Orofacial changes of patients with congenital Zika syndrome in Northeast Brazil: an integrative literature review

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ABSTRACT | In 2015, in Northeast Brazil, cases of microcephaly associated with the outbreak of zika virus in South America were identified. This virus is transmitted by the biological vector *Aedes aegypti*, which also transmits dengue, yellow fever, and chikungunya viruses. The congenital Zika syndrome affected newborns with head circumference smaller than 32 cm, compromising their central nervous system. Besides ocular lesions, hyperexcitability, and hypertonia, newborns also showed intracranial calcifications in imaging exams. If children with congenital Zika syndrome suffer maxillofacial alterations during embryonic development, they could have delayed tooth eruption and malformations. This study aims to perform an integrative review of the current literature about the health conditions of children with congenital Zika virus infection and the possible alterations of their oral cavity. This integrative literature review was performed by searching scientific articles in the PubMed, SciELO, and MEDLINE electronic databases with the descriptors "Zika Virus Infection", "Zika Virus", and "Microcephaly", which deal with clinical case reports and were indexed between 2016 and 2021. About 26 articles published entirely in English were analyzed after meeting the eligibility criteria. The studies contributed to better treatment conducts by showing the neurological, functional, and oral alterations in children with congenital Zika syndrome, including periodontal diseases, malocclusions, dental caries, bruxism, micrognathia, ankyloglossia, short labial frenum, dental trauma, and dysphagia.

DESCRIPTORS | Congenital Zika Syndrome ; ZIKV Infection; Zika Virus.

RESUMO | **Alterações orofaciais dos pacientes portadores de síndrome congênita de Zika no nordeste brasileiro: uma revisão integrativa da literatura** • No nordeste brasileiro, no ano de 2015, foram identificados casos de microcefalia associados ao surto de Zika vírus no continente sul-americano, transmitido pelo vetor biológico *Aedes Aegypti*, também transmissor dos vírus da dengue, febre amarela, Chikungunya. A síndrome congênita de Zika manifestou-se em recém-nascidos com perímetro cefálico menor de 32 cm, comprometendo o sistema nervoso central, apresentando em exames de imagem calcificações cerebrais, além de lesões oculares, hiperexcitabilidade e hipertonia. As crianças portadoras de síndrome congênita de Zika apresentam possíveis alterações maxilofaciais durante o desenvolvimento embrionário, ocasionando atraso na cronologia de erupção dentária e possíveis malformações. Este estudo busca realizar uma revisão integrativa da literatura atual sobre as condições de saúde e possíveis alterações na cavidade oral das crianças portadoras de infecção congênita por Zika vírus. A revisão integrativa da literatura foi realizada por meio de uma busca de artigos científicos na base de dados eletrônica PubMed, SciELO e MEDLINE, utilizando os descritores "Zika Virus Infection", "Zika Virus" e "Microcephaly", indexados no período de 2016 a 2021, que tratavam de relato de caso clínico. Após os critérios de elegibilidade, foram analisados integralmente 26 artigos publicados em língua inglesa. Os estudos mostraram as principais alterações bucais presentes nas crianças portadoras da síndrome congênita de Zika, como doenças periodontais, maloclusões, cárie dentária, bruxismo, micrognatia, anquiloglossia, encurtamento do freio labial, traumatismos dentários e disfagia, assim como as neurológicas e funcionais dos indivíduos, contribuindo para melhores condutas de tratamento.

DESCRITORES | Síndrome Congênita de Zika; Infecção por ZIKV; Vírus Zika.

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INTRODUCTION

According to the World Health Organization (WHO), microcephaly is a congenital anomaly in which a newborn's cephalic perimeter is shorter than 32 cm even after 39 weeks of gestational age. Since it can be transmitted prenatally (congenital), perinatally, and postnatally (acquired), gestational monitoring is essential.[1]

Zika is a single-stranded RNA virus with African and Asian strains. This neurotropic flavivirus transmitted by Aedes aegypti was first identified in 1947 in forests of Entebbe, Uganda, in a blood sample of a rhesus macaque.[2] Because of the virus's wide geographic distribution, pandemics rapidly emerged Zika is expected to continue spreading by its transmitting agent.[1-3]. The first human cases were found in 1952-1954 in Nigeria and Tanzania. A Zika virus epidemic became a risk from 2005. The virus caused great damage to the French Polynesia in 2012, reaching Europe in 2013 and Brazil on April 29th, 2015.

The Zika virus disease is asymptomatic. Similarly to dengue, it is usually a mild febrile illness which causes cutaneous rash, arthralgia, or non-purulent conjunctivitis. Symptoms usually last up to a week.[3] This disease currently has no specific treatment or vaccine, but possible randomized clinical trials on vaccine production are being conducted. Laboratory diagnosis mainly detects viral RNA genome by reverse transcriptase-polymerase chain reaction (RT-PCR) or virus isolation and specific IgM or IgG antibodies by serological tests.[4]

Six months after the Zika virus outbreak began, an unusual number of babies were born with microcephaly.[5] They were mainly infected by the virus by maternal-fetal transmission by the amniotic fluid. The virus was found in two women pregnant with babies with microcephaly in the state of Paraíba, Brazil, and in tissue samples from a stillborn baby.[4] The Brazilian and the French Polynesia Ministry of Health associated congenital malformation with Zika V infection. Both countries also agreed that pregnant women were infected during the first and second trimesters of gestation.[5]

Brazil's Live Birth Information System (Sistema de Informações Sobre Nascidos Vivos – SINASC) notified 141 suspected cases of microcephaly in 2015 in in the states of Pernambuco, Paraíba, and Rio Grande do Norte, in northern Brazil. The Brazilian Ministry of Health declared this a public emergency.[6] The Evandro Chagas Institute of the Ministry of Health isolated the Zika virus from the brain of a stillborn child by detecting it in cerebrospinal fluid (CSF), brain, and viscera fragments.[7] As a result, IgM antibodies to the Zika virus were detected in the CSF of 12 children with microcephaly. The Ministry of Health's prevention policies aimed to create a vaccine to control congenital Zika.[8]

Studies from the Altino Ventura Foundation showed brain calcifications in CT scans and myopia, macular atrophy, and optic nerve hypoplasia in eye exams.[9]

The most prevalent alterations caused by microcephaly are intellectual disability, cerebral palsy, epilepsy, dysphagia, and behavioral disorders such as excessive crying, global hypertonia, seizures, epileptic seizures, and epileptic spasms.[10] Patients with microcephaly are most likely to develop oral diseases even if the virus did not affect their oral cavity during pregnancy. Oral hygiene is the best method of prevention and care against these oral diseases, which can directly and negatively impact the lives of these patients.[11]

Microcephaly is a genetic alteration that occurs during the neuronal proliferation phase, between the 3rd and 4th month of gestation. From the 3rd to the 5th month, imaging exams show malformations in fetal cortical development, neuronal migration disorders, and diffuse calcifications that cause neuronal death.[12] Zika virus's pathogenesis greatly affects the central nervous system, increasing susceptibility to postnatal cortical development.[13]

The WHO classifies microcephaly by the following standards: Microcephaly, in which the newborn's (NB) head circumference is 2 standard deviations below the mean for gestational age and gender; and Severe Microcephaly, in which the NB's head circumference is 3 standard deviations below the mean.[14]

Over the past few decades, microcephaly incidence ranged from 1:6,250 cases to 1:8,500 cases, affecting mostly male children. In 2015, however, Brazil reached an excess number of cases without sex or skin color differences, and pregnant women of poorer socioeconomic conditions were the most affected.[15] These cases are monitored by SINASC by Code Q.02.

Patients with microcephaly have a small head circumference and could also present hearing loss, poor motor coordination, myopia, macular atrophy, optic nerve hypoplasia, hyperactivity, seizures, epilepsy, autism, cerebral palsy, ADHD, muscle rigidity, dysphagia, among others.[16]

Clinical diagnosis is made by measuring the head circumference using a flexible, non-elastic tape measure. The fetal head is measured at its greatest circumference, above the superciliary arches and the ears, and prominent at the posterior skull base. Laboratory diagnosis is done by collecting serum/plasma from the newborn's CSF to confirm infection by Zika virus.[17] Molecular biological tests and serological testing can also be conducted using RT-PCR with serum, amniotic fluid, cerebrospinal fluid (CSF), saliva, and urine. Immunohistochemistry tests and serological testing such as ELISA IgM and IgG or PRNT detect Zika in the newborn's umbilical cord. Neuronal migration disorders, calcifications, ventricular dilatations, and loss of brain tissue can be visualized by computed tomography (CT) scans. Obstetric Ultrasonography is indicated for diagnosing structural abnormality of the central nervous system (CNS) and monitoring fetal and cerebral growth. Transfontanellar ultrasonography is used for more detailed examinations.[18]

The Brazilian Ministry of Health proposed to create a preventive vaccine against the Zika virus. Other countries, including the USA, are also developing this vaccine. However, the treatment of patients with microcephaly requires a multidisciplinary team with physicians, psychologists, physical therapists, speech therapists, dentists, social workers, nutritionists, nurses, etc. This study focuses on dental care for patients with microcephaly.[18]

Guiding question: what are the orofacial changes associated with congenital Zika syndrome?

METHODOLOGY

Search strategy

This integrative literature review was conducted by searching scientific articles in the electronic databases PubMed, Medline, and Portal CAPES, using the descriptors "Zika Virus Infection", "Zika Virus", and "Microcephaly" combined with the associations and outcomes of interest, as described in Figure 1.

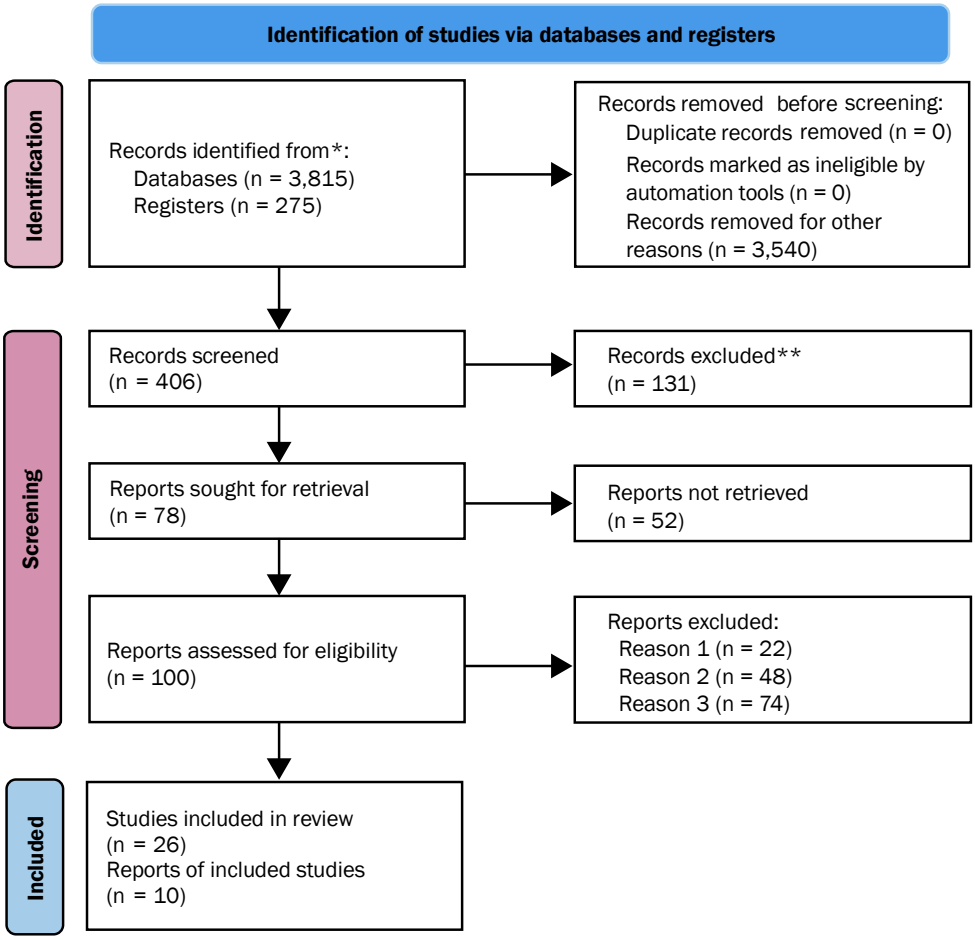

FIGURE 1 | Flowchart of the search strategy.
Source: PRISMA 2020 statement (Authors, 2021).

Selection of articles

The articles were assessed and selected by two separate researchers, who later compared their selected texts to reach consensus. If the researchers disagreed or doubted which articles to include in the study, they were joined by a third researcher. Articles that were indexed in both databases were considered only once. Then, selection had two phases: (1) reading the abstracts, and (2) qualitative analysis of the full texts.

Eligibility criteria

The inclusion criterion for article selection were: original articles available in full, published in English and Portuguese and indexed between 2016 and August 2020; articles regarding the oral health of patients with congenital Zika syndrome; clinical and laboratory mean studies that associate microcephaly with Zika virus; and studies regarding assistance and promotion of the oral health of patients with special needs. The following were not included: case-control studies, research with animal use, articles that relate microcephaly to other pathologies, articles that assess diagnoses of ZIKV, and etiological factors for congenital Zika syndrome in Northeast Brazil.

Our methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Articles that

did not fit the inclusion criteria and repeated articles were excluded. After a full reading of the remaining articles was performed, our final sample included 26 articles.

Theses, dissertations, and monographs were not used, since they are impractical to search for and were not included in database.

RESULTS AND DISCUSSION

Results

This study aimed to analyze the literature on congenital Zika syndrome. We observed the clinical and pathological characteristics and diagnostic methods of the disease, assessing the patient as a whole and following the principles of the Brazilian Unified Health System (Sistema Único de Saúde – SUS): equity, universality, and social equality. Our integrative review found recent studies on how the virus originated and spread until the first cases of Zika virus infection appeared. We observed the virus's stages of development and pathological advances, diagnosis by clinical and laboratory tests, risk factors and lesions associated with congenital infection, and the use of scientific means to create a vaccine for both treatment and prevention of the disease, as shown in Table 1.

Twenty-six scientific articles were selected according to the criteria. Results showed that the oral cavity of patients with congenital Zika syndrome changed. Among these articles, 10 were selected for evaluation and description of data (Table 1): 1 Retrospective Study, 5 Cross-Sectional Studies, 2 Longitudinal Studies, 1 Scopus Review, and 1 Case Series.

TABLE 1 | Selection of articles according to the author, type of study, objectives, methodology, results, and conclusion.

Author and Study	Objective	Methodology	Results	Conclusion
Leal et al., 2017, retrospective study[1]	To assess the characteristics of dysphagia in nine children in Brazil with microcephaly caused by congenital Zika virus infection.	A descriptive, retrospective study of a case series was conducted by reviewing the medical records of nine children in Brazil with dysphagia and microcephaly caused by congenital Zika syndrome (CZS) who were diagnosed during the 2015 microcephaly epidemic.	All babies had some degree of neurological damage, with delays in development and limb hypertonia. Most babies had abnormal tongue movements, which contributes to dysphagia.	Affected children had marked oral dysfunction and dystonic tongue movements and lacked pharyngeal sensitivity, which increases the risk of aspiration, especially of liquid foods.
Fonteles et al., 2018, cross-sectional and descriptive study[10]	To assess the lingual frenulum of children with congenital Zika syndrome (CZS).	Data collection and orofacial assessment of babies with congenital Zika syndrome (CZS).	The lingual frenulum was visible in 34 (63%) infants, whereas 20 (37%) infants required a specific maneuver to retract the tongue for visibility.	Children with CZS had a short lingual frenulum.
Cavalcanti et al., 2018, longitudinal study[19]	To investigate the occurrence of signs and symptoms related to primary tooth eruption in children with congenital Zika syndrome.	79 children were assessed for 24 months. Their medical records were analyzed. The data were presented using descriptive and inferential statistics (chi-square test).	94.9% of children showed two or more signs and symptoms related to tooth eruption simultaneously, including increased salivation (91.1%), irritability (86.1%), and itchy gums (83.5%).	Children with congenital Zika syndrome had increased salivation, irritability, and itchy gums, all related to primary teeth eruption.
Carvalho et al., 2019, observational cross-sectional study[20]	To investigate possible soft-tissue, bone, and / or dental malformations in patients with congenital Zika virus syndrome.	30 children born with ZIKV and 30 children born without ZIKV (control group) were included in the study and assessed for 24 consecutive months.	Babies with ZIKV showed a high prevalence of inadequate resting tongue posture, micrognathia, changes in the shape and / or number of teeth, alterations in the sequence of tooth eruption and muscle spasms, delayed eruption, and narrow arched palate.	Children with ZIKV were more inclined to have delayed primary tooth eruption, inadequate tongue posture, and short labial and lingual frenulum.

Continue...

TABLE 1 | Continuation

Author and Study	Objective	Methodology	Results	Conclusion
Silva, 2020, longitudinal study[21]	To assess the presence of dental anomalies in 13 babies diagnosed with congenital ZIKV syndrome.	The first 29 reported cases of children with microcephaly admitted to special maternal and childcare units between July and October 2015 were assessed. Of these children, three died and 13 lived in other municipalities; thus, only 13 patients remained for assessment in Recife, PE.	Dental radiographs showed that, in the first half, all children had dental germs; at the end of the study, they had incomplete primary dentition.	Abnormal chronology of tooth eruption and tooth development disorders in children with microcephaly who were infected by ZIKV indicate that viruses could affect odontogenesis.
Ribeiro RA, 2020, cross-sectional and observational study[22]	To assess the oral and maxillofacial characteristics of children with microcephaly associated with congenital Zika syndrome.	Assessment of 61 patients with microcephaly / CZS born between June 2015 and September 2017 and of a control group with 58 non-CZS children born in the same period.	Narrow palate and late primary tooth eruption were prevalent in the group with microcephaly caused by Zika.	Children with microcephaly caused by congenital Zika infection showed functional, oral, and maxillofacial changes and smaller facial development.
Oliveira, 2020, cross-sectional study[23]	To investigate oral and maxillofacial outcomes in children with congenital Zika syndrome.	Assessment of 45 children with CZS and of 50 healthy controls in the state of Sergipe, Brazil, from February 2018 to June 2018.	Patients with CZS were oral breathing, had difficulty swallowing, excessive salivation, abnormal attachment of the upper lip frenulum, high-arched palate, dental enamel defects, and late tooth eruption.	Children with CZS had more problems related to breastfeeding, low weight, and oral and maxillofacial abnormalities.
D'Agostino ÉS, 2020, cross-sectional study[24]	To describe the chronology and sequence of primary teeth in children with microcephaly caused by fetal exposure to the Zika virus.	Assessment of 74 children from a neuropediatric referral unit in Salvador, Bahia, in 2017.	The average eruption time is 17.92 months for maxillary teeth and 11.57 months for the mandible teeth. The first teeth erupted in the lower arch, and the molars and / or canines erupted before the incisors.	The chronology and eruption sequence of primary teeth changed.
Silva Sobrinho, 2021, scope review[25]	To analyze published scientific evidence on the most common orofacial disorders in children with microcephaly associated with ZIKV infection.	PubMed, EMBASE, Scopus, and Health Virtual Library databases were used for research.	11 studies conducted in Northeast Brazil between 2018 and 2020 were selected.	The chronology of tooth eruption and teeth and oral structures changed the most.
Aragón et al., 2021, case series[11]	To describe the dental, occlusal, and craniofacial characteristics of three children with congenital Zika virus infection.	Case report of three children with congenital microcephaly caused by Zika virus.	The children had a short upper third of the face, hypertonic masticatory muscles and hypotonic swallowing muscles, dysphagia, dyslalia, bruxism, labial incompetence, tongue interposition, hypersalivation, and epilepsy. The complete primary teeth with normal dental morphology were affected by altered tooth eruption, dental caries, and dental malocclusion.	The children's dental formula and dental morphology of the primary dentition did not change. However, they have severe chewing and speech limitations, facial disproportion, and occlusal problems.

Source: Authors (2021).

Discussion

In 2015, in Northeast Brazil, mainly in the state of Pernambuco, the number of children born with microcephaly increased significantly, indicating a possible association with Zika virus infection during pregnancy. About 29 babies with microcephaly were admitted in the main public hospitals of Pernambuco, which are the Pediatric Infectious Diseases Unit of the University Hospital Oswaldo Cruz, University of Pernambuco, and the Professor Fernando Figueira Institute of Integral Medicine. Thus, the Pernambuco Health Department notified an unusual incidence of microcephaly cases to the Brazilian Ministry of Health.[21]

We agree that ZIKV infection during pregnancy can cause severe defects and abnormalities in the neurological and craniofacial development of children. Babies infected with congenital Zika virus develop problems such as epilepsy, vision loss, and developmental delays as they grow. The new congenital Zika syndrome should be classified as a TORCH infection (toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes), which are some of the most common infections associated with mother-to-child infections transmitted during pregnancy that cause congenital anomalies, including maxillofacial disorders.[21]

Ameloblasts that synthesize the enamel of the tooth crown are formed during embryonic teeth development. Once damaged, the enamel cannot recover. The formation of dental tissues, enamel, and dentin depends on coordinated cellular interactions between the oral epithelium and the ectomesenchyme, derived from the neural crest.

Dental radiographs obtained during the patients' first trimester of life aimed to verify the extent of ZIKV infection and its impact on the development of dental germs. The results revealed that children born with congenital Zika syndrome have dental germs. Radiolucency in the teeth pre and post-eruption confirmed that the tooth tissue underwent calcification disorder during enamel formation. Panoramic radiographs also showed both qualitative and quantitative dental development anomalies, prevalent in children with neurological disorders.[12,21]

To answer the guiding question, children with congenital ZIKV infection have short labial and lingual frenulum, narrow palate, interfered tooth eruption, hypersalivation, muscle spasms, hyperplasia of the alveolar ridge, no cleft lip or palate, agenesis of upper and lower deciduous incisors, microdontia, micrognathia, supernumerary teeth, eruption cysts, dental hypoplasia, and diffuse opacity enamels. Infections during gestation are considered a risk factor for dental lesions and congenital anomalies in embryos.

FINAL CONSIDERATIONS

Finally, we conclude that the association of Zika virus with microcephaly cases in Brazil can be proved by scientific evidence. However, we observed that scientific and clinical studies should be more accessible to dental surgeons, whereas microcephaly patients need more retrospective, randomized clinical studies regarding treatment conduct and the use of medicines.

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