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# Congenital Zika Virus Infection: a Review with Emphasis on the Spectrum of Brain Abnormalities

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## Abstract

**Purpose of Review** In 2016, the World Health Organization declared the Zika virus (ZIKV) outbreak a Public Health Emergency of International Concern following a cluster of associated neurological disorders and neonatal malformations. Our aim is to review the clinical and neuroimaging findings seen in congenital Zika syndrome.

**Recent Findings** ZIKV injures neural progenitor cells in the hippocampus, a brain region important for learning, memory, cognition, and emotion/stress response. Positron emission tomography has revealed global neuroinflammation in ZIKV infection in animal models.

**Summary** Congenital Zika syndrome is associated with a spectrum of brain abnormalities, including microcephaly, parenchymal calcifications, malformations of cortical development and defective neuronal migration, corpus callosum abnormalities, ventriculomegaly, and brainstem and cerebellar abnormalities.

**Keywords** Zika virus · Zika virus infection · Microcephaly · Neuroimaging

## Introduction

Zika virus (ZIKV) is a positive-sense single-stranded RNA virus belonging to the *Flaviviridae* family [1]. It was first isolated in 1947 from the serum of a sentinel Rhesus monkey in the Zika forest of Uganda [2]. In 2007, the virus emerged in the Federated States of Micronesia and affected approximately 75% of the population (approximately 5000 infections) within a few months [3]. During the first 60 years of its known existence, fewer than 20 human infections were recorded [4]. In November 2016, the transmission of ZIKV spread to over 48 countries [5].

## Transmission

ZIKV is transmitted primarily by the *Aedes* mosquito species, especially by *Aedes aegypti* and *Aedes albopictus*, but can also be transmitted from human to human through blood transfusions, sexual intercourse, and during pregnancy [6]. Vertical transmission occurs presumably through the placenta, although can also occur through breast milk or by a blood-borne route [7]. The risk of developing congenital Zika Syndrome (CZS) is increased when the infection occurs in the first trimester [8].

## Definition of Congenital Zika Syndrome

CZS results from vertical transmission of ZIKV from an infected woman to the fetus during pregnancy [7]. Although many of the signs and symptoms of this syndrome are shared by other congenital infections, five features differentiate CZS from other congenital infections: (1) severe microcephaly with partially collapsed skull, (2) thin cerebral cortices with

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subcortical calcifications, (3) macular scarring and focal pigmentary retinal mottling, (4) congenital contractures, and (5) marked early hypertonia [9].

Suspected cases of CZS can be classified, based on neuroimaging and laboratory results for ZIKV and other relevant infections. Definite cases are those with laboratory evidence of ZIKV infection. Probable cases present with characteristic neuroimaging findings without laboratory evidence of ZIKV infection, but negative laboratory results for other congenital infections [10].

## Possible Explanations for the Outbreak of ZIKV

A single serine-to-asparagine substitution in the viral polyprotein substantially increased ZIKV infectivity. Evolutionary analysis indicates that this sequence variation occurred just before the outbreak in French Polynesia and has been maintained during subsequent spread to the Americas [11]. The outbreak of ZIKV can also be explained based on the structural similarity between ZIKV and dengue viruses. The antibodies produced against these flaviviruses can cross-react without neutralization of the virus and can also enhance ZIKV infection [12], a process known as antibody-dependent enhancement [13].

In addition to previous explanations for the outbreak of ZIKV listed above, ZIKV infection of the vector *A. aegypti* can also cause neuroexcitation in mosquitoes, that could contribute to increased diurnal locomotion activity compared with uninfected females, increasing the chances of transmission to new susceptible hosts [14].

## Decline in ZIKV Incidence

In 2017, there was a marked decline in reported ZIKV cases and its severe disease manifestations [15]. In addition, there has also been a relevant decline in the incidence of dengue and chikungunya cases in Brazil, suggesting a possible role for climatic and other factors affecting mosquito density or cross-immunity between arboviruses [16].

## Neuropathology

### Pathogenesis

The microcephaly and structural brain abnormalities associated with CZS are the consequences of in utero destruction of neural progenitor cells and persistent inflammatory response–associated molecules [5]. It is also known that ZIKV infection suppresses cranial osteogenesis, which can be associated with craniofacial bone malformations. Combined with neural progenitor cell loss and the resulting microcephaly, these can

account for the cardinal features of ZIKV-mediated birth defects [17].

## Neurotropism and Histopathological Findings

The spectrum of histopathological findings can be summarized as follows: (1) malformations of cortical development, represented by abnormal bands of germinal matrix towards the cortex, meningeal glioneuronal heterotopias, polymicrogyria, and cortical dysplasia; (2) destructive lesions with neuronal degeneration, apoptosis, and coarse and filamentous calcification; (3) inflammation with predominance of T lymphocytes CD8+; and (4) hypoplastic lesions characterized by lack of descending fibers leading to hypoplasia of the pons, pyramids, and spinal corticospinal tracts [18]. In ZIKV-infected mice, positron emission tomography (PET) imaging revealed global neuroinflammation affecting the whole brain [19].

## Concerns About Persistence of the Virus in Blood and Tissues

Viral persistence in the maternal blood seems to be associated with a failure of antiviral immunological clearance or the consequence of maternal reseeding from fetal infection [20]. In an autopsy of a 5-month infant with CZS, ZIKV RNA was detected in the brain, indicating viral persistence after a first trimester of gestation infection [21]. The transmission of ZIKV by breastfeeding can be the cause of postnatal microcephaly in previously healthy infants [22]. Infants born to mothers exposed to ZIKV during pregnancy showed progression of developmental, motor, and neurologic abnormalities even if they were born asymptomatic [23]. ZIKV exposure in the adult brain could have an effect on long-term memory or an increased risk for depression [24].

## Clinical Spectrum of Disease

### Adult Features (Including Symptoms During Pregnancy)

ZIKV infection has a self-limited course and 80% of the infected patients are asymptomatic [25]. The most frequent symptoms are conjunctivitis, mild fever, headache, skin rash, and diarrhea [5]. Autoimmune disorders caused by ZIKV can also occur in adults, including Guillain-Barré syndrome (GBS), transverse myelitis, and acute meningoencephalitis [26]. Stroke is also a complication from ZIKV vasculitis [27].

## Clinical Features of Congenital Zika Syndrome

Children affected by CZS may develop severe symptoms, including often moderate to severe global neurodevelopmental delay, epilepsy, blindness, hearing loss, and hypotonia [28]. Among 48 infants with CZS, 85.4% had irritability, becoming the most common described symptom, followed by upper motor neuron/extrapyramidal manifestations (56.3%), epileptic seizures (50%), and dysphagia (14.6%) [29•]. Additionally, the nature of muscle tone abnormalities can change over time (e.g., hypotonia develops into spasticity) [30]. Extrapyramidal findings were predominantly characterized as dyskinesia and dystonias [31]. Prominent contractures of at least one joint were present in approximately 42% of cases, although arthrogryposis multiplex congenita was seen only in 10% of cases [32].

In patients with epilepsy, the main seizure types included infantile spasms (72% of the infants), focal motor seizures (21%), and tonic seizures (4%). The main electroencephalographic patterns were focal epileptiform discharges (51%), multifocal epileptiform discharges (44%), hypsarrhythmia (11%), and burst-suppression (8%) [33]. Microcephaly was present in 69% of children diagnosed with CZS. In these children, 67% were diagnosed with microcephaly at birth and 33% developed postnatal microcephaly, mainly during the first year of life. Time of diagnosis is also variable, with 46% of infants diagnosed at birth and 54% within 10 months of life [23].

Among infants with congenital ZIKV infection, there is a group of children with normal head circumference at birth who develop progressive microcephaly during the first year of life [34]. Even in the absence of abnormalities identified by prenatal and postnatal testing, the potential for long-term neurocognitive deficits remains [35–39].

Hyperactivity, severe irritability, and self-injurious behaviors have also been reported in infants with CZS [29•].

## Complementary Investigation of ZIKV Infection and CZS

### Laboratory Methods

Pregnant women with possible ZIKV exposure, who have a fetus with prenatal ultrasound findings consistent with CZS, should be tested by nucleic acid amplification test (NAAT) and IgM levels in maternal serum and NAAT in maternal urine. Consideration of amniocentesis should be individualized because data about its usefulness in diagnosing congenital ZIKV infection are limited [40]. Confirmation of an in utero infection can be made through a positive RTPCR in cord blood, neonatal blood, urine, placenta, or cerebrospinal fluid (CSF), as well as by the presence of specific IgM [41].

## Neuroimaging Findings

### General Aspects

The reported risk of fetal/infant abnormalities with maternal ZIKV infection ranges between 1 and 29% [42]. The most prevalent brain congenital defects reported are the following: calcifications at the cortical-subcortical junction (Fig. 1a, b) (92.9%); basal ganglia calcification (Fig. 1c) (57%); periventricular calcifications (29.5%); ventriculomegaly (Fig. 1d, e, g, i, j, k, l) (63.1%); cerebellar abnormalities (Fig. 1d, j, k, l) (47.9%); corpus callosum abnormalities (Fig. 1d, g, h, l) (46.2%); and microcephaly (39.7%) (Fig. 1d), almost 100% when the infection occurs in the first trimester of pregnancy [43•].

### Brain Calcifications

Brain calcifications are common in CZS, occurring in 88–100% of patients [44], especially involving the gray-white matter junction (Fig. 1a, b) [45]. Calcifications were also identified in basal ganglia (Fig. 1c), thalamus, cortex, and periventricular regions. In patients with periventricular calcifications (Fig. 1i), these were associated with areas of parenchymal thinning [46•].

Cortical-subcortical calcifications were located mainly in the frontal (Fig. 1a, b) (100%) and parietal (68.7%) lobes, and less frequently in the occipital (50%) and temporal (43.7%) lobes. Brain calcifications described in CZS can also be punctate and coarse (Fig. 1a, b) [47]. In some cases, a layered calcification appearance can be seen in cortical gray and white matter [48•].

### Microcephaly

The definition of microcephaly varies from fetus to child [49]. It is defined as a fetal or newborn head circumference (HC) below the third percentile or, at least, two standard deviations (SDs) below the mean for sex, age, and ethnicity [50]. Severe microcephaly is defined as a HC below the parameters mentioned above [51]. Microcephaly is present in 39.7% of infants and, when the infection occurs in the first trimester, in almost 100% of affected individuals [43•]. Among microcephalic infants, severe microcephaly is identified in 54.9% of them [52••].

As consequence to microcephaly, redundant skin of the scalp has been described in 67.4% of infants. Redundant skin could be best demonstrated by manually creating folds in the scalp and is evident in the forehead (37.3%) or in the occipital and nuchal regions (Fig. 1d) (47%) [32]. Skin redundancy is best explained by the collapse of the skull, which previously had larger dimensions. The latter can be the result of the decreased brain size or the suppressed cranial osteogenesis

**Fig. 1** Brain images of infants diagnosed with CZS. CT scan slices: images **a**, **c**, **i**, **j**, and **k**. MRI images: **b**, **d**, **e**, **f**, **g**, **h**, **k**, and **l**. **a** (CT) and **b** (MRI): coarse and punctate calcifications at the cortico-subcortical junction, predominating in the frontal lobes. **c**: basal ganglia calcifications. **d**: marked microcephaly with redundant scalp skin in the occipital region. **e**: marked dilatation of supratentorial ventricular system, simplified gyral pattern of the brain, and prominence of the subarachnoid space in the frontal regions. **f**: malformations of cortical development compatible with polymicrogyria in the frontal lobes with sparing of posterior cortical areas. **g**: thin/hypoplastic corpus callosum. **h**: short corpus callosum with dysgenetic aspect. **i** and **j**: tetraventricular dilatation, simplified gyral pattern of the brain, cerebellar and pons hypoplasia, and cortico-subcortical and periventricular calcifications. **k**: asymmetric cerebellar hypoplasia with greater involvement of the right hemisphere, marked dilatation of the lateral ventricles with thinning of cerebral mantle, and prominence of cisterna magna. **l**: severe cerebellar hypoplasia
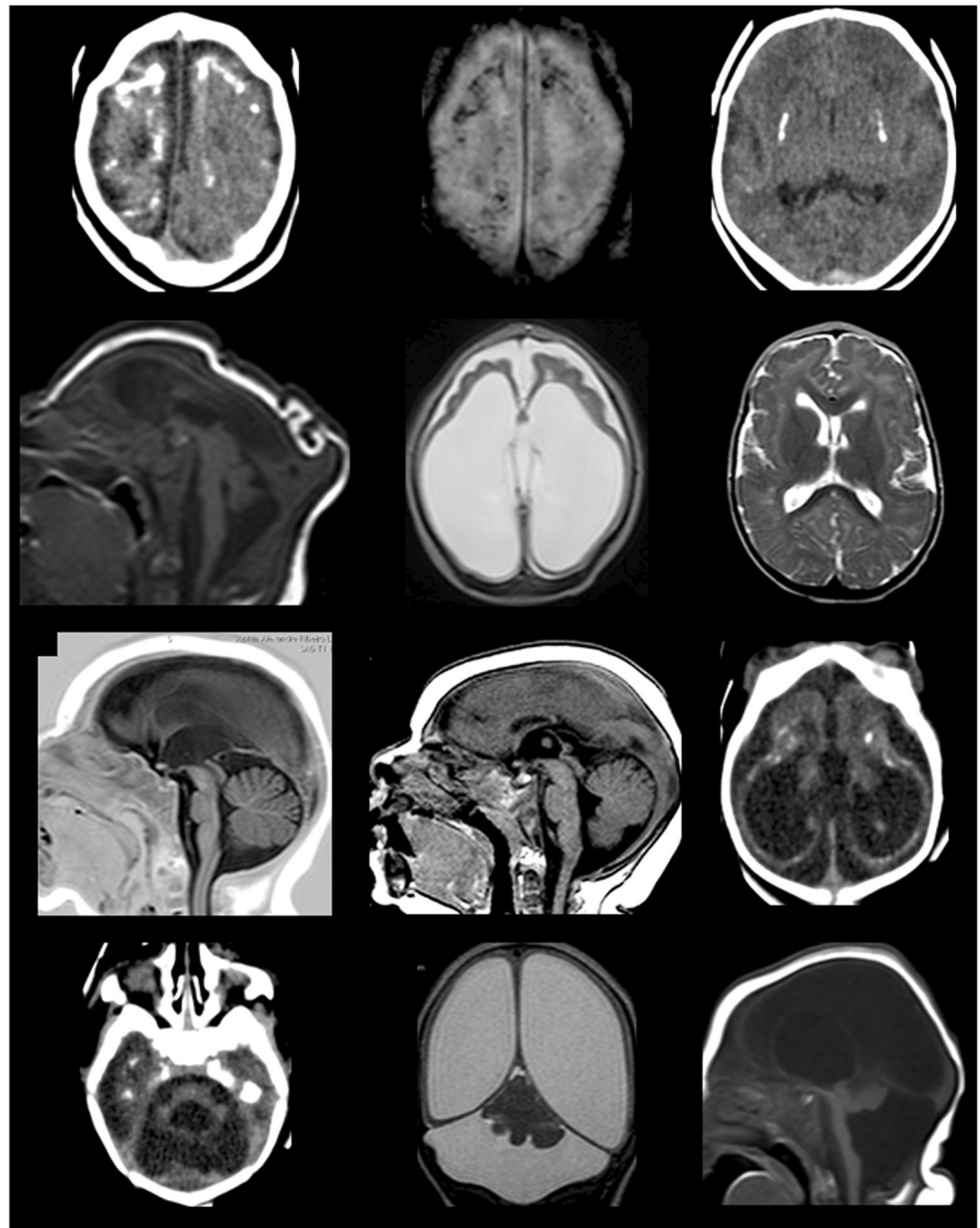


caused by ZIKV [17, 44]. Periorbital fullness, epicanthal folds, and mild retrognathia are the main facial features of these infants [32].

## Malformations of Cortical Development

Malformations of cortical development were present in 89% of the cases, most frequently affecting the frontal lobes. Among them, lissencephaly-pachygyria spectrum and other focal migrational/post migrational abnormalities were the most frequent findings [53]. Other observed abnormalities included areas of polymicrogyria (Fig. 1f) accompanied by gyral simplification (Fig. 1d, e, g, i, k, l) [54]. These abnormalities are usually asymmetric. Overall, the sulci were less prominent and widening of the sylvian and interhemispheric fissures was also found in neonates, as well as abnormal myelination [46•]. Gray matter heterotopia is rare [44].

Associated with the frequent finding of malformations of cortical development, infants with CZS have large reductions in parenchymal volume. In some cases, this is accompanied by enlargement of the subarachnoid spaces (Fig. 1e, i) [54–57]. Ventriculomegaly (Fig. 1d, e, g, i, j, k, l) occurs in 63% of patients with CZS [43•].

## Corpus Callosum Abnormalities

Corpus callosum abnormalities are a common finding in CZS and occur in about 46% of cases [43•]. Typically, there is a

thin, hypoplastic (Fig. 1d, g, l), dysmorphic (Fig. 1h), or absent corpus callosum. Formation of the corpus callosum occurs between 8 and 20 weeks of gestational age [55, 58], suggesting that at least in some cases the insult to CNS morphology occurs concurrent with corpus callosum development.

## Hydrocephalus

Among infants with CZS, approximately 18% had progressive ventriculomegaly and 5% had communicating hydrocephalus associated with increased frequency of seizures and worsening neurological impairment [59]. Hydrocephalus occurred without remarkable increase in the head circumference, and 92% of these children remained microcephalic [60].

## Posterior Fossa Abnormalities

Cerebellar and brainstem hypoplasia (Fig. 1d, j, k, l) were present, respectively in 24% and 20% of these infants [52, 61]. The cerebellar hemispheres usually had symmetric involvement, although asymmetric unilateral cerebellar hypoplasia (Fig. 1k) has been reported. The brainstem hypoplasia frequently involved the pons (Fig. 1d, g, j, l) [58••]. Brainstem and cerebellar calcifications occurred, respectively in 9.9% and 2.9% of infants [52, 61–63].

## Spinal Cord and Skeletal Anomalies (Including Arthrogryposis)

The spectrum of neurological abnormalities in CZS also includes spinal cord injuries. Immunohistochemistry showed immunoreactivity for the ZIKV proteins in the gray matter of the spinal cord [64]. Needle electromyography showed moderate signs of remodeling of the motor units (polyphasic motor unit potentials with increased amplitude and duration) and a reduced recruitment pattern, suggesting chronic involvement of peripheral motor neurons [65].

The spinal cord is also abnormally shaped because of small corticospinal tracts, in addition to motor neuron degeneration and loss. Gliosis, small, or coarse foci of calcifications have also been described [45].

Reduction in the thickness of spinal cord segments is present in 83% of patients with CZS. The thoracic segment is the most often compromised, encompassing the totality of these infants with thinned spinal cords. Additional findings include a reduction of the anterior nerve roots of the conus medullaris. Moreover, there are reports of congenital hip dysplasia, more frequent among infants with arthrogryposis. In addition, half of these infants with arthrogryposis had a prominent anterior median fissure of the spinal cord, a feature not identified in any of the children without arthrogryposis [66]. Clubfoot and

arthrogryposis were reported each one in 10.4% of newborns with CZS [67].

## Ocular Abnormalities

Ocular features of CZS are mainly characterized by macular pigment mottling, neuroretinal atrophy with macular involvement, iris coloboma, and changes in the retinal vasculature [68]. Eye abnormalities were described in about 44% of infants with CZS. The most frequent findings were the following: macular lesions (pigmentary maculopathy, pigment mottling, lacunar maculopathy, or macular chorioretinal atrophy with and without hyperpigmented borders), present in all patients with ocular lesions; followed by optic nerve abnormalities (55%); chorioretinal atrophy/scarring (21%); and focal pigment mottling of the retina (14%) [43•]. Microphthalmia occurs in only 4.2% of patients [69].

## Neuroimaging Findings in Children with Congenital ZIKV Infection Without Microcephaly

The main neuroimaging findings in children with CZS without microcephaly include malformations of cortical development (predominantly affecting the anterior part of the brain); calcifications, usually at the corticomedullary junction, decreased brain volume, and ventriculomegaly. Hypoplasia of the corpus callosum, cerebellum, and brainstem, as well as delayed myelination, was also reported [34]. Cranial nerve enhancement and cerebral infarction may be among the expanding list of neurological findings in congenital ZIKV infection in normocephalic newborns with intrauterine virus exposure [70]. It suggests that there may be a wide spectrum of findings associated with CZS and that the microcephaly may be the most severe end of this spectrum [71].

## Neuroimaging Findings of Acquired Zika Virus Infection

Neuroimaging findings of postnatally acquired ZIKV infection include a heterogeneous spectrum of diseases affecting the brain, peripheral nerves, and spinal cord [72]. ZIKV-related Guillain-Barré syndrome (GBS) presented as post-contrast enhancement of the conus medullaris and cauda equina nerve roots on spine MRI (most commonly seen in the anterior nerve roots). On brain MRI, the cranial nerves may show post-contrast enhancement, especially the facial (VII) and trigeminal (V) nerves [73].

ZIKV-related acute transverse myelitis (ATM) usually involves more than 3 spine segments in length [74]. The spectrum of meningoencephalitis, presented as asymmetric subcortical hyperintense lesions, was best seen on fluid-sensitive pulse sequences, with cytotoxic edema and at times with foci of restricted diffusion [75, 76]. Acute disseminated

encephalomyelitis (ADEM) has also been described with multiple ill-defined, asymmetric lesions involving the subcortical and deep white matter and deep gray matter nuclei [77].

## Neuroimaging Techniques

### Prenatal Ultrasonography

Doppler ultrasonography during pregnancy can detect congenital abnormalities with low sensitivity, but higher specificity [78]. Brain abnormalities observed by ultrasonography in fetuses affected by ZIKV include abnormal head shape, declining head measurements on serial scans, cerebral atrophy, increased extra-axial fluid, micro-calcification, and cerebellar hypoplasia. Even if the first evaluation is normal, it is necessary to follow up potentially affected fetuses throughout the pregnancy because abnormalities might not be apparent until the third trimester [79].

Among 92 fetuses from pregnant women diagnosed during pregnancy with ZIKV infection, eleven (12%) had ZIKV-associated abnormal findings, comprising (1) major CNS abnormalities (11% of fetuses) characterized by microcephaly (8%), calcifications (10%), ventriculomegaly (7%), Blake pouch cyst (3%), cerebellar vermis hypoplasia (3%), agenesis of the corpus callosum (2%); (2) fetal growth restriction (8%); and (3) arthrogryposis (1%). Postnatal neuroimaging was performed in 68 neonates, of whom 23 (34%) had abnormal results [80].

### Prenatal MR Imaging

Fetal magnetic resonance imaging (F-MRI) may be useful to diagnose cortical development disorders compared with ultrasound [57]. F-MRI can also better describe than prenatal ultrasonography the following abnormalities: corpus callosum dysgenesis (hypogenesis, agenesis, hypoplasia), myelination status according to the stage of development (normal or delayed), and cerebral ventricular enlargement due to white matter hypoplasia (mainly affecting the posterior aspect of the lateral ventricles) [81].

Malformations of cortical development in CZS are described as polymicrogyria, schizencephaly, and lissencephaly-pachygyria spectrum, but F-MRI usually is not able to distinguish among these findings. F-MRI may improve the identification of brain malformations such as cerebral atrophy and microphthalmia. A frequent and typical finding at F-MRI is redundant scalp skin in the occipital region, which may also be seen at postnatal imaging or even during physical examination of the newborn [26]. Conversely, when compared with ultrasound, prenatal MRI is less sensitive in the detection of parenchymal calcifications [82].

### Postnatal Transfontanellar Ultrasonography

Postnatal transfontanellar ultrasonography is the examination of choice for the assessment of newborns. It is an inexpensive and safe modality for the first-line investigation of suspected neonates. Both brain parenchyma and the ventricular system can be evaluated by ultrasound [83], although the fontanelles may be closed due to a collapse of the upper cranial bones [9, 84].

Postnatal transfontanellar neurosonography showed ventriculomegaly in 28% of newborns. Cerebral calcifications were detected in 34.9% of newborns; neuronal migrational abnormalities were present in 31.1%; dysgenesis of the corpus callosum in 26%; cerebellar atrophy and dilatation of the 4th ventricle in 16.2% and 17.3% of cases, respectively [85].

### Postnatal Computed Tomography

The main findings in brain computed tomography (CT) are calcifications (predominantly at the cortico-subcortical junction, in the frontal lobes), malformation of cortical development, cerebral volume reduction, and ventriculomegaly and prominence of the occipital bone [47].

CT is the best imaging modality for the identification and delineation of calcifications [86]. Compared with prenatal ultrasound, CT was able to detect cerebellar vermis hypoplasia and corpus callosum dysgenesis that was undetected at the prenatal scan [87].

Head CT scans with 3D reconstructions are useful to demonstrate craniofacial disproportion with depression of the frontal and parietal bones, overlapping sutures, cranial bone collapse, and prominent appearance of the occipital and frontal regions. Small fontanels may be best seen on the bone window [58••].

### Postnatal Magnetic Resonance Imaging

Malformations of cortical development and sulcation are common imaging findings in ZIKV-infected children and are best assessed with postnatal MR imaging [88]. Delayed myelination and demyelination are observed in some cases and may be associated with secondary thinning of the corpus callosum, events better depicted by MR imaging [9].

Although MRI is less sensitive than CT for calcifications, in this study, most of the calcifications were identified on T1-weighted or susceptibility-weighted imaging [61••]. MRI is also useful to detect brainstem and cerebellar abnormalities [57].

Other features of CZS better visualized by postnatal MRI include intraventricular septations, gray matter heterotopia, and schizencephaly [56•]. In addition, MRI is able to better visualize polymicrogyria, most

frequently seen in the frontal lobes [87]. MRI also allows superior visualization of brainstem hypoplasia, cerebellar hemispheric volume loss, and other described abnormalities such as pseudocysts [89]. Table 1 summarizes the spectrum of brain and systemic abnormalities in CZS.

## Differential Diagnosis

The main differential diagnoses of CZS include congenital infections such as toxoplasmosis, rubeola, cytomegalovirus, and herpes simplex (TORCH); and heritable disorders like Aicardi-Goutières syndrome, band-like

**Table 1** Main neurological findings on CZS [32, 43, 47, 51–54, 58–62, 66, 68, 72]

| Frequency | Abnormalities | Comments |
|---|---|---|
| 88–100% | Brain calcifications | |
| 92% | Cortical-subcortical junction Basal ganglia periventricular | CT is the best modality to detect calcifications. Cortical - subcortical calcifications are located mainly in the frontal and parietal lobes (in respectively 100% and 68.7% of patients with CZS and brain calcifications). They can be punctate and/or coarse. |
| 57% | | |
| 29% | | |
| 89% | Malformations of cortical development | |
| | Lissencephaly - pachygyria, polymicrogyria, cortical dysplasia, heterotopia, schizencephaly | The malformations are usually asymmetric, most frequently affecting the frontal lobes. Overall, the sulci are less prominent and wide Sylvian and interhemispheric fissures are found in neonates. Gray matter heterotopia is rare. |
| 63% | Ventriculomegaly | |
| 42% | Supratentorial ventriculomegaly | Decreased brain volume and diffuse cortical atrophy are often observed, with associated findings of enlarged supratentorial subarachnoid spaces, ventriculomegaly, and open Sylvian fissures. Some patients have progressive ventriculomegaly and hydrocephalus. |
| 21% | Global ventriculomegaly | |
| 5% | Hydrocephalus | |
| 46% | Corpus callosum abnormalities | |
| | Hypoplasia, dysgenesis, or absence of corpus callosum | Associated with an abnormal rotation of the hippocampi and thickened fornices. |
| | Microcephaly | |
| 39% | Microcephaly | Present in almost 100% when the infection occurs in the first trimester. Redundant skin of the scalp occurs in 67.4% of infants (mainly in the occipital and nuchal regions). Head CT scans with 3D reconstructions are useful to demonstrate craniofacial disproportion. |
| 21% | Severe microcephaly | |
| | Posterior fossa abnormalities | |
| 24% | Cerebellar hypoplasia | Other abnormalities include Dandy-Walker malformation, cerebellar dysplasia, and enlarged cisterna magna. |
| 20% | Brainstem hypoplasia | |
| 10% | Brainstem calcifications | |
| 3% | Cerebellar calcifications | |
| | Spinal cord and skeletal anomalies and arthrogryposis | |
| 83% | Thickness reduction of spinal cord segments | Thickness of all segments of the spinal cord is reduced, with the thoracic segment most compromised. Gliosis, small, or coarse foci of calcification are also described. |
| 10% | Clubfoot | |
| 10% | Arthrogryposis | |
| 44% | Ocular abnormalities | |
| 44% | Macular lesions | |
| 24% | Optic nerve abnormalities | Ocular features of CZS are mainly composed of macular pigment mottling, neuroretinal atrophy with macular involvement, iris coloboma, and changes in retinal vasculature. |
| 9% | Chorioretinal atrophy/scarring | |
| 4% | Microphthalmia | |

*Abbreviations*: *CT*, computed tomography; *CZS*, congenital Zika syndrome; *3D*, three-dimensional

cerebral calcifications associated with pathogenic sequence variations in *OCLN* (a.k.a. "pseudo-TORCH syndrome," and *RNASET2*-related leukodystrophy, that may manifest with findings similar to those of congenital ZIKV infection [86].

## Treatment and Prevention Perspectives

Current treatment protocols for ZIKV infection mostly involve symptomatic care and rehabilitation. At present, there are no specific ZIKV vaccines or therapies available [90]. Antivirals used for the treatment of hepatitis C virus, including sofosbuvir and other antiviral agents such as favipiravir, have been used for potential treatment of ZIKV infection in animal models [91]. The antimalarial drug chloroquine inhibits ZIKV infection limiting vertical transmission of ZIKV infection and fetal growth defects when used in pregnant mice [92]. Several candidate ZIKV vaccines are currently under development, being already on phase 1 clinical trials [93]. Surgical interventions, such as ventriculoperitoneal shunt procedure, are indicated for children with progressive ventricular enlargement due to hydrocephalus [59, 60].

## Conclusions

The heterogeneous spectrum of abnormalities in CZS is characterized by multisystem involvement. Main brain features observed are parenchymal calcifications, malformations of cortical development, callosal abnormalities, and brainstem and cerebellar abnormalities.

Imaging techniques such as ultrasound, MRI, or CT may be performed in the prenatal and/or in the postnatal periods. More studies will be required to further understand the entire spectrum of the brain abnormalities, including new techniques in radiology and nuclear medicine, in addition to new molecular studies to explore better the complexity of ZIKV infection.

### Compliance with Ethical Standards

**Conflict of Interest** Leão VHP, Aragão MM, Pinho RS, Hazin AN, Paciorkowski AR, Penalva de Oliveira AC, and Masruha, MR each declare no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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