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# ORAL FINDINGS IN CHILDREN WITH CONGENITAL ZIKA SYNDROME: A CASE SERIES

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**ABSTRACT:** To describe the oral findings observed in a case series of children with Congenital Zika Syndrome (CZS). The patients attending in a Basic Unit of Health from a municipality in northeast Brazil were evaluated by means of anamnesis and clinical oral examination. All procedures were carried out by a single researcher. The final sample consisted of 12 subjects (six males and six females), with ages ranging from 36-40 months old. It was observed higher percentage of children that tooth brushing twice a day and with nocturnal bottle feeding habit. The most prevalent oral findings were presence of visible biofilm, bruxism and delayed tooth eruption. The results suggest that some oral alterations might be part of the phenotypic spectrum of CZS. This study can potentially help dentists to understand the importance to establishment early diagnosis and intervention of oral conditions, with a multidisciplinary approach focused on health promotion and individual well-being.

**KEY WORDS:** Microcephaly; Oral health; Oral manifestations; Zika virus infection.

## ACHADOS BUCAIS EM CRIANÇAS COM A SÍNDROME CONGÊNITA ZIKA: UMA SÉRIE DE CASOS

**RESUMO:** O objetivo deste trabalho é descrever os principais achados orais observados em uma série de casos de crianças com a Síndrome Congênita do Zika (CZS). Os participantes foram selecionados dentre os pacientes atendidos em uma Unidade Básica de Saúde de um município do Nordeste do Brasil, os quais foram avaliados (anamnese e exame clínico oral) por um único pesquisador. A amostra final foi composta por 12 sujeitos (seis homens e seis mulheres), com idade entre 36 e 40 meses. Observou-se maior percentual de crianças que escovam os dentes duas vezes ao dia e utilizam mamadeira noturna. Os achados bucais mais prevalentes foram a presença de biofilme visível, bruxismo e retardo na erupção dentária. Os resultados sugerem que algumas alterações bucais podem fazer parte do espectro fenotípico da CZS e ressalta a importância de um diagnóstico precoce e uma abordagem multidisciplinar focada na promoção da saúde e no bem-estar individual.

**PALAVRAS-CHAVE:** Infecção por Zika virus; Manifestações bucais; Microcefalia; Saúde bucal.

## INTRODUCTION

At the end of 2015, the local medical community of northeastern Brazil observed an increase in cases of microcephaly in newborns. This epidemic has captured the attention of World Health Organization and the world's media because it was raised a possible association between Zika virus (ZIKV) infection in pregnancy and fetal malformations[1]. On November 11th 2015, Brazil declared a public health emergency and began undertaking clinical, laboratory and ultrasound analysis of affected newborn babies and their mothers[2].

With the advancement of researches, in 2016 it was confirmed the causal relationship between ZIKV infection in pregnant women and the occurrence of severe abnormalities in the newborn who contracted the virus in utero, known as Congenital Zika Syndrome (CZS). The full phenotypic spectrum of this syndrome remains to be elucidated, but it is known that it may include brain, ocular, hearing and musculoskeletal abnormalities[3]. Although congenital microcephaly has been a hallmark of intrauterine infection by the ZIKV, accepted as the tip of the iceberg, this condition is considered a sign of extensive encephalopathic changes. It is important to emphasize that the absence of microcephaly at birth does not exclude the diagnosis of CZS.

The investigations itself has made progress on case reporting and definition of suspected, confirmed and discarded cases, new therapeutic approaches and lifelong care. Protocols, manuals and patient flows were created; financial and human resources were allocated to qualify care and define paths in the health care network. Many knowledge related to the confrontation of this situation were produced, unprecedented in the world. It was a gain for the country, in terms of management and qualification of professionals and preparation of immediate and mediating responses, with the support of national and international bodies.

However, even with the adoption of strategies to limit ZIKV transmission through the control and reduction of vector mosquito, the continuous number of cases of CZS throughout the national territory, drawing the attention of experts and general population. According to data from the Brazilian Ministry of Health, in 2018 a total of 2.819 cases of newborns and children with alterations in growth and development possibly related to ZIKV infection were confirmed. Of these cases 1.843 is concentrated in the northeast region of the country[4]. According to Cavalcanti[5]children with microcephaly resulting from CZS present oral characteristics, such as alteration of muscle tone (hypotonia or hypertonia), that can interfere with the sucking, swallowing, lip-forming dynamics and breathing. Therefore, considering that ZIKV has a nervous tissue tropism, that the dental blade is formed from cells that originate from the neural crest and that infections at the beginning of gestation may have especially serious repercussions for the baby,[6] it is essential the dentists to know how to recognize possible oral manifestations and their limiting factors in care, in order to adequately proceed with the dental treatment and rehabilitation of the children[7-9].

Once that there is no description in the dental literature of a protocol that guides clinical care or scientific studies that reliably describe orofacial and dental alterations in these children,[5] the objective of this study is to describe and discuss the oral findings observed in a group of children with CZS from a municipality in northeast Brazil.

## METHOD

This is an observational, descriptive, cross-sectional study of a group of patients described as a case series. A convenience sample was evaluated from a population of patients attending in a Basic Unit of Health considered reference center for dental care from children with CZS of the city of Maceió, Brazil. The municipality, capital of the State of Alagoas, has estimated population of 1.012,387 inhabitants, infant mortality rate of 12.18 cases per 1.000 live births and Human Development Index of 0.721. Since 2015 Alagoas State accounts for 105 confirmed cases of children with evidence of congenital ZIKV infection, of which eight evolved to fetal or neonatal death[4].

As inclusion criteria, only those patients aged more than 3 years old (≥ 36 months), born and resident in Maceió and with confirmed diagnosis of CZC were

selected. Debilitating health status impeding the proposed clinical evaluation was the exclusion criteria.

Data were obtained, between February and April 2019, from parents/legal guardians anamnesis as well as from oral examination of children. Collections procedures were carried out by a single researcher, who was previously trained and calibrated.

Detailed anamnesis including questioning about age, gender, oral hygiene practices and dietary habits was performed. Each child was examined while seated on a dental chair or lying on the parents' lap, with the aid of artificial light. Depending on the degree of cooperation, the child was immobilized by their caregiver. The nomenclature adopted by the American Dental Association[10] was used for tooth identification.

Clinical evaluation was conducted with the help of an assistant to note the following variables: dental caries experience/dmft index (number of decayed, missing and filled primary teeth;[11]presence of visible biofilm; malocclusions[12]; oral deleterious habits; enamel defects of opacity (enamel (a qualitative defect of the enamel characterized by changes in translucency) or hypoplasia (a quantitative defect with reduction in the enamel thickness); soft tissue lesions and others oral manifestations such as dental eruption alterations, palatal shape, gingival alterations and dental anomalies (changes in crown shape as twinning, fusion, accessory cuspids and invaginated tooth, changes in size as micro and macrodontia, and number of changes as anodontia, hypodontia/oligodontia and hyperdontia/supernumerary teeth)[13].

After the collection, data were entered in the database for analysis of absolute and relative frequency and then descriptively evaluated.

The project was submitted to and approved by the local Research Ethics Committee (CAAE:57837016.4.0000.0039). Parents or legal guardians of research subjects read and signed a declaration of free and informed consent. For guaranteeing complete confidentiality and anonymity, the participants were named as "subject" and a number (Subject 1, Subject 2…).

**RESULTS**

From an initial sample of 35 patients with CZS, only 12 were eligible according to the inclusion and exclusion criteria. The final sample consisted of six males and six females children with ages ranging from 36–40 months old (mean = 37.4, standard error = 1.11). Data pertaining to factors related to oral hygiene practices demonstrated that eight subjects(66.6%) tooth brushing twice a day and all them brushing with fluoride toothpaste. In relation to dietary habits, nocturnal bottle feeding (66.6%) was most prevalent than breastfeeding ≥12 months (8.33%) (Table 1).

Table 2 shows the oral findings of the patients. It was observed that only one child evaluated had already experienced dental caries (dmft group = 1.5, standard error = 4.97). Visible biofilm was detected in eight cases(66.6%) whereas two subjects (16.6%) presented anterior open-bite as malocclusion. With regard to oral deleterious habits, one could find two types, with the most frequent ones being bruxism (58.3%) and pacifier sucking (41.6%). In the analysis of enamel defects, opacity and hypoplasia were observed associated in two subjects (16.6%). Delayed tooth eruption was presented in seven children (58.3%) and others oral manifestations as narrow and deep palate and gingival hyperplasia were detected in five them (41.6%). No patients had soft tissue lesions or cleft palates. Dental anomalies, as change in crown shape, was observed in one child (8.3%) (Figures 1-3).

**Table 1.** Sample characterization and factors related to oral hygiene practices and dietary habits

| Subject | Age (months) | Gender | Daily frequency of toothbrushing | Fluoride toothpaste | Breastfeeding ≥12 months | Nocturnal bottle feeding |
|---|---|---|---|---|---|---|
| 1* | 37 | M | 2 | + | - | - |
| 2 | 36 | M | 2 | + | - | + |
| 3 | 38 | M | 2 | + | - | + |
| 4 | 40 | M | 2 | + | - | + |
| 5 | 38 | M | 1 | + | + | - |
| 6 | 38 | M | 3 | + | - | + |
| 7 | 36 | F | 3 | + | - | + |
| 8 | 36 | F | 2 | + | - | + |
| 9* | 38 | F | 1 | + | - | - |
| 10* | 37 | F | 2 | + | - | - |
| 11 | 37 | F | 2 | + | - | + |
| 12 | 38 | F | 2 | + | - | + |
| Absolute (relative frequency) | | | | 12 (100%) | 1 (8.33%) | 8 (66.6%) |

**Table 2.** Oral findings in 12 children with Congenital Zika Syndrome

| Subject | dmft | Visible Biofilm | Malloclusion | Oral Deleterious Habits | | Enamel Defects | | Others Oral Manifestations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Anterior open-bite | Bruxism | Pacifier sucking | Opacity | Hypoplasia | Delayed tooth eruption | Narrow and deep palate | Gingival hyperplasia | Dental anomalies |
| 1 | 0 | - | - | - | + | - | - | + | - | - | - |
| 2 | 0 | + | - | - | + | + | + | - | + | - | - |
| 3 | 0 | + | - | + | - | + | + | + | - | - | - |
| 4 | 0 | - | - | + | - | - | - | - | - | - | - |
| 5 | 18 | + | - | + | - | - | - | + | + | + | - |
| 6 | 0 | + | - | - | - | - | - | - | - | - | - |
| 7 | 0 | - | + | + | + | - | - | - | + | + | - |
| 8 | 0 | + | + | + | + | - | - | + | + | + | + |
| 9 | 0 | + | - | + | - | - | - | + | + | - | - |
| 10 | 0 | - | - | - | - | - | - | + | - | + | - |
| 11 | 0 | + | - | - | - | - | - | + | - | + | - |
| 12 | 0 | + | - | + | + | - | - | - | - | - | - |
| Absolute (relative frequency) | | 8 (66.6%) | 2 (16.6%) | 7 (58.3%) | 5 (41.6%) | 2 (16.6%) | 2 (16.6%) | 7 (58.3%) | 5 (41.6%) | 5 (41.6%) | 1 (8.3%) |

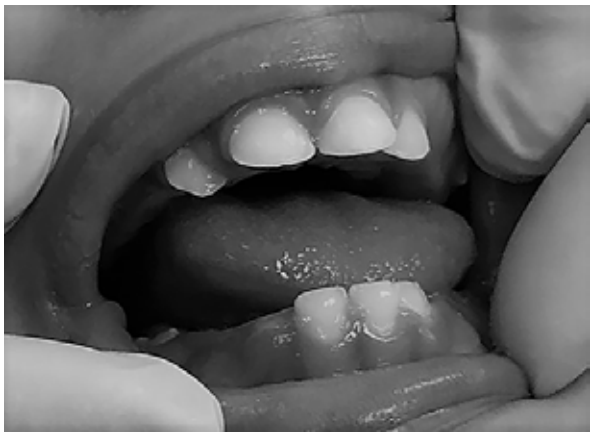

**Figure 1**. Frontal view exhibiting delayed tooth eruption in a child with Congenital Zika Syndrome (subject 1). Note the absence of teeth 82 and 83

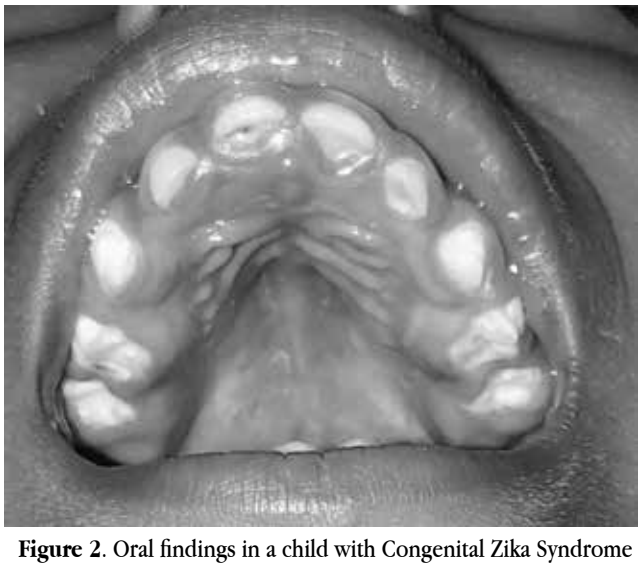

**Figure 2**. Oral findings in a child with Congenital Zika Syndrome (subject 5): presence of dental caries, narrow and deep palate and gingival hyperplasia

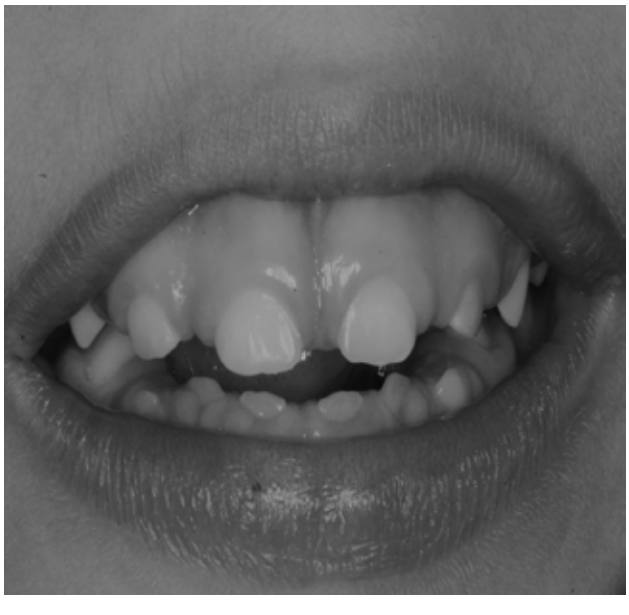

**Figure 3**. Oral findings in a child with Congenital Zika Syndrome (subject 7): anterior open-bite and generalized gingival overgrowth.

## DISCUSSION

This article brings a series of cases wich all children with CZS had at least one of the evaluated oral findings. Of these patients, one presented 18 decayed teeth. This child, despite being 38 months old, was the only one in the sample to prolonged demand breastfeeding. In addition, tooth brushing was performed once a day, reflecting the clinical aspect of visible biofilm.

Early Childhood Caries (ECC) may be defined as the presence of ≥1 decayed (noncavitated or cavitated lesions), missing (due to caries) or filled tooth surfaces in any primary tooth in a child ≤71 months of age[14]. It is known that ECC is disproportionately found in certain segments of the childhood population[15] and this question remains uncertain regarding children with CZS, since there are no published studies for a comparative analysis.

Over the last decades, researchers from several countries have analyzed a possible association between various risk factors and ECC. Kirthiga *et al*.[16]. systematically reviewed the literature and identified that the two strongest risk factors associated with ECC were the presence of enamel defects and high levels of mutans streptococci. Significant secondary risk factors were the presence of dentinal caries, frequent consumption of sweetened foods, poor oral hygiene and the presence of visible plaque.

In other systematic review[17], the breastfeeding up to 2 years of age does not increase risk of ECC as compared with breastfeeding up to 1 year. According to the authors, providing access to fluoridated water and limiting sugars in bottles and complementary foods are justified approaches to ECC prevention. In the present study, nocturnal bottle feeding habit was absent in only four children. Of these, three underwent surgical gastrostomy for enteral nutrition.

For areas without access to public water supplies to fluoridate, as the municipality of Maceió, exposure to fluoride via alternative means is required[17]. As would be expected, because it is a group of children assisted by a reference center for dental care, all performed tooth brushing with fluoride toothpaste. American Dental Association[18] recommends brush teeth using fluoride toothpaste twice per day (morning and night) in an

amount not more than a smear or the size of a grain of rice from eruption of the first tooth to age 3 years.

In this study, although parents/legal guardians report adequate oral hygiene practices, eight of 12 children (66.6%) met visible biofilm. The explanation for these results may be theoretically related to the difficulty of the caregivers to effectively perform tooth brushing of the child, probably due to muscle tone and undesirable behaviors, such as irritability and crying.

As for the enamel defects, another aspect observed was the presence of teeth with opacity and hypoplasia, especially in the anterior teeth, in only two caries-free children. This finding tends to disagree with the literature[6]which points that children with microcephaly by CZS present with greater enamel defects in the primary teeth and this increases the risk of dental caries.

Gerlach et al.[19]reported that nutritional changes, vascular perfusion disorders, as well as disorders in calcium metabolism can cause enamel defects, being observed the most severe in children with shorter gestation time, neonatal asphyxia, low birth weight and malnutrition. So, it is important to investigate whether children with the CZS were born at term, normal weight and nourished. Waes and Stöckli[20] consider that the type and form of defect are related to the chronological development of the affected teeth as well as the duration (acute or chronic) and the intensity of the etiologic factors on teeth in formation.

Data on frequency of oral deleterious habits indicated that nine (75%) subjects exhibited at least one parafunction. The majority of the patients had signs and/or symptoms of bruxism (58.3%), which represent a challenge for dental care. This result surpasses those of Siqueira *et al.*[6] who reported bruxism in 20.3% of children with CZS. Furthermore, there is also a considerable discrepancy in the literature regarding the prevalence of bruxism in normoreactive children (5.9% to 49.6%) and these variations present possible associations with the diagnostic criteria used in the studies[21].

According to the minimal criteria of the American Academy of Sleep Medicine[22], childhood bruxism is characterized by involuntary nocturnal and/or diurnal activity of the masticatory muscles, rhythmic or spasmodic, with parental reporting of the child's grinding or clenching of teeth. Several etiological factors may be associated with this disorder, such as local, systemic, hereditary, psychosocial and behavioral factors[23,24], which tends to make it more difficult their identification particularly in individuals with disabilities.

Due to the broad spectrum of clinical and neurodevelopmental features in children with sequelae of ZIKV infection, the evaluation of psychological risk factors for bruxism, such as stress and anxiety, will depend on professional experience. Initially, the dentist needs to collect from the caregivers as much information as possible through the anamnesis, since the children cannot verbalize their feelings. Another strategy should be focused on the detection of neurological disorder that could account for the abnormal movements of the mouth and jaw during sleep. The cases studied present chronic irritability and convulsions in different intensities and frequencies. In this context, it is important to communicate with the neurologist to analyze the need for adjusting doses of anticonvulsant drugs in the presence of bruxism associated with the report of constant agitation of the child.

Another oral characteristic found in studied children was the presence of anterior open-bite. According to a recent study[25] the sucking habits increase over jet, reduce overbite and increase open-bite prevalence. The authors emphasize that for the first 3-4 years of life, the damage is more limited to the previous part and at least two years of non-nutritional sucking habits are necessary to produce specific effects on occlusion. Thus, in our research, it would be precocious to point out the relationship between pacifier sucking and the malocclusion detected, because of the five children with the habit installed, only two (16.6%) had anterior open-bite. In addition to this environmental factor, it is also necessary to consider the influence of other causes, such as heredity or a possible dental-facial characteristic of syndrome.

Among children with some congenital deficiency, in particular those with alterations in the Nervous System, it is possible frequently verify altered occlusion parameters. Vellappally *et al.*[26] investigated children with neurological complications, which were included cerebral palsy, Down syndrome and intellectual deficit

and of the 243 samples examined, 93% have a type of malocclusion, requiring orthodontic treatment.

The present study found alterations in palatal shape of five subjects. There is scientific evidence of a strong association between abnormal orofacial growth, as ogival palate, and sleep breathing disorders[27,28]. However, Milanesi *et al*.[29] reported that hard palate depth may not be a mouth breathing consequence and they alerted that pacifier is associated with reduced maxillary intercanine distance and altered resting tongue position, showing that this habit may be associated with alterations in hard palate shape. These confirmations may help explain the prevalence (41.6%) of narrow and deep palate in our research.

In one child (subject 8) was observed discreet change in crown shape of teeth 71 and 81, which present the irregular incisal edge and similar to a cusp tip. At the same time that other dental anomalies were not found in this sample, such changes in size and number of changes. Shrestha *et al*.[30] emphasize that although asymptomatic, these dental anomalies can lead to clinical problems which include compromised esthetics, occlusal interference, accidental cusp fracture, interference with tongue space causing difficulty in speech and mastication. Therefore, understanding the various diagnostic criteria and appropriate treatment strategies are important to patient outcome.

Our findings also involved the presence of gingival hyperplasia in five patients, in the form of a generalized gingival overgrowth or of a gingival fibrosis/edema located in areas of dental eruption. This phenomenon can be related to local factors (biofilm accumulation) as well as a side effect from the administration of some drugs, as anticonvulsants (drug-induced gingival hyperplasia).

Since the eruption of primary teeth occurs over a broad chronological age range, only five studied subjects presented complete deciduous dentition. In this study a tooth was considered to have erupted when any part of its crown was visible in the oral cavity. Delayed eruption eruption was considered when the tooth was not visible in the oral cavity six months after the normal chronology of tooth eruption, proposed by Lunt and Law[31].

Seven children (58.3%) with dental eruption alteration showed absence of at least two deciduous molars. In addition to these teeth, in subjects 1 and 11 one of unerupted anterior teeth was also encountered. Similarly, Siqueira *et al*.[6] reported that children with microcephaly present with greater delays in chronology of eruption of the primary teeth than normoreactive children.

Variations in the eruption timing of primary teeth are considered multifactorial and depending on infants' ethnicity and community, likely in response to variation in environmental, developmental and genetic factors. Some reports[32-34] have associatedpremature delivery and low infant birth weight with eruption delayed of primary teeth. However, when analyzing the impact of gender and prematurity on chronology of first deciduous tooth eruption in children with microcephaly associated with presumed or confirmed ZIKV, Aguiar *et al*.[35] cited that girls had lower average eruption time when compared to boys in both chronological age and age corrected for prematurity.

In this study, some children use parenteral feeding and others present diet of liquid-to-pasty consistency by a nursing bottle. In fact, lack of chewing solid foods may not stimulate gingival mucosal rupture and consequently inhibit dental eruption. This relationship tends to be considered a "two-way street". Literature points out that the delay in the eruption of deciduous dentition can interfere with masticatory patterns and causes feeding problems, contributing to malnutrition and to the development of malocclusion[6,35,36].

The authors acknowledge that the use of convenience sampling and a lack of control group are major limitations of our study. Another constraint was the absence of radiographic information, so that only alterations through anamnestic finding and clinical examination could be evaluated. In this way, we think it is early to point out the oral findings observed in this research as the pathognomonic signs of the syndrome or occasional cases. Therefore, it is suggested the future realization of comparative and longitudinal studies with a larger sample size, besides the need for complementary tests. Panoramic radiographic evaluation may assist in the identification of other dental anomalies and elucidate if cases of delayed tooth eruption are only deviates from norms or absence of tooth germ formation. In cases of

radiographic confirmation of the delay in dental eruption due to gingival fibrosis, the child should be treated as soon as possible by surgically exposing the impacted tooth (ulectomy).

For finish, it is essential to remember that children with CZS are also vulnerable to a range of secondary health conditions, such as respiratory illness, malnutrition and oral diseases, which will persist into adulthood due to the presence of serious neurological damage. Thus, promoting the health of these population is imperative. Health promotion messaging should be mostly directed to family members, as they are usually the main caregiversto children. Therefore, the dentist to be aware of the educational and preventive needs of these patients, providing caregivers with an adequate dental care orientation in the 1st months of life regarding oral hygiene and eating habits, establishing a preventive program with regular consultations, adequate control of the dental biofilm and rational use of fluoride, providing children and their family a better quality of life[5,7,37].

Thus, thinking about caring is first to know the care line and thinking about it for all children with suspected/confirmed microcephaly, regardless of origin. It is also to live with uncertainties related to the behavior of the virus in the body and what the possible changes in child development. Besides as we do not know until when the changes related to congenital infection may arise, it is fundamental to strengthen the surveillance of infant developmental milestones for all children in Primary Care, especially those whose mothers had a history of rash during the gestation. And, within the development of children, oral health is fundamental so that the child grows with healthy teeth and is accompanied by qualified professionals.

## CONCLUSION

Based on the study design, the clinical findings in the studied group, as presence of visible biofilm, bruxism and delayed tooth eruption, lead us to suppose that some oral alterations might be part of the phenotypic spectrum of CZS. Generalizing our results, it could potentially help dentists to understand the importance to establishment early diagnosis and intervention of oral conditions, with a multidisciplinary approach focused on health promotion and individual well-being.

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