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ORIGINAL ARTICLE

Systemic Manifestations, Tooth Eruption and Enamel Defects in Children with Congenital Zika Virus Syndrome: 36-Month Follow-up Case Series

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ABSTRACT

Objective: To describe systemic manifestations, the characteristics related to tooth eruption, and the occurrence of enamel defects in children with Congenital Zika Virus Syndrome (CZS). **Material and Methods:** Prospective case series based on nine children with confirmed CZS diagnosis assisted at a reference center in a municipality in the Northeast Region of Brazil. Through a structured interview directed to mothers, information related to prenatal, delivery, and postpartum periods was collected. Tooth eruption was monitored through clinical examinations for 36 months. The modified developmental defect of enamel index (DDE) was used to identify opacities and hypoplasia. Data were presented using descriptive statistics. **Results:** A high proportion (77.8%) had microcephaly, and 55.5% had low birth weight. Musculoskeletal disorders, swallowing difficulty, and self-injury practices were present in all children. Among the systemic findings, visual impairment (77.8%) and seizures (77.8%) were widely reported. Concerning disorders related to the stomatognathic system, bruxism (66.7%) and difficulty in sucking (33.3%) were present. For most children (77.8%), the deciduous right lower central incisor was the first tooth to erupt (minimum 8 months and maximum 17 months). Enamel defects were diagnosed in only two children (22.2%). **Conclusion:** A wide range of systemic manifestations was observed in children with CZS, including visual impairment and musculoskeletal disorders. Delayed eruption of the first deciduous tooth was also observed. Enamel defects were present in a small proportion of children.

Keywords: Arbovirus Infection; Craniofacial Abnormalities; Microcephaly; Tooth Eruption; Dental Enamel.

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Introduction

Congenital Zika Virus Syndrome (CZS) corresponds to a set of abnormalities observed in fetuses and later manifested in different ways and degrees of severity throughout the development of children. Diagnosable neurological damages include brain calcifications, ventriculomegaly, and cortical malformations due to neuronal migration disorders [1].

Recently, a comparative analysis of samples infected and not infected with Zika Virus (ZIKV) has shown that neonates with CZS present a reduction in collagen, both in RNA and protein levels. In addition, there are numerous single nucleotide polymorphisms in genes encoding collagen, and these findings are associated with osteogenesis imperfecta and arthrogryposis [2].

The most striking clinical feature of CZS is microcephaly [3]. As a consequence of this smaller cranial dimension, newborns have excess skin tissue in some areas of the scalp and face [4] and, in certain situations, oversized features, in view of the occurrence of forehead inclination, prominence of supraorbital ridges, and apparent proptosis. This disease is also associated with the occurrence of strabismus, nystagmus, and reduced and inconsistent response to visual and auditory stimuli, as well as irritability, excessive crying, and epileptic activity [4].

Dysphagia for liquid and solid foods has also been a frequently reported alteration resulting from the infection [5]. In addition, difficulties in suction dynamics and lip sealing also make up the spectrum of manifestations [6].

Delays in the chronology of eruption of deciduous teeth, alterations in the emergence sequence in the oral cavity [7-9], and the occurrence of disturbances in the development of the dental organ in number, shape, and structure indicate a possible role of ZIKV in odontogenesis [8]. Defects in dental enamel development, such as demarcated opacities and hypoplasia, have been reported in the deciduous dentition of children with CZS, evaluated for a period of 18 [9] to 36 months [8]. The distribution of occurrences was more frequent in the anterior teeth of the upper and lower arches, as well as in the posterior teeth located in the mandibular dental arch [8].

In view of the above, the aim of the present study was to describe the systemic manifestations and findings regarding the chronology of deciduous teeth eruption and defects in the dental enamel structure in children with Congenital Zika Virus Syndrome, assisted at a referral center in the state of Paraíba, Brazil.

Material and Methods

Study Design and Participants

This prospective case series was based on nine children. The research was conducted in the municipality of Campina Grande, State of Paraíba, in the Northeast Region of Brazil. The selection of participants took place at the Rehabilitation Specialized Center (RSC), a municipal reference institution for the care of patients with special needs, including children with CZS.

At RSC, 79 children with CZS were registered in 2016. The following inclusion criteria were adopted: children whose mothers/caregivers were 18 years of age or older and had no previous history of treatment for psychiatric disorders; children residing in the municipality of Campina Grande, Brazil; children regularly attended in dental appointments, whose purpose was to monitor the eruption chronology. Therefore, after adopting these criteria, nine children composed the sample of the present investigation.

Data Collection

Prior to carrying out examinations, a researcher conducted a face-to-face interview with the mothers of participating children, aiming to collect information about prenatal care (pregnancy period when Zika infection occurred), delivery (gestational age and type of delivery) and postpartum information (child's sex, weight, head circumference at birth, clinical manifestations related to the spectrum of the syndrome and occurrence of dental eruption disorders) [10]. "Low birth weight" was considered when the child weighed less than 2,500g [11]. In addition, microcephaly was considered present when the head circumference measured -2 standard deviations below the specific mean for sex and gestational age, and the severe subtype was verified in children, with -3 standard deviations below the mean [12].

Clinical Exam

Clinical examinations were performed in a reserved place, with natural light, by a single researcher. The technique used was the knee-knee position, with the infant in the supine position, with the head and part of the trunk on the examiner's lap and the rest of the body on the mother's lap, to allow systematic inspection by quadrant [13]. Children were examined at monthly intervals during the first year of life. In the initial consultation, mothers were instructed to contact the researcher when observing the emergence of a new tooth; however, consultations were rescheduled, after 12 months of age, every three months, for 36 months (2016-2019). A tooth was considered to erupt when any part of its crown was visible in the oral cavity. Eruption chronology and eruption delay were established based on a table modified by Lunt and Law [14]. The modified Developmental Defects of Enamel (DDE) index was used, and according to the macroscopic characteristic of the defect, it was classified into demarcated opacity, diffuse opacity, and hypoplasia [15].

Data Analysis

Data were entered into a database in the SPSS software, version 21.0 (IBM Corporation, Chicago, IL, USA) and presented using descriptive statistics (absolute and percentage distributions, minimum and maximum amplitude, mean and standard deviation).

Ethical Clearance

The study was approved by the Research Ethics Committee of the Federal University of Paraíba, under Opinion No. 2.040.765, being carried out in accordance with Brazilian provisions. All mothers were informed about the objectives and procedures of the study and signed an informed consent form.

Results

Table 1 presents information about the gestational period, delivery, and the neonate. Most children were male (66.7%), with gestational age ranging from 34 to 41 weeks, with a predominance of normal delivery (66.7%) and maternal ZIKV infection in the first trimester of pregnancy (66.7%). Most children were born at term (77.8%), and the mean weight was 2,478g (±0.700). However, more than half of the children (55.5%) had low birth weight, and severe microcephaly was observed in 77.8% of cases.

With regard to clinical manifestations (Table 2), it was found that visual impairment and seizures affected 77.8% of cases, while 55.5% manifested irritability. Musculoskeletal disorders were present in all children, in different ways, from changes in muscle tone (hypertonia or hypotonia) to the occurrence of arthrogryposis multiplex.

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Table 1. Distribution of children affected by the Zika virus according to characteristics of the gestational period and birth.

Case	Gender	Gestational Period of Zika Infection Occurrence	Type of Delivery	Gestational Age	Gestational Age Classification	Birth Weight (g)	Low Birth Weight	Head Circumference at Birth (cm)	Microcephaly/ Classification
1	Female	3rd Trimester	Cesarean	39	Full-term	3,150	No	30	Yes/Severe
2	Female	1st Trimester	Vaginal	34	Pre-term	1,060	Yes	23	Yes/Severe
3	Female	1st Trimester	Cesarean	39	Full-term	2,645	No	29	Yes/Severe
4	Male	1st Trimester	Vaginal	38	Full-term	1,980	Yes	27	Yes/Severe
5	Male	1st and 2nd Trimester	Vaginal	41	Full-term	2,495	Yes	30	Yes/Severe
6	Male	1st Trimester	Vaginal	40	Full-term	3,460	No	32	No
7	Male	2nd Trimester	Vaginal	38	Full-term	2,480	Yes	28,5	Yes/Severe
8	Male	3rd Trimester	Vaginal	40	Full-term	2,846	No	29	Yes/Severe
9	Male	1st Trimester	Cesarean	35	Pre-term	2,190	Yes	31	No

Alterations in orofacial muscles with consequent repercussions on sucking dynamics were reported by 33.3% of mothers. Regarding behavioral habits involving structures of the stomatognathic complex, 66.7% of children manifested bruxism during the day or at night. In all cases evaluated, self-injury episodes have been identified (Table 2).

Table 2. Clinical manifestations presented by children with Congenital Zika Virus Syndrome.

Case	Visual Impairment	Hearing Impairment	Skeletal Muscle Disorder	Seizures	Irritability	Sucking Difficulty	Swallowing Difficulty	Self-Injury	Bruxism
1	Yes	No	Yes	No	No	No	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
3	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
4	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes
5	Yes	*	Yes	Yes	Yes	No	Yes	Yes	Yes
6	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
7	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
8	*	No	Yes	Yes	No	No	Yes	Yes	Yes
9	No	No	Yes	No	Yes	No	Yes	Yes	No

*Data not reported.

The deciduous lower right central incisor was the first tooth to erupt (77.8%), and its presence in the oral cavity was detected in children aged at least 8 months and at most 17 months. A defect in the dental enamel development was observed in two cases, hypoplasia being verified in case 7 and demarcated opacity in case 9. Only two children had eruption cysts. At 36 months, 77.8% of children had complete deciduous teeth (Table 3).

Mothers reported that in the period of eruption of deciduous teeth, children manifested signs and symptoms of a systemic and local nature. Episodes of irritation, increased salivation, and gingival itching were frequently reported, with all these affections presenting a frequency of 88.9% (Table 4).

Table 3. Distribution of children according to characteristics related to tooth eruption and enamel defects.

Case	1st Erupted Tooth	Age at Eruption of the 1st Tooth	Enamel Defect	Type of Defect	Eruption Cyst	Number of teeth at 36 months
1	81	11 Months	No	----	No	18
2	61	13 Months	No	----	Yes	19
3	81	09 Months	No	----	No	20
4	81	13 Months	No	----	No	20
5	61	15 Months	No	----	No	20
6	81	08 Months	No	----	No	20
7	81	13 Months	Yes	Hypoplasia	No	20
8	81	09 Months	No	----	No	20
9	81	17 Months	Yes	Demarcated Opacity	Yes	20

Table 4. Distribution of children according to type of disorder related to tooth eruption.

Case	Eruption-Related Disorder	Type of Disorder						
		Irritation	Restless Sleep	Coryza	Fever	Diarrhea	Increased Salivation	Itchy Alveolar Ridge
1	Yes	Yes	Yes	No	No	No	No	Yes
2	Yes	Yes	No	Yes	Yes	No	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	No	No	No	No	Yes	Yes
5	Yes	Yes	Yes	No	Yes	No	Yes	Yes
6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
7	Yes	Yes	No	Yes	Yes	No	Yes	Yes
8	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
9	Yes	No	Yes	Yes	Yes	No	Yes	Yes

Discussion

Case series studies include the description of characteristics and outcomes among individuals in a group with a disease or exposure (which may be an intervention) over a period of time and without a control group. Data were retrospectively or prospectively collected, and there was no randomization [16].

In the first quarter of 2015, Brazil registered an outbreak of ZIKV infection in the Northeastern region of the country [17]. That same year, initially in the state of Pernambuco and later in other states in the same region, such as Bahia and Paraíba, health authorities reported an increase in the number of infants born with microcephaly. The evidence of an increase in the prevalence of microcephaly was confirmed by the Ministry of Health (MS), which identified an alteration in the pattern of occurrence of head reduction and/or alterations in the central nervous system (CNS), possibly in association with congenital infection. In this context, the Ministry of Health declared a Public Health Emergency of National Importance (ESPIN) through Ordinance 1.813 of November 11, 2015 [18].

In early 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Importance (PHEIC), although the relationship between the "microcephaly/neurological alterations" outcome and the possible causal factor "congenital ZIKV infection" had not been fully clarified [19].

In this sense, data from CZS surveillance registered, in the Brazilian territory, between 2015 and 2020, a total of 18,828 suspected cases of the syndrome, among which 3,523 (18.7%) were confirmed. The diagnosis was made through the evaluation of newborns (n=2,742), children with a mean age of 9 months (n=543), and stillbirths, fetuses, and spontaneous abortions (n=238) [20].

Maternal-fetal ZIKV transmission can occur in all trimesters of pregnancy, regardless of whether the maternal infection is symptomatic or asymptomatic [21]. In the present study, for more than half of mothers (66.7%), ZIKV infection occurred in the first three months of pregnancy, corroborating the findings of Aragão et al. [22]. It is noteworthy that, as already reported in the literature, the first gestational trimester is a phase in which the risk is higher for any type of infection, as in this period, there is a greater chance of the virus, whatever it may be, to cross the placental barrier [23]. However, specifically with regard to ZIKV, given the severity of systemic repercussions, all measures to prevent maternal infection throughout pregnancy are valid [18].

Data reported in this investigation showed that male children were predominantly affected, similar to previous findings [8,10,24,25]. Most mothers reported that their children were born via normal delivery, with a gestational age of less than 37 weeks and weighing less than 2,500g. With regard to childbirth, it is necessary to reaffirm the prerogatives established by national protocols, which ratify that care during childbirth and birth should not be modified exclusively due to the suspicion or confirmation of ZIKV infection or microcephaly [12]. As previously mentioned, most children were born at term, corroborating recent findings [8]. Regarding weight, other case series of children exposed to ZIKV during pregnancy also showed that the occurrence of low birth weight could be high [26,27].

In this study, although all children had confirmed CZS diagnosis, cases 6 and 9 did not have microcephaly at birth. However, among the other cases that composed this study, the severe subtype was a common finding established through the occurrence of -3 standard deviations below the mean [12].

Monitoring the development of children with CZS revealed a wide spectrum of congenital and postnatal manifestations [4,10]. Thus, it was found that musculoskeletal disorders, seizures, and visual impairment were conditions reported by mothers. In this sense, it is important to highlight that, although all children presented impairment of the musculoskeletal system, manifestations were different in number and severity, but it is possible to mention the occurrence of abnormalities in muscle tone, motor impairment, and multiple congenital contractures. Seizures, in turn, have been described as one of the main CZS complications in early childhood [8,10,28,29]. Regarding the findings that compromise vision, some cases presented high severity, so assessing visual acuity and visual development with age-matched control has been recommended [30].

Regarding the stomatognathic system, some aspects are relevant and deserve special attention from the dentist. First, all children had swallowing difficulties. Similar to the present study, another study has shown that dysphagia can develop in infants over three months of age and is characteristically severe [31]. Furthermore, Leal et al. [31] concluded that all infants with some degree of neurological damage had some abnormality in the oral phase of swallowing. Eight of the nine infants did not have respiratory and oral tract sensitivity, leading to delays in the onset of the pharyngeal phase of swallowing. Episodes of high irritability, bruxism, and self-injury, as seen in this group of children, have been previously described [8,10,25,29].

In one-third of children, the oral sucking process was compromised; in the same way, in a previous study in which 77 children with microcephaly resulting from CZS aged 5-36 months were evaluated, alteration in the muscle tone of the oral region was observed, with direct reflection on the suction dynamics [6].

In the evaluation of the tooth eruption chronology based on the proposal modified by Lunt and Law [14], the first teeth to erupt in the oral cavity are the deciduous lower central incisors. These teeth usually erupt when the child is between 6 and 10 months of age, which occurred for only one-third of the sample. In this study, one of the children had a severe delay in the eruption of the first deciduous tooth, occurring only in the 17th month of life. Overall, the pattern of delay is consistent with previous studies [7-10,24,32-34]. In cases 2 and 5, alteration in the sequence of eruption of deciduous teeth was observed, as the maxillary central incisors were the first teeth to erupt; in addition, the event occurred beyond the expected time, at 13 and 15 months, respectively. Therefore, it is acceptable to say that children born from mothers infected with ZIKV need a longer time for the complete eruption of the deciduous dentition [8].

It was possible to observe the occurrence of disorders related to the phase of eruption of the deciduous teeth, so all children presented a set of manifestations that included between 3 and 7 signs reported by mothers, which is corroborated by a previously published cohort study [35]. As reported in the literature, there are signs and symptoms to be expected at this time. This is because the consequent degranulation and local release of mediators, such as histamine, leukotrienes, prostaglandins, proteases, cytokines, and growth factors, contribute to the understanding of some of the local manifestations attributed to the tooth eruption phase, such as itching, inflammation, redness, and sialorrhea [36]. Specifically regarding the occurrence of fever, although most mothers attribute its occurrence to the "tooth eruption" outcome, the subjectivity of such finding should be highlighted. In addition, evidence provided by a systematic review with meta-analysis showed that the eruption of deciduous teeth is associated with increased temperature, but such elevation was not characterized as fever [37].

Silva et al. [8] reported that the most common complication in deciduous dentition development was eruption cysts. They also reported that they appeared before the teeth eruption and justified that the high incidence may be associated with malnutrition and that part of the sample was fed by gastric tubes. In the present investigation, only two children were diagnosed with eruption cysts, which occurred in the anterior region in both jaws.

Defects in the adamantine structure were also detected in this study, which, despite being present in only two children (cases 7 and 9), affected more than one tooth in a different way. In case 7, the presence of hypoplasia was evidenced in different groups of teeth, such as incisors, canines, and molars, while in case 9, demarcated opacity was diagnosed in the maxillary central and lateral incisors. Silva et al. [8] found that dental opacity was present in nine teeth of three children and was more prevalent on the buccal surfaces of upper incisors and canines and the occlusal surfaces of lower molars. One child had enamel hypoplasia in four teeth, maxillary incisors, and mandibular molars.

Among the limitations of the present study, the difficulty of monitoring children stands out since most families live in other locations and depend on the public transport service, a fact that culminated in the permanence of these children in the assistance center for a limited period for the performance of therapeutic interventions. In addition, due to the worsening of the health condition and death of some children, the evaluation of the tooth eruption chronology was interrupted and/or became unfeasible. However, case series are especially important when a new disease or treatment emerges, as they provide descriptive information and contribute to the construction of knowledge and the generation of hypotheses [16].

The findings of the present investigation are added to those of other studies that bring to light current knowledge and a greater amount of information about the systemic and oral repercussions of intrauterine exposure to Zika virus. The aim is to provide health professionals directly involved in care with a direction for

implementing preventive and intervention actions. Finally, regarding aspects related to oral health, it is worth mentioning the need to monitor these children in the medium and long term so that it is possible to monitor their growth and development of their oral structures [32].

Conclusion

In children with congenital Zika virus syndrome, a broad spectrum of systemic manifestations has been observed. The period of eruption of the first deciduous tooth was quite variable but mostly occurred after the age of 12 months. In addition to delays in the tooth eruption chronology, a process accompanied by significant physical and psychological discomfort, defects in the enamel structure were also identified, albeit in a small proportion. The multidisciplinary work in the management and health care of these children constitutes a relevant strategy to face these problems. Therefore, taking care of this population in the most diverse areas is essential, as well as monitoring the factors involved in these disorders.

Authors' Contributions

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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

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Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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