 (12.0)	3.70	1.63−8.40
Dental enamel defects	16 (35.6)	8 (16.0)	2.22	1.05−4.69
Delay in dental eruption	8 (17.8)	1 (2.0)	8.89	1.16−68.32

CI, confidence interval; *CZS,* congenital Zika syndrome; *PR,* prevalence ratio.

DISCUSSION

CZS encompasses a spectrum of signs and symptoms observed in infants who were exposed to ZIKV during the gestational period.[37] The emerging CZS phenotype seems to be associated with ZIKV neurotropism and includes severe microcephaly, macular lesions, craniofacial malformations, and significant neurologic impairment.[38] In addition, it has been reported that children with CZS present severe motor impairment and low functional capacity,[39] which can lead to dyspraxia, with implications for breastfeeding, feeding (chewing and swallowing), and child development.[40] In this study, we investigated the oral and maxillofacial outcomes in children with CZS, as well as the presence of nonnutritive sucking habits, functional habits, and features related to breastfeeding and nutrition of these children.

In the present study, we found that the nonexclusive breastfeeding up to age 6 months was more frequent among children with CZS, which may be related to the underdevelopment of the maxilla, a decrease in the tonus of the perioral and chewing muscles, changes in lip posture, and tongue movement difficulties. A similar condition has also been observed in children with cerebral palsy, who usually are also exclusively

breastfed for a shorter period.[41-43] Although there is evidence showing an association between breastfeeding problems and the development of nonnutritive sucking habits (NNHS) in children with cerebral palsy,[44,45] no differences were found in the use of pacifier use or finger sucking among the groups in this study. However, the high prevalence of pacifier use among children in the present study may be related to the development of an artificial habit to satisfy the need for sucking or a cultural norm encouraged by parents who give pacifiers to children at early ages.[46]

It has been suggested that in children with CZS, mouth breathing and dysphagia may also be associated with hypotonia of the labial and facial muscles and with habitual projection of the tongue between teeth and out of the oral cavity.[22] In addition, these children can have reduced pharyngeal motility, tactile hypersensitivity, and gastroparesis, contributing to the development of swallowing disorders.[23] In the present study, the prevalence of swallowing difficulties was 6-fold higher among children with CZS, reflecting the spectrum of the neurologic manifestations of the disease. In a case series presented by Leal et al.,[23] severe dysphagia, with an increased risk of aspiration, was observed in 8 of 9 children with CZS who had.

Problems with oral motor dysfunction, including those related to breastfeeding and swallowing observed in children with CZS, may lead to serious nutritional complications. Recently, it has been shown that children with CZS present worsening of their nutritional status during the first 2 years of life, especially in relation to age-adjusted height and cephalic circumference.[39,40] In addition, there has been a high prevalence of inappropriate nutritional practices, such as low food diversification, consumption of ultraprocessed products, and low lipid intake among these children.[47] In the present study, among children with CZS, we observed higher prevalence of high intake of ultraprocessed foods, as well as higher prevalence of low weight and need for micronutrient supplementation, compared with the control group. The use of gastrostomy or jejunostomy was also observed in about 15% of the children with CZS. Access to the stomach lumen and the upper small intestine obtained through tube placement has been indicated for patients unable to eat orally and who require long-term nutritional support.[48] For these children, adequate nutritional support can restore linear growth, normalize weight, decrease irritability and spasticity, reduce the frequency of hospitalization, and improve their overall health and quality of life.[49]

Excessive salivation has been associated with comorbidities, such as cerebral palsy, severe mental retardation, and hypoxic encephalopathy. It affects the well-being of children with disabilities and demands more work from caregivers.[50] The results of this study demonstrated a high prevalence of excessive salivation in children with CZS. According to Cavalcanti et al.,[22] excessive salivation in children with CZS may be related to the continued use of medications for seizure disorders commonly present in these individuals. Studies have shown that in children with cerebral palsy, dysfunctional oral motor control appears to be responsible for the presence of excess saliva in the mouth, although salivary flow is similar to that observed in healthy children.[51,52] Because the neural control mechanisms of salivary secretion are complex[53] and the brain lesions involved in congenital ZIKV infection are severe, further studies are needed to identify the factors associated with excessive salivation in these children.

There is emerging evidence that in children with CZS, there may be higher prevalence of oral and maxillofacial alterations, including delayed teeth eruption and enamel defects, palatine narrowing, ankyloglossia, abnormal insertion of the upper labial frenulum, inadequate tongue posture and micrognathia.[21,54] Similar results were observed in the present study, suggesting that the neurologic changes resulting from ZIKV infection lead to a delay in the child's physical development, with negative repercussions in the oral and maxillofacial region. In addition, ZIKV infection of the cephalic neural crest cells[55] may contribute to the development of these craniofacial anomalies and dental alterations.

It has been demonstrated that neural crest cells are a population of embryonic cells that contribute to the formation of various craniofacial structures, including teeth.[56,57] There is evidence that congenital viral infections, such as cytomegalovirus infection, may impair the distribution of dentin's amelogenin, enamelin, and sialoprotein and lead to the development of enamel defects.[58] However, the mechanisms by which ZIKV induces enamel defects are still unknown. In addition, although carious lesions in children with CZS were not identified in the present study, guidance for oral and nutritional hygiene and close monitoring are necessary because enamel defects and high consumption of cariogenic foods increase the risk of demineralization and the development of dental caries.

Our study findings need to be considered in light of some of its limitations: (1) lack of access to radiographic and cephalometric evaluation data, which limited our ability to analyze the dental structures and skeletal problems; (2) absence of data on videofluoroscopic swallowing and, thus, diagnostic information about the pharyngeal phase of swallowing; (3) lack of data on electromyographic assessments, which limited our ability to examine the state of muscle tone and spasticity; (4) a potential bias in the reporting of mothers, especially regarding breastfeeding and feeding; and (5) selection of participants by using a nonprobability sampling method and the use of bivariate

analysis to summarize the relationship between groups. Although we have used an appropriate ratio measure, a multivariate setting was not analyzed. Laboratory tests, other anthropometric and body composition measures, and assessments of the nutritional needs of these children should be performed in future studies. Despite these limitations, this study provided valuable data that may help understand the spectrum of CZS.

CONCLUSIONS

In children with CZS, there is higher prevalence of functional habits, problems related to breastfeeding, ultraprocessed food intake, and low weight compared with healthy children. Hypoplasia of the middle third of the face, abnormal insertion of the upper labial frenulum, ogival palate, enamel defects, and eruption delay are also more common among children with CZS.

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