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FOCUS SESSION

Imaging findings in congenital Zika virus infection syndrome: an update

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Abstract
Background Zika virus (ZIKV) is a neurotropic and neurotoxic RNA Flavivirus prompt to cause severe fetal brain dysmorphisms during pregnancy, a period of rapid and critical central nervous system development. A wide range of clinico-radiological findings of congenital ZIKV infections were reported in the literature, such as microcephaly, overlapping sutures, cortical migrational and corpus callosum abnormalities, intracranial calcifications, ventriculomegaly, brain stem and cerebellar malformations, spinal cord involvement, and joint contractures. ZIKV is also related to other severe neurological manifestations in grown-up individuals such as Guillain-Barré syndrome and encephalomyelitis.
Purpose Our purpose is to review the radiological central nervous system abnormalities of congenital ZIKV infection syndrome on different imaging modalities.

Keywords Zika · ZIKV · Microcephaly · Congenital malformation · Brain calcifications · Ventriculomegaly · Arthrogryposis

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Introduction

Zika virus has shown striking capacity to knock out neurogenesis [1–3] and increase neuronal apoptosis over progenitor cells [3–5] or even on differentiated cells [6]. This neurotropic and neurotoxic RNA Flavivirus virus can be transmitted through the bite of infected female mosquito vectors [4, 7–11], sexually [2, 11], or by vertical transmission as the virus is able to cross the fetal-placental barrier [7, 12–15].

Different studies detected Zika virus (ZIKV) infection in fetal cerebral tissue [6, 12, 13, 16–20], in cerebral spinal fluid [13, 17, 20, 21] and meninges [7, 17] of microcephalic newborns, in umbilical cord [19], and in the amniotic fluid [6, 7, 13, 14, 16, 18, 20] and placenta [1, 7, 13, 15, 20] of pregnant mothers. Suspicion of maternal ZIKV infection should be raised in women who experience low-grade fever, arthralgia, headache, conjunctivitis, myalgia, and a characteristic rash during pregnancy [1, 9–11, 19].

Adverse pregnancy outcomes due to maternal ZIKV infection seem to be related to the gestational time of infection [17], presenting a potential peak risk during 14 to 17 gestational weeks. According to Johansson [22], the risk of adverse events may be higher in symptomatic infections. Nevertheless, mild and undetected infections also contribute substantially to a great number of fetal infections [1, 22].

In this paper, we will review the imaging findings of congenital ZIKV infection syndrome (CZS) and comment some possible explanations for the most common abnormalities.

Imaging instruments and findings

Imaging techniques are essential tools for the in vivo detection of major abnormalities related to CZS, with prognostic importance. Here, the most relevant features of each radiological

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technique are addressed, followed by an update on CZS imaging findings.

Ultrasonography

Ultrasonography is a low-cost noninvasive technique that lacks the use of ionizing radiation and is ideal for monitoring fetal anatomy, biometrical indices, amniotic fluid levels, and placental health [7, 20, 23]. Other related methods are ultrasound-guided transabdominal amniocentesis to investigate causes of congenital fetal damage [13, 18, 20, 23]; transfontanellar ultrasonography [40]; and Doppler scans to evaluate major arteries and veins [7, 13, 20, 24], fetal growth restriction, and oligohydramnios [45].

When fetal cranial circumference (CC) is below two standard deviations (SD) from the expected mean value for gestational age, with or without other central nervous system (CNS) anomalies, fetal ZIKV infection should be considered or ruled out [25]. When CC is below three SD, newborns are considered to have severe microcephaly [1, 25].

Computed tomography

Computed tomography (CT) scan uses ionizing radiation and allows multiplanar reformations (MPR) and 3D reconstructions, which are especially useful as a screening method for cranial and skeletal anomalies. CT requires immobility, so sedation may be necessary, especially in older infants [26].

Fetal and postnatal magnetic resonance

It is an expensive imaging technique with more restrained availability in the public health system, with, however, an enormous advantage regarding the high quality and detailed images that can be obtained [7, 23, 25].

Imaging findings

The most striking findings are intrauterine fetal growth retardation [6, 14, 16, 23], cerebral atrophy (small brain) with microcephaly (small head, with craniofacial disproportion) [4, 7–10, 12, 13, 16, 17, 20, 27], ventriculomegaly (usually asymmetrical) [7, 13, 17, 20, 26, 28, 29], and brain calcifications (particularly in the gray-white matter junction, the basal ganglia, and/or the thalamus) [7–9, 12, 16, 17, 23, 27–29] (Fig. 1).

Nevertheless, CZS has a wide range of other clinical-radiological findings such as skull collapse with overlapped sutures with redundant scalp skin, prominent occipital bone [7, 23, 26, 30, 31], cortical and white matter volume loss, callosal abnormalities, defective neuronal migration (agyria, pachygyria, polymicrogyria), cerebellar hypoplasia or maldevelopment, ventriculomegaly [7, 13, 20, 26, 30], intraventricular septations [7, 13, 26, 30], subependymal cysts [13, 23], brain stem abnormalities [7, 13, 20, 23], thalamus absence [7], degeneration of the long descending tracts in the brain stem and spinal cord [12, 17, 32], and arthrogryposis [7, 8, 20, 26, 27, 30]. Although amniotic fluid volume may be completely normal during pregnancy [20], there are reports of both polyhydramnios and oligohydramnios [7, 18, 19, 33]. Single umbilical artery [19] and fetal hydrops [1] have also been addressed.

Supratentorial brain anomalies

Microcephaly

Microcephaly is the most recognized manifestation of CZS [1, 25, 30], accompanied by craniofacial disproportion and decreased vertical size of the skull [26, 30, 31]. This finding is commonly associated with redundant skin [26, 30] that may be particularly evident in the forehead or in the occipital and nuchal regions [20, 30]. Craniofacial abnormalities have also been described, such as hypertelorism, flat midface, low nasal bridge, and short nose [1].

Small birth head size for gestational age indicates possible brain growth impairment [1, 20, 27, 31, 34], which is an import risk factor for motor and cognitive development. Microcephaly may be due to viral effects on neuronal formation during embryogenesis, but can also take place as a part of fetal brain disruption sequence (FBDS) [20, 30, 31, 34, 35] even in the late stages of the third trimester wherein fetal brain tissue destruction occurs secondary to different forms of vascular injury with interruption of blood supply to the central nervous system [29, 35]. FBDS is described as a rare cause of extreme microcephaly with normal brain growth throughout the first 18 weeks of gestation. Brain destruction and volume loss leads to diminished intracranial pressure with fetal skull collapse and consequent overlapping sutures, scalp rugae with normal hair patterning, redundant and folded skin, and marked neurological impairment [10, 27, 30, 31, 35] (Fig. 2).

Del Campo et al. [30] describe skull collapse with normal hair patterning in most microcephalic CZS children evaluated in their study (fetus usually later than 16 weeks). It is interesting to notice that hair scalp patterns depend on underlying brain growth from 10 to 16 gestational weeks. They also observed some severe microcephalic cases with abnormal hair patterns, suggesting that the onset of events leading to these dysmorphic features took place prior to 16 gestational weeks and has been described elsewhere as a possible consequence of interrupted neurogenesis with severe brain injury [1].

Although some authors did not observe changes in umbilical and cerebral blood flow (even in the most severe cases) [7, 12, 20], Doppler flow studies can be used in the evaluation of these major arterial branches [7, 13], even when possible

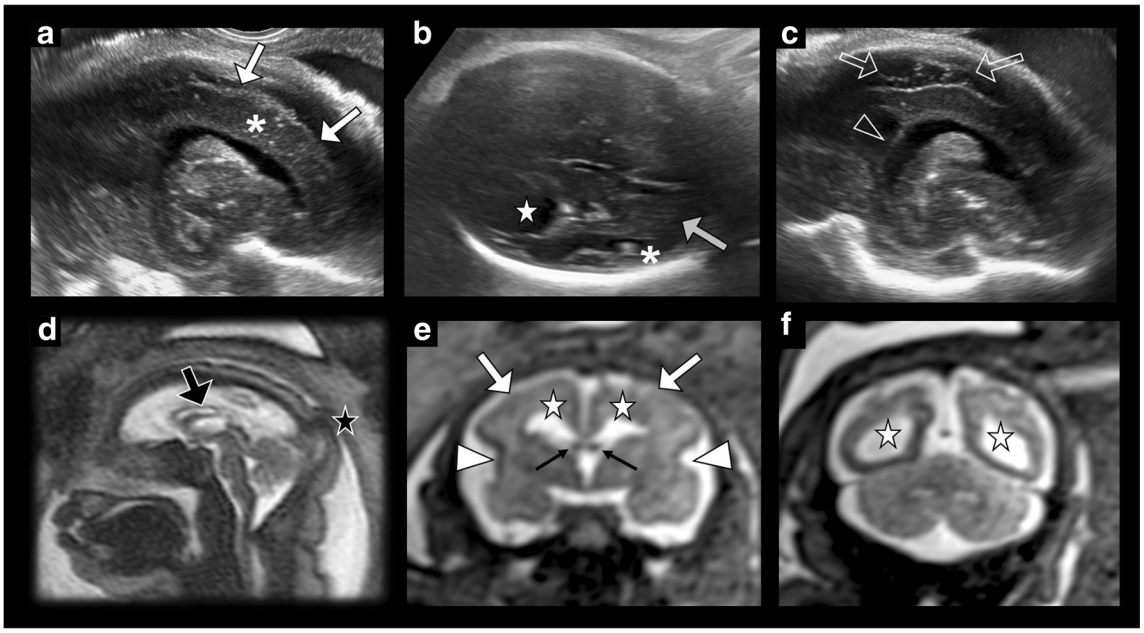

Fig. 1 Prenatal **a**–**c** ultrasonography and **d**–**f** magnetic resonance in confirmed fetal Zika virus infections. **a**, **b**, **e** Simplified gyral pattern with agyria and pachygyria (solid arrow). **a**, **b** Subcortical calcifications (white asterisk). **d** Microcephaly with prominent occiput (black star) and hypoplastic corpus callosum (black arrow). **e** Thickened fornices (black thin arrows). **b**, **e**, **f** Ventriculomegaly with **f** occipital horns dilated out of proportion to the **e** frontal horns due to parieto-occipital gray and white matter loss (white star), and **c** intraventricular septation adjacent the atrium (open arrowhead). **c** Enlarged extra-axial subarachnoid space (open arrow)

FBDS is suspected. Besides, the findings of normal umbilical and uterine artery Doppler ultrasounds suggest that fetal growth restriction is related to fetal infection [20].

Microcephaly is a nonspecific finding and the differential diagnosis includes a wide range of other conditions such as the classic TORCH infections, human immunodeficiency and chikungunya viruses, teratogens (such as radiation, antiepileptic drugs, alcohol, cocaine, antiepileptic drugs, lead, or mercury intoxication), maternal malnutrition, and genetic disorders [20, 25, 27, 31, 36]. In addition, although microcephaly is

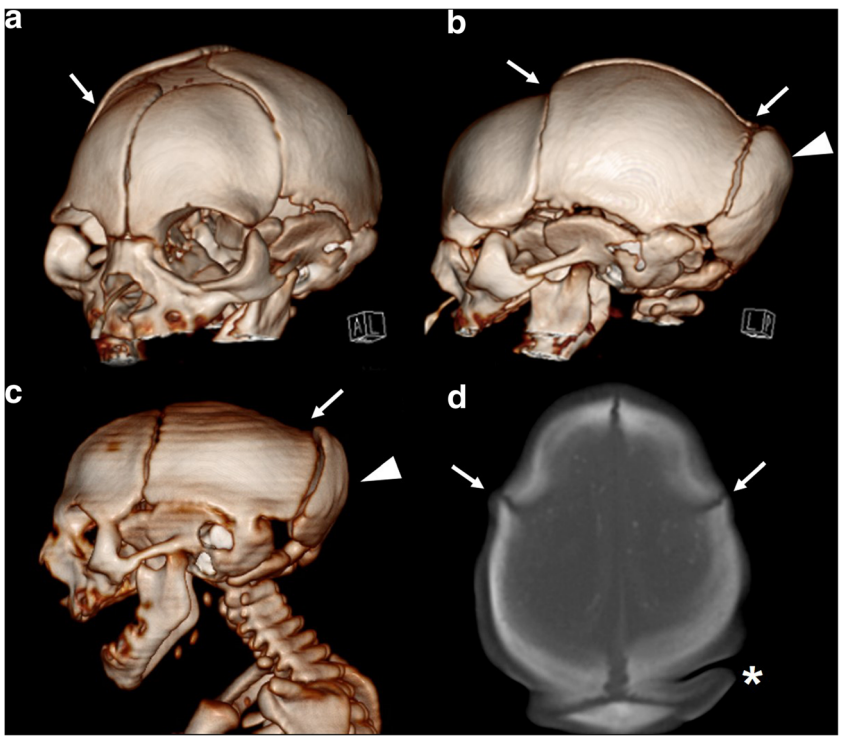

Fig. 2 Postnatal computed tomography (CT) with multiplanar reformations with **a**–**c** 3D reconstructions of an infant with congenital Zika infection. **a**–**d** Cranial vault partial collapse with overlapped sutures (arrows), prominent occiput (arrowhead), and scalp rugae (asterisk)

considered the most common reported sign of CZS, ZIKV-positive newborns with normal head size but severe brain development disruption and brain tissue destruction have been described [1, 13, 17]. Those less common presentations were usually also associated with brain stem calcification and marked hydrocephalus [13, 17].

Cortical development abnormalities and defective neuronal migration

Cortical development abnormalities (CDA) are believed to be related to the death of cortical progenitor cells caused by the virus [25], being best evaluated by MR imaging. CDA associated with CSZ findings are usually asymmetrical and include more frequently irregular areas of sulci and/or gyri, and focal cortical malformation, agyria, and polymicrogyria or pachygyria [7, 13, 20, 26, 28, 29] (Fig. 3). Most infected neonates presented shallow sulci and wide interhemispheric and Sylvian fissures as well as anomalous myelination [13, 28]. Simplified gyral pattern refers to few gyri and shallow sulci, being related to abnormal neuronal and glial proliferation, with deficits in cell production and/or white matter development. Polymicrogyria and pachygyria are predominantly found in the frontal lobes, while a simplified gyral pattern is more found in the parieto-occipital lobes, or diffusely [25, 28]. Pachygyria happens early in pregnancy, between the 12th and 16th gestational weeks [25], and is related to abnormal neuronal migration [25, 28]. Herein, areas of flat, broad, and thickened gyri are observed [25]. Abnormalities in cortical migration and heterotopias [1, 17, 38], cerebellar cortical dysplasia [17], and meningeal glioneuronal heterotopia [17, 38] were also reported.

Interruption in late stages of neuronal migration and cortical organization can lead to polymicrogyria originating only after the 20th gestational week [37]. Due to the presence of numerous microgyri and microsulci, the cortex is thickened, and the cortical and subcortical surface junctions are irregular [23, 25, 39].

Parenchymal calcifications

Fetal or newborn brain calcification detection is a strong hallmark of congenital infection (Fig. 4), which is usually the first diagnostic hypothesis when identified. CT remains the best imaging method for its identification and delineation as it appears as a hyperdense focus [25]. Brain calcification can

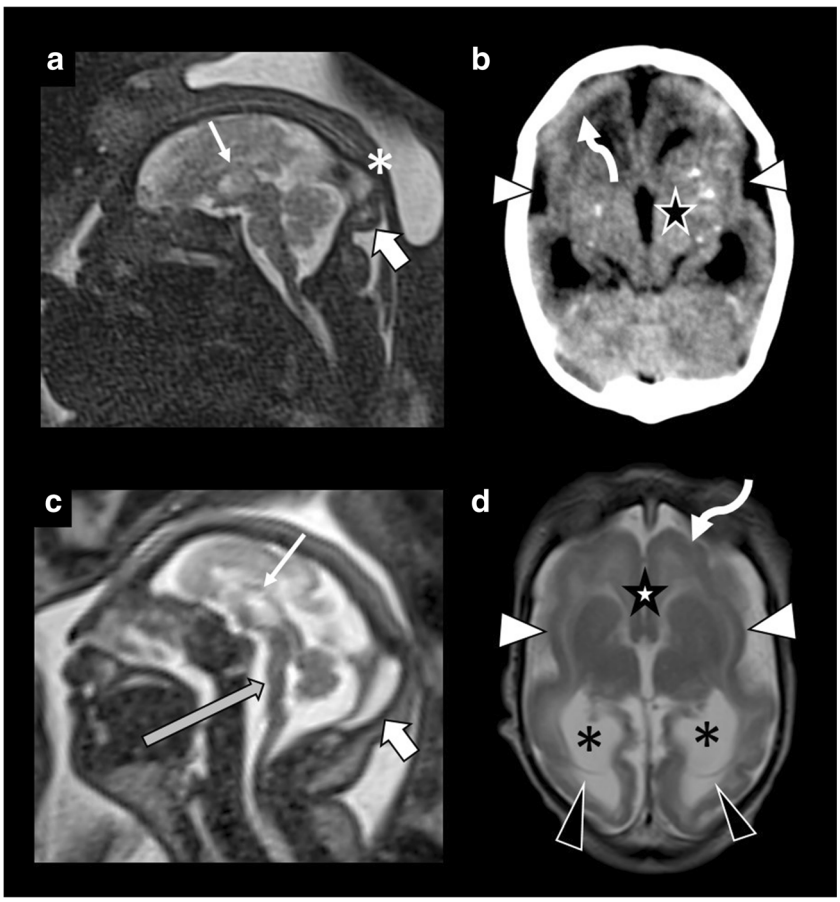

Fig. 3 **a**, **c** Prenatal magnetic resonance and postnatal **b** computed tomography (CT) and **d** MR of congenital Zika infection cases. **a**, **c** Microcephaly and reduced brain volume, craniofacial disproportion with decreased vertical size of the skull, and prominent occipital bone (thick arrow). **a** Enlarged torcula filled with heterogeneous material probably related to thrombus presence (white asterisk). **a**, **c** Hypoplastic corpus callosum (thin arrow) and **c** brain stem (gray long arrow). **b**, **d** Shallow sulci and Sylvian fissure with hypodeveloped opercula and insular cortex (solid arrowhead). **b**, **d** Cortico-subcortical hypointensity with thickened blurred borders (curved arrow). **d** Ventriculomegaly with dilated occipital horns (black asterisk) and intraventricular septations (black arrowhead). **b** Brain calcifications as hyperdense foci on CT scan (black star)

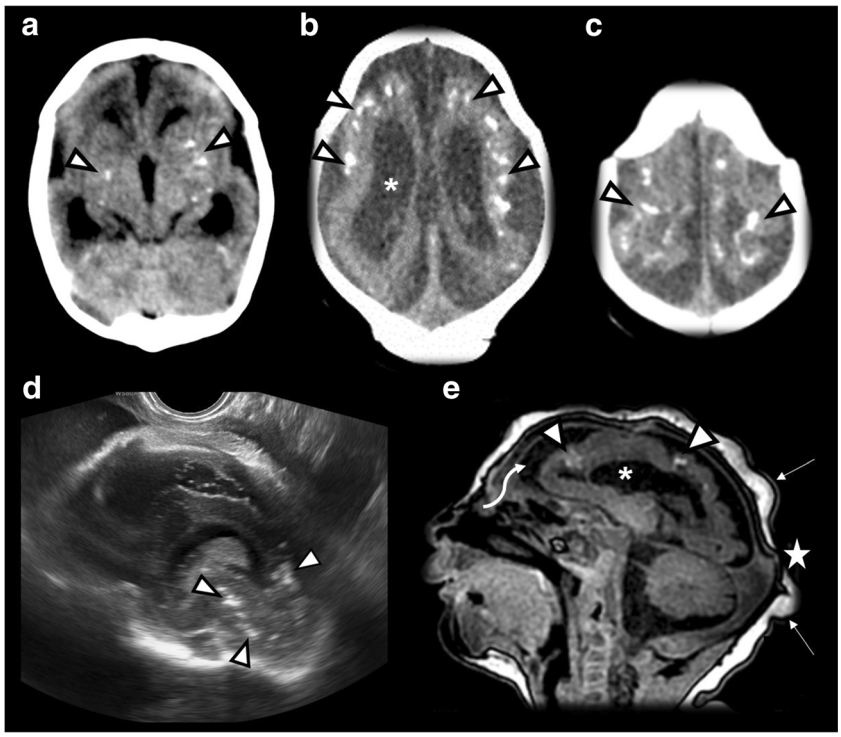

Fig. 4 Numerous parenchymal calcifications (arrowheads) due to congenital Zika infections on **a**–**c** computed tomography, **d** gestational ultrasound, and **e** T1-weighted magnetic resonance. Other findings: ventriculomegaly (white asterisk), prominent occiput (star), scalp rugae (thin arrows), and enlarged extra-axial subarachnoid spaces (curved arrow)

also be depicted postnatally by transfontanellar ultrasonography (US) as hyperechoic foci [20, 24, 25].

Oliveira-Szjenfeld et al. considered brain calcifications as an inclusion criterion for the presumed ZIKV infection and served as well to rule out microcephaly due to causes other than infection such as other congenital syndromes or unrecognized prematurity [13]. Calcifications in CZS infection could affect cortical regions, gray-white matter junction, basal ganglia and/or thalamus, brain stem, cerebellum, or periventricular regions [4, 13, 20, 26, 30]. When present, periventricular calcifications were related to areas of severe parenchymal thinning [13, 20]. In some cases, a layered calcification appearance was seen with cortical, gray, and white matter [13].

A candelabra-like pattern of basal ganglia calcification was described by Schaub et al. in two cases of an US follow-up study of ZIKV-infected fetuses, suggesting lenticulostriate vasculopathy. This pattern is nonspecific and can also be observed in congenital cytomegalovirus infection [20].

In another study, postnatal CT scans detected intracranial calcifications preferentially in the cerebral hemispheres, mainly involving the frontal and parietal lobes. Calcifications were also detected in the basal ganglia and in the thalamus [25, 29, 40], and less frequently in the brain stem and cerebellum [25]. Calcification's morphology was varied: punctiform, in band, coarse, or even isolated calcium spots [25].

The best MR sequences to demonstrate intracranial calcifications were reported to be the susceptibility magnetic weighted (SWi) and T2* gradient echo sequences, where calcifications appear as dark hypointense foci. Differential diagnoses for such signal presentation on those sequences are iron deposition and hemosiderin/ferritin. Calcifications may show hyperintense signal on T1-weighted MR images, with possible differential diagnoses being melanin, methemoglobin, manganese deposition, or lipid [25].

Intraparenchymal calcifications tend to be more severe in CZS than in other TORCH infections [13] and frequently are observed in the gray-white matter junction [7, 13, 40]. On one hand, cytomegalovirus intracranial calcifications are frequently periventricular [25, 31], although asymmetric basal ganglia, cortical, and white matter calcifications may also be observed [25]. Congenital toxoplasmosis has hydrocephalus and periventricular, thalamic, basal ganglia, and cortical calcifications (present in 50–80% of cases) as main changes [25].

Calcifications may represent "scars" secondary to brain cell destruction, with calcium deposition over time [13, 25, 31].

Subependymal cysts

The subependymal area is closely related to the lateral ventricle boundaries and the germinal matrix, where neuronal precursor cells are initially located. Subependymal pseudocysts can be observed in this region and are commonly depicted before and after birth, mostly carrying a favorable prognosis. Nevertheless, they can be related to infectious intrauterine diseases such as that by cytomegalovirus and CZS, especially when isolated and in the occipital localization [23].

Callosal abnormalities

Another common feature in confirmed or presumed CZS infection is abnormalities in the corpus callosum [7, 13, 20, 23, 28] (Figs. 1 and 3) which are easily detected on US and MR imaging. This finding is more difficult to be recognized on CT scans, but should be considered when pronounced colpocephaly without visualization of the body of the corpus callosum is detected [13]. Melo et al. [7] suggest that changes in the corpus callosum may be related to decreased number of neuronal cells and/or the interference in the neuronal migration process by the ZIKV itself. Schaub et al. [20] reported progressive and severe corpus callosum hypoplasia with normal pericallosal artery in all Doppler scans obtained in a sequential ultrasound assessment follow-up study, probably due to insufficient development of fibers that cross the midline. They observed normal corpus callosum embryological formation without vascular compromise.

Ventriculomegaly

Although many cases of CZS are associated with microcephaly, sometimes a normal head circumference is observed during pregnancy or after birth, even when extensive brain compromise is detected. This could be due to severe ventriculomegaly [4, 7, 13, 17] which masks a small microcephalic brain [25, 28], presumably related to obstructed ventricles [10]. As a consequence, isolated fetal head circumference measurement may not be a good prognosis predictor in congenital ZIKV infection [20]. Ventriculomegaly could range from mild to severe [7–9, 12, 13, 17, 23, 28]. The occipital horns of the lateral ventricles are often dilated out of proportion to the frontal horns due to parieto-occipital volume loss [13, 25] (Fig. 1). Some infants present with reduced cerebrospinal fluid (CSF) absorption or obstruction of its pathways leading to hydrocephalus and usually with severe brain stem calcification [13, 25]. Intraventricular septations typically occur in occipital horns and may also be observed pre- and/or postnatally [13, 18] (Figs. 1 and 3).

Enlarged extra-axial subarachnoid space

Although these findings can be considered normal variations, they were reported to be more frequent in CZS, especially in the most severe cases [20, 28], probably due to brain atrophy or cortical underdevelopment [13, 23, 28] (Figs. 1 and 4). Prominent extra-axial spaces were frequently observed despite ventriculomegaly [4, 13, 23, 28, 30].

Infratentorial brain anomalies

Brainstem and cerebellar abnormalities

Posterior fossa changes included brain stem abnormalities such as thin and atrophic pons (Fig. 3) or a kink at the pontomedullary junction, thinned spinal cord, enlarged cisterna magna [7, 13, 20, 23, 28], and hypoplastic cerebellar vermis and/or hemispheres [7, 8, 13, 16, 20, 28, 29].

Melo et al. describe fetal deaths shortly after birth due to respiratory failure in severely affected infants with slender brain stem. Indeed, fetal MR imaging may play an important role on the evaluation of newborn survival based on brain stem abnormalities [7].

Calcifications and hypoplasia were noticed in the brain stem, mainly in the pons, and in the cerebellum of infants with CZS [28], possibly secondary to Wallerian degeneration and/or development arresting of pontocerebellar connections and the corticobulbar and corticospinal tracts [25, 38].

Dysmorphic brain stem associated with aqueduct stenosis is a more severe manifestation of infection and can lead to secondary supratentorial hydrocephaly [4, 13, 17].

Spinal cord and congenital contractures

Multiple congenital joint contractures (arthrogryposis) can be even detected with US during pregnancy [7, 13, 26, 31]. The early development of arthrogryposis can be a consequence of degeneration of motor neurons of long descending tracts (including corticospinal tracts) in the brain stem and spinal cord [12, 17, 41], interfering with neuromuscular signaling and leading to reduced fetal movements or akinesia [8, 25, 31, 41] and fixed postures and deformities [25, 31] (Fig. 5).

Spine MRI of patients with ZIKV infection and arthrogryposis shows apparent thinning of the spinal cord and specifically reduced ventral roots of the medullary cone [25].

Aragão et al. observed that most babies with CZS presented some degree of spinal cord thickness reduction. This reduction was predominant in the thoracic segment in cases without arthrogryposis and compromised the whole spinal cord in cases of arthrogryposis [25, 42].

It is important to note that congenital arthrogryposis has also been associated with other intrauterine infections such as rubella, varicella, and Coxsackie B [31].

Ocular findings

Although posterior segment compromise (retina and optic nerve) is the most prevalent in ZIKV infection [25, 26, 33, 42], asymmetrical microphthalmia [1, 17, 31], cataracts, herniation of the orbital fat into the cranial vault [13, 17, 18, 43], glaucoma [1], intraocular calcifications, iris coloboma [25, 26, 33], and lens subluxation were also described [25, 33].

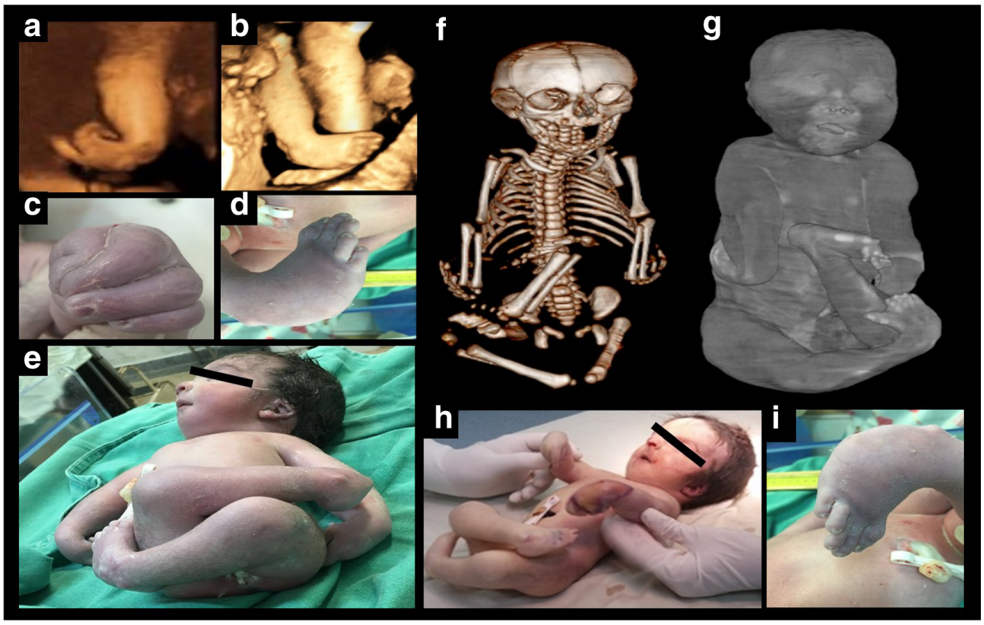

Fig. 5 Different cases of congenital Zika arthrogryposis. Multiple joint and limb congenital contractures are observed involving superior and inferior limbs, with limitations of passive and active range of motion. **a**, **b** Gestational 3D ultrasonography and **f**, **g** computed tomography (CT) images including 3D CT **f** bone and **g** surface reconstructions. Contractures of **a**, **c**, **d**, **i** digits and **b**, **d**, **i** abnormal feet anatomy (talipes equinovarus) are easily recognized with **f** hip deformity

The main risk factors associated with ocular findings are the gestational trimester when the infection occurred and the severity of microcephaly at birth. Babies exposed to ZIKV in the first trimester of pregnancy or those born with severe microcephaly have a greater chance of ocular abnormalities at birth [25, 33, 43].

Conclusions

Zika was declared an international public health emergency concern by the World Health Organization (WHO) in 2016 [28, 44], as it became the first new major infectious disease linked to human birth defects discovered in more than half a century [34]. In most cases, maternal ZIKV infection is often mild or not detected. Nevertheless, exposure to ZIKV during pregnancy can lead to devastating effects on the developing fetus [25]. Although most CZS infections may be related to severe fetal central nervous system compromise, pregnancies are considered low risk where a high prevalence of vaginal (78%) and term (91%) deliveries are reported [26].

Ultrasonography (gestational or transfontanellar) must be the first imaging method in the evaluation of CZS. Nevertheless, the fontanelles are usually small or even closed at birth due to microcephaly, which can hinder examination [20, 26, 30, 31]. Although more expensive than US, and despite the use of ionizing radiation, CT is a faster imaging technique, with high sensibility to detect calcifications and capable to check other CNS malformations. Fetal and/or postnatal MR and CT are complementary tools to gestational, fetal, and neonatal US findings [7, 23]. CT is widely available and less expensive than MR. On the other hand, MR radiation free is the best choice for detailed evaluation of CNS components (brain and spinal cord), also allowing clear demonstration of brain calcifications [25]. However, it is a time-consuming examination that usually requires sedation.

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Compliance with ethical standards

Conflict of interest All authors reported no conflicts of interest.

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