



Picture of the Month

Intrauterine Zika virus infection and microcephaly: correlation of perinatal imaging and three-dimensional virtual physical models

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Zika virus (ZIKV) belongs to the same family of flaviviruses as dengue (DENV) and chikungunya (CHIKV) and, the *Ae. aegypti* and *Ae. albopictus* mosquitoes are recognized as transmitting agents. Zika virus was first identified in Uganda in 1947 and few cases were reported in humans until 2007 when a ZIKV outbreak occurred in Yap, Micronesia¹. The first autochthonous transmission of ZIKV infection was reported in Brazil in June 2015² and ZIKV has now reached the Americas, most likely as a result of travel to and from the 2014 FIFA World Cup in Brazil³.

In adults, ZIKV infection causes cutaneous rash, fever, general illness and symptoms overlapping those of Guillain–Barré syndrome⁴.

Microcephaly is a neurodevelopmental disorder characterized by a normally structured but small brain, with recognized multifactorial causes such as mutations involving microcephalin (*MCPH1*) and abnormal spindle-like microcephaly-associated (*ASPM*) genes, and is associated with genetic syndromes, brain injury, metabolic disorders such as alaninuria or exposure to teratogenic drugs and chemicals⁵.

A dramatic surge in birth defects, particularly of fetuses and newborns with microcephaly, has been reported recently in Brazil⁶. In 2015, the State of Pernambuco, Brazil registered 646 newborns with microcephaly and, to date, about 4000 cases have been recorded in Brazil⁷, compared to an average of 10 cases of microcephaly per year in 2010–2014. Recently, the World Health Organization (WHO) declared the spreading of ZIKV infection a global public health emergency⁸. Postponement of pregnancy has been suggested and guidelines for pregnant women have been released in order to potentially avoid the teratogenic effect of ZIKV, as no medical treatment or vaccine is currently available⁹.

We report here imaging findings in a 27-year-old primigravida with no family history of congenital anomalies or

consanguinity who was referred at 12 weeks of gestation for symptoms consistent with those of ZIKV infection, namely fever, maculopapular rash and arthralgia. She lived in a peripheral area of Rio de Janeiro city, exposed to untreated sewage. Serology testing for TORCH, DENV and CHIKV were negative. First- and second-trimester ultrasound examinations, performed at 12 and 21 weeks of gestation, respectively, showed normal fetal anatomy. The mother was referred to the Department of Radiology, Clínica de Diagnóstico por Imagem (CDPI), at 37 weeks for ultrasound investigation of suspected microcephaly on a 32-week scan. The ultrasound examination was carried out using a Voluson E8 (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound apparatus equipped with transabdominal (RAB 4–8D) and transvaginal two- and three-dimensional (3D) volumetric probes (RIC 5–9 W).

Microcephaly, defined as biparietal diameter (BPD) and head circumference (HC) > 3 standard deviations (SD) below the mean for gestational age using Brazilian-based reference ranges¹⁰, and diffuse brain calcifications were identified (Figure 1).

Fetal magnetic resonance imaging (MRI) confirmed microcephaly and was better than ultrasound in demonstrating brain pathology such as reduced gyration and asymmetric colpocephaly (Figure 2).

Induction of labor with vaginal misoprostol (25 µg/4 h) for severe maternal anxiety failed and a Cesarean section was performed at 38 + 2 weeks. A male newborn was delivered, weighing 2210 g with 1- and 5-min Apgar scores of 8 and 9, respectively (Figure S1). Neonatal HC was 29.0 cm. Transfontanelar ultrasound examination identified subcortical and periventricular calcifications with ventricular dilatation.

Postnatal computed tomography (CT) with 3D post-processing, performed 10 days after delivery, enabled reconstruction of the microcephaly; in addition, cortical atrophy, brain calcifications and small anterior fontanel

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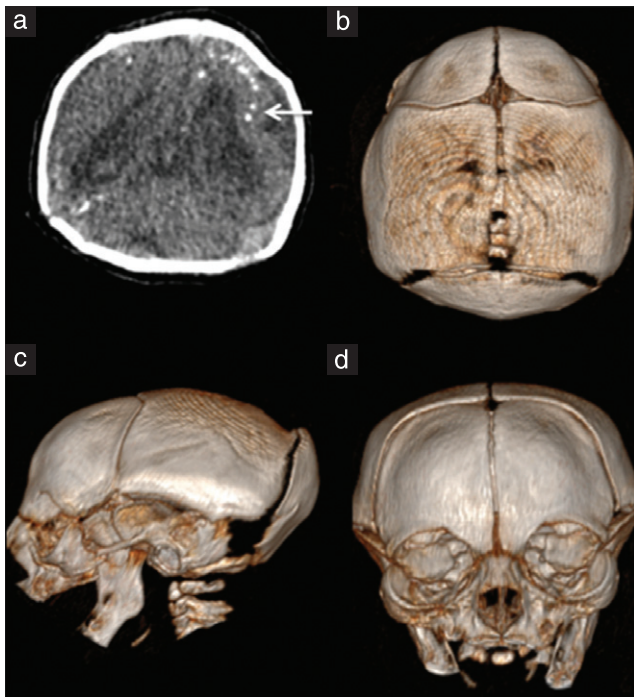


Figure 3 Postnatal computed tomographic imaging in neonate 10 days after delivery (a) and three-dimensional reconstruction in axial (b), sagittal (c) and coronal (d) views, showing microcephaly and cortical atrophy. Note brain calcifications (arrow) and small anterior fontanel, with premature closure of metopic and coronal sutures.

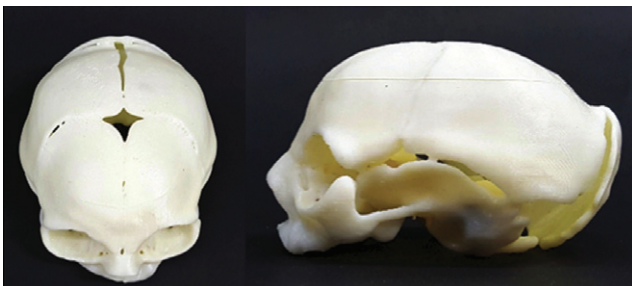


Figure 4 Three-dimensional virtual physical model of skull of neonate with microcephaly, constructed using data from computed tomography, printed on thermoplastic acrylonitrile butadiene styrene. Microcephaly, small anterior fontanel and premature closure of metopic and coronal sutures are clearly reconstructed.

In February 2016, Mlakar *et al.*¹⁷ proved ZIKV infection was associated with microcephaly by demonstrating ZIKV in fetal brain tissue using an RT-PCR assay. The complete ZIKV genome was recovered from the fetal brain of the aborted fetus at 29 weeks of gestation. The mother had had a high fever, severe musculoskeletal and retroocular pain and a generalized maculopapular rash at 13 weeks of gestation while she was living in Natal, the Capital of Rio Grande do Norte State in Brazil. Postmortem examination of the fetus revealed microcephaly (an abnormally small brain) with almost complete agyria, hydrocephalus and multifocal dystrophic calcifications in the cortex and subcortical white matter, with associated cortical displacement.

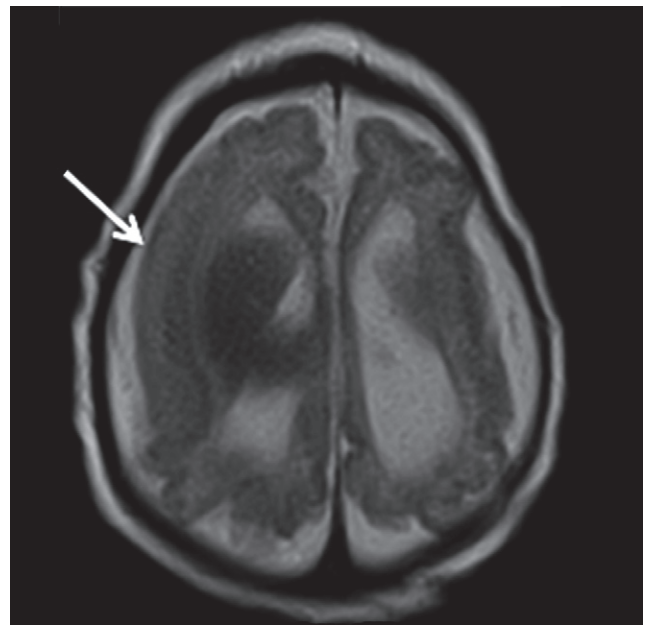


Figure 5 Axial T2-weighted brain magnetic resonance imaging in neonate at 1 month, performed without sedation or intravenous contrast, showing frontoparietal area of smoothness on the cortical surface, compatible with pachygyria (arrow). The cephalic circumference is 32.0 cm.

In our case, the diagnosis of maternal ZIKV infection was assessed retrospectively because RT-PCR identification of ZIKV was not available at the time of acute maternal infection (June 2015) and ZIKV infection was not epidemic. In addition, results of serological testing for DENV, CHIKV and TORCH were negative. Brain calcifications detected prenatally raised the suspicion of an intrauterine infection. Moreover, perinatal imaging by MRI and CT scan enabled the diagnosis of pachygyria, corpus callosal dysgenesis and small anterior fontanel with premature closure of metopic and coronal sutures.

3D virtual physical models have been shown to enhance parents' understanding of fetal pathology, aiding in counseling and perinatal care, and to improve maternal–fetal attachment, especially in blind women^{18–21}. 3D virtual models can be produced from 3D volume ultrasound, CT and MRI data in varied materials such as polyamide, metal and ceramics powder, photosensible resins, thermoplastic filaments and others. The construction process represents the sequential upward superimposition of slices according to the physical characteristics of the material resulting in an accurate tactile 3D model of the fetus, exhibiting complete surface details of the congenital anomaly¹⁹.

In the presented case, a 3D virtual physical model reconstructed the typical skull anomaly seen in microcephaly, the small anterior fontanel and the premature closure of the cranial sutures. We believe that a 3D virtual model of fetal pathology could be helpful for healthcare providers and parents-to-be, and may improve counseling in cases of intrauterine ZIKV infection and microcephaly.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

 **Figure S1** Newborn baby with microcephaly.

Figure S2 Three-dimensional virtual physical model of neonate with microcephaly, constructed using data from computed tomography 10 days after delivery.

Figure S3 (a,b) Magnetic resonance imaging (MRI) of upper level of the brain in 1-month old neonate with microcephaly, without sedation or intravenous contrast. (a) Axial T2-weighted MRI showing right posterior parieto-occipital area with numerous small gyri that can be associated with cortical development malformation (polymicrogyria). (b) Axial T1-weighted MRI showing multiple subcortical frontoparietal hyperintense foci (arrow), consistent with the calcifications seen on previous computed tomography and ultrasound. (c) Three-dimensional reconstruction of infant's head using data from MRI.

Videoclip S1 The printing process of a three-dimensional virtual physical model of the fetal cranium in a case of microcephaly using thermoplastic acrylonitrile butadiene styrene.