Development of Infants With Congenital Zika Syndrome: What Do We Know and What Can We Expect?

Anne C. Wheeler, PhD

abstract The association between Zika virus infection during pregnancy and severe birth defects in infants has led to worldwide attention focused on the mechanisms of the disease and the prevention of future exposure. Surveillance efforts around the world continue with the goal of identifying and monitoring all potentially exposed women and their newborns. For infants who were born with congenital Zika syndrome (CZS) and their families, an uncertain future awaits. As infants who were born with CZS during the most recent outbreak enter their second year of life, new developments in the outcomes of the condition continue to unfold, providing some insight into the likely long-term sequelae. In this article, I review the literature on emerging findings regarding the impact of CZS on the developing infant and provide some predictions regarding the long-term outcomes and lifetime needs of these children and their families.

RTI International, Research Triangle Park, North Carolina

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Address correspondence to Anne Wheeler, PhD, RTI International, 3040 E. Cornwallis Rd, PO Box 12194, Research Triangle Park, NC 27709. E-mail: acwheeler@rti.org

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Congenital Zika syndrome (CZS) encompasses the spectrum of symptoms observed in infants who have been exposed to the Zika virus (ZIKV) in utero.¹ ZIKV is a *Flavivirus* that is most often transmitted via mosquitos, but it can be transmitted sexually also. It has emerged in recent years as a significant human pathogen primarily because of the impact it has on the neonate; researchers in previous reports considered ZIKV to be relatively harmless with few to no symptoms reported by those who were infected. However, prenatal exposure to ZIKV is now known to increase the risk for severe microcephaly in infants. It is also now clear that CZS has variable presentation, severity, and prognosis depending in part on head circumference (HC) at birth, and it is compounded by additional central nervous system (CNS) damage.² Although the most severe phenotype appears to be associated with exposure during the first trimester,^{3,4} reports of confirmed CZS after exposure during all 3 trimesters have been reported, and nearly half of the infants who are exposed to Zika in utero appear to have abnormalities either at birth or have acquired them over the first year of life.^{5,6}

A handful of infants who were born with CZS have died prenatally, at birth, or in their first year of life,^{7–9} and complications associated with respiratory infection, dysphagia, and epilepsy may prove fatal for the most severely affected infants. However, most infants who were exposed to Zika in utero are expected to survive, and their predicted life span is comparable with that of others who have conditions associated with microcephaly, epilepsy, and intellectual disability. Researchers in studies of other *Flaviviruses*, including West Nile virus and the dengue virus, have observed neurologic complications and long-term sequelae in people who are infected with these diseases.^{10–12} The

emerging phenotype of CZS appears to be associated with a fetal brain disruption sequence, including severe microcephaly, overlapping sutures, prominent occipital bone, scalp rugae with normal hair patterning, and significant neurologic impairment.^{13,14} Infants with CZS have also been reported to have neuropathology resembling other common congenital infections, such as toxoplasmosis or cytomegalovirus,¹⁵ which also have overlapping clinical presentations.¹⁶ The literature on these conditions may shed light on treatment options and prognoses for some infants with CZS. However, researchers in a recent review concluded that CZS differs from other congenital infections because of 5 distinct features: (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.¹⁷

Case studies are being reported as new findings emerge, and several recent reviews highlight what is currently known about outcomes in the first year of life.^{2,17–19} A considerable knowledge gap remains about the neurodevelopmental sequelae of children who are affected by CZS; clearly, however, the long-term impacts will be severe for many children and their families.²⁰ Our goal in this article is to describe what is known about the neurodevelopment and behavioral profiles of infants with CZS and make some predictions about what we might expect for these children as they get older. These predictions are informed by the known and suspected impacts of Zika on the developing brain and by findings from the literature on children with similar CNS dysfunctions but without CZS.

IMPACT OF ZIKA ON THE DEVELOPING BRAIN

The most obvious symptom linked to CZS is microcephaly, which is reported in up to 91% of cases.¹⁹ Microcephaly is defined in most cases as an occipitofrontal head circumference (OHC) between the glabella and occipital protuberance of ≥ 2 SDs below the mean for age based on growth charts provided by the Centers for Disease Control and Prevention²¹ or the International Fetal and Newborn Growth Consortium for the 21st Century international standards.²² Severe microcephaly is defined by OHC values of >3 SDs below the mean. Many newborns with CZS have OHCs between 3 and 4 SDs below the mean at birth,²³ although variations in the initial definitions of microcephaly may have skewed early findings.²⁴ In general, microcephaly is associated with reduced brain volumes, a lack of or abnormal development of the neurons, and subsequent reduced numbers of neurons in the gray matter.²⁵ Cerebral palsy, intellectual disabilities, and epilepsy are all strongly associated with microcephaly regardless of etiology^{21,26}; all of these comorbid conditions should be expected and monitored in CZS cases.

Although microcephaly is the most obvious symptom of CZS, emerging reports suggest that microcephaly is just the tip of the iceberg with regard to associated developmental and medical features. Electromyography and brain imaging studies have identified neurologic lesions involving the CNS and peripheral nervous system with downstream effects on the musculoskeletal, auditory, and ophthalmologic systems. Consequently, hip dysplasia, subluxation of large joints, abnormal posturing of extremities, conductive hearing loss, and abnormalities of the retina and optic nerve have all been observed.²⁷ Exaggerated primitive reflexes, abnormal posturing,

pneumonia and other respiratory problems, dysphagia, reflux and other gastrointestinal problems, epilepsy, and hydrocephalus are features that are being reported by clinicians in Brazil who work closely with infants with CZS.^{23,27,28}

Importantly, not all infants who are exposed to Zika in utero have obvious abnormalities at birth. Many of these infants have less obvious impairments that become evident only over time. Researchers in recent studies have found that ZIKV replication in the infant brains continues after birth,²⁹ and the brain growth of prenatally exposed infants continues to decelerate after birth.²⁸ A recent description of 13 infants with prenatal Zika infection without microcephaly at birth showed that all the infants had brain abnormalities that were consistent with CZS.²⁸ Surprisingly, head growth decelerated after birth, and by 5 months of age, 11 infants had microcephaly. Ocular and neurologic findings were found in the absence of microcephaly in a 6-day-old infant.³⁰

Our understanding of the impact of Zika on the brain is still rudimentary; clearly, however, the compounding effects of microcephaly with the additional CNS dysfunctions described in CZS are likely to result in widely variable but largely severe long-term outcomes. In the following sections, I outline suspected longitudinal neurodevelopmental and behavioral outcomes of CZS.

LIKELY IMPACT ON COGNITIVE DEVELOPMENT

Cognitive outcomes will be associated with HC at birth (the smaller the HC, the worse the outcome), with impairments ranging from mild developmental delays to severe motor and intellectual deficits. The risk for intellectual disability in non-CZS-associated microcephaly is ~10.5% when HC is between -2 and 3 SDs, 51.2% when HC is between -3 and 4

SDs, and 100% for HC smaller than -4 SDs.^{31,32} Approximately two-thirds of infants with CZS are reported to have severe microcephaly (an HC of ≥ 3 SDs below expectations)^{23,33,34}; nearly all of these infants are expected to have some level of intellectual disability, most likely in the severe-to-profound range.

The level of impairment is likely to be even more severe given the additional sensory-motor complications being reported. Visual and hearing impairments will further reduce the ability of the children to engage with and learn from their environments and will lead to additional impairments in functional skill obtainment. Although the impact of CZS on cognitive development will certainly vary depending on the severity of microcephaly and other CNS impacts, many of the most severely affected children are not expected to obtain developmental skills beyond the infant-toddler age range. Indeed, crude reports of developmental progress in infants with CZS in Brazil suggest that at their first birthday, many are functioning at the ~2- to 3-month age level.³⁵

Our expectations are not clear regarding the long-term cognitive impacts for those with later exposure and who acquired microcephaly over the first year of life. Based on literature on other conditions with later-onset microcephaly, these infants should be expected to have some level of cognitive impairment, although it is likely to be less severe than in those with microcephaly at birth. Children with later exposure may have delays in attaining cognitive milestones and will likely require ongoing developmental, educational, and social-emotional support.

LIKELY IMPACT ON COMMUNICATION SKILLS

The ability to understand and produce language is strongly associated with cognitive

functioning; therefore, the severity of language impairment is expected to be consistent with the level of intellectual impairment. Reports of comorbid hearing impairments³⁶ suggest that communication may be especially difficult for children with CZS.

Motor and cognitive impairments usually result in more difficulty in the production of speech than in the ability to understand language³⁷; therefore, some children with CZS may be able to understand verbal communication but be unable to express themselves in words. Although many children with CZS may never produce meaningful speech, some may be able to communicate through vocalizations or nonverbal gestures. Alternative and augmentative communication techniques, including the use of assisted communication devices, may be useful for children with CZS to communicate their basic needs and wants.

LIKELY IMPACT ON MOTOR DEVELOPMENT

Motor development for children with CZS is complicated not only by the level of cognitive impairment but also by congenital contractures, hypotonia, and extrapyramidal involvement. The combination of these impairments is likely to result in extreme delays in reaching motor development milestones. Early reports of motor development suggest that many infants with CZS are not able to roll over, sit, or, in some cases, even hold their heads up independently. A significant percentage of children with CZS will likely never become ambulatory; those who do learn to walk may have challenges with gait, agility, and/or endurance. Seizures and tremors, if uncontrolled, can erode obtained motor skills over time.

Motor impairments can also lead to other severe consequences.

Dyspraxia, or motor planning impairments, is likely; in addition to causing delayed motor development, dyspraxia can also have implications for feeding (eg, chewing and swallowing). Dysphagia has resulted in a failure to thrive in several infants with CZS, and many others have needed feeding tubes.²³

LIKELY IMPACT ON BEHAVIOR

Long-term social, emotional, and behavioral challenges are probable in children with CZS. Facial distortions, hyperactivity, and severe irritability, including almost constant crying and an inability to be soothed, have been reported in infants with CZS.²³ Pain, difficulties with regulating sensory input, frustrations with communication, and ambulatory challenges are all highly likely to contribute to irritability. Parental reports, as well as EEG findings, suggest that sleep patterns are abnormal in infants with CZS,³⁸ and this is likely driven by (and contributes to) the irritability. If these sleep difficulties continue into childhood, they will likely contribute to behavioral challenges in areas such as attention regulation and agitation.

Self-injurious behaviors (eg, head banging and eye poking) as a result of sensory seeking are common among children with visual and/or auditory impairments and intellectual disability,³⁹ so these behaviors should be expected and monitored in children with CZS. Children with milder phenotypes may be more likely to have behavioral issues if patterns in CZS mirror other conditions with a spectrum of outcomes. Individuals with milder microcephaly may have typical or low-average cognitive abilities; however, they may also have more behavioral issues than those without CZS because of other CNS challenges, including difficulty regulating sensory input.

Other conditions acquired through prenatal exposure to infections, such as rubella, have been associated with later schizophrenia and autism spectrum disorder.^{40–43} Higher-than-expected rates of comorbid autism spectrum disorder have also been described among children with visual and auditory impairments^{44,45} as well as those with both syndromic and nonsyndromic intellectual disability.^{46,47} Therefore, infants with CZS are at increased risk for these later psychiatric disorders, although the severity of the intellectual disability is likely to make a diagnosis of these conditions difficult. Thus far, anecdotal reports suggest that infants with CZS do appear to show some interest in and engagement with others and a preference for caregivers, suggesting that sociability could be a strength in these infants. However, only time and careful monitoring of these symptoms will provide a better estimate of risk for these additional comorbid conditions.

LIKELY IMPACT ON FUNCTIONAL SKILL DEVELOPMENT

Because infants with CZS have multiple vulnerabilities, they are likely to be extremely limited in their development of functional skills. Activities of daily living will be compromised, and most children with CZS will require lifelong care. Many will not obtain even the most basic self-help skills; however, many activities of daily living, such as self-feeding, dressing, and toileting, may be obtainable by some with early intervention and ongoing support. Given what we know of other neurologic impairments, individual and environmental variables (such as maternal education, formal and informal support systems, access to quality early-intervention services, and maternal and child nutrition) will have a mediating or moderating effect on infant outcomes. Parents' use of strategies to provide motor,

literacy, language, and other sensory stimulation and integrate them into family routines will be critical for maximizing outcomes. Therefore, it will be imperative to consider family adaptation and the potential toll that stress related to raising a child with severe, lifelong disabilities may have on parent and family well-being (see Bailey et al in this issue).

DISCUSSION AND IMPLICATIONS FOR PEDIATRICIANS

The outbreak of ZIKV and its link to microcephaly and other abnormalities in infants who are exposed in utero pose a major public health concern.^{48,49} As of this writing, >40 000 cases of confirmed Zika infection have been reported among individuals in the United States and its territories.⁵⁰ Of these cases, ~5000 are in pregnant women, and of those who have given birth, approximately one-quarter of them have had negative outcomes (birth defects or pregnancy loss). We do not fully understand how preventive measures might change Zika's effects on children in the United States, but close surveillance of potentially affected infants and their families will be needed.

To date, we do not know if children who are exposed to Zika postnatally, either through direct exposure (a mosquito bite) or indirect exposure (through fluid via a contaminated family member [eg, breast milk]), will experience long-term negative outcomes. Adult infections have been linked to other neurologic illnesses, such as Guillain-Barré syndrome. Case reports of infants who were infected during the peripartum period during the outbreak in French Polynesia suggest that there is less of a concern for these infants.⁵¹ They may have risks similar to the symptoms of Zika infection in adults (eg, rash and fever) as opposed to the more severe effects in those who are exposed during critical prenatal brain

development. However, given the lack of long-term studies to confirm this hypothesis, precautions to protect newborns and young children from Zika exposure should continue to be a priority.

Rapid discoveries in the mechanisms of disease and potential vaccines and early treatments are being developed through animal models,⁵² which will hopefully prevent or alleviate the comorbidities of CZS. However, for those children and families who are now living with CZS, the provision of the most up-to-date information and proper support, monitoring, and treatment are critical. A coordinated, interdisciplinary approach to care will be necessary to treat the multiple needs of these children. Guidelines and overviews for providers published by the Centers for Disease Control and Prevention,⁵³ the National Institutes of Health,¹⁸ and the World Health Organization⁵⁴ outline steps for identifying and assessing pregnant women and newborns who are suspected to have been exposed to Zika. Various professionals, including early-intervention providers and pediatricians, are opening new discussions about factors for long-term surveillance and treatment and are most likely to be on the frontlines of care for these infants and their families.^{55,56} It will be essential for these professionals to stay abreast of the evolving knowledge of CZS to provide the most effective treatment to all those who are affected by ZIKV.

ABBREVIATIONS

CNS: central nervous system
CZS: congenital Zika syndrome
HC: head circumference
OHC: occipitofrontal head circumference
ZIKV: Zika virus

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