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ORIGINAL ARTICLE

CONGENITAL ZIKA VIRUS SYNDROME-RELATED ANOMALIES DETECTED OVER THE SEVEN-YEAR HISTORY OF THE EPIDEMIC: a literature review

ANOMALIAS CONGÊNITAS RELACIONADAS À SÍNDROME DO ZIKA VÍRUS DETECTADAS AO LONGO DE SETE ANOS DE HISTÓRIA DA EPIDEMIA: uma revisão da literatura

ANOMALÍAS CONGÉNITAS RELACIONADAS CON EL SÍNDROME DEL VIRUS DEL ZIKA DETECTADAS DURANTE LOS SIETE AÑOS DE HISTORIA DE LA EPIDEMIA: una revisión de la literatura

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RESUMO: Em 2015, foi registrado um aumento alarmante da microcefalia no Brasil, associada à epidemia do vírus Zika (ZV). Os efeitos teratogênicos do ZV, no entanto, não se restringem apenas à microcefalia. Descrever as estruturas corporais afetadas pelo potencial teratogênico da síndrome congênita do Zika vírus (SCZV), a fim de fornecer um panorama das anomalias detectadas e disponibilizar esse conhecimento aos profissionais de saúde e à comunidade científica. Foi realizada revisão narrativa entre junho de 2020 e janeiro de 2022 nas bases de dados do Portal de Periódicos CAPES, MEDLINE, Scopus, LILACS e SciELO. Foram incluídas publicações científicas que abordaram estruturas orgânicas fetais afetadas pelos efeitos teratogênicos da SCZV. Trinta e dois estudos foram incluídos nesta revisão e identificaram anomalias no crânio, estruturas orofaciais, sistema nervoso, articulações, via visual e vísceras torácicas. Os efeitos teratogênicos da SCZV afetam um amplo espectro de estruturas corporais. As crianças acometidas pela SCZV ainda requerem abordagem multidisciplinar de saúde, portanto o presente estudo é uma fonte de informação útil para esses profissionais.

Palavras-Chave: Zika vírus. Infecção por Zika vírus. Anomalias congênitas. Síndrome congênita do Zika vírus. Microcefalia.

ABSTRACT: In 2015, an alarming increase in microcephaly was recorded in Brazil, being associated to Zika virus (ZV) epidemic. The teratogenic effects of ZV, however, are not restricted to microcephaly only. To describe the body structures affected by the teratogenic potential of Zika virus congenital syndrome (ZVCS), in order to provide an overview of the anomalies detected and make this knowledge available to health professionals and to the scientific community. A narrative review was carried out between June 2020 and January 2022 in Portal de Periódicos CAPES, MEDLINE, Scopus, LILACS and SciELO databases. Scientific publications that addressed fetal organic structures that were affected by the teratogenic effects of ZVCS were included. Thirty-two studies were included in this review and identified anomalies in cranium, orofacial structures, nervous system, joints, visual pathway and thoracic viscera. The teratogenic effects of ZVCS affect a broad spectrum of body structures. The children affected by ZVCS still require multidisciplinary health approach, so the present study is a helpful source of information for such professionals.

Keywords: Zika virus. Zika virus infection. Congenital abnormalities. Congenital Zika Syndrome. Microcephaly.

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Introduction

Zika virus (ZV) is an arbovirus that belongs to the family Flaviviridae, being first detected in monkeys in Uganda (1947) (DICK *et al.*, 1952). In 1978, the first relate of ZV contamination in humans was described in Nigeria; Nevertheless, over 80% of the infected people did not exhibit any symptom, or only presented with a mild flu-like condition. From Africa, this virus spread to Asia in the 1970s, to the Pacific Ocean islands in 2007 and, around 2015, to large areas of South and Central Americas, thus characterizing an epidemic status (GRASSI *et al*., 2016; MLAKAR *et al*., 2016).

In 2015, health professionals observed an extremely alarming increase in microcephaly records in Brazil, from about 150 cases per year in 2014 (ABREU *et al.*, 2016) to 1,248 records in 2015 (FLOR *et al.*, 2017). Considering the ongoing ZV epidemic on this year, a possible association between the disorder and the virus was raised, being confirmed in 2016 (ABREU *et al.*, 2016; MLAKAR *et al.*, 2016; FLOR *et al.*, 2017; KROW-LUCAL *et al.*, 2018).

The teratogenic effects of ZV, however, are not restricted to microcephaly only. Children exposed to the virus throughout the gestational period presented with further anomalies in spinal cord, nerves, joints, ocular and auditory systems, among others (ALVINO *et al.*, 2016; RIBEIRO *et al.*, 2017; SANTANA *et al.*, 2019), leading to numerous functional disabilities, such as delays in neuropsychomotor development, visual and auditory disorders, dysphagia and severe seizures (ALVES *et al.*, 2018; COLUCCI, 2016). Thus, considering the broad spectrum of organic systems affected, the concept of Zika Virus congenital syndrome (ZVCS) was defined.

The Zika epidemic in 2015/2016 represented one of the greatest public health emergencies in history, comprising more than 216,000 cases of people infected in Brazil in 2016. This number has been decreasing over the past years, however, in 2020, 7,387 probable cases were still registered (BRASIL, 2021).

In Brazil, the history of children who were affected by the ZVCS has completed seven years, and these patients are permanently dependent on multidisciplinary care in order to achieve better quality of life. Nevertheless, the scientific interest on the topic has been significantly decreasing, given the small number of studies published between 2018 and 2022. In spite of this, additional investigations on the functional changes and disabilities of children with ZVCS remain necessary. Thus, this study aims to describe the body structures affected by the teratogenic potential of ZVCS, in order to systematize the anomalies detected and make this knowledge available to health professionals and to the scientific community.

Methods

The present narrative review was carried out between June 2020 and January 2022, and included scientific publications that addressed fetal organic structures that were affected by the teratogenic effects of ZVCS, published between 2016 and 2022. The research encompassed the following databases: *Portal de Periódicos* CAPES, MEDLINE (via PubMed), Scopus, LILACS and SciELO (via *Biblioteca Virtual da Saúde)*. The search strategy comprised the following descriptors and keywords: Zika virus, Zika Virus Infection, Congenital abnormalities, Congenital Zika Syndrome, and Microcephaly; Their variations in Portuguese were also applied.

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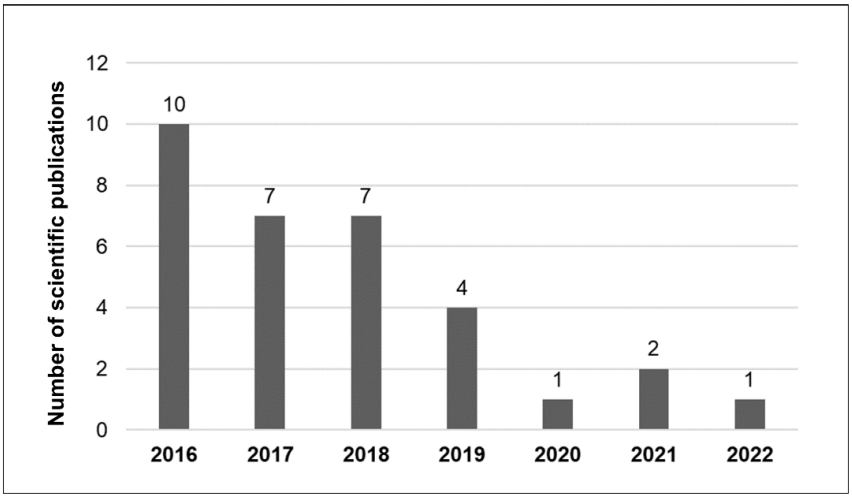
The number of studies that addressed the teratogenic potential of ZV and were included in this review are exhibited in Figure 1.

Figure 1. Number of studies included in this review per publication year.



Results and Discussion

Publications demonstrate that ZV is a teratogenic agent that may lead to morphological abnormalities in several body structures. In the present review, the included studies identified anomalies in cranium, orofacial structures, nervous system, joints, visual pathway and thoracic viscera, which are summarized in Table 1.

Table 1. Body structures affected by the teratogenic potential of Zika virus congenital syndrome and their respective anomalies detected by the studies included in this review.

Body structure	Anomalies detected	Authors
Cranium	Microcephaly	Ribeiro *et al*., (2017); Schuler-Faccini *et al*., (2016); Aguilar Ticona *et al.*, (2021); Freitas *et al.*, (2016).
	Occipital prominence and skull sutures eversion	Ribeiro *et al*., (2017); Schuler-Faccini *et al*., (2016).
	Redundant scalp	Ribeiro *et al*., (2017); Schuler-Faccini *et al*., (2016); Lima *et al*., (2016).
Nervous system	Decreased brain volume	Mlakar *et al*., (2016); Ribeiro *et al*., (2017); Schuler-Faccini *et al*., (2016); Cabral *et al*., (2017); Eickmann *et al*., (2016).
	Myelination delay	
	Decreased number of neurons	
	Cerebral asymmetries	
	Corpus callosum hypoplasia	
	Ventriculomegaly	
	Periventricular and cortical calcifications	Ribeiro *et al*., (2017); Alves *et al.*, (2018); Carvalho *et al.*, (2019).
	Spinal cord thinning	Mlakar *et al*., (2016); Ribeiro *et al*., (2017).
	Decrease number of axons in spinal nerves	

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Body structure	Anomalies detected	Authors
Joints	Arthrogryposis	Alvino *et al.*, (2016); Van Der Linden *et al.*, (2016); Aragão *et al.*, (2017).
	Congenital clubfoot	Alvino *et al.*, (2016).
Orofacial region	Delayed tooth eruption	Carvalho *et al.*, (2019); D'agostino (2018); Siqueira *et al.*, (2018); Marinho *et al.*, (2020).
	Alteration in tooth eruption sequence	
	Changes in shape and number of theeth	
	Tooth enamel opacity and hypoplasia	
	High-arched palate	
	Gingival hyperplasia	
	Labial and lingual frenulum shortening	
	Dolicocephalic facial pattern	
Visual pathway	Chorioretinal atrophy	Freitas *et al.*, (2016); Ventura *et al.*, (2016); Roth *et al.*, (2018).
	Focal pigment spots in the macular area	
	Optic nerve hypoplasia and cupping	
Thoracic viscera	Patent ductus arteriosus	Santana *et al.*, (2019).
	Atrial and ventricular septal defects	
	Right atrium and ventricle dilatation	
	Pulmonary hypoplasia	Sousa *et al.*, (2017).
	Reduced lung weight	

Cranial abnormalities

Cranial abnormalities in ZVCS may comprise microcephaly, occipital prominence, skull sutures eversion, besides redundant scalp, which will be better detailed as follows.

Microcephaly

Microcephaly, classified as a disruption, has become the most prominent and popular sign of ZVCS. This sign is characterized by the occurrence of a small congenital skull.

Disruption is the interruption of the normal course of a process. In the health sciences field, it is defined as a morphological abnormality observed in an organ, part of it or even in a large region of the body, resulting from a disarrangement on the originally normal development process, which is compromised by interference of an extrinsic factor. In the ZVCS, the extrinsic factor that leads to this disruption is the ZV infection itself, which crosses the placental barrier, reaches the brain tissue and interferes with brain growth, and may even lead to degeneration accompanied by regression in brain size. Consequently, skull growth, which accompanies brain growth, is also interfered with.

About 90% of microcephalies are associated with mental retardation. The remaining 10% fall into hereditary microcephalies, in which the skull is smaller than the average size, but there is no impairment in cognitive development (RIBEIRO *et al.*, 2017; SCHULER-FACCINI *et al.*, 2016). Throughout the prenatal period, several fetal's anthropometric parameters are evaluated, including body length and weight, head, chest and abdominal circumferences. Head circumference, also called occipitofrontal circumference, is assessed in newborns by placing a measuring tape over the forehead, just above the eyes, above the ears, and over the occipital protuberance. When the head circumference falls into 2 standard deviations below the average line for a given age or gender, microcephaly is considered. In term newborns, head

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circumference is expected to be between 31.5 to 36.2 cm for girls and between 31.9 to 37 cm for boys. Also, if the occipitofrontal circumference is less than 32cm at birth, the possibility of microcephaly should be considered (AGUILAR TICONA *et al.*, 2021; FREITAS *et al.*, 2017; SCHULER-FACCINI *et al.*, 2016).

In addition, if the patient is diagnosed with microcephaly, a cranial tomography should be carried out. In case there are findings suggestive of congenital infection, the clinical assessment should consider an echocardiogram, besides blood, cerebrospinal fluid (CSF) and urine tests, ophthalmologic evaluation with fundoscopic examination and otoacoustic emission assessment (SCHULER-FACCINI *et al.*, 2016).

Occipital prominence and skull sutures eversion

Occipital prominence and skull sutures eversion are frequent findings in ZVCS, being associated with microcephaly. This association is a result of the brain development disruption, which leads to a sudden blockage in the stimulation of skull bones growth, culminating in an alteration in the shape of the bones. Thus, the occipital prominence is easily palpable and the eversion of the sutures can be visualized on imaging exams as prominences on the skull surface along the sutures (RIBEIRO *et al.*, 2017; SCHULER-FACCINI *et al.*, 2016).

Redundant scalp

The scalp encompasses the following layers, from the most superficial to the deepest ones: skin, dense connective tissue, aponeurotic layer, loose connective tissue and pericranium (DRAKE *et al.*, 2015). Just like the skull bones, the scalp also accompanies the brain growth until the disruption caused by the ZV occurs. Consequently, a leftover skin, characterized by folds in the scalp, becomes visible and palpable on the skull surface, especially in the nape region, therefore characterizing the redundant scalp (SCHULER-FACCINI *et al.*, 2016; RIBEIRO *et al.*, 2017; LIMA *et al.*, 2019).

Nervous system anomalies

Encephalon hypoplasia

Hypoplasia describes the deficient development of an organ or structure. A classical finding in encephalon hypoplasia is agyria, which is commonly observed in ZVCS as a consequence of the impairment in brain gyri formation. This process results in simplification of gyral patterns, less deep and less visible cerebral sulci, smaller brain volume, myelination delay, fewer neurons, thinning of the corpus callosum, cerebral asymmetries and a compensatory increase in the CSF space. Neuroimaging tests also exhibit poor development of the basal ganglia, as well as pontocerebellar hypoplasia.

As a compensation for the reduction in brain volume, an increase in the dimensions of the confluence of dura mater's venous sinuses can be observed. The presence of ventriculomegaly is directly related to the reduction in brain volume and may therefore stimulate skull bones growth in order to reach an average occipitofrontal circumference. Thus, the child with ZVCS will not necessarily present with a small skull suggestive of microcephaly (RIBEIRO *et al.*, 2017;).

Such abnormalities in brain structures cause delays in neuropsychomotor development, with functional impairments related to balance and motor coordination (MLAKAR *et al.*, 2016; RIBEIRO *et al.*, 2017; SCHULER-FACCINI *et al.*, 2016; CABRAL *et al.*, 2017; EICKMANN *et al.*, 2016). In addition,

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brain anomalies provide epileptic conditions, and 40% of individuals have episodes of constant epilepsy (SOBROSA, 2018).

Calcifications

Nervous tissue lesions caused by ZV induce scar formation with calcium deposits. Therefore, calcifications are frequent signs in ZVCS, especially in the cortical-subcortical transition. The calcifications observed in other congenital syndromes are usually in periventricular and cortical areas (RIBEIRO *et al.*, 2017; SCHULER-FACCINI *et al.*, 2016; EICKMANN *et al.*, 2016; VAN DER LINDEN *et al.*, 2016; PIRES *et al.*, 2019; PIMENTEL, 2021). In ZVCS, calcifications can be found even in periventricular and cortical regions, especially in newborns in which there was a significant loss of brain parenchyma volume, making it difficult to precisely locate the calcifications (congenital syndromes are usually in periventricular and cortical areas (RIBEIRO *et al.*, 2017; ALVES *et al.*, 2018; CARVALHO *et al.*, 2019).

Spinal cord and spinal nerves anomalies

Proportionately to the brain volume reduction observed in ZVCS, spinal cord thinning is also evident, involving its descending anterior tracts and reduction in the number of axons in spinal nerves (RIBEIRO *et al.*, 2017; SCHULER-FACCINI *et al.*, 2016).

Joint anomalies

There is evidence that the greater severity of developmental changes in the brain, spinal cord and spinal nerves, the greater the incidence of joint abnormalities in children with ZVCS. Thus, the importance of orthopedic monitoring is reinforced, as musculoskeletal deformities secondary to neurological impairments may occur (ALVINO *et al.*, 2016; SCHULER-FACCINI *et al.*, 2016; ARAGAO *et al.*, 2017). Considering this scenario, arthrogryposis and congenital clubfoot were reported as the main joint anomalies found in ZVCS.

Arthrogryposis is defined as congenital joint contractures involving at least two different areas of the body, mainly in the upper and lower limbs, being frequent in ZVCS (ALVINO *et al.*, 2016; RIBEIRO *et al.*, 2017; VAN DER LINDEN *et al.* , 2016; ARAGAO *et al.*, 2017).

The pathological mechanism for such disorder is related to the absence of active fetal movements (akinesia), usually around the eighth week of pregnancy. However, fetal akinesia for at least three weeks is already capable of causing changes in the joint system that result in fibrosis of the periarticular structures. Besides, direct injury to peripheral motor nerves also seems to influence on this scenario. Therefore, ZV infection in the early stages of embryogenesis may cause peripheral motor nerve damage and fetal akinesia, with consequent joint stiffness and arthrogryposis (ALVINO *et al.*, 2016).

Van der Linden *et al.* (2016) state that arthrogryposis is another consequence of ZVCS, but its occurrence is not directly correlated to the severity of the case, as babies without microcephaly – a less severe condition – could also present with arthrogryposis. On the other hand, Aragão *et al.* (2017) pointed out a correlation between the presence of arthrogryposis and more severe brain tissue damage, with greater number of cerebral and infratentorial calcifications, besides greater cerebellum and brainstem hypoplasia.

Furthermore, arthrogryposis may also be accompanied by congenital clubfoot. This type of joint alteration requires management by a multidisciplinary team that involves pediatricians, orthopedists,

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physical therapists and occupational therapists. Treatment includes the use of orthotics, surgery and rehabilitation (ALVINO *et al.*, 2016).

Orofacial anomalies

The orofacial alterations that affect patients with ZVCS are: delayed tooth eruption, which mainly affects the lateral incisors; alterations in tooth eruption sequence, as well as changes in the shape and number of teeth. Besides, tooth enamel analysis evidenced opacity and hypoplasia of such tooth layer.

Inadequate tongue posture is also characteristic of ZVCS and causes palate abnormal growth, which becomes deeper and narrower, being classified as high-arched palate. Periodontal diseases, gingival hyperplasia, and shortening of the labial and lingual frenulum are also evident in children with ZVCS.

In addition, patients with such disorder exhibit a typical dolichocephalic facial pattern, which is defined as an elongated skull, whose transverse diameter is much smaller than the anteroposterior diameter (CARVALHO *et al*., 2019; D'AGOSTINO, 2018; SIQUEIRA *et al.*, 2018; MARINHO *et al.*, 2020).

These orofacial imbalances suggest disharmonies of the stomatognathic system and may compromise the dynamics of craniofacial growth, causing chewing, swallowing, phonation and breathing disfunctions (MARINHO *et al.*, 2020). In addition, the findings reinforce the importance of dental surgeon participation in the multidisciplinary teams that supports patients with ZVCS.

Visual pathway anomalies

Ophthalmologic lesions are quite common in children with ZVCS. Focal pigment spots and chorioretinal atrophy, with a predilection for the macular area, as well as optic disc abnormalities are frequent, which compromise visual acuity. Therefore, it is essential that these children undergo a routine ophthalmological evaluation, which may even help in the differential diagnosis between ZVCS and other congenital syndromes.

Moreover, eye retinographies of babies with ZVCS commonly demonstrate two anomalies related to the optic nerve: hypoplasia of the optic nerve, due to nerve malformation, as well as increased cupping of such nerve. The latter finding leads to slow and progressive retinal ganglion cells death as a result of deficient vascularization and nutrition, with a consequent reduction in the number of optic nerve fibers (FREITAS *et al.*, 2016; VENTURA *et al.*, 2016; ROTH *et al.*, 2022).

Thoracic viscera anomalies

Zika virus infection in adults has been associated with changes in several organs, including heart, lungs, liver and kidneys. Cardiological changes, such as myocarditis, ventricular dilatation, arrhythmias and heart failure due to Zika virus infection have already been reported in adults (MINHAS *et al*., 2017; FERREIRA *et al*., 2018). Nevertheless, few studies investigated anomalies in such organs in the spectrum of ZVCS.

Brasil *et al.* (2016), suggested a possible association between congenital heart anomaly and ZV infection in the fetal period. This possibility is corroborated in the study carried out by Orofino *et al.* (2018), which evaluated 120 children exposed to ZV during the fetal period. The findings indicated that half of the sample presented with persistent ductus arteriosus, atrial or ventricular septal defects, though none of the cases was considered severe.

Posteriorly, another study comprising children with ZVCS who underwent echocardiography exams identified structural changes in the pulmonary veins, atrioventricular septum malformation and patent ductus arteriosus in a two-month-old baby, compromising oxygenation level in arterial blood for the systemic circulation. In addition, the authors also identified right atrium and ventricle dilatation in a two-year-old and in a four-month-old children with ZVCS (SANTANA *et al.*, 2019).

Pulmonary changes related to congenital Zika virus infection were also identified in a study conducted by Sousa et al in 2017 (SOUSA *et al.*, 2017). In this study, it was observed that all infected neonates had pulmonary hypoplasia, with reduced relative lung weight. These findings were associated with clinical features, such as intra-alveolar hemorrhage, interstitial lymphocytic pulmonary infiltration and expansion of alveolar septa.

Conclusions

The present review gathered knowledge regarding body structures affected by the teratogenic potential of ZVCS, being a helpful source of information to health professionals, as well as to the scientific community.

Despite the teratogenic potential of ZV, the large number of children who have this congenital syndrome and the lack of a vaccine to prevent new cases, the number of scientific studies related to the ZVCS have reduced in recent years. Such fact has been justified by the lack of interest of scientific journals, due to the fact that such congenital syndrome is considered a local problem.

Nevertheless, the continuity of developing basic and applied scientific research on this topic is essential for improving techniques to prevent the emergency of new ZV epidemics, as well as for better understanding the mechanisms underlying the congenital anomalies found in the children infected.

Finally, the advancement of scientific knowledge on all aspects involving the ZVCS should be encouraged, in search of greater effectiveness in the therapeutic management of this syndrome, as the children affected are now reaching their seventh year of life and will keep on demanding multidisciplinary health approach.

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