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Clinical manifestations and management of congenital Zika virus infection: A systematic review

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ABSTRACT

Objective: The general objective of the present study is to analyze the scientific production on Congenital Zika Virus Infection, seeking to identify the main clinical manifestations, as well as the

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main methods used in the treatment of this pathology. Methodology: It is a systematic review focused on understanding the main aspects of Congenital Zika Virus Infection. The research was guided by the question: "What are the main signs and symptoms of congenital Zika virus infection in the pediatric population, as well as what are the therapeutic resources used in clinical practice?" . To find answers, searches were performed in the PubMed database using three descriptors combined with the Boolean term "AND". This resulted in 010 articles. 12 articles were selected for analysis. Results: Congenital Zika syndrome (CZS) emerges as a complex and multifaceted challenge whose implications go beyond the boundaries of public health. Babies exposed to the Zika virus during pregnancy face a range of clinical manifestations, from microcephaly to eye anomalies and neurological disorders. Prevention, therefore, takes on a crucial role: educating pregnant women about the risks and promoting protective measures, such as the use of repellents and mosquito nets, is imperative. Conclusion: Although we do not yet have a licensed Zika vaccine, research efforts continue to explore this possibility. In addition, long-term surveillance is essential to fully understand the effects of the virus. In this scenario, awareness, interdisciplinary collaboration, and a commitment to the well-being of future generations are our best allies in the fight against this potentially devastating syndrome.

Keywords: Zika Virus, Clinical Picture, Pediatrics.

INTRODUCTION

Zika Virus (ZIKV) is an enveloped RNA virus with an icosahedral structure, containing a single-stranded RNA of positive polarity. It belongs to the genus *Flavivirus* and is part of the *Flaviviridae family*, being related to other viruses such as dengue (DENV), yellow fever (YFV), Japanese encephalitis (JEV), Chikungunya (CHIKV) and West Nile. The Zika genome is composed of a single open reading frame, which encodes a single polyprotein. This polyprotein is processed by cellular enzymes and viral proteases into 10 different proteins. Viral proteins include three structural proteins [envelope (E), membrane (M), and capsid (C)], which make up the viral particle, and seven non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5), which are essential for the processing, replication, and assembly of new viruses. ZIKV transmission occurs through mosquitoes of the genus *Aedes* active during the day (such as A. aegypti and A. albopictus), sexual contacts, blood transfusions, and vertical transmission (GIRALDO et al., 2023) (AURITI et al., 2021).

Although ZIKV was first identified in the Ugandan jungle in 1947, global concern grew significantly during the Zika pandemic between 2015 and 2016, when the severe teratogenic effects of infection during pregnancy became evident. In Brazil, the incidence of congenital Zika syndrome (CZS) was 49.9 cases per 10,000 live births. Pregnant women are particularly vulnerable to viral infections during the first and second trimesters, periods when there is a high risk of birth harm to the fetus. Among fetuses exposed to ZIKV, fetal loss occurred in 14% of cases, and severe complications, compatible with Congenital Zika Syndrome (CZS), were observed in 21%. These congenital malformations, which include cortical atrophy with microcephaly and functional impairments such as dysphagia and epilepsy, can arise after both symptomatic and asymptomatic infections (GIRALDO et al., 2023) (AURITI et al., 2021) (ARORA; LAKSHMI, 2021).

During the 2015-2016 period, Brazil reported more than 200,000 probable cases of ZIKV and nearly 2,000 cases of microcephaly. Due to the rapid spread and large number of suspected cases, ZIKV infection was declared a Public Health Emergency of International Concern on February 1, 2016. Soon after, in March 2016, the World Health Organization announced that there was scientific consensus causally linking congenital brain anomalies to ZIKV infection. After 2017, the number of CZS cases decreased dramatically, ranging from 39 confirmed cases in 2018 to just two in 2022 in various regions of the country. Despite this drop, a significant number of suspected cases of CZS (n=2,960) are still under investigation, suggesting that the real burden of the disease may be underestimated (LIANG et al., 2019) (MARTELLI et al., 2024).

Maternal exposure to ZIKV causes a diffuse placental lesion, characterized by trophoblastic hyperplasia, focal regions of necrosis, and loss of embryonic blood vessels, changes that probably contribute to adverse outcomes in the fetus, even in the absence of fetal infection. An increase in the

number of macrophages and Hofbauer cells was observed, which promotes the production of matrix metalloproteinases, responsible for degrading collagen, as well as TNF-α, activating the trafficking of immune cells. CD68+ and CD8+ T cells were widely detected in infected placentas, with high expression of cytokines (IFN-γ and TNF-α) and other immune mediators (RANTES/CCL5 and VEGFR-2), confirming excessive inflammation and dysfunction in vascular permeability. In addition, in the presence of ZIKV infection, the Bcl-2 protein has been shown to be overexpressed in third-trimester syncytiotrophoblastic cells, resulting in increased cell apoptosis and persistence of viral particles in the placenta (AURITI et al., 2021).

The AXL receptor appears to be the main entry cofactor of ZIKV into human umbilical vein endothelial cells (HUVECs), allowing the virus to enter the fetal bloodstream and reach other fetal tissues. AXL mRNA has also been found in human neural progenitor cells (NPCs) and other brain cells (such as radial glial cells, microglial cells, and astrocytes), suggesting a susceptibility of these cells and explaining the related brain anomalies (AURITI et al., 2021).

This systematic review article aims to compile and evaluate the existing scientific evidence on the clinical manifestations and management of Congenital Zika Syndrome. The intention is to provide a comprehensive and up-to-date view, which not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and clinical practices. By offering an in-depth analysis of the evidence, this study aims to serve as a resource for health professionals, researchers, and academics, helping to optimize diagnostic and therapeutic approaches to this condition.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of the clinical manifestations of Congenital Zika Virus Infection in pediatric patients, as well as to demonstrate the main methods used in the treatment of the condition, aiming to ensure a greater clinical elucidation of this pathology. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main signs and symptoms of congenital Zika Virus infection in the pediatric population, as well as what are the therapeutic resources used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Three descriptors were used in combination with the Boolean term "AND": Zika Virus Infection, New born, and Zika Virus. The search strategy used in the PMC database was: Zika Virus Infection AND newborn and Zika Virus and newborn. From this search, 101 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes

proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 101 articles were found. After applying the inclusion and exclusion criteria, 26 articles were selected from the PubMed database, and a total of 12 studies were used to compose the collection.

DISCUSSION

Congenital Zika syndrome is the most serious complication that can occur during pregnancy in women infected with Zika virus (ZIKV). Regardless of whether the mother has symptoms or not, fetuses have a 5% to 14% risk of developing this syndrome and a 4% to 6% risk of microcephaly. The highest risk of developing congenital Zika syndrome occurs in the first trimester of pregnancy (between 8% and 15%), compared to the following two trimesters (between 4% and 5%). The main signs and symptoms associated with this syndrome include microcephaly, calcifications in the brain (particularly in the parenchymal or cerebellar regions), ventriculomegaly, hypoplasia or atrophy of the central nervous system, arthrogryposis, ocular anomalies, and low birth weight for gestational age. (SCOTTO et al., 2023)

Microcephaly is the first and most evident anomaly observed in children born to mothers with ZIKV infection. It is defined as a head circumference below normal standards specific to the age and sex of the newborn. Specifically, microcephaly is considered when the occipitofrontal head circumference is below two standard deviations in relation to the mean for gestational age and sex, according to the INTERGROWTH-21 standard. In more severe cases, head circumference may be below three standard deviations from the mean. In addition to microcephaly, other brain anomalies may be present, even in the absence of this condition, resulting from disruptions in brain development during pregnancy, with cranial collapse and disturbance in nerve and glial cell migration. (SCOTTO et al., 2023)

In a study of seventy-one Brazilian children with prenatal ZIKV infection, the most common abnormalities included calcifications (especially at the cortico-subcortical junction of the white matter), cerebral cortex malformations, ventriculomegaly, reduced brain volume, cerebellar hypoplasia, and dysgenesis of the corpus callosum. Other less frequent brain abnormalities included cerebellar hypoplasia, lissencephaly, and pachygyria (changes in cerebral convolutions). In addition to microcephaly, congenital ZIKV infection may also be associated with low birth weight, excess skin on the scalp, facial disproportion, swallowing difficulties, hypertonia/spasticity, tremors/seizures, and hearing impairment. These conditions result from tissue damage, especially during the first three months of gestation, leading to anomalies in the macroscopic (malformations)

and microscopic (dysplasia) development of the central nervous system, often related to microcephaly. (SCOTTO et al., 2023)

Congenital infections, such as those caused by Toxoplasma gondii and cytomegalovirus, have also been linked to serious brain changes, such as calcifications and ventriculomegaly. However, unlike these other infections, Zika virus (ZIKV) infection is known to be directly associated with severe cases of microcephaly. This condition manifests with a partially collapsed skull, thin cerebral cortex with subcortical, calcifications, retinal scarring, and other eye changes. These effects result from significant viral tropism by the neural and ocular progenitor cells of the fetus. In addition, congenital contractures (bone deformities) can also be linked to ZIKV infection during pregnancy, although they are less frequent. In summary, these findings can also occur in similar congenital syndromes such as toxoplasmosis, syphilis, and chickenpox. (FREITAS et al., 2020)

Oral, facial, and dental changes are common in CZS. Tooth development, known as odontogenesis, begins around the sixth week of intrauterine life and involves cells migrating from the neural crest, which is the same embryonic tissue from which the center originates the nervous system. Disturbances during this period can affect the physiology and morphology of dental tissues, leading to changes in their internal and external anatomy. Among children with ZIKV-associated microcephaly, notable changes in the region include altered eruption chronology, tooth morphology, oral structures, and gnathic bones, as well as other modifications such as hypersalivation and infant irritation. (SCOTTO et al., 2023)

According to a recent Brazilian cross-sectional observational study of 61 patients with microcephaly/CZS, narrow palate and anterior tongue projection are significantly more prevalent in the microcephaly/CZS group compared to normal development. The microcephaly group also demonstrates reduced measurements of facial width, jaw width, height of the upper third of the face, and monthly growth of head circumference; These changes in palate shape may result from the impact of ZIKV on cranial neural crest cells, affecting normal craniofacial development. In addition, the narrow palate may be associated with the orofacial muscle hypotonia commonly seen in children with CZS. Abnormalities in tongue posture, presence of narrow palatine vaults, and changes such as macroglossia and ankyloglossia

They are frequently reported by many authors. Microcephaly caused by ZIKV contributes to orofacial disproportions, decreased skull size, retrognathia, and micrognathia. Changes in lip posture at rest, increased tongue tone, decreased cheek tone, and abnormal insertion of the upper labial frenulum have also been documented. (SCOTTO et al., 2023)

Children with CZS often have eating disorders, swallowing difficulties, and a higher prevalence of low birth weight. Palate shape has been significantly associated with dysphagia in patients with CZS. Dysphagia is linked to the loss of voluntary activity during the oral swallowing

phase, commanded by the cerebral cortex, and is a consequence of oral motor dysfunctions that can lead to serious nutritional complications. Hypersalivation, irritability, and gingival itching are also reported symptoms. These findings suggest that children with CZS may be prone to developing malocclusions, with a considerable proportion already exhibiting anterior open bite. In addition, bruxism was observed in one-fifth of patients with microcephaly. Mouth breathing, functional habits, breastfeeding problems, intake of ultra-processed foods, and low weight are more prevalent in children with CZS compared to healthy children. Clinical evaluations of CZS patients with mild and moderate/severe oropharyngeal dysphagia have shown poor lip sealing, lack of sucking-swallowing-breathing coordination, and absence of pauses to breathe during sucking. Proper lip closure is significantly associated with efficient lip sealing and swallowing success. (SCOTTO et al., 2023)

In research studies, it has been observed that Zika virus, when infecting mice, can cause acute kidney injury and increase the levels of related biomarkers. In addition, children with congenital Zika syndrome (CZS) and severe microcephaly often have urinary tract disorders such as neurogenic bladder, urinary tract infections, and abnormalities detected by ultrasound. However, more research is still needed to fully understand the long-term impact of Zika virus on the urinary system. (ANTONIOU et al., 2021)

Ocular manifestations associated with congenital Zika syndrome (CZS) include several abnormalities, such as changes in the pigment epithelium of the retinal macula, optic nerve hypoplasia, chorioretinal atrophy, colobomas, and microphthalmia. These conditions affect visual function and are usually identifiable in early childhood in affected children. However, it is important to note that eye abnormalities do not usually progress over time. An interesting finding, which has similarities to congenital rubella syndrome, is that about 10% of children exposed to Zika virus during pregnancy had congenital heart defects in prospective studies. In addition, long-term follow-up studies have revealed that approximately 15% of these children may experience severe neurodevelopmental problems and neurosensory abnormalities by the age of 3. It is worth noting that not all children with anomalies at birth develop later neurological complications. Similarly, babies initially considered normal at birth, after maternal exposure to Zika virus during pregnancy, may have abnormal developmental outcomes years later. (AMARAL et al., 2021)

Severe microcephaly, characterized by an abnormally small skull size, is often diagnosed before birth through fetal ultrasound and MRI. When there is a sudden stop in intrauterine brain growth, but not in the growth of scalp skin, an excess of redundant skin on the scalp may be observed. In addition, the fontanelle (the soft area at the top of the skull) is usually already closed in babies with severe microcephaly. Postnatal imaging tests, such as computed tomography, show punctate calcifications with a characteristic banded distribution, located at the junction between the cortical and medullary layers of the brain. These calcifications are often found in the basal ganglia

and, less frequently, in the thalamus. Ventriculomegaly (enlargement of the cerebral ventricles) is common in almost all infants with severe microcephaly. Interestingly, occipital cysts, which used to be highly suggestive of congenital cytomegalovirus (CMV) infection, are also seen in cases of Zika virus (ZIKV) infection. In addition, infants with normal head size at birth but who were exposed to ZIKV during pregnancy may present with asymmetric calcifications at the cortico-subcortical junction, frontal cortical malformations, mild ventriculomegaly, and delayed myelination. In some more severe cases, progressive ventriculomegaly may require the insertion of a ventriculoperitoneal shunt to relieve clinical symptoms. (DE VRIES, 2019)

There is currently no licensed vaccine or specific drug to prevent or treat ZIKV infection. Primary prevention should focus on educating pregnant women. All non-essential travel to destinations with a risk of Zika should be avoided. If travel cannot be avoided or if women live in risk areas, appropriate protective measures must be taken. Mosquito bites can be prevented by covering exposed skin and using appropriate insect repellents, such as picaridin or diethyltoluamide (DEET). It is best to stay in air-conditioned rooms and sleep under a mosquito net. Women who have traveled to high-risk areas should wait at least 2 months before trying to conceive, regardless of symptoms. Men should wait at least 6 months, due to the persistence of viral particles in the male reproductive organs. On the other hand, condoms should be used to avoid contracting ZIV through sexual contact if partners have recently traveled to a Zika-affected area, although it is an unpopular practice. (AURITI et al., 2021).

There are at least nine candidate vaccines for the Zika vaccine under clinical evaluation and 25 in non-clinical development to date. The Target Product Profile outlined by the World Health Organization for vaccine use in response to outbreaks would target people aged nine years and older, with coverage of 80% of the population, in order to prevent infection of the fetus up to one year after completion of the primary series. Initial challenges to vaccine development are concerns that a ZIKA vaccine could result in an autoimmune trigger of GBS. Animal studies have provided clues suggesting that neutralizing antibodies provide immune protection and sufficient titers protect against infections in the reproductive system, but this requires clinical confirmation. (EVANS-GILBERT, 2020)

Current WHO guidance recommends that infants born to mothers with suspected, probable, or confirmed ZIKV infection during pregnancy, even without microcephaly, should be evaluated for signs of neurodevelopmental abnormalities and feeding difficulties during follow-up visits at at least 3, 9, and 24 months of age. Infants with CZVS who present with irritability, seizures, and swallowing dysfunction or dysphagia should receive comprehensive neurodevelopmental evaluation and supportive therapy. (MARTINEZ et al., 2020)

CONCLUSION

Congenital Zika syndrome (CZS) emerges as a complex and multifaceted challenge whose implications go beyond public health boundaries. Babies exposed to the Zika virus during pregnancy face a range of clinical manifestations, from microcephaly to eye anomalies and neurological disorders. Prevention, therefore, plays a crucial role: educating pregnant women about the risks and promoting protective measures, such as the use of repellents and mosquito nets, is imperative. Although we do not yet have a licensed Zika vaccine, research efforts continue to explore this possibility. In addition, long-term surveillance is essential to fully understand the effects of the virus on the urinary system and other areas. In this scenario, awareness, interdisciplinary collaboration, and a commitment to the well-being of future generations are our best allies in the fight against this potentially devastating syndrome.

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