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Congenital Zika Syndrome: Characterizing the Pattern of Anomalies for Pediatric Healthcare Providers

Cynthia A. Moore, MD, PhD¹, J. Erin Staples, MD, PhD², William B. Dobyns, MD³, André Pessoa, MD⁴, Camila V. Ventura, MD^{5,6,7}, Eduardo Borges da Fonseca, MD, PhD^{8,9}, Erlane Marques Ribeiro, MD, PhD^{4,10}, Liana O. Ventura, MD^{5,6}, Norberto Nogueira Neto, MD⁸, J. Fernando Arena, MD, PhD¹¹, and Sonja A. Rasmussen, MD, MS¹²

¹National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA

²National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, CO

³University of Washington and Seattle Children's Research Institute, Seattle, WA

⁴Hospital Infantil Albert Sabin, Fortaleza, Ceará, Brazil

⁵Altino Ventura Foundation, Recife, Pernambuco, Brazil

⁶HOPE Eye Hospital, Recife, Pernambuco, Brazil

⁷Federal University of São Paulo (UNIFESP), São Paulo, São Paulo, Brazil

⁸NOVA Diagnóstico Por Imagem, João Pessoa, Paraíba, Brazil

⁹Federal University of Paraíba (UFPB), João Pessoa, Paraíba, Brazil

¹⁰Estacio Faculdade de Medicina de Juazeiro do Norte, Juazeiro do Norte, Ceará, Brazil

¹¹Carter Consulting, Atlanta, GA

¹²Center for Surveillance, Epidemiology and Laboratory Services, Centers for Disease Control and Prevention, Atlanta, GA

Abstract

Corresponding author: Cynthia A. Moore, MD, PhD, Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Mail stop E-86, 4770 Buford Hwy., NE, Atlanta, GA 30341 cam0@cdc.gov.

Author Contributions

Dr. Moore had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Drs. Moore, Rasmussen, Dobyns, Pessoa, Ribeiro.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Drs. Moore, Staples, Rasmussen, Dobyns, Fonseca, Pessoa, Ribeiro.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: Drs. Moore, Arena, Fonseca, Pessoa, Ribeiro

Study supervision: Drs. Moore, Dobyns, Pessoa, L. Ventura

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Importance—Zika virus infection can be passed prenatally from a pregnant woman to her fetus. There is sufficient evidence to conclude that intrauterine Zika virus infection is a cause of microcephaly and serious brain anomalies, but the full spectrum of anomalies has not been delineated. To inform pediatric healthcare providers who may be called upon to evaluate and manage affected infants and children, we review the most recent evidence to better characterize congenital Zika syndrome.

Observations—We reviewed published reports of congenital anomalies occurring in fetuses or infants with presumed or laboratory-confirmed intrauterine Zika virus infection. Congenital anomalies were considered in the context of the presumed pathogenetic mechanism related to the neurotropic properties of the virus. We conclude that congenital Zika syndrome is a recognizable pattern of structural anomalies and functional disabilities secondary to central and perhaps peripheral nervous system damage. Although many of the components of this syndrome such as cognitive, sensory and motor disabilities are shared by other congenital infections, there are five features that are rarely seen with other congenital infections or are unique to congenital Zika virus infection: severe microcephaly with partially collapsed skull; thin cerebral cortices with subcortical calcifications; macular scarring and focal pigmentary retinal mottling; congenital contractures; and marked early hypertonia and symptoms of extrapyramidal involvement.

Conclusions and Relevance—Although the full spectrum of adverse reproductive outcomes caused by Zika virus infection is not yet determined, a distinctive phenotype, the congenital Zika syndrome, has emerged. Recognition of this phenotype by healthcare providers for infants and children can help ensure appropriate etiologic evaluation as well as comprehensive clinical investigation to define the range of anomalies in an affected infant and determine essential follow-up and ongoing care.

Introduction

Zika virus (ZIKV) infection, contracted through the bite of an infected mosquito or through sexual or other modes of transmission, can be passed prenatally from mother to fetus.¹ The virus was first identified in the Region of the Americas in early 2015 when local transmission was reported in Brazil.² Six months later a notable increase in the number of infants with congenital microcephaly was observed in northeast Brazil.^{3,4} Clinical, epidemiologic, and laboratory evidence led investigators to conclude that intrauterine ZIKV infection was a cause of microcephaly and serious brain anomalies.^{5–7} However, as with other newly-recognized teratogens, these features likely represent a portion of a broader spectrum.

A comprehensive review of the English literature, identified by searching MEDLINE and EMBASE for “Zika” from inception through September 30, 2016, was done to better characterize the spectrum of anomalies in fetuses and infants with presumed or laboratory-confirmed ZIKV infection. A constellation of anomalies that is both consistent and unique, called congenital Zika syndrome (CZS), has emerged but specific components and presumed pathogenetic mechanisms previously have not been well-delineated.^{8–10}

ZIKV has spread to over 50 countries in the Americas and three United States territories, and, most recently, local transmission was confirmed in the continental US in the state of

Florida (<http://www.cdc.gov/zika/geo/index.html>). Mosquito-borne transmission of ZIKV in other areas of the US is possible based on the estimated range of its vectors (*Aedes aegypti* and *Aedes albopictus*) (<http://www.cdc.gov/zika/vector/range.html>). Recognition of the CZS phenotype by pediatric healthcare providers will help ensure appropriate and timely evaluation and follow-up of affected infants.

Congenital Zika Syndrome

Clinical features of CZS are a consequence of direct neurological damage and severe intracranial volume loss. Among 34 published reports with sufficient clinical information on at least one component of CZS were single case descriptions (11),^{11–21} case series (21),^{10,22–41} one cohort study,⁴² and one case-control study.⁷ Two reports contained information on pregnancies in French Polynesia,^{22,27} 29 in Brazil, and one each in the US, Spain and Finland with exposure outside the countries of birth.^{11,13,18} For discussion purposes, these clinical components can be divided into structural and functional components recognizing the overlap between these categories. Structural components include cranial morphology, brain anomalies, ocular anomalies, and congenital contractures. Functional components are exclusively related to neurologic impairment. Intrauterine growth restriction and low birth weight have been reported in infants with presumed and laboratory-confirmed congenital ZIKV infection;^{22,35} however, its relation to the CZS phenotype and pathogenetic mechanism has not been described.

Cranial Morphology

Severe microcephaly (more than 3 SD below the mean) observed with intrauterine ZIKV infection can be accompanied by findings consistent with fetal brain disruption sequence (FBDS).^{43,44} FBDS is characterized by severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, in addition to severe neurologic impairment (Figures 1, 2). There is often extreme craniofacial disproportion with depression of the frontal bones and parietal bones which can overlap.⁴³ Typically, affected fetuses are noted to have decreasing head circumferences in utero.³⁴

The FBDS phenotype has been reported in an infant with laboratory-confirmed ZIKV infection,¹¹ in a neuroimaging report documenting cranial bone collapse in infants born to mothers with suspected ZIKV infection during pregnancy,¹² and a recent case series of infants with probable ZIKV-associated microcephaly.³⁶ In three of the largest case series reporting 35, 48 and 104 infants primarily with suspected congenital ZIKV infection,^{31,35,36} approximately two-thirds of infants had severe microcephaly. In the recent case series, most infants with probable congenital ZIKV infection were noted to have craniofacial disproportion (95.8%) and to a lesser degree biparietal depression (83.3%), prominent occiput (75%) and excess nuchal skin (47.9%).³⁶ Features supportive of the FBDS phenotype scattered through published reports include redundant scalp,^{25,34,37,39} occipital prominence and/or overlapping sutures^{12,18,20–22,24,25,36} and typical craniofacial appearance with disproportion.^{11,25,31,32,38} The FBDS phenotype is also prevalent in ZIKV-related media (<http://www.apimages.com/Collection/Landing/Photographer-Felipe-Dana-Brazil-Zika-Birth-Defects/5437af63923a4384a8b27854132305a5>). Among infants with severe

microcephaly the pattern appears to be consistent, although the degree of cranial vault deformation varies.

The FBDS phenotype is hypothesized to be a result of loss in brain volume and decrease in intracranial pressure, and is not specific to the etiologic agent.^{43,44} While FBDS is not unique to CZS, the phenotype was previously rarely reported; a literature review published in 2001 identified a total of 20 cases.⁴⁴ To date, published series have not provided sufficient descriptors to estimate the proportion of infants with the FBDS phenotype among those with severe microcephaly and presumed or laboratory-confirmed ZIKV infection.

Brain Anomalies

Gross brain pathology from infants with presumed or laboratory-confirmed ZIKV infection, primarily from neuroimaging, closely resembles neuropathology associated with congenital cytomegalovirus (CMV).⁴⁵ The most notable difference is the distribution of intracranial calcifications, i.e., typically subcortical in congenital ZIKV infection and periventricular in CMV.^{45,46} Such calcifications are likely dystrophic and related to cell death, either by necrosis, apoptosis or both.⁴⁷

A prospective series of pregnant women tested for ZIKV infection because of rash found that 7/42 (16.7%) of women who underwent fetal ultrasonography had fetuses with calcifications or other central nervous system (CNS) anomalies.⁴² Postnatal CT scan and MR imaging have identified a spectrum of abnormalities that include, in decreasing frequency, diffuse, primarily subcortical calcifications; increased fluid spaces—ventricular and extra-axial; marked cortical thinning with abnormal gyral patterns (most consistent with polymicrogyria); hypoplasia or absence of the corpus callosum; decreased myelination; and cerebellar or cerebellar vermis hypoplasia (Figure 2)^{22,24,28,33–39} In addition, calcifications have been identified in the basal ganglion as well as the brainstem in some affected infants.³⁷ Some of these brain abnormalities can be detected prenatally with ultrasound or MR imaging;^{27,33,34,37} however, with severe microcephaly the anterior fontanel is often small or closed^{25,34} making tranfontanellar ultrasound in the newborn difficult.

The CNS damage seen with prenatal ZIKV infection is likely due to direct cellular injury as ZIKV RNA^{13,15,30} and live virus¹³ has been identified in brain tissue of infants with microcephaly. Studies in experimental models have implicated neural progenitor cells as a primary ZIKV target;^{48–50} however, immature neurons were also infected to a lesser extent.¹³ On microscopic examination of a ZIKV-infected fetal brain, apoptotic neurons that were primarily intermediately-differentiated postmigratory neurons were observed.¹³ These findings support direct neural cell injury by ZIKV and suggest disruption of existing immature neurons, as well as decreased proliferation and impaired migration due to loss of progenitor cells. Expression studies of candidate viral entry receptors such as AXL suggest that several other cell types including astrocytes, endothelial cells, and microglia might also be ZIKV targets.⁵¹

Ocular anomalies

Structural eye anomalies (in particular, microphthalmia and coloboma), cataracts, intraocular calcifications, and posterior ocular findings have been reported in infants with presumed and

laboratory-confirmed prenatal ZIKV infection; however, posterior findings have been the most prevalent.^{23,26,31,33,34,39,40,41,52} Case series report chorioretinal atrophy, focal pigmentary mottling of the retina, and optic nerve atrophy/anomalies.^{26,32,35,39–41,53} Series of 20 or more infants with presumed ZIKV-associated microcephaly report ocular findings in 24–55%^{26,31,40} In one study, testing for ZIKV IgM was performed in 24/40 (60%) of infants with microcephaly and was positive in the cerebrospinal fluid (CSF) in 100% of those tested.⁴⁰ The proportion of infants with ocular lesions did not differ in those with and without testing.⁴⁰ In that series, first trimester maternal infection and smaller head circumference significantly correlated with the presence of abnormal ocular findings.⁴⁰

The pathogenesis of the posterior eye lesions is unknown but might be due to direct cellular damage by ZIKV or inflammatory sequelae. Active chorioretinitis, a possible precursor of chorioretinal atrophy, has not been reported in infants with congenital ZIKV infection, and the pattern of ocular findings differs from those in other congenital infections.⁵⁴ In particular, retinal lesions including well-defined chorioretinal atrophy and gross pigmentation, generally affecting the macular region, are unique to ZIKV infection (Figure 3).

Congenital contractures

Congenital contractures involving one or multiple joints (i.e., arthrogryposis multiplex congenita or arthrogryposis) have been reported in fetuses and infants with presumed or laboratory-confirmed congenital ZIKV infection.^{18,22,34,35,39} The clinical picture of congenital contractures varies among affected infants in regard to type (proximal or distal), laterality, upper or lower limb, and severity, likely reflecting variations in neurologic damage (Figure 4). The three largest case series of infants with microcephaly also reporting congenital contractures found that, among 35, 48 and 52 infants with microcephaly and presumed congenital ZIKV infection, isolated clubfoot occurred in 14%, 10.4% and 3.8% and arthrogryposis in 11%, 10.4 % and 5.7%, respectively.^{34–36} Among a series of 104 infants under clinical investigation, 7 (6.7%) with presumed (5 infants) and laboratory-confirmed (2 infants) congenital ZIKV infection had arthrogryposis; six of these infants had a head circumference of at least 2 SD below the mean.³⁹ All had bilateral congenital hip dislocation which previously has been reported to occur in 30–40% of children with arthrogryposis of various etiologies and 3/7 had dislocation or partial dislocation of one or both knees.^{39,55}

Neurogenic factors that impact the corticospinal tract, motor neurons, or their interactions can cause fetal motor abnormalities, leading to diminished fetal movements and contractures.^{55,56} The specific mechanism for contractures with prenatal ZIKV infection is not fully understood. Among 7 infants with arthrogryposis, MR imaging of the spine in 4 was consistent with thinning of the cord and reduction in the ventral roots.³⁹ In these 7 infants, electromyographic findings suggested chronic involvement of peripheral motor neurons as well as central motor neurons.³⁹ No pathologic examination of the spinal cord from an affected infant has been published. The brainstem and spinal cord of one fetus with ZIKV infection showed Wallerian degeneration of the long descending tracts; but the fetus was not reported to have contractures, despite documentation of decreased fetal

movement.¹⁵ Previous reports of infants with the FBDS phenotype have not described congenital contractures; intrauterine infection with other viruses (e.g., rubella, varicella and coxsackie B) has been implicated in infants with arthrogryposis.^{57,58}

Neurological Sequelae and Prognosis

Information on long-term medical and developmental outcomes for infants with CZS is sparse. Based on data on infants with FBDS, development in infants with CZS is likely to be severely impaired. In a 2001 review of FBDS, 19/20 infants had severe neurological impairment; among 13 surviving infants, none had developmental skills that exceeded 2 months.⁴⁴ Three infants born after the 2013–2014 ZIKV outbreak in French Polynesia and presumed to have been infected *in utero* had severe neurological sequelae including motor and cognitive disabilities, seizures, and swallowing difficulties leading to failure to thrive; one infant had severe vision loss and suspected hearing impairment.²² In a series of newborns with microcephaly and presumed congenital ZIKV infection, 12% (2/16) of those with severe microcephaly (head circumference <30 cm) and 9% overall had abnormal otoacoustic emission testing.³⁵ Profound sensorineural hearing loss was reported in an infant with characteristic brain imaging findings and CSF positive for ZIKV IgM,¹⁴ and sensorineural hearing loss was documented in 4/69 infants with microcephaly and laboratory evidence of congenital ZIV infection.²⁹ Neurological examination of affected infants has shown hypertonia and spasticity, irritability manifested by excessive crying, dysphagia, and less frequently, hypotonia.^{35,36} Abnormal activity on electroencephalogram was seen in 13/27 (48%) infants with presumed congenital ZIKV infection and 14 (52%) additional infants had either focal or multifocal discharges.³⁶ In addition, tremors and posturing consistent with extrapyramidal dysfunction have been reported.^{11,35,36}

Data on mortality associated with suspected or confirmed congenital ZIKV infection are sparse, but prognosis was poor among infants with FBDS in the 2001 review; 7/20 infants died of pneumonia at an average age of 6 months.⁴⁴ Recently, mortality rates at a median of 8 days for 76 infants with laboratory-confirmed ZIKV infection was 41.1 per 1000.¹⁰

Differential Diagnosis

Infants with suspected congenital Zika infection should have a comprehensive evaluation as the differential diagnosis of CZS includes both infectious and genetic etiologies.⁵⁸ Although the brain findings in CMV and CZS are the most similar among congenital infections, the FBDS phenotype has rarely been described in congenital CMV,⁴³ despite published imaging studies of fetuses with CMV consistent with FBDS.⁴⁶ Microcephaly occurs with congenital infections with a number of other virus such as human immunodeficiency virus, varicella zoster virus, and rubella virus;⁴⁵ however, additional clinical findings (e.g., hepatomegaly and rash) help to differentiate these etiologies from ZIKV infection.^{8,60} To date no hematologic, hepatic, or renal laboratory abnormalities have been documented in infants with congenital ZIKV infection.

Several genetic etiologies share some similarities with CZS including Aicardi-Goutières syndrome,⁶¹ “pseudo-TORCH” syndrome,^{62,63} and mutations in the following genes: *JAM3*,

NDE1, and *ANKLE2*.^{64–66} Familial occurrence of the FBDS phenotype has also been reported, and for these cases, the term fetal brain arrest has been proposed.^{67–69}

Discussion

Limitations of this review include the absence of testing for ZIKV infection as well as the incomplete description of the full range of anomalies in most reported infants. In addition, because many reports focus on a single component of the syndrome, some infants may be included in more than one report. Although the numbers are small, recent reports provide evidence that the distinctive brain and eye anomalies of congenital ZIKV infection can occur without microcephaly;^{10,17,22,36,39,70} however, for some infants hydrocephaly was the underlying cause of the normal head circumference measurement.^{17,37} Expansion of the CZS phenotype to include infants with microcephaly but without brain anomalies has been suggested in a recent case-control study, however, it is unclear if these infants represented the effects of intrauterine growth restriction because information on other growth parameters at birth was not provided.⁷¹ Finally, postnatal development of microcephaly has also been reported.³⁶

The vast majority of clinical descriptions of ZIKV-affected infants available at this time understandably are from Brazil. Two case reports in this review document probable exposure in additional countries in the Americas^{13,18} and infants with microcephaly presumed secondary to congenital ZIKV infection have been reported in press releases from a number of countries in this region. A preliminary report from Colombia of 4 infants with laboratory-confirmed congenital Zika virus infection had the following brief summary of anomalies among those infants: abnormal brain findings by ultrasound (1 infant), abnormal hearing evaluations (3 infants), and other neurologic findings including hypotonia, poor suck or swallow, and arthrogryposis of the lower limbs (number not specified). These findings are consistent with the congenital Zika syndrome phenotype.⁷¹

Based on the available data, it appears that the most common timing of infection, as determined by maternal symptoms, is late first and early second trimester; however, third trimester infection is also reported among affected infants.^{10,38} Although no definitive correlation between timing of infection and severity of the phenotype has been documented, among a case series of 1,501 live births with complete investigation, head circumference Z scores varied by the reported trimester of exposure with those in the first trimester showing greatest negative scores.¹⁰ A recent report of 2 infants with laboratory-confirmed ZIKV infection due to exposure in the third trimester showed brain abnormalities including subependymal cysts in both infants and lenticulostriate vasculopathy in one.³⁸ These findings have been associated with other congenital infections and the significance in congenital ZIKV infection is not yet known; however, lenticulostriate vasculopathy has been documented prenatally in a Zika-affected fetus³³ and recently been identified as a high-risk marker for hearing loss in congenital CMV infection.⁷² In contrast, among 1,850 pregnant women in Colombia, more than 90% reportedly with third trimester infection, no apparent anomalies were noted in their infants;⁷¹ however, efforts to monitor the effect of ZIKV infection during pregnancy are ongoing.

Complete clinical descriptions of additional affected fetuses, infants, and young children are needed to help verify conclusions built on sparse data and to go beyond the current phenotype which likely represents a portion of a broader spectrum (<http://www.who.int/bulletin/volumes/94/6/16-176990>). In particular, more data are needed on infants with congenital ZIKV infection who do not have microcephaly at birth and the brain findings in these infants. In addition, knowledge about the frequency in which the various components co-occur in an infant is also lacking at this time.

At present the majority of reported congenital anomalies are consistent with the neurotropic nature of the virus; however, there are sporadic reports of anomalies that tend to have the highest birth prevalence in most populations, e.g., congenital heart defects, and are not consistent with current understanding of the pathogenetic mechanisms in CZS. Addition of these types of congenital anomalies to CSZ phenotype will likely require epidemiologic studies to help exclude coincidental associations as well as and determine a more complete phenotype for CZS.⁷³

Conclusion

Based on our review, ZIKV infection in pregnancy appears to be the cause of a recognizable pattern of congenital anomalies that is consistent and unique. Although many of the components of this syndrome such as cognitive, sensory and motor disabilities are shared by other congenital infections, five features differentiate congenital Zika syndrome from other congenital infections: severe microcephaly with partially collapsed skull; thin cerebral cortices with subcortical calcifications; macular scarring and focal pigmentary retinal mottling; congenital contractures; and marked early hypertonia with symptoms of extrapyramidal involvement (Table). Recognition of this phenotype by pediatric healthcare providers will help ensure appropriate and timely evaluation and follow-up of affected infants.

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References

1. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. *N Engl J Med*. 2016; 374(16): 1552–1563. [PubMed: 27028561]
2. Zanolini C, de Melo VC, Mosimann AL, Dos Santos GI, Dos Santos CN, Luz K. First report of autochthonous transmission of Zika virus in Brazil. *Mem Inst Oswaldo Cruz*. 2015; 110(4):569–572. [PubMed: 26061233]
3. Kleber de Oliveira W, Cortez-Escalante J, De Oliveira WT, et al. Increase in reported prevalence of microcephaly in infants born to women living in areas with confirmed Zika virus transmission during the first trimester of pregnancy – Brazil, 2015. *MMWR Morb Mortal Wkly Rep*. 2016; 65(9):242–247. [PubMed: 26963593]
4. Pan American Health Organization. World Health Organization. Regional Office for the Americas. Epidemiological Alert: Neurological syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas. 2015. http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=&gid=32405&lang=en. Accessed 2016 July 7

5. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects—reviewing the evidence for causality. *N Engl J Med*. 2016; 374(20):1981–1987. [PubMed: 27074377]
6. World Health Organization. Zika situation report. Zika virus, Microcephaly and Guillain-Barré syndrome. Apr. 2016 <http://www.who.int/emergencies/zika-virus/situation-report/7-april-2016/en/>
7. de Araujo TV, Rodrigues LC, de Alencar Ximenes RA, et al. Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study. *Lancet Infect Dis*. 2016 Sep 15. [Epub ahead of print].
8. Miranda-Filho DB, Martelli CM, Ximenes RA, et al. Initial description of the presumed congenital Zika syndrome. *Am J Public Health*. 2016; 106(4):598–600. [PubMed: 26959258]
9. Chan JF, Choi GK, Yip CC, Cheng VC, Yuen KY. Zika fever and congenital Zika syndrome: An unexpected emerging arboviral disease. *J Infect*. 2016; 72(5):507–524. [PubMed: 26940504]
10. Franca GV, Schuler-Faccini L, Oliveira WK, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. *Lancet*. 2016; 388(10047):891–897. [PubMed: 27372398]
11. Culjat M, Darling SE, Nerurkar VR, et al. Clinical and imaging findings in an infant with zika embryopathy. *Clin Infect Dis*. 2016; 63(6):805–811. [PubMed: 27193747]
12. Dain Gandelman Horovitz D, da Silva Pone MV, Moura Pone S, Dias Saad Salles TR, Bastos Boechat MC. Cranial bone collapse in microcephalic infants prenatally exposed to Zika virus infection. *Neurology*. 2016; 87(1):118–119. [PubMed: 27378805]
13. Driggers RW, Ho CY, Korhonen EM, et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. *N Engl J Med*. 2016; 374(22):2142–2151. [PubMed: 27028667]
14. Leal MC, Muniz LF, Neto SS, Linden V, Ramos RC. Sensorineural hearing loss in a case of congenital Zika virus. *Braz J Otorhinolaryngol*. 2016 Jun 30. [Epub ahead of print].
15. Mlakar J, Korva M, Tul N, et al. Zika virus associated with microcephaly. *N Engl J Med*. 2016; 374(10):951–958. [PubMed: 26862926]
16. Moron AF, Cavalheiro S, Milani H, et al. Microcephaly associated with maternal Zika virus infection. *BJOG*. 2016; 123(8):1265–1269. [PubMed: 27150580]
17. Oliveira DB, Almeida FJ, Durigon EL, et al. Prolonged shedding of zika virus associated with congenital infection. *N Engl J Med*. 2016; 375(12):1202–1204. [PubMed: 27653589]
18. Perez S, Tato R, Cabrera JJ, et al. Confirmed case of Zika virus congenital infection, Spain, March 2016. *Euro Surveill*. 2016; 21(24):doi: 10.2807/1560-7917.ES.2016.21.24.30261
19. Ventura CV, Maia M, Bravo-Filho V, Gois AL, Belfort R Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. *Lancet*. 2016; 387(10015):228.
20. Werner H, Fazecas T, Guedes B, et al. Intrauterine Zika virus infection and microcephaly: correlation of perinatal imaging and three-dimensional virtual physical models. *Ultrasound Obstet Gynecol*. 2016; 47(5):657–660. [PubMed: 26923098]
21. Werner H, Sodre D, Hygino C, et al. First trimester intrauterine Zika virus infection and brain pathology: prenatal and postnatal neuroimaging findings. *Prenat Diagn*. 2016; 36(8):785–789. [PubMed: 27316349]
22. Besnard M, Eyrolle-Guignot D, Guillemette-Artur P, et al. Congenital cerebral malformations and dysfunction in fetuses and newborns following the 2013 to 2014 Zika virus epidemic in French Polynesia. *Euro Surveill*. 2016; 21(13)
23. Calvet G, Aguiar RS, Melo AS, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. *Lancet Infect Dis*. 2016; 16(6):653–660. [PubMed: 26897108]
24. Cavalheiro S, Lopez A, Serra S, et al. Microcephaly and Zika virus: neonatal neuroradiological aspects. *Childs Nerv Syst*. 2016; 32(6):1057–1060. [PubMed: 27080092]
25. de Fatima Vasco Aragao M, van der Linden V, Brainer-Lima AM, et al. Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study. *BMJ*. 2016; 353:i1901. [PubMed: 27075009]
26. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. *JAMA Ophthalmol*. 2016 Feb 9. [Epub ahead of print].

27. Guillemette-Artur P, Besnard M, Eyrolle-Guignot D, Jouannic JM, Garel C. Prenatal brain MRI of fetuses with Zika virus infection. *Pediatr Radiol*. 2016; 46(7):1032–1039. [PubMed: 27090801]
28. Hazin AN, Poretti A, Cruz DD, et al. Computed tomographic findings in microcephaly associated with Zika virus. *N Engl J Med*. 2016; 374(22):2193–2195.
29. Leal MC, Muniz LF, Ferreira TS, et al. Hearing loss in infants with microcephaly and evidence of congenital Zika virus infection – Brazil, November 2015–May 2016. *MMWR Morb Mortal Wkly Rep*. 2016; 65(34):917–919. [PubMed: 27585248]
30. Martinez RB, Bhatnagar J, de Oliveira Ramos AM, et al. Pathology of congenital Zika syndrome in Brazil: a case series. *Lancet*. 2016; 388(10047):898–904. [PubMed: 27372395]
31. Microcephaly Epidemic Research G. Microcephaly in Infants, Pernambuco State, Brazil, 2015. *Emerg Infect Dis*. 2016; 22(6):1090–1093. [PubMed: 27071041]
32. Miranda HA 2nd, Costa MC, Frazao MA, Simao N, Franchischini S, Moshfeghi DM. Expanded spectrum of congenital ocular findings in microcephaly with presumed Zika infection. *Ophthalmology*. 2016; 123(8):1788–1794. [PubMed: 27236271]
33. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol*. 2016; 47(1):6–7. [PubMed: 26731034]
34. Sarno M, Aquino M, Pimentel K, et al. Progressive lesions of central nervous system in microcephalic fetuses with suspected congenital Zika virus syndrome. *Ultrasound Obstet Gynecol*. 2016 Sep 19. [Epub ahead of print].
35. Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly — Brazil, 2015. *MMWR Morb Mortal Wkly Rep*. 2016; 65(3):59–62. [PubMed: 26820244]
36. Silva AAM, Ganz JSS, Sousa PS, et al. Early growth and neurologic outcomes of infants with probable congenital Zika virus syndrome. *Emerg Infect Disease*. 2016 Nov. [Aug 25]. doi: 10.3201/eid2211.160956
37. Soares de Oliveira-Szejnfeld P, Levine D, Melo AS, et al. Congenital brain abnormalities and Zika virus: what the radiologist can expect to see prenatally and postnatally. *Radiology*. 2016; 281(1): 203–218. [PubMed: 27552432]
38. Soares de Souza A, Dias CM, Braga FD, et al. Fetal infection by Zika virus in the third trimester – report of 2 cases. *Clin Infect Dis*. 2016 Sep 6. [Epub ahead of print].
39. van der Linden V, Filho EL, Lins OG, et al. Congenital Zika syndrome with arthrogryposis: retrospective case series study. *BMJ*. 2016; 354:i3899.doi: 10.1136/bmj.i3899 [PubMed: 27509902]
40. Ventura CV, Maia M, Travassos SB, et al. Risk factors associated with the ophthalmoscopic findings identified in infants with presumed Zika virus congenital infection. *JAMA Ophthalmol*. 2016; 134(8):912–918. [PubMed: 27228275]
41. Ventura CV, Maia M, Ventura BV, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. *Arq Bras Oftalmol*. 2016; 79(1):1–3. [PubMed: 26840156]
42. Brasil P, Pereira JP Jr, Raja Gabaglia C, et al. Zika virus infection in pregnant women in Rio de Janeiro – preliminary report. *N Engl J Med*. 2016 Mar 4. [Epub ahead of print].
43. Russell LJ, Weaver DD, Bull MJ, Weinbaum M. In utero brain destruction resulting in collapse of the fetal skull, microcephaly, scalp rugae, and neurologic impairment: the fetal brain disruption sequence. *Am J Med Genet*. 1984; 17(2):509–521. [PubMed: 6702901]
44. Corona-Rivera JR, Corona-Rivera E, Romero-Velarde E, Hernandez-Rocha J, Bobadilla-Morales L, Corona-Rivera A. Report and review of the fetal brain disruption sequence. *Eur J Pediatr*. 2001; 160(11):664–667. [PubMed: 11760023]
45. Parmar H, Ibrahim M. Pediatric intracranial infections. *Neuroimaging Clin N Am*. 2012; 22(4): 707–725. [PubMed: 23122263]
46. Averill LW, Kandula VV, Akyol Y, Epelman M. Fetal brain magnetic resonance imaging findings in congenital cytomegalovirus infection with postnatal imaging correlation. *Semin Ultrasound CT MR*. 2015; 36(6):476–486. [PubMed: 26614131]

47. Fujita H, Yamamoto M, Ogino T, et al. Necrotic and apoptotic cells serve as nuclei for calcification on osteoblastic differentiation of human mesenchymal stem cells in vitro. *Cell Biochem Funct.* 2014; 32(1):77–86. [PubMed: 23657822]
48. Garcez PP, Loiola EC, Madeiro da Costa R, et al. Zika virus impairs growth in human neurospheres and brain organoids. *Science.* 2016
49. Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. *Cell Stem Cell.* 2016; 18(5):587–590. [PubMed: 26952870]
50. Qian X, Nguyen HN, Song MM, et al. Brain-region-specific organoids using mini-bioreactors for modeling zikv exposure. *Cell.* 2016; 165(5):1238–1254. [PubMed: 27118425]
51. Nowakowski TJ, Pollen AA, Di Lullo E, Sandoval-Espinosa C, Bershteyn M, Kriegstein AR. Expression analysis highlights AXL as a candidate Zika virus entry receptor in neural stem cells. *Cell Stem Cell.* 2016; 18(5):591–596. [PubMed: 27038591]
52. Ventura CV, Maia M, Bravo-Filho V, Gois AL, Belfort R Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. *Lancet.* 2016a; 387(10015):228.
53. Valentine G, Marquez L, Pammi M. Zika virus-associated microcephaly and eye lesions in the newborn. *J Pediatric Infect Dis Soc.* 2016; 5(3):323–328. [PubMed: 27405738]
54. Mets MB, Chhabra MS. Eye manifestations of intrauterine infections and their impact on childhood blindness. *Surv Ophthalmol.* 2008; 53(2):95–111. [PubMed: 18348876]
55. Kowalczyk B, Felus J. Arthrogryposis: an update on clinical aspects, etiology, and treatment strategies. *Arch Med Sci.* 2016; 12(1):10–24. [PubMed: 26925114]
56. Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update. *J Bone Joint Surg Am.* 2009; 91(Suppl 4):40–46.
57. Hall JG, Reed SD. Teratogens associated with congenital contractures in humans and in animals. *Teratology.* 1982; 25(2):173–191. [PubMed: 7101197]
58. Konstantinidou A, Anninos H, Spanakis N, et al. Transplacental infection of coxsackievirus B3 pathological findings in the fetus. *J Med Virol.* 2007; 79(6):754–757. [PubMed: 17457913]
59. Russell K, Oliver SE, Lewis L, et al. Update: Interim guidance for the evaluation and management of infants with possible congenital Zika virus infection – United States, August 2016. *MMWR Morb Mortal Wkly Rep.* 2016; 65(33):870–878. [PubMed: 27559830]
60. Degani S. Sonographic findings in fetal viral infections: a systematic review. *Obstet Gynecol Surv.* 2006; 61(5):329–336. [PubMed: 16635273]
61. La Piana R, Uggetti C, Roncarolo F, et al. Neuroradiologic patterns and novel imaging findings in Aicardi-Goutieres syndrome. *Neurology.* 2016; 86(1):28–35. [PubMed: 26581299]
62. Briggs TA, Wolf NI, D'Arrigo S, et al. Band-like intracranial calcification with simplified gyration and polymicrogyria: a distinct “pseudo-TORCH” phenotype. *Am J Med Genet A.* 2008; 146A(24):3173–3180. [PubMed: 19012351]
63. O'Driscoll MC, Daly SB, Urquhart JE, et al. Recessive mutations in the gene encoding the tight junction protein occludin cause band-like calcification with simplified gyration and polymicrogyria. *Am J Hum Genet.* 2010; 87(3):354–364. [PubMed: 20727516]
64. Mochida GH, Ganesh VS, Felie JM, et al. A homozygous mutation in the tight-junction protein JAM3 causes hemorrhagic destruction of the brain, subependymal calcification, and congenital cataracts. *Am J Hum Genet.* 2010; 87(6):882–889. [PubMed: 21109224]
65. Paciorkowski AR, Keppler-Noreuil K, Robinson L, et al. Deletion 16p13.11 uncovers NDE1 mutations on the non-deleted homolog and extends the spectrum of severe microcephaly to include fetal brain disruption. *Am J Med Genet A.* 2013; 161A(7):1523–1530. [PubMed: 23704059]
66. Yamamoto S, Jaiswal M, Charng WL, et al. A drosophila genetic resource of mutants to study mechanisms underlying human genetic diseases. *Cell.* 2014; 159(1):200–214. [PubMed: 25259927]
67. Abdel-Salam GM, Abdel-Hamid MS, El-Khayat HA, et al. Fetal brain disruption sequence versus fetal brain arrest: A distinct autosomal recessive developmental brain malformation phenotype. *Am J Med Genet A.* 2015; 167A(5):1089–1099. [PubMed: 25755095]
68. Alexander IE, Tauro GP, Bankier A. Fetal brain disruption sequence in sisters. *Eur J Pediatr.* 1995; 154(8):654–657. [PubMed: 7588968]

69. Schram A, Kroes HY, Sollie K, Timmer B, Barth P, van Essen T. Hereditary fetal brain degeneration resembling fetal brain disruption sequence in two sibships. *Am J Med Genet A*. 2004; 127A(2):172–182. [PubMed: 15108206]
70. Ventura CV, Maia M, Dias N, Ventura LO, Belfort R Jr. Zika: neurological and ocular findings in infant without microcephaly. *Lancet*. 2016; 387(10037):2502. [PubMed: 27287830]
71. Pacheco O, Beltran M, Nelson CA, et al. Zika virus disease in Colombia – Preliminary report. *N Engl J Med*. 2016 Jun 15. [Epub ahead of print].
72. Bilavsky E, Schwarz M, Pardo J, et al. Lenticulostriated vasculopathy is a high-risk marker for hearing loss in congenital cytomegalovirus infections. *Acta Paediatr*. 2015; 104(9):e388–394. [PubMed: 26018986]
73. Gerardin P, Randrianaivo H, Schaub B, Cesaire R, Doray B, LaBeaud AD. Congenital Zika syndrome: time to move from case series to case-control studies and data sharing. *BMJ*. 2016; 354:i4850. [PubMed: 27629599]

Figure 1. Cranial morphology supporting fetal brain disruption sequence (FBDS) phenotype in congenital Zika syndrome

A) Lateral view of an infant with congenital Zika virus infection. Note the severe decrease in cranial vault, irregularity of the skull, and scalp rugae.

B) Note typical scalp folds or rugae in a 3-month-old infant with presumed congenital Zika virus infection.

C) Lateral skull radiograph in a newborn showing partial collapse of the cranial bones with prominent occiput.

D) Fetal MRI showing same phenotype at 29 weeks' gestation. White arrow indicates occipital area.

E) 3D skull reconstruction in a 3-month-old infant showing downward displacement of the frontal and temporal bones while occipital bone appears stable.

Figure 2. Brain findings in infants with presumed congenital Zika syndrome

CT scan in one infant and MRI in another infant with prenatal Zika exposure show very low forehead and small cranial vault (D), striking volume loss shown by enlarged extra-axial space and ventriculomegaly (all images), poor gyral development with few and shallow sulci (long white arrows in A and E), poor gyral development with irregular “beaded” cortex most consistent with polymicrogyria (black arrows in F), scattered punctate calcifications (white arrowheads in A, B, C and E), flattened pons and small cerebellum (black arrowhead and asterisk in D). The occipital “shelf” caused by skull collapse is seen in both children (large white arrows in C and D).

Figure 3. Wide-angle fundus images (RetCam®) of a male infant with congenital Zika infection
A) Right eye: Optic nerve hypoplasia with the double-ring sign, increased cup-to-disk ratio, attenuated blood vessels, gross pigment mottling and chorioretinal scar in the macular region.
B) Left eye: Optic nerve hypoplasia with the double-ring sign, increased cup-to-disk ratio, attenuated blood vessels, gross pigment mottling and chorioretinal scar in the macular region.

Figure 4. Infants with congenital Zika infection and microcephaly and arthrogryposis
A) Newborn infant with bilateral contractures of the hips and knees, bilateral talipes calcaneovalgus, and anterior dislocation of the knees. Hips are bilaterally dislocated.
B) Newborn infant with bilateral contractures of the shoulders, elbows, wrists, hips, knees, and right talipes equinovarus. Hips are bilaterally dislocated.

Table

Clinical findings comprising a unique pattern of congenital anomalies in infants with the congenital Zika virus infection – congenital Zika syndrome

Clinical feature	Findings in infants with confirmed congenital Zika infection	Differential diagnoses	Findings potentially unique to infants with congenital Zika virus (ZIKV) infection
Cranial morphology	<ul style="list-style-type: none"> Fetal brain disruption sequence (FBDS) <ul style="list-style-type: none"> Severe microcephaly Overlapping cranial sutures Prominent occipital bone Redundant scalp skin Neurologic impairment 	<ul style="list-style-type: none"> Congenital cytomegalovirus infection Possibly other congenital infections Gene mutations in <i>JAM3</i>, <i>NDE1</i>, and <i>ANKLE2</i> 	FBDS phenotype not unique to congenital ZIKV infection but rarely reported prior to 2015 when local transmission of ZIKV confirmed in Brazil
Brain anomalies	<ul style="list-style-type: none"> Cerebral cortex thinning Abnormal gyral patterns Increased fluid spaces (ventriculomegaly or extra-axial) Subcortical calcifications Corpus callosum anomalies Decreased white matter Cerebellar (vermis) hypoplasia 	<ul style="list-style-type: none"> Congenital cytomegalovirus infection Possibly other congenital infections Genetic syndromes, in particular Aicardi-Goutieres syndrome and pseudo-TORCH syndrome Gene mutations in <i>JAM3</i>, <i>NDE1</i>, and <i>ANKLE2</i> 	Subcortical location of calcifications in congenital ZIKV infection unique among other congenital infections and genetic syndromes
Ocular anomalies	<ul style="list-style-type: none"> Structural anomalies (microphthalmia, coloboma) Cataracts Posterior anomalies <ul style="list-style-type: none"> Chorioretinal atrophy Focal pigmentary mottling Optic nerve hypoplasia/atrophy 	<ul style="list-style-type: none"> Congenital infections 	Chorioretinal atrophy and focal pigmentary mottling, both affecting the macula, unique among other congenital infections
Congenital contractures	<ul style="list-style-type: none"> Unilateral or bilateral clubfoot Arthrogryposis multiplex congenita 	<ul style="list-style-type: none"> Congenital infections (rubella, varicella, coxsackie B only) 	Contractures not previously reported with the FBDS phenotype
Neurologic sequelae	<ul style="list-style-type: none"> Motor disabilities Cognitive disabilities Hypertonia/spasticity Hypotonia Irritability/excessive crying Tremors and extrapyramidal symptoms 	<ul style="list-style-type: none"> Congenital cytomegalovirus infections Other congenital infections 	Early pyramidal and extrapyramidal symptoms unusual among other congenital infections

Clinical feature	Findings in infants with confirmed congenital Zika infection	Differential diagnoses	Findings potentially unique to infants with congenital Zika virus (ZIKV) infection
	<ul style="list-style-type: none">Swallowing dysfunctionVision impairmentHearing impairmentEpilepsy		

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