

# Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians

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**IMPORTANCE** Zika virus infection can be prenatally passed 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 clinicians who may be called on to evaluate and treat 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. We conducted a comprehensive search of the English literature using Medline and EMBASE for *Zika* from inception through September 30, 2016. 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 5 features that are rarely seen with other congenital infections or are unique to congenital Zika virus infection: (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) 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 clinicians for infants and children can help ensure appropriate etiologic evaluation and comprehensive clinical investigation to define the range of anomalies in an affected infant as well as determine essential follow-up and ongoing care.

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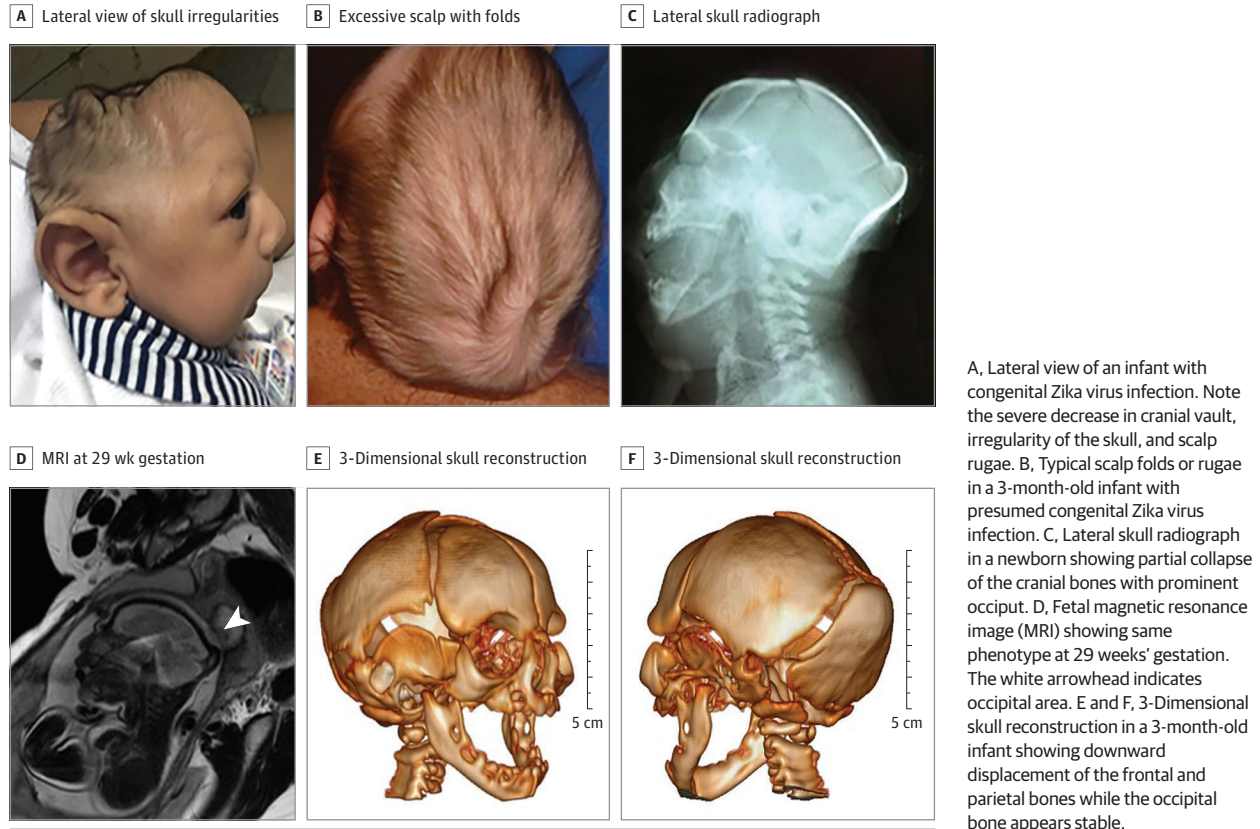
Contracted through the bite of an infected mosquito or through sexual or other modes of transmission, Zika virus (ZIKV) infection can be prenatally passed from mother to fetus.<sup>1</sup> The virus was first identified in the region of the Americas in early 2015, when local transmission was reported in Brazil.<sup>2</sup> Six months later, a notable increase in the number of infants with congenital microcephaly was observed in northeast Brazil.<sup>3,4</sup> Clinical, epidemiologic, and laboratory evidence led investigators to conclude that intrauterine ZIKV infection was a cause of microcephaly and serious brain anomalies.<sup>5-7</sup> 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 Sep-

tember 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.<sup>8-10</sup>

Zika virus infection has spread to more than 45 countries in the Americas and 3 US territories, and, most recently, local transmission was confirmed in the continental United States in the state of Florida.<sup>11</sup> Mosquito-borne transmission of ZIKV in other areas of the United States is possible based on the estimated range of its vectors (*Aedes aegypti* and *Aedes albopictus*).<sup>12</sup> Recognition of the CZS phenotype by pediatric clinicians will help ensure appropriate and timely evaluation and follow-up of affected infants.

**Figure 1. Cranial Morphology Supporting Fetal Brain Disruption Sequence Phenotype in Congenital Zika Syndrome**



## Congenital Zika Syndrome

Clinical features of CZS are a consequence of direct neurological damage and severe intracranial volume loss. Of the 34 published reports with sufficient clinical information on at least 1 component of CZS, 11 were single case descriptions,<sup>13-23</sup> 21 case series,<sup>10,24-43</sup> 1 cohort study,<sup>44</sup> and 1 case-control study.<sup>7</sup> Two reports contain information on pregnancies in French Polynesia<sup>24,29</sup> and 29 in Brazil; and there were 2 such reports in the United States<sup>13,15</sup> and 1 in Spain,<sup>20</sup> with exposure outside the countries of birth. 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<sup>24,37</sup>; however, its relation to the CZS phenotype and pathogenetic mechanism has not been determined.

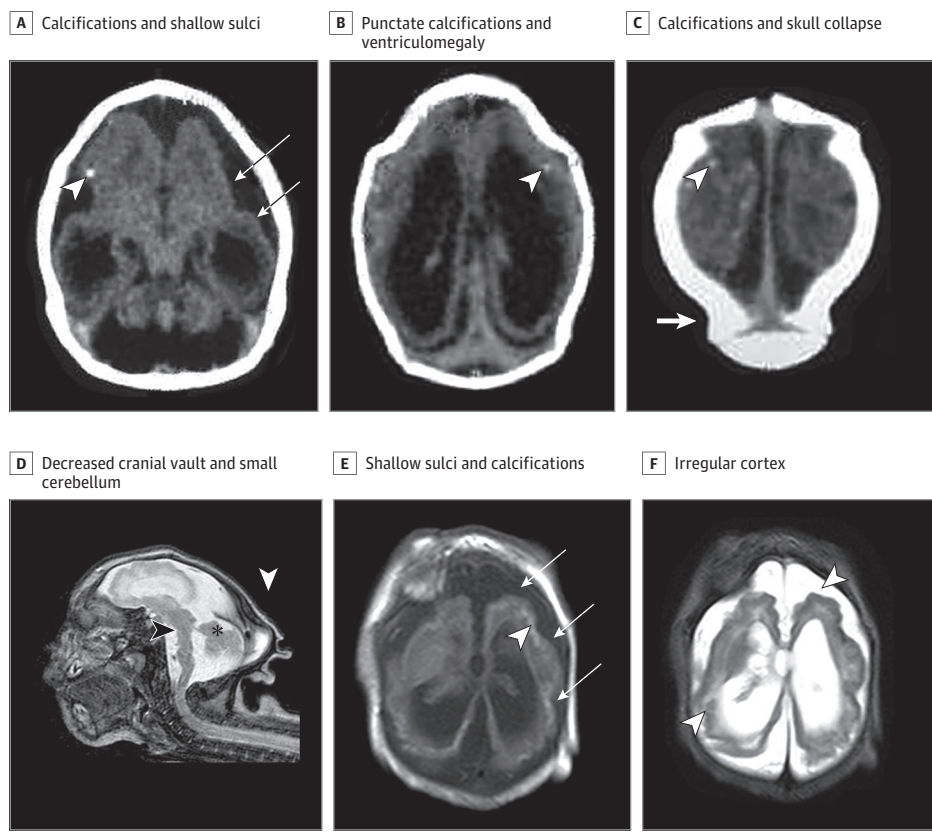
### Cranial Morphology

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).<sup>45,46</sup> Fetal brain

disruption sequence is characterized by severe microcephaly, overlapping cranial sutures, prominent occipital bone, and redundant scalp skin, in addition to severe neurologic impairment (Figure 1 and Figure 2). There is often extreme craniofacial disproportion with depression of the frontal bones and parietal bones, which can overlap.<sup>45</sup> Typically, affected fetuses are noted to have decreasing head circumferences in utero.<sup>36</sup>

The FBDS phenotype has been reported in an infant with laboratory-confirmed ZIKV infection,<sup>13</sup> in a neuroimaging report documenting cranial bone collapse in infants born to mothers with suspected ZIKV infection during pregnancy,<sup>14</sup> and a recent case series of infants with probable ZIKV-associated microcephaly.<sup>38</sup> In 3 of the largest case series reporting 35, 48, and 104 infants primarily with suspected congenital ZIKV infection,<sup>33,37,38</sup> 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%).<sup>38</sup> Features supportive of the FBDS phenotype scattered through published reports include redundant scalp,<sup>27,36,39,41</sup> occipital prominence and/or overlapping sutures,<sup>14,20,22-24,26,27,38</sup> and typical craniofacial appearance with disproportion.<sup>13,27,33,34,40</sup> The FBDS phenotype is also prevalent in ZIKV-related media.<sup>47</sup> Among infants with severe microcephaly, the pattern appears to be consistent, although the degree of cranial vault deformation varies.

Figure 2. Brain Findings in Infants With Presumed Congenital Zika Syndrome



Computed tomographic scan in 1 infant and magnetic resonance imaging in another infant with prenatal Zika exposure show scattered punctate calcifications (A, B, C, and E; white arrowheads), 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 (A and E; long white arrows), poor gyral development with irregular "beaded" cortex most consistent with polymicrogyria (F, white arrowheads), flattened pons and small cerebellum (D; black arrowhead and asterisk). The occipital "shelf" caused by skull collapse is seen in both infants (C, white arrow and D, white arrowhead).

The FBDS phenotype is hypothesized to be a result of loss in brain volume and decrease in intracranial pressure, and it is not specific to the etiologic agent.<sup>45,46</sup> 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.<sup>46</sup> To our knowledge, 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 to date.

### 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).<sup>48</sup> The most notable difference is the distribution of intracranial calcifications (ie, typically subcortical in congenital ZIKV infection and periventricular in CMV).<sup>48,49</sup> Such calcifications are likely dystrophic and related to cell death, either by necrosis, apoptosis, or both.<sup>50</sup>

A prospective series of pregnant women tested for ZIKV infection because of rash found that 7 of 42 women (16.7%) who underwent fetal ultrasonography had fetuses with calcifications or other central nervous system anomalies.<sup>44</sup> Postnatal computed tomographic scan and magnetic resonance 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 abnor-

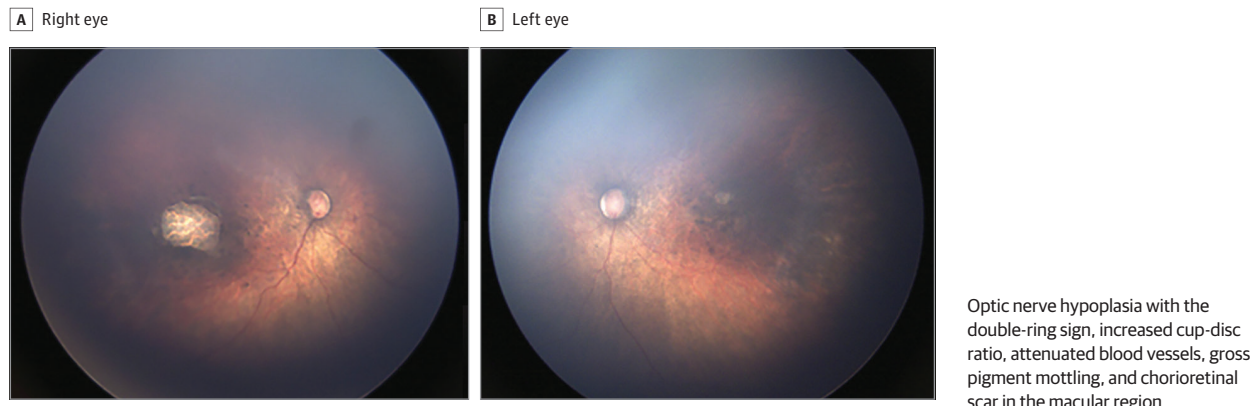
mal gyral patterns (most consistent with polymicrogyria); hypoplasia or absence of the corpus callosum; decreased myelination; and cerebellar or cerebellar vermis hypoplasia (Figure 2).<sup>24,26,30,35-41</sup> In addition, calcifications have been identified in the basal ganglion and brainstem in some affected infants.<sup>39</sup> Some of these brain abnormalities can be detected prenatally with ultrasonography or magnetic resonance imaging<sup>29,35,36,39</sup>; however, with severe microcephaly, the anterior fontanel is often small or closed,<sup>27,36</sup> making tranfontanellar ultrasonography in the newborn difficult.

The central nervous system damage seen with prenatal ZIKV infection is likely due to direct cellular injury, as ZIKV RNA<sup>15,17,32</sup> and live virus<sup>15</sup> have been identified in the brain tissue of infants with microcephaly. Studies in experimental models have implicated neural progenitor cells as a primary ZIKV target<sup>51-53</sup>; however, immature neurons were also infected to a lesser extent.<sup>15</sup> On microscopic examination of a ZIKV-infected fetal brain, postmigratory neurons—primarily intermediately differentiated—were apoptotic.<sup>15</sup> 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.<sup>54</sup>

### Ocular Anomalies

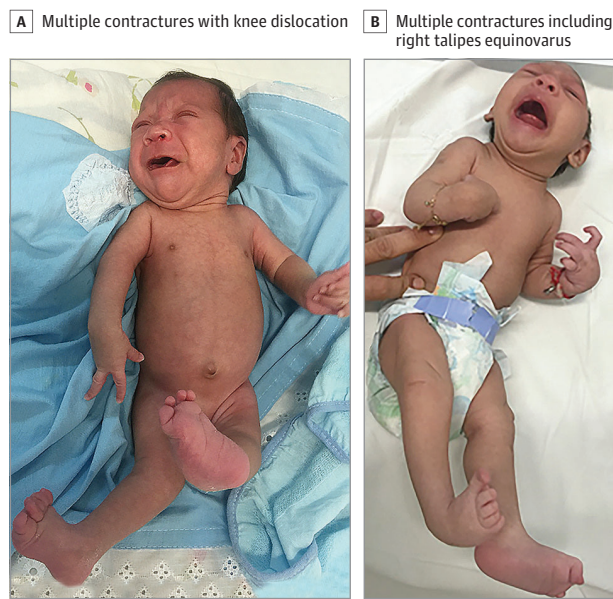
Structural eye anomalies (in particular, microphthalmia and coloboma), cataracts, intraocular calcifications, and posterior ocular find-

Figure 3. Wide-Angle Fundus Images (RetCam) of a Male Infant With Congenital Zika Infection



Optic nerve hypoplasia with the double-ring sign, increased cup-disc ratio, attenuated blood vessels, gross pigment mottling, and chorioretinal scar in the macular region.

Figure 4. Infants With Congenital Zika Infection, 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.

ings have been reported in infants with presumed and laboratory-confirmed prenatal ZIKV infection; however, posterior findings have been the most prevalent.<sup>21,25,28,33,35,36,41-43</sup> Case series report chorioretinal atrophy, focal pigmentary mottling of the retina, and optic nerve atrophy/anomalies.<sup>28,34,37,41-43,55</sup> Series of 20 or more infants with presumed ZIKV-associated microcephaly report ocular findings in 24% to 55%.<sup>28,33,42</sup> In one study, testing for ZIKV IgM was performed in 24 of 40 infants (60%) with microcephaly and the results were positive in the cerebrospinal fluid in 100% of those tested.<sup>42</sup> The proportion of infants with ocular lesions did not differ in those with and without testing.<sup>42</sup> In that series, first trimester maternal infection and smaller head circumference significantly correlated with the presence of abnormal ocular findings.<sup>42</sup>

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.<sup>56</sup> 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 1 or multiple joints (ie, arthrogryposis multiplex congenita or arthrogryposis) have been reported in fetuses and infants with presumed or laboratory-confirmed congenital ZIKV infection.<sup>20,24,36,37,41</sup> 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 3 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.<sup>36-38</sup> 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; 6 of these infants had a head circumference of at least 2 SD below the mean.<sup>41</sup> All had bilateral congenital hip dislocation, which previously has been reported to occur in 30% to 40% of children with arthrogryposis of various etiologies and 3 of 7 had dislocation or partial dislocation of 1 or both knees.<sup>41,57</sup>

Neurogenic factors that affect the corticospinal tract, motor neurons, or their interactions can cause fetal motor abnormalities, leading to diminished fetal movements and contractures.<sup>57,58</sup> The specific mechanism for contractures with prenatal ZIKV infection is not fully understood. Among 7 infants with arthrogryposis, magnetic resonance imaging of the spine in 4 was consistent with thinning of the cord and reduction in the ventral roots.<sup>41</sup> In these 7 infants, electromyographic findings suggested long-term involvement of peripheral motor neurons and central motor neurons.<sup>41</sup> To our knowledge, no pathologic examination of the spinal cord from an affected infant has been published. The brainstem and spinal

cord of 1 fetus with ZIKV infection showed Wallerian degeneration of the long descending tracts; however, the fetus was not reported to have contractures, despite documentation of decreased fetal movement.<sup>17</sup> Previous reports of infants with the FBDS phenotype have not described congenital contractures; intrauterine infection with other viruses (eg, rubella, varicella, and coxsackie B) has been implicated in infants with arthrogryposis.<sup>59,60</sup>

### 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 of 20 infants had severe neurological impairment; among 13 surviving infants, none had developmental skills that exceeded 2 months.<sup>46</sup> 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; 1 infant had severe vision loss and suspected hearing impairment.<sup>24</sup> In a series of newborns with microcephaly and presumed congenital ZIKV infection, of 23 with otoacoustic emission testing, 12.5% (2/16) of those with severe microcephaly and 8.7% (2/23) overall had abnormal results.<sup>33</sup> Profound sensorineural hearing loss was reported in an infant with characteristic brain imaging findings and cerebrospinal fluid positive for ZIKV IgM,<sup>16</sup> and sensorineural hearing loss was documented in 4 of 69 infants (5.8%) with microcephaly and laboratory evidence of congenital ZIKV infection.<sup>31</sup> Neurological examination of affected infants has shown hypertonia and spasticity, irritability manifested by excessive crying, dysphagia, and, less frequently, hypotonia.<sup>37,38</sup> Abnormal activity on electroencephalogram was seen in 13 of 27 infants (48%) with presumed congenital ZIKV infection and 14 infants (52%) had either focal or multifocal discharges.<sup>38</sup> In addition, tremors and posturing consistent with extrapyramidal dysfunction have been reported.<sup>13,37,38</sup>

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 of 20 infants (35%) died of pneumonia at a mean age of 6 months.<sup>46</sup> Recently, mortality rates at a median of 8 days for 76 infants with laboratory-confirmed ZIKV infection was 41.1 per 1000.<sup>10</sup>

### Differential Diagnosis

Infants with suspected congenital ZIKV infection should have a comprehensive evaluation, as the differential diagnosis of CZS includes both infectious and genetic etiologies.<sup>61</sup> 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,<sup>45</sup> despite published imaging studies of fetuses with CMV consistent with FBDS.<sup>49</sup> Microcephaly occurs with congenital infections with a number of other virus such as human immunodeficiency virus, varicella-zoster virus, and rubella virus<sup>48</sup>; however, additional clinical findings (eg, hepatomegaly and rash) help to differentiate these etiologies from ZIKV infection.<sup>8,62</sup> To our knowledge, no hematologic, hepatic, or renal laboratory abnormalities have been documented in infants with congenital ZIKV infection to date.

Several genetic etiologies share some similarities with CZS including Aicardi-Goutières syndrome,<sup>63</sup> "pseudo-TORCH" syndrome,<sup>64,65</sup> and mutations in the *JAM3*, *NDE1*, and *ANKLE2* genes.<sup>66-68</sup> Familial occurrence of the FBDS phenotype has also been reported, and for these cases, the term *fetal brain arrest* has been proposed.<sup>69-71</sup>

### Discussion

Most clinical descriptions of ZIKV-affected infants available at this time are from Brazil. Two case reports in this review document probable exposure in additional countries in the Americas<sup>15,20</sup> 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 ZIKV infection had the following brief summary of anomalies among those infants: abnormal brain findings by ultrasonography (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 CZS phenotype.<sup>72</sup>

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.<sup>10,40</sup> Although no definitive correlation between timing of infection and severity of the phenotype has been documented, among a case series of 1501 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.<sup>10</sup> 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.<sup>40</sup> 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 fetus<sup>35</sup> and recently has been identified as a high-risk marker for hearing loss in congenital CMV infection.<sup>73</sup> In contrast, among 1850 pregnant women in Colombia, more than 90% reportedly with third trimester infection, no apparent anomalies were noted in their infants<sup>72</sup>; 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.<sup>74</sup> 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, as well as whether any component(s) are mandatory features, is lacking at this time.

At present, most 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 (eg, congenital heart defects) and are not consistent with current understanding of the pathogenetic mechanisms in CZS. Addition of these types of congenital anomalies to the

Table. Clinical Findings Comprising a Unique Pattern of Congenital Anomalies in Infants With Congenital ZIKV Infection: Congenital Zika Syndrome

Clinical Feature	Findings in Infants With Confirmed Congenital ZIKV Infection	Differential Diagnoses	Findings Potentially Unique to Infants With Congenital ZIKV Infection
Cranial morphology	FBDS: severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and neurologic impairment	Congenital cytomegalovirus infection; possibly other congenital infections; and 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 was confirmed in Brazil
Brain anomalies	Cerebral cortex thinning; abnormal gyral patterns; increased fluid spaces (ventriculomegaly or extra-axial); subcortical calcifications; corpus callosum anomalies; decreased white matter; and cerebellar (vermis) hypoplasia	Congenital cytomegalovirus infection; possibly other congenital infections; genetic syndromes, in particular Aicardi-Goutières syndrome and pseudo-TORCH syndrome; and 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	Structural anomalies (microphthalmia, coloboma); cataracts; and posterior anomalies: chorioretinal atrophy, focal pigmentary mottling, and optic nerve hypoplasia/atrophy	Congenital infections	Chorioretinal atrophy and focal pigmentary mottling, both affecting the macula, unique among other congenital infections
Congenital contractures	Unilateral or bilateral clubfoot and arthrogryposis multiplex congenita	Congenital infections (rubella, varicella, and coxsackie B only)	Contractures not previously reported with the FBDS phenotype
Neurologic sequelae	Motor disabilities; cognitive disabilities; hypertonia/spasticity; hypotonia; irritability/excessive crying; tremors and extrapyramidal symptoms; swallowing dysfunction; vision impairment; hearing impairment; and epilepsy	Congenital cytomegalovirus infections and other congenital infections	Early pyramidal and extrapyramidal symptoms unusual among other congenital infections

Abbreviations: FBDS, fetal brain disruption sequence; ZIKV, Zika virus.

CZS phenotype will likely require epidemiologic studies to help exclude coincidental associations and determine a more complete phenotype for CZS.<sup>75</sup>

### Limitations

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 1 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<sup>10,19,24,38,39,41,76</sup>; however, for some infants, hydrocephaly was the underlying cause of the normal head circumference measurement.<sup>19,39</sup> 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 whether these infants represented the effects of intrauterine growth restriction because information on other growth para-

eters at birth was not provided.<sup>72</sup> Finally, postnatal development of microcephaly in an infant with presumed in utero exposure has also been reported.<sup>38</sup>

### Conclusions

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, 5 features differentiate CZS from other congenital infections: (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) marked early hypertonia with symptoms of extrapyramidal involvement (Table). Recognition of this phenotype by pediatric clinicians will help ensure appropriate and timely evaluation and follow-up of affected infants.

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*Supervision:* Moore, Dobyns, Pessoa.

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