BOCA
BOLETIM DE CONJUNTURA

# COMMONLY AFFECTED BRAIN AREAS IN CHILDREN WITH CONGENITAL ZIKA SYNDROME: ANATOMICAL PATTERNS AND FUNCTIONAL CONSEQUENCES

# ÁREAS DO CÉREBRO COMUMENTE AFETADAS EM CRIANÇAS COM SÍNDROME CONGÊNITA DO ZIKA: PADRÕES ANATÔMICOS E CONSEQUÊNCIAS FUNCIONAIS

# ÁREAS CEREBRALES COMÚNMENTE AFECTADAS EN NIÑOS CON SÍNDROME CONGÉNITO DEL ZIKA: PATRONES ANATÓMICOS Y CONSECUENCIAS FUNCIONALES

10.56238/bocav25n77-023

**Leila Maria Guissoni Campos**[1]

## ABSTRACT

Congenital Zika Syndrome (CZS) affects the fetal central nervous system (CNS) during pregnancy, resulting in specific neurological, cognitive and functional consequences. As this syndrome has only recently been identified, the full extent of its phenotypic and functional expression throughout childhood remains unclear. Objective: This review aims to explore anatomical patterns of major brain involvement in children with CZS, while also integrating emerging evidence on associated motor, cognitive and behavioural impairments. Methods: A review was conducted of studies involving children with microcephaly and confirmed Zika virus (ZIKV) infection. Neuroimaging findings were analyzed in relation to clinical advances, with particular attention to the CNS regions most and least affected by ZIKV. Results: Most studies report a predominance of major morphological anomalies in the cortical and subcortical regions, with the cerebellum and brainstem being relatively unaffected. Combined with the chronology of brain development and the possible differential expression of viral receptors, these findings reinforce the hypothesis that ZIKV's preference for certain cell populations plays a central role in the pathogenesis of the syndrome. Furthermore, the blood–brain barrier may contribute to the regional selectivity of the infection, providing partial protection to certain regions. Conclusions: A deeper understanding of the complex interplay between the pathophysiological mechanisms of the virus, neuroanatomical development and clinical manifestations is essential to improve our understanding of the CZS phenotype.

**Keywords:** Microcephaly. Development. Zika Virus. Brainstem.

## RESUMO

A síndrome congênita do Zika (SCZ) afeta o sistema nervoso central (SNC) fetal durante a gravidez, resultando em consequências neurológicas, cognitivas e funcionais específicas. Como essa síndrome foi identificada recentemente, o espectro completo de sua expressão

[1] Dr. in Morphofunctional Sciences. Universidade de São Paulo (USP), Universidade de Marília (UNIMAR).
E-mail: guissoni.campos@gmail.com Orcid: https://orcid.org/0000-0002-2344-4750
Lattes: http://lattes.cnpq.br/5621196835928915

fenotípica e funcional ao longo da infância ainda não está claro. Objetivo: esta revisão tem como objetivo explorar os padrões anatômicos de comprometimento cerebral em crianças com CZS, integrando também evidências emergentes sobre associação com distúrbios motores, cognitivos e comportamentais. Métodos: foi realizada uma revisão de estudos envolvendo crianças com microcefalia e confirmação de infecção pelo Zika vírus (ZIKV). Os achados de neuroimagem foram analisados em relação aos avanços clínicos, com atenção particular às regiões do SNC mais e menos afetadas pelo ZIKV. Resultados: a maioria dos estudos relata uma predominância de grandes anomalias morfológicas nas regiões corticais e subcorticais, com o cerebelo e o tronco encefálico relativamente pouco afetados. Juntamente com a cronologia do desenvolvimento cerebral e a possível expressão diferencial de receptores virais, esses achados reforçam a hipótese de que a preferência do ZIKV por certas populações de células desempenha um papel central na patogênese da síndrome. Além disso, a barreira hematoencefálica pode contribuir para a regionalidade da infecção, proporcionando proteção parcial a determinadas regiões. Conclusões: um entendimento mais aprofundado da complexa interação entre os mecanismos fisiopatológicos do vírus, o desenvolvimento neuroanatômico e as manifestações clínicas é essencial para aprimorar nossa compreensão do fenótipo da SCZ.

**Palavras-chave:** Microcefalia. Desenvolvimento. Vírus Zika. Tronco Encefálico.

**RESUMEN**

El síndrome congénito del Zika (CZS) afecta al sistema nervioso central (SNC) fetal durante la gestación, lo que provoca consecuencias específicas en el ámbito neurológico, cognitivo y funcional. Al ser esta enfermedad de reciente identificación, se desconoce la expresión fenotípica y funcional completa a lo largo de la infancia. El objetivo de esta revisión es explorar los patrones anatómicos de afectación cerebral en niños con CZS, integrando también la evidencia emergente sobre las alteraciones motoras, cognitivas y de comportamiento asociadas. Métodos: se realizó una revisión de estudios que incluían a niños con microcefalia y confirmación de infección por el virus del Zika (ZIKV). Se analizaron las imágenes neurológicas en relación con los avances clínicos, prestando especial atención a las regiones del SNC más y menos afectadas por el ZIKV. Resultados: la mayoría de los estudios informan de una mayor prevalencia de anomalías morfológicas importantes en las regiones corticales y subcorticales, mientras que el cerebelo y el tronco encefálico resultan relativamente menos afectados. Junto con la cronología del desarrollo cerebral y la posible expresión diferencial de los receptores virales, estos resultados refuerzan la hipótesis de que la preferencia de ZIKV por determinadas poblaciones celulares desempeña un papel central en la patogénesis del síndrome. Además, la barrera hematoencefálica puede contribuir a la selectividad regional de la infección, proporcionando una protección parcial a ciertas regiones. Conclusiones: es esencial comprender mejor la compleja interacción entre los mecanismos patogénicos del virus, el desarrollo neuroanatómico y las manifestaciones clínicas para mejorar nuestra comprensión del fenotipo CZS.

**Palabras clave:** Microcefalia. Desarrollo. Virus Zika. Tronco Encefálico.

## 1 INTRODUCTION

Congenital intracranial infections can be transmitted transplacentally during fetal development or when passing through an infected birth canal. These infections can be caused by a variety of viruses, protozoa, bacteria and fungi, all of which can significantly affect the central nervous system (CNS) (Sahu et al., 2009). In recent years, congenital Zika syndrome (CZS), which is caused by infection with the Zika virus (ZIKV), has emerged as a major public health concern, particularly in Latin America (Quicke, 2016).

The ZIKV epidemic gained prominence in mid-2015 when an increase in microcephaly cases among newborns was identified in north-eastern Brazil (Campos et al., 2015; Heukelbach et al., 2016). Since then, the clinical phenotype of CZS has been systematically characterised and described, revealing a combination of brain malformations, physical anomalies, and severe functional impairments (del Campo et al., 2017; Mehrjardi et al., 2017; Schuler-Faccini et al., 2016).

ZIKV belongs to the Flavivirus genus, which comprises approximately 70 viruses. Its high mutation rate and lack of proofreading mechanisms during RNA replication confer a high degree of adaptability and genomic variability (Huang, 2014). These features partly explain its neurotropism and the severity of neurological damage when infection occurs during critical stages of embryogenesis and fetal organogenesis. Therefore, the stage of fetal development at the time of infection is a key determinant of the extent of neurological impairment (Sahu et al., 2009).

Phenotypically, CZS is classically defined by five core features: severe microcephaly with craniofacial disproportion; presence of cortical and subcortical calcifications; ophthalmological abnormalities (macular scarring and retinal pigment mottling); congenital contractures; and early hypertonia with extrapyramidal signs (Aragão et al., 2016; Aragão et al., 2017; Duarte, 2017; Melo et al., 2020; Moore et al., 2017; van der Linden et al.).

The microcephaly observed in cases of CZS reflects a profound disruption to neurological development. This is manifested both functionally and morphologically as reduced brain volume and head circumference. Key clinical features include severe microcephaly, subcortical calcifications, cortical thinning, ophthalmological abnormalities (such as macular lesions and retinal pigmentary changes), congenital joint contractures and generalized hypertonia with pyramidal and extrapyramidal signs. Less frequently, anomalies are also observed in the infratentorial structures, namely the brainstem and cerebellum (Aragão et al., 2016; Aragão et al., 2017; Duarte, 2017; Moore et al., 2017).

Despite the extensive phenotypic characterization of CZS (Carvalho et al., 2017; Mehrjardi et al., 2017; Pinato et al., 2018; Schuler-Faccini et al., 2016; van der Linden et al.,

2016), discussion remains limited regarding the factors that govern the specific pattern and severity of involvement across different brain regions. This is a significant gap because the integrity of discrete neural structures is fundamental to cognitive, autonomic and behavioural functions. Hence, multiple morphological anomalies can broadly compromise CNS function and give rise to a spectrum of functional deficits (Carvalho et al., 2017; del Campo et al., 2017; Moore et al., 2017).

Furthermore, clinical studies demonstrate that children with CZS frequently exhibit severe motor impairments, such as spasticity, dystonia and arthrogryposis, which are consistent with the cortical and subcortical lesions observed on neuroimaging (van der Linden et al., 2018; Melo et al., 2020). These motor deficits typically result in pronounced delays in postural control and locomotion, with many children being unable to sit or walk independently by the age of two (Ribeiro et al., 2022).

In addition to motor deficits, significant cognitive impairments have been widely reported. These include severe intellectual disability, reduced attentional capacity, and language acquisition difficulties. These deficits correlate with cortical thinning and reduced gyrification, particularly in the frontal and temporal regions (Oliveira-Szejnfeld et al., 2016; Almeida et al., 2019). Behaviorally, irritability, sleep disturbances, and diminished responsiveness to social stimuli have been documented, suggesting affective dysregulation and sensory processing impairments. These phenomena are potentially linked to lesions in limbic structures and thalamocortical circuits (Pinato et al., 2018; van der Linden et al., 2018).

The long-term functional consequences of these neurodevelopmental impairments include high caregiver dependence for basic activities, profound communication challenges, and limited social engagement. These consequences negatively affect the quality of life of children and their families (Leal et al., 2017; Lima et al., 2025). In this context, the present review aims to delineate the morphological pattern of brain involvement and its functional sequelae by examining correlations with motor, cognitive, and behavioral outcomes documented in the literature.

By integrating structural and functional data, we aim to enhance our comprehension of the mechanisms underlying the neurological phenotype of CZS and inform the development of more effective clinical protocols. Characterizing these patterns of cerebral involvement may enable more accurate prognostication of neurological dysfunction and guide individualized clinical interventions and rehabilitation strategies.

## 2 MATERIAL AND METHODS

### 2.1 DATABASES AND SEARCH STRATEGY

The databases were used for the research: PubMed, LILACS, EMBASE, Cochrane Library, Web of Science and q. Search strategies formulated in English were based on DeCS/MeSH (Health Sciences Descriptors/Medical Subject Headings) terms: keywords “Zika virus”, “neuroimaging”, “magnetic resonance imaging (MRI)”, “computed tomography (CT)”, articulated with the Boolean operator “AND” and the term “Zika virus”.

### 2.2 INCLUSION AND EXCLUSION CRITERIA

The initial screening of the search strategies involved restricting the publication date of articles to between 2016 and 2025. Prospective cohort studies involving follow-up, case-control studies, neuroimaging, case series with a confirmed CZS diagnosis (laboratory or clinical radiological), and studies evaluating neurological outcomes were considered. Consequently, letters, abstracts, editorials, conference proceedings and experimental studies involving animals were disregarded in the final selection process. Studies without clear delimitation of the CZS group or without data on neurological characteristics were disregarded. Article selection and bias determination were performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol and the Cochrane Handbook for Systematic Reviews of Interventions (Cumpston et al., 2019; Page et al., 2021, 2022). Data extraction was performed using the PICO method (Population, Intervention, Comparison, and Outcome).

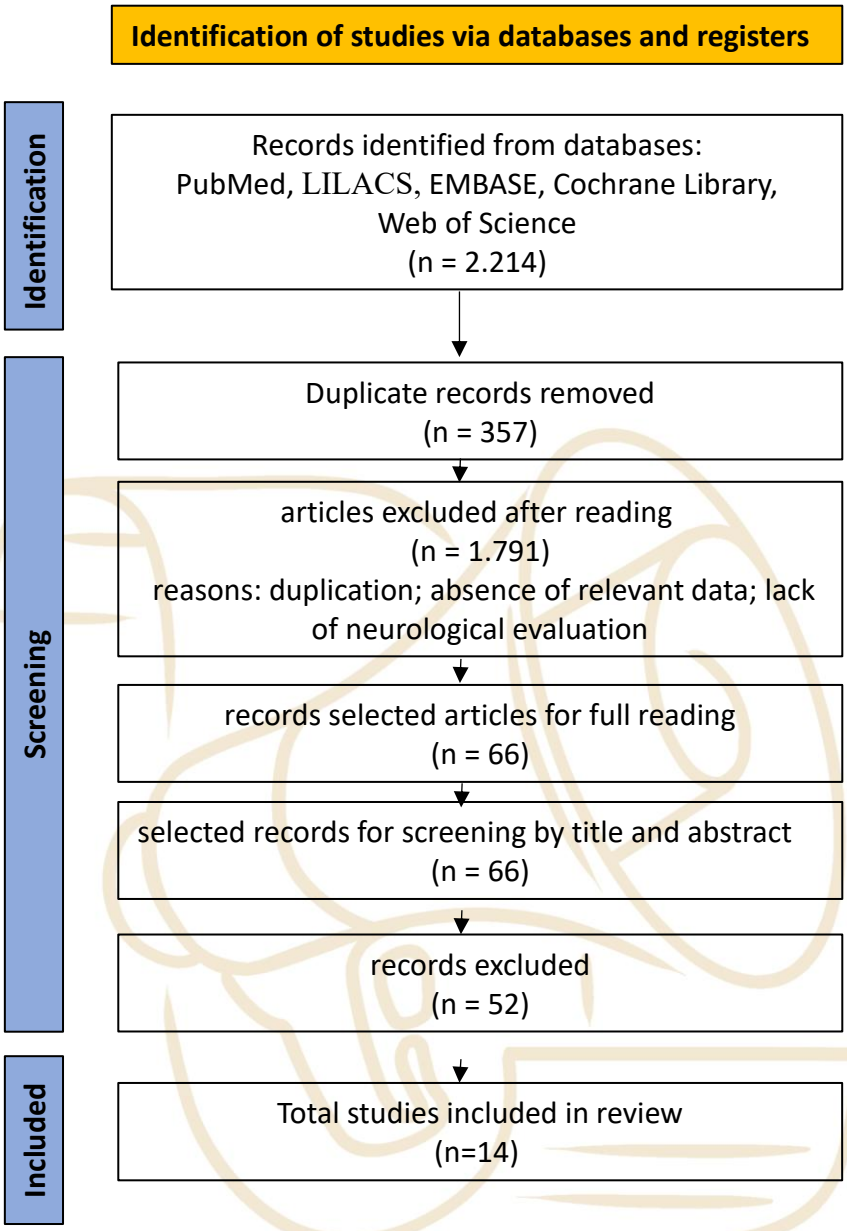
## 3 RESULTS

Initially, 2.214 publications were selected following research involving the application of two filters: temporality (2016–2025) and open access. Following the inclusion and exclusion processes, 14 articles were selected for the review (Fig 1).

Flowchart of the paper selection process.

**Figure 1**

*Flowchart of the paper selection process. Identification of studies via databases. (Author)*




All included studies presented primary data obtained using neuroimaging, MRI and/or CT scans in individuals with confirmed or presumed Zika virus infection. The studies comprised clinical cohorts, case series and descriptive diagnostic investigations conducted between 2016 and 2025. Critical exclusion was conducted based on predefined eligibility criteria and the clinical applicability of the neuroimaging data.

## 3.1 PREDOMINANT NEUROLOGICAL INVOLVEMENT

An integrated analysis of these studies reveals consistent patterns of morphological abnormalities that are compatible with severe microcephaly. These abnormalities include cortical thinning, subcortical calcifications, ventriculomegaly, and cortical malformations.

Frequently observed features include enlarged ventricles, multiple punctate calcifications, and diffuse cortical thinning. In some cases, lissencephaly is present, which is characterized by a smooth cortical surface with reduced sulcation, indicating neuronal migration defects (Aragão et al., 2016; Ribeiro et al., 2020). In addition to cortical changes, focal white matter lesions have been identified, with fewer abnormalities noted in the cerebellum. However, the cerebellum and brainstem generally demonstrate preserved morphology with no major structural anomalies evident in most evaluated cases (Aragão et al., 2016; Aragão et al., 2017; Castro et al., 2023; de Castro et al., 2017; Peixoto Filho et al., 2018; Pires et al., 2018). Table 1.

**Table 1**

*Description of the main brain areas showing signs of neurological involvement and morphological preservation, based on literature data on microcephaly caused by ZIKV infection.(Author)*

| BRAIN | CEREBELLUM | BRAINSTEM |
|---|---|---|
| • Craniofacial disproportion;<br>• Scattered brain calcifications in cortical and subcortical areas;<br>• Global and diffuse reduction in brain volume;<br>• Atrophy – thinning;<br>• Ventricular dilation;<br>• Reduction in the number of gyri and sulci;<br>• Thickened gyri;<br>• Decreased white matter;<br>• Mild craniofacial disproportion;<br>• Reduced number of calcifications in cortical and subcortical areas;<br>• Mild ventricular dilation;<br>• Mild reduction in the number of gyri and sulci;<br>• Decreased white matter; | • Slight asymmetry<br><br>• Habitual Neuro-Morphological Pattern ( in most of the childrens) | • Habitual Neuro-Morphological Pattern |

The severity of these malformations, particularly the degree of microcephaly at birth, is strongly correlated with the risk of neurological complications. Longitudinal studies indicate that more severe microcephaly often progresses to multiple functional deficits, including neuropsychomotor delay, delayed communication and auditory skills, dysphagia, epilepsy, severe cerebral palsy, sensory disturbances (e.g., hearing and vision loss), sleep disorders, persistence of primitive reflexes, dystonia, and urinary incontinence (Almeida et al., 2022; Leal et al., 2017; Pool et al., 2019; Sanz-Cortés et al., 2018; Ventura et al., 2016). Most of the reviewed studies were conducted in Brazil, which experienced the majority of epidemic cases. Each study used at least one imaging technique for diagnosis, particularly magnetic resonance imaging and computed tomography, as shown in Table 2. This table summarizes the main methodological details and clinical results of the included articles.

**Table 2**

*US – Ultrasound; CT – Computed Tomography; head circumference (HC); MRI – Magnetic Resonance Imaging; (Author)*

| AUTHOR (YEAR) | COUNTRY | STUDY TYPE | SAMPLE SIZE | IMAGING TECHNIQUES | MAIN FINDINGS | DOI |
|---|---|---|---|---|---|---|
| **ARAGÃO et al. (2016)** | Brazil | Case series | 23 | CT, MRI | Brain calcifications at cortico-subcortical junction, cortical malformations, corpus callosum abnormalities, ventriculomegaly, cerebellar and brainstem hypoplasia. | https://doi.org/10.1136/bmj.i1901. |
| **ARAGÃO et al. (2017)** | Brazil | Comparative case series | 77 | CT, MRI | Calcifications, corpus callosum abnormalities, ventriculomegaly, enlarged cisterna magna, polymicrogyria | https://doi.org/10.3174/ajnr.A5216 |
| **CASTRO et al. (2023)** | Brazil | Case report | 1 | US, MRI, CT | Multiple cerebral calcifications, parenchymal atrophy, ventricular dilatation, microcephaly. | https://doi.org/10.1080/15513815.2022.2118559 |
| **Daza et al. (2021)** | Colombia | Cohort | 31 | CT, MRI | ophthalmologic abnormalities and HC | https://doi.org/10.1002/bdr2.1947 |
| **de CASTRO et al. (2017)** | Brazil | Case series | 8 | CT, MRI | Ventriculomegaly, microcephaly, cerebellar atrophy, brainstem hypoplasia, corpus callosum hypogenesis, focal calcifications. | https://doi.org/10.1590/0004-282X20170134 |
| **HAZIN et al. (2016)** | Brazil | Case series | 23 | Clinical exams and CT | Cortical malformations, | https://doi.org/10.1056/NEJMc1603617 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | calcifications basal ganglia and in the thalamus, ventriculomegaly, Cerebellar hypoplasia. | |
| **LAGE et al. (2019)** | Brasil | Retrospective Cross-sectional | 102 | MRI, CT | cerebral atrophy, ventriculomegaly, malformation of cortical, and cortical–subcortical calcifications | https://doi.org/10.3390/ijerph16030309 |
| **PEIXOTO FILHO et al. (2018)** | Brazil | Descriptive study | 9 | Clinical assessment and CT, MRI | Microcephaly, calcifications, ventriculomegaly | https://doi.org/10.1590/0100-3984.2016.0135 |
| **PIRES et al. (2018)** | Brazil | Case series | 8 | CT, MRI | periventricular and/or parenchymal calcifications, asymmetrical ventriculomegaly, pachygyria, corpus callosum dysgenesis, cerebral cortex and reduced gyration and sulcation | https://doi.org/10.1007/s00381-017-3682-9 |
| **POOL et al. (2019)** | Brazil | Cohort | 110 | 3D CT | Calcifications, cortex malformations, brain volume reduction, cerebellar hypoplasia, corpus callosum abnormalities, correlated with clinical symptoms. | https://doi.org/10.1001/jamanetworkopen.2019.8124 |
| **REGADAS et al. (2018)** | Brazil | Case report | 1 | US, MRI | cranial and encephalic changes, circumference reduction, cerebral calcifications and ventriculomegaly. | https://doi.org/10.1590/1806-9282.64.01.11 |
| **RIBEIRO et al. (2020)** | Brazil | Case series | 34 | CT, MRI | calcifications, ventriculomegaly, dysgenesis of the corpus callosum, craniofacial | https://doi.org/10.1590/0037-8682-0557-2019 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | disproportion occipital prominence cerebellar hypoplasia and pontine hypoplasia | |
| **SANZ-CORTÉS et al. (2018)** | Colombia | Cohort | 12 | US, neurosonography, MRI, CT | Brain volume loss, calcifications, callosal anomalies, cortical malformations, ventriculomegaly | https://doi.org/10.1016/j.ajog.2018.01.012 |
| **WERNER et al. (2016)** | Brazil | Case report | 1 | US, MRI, CT | Pachygyria, reduced gyrification, ventriculomegaly, corpus callosum dysgenesis. Brain calcifications detected on US, not MRI. | https://doi.org/10.1002/pd.4860 |

These findings highlight the importance of structured clinical protocols, multidisciplinary team training, and future research focused on rehabilitation and functional support for children with CZS. A detailed understanding of morphological alterations can enable more accurate prognostication and guide therapeutic strategies tailored to the specific neurofunctional needs of this population.

## 4 DISCUSSION

This study examined morphological aspects associated with microcephaly in the context of CZS, characterizing the differential involvement of more- and less-affected brain regions.

### 4.1 REGIONAL VULNERABILITY AND MORPHOLOGICAL INVOLVEMENT

The specialized literature highlights recurrent neuroanatomical abnormalities in cortical and subcortical territories. These abnormalities include cortical thinning, cerebral cortex malformations, subcortical calcifications, ventriculomegaly, and corpus callosum hypoplasia. These abnormalities are often accompanied by peripheral and ophthalmologic alterations (Duarte, 2017; Moore et al., 2017). In addition to these intracerebral structural changes, impaired fetal cranial bone development—possibly resulting from suppressed osteogenesis—has also been described. This contributes to the syndrome's characteristic craniofacial deformities (Yan et al., 2019).

These variations in morphological involvement appear to reflect ZIKV selective affinity for cortical neural progenitor cells, especially during embryonic development (Dang et al., 2016; Lazear et al., 2016; Lemke & Rothlin, 2008; Li et al., 2016; Miner et al., 2016; Tang et al., 2016). Experimental studies suggest that different cell populations within the nervous and immune systems exhibit varying degrees of susceptibility to ZIKV infection. This may explain why structures such as the brainstem and cerebellum are relatively preserved (Hafizi & Dahlbäck, 2006; Meertens et al., 2017; Retallack et al., 2016).

Most of the reviewed studies link microcephaly and/or congenital CNS abnormalities to an infectious etiology characterized by the destruction of neural progenitor cells during intrauterine life, often accompanied by a persistent inflammatory response (Almeida et al., 2019; Aragão et al., 2017; Dang et al., 2016; Krow-Lucal et al., 2018; Tang et al., 2016).

Morphologically, the brainstem and cerebellum exhibit a lower degree of anatomical compromise in most evaluated cases, maintaining their typical structural pattern (Aragão et al., 2016; Aragão et al., 2017; Castro et al., 2023; de Castro et al., 2017; Peixoto Filho et al., 2018; Pires et al., 2018). This relative preservation may be associated with reduced expression of viral receptors in these regions or with their specific embryonic developmental characteristics, which occur at later stages or under more protected conditions (Cho et al., 2013; Wang et al., 2017; Zegenhagen et al., 2016).

The tropism of ZIKV for cortical progenitor cells is well-established in the literature. During the first and second trimesters of gestation—a critical period for cerebral cortex development—these cells exhibit a high proliferation rate, favoring viral entry and exacerbating structural damage in regions responsible for motor, cognitive, and behavioral function (Cho et al., 2013; Dang et al., 2016; Fensterl et al., 2012; Lazear et al., 2016; Li et al., 2016; Miner et al., 2016; Sharon & Pasko, 2022; Tang et al., 2016).

At the cellular level, the TAM receptor family (TYRO3, AXL, and MERTK) is involved in mediating ZIKV entry into neural cells, particularly through the AXL receptor. High AXL expression in cortical progenitor cells promotes viral endocytosis, modulates the immune response, and facilitates viral replication (Chen et al., 2018; Kim et al., 2017; Lemke & Rothlin, 2008; Mercer et al., 2010).

Conversely, lower expression of these receptors in the cerebellum and brainstem may explain why these areas are more resistant to viral infection (Cho et al., 2013; Fensterl et al., 2012; Hafizi & Dahlbäck, 2006; Meertens et al., 2017; Retallack et al., 2016). However, evidence suggests that additional receptors and alternative mechanisms may also mediate infection in certain contexts (Das et al., 2009; Hasan et al., 2017; Shi & Gao, 2017).

The discrepancy between the high involvement of cortical and subcortical regions and the lower virulence of brainstem and cerebellar structures underscores the need for further investigation into the mechanisms underlying the differential vulnerability of brain regions to ZIKV. Some hypotheses suggest that developing physiological barriers, such as the blood-brain barrier, may offer specific protection to certain brain regions (Liebner et al., 2018). However, this possibility remains to be explored further.

Understanding the interplay between viral mechanisms, the timing of neuroembryonic development, and the regional distribution of viral receptors is crucial to explaining the injury patterns observed in SCZ and their functional implications. This information is essential for anticipating clinical outcomes, planning longitudinal care, and improving intervention strategies for affected children.

## 4.2 ASSOCIATED NEUROLOGICAL AND FUNCTIONAL IMPAIRMENT

Morphological abnormalities observed through imaging studies are closely associated with a spectrum of neurological impairments in children with CZS. Studies show that cases with more severe microcephaly or extensive brain lesions tend to exhibit significant developmental delays, severe motor and sensory impairments, and global neurodevelopmental delays (Aragão et al., 2016; Aragão et al., 2017; Duarte, 2017; Melo et al., 2020; Moore et al., 2017; Oh et al., 2017; van der Linden et al., 2018).

Identifying possible patterns of morphological impairment contributes to understanding the origin of the functional deficiencies observed in this group. Studies have revealed that the cerebellum and brainstem tend to exhibit lesser morphological involvement in most cases. Structural alterations in cortical and subcortical regions define the neurological phenotype and directly impact a child's overall functioning. This includes total dependence on caregivers, impaired autonomy, and severe limitations in social, educational, and daily living activities (Aragão et al. , 2016; Aragão et al., 2017; Castro et al., 2023; de Castro et al., 2017; Lima et al., 2025; Peixoto Filho et al., 2018; Pires et al., 2018).

Frequently described alterations in cortical and subcortical regions include reduced cortical thickness, subcortical calcifications, corpus callosum hypoplasia, and malformations of cortical development. These alterations are associated with significant motor impairments, including spasticity, dystonia, hyperreflexia, and arthrogryposis (Melo et al., 2020; Ribeiro et al., 2022; van der Linden et al., 2018). These alterations result in significant delays in motor development, including postural and gait control. The absence of trunk support or ambulation is common even after two years of age (Ribeiro et al., 2022).

In the cognitive domain, the observed morphological pattern closely correlates with severe intellectual deficits, attention difficulties, limitations in language acquisition, and global neurodevelopmental delay (del Campo et al., 2017; Mehrjardi et al., 2017; Oliveira-Szejnfeld et al., 2016; Pinato et al., 2018; Ribeiro et al., 2022; Schuler-Faccini et al., 2016). Hypoplasia of the frontal and temporal regions, associated with reduced cortical gyrification, has been identified as the anatomical basis of these cognitive manifestations (Almeida et al., 2019; Almeida et al., 2022; Oliveira-Szejnfeld et al., 2016).

In addition to motor and cognitive deficits, the functional consequences of SCZ include relevant behavioral changes. Persistent irritability, low responsiveness to social stimuli, sleep disturbances, and sensory hyperresponsiveness are frequently reported. These symptoms suggest dysfunction in critical neural circuits for affective and sensory regulation, such as the limbic and thalamocortical systems (Pinato et al., 2018; van der Linden et al., 2018).

Given the complexity of the clinical and functional picture observed in schizophrenia, it is essential to understand how structural morphological alterations translate into neurodevelopmental impairments. This understanding is crucial for formulating individualized intervention strategies based on each child's neurofunctional profile. Furthermore, a longitudinal, interdisciplinary approach to monitoring these patients must consider neuropsychomotor developmental dynamics and overlapping functional deficits throughout childhood.

## 5 CONCLUSION

Although the cerebellum and brainstem exhibit less morphological involvement in most cases of CZS, this preservation is insufficient to offset the devastating effects of the extensive cortical and subcortical lesions commonly observed in this condition. Structural alterations in these critical regions directly correlate with the severity of motor, cognitive, and behavioral deficits in affected children.

Together with the chronology of brain development and possible differential expression of viral receptors, these findings reinforce the hypothesis that ZIKV tropism for certain cell populations plays a central role in the pathogenesis of the syndrome. Additionally, it is proposed that the developing blood-brain barrier contributes to the regional selectivity of the infection by partially protecting structures such as the cerebellum and brainstem.

Understanding the complex interplay between the virus's pathophysiological mechanisms, neuroanatomical development, and clinical manifestations is essential to deepening our understanding of the CZS phenotype. While challenging, this understanding

is essential for guiding early intervention, rehabilitation, and longitudinal monitoring strategies to mitigate functional impacts and improve the prognosis of affected children.

## ACKNOWLEDGMENTS

The author would like to thank the Graduate Program in Structural and Functional Interactions in Rehabilitation – UNIMAR.

## CONFLICT OF INTEREST

The author declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data and all supplementary materials associated with this article are available upon request and can be obtained from the corresponding author upon reasonable request.

## REFERENCES

Almeida, I. M. L. M., et al. (2019). Clinical and epidemiological aspects of microcephaly in the state of Piauí, northeastern Brazil, 2015–2016. Journal of Pediatrics (Rio J.), 95(4), S6. https://doi.org/10.1016/j.jped.2018.04.013

Almeida, L. C., et al. (2022). Hearing and communicative skills in the first years of life in children with congenital Zika syndrome. Brazilian Journal of Otorhinolaryngology, 88(1), 112–117. https://doi.org/10.1016/j.bjorl.2020.05.007

Aragão, M. F. V. V., et al. (2016). Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study. BMJ, 353, i1901. https://doi.org/10.1136/bmj.i1901

Aragão, M. F. V. V., et al. (2017). Nonmicrocephalic infants with congenital Zika syndrome suspected only after neuroimaging evaluation compared with those with microcephaly at birth and postnatally: how large is the Zika virus 'iceberg'? AJNR American Journal of Neuroradiology, 38(7), 1427–1434. https://doi.org/10.3174/ajnr.A5216

Campos, G. S., Bandeira, A. C., & Sardi, S. I. (2015). Zika virus outbreak, Bahia, Brazil. Emerging Infectious Diseases, 21(10), 1885–1886. https://doi.org/10.3201/eid2110.150847

Carvalho, M. D. C. G., et al. (2017). Sleep EEG patterns in children with congenital Zika virus syndrome. Clinical Neurophysiology, 128(9), 2040–2047. https://doi.org/10.1016/j.clinph.2016.11.004

Castro, P. T., et al. (2023). Prenatal and postnatal Zika intrauterine infection: diagnostic imaging techniques and placental pathology. Fetal and Pediatric Pathology, 42(2), 207–215. https://doi.org/10.1080/15513815.2022.2118559

Chen, J., et al. (2018). AXL promotes Zika virus infection in astrocytes by antagonizing type I interferon signalling. Nature Microbiology, 3(3), 302–309. https://doi.org/10.1038/s41564-017-0092-4

Cho, H., et al. (2013). Differential innate immune response programs in neuronal subtypes determine susceptibility to infection in the brain by positive-stranded RNA viruses. Nature Medicine, 19(4), 458–464. https://doi.org/10.1038/nm.3108

Cumpston, M., et al. (2019). Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database of Systematic Reviews, 2019(10), ED000142. https://doi.org/10.1002/14651858.ED000142

Das, S., et al. (2009). Heat shock protein 70 on Neuro2a cells is a putative receptor for Japanese encephalitis virus. Virology, 385(1), 47–57. https://doi.org/10.1016/j.virol.2008.10.025

Daza, M., et al. (2021). Clinical and neurodevelopmental outcomes based on brain imaging studies in a Colombian cohort of children with probable antenatal Zika virus exposure. Birth Defects Research, 113(18), 1299–1312. https://doi.org/10.1002/bdr2.1947

De Castro, J. D. V., et al. (2017). Presumed Zika virus-related congenital brain malformations: the spectrum of CT and MRI findings in fetuses and newborns. Arquivos de Neuro-Psiquiatria, 75(10), 703–710. https://doi.org/10.1590/0004-282X20170134

Del Campo, M., et al. (2017). The phenotypic spectrum of congenital Zika syndrome. American Journal of Medical Genetics Part A, 173(4), 841–857. https://doi.org/10.1002/ajmg.a.38170

Dang, J., et al. (2016). Zika virus depletes neural progenitors in human cerebral organoids through activation of the innate immune receptor TLR3. Cell Stem Cell, 19(2), 258–265. https://doi.org/10.1016/j.stem.2016.04.014

Duarte, G., et al. (2017). Zika virus infection in pregnant women and microcephaly. Revista Brasileira de Ginecologia e Obstetrícia, 39(5), 235–248. https://doi.org/10.1055/s-0037-1603450

Fensterl, V. L., et al. (2012). Interferon-induced Ifit2/ISG54 protects mice from lethal VSV neuropathogenesis. PLoS Pathogens, 8, e1002712. https://doi.org/10.1371/journal.ppat.1002712

Hasan, S. S., et al. (2017). A human antibody against Zika virus crosslinks the E protein to prevent infection. Nature Communications, 8, 14722. https://doi.org/10.1038/ncomms14722

Hafizi, S., & Dahlbäck, B. (2006). Signalling and functional diversity within the Axl subfamily of receptor tyrosine kinases. Cytokine & Growth Factor Reviews, 17(4), 295–304. https://doi.org/10.1016/j.cytogfr.2006.04.004

Hazin, A. N., et al. (2016). Computed tomographic findings in microcephaly associated with Zika virus. New England Journal of Medicine, 374, 2193–2195. https://doi.org/10.1056/NEJMc1603617

Heukelbach, J., et al. (2016). Zika virus outbreak in Brazil. Journal of Infection in Developing Countries, 10(2), 116–120. https://doi.org/10.3855/jidc.8217

Huang, Y. J., Higgs, S., & Vanlandingham, D. L. (2014). Flavivirus–mosquito interactions. Viruses, 6(11), 4703–4730. https://doi.org/10.3390/v6114703

Kim, S. Y., Li, B., & Linhardt, R. J. (2017). Pathogenesis and inhibition of flaviviruses from the carbohydrate perspective. Pharmaceuticals (Basel), 10(2), Article 44. https://doi.org/10.3390/ph10020044

Krow-Lucal, E. R., et al. (2018). Association and birth prevalence of microcephaly attributable to Zika virus infection among infants in Paraíba, Brazil, in 2015–16: a case-control study. The Lancet Child & Adolescent Health, 2(3), 205–213. https://doi.org/10.1016/S2352-4642(18)30020-8

Lage, M.-L. C., et al. (2019). Clinical, neuroimaging, and neurophysiological findings in children with microcephaly related to congenital Zika virus infection. International Journal of Environmental Research and Public Health, 16(3), Article 309. https://doi.org/10.3390/ijerph16030309

Lazear, H. M., et al. (2016). A mouse model of Zika virus pathogenesis. Cell Host & Microbe, 19(5), 720–730. https://doi.org/10.1016/j.chom.2016.03.010

Leal, M. C., et al. (2017). Characteristics of dysphagia in infants with microcephaly caused by congenital Zika virus infection, Brazil, 2015. Emerging Infectious Diseases, 23(8), 1253–1259. https://doi.org/10.3201/eid2308.170354

Lemke, G., & Rothlin, C. V. (2008). Immunobiology of the TAM receptors. Nature Reviews Immunology, 8(5), 327–336. https://doi.org/10.1038/nri2303

Li, C., Xu, D., & Sim, Q. (2016). Zika virus disrupts neural progenitor development and leads to microcephaly in mice. Cell Stem Cell, 19(1), 120–126. https://doi.org/10.1016/j.stem.2016.04.017

Liebner, S., et al. (2018). Functional morphology of the blood-brain barrier in health and disease. Acta Neuropathologica, 135(3), 311–336. https://doi.org/10.1007/s00401-018-1815-1

Lima, P. H. M., et al. (2025). Perception of quality of life by primary caregivers of children with congenital Zika syndrome: a cross-sectional study. Maternal and Child Health Journal, 29(3), 363–375. https://doi.org/10.1007/s10995-025-04057-y

Meertens, L., et al. (2017). Axl mediates Zika virus entry in human glial cells and modulates innate immune responses. Cell Reports, 18(2), 324–333. https://doi.org/10.1016/j.celrep.2016.12.045

Mehrjardi, M. Z., et al. (2017). Neuroimaging findings of congenital Zika virus infection: a pictorial essay. Japanese Journal of Radiology, 35(3), 89–94. https://doi.org/10.1007/s11604-016-0609-4

Melo, A., et al. (2020). Motor function in children with congenital Zika syndrome. Developmental Medicine & Child Neurology, 62(2), 221–226. https://doi.org/10.1111/dmcn.14227

Mercer, J., Schelhaas, M., & Helenius, A. (2010). Virus entry by endocytosis. Annual Review of Biochemistry, 79, 803–833. https://doi.org/10.1146/annurev-biochem-060208-104626

Miner, J. J., et al. (2016). Zika virus infection during pregnancy in mice causes placental damage and fetal demise. Cell, 165(5), 1081–1091. https://doi.org/10.1016/j.cell.2016.05.008

Moore, C. A., et al. (2017). Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. JAMA Pediatrics, 171(3), 288–295. https://doi.org/10.1001/jamapediatrics.2016.3982

Oh, Y., et al. (2017). Zika virus directly infects peripheral neurons and induces cell death. Nature Neuroscience, 20(9), 1209–1212. https://doi.org/10.1038/nn.4612

Oliveira-Szejnfeld, P. S., et al. (2016). Congenital brain abnormalities and Zika virus: what the radiologist can expect to see prenatally and postnatally. Radiology, 281(1), 203–218. https://doi.org/10.1148/radiol.2016161584

Page, M. J., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Revista Española de Cardiología, 74(9), 790–799. https://doi.org/10.1016/j.rec.2021.07.010

Page, M. J., et al. (2022). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews / Declaración PRISMA 2020. Revista Panamericana de Salud Pública, 46, e112. https://doi.org/10.26633/RPSP.2022.112

Peixoto Filho, A. A. A., et al. (2018). Computed tomography and magnetic resonance imaging findings in infants with microcephaly potentially related to congenital Zika virus infection. Radiologia Brasileira, 51(2), 119–122. https://doi.org/10.1590/0100-3984.2016.0135

Pinato, L., et al. (2018). Sleep findings in Brazilian children with congenital Zika syndrome. Sleep, 41(3), zsy009. https://doi.org/10.1093/sleep/zsy009

Pires, P., et al. (2018). Neuroimaging findings associated with congenital Zika virus syndrome: case series at the time of first epidemic outbreak in Pernambuco State, Brazil. Child's Nervous System, 34(5), 957–963. https://doi.org/10.1007/s00381-017-3682-9

Pool, K.-L., et al. (2019). Association between neonatal neuroimaging and clinical outcomes in Zika-exposed infants from Rio de Janeiro, Brazil. JAMA Network Open, 2(7), e198124. https://doi.org/10.1001/jamanetworkopen.2019.8124

Quicke, K. M., et al. (2016). Zika virus infects human placental macrophages. Cell Host & Microbe, 20(1), 83–90. https://doi.org/10.1016/j.chom.2016.05.015

Regadas, V. C., et al. (2018). Microcephaly caused by congenital Zika virus infection and viral detection in maternal urine during pregnancy. Revista da Associação Médica Brasileira, 64(1), 11–14. https://doi.org/10.1590/1806-9282.64.01.11

Retallack, H., et al. (2016). Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proceedings of the National Academy of Sciences of the United States of America, 113(50), 14408–14413. https://doi.org/10.1073/pnas.1618029113

Ribeiro, B. N. F., Muniz, B. C., & Marchiori, E. (2020). Evaluation of the frequency of neuroimaging findings in congenital infection by Zika virus and differences between computed tomography and magnetic resonance imaging. Revista da Sociedade Brasileira de Medicina Tropical, 53, e20190557. https://doi.org/10.1590/0037-8682-0557-2019

Ribeiro, C. T. M., et al. (2022). Gross motor function in children with congenital Zika syndrome from Rio de Janeiro, Brazil. European Journal of Pediatrics, 181(2), 783–788. https://doi.org/10.1007/s00431-021-04270-1

Sahu, R. N., Kumar, R., & Mahapatra, A. K. (2009). Central nervous system infection in the pediatric population. Journal of Pediatric Neurosciences, 4(1), 20–24. https://doi.org/10.4103/1817-1745.49102

Sanz-Cortés, M., et al. (2018). Clinical assessment and brain findings in a cohort of mothers, fetuses and infants infected with Zika virus. American Journal of Obstetrics and Gynecology, 218(4), 440.e1–440.e36. https://doi.org/10.1016/j.ajog.2018.01.012

Schuler-Faccini, L., et al. (2016). Possible association between Zika virus infection and microcephaly — Brazil, 2015. MMWR Morbidity and Mortality Weekly Report, 65(3), 59–62. https://doi.org/10.15585/mmwr.mm6503e2

Sharon, M. K., & Pasko, R. (2022). Development of prefrontal cortex. Neuropsychopharmacology, 47(1), 41–57. https://doi.org/10.1038/s41386-021-01137-9

Shi, Y., & Gao, G. F. (2017). Structural biology of the Zika virus. Trends in Biochemical Sciences, 42(6), 443–456. https://doi.org/10.1016/j.tibs.2017.02.009

Tang, H., et al. (2016). Zika virus infects human cortical neural progenitors and attenuates their growth. Cell Stem Cell, 18(5), 587–590. https://doi.org/10.1016/j.stem.2016.02.016

Van der Linden, V., et al. (2016). Description of 13 infants born during October 2015–January 2016 with congenital Zika virus infection without microcephaly at birth — Brazil. MMWR Morbidity and Mortality Weekly Report, 65(47), 1343–1348. https://doi.org/10.15585/mmwr.mm6547e2

Ventura, C. V., et al. (2016). Risk factors associated with the ophthalmologic findings identified in infants with presumed Zika virus congenital infection. JAMA Ophthalmology, 134(8), 912–918. https://doi.org/10.1001/jamaophthalmol.2016.1784

Wang, Z.-Y., et al. (2017). Axl is not an indispensable factor for Zika virus infection in mice. Journal of General Virology, 98(8), 2061–2068. https://doi.org/10.1099/jgv.0.000886

Werner, H., et al. (2016). First-trimester intrauterine Zika virus infection and brain pathology: prenatal and postnatal neuroimaging findings. Prenatal Diagnosis, 36(8), 785–789. https://doi.org/10.1002/pd.4860

Yan, Y., et al. (2019). Zika virus induces abnormal cranial osteogenesis by negatively affecting cranial neural crest development. Infection, Genetics and Evolution, 69, 176–189. https://doi.org/10.1016/j.meegid.2019.01.023

Zegenhagen, L., et al. (2016). Brain heterogeneity leads to differential innate immune responses and modulates pathogenesis of viral infections. Cytokine & Growth Factor Reviews, 30, 95–101. https://doi.org/10.1016/j.cytogfr.2016.03.006