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Pathogenesis of Non-Zika Congenital Viral Infections

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A widespread epidemic of Zika virus (ZIKV) infection was reported in 2015 from South and Central America and the Caribbean. Although the full spectrum of ZIKV infection of the newborn has yet to be determined, other maternal viral infections resulting in transmission to the fetus provide instructive lessons that can be applied to the prospective evaluation of individuals with ZIKV infection. This review focuses on those other congenital infections, including rubella, congenital cytomegalovirus, human immunodeficiency virus, hepatitis B virus, and neonatal herpes simplex virus, from which lessons for the evaluation of ZIKV in the newborn can be applied.

Keywords. Zika; congenital infections; rubella; hepatitis B; neonatal herpes simplex infection.

A widespread epidemic of Zika virus (ZIKV) infection was reported in 2015 from South and Central America and the Caribbean [1–3]. By December 2015, the Brazil Ministry of Health estimated >1 000 000 cases of ZIKV infection in adults [4, 5]. In September of the same year, clinicians began to identify an increased number of babies born with microcephaly in the same area in which ZIKV infection was detected [6–8]. This observation resulted in generalized concern for maternofetal transmission by ministries of health worldwide, including the World Health Organization, the Centers for Disease Control and Prevention, and the Brazil Ministry of Health. The possibility and, indeed, introduction of Zika-infected *Aedes aegypti* and *Aedes albopictus* to North America has heightened scientific investment by the US Department of Health and Human Services.

While the full spectrum of ZIKV infection of the newborn has yet to be determined, other maternal viral infections resulting in transmission to the fetus provide instructive lessons that can be applied to the prospective evaluation of individuals with ZIKV infection. These include rubella, congenital cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), and neonatal herpes simplex virus (HSV) infections. Congenital rubella syndrome has virtually been eliminated from the developed world, following universal vaccination programs of young children. However, the remaining perinatal infections still are significant causes of morbidity and, in some cases, mortality. Likely, the most analogous infection is congenital CMV infection, which can produce profound effects on the fetus, including microcephaly, sensorineural hearing loss, chorioretinitis, and other neurologic defects. This review will focus on those other congenital infections from which lessons for the evaluation of ZIKV in the newborn can be applied. Parallels and differences will be noted.

RUBELLA

Primary rubella infection during pregnancy, particularly during the first trimester, represents a major risk for congenital infection via placental transmission [9]. The timing of maternal infection correlates with fetal outcome, with up to 85% of fetuses affected if primary infection occurs in the first 12 weeks of gestation [10]. Beyond the first trimester, the risk of transmission diminishes considerably, although congenital infection is still possible. Reinfection can occur in persons with a past history of natural rubella infection or in those who have been immunized; fetal transmission after maternal reinfection is rare [11].

Congenital rubella infection may result in fetal death or premature labor. Affected infants often have multiple serious birth defects (ie, congenital rubella syndrome [CRS]), including sensorineural hearing loss (SNHL), cataracts, cardiovascular defects, microcephaly, neurodevelopmental impairment, intrauterine growth restriction, and thrombocytopenia. The classic CRS triad consists of cardiac, ophthalmic, and auditory sequelae. When transmission of infection occurs beyond the first trimester, adverse effects are less common, with SNHL being the most common sequela.

Prior to the implementation of effective vaccination programs, it is estimated that >100 000 infants were born with CRS globally each year, mostly in developing countries [12]. Control of endemic rubella infection and CRS can occur through the use of live attenuated vaccines in all children during the second year of life to eradicate rubella from the community, therefore preventing infection in pregnant women. Whenever possible, women of childbearing age who are not immune to rubella should also be identified and immunized. In countries reporting to the World Health Organization (WHO), the introduction of rubella-containing childhood immunization schedules has led

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to a 95% decrease in rubella infections, from 670 894 reported cases in 2000 to 33 068 reported cases in 2014 [13]. Notably, the 2014 WHO surveillance data had a great number of countries reporting rubella compared to the 2000 data (162 vs 102 countries reporting, respectively). One hundred forty-one cases of CRS were reported to the WHO in 2014, although CRS cases are likely often underreported [13]. Elimination of CRS has proven to be an achievable goal in countries with appropriate vaccine uptake [14]. Importantly, universal vaccination to prevent rubella is a model by which fetal transmission of ZIKV can be prevented. Such vaccines are discussed elsewhere in this monograph.

CONGENITAL CYTOMEGALOVIRUS INFECTION

Cytomegalovirus infections are ubiquitous in humans and are an important cause of congenital infection and a leading cause of SNHL worldwide [15–17]. It is estimated that, in the United States, between 20 000 and 30 000 newborns each year are infected with CMV. The number of infants with congenital CMV infection is actually much higher in developing countries because of the direct correlation with maternal CMV [15, 17, 18]. Unlike rubella, toxoplasmosis, and, apparently, Zika where intrauterine transmission occurs as a result of maternal infection acquired during pregnancy (primary infection), congenital CMV infection can occur in infants born to mothers who have had CMV infection prior to pregnancy (nonprimary infection) [19–25]. In fact, congenital CMV infection following a nonprimary maternal infection accounts for two-thirds to three-quarters of all congenital CMV infections in highly seroimmune populations [22–29]. Young maternal age and non-Hispanic black race have been associated with increased risk of congenital CMV infection [17, 30–35]. The argument that maternal immunity to CMV limits intrauterine transmission is supported by the finding that the rate of intrauterine infection in women with preexisting CMV immunity (nonprimary maternal infection) is about 1%–1.5%, which is about 20- to 30-fold less than in women with primary CMV infection during pregnancy [15, 20, 26, 36, 37]. However, the number of women undergoing primary CMV infections during pregnancy is considerably smaller than the number with nonprimary infections, especially in highly seropositive populations. In populations with near-universal seroimmunity, it is likely that most infants with congenital CMV infection are born to women with nonprimary infection [26, 28, 38, 39]. From existing reports, fetal Zika infection occurs after primary maternal infection.

Congenital CMV infection is a leading cause of childhood permanent hearing loss and neurodevelopmental disabilities [15, 16, 40]. Congenital CMV-associated SNHL accounts for about 25% of all SNHL in children [41]. The number of children with congenital CMV-related disabilities is similar to or exceeds the number of children with better-known conditions such as Down syndrome or spina bifida [42]. The majority of the 20 000–30 000 children born with congenital CMV infection each year in the United States (approximately 85%–90%) do not exhibit any clinical abnormalities at birth (asymptomatic congenital CMV infection) [21, 23, 43–45]. The remaining 10%–15% born with clinical abnormalities are categorized as having clinically apparent or symptomatic congenital infection. The infection may involve multiple organ systems with particular predilection for the reticuloendothelial system and central nervous system (CNS) [43]. The most commonly observed clinical findings are petechial rash, jaundice, hepatomegaly, splenomegaly, and microcephaly. Ophthalmologic examination is abnormal in approximately 10% of infants with symptomatic congenital CMV infection, with chorioretinitis and/or optic atrophy most commonly observed.

Laboratory abnormalities in children with symptomatic infection reflect the involvement of the hepatobiliary and reticuloendothelial systems and include conjugated hyperbilirubinemia, thrombocytopenia, and elevations of hepatic aminotransferases in more than half of symptomatic newborns [46–48]. Neuroimaging is abnormal in approximately 50%–70% of children with symptomatic infection at birth and intracerebral calcification is the most common abnormality [49, 50]. Although a number of nonspecific neuroimaging findings have been reported including ventricular dilatation, cysts, and lenticulostriate vasculopathy in infants with congenital CMV, the significance of these findings is not clear.

Approximately half of the infants with symptomatic infection will develop sequelae including SNHL, cognitive, and motor deficits [23, 44, 46–48, 51–55]. Predictors of adverse neurological outcome in children with symptomatic congenital CMV infection include microcephaly, the presence of other neurologic abnormalities at birth or in early infancy, neuroimaging abnormalities detected within the first month of life, and the presence of multiple clinical findings [44, 47, 49, 55–60]. Approximately 7%–15% of asymptomatic children will develop SNHL. Approximately one-half of children with asymptomatic infection who develop hearing loss will have bilateral deficits, which can vary from mild high frequency loss to profound impairment [23, 54, 61–64]. In addition, hearing loss in these children is often progressive and/or late onset, requiring ongoing monitoring [54, 61, 63, 64]. Other neurological complications may also occur in asymptomatic congenital CMV infection, and, although the data are sparse, are thought to occur at a much lower frequency than in symptomatic infection [64].

Decades of natural history studies of CMV infections during pregnancy have provided a solid framework for current and future studies of ZIKV infection during pregnancy. The utilization of a template derived from descriptions of CMV during pregnancy for studies of perinatal ZIKV infections is justified by the similarities of proposed mechanisms of CNS damage during both CMV and Zika infections that occur early in CNS development. These include virus-induced destruction of neural progenitor cells, alterations in the proliferative capacity of neural progenitor cells, and damage to the supporting vasculature.

The catastrophic outcome of these infections very early in CNS development is evident in both postmortem and imaging studies of infants with congenital CMV and ZIKV infections and commonly include significant structural damage to the brain and spinal cord [64] (Table 1). In contrast, intrauterine infections later in pregnancy result in less dramatic evidence of CNS damage but nonetheless can be associated with a variety of disorders of neuronal cell positioning and cellular connectivity that often lead to a number of neurological abnormalities, including dysfunction of perceptual pathways such as hearing [64]. However, several lines of evidence provided by studies in experimental animals that model CMV and ZIKV infections in human fetuses argue that a host derived inflammatory component could contribute to disease in infections that are acquired later in gestation [64]. Thus, the commonalities in the pathogenesis of CNS damage resulting from either CMV or ZIKV infection of the fetus argue that a similar spectrum of neurological deficits can be expected following either infection and, in both cases, can be directly related to developmental status of the fetal CNS at the time of infection. How these findings will ultimately mirror ZIKV infection of infants can only be determined by similar large prospective studies.

These lessons from studies of congenital CMV infections should be considered in designing natural history studies of infants born to women infected with Zika during pregnancy. Thus far, it is likely that only a small fraction of the total number of congenitally ZIKV-infected infants have presented with the stigmata of congenital ZIKV infection and that the vast majority of infected infants will only be identified by laboratory testing in the newborn period. Although congenitally Zika-infected infants with subclinical presentations will almost assuredly have more favorable long-term outcomes than infants with obvious CNS structural abnormalities, it is also very likely that many of these infants will be at risk for neurodevelopmental sequelae that mirror those described in infants with congenital CMV infections. Importantly, early identification of infants with neurodevelopmental abnormalities coupled with appropriate interventions offers the possibility of improved long-term outcomes.

Table 1. Imaging Findings in Congenital Cytomegalovirus and Congenital Zika Virus Infections

Congenital CMV Infection	Congenital Zika Syndrome
Calcifications, ventricular dilation, cortical atrophy, white matter changes (CT) [49]	Calcifications, ventricular dilation, white matter changes, cerebellar hypoplasia, hypogyria, basal ganglia changes (CT) [69]
Calcifications, cerebellar hypoplasia, white matter changes (MRI) [65]	Calcifications, cortical atrophy, ventricular dilation, cerebellar atrophy (US, CT) [70]
Calcifications, hypogyria, lissencephaly [66]	Calcifications, cortical loss, ventricular dilation, cerebellar atrophy, white matter changes, basal ganglia abnormalities (CT, MRI) [71]
Cerebellar hypoplasia, hypogyria, lissencephaly, white matter changes (MRI) [67]	
Ventricular dilation, oligo/pachygyria (MRI) [68]	

Abbreviations: CMV, cytomegalovirus; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

HUMAN IMMUNODEFICIENCY VIRUS

Human immunodeficiency virus, a member of the family of retroviruses, is estimated to have been responsible for the death of approximately 5 million children since 1981 when it was first recognized as the cause of AIDS [72]. The HIV pandemic has affected every continent, but some areas have been disproportionately affected. Of the estimated 33 million individuals currently infected with the virus, two-thirds live in sub-Saharan Africa.

In young children, infections occur predominately by transmission from infected mothers to their infants. Transmission can occur in utero, intrapartum, or postpartum through breastfeeding. The Centers for Disease Control and Prevention (CDC) estimates that approximately 8500 women with HIV give birth to infants in the United States annually [73]. Globally, the number of seropositive women delivering infants annually is not known, but with prevalence rates ranging from 15% to 40% among countries in southern Africa, an area most affected by the epidemic, the number of pregnant seropositive women delivering each year is substantial [74]. A major risk factor for transmission is maternal viral load [75].

During the past 2 decades, there has been substantial progress in prevention of perinatal HIV type 1 (HIV-1) infection in children because of identification and treatment of HIV-infected pregnant women during pregnancy and delivery and subsequent prophylaxis of their infants with antiretroviral therapy (ART).

Countries with ready access to antiretroviral drugs (ARVs) have seen the most significant decline in infections. With improved access to ARVs in priority countries in Africa, the number of new infections in infants from 2009 to 2012 decreased by almost 40% [76].

Both the life cycle of HIV and the pathogenesis of HIV infection are complex. HIV infects a number of cell types but its primary target is the activated $CD4^+$ T lymphocyte, a cell that is central in the immune response. Soon after infection, there is a rapid increase in viral replication and dissemination of virus to the lymph nodes, gastrointestinal tract, and other lymphoid organs [77, 78]. In older individuals with a primary infection, the number of viral copies can reach 10^6 per mL of plasma [77] but there is a decrease in viral copy number to a new set point within weeks after activation of the immune response. In infants, the viral load increases to a similar level but, untreated, can remain at this level for years [78]. Over time, with sustained viral replication, and infection and destruction of $CD4^+$ lymphocytes, there is a progressive loss of the memory and naive $CD4^+$ T-lymphocyte population. The resulting immunodeficiency is associated with the myriad of disease manifestations,

both infectious and noninfectious. Because the virus establishes a latent infection in $CD4^+$ lymphocytes, the infection remains life-long even with therapy.

Most infants with intrauterine or perinatally acquired infection are asymptomatic at birth [79, 80]. Compared to older individuals, disease onset in untreated infants occurs much sooner and can progress rapidly in many children [80]. Failure to thrive, hepatosplenomegaly, lymphadenopathy, developmental delay, and oral thrush are common manifestations within the first few months of life. Progressive encephalopathy characterized by loss of developmental milestones, spasticity, and acquired microcephaly also occurs in some children [79, 80]. Basal ganglia calcifications and cerebral atrophy are characteristic findings on computed tomography. *Pneumocystis jirovecii* pneumonia is the most common opportunistic infection in young children and can occur before 1 year of age [81, 82].

The availability of ARVs has changed the prognosis for individuals with HIV infection. Prior to ART, an estimated 20% of children with HIV died by 2 years of age [83]. For children and adults, HIV infection is now considered a chronic infection that can be managed with ARVs. Therapy with ARVs suppresses viral replication and improves and maintains immune function if started early. With adherence to their medication, most children can remain asymptomatic.

HIV infection in infants is similar to congenital ZIKV infection in the timing and mechanisms of mother-to-child transmission. Like HIV, ZIKV-infected infants may be asymptomatic at birth but then develop disease within the first few months of life. The primary clinical manifestation they share is neurologic disease, particularly microcephaly, a finding that does not occur in HIV-treated infants who receive therapy early.

HEPATITIS B VIRUS

Hepatitis B virus is estimated to infect >350 million people worldwide with the main public health burden due to the effects of chronic liver disease and hepatocellular carcinoma [84].

It is a hepatotropic virus that replicates in hepatocytes and is released into the bloodstream. The virus is present in all body fluids including blood, saliva, breast milk, and semen and is transmitted by percutaneous and permucosal contact and perinatal transmission [85]. It can survive on surfaces outside the body for at least 7 days, remaining infectious [86]. There are extrahepatic diseases related to HBV and it is estimated to be associated with 20% of membranous nephropathy cases in children [87].

Babies with perinatal infection with HBV are asymptomatic initially; however, approximately 90% will progress to chronic infection. Of those chronically infected, roughly 10%–30% will develop chronic hepatitis, of whom 20%–50% will progress to cirrhosis and 10% will subsequently develop hepatocellular carcinoma. In contrast, only 20%–50% in children 1–5 years of age and 5% in adults progress from acute to chronic infection with attendant complications [88].

Key proteins involved in the pathogenesis are the nucleocapsid core protein/ hepatitis B core antigen (HBcAg), which is retained in infected hepatocyte; the precore protein/hepatitis B e antigen (HBeAg), which is secreted into blood and essential for establishment of persistent infection; and the envelope glycoprotein/hepatitis B surface antigen (HBsAg), which is secreted into blood and is highly immunogenic [89].

Humoral antibody contributes to clearance of circulating viral particles and prevention of viral spread within the body. T-cell–mediated immune responses are required for elimination of infected hepatocytes and viral clearance. Persistent HBV infection results from an inefficient CD4 T-cell priming early in infection with the subsequent development of an ineffective CD8 T-cell response [89].

Neonatal tolerance to HBV is thought to be responsible for persistent infection. This tolerance is thought to be induced by the HBeAg that crosses the placenta as demonstrated in a transgenic mouse model. HBeAg has been shown to suppress the antibody and T-cell response to HBcAg [89].

Infants at greatest risk of infection are born to younger women who are HBeAg positive, have a high viral load, or receive <3 hepatitis B vaccine doses at the recommended times [90].

Unlike ZIKV, there is a highly effective vaccine that can prevent the transmission of HBV [91], a likely goal for a ZIKV vaccine. For pregnant women who are identified as HBsAg positive, their babies should receive a dose of HBV-specific immunoglobulin in addition to the vaccine, which helps prevent perinatal transmission up to 90% [92]; there is also an opportunity for immunoprophylaxis with high-titered Zika antibody products. Furthermore, antiviral therapy in high-risk mothers reduces but does not prevent transmission [93].

Antiviral medications are licensed for treatment of both children and adults who develop chronic HBV infection to help prevent the progression to cirrhosis and decrease the risk of developing hepatocellular carcinoma.

NEONATAL HERPES SIMPLEX VIRUS INFECTION

Approximately 85% of all cases of neonatal HSV infection are acquired by intrapartum contact of the fetus with infected maternal genital secretions. An additional 10% are acquired postnatally as a consequence of direct contact with an infected individual and 5% result from in utero transmission, resulting in congenital disease that is manifest at the time of birth. The overall incidence of neonatal HSV infection is estimated to range from 1 in 3000 to 1 in 20 000 live births. The risk of transmission to the fetus is greatest for women who experience a primary infection during the third trimester of gestation, resulting in an estimated 25%–60% incidence of transmission to newborns. Importantly, just as is the case with ZIKV infection, maternal primary infection is usually asymptomatic [94–96].

Children with congenital HSV infection, albeit rare, most closely resemble babies with congenital Zika infection. These

babies can present with combinations of microcephaly, retinitis, microphthalmia, skin scarring, and limb abnormalities. Babies with congenital HSV infection have a uniformly poor outcome with mortality in the first month of life in excess of 60% [97].

With the exception of congenital HSV infection, children who acquire neonatal herpes present between day 7 and day 21 of life, depending upon clinical manifestations. Children with disease caused by HSV infection present in 1 of 3 fashions. Disease can be localized to the skin, eye, and mouth, occurring in approximately 45% of newborns. These babies present at day 7–11 of life on average. Children with encephalitis, accounting for approximately 35% of newborns, present on average at 2 weeks of life. These children may or may not also have skin, eye, or mouth involvement. Finally, children with multiorgan disseminated disease account for 25% of cases, presenting at approximately 7–11 days of life [97, 98].

Prognosis with therapy varies according to disease classification. For those children with multiorgan disseminated disease, the mortality is approximately 35%. Approximately, 3 of 4 of these children will have CNS disease as well, with attendant complications. Those children with encephalitis, but without multiorgan involvement, have a lower mortality of 3%–5%, but the risk for significant neurologic impairment is high. These children can have impaired intellectual potential, seizure disorders, spasticity, and not infrequently, microcephaly. Notably, children with CNS disease caused by HSV-2 have a poorer outcome than those babies with HSV-1 infection, for unknown reasons. Last, children with disease localized to the skin, eye, and mouth have the best prognosis. In the absence of asymptomatic CNS involvement, these children virtually all develop normally but will have recurrent lesions [99, 100].

Contrasts to ZIKV infection are indicated. First, an antiviral drug exists for the treatment of neonatal HSV infection, namely acyclovir, whereas none is currently available for Zika. Second, suppressive acyclovir therapy, when administered for 6 months following newborn infection, results in an improved neurologic outcome, implying that HSV can replicate subclinically in CNS. Such remains unknown for Zika. Thus, long-term studies are mandatory. Third, the question of asymptomatic neonatal HSV infection has been debated; contact of newborns with infected maternal genital secretions may lead to late-onset abnormalities that have yet to be identified [99–102].

DISCUSSION

These 5 congenital viral infections provide important lessons for ongoing and future studies of ZIKV infection in both the newborn and developing infant. First, it is well established that women are infected by HSV that is transmitted from an asymptomatic male sexual partner, resulting in newborn disease. The contribution of male-to-female Zika transmission resulting in congenital infection remains to be defined but clearly is highly probable. Second, only through prospective cohort studies has it been possible to define the spectrum of sequelae in babies with congenital CMV, rubella, HIV, and HSV infections and, importantly, those abnormalities that appear later in life. Such will be the same for the apparently asymptomatically infected newborn whose mother had Zika infection, as was recently suggested by CDC investigators based on a nonhuman primate study [103]. Third, chronic subclinical replication of the lytic virus HSV can lead to significant neurologic impairment to a greater extent than CMV infection. With HSV, however, long-term therapy can improve outcome. Currently, no antiviral drugs exist for either the prevention or treatment of ZIKV infections in either mother or infant. Fourth, this review cannot fully address the need for antiviral therapy but with the introduction of safe drugs, the natural history of Zika will need to be redefined as it has been for CMV, HIV, and HSV infections. Finally, only rubella has been amenable to prevention by vaccination. Hopefully the same will be true for ZIKV in endemic areas.

Notes

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