# Congenital Zika Syndrome

Subjects: Allergy
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Zika virus (ZIKV) is a single-stranded ribonucleic acid (RNA) flavivirus transmitted by arthropod vectors, in particular, Aedes aegypti (or yellow fever mosquito, also responsible for the transmission of Dengue and Chikungunya) and Aedes albopictus (or Asian tiger mosquito, also responsible for the transmission of Chikungunya and West Nile virus). The virus replicates in the insect's epithelial cells and, eventually, in the salivary glands.

Keywords: Zika virus ; pregnancy ; microcephaly ; prenatal diagnosis ; neuroimaging ; long-term outcomes ; single nucleotide polymorphisms (SNPs)

## 1. Introduction

ZIKV is a single-stranded ribonucleic acid (RNA) flavivirus transmitted by arthropod vectors, in particular, Aedes aegypti (or yellow fever mosquito, also responsible for the transmission of Dengue and Chikungunya) and Aedes albopictus (or Asian tiger mosquito, also responsible for the transmission of Chikungunya and West Nile virus). The virus replicates in the insect's epithelial cells and, eventually, in the salivary glands. ZIKV infection used to be considered a tropical disease, but global interest has increased since 2015 due to an epidemic of neonatal microcephaly in Brazil. The virus has been found capable of crossing the placenta in all gestational periods, but mainly in the first trimester. The infection has also been shown to be transmissible sexually and through transfusions [1]. Another important aspect is that the vector Aedes aegypti varies seasonally in the United States [2]. No treatment or vaccine as yet exists for ZIKV. Symptomatic infection is characterized by low-grade fever, maculopapular rash, arthralgia, and conjunctivitis (some cases of Guillain-Barré syndrome have also been reported in adults); although the symptoms may last for about 5–7 days, 80% of cases are asymptomatic, which greatly complicates the diagnosis in pregnancy. Congenital ZIKV infection may accurately be viewed as a newcomer of the TORCH complex, an acronym that stands for toxoplasmosis, others (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), herpesvirus (HSV), given the characteristics it shares with such well-known pregnancy diseases with mild symptoms in the mother, vertical transmission, severe anomalies in the new-born and maternal therapy, which often fails to improve the prognosis [3]. Although it is a relatively new disease, many national and international associations have already drawn up guidelines for ZIKV infection in pregnancy [4], stressing the need for wide-ranging interventions via family-based support programmes aimed at addressing the special needs of children with CZS neurodevelopmental disability in low- and middle-income countries [5][6], as well as the socioeconomic struggles and psychological impact burdening their families [7][8]. All such issues have been further worsened by the COVID-19 pandemic. As the SARS-CoV-2 curve of infections grew at the height of the pandemic, so did the strain caused by ZIKV on public health facilities in countries where CZS already posed a threat long before the current pandemic [9][10]. The two diseases do bear similarities in terms of clinical manifestations, particularly in the early stages; such an ambiguity can cause delays in diagnosis and treatment interventions, thus, fostering the spread of infection and raising the risk of adverse clinical outcomes. Delays in diagnosis and treatment due to symptoms similar to COVID-19 and other infectious diseases such as Dengue and typhoid fever have also been reported. In India and Pakistan [11][12], the similarity between COVID-19 symptoms and other diseases has reportedly caused misdiagnosis and possible underreporting.

## 2. Pathogenesis

ZIKV has a unique ability among flaviviruses to cross the placental barrier (for example, Dengue virus does not have the same capacity) [13]. Hypothesized transmission routes are: direct infection of the syncytiotrophoblast layer, passage through ruptures in the syncytiotrophoblast layer, crossing of the syncytiotrophoblast layer through non-replicative routes (for example antibody-mediated transcytosis), infection of extravillous trophoblast or other more permissive placental cells (for example, cell of the maternal microvasculature and/or decidua), transmission to the fetus and/or villous core through maternal cells (most probably of immune origin), ascending vaginal infection [14]. The placental damage caused by the virus is related to local inflammation and/or metabolic alterations with mitochondrial dysfunction and loss of function of membrane lipids; the latter seem to rearrange themselves and to support viral replication [15]. ZIKV can reportedly

upregulate the innate immune response of the decidua (an aspect in common with CMV), while some findings also show that the mechanism of damage of the maternal-fetal interface is not inflammation-mediated, but only related to the upregulation of apoptosis in placental cells [16]. Once the ZIKV has reached the fetal bloodstream, given its marked neurotropism, the damage is mainly neuronal. The pathogenetic mechanism has been hypothesized to be inflammatory initially for toxoplasma, CMV and rubella, the three most studied etiological agents that cause microcephaly by congenital infection [17]. Studies have also shown how the marked neurotropism of the virus may depend on a specific receptor on neural progenitor cells. In murine animal models, ZIKV infection has, at times, exhibited interference with cell cycle progression; neuronal cells may, therefore, become unable to migrate in the genesis of the telencephalon; for this reason, neurospheres and brain organoids cannot develop [18]. Reportedly, 1 to 42% of embryos or fetuses that are exposed to ZIKV infection in utero develop congenital Zika syndrome (CZS) [19]. Still, it is worth noting that the discovery of the viral teratogenic potential associated with ZIKV is relatively recent; hence, the degree of susceptibility and the mechanisms involved in the adverse effects on embryos and developing fetuses exposed to it are still not fully understood [20]. It is, therefore, essential to evaluate how susceptibility to ZIKV teratogenesis can be affected by environmental and genetic factors (e.g., the inflammatory process of response to ZIKV as risk or protective factors for CZS and the involvement of genetic variants in such dynamics).

## 3. Genetic Risk Factors

Technological advances are increasingly contributing to clarifying the key factors that affect and shape the dynamics of emerging infections, including ZIKV. Techniques such as genome-wide association studies [21], high-throughput sequencing [22] and screening based on clustered regularly interspaced short palindromic repeat (CRISPR) [23][24] has made it possible to identify human single nucleotide polymorphisms (SNPs), which may substantially affect the outcome of infectious diseases [25]. Polymorphisms in NOS2 and TNF genes have been reported to play a role in the development of CZS, with a higher risk in the first trimester, and of severe microcephaly. Specifically, genes closely linked to immune and inflammatory response, such as VEGFA, PTGS2, NOS3, TNF, and NOS2, with functional genetic variants, can exhibit different allelic, genotypic, and haplotypic frequencies in children with CZS [26]. A higher prevalence of the rs2297518 allele A in the NOS2 gene has also been observed in children with CZS. Significantly, the iNOS protein activity is somehow influenced by functional polymorphism NOS2 rs2297518. Enhanced protein activity and a higher level of nitric oxide (NO) are also presumably associated with A allele [27][28]. Neurogenesis and neurodevelopment have, in turn, been found to be substantially influenced by NO, whose dysregulation may impact the progression of various neurodevelopmental, neurobehavioral, and neurodegenerative disorders [29]. The rate of progression and development could be influenced by NO dysregulation linked to the individual response to ZIKV infection and by the patient's genotype, even to the point of bringing about a congenital anomaly. Furthermore, CZS pathogenesis may be affected by single nucleotide variants: rs2076469 at the DISP3 gene and other rare variants in the IL12RB2 gene, due to their possible protective value and connection with neuronal proliferation and differentiation. Both phenotypes have been found altered in CZS patients, which may impact early immune-response to ZIKV infection [30][31][32]. Recent findings also reflect how two genes prominently involved in the regulation of bone development and cell–cell adhesion, FGFR3 and ITGB4, are upregulated in the brains of CZS patients [33].

## 4. Reverse Genetics and Recombinant ZIKV

The complex ways in which the pathology of ZIKV infection is affected by genetic traits will be instrumental in laying out therapeutic pathways and enhancing surveillance and prevention capabilities to counter the spread of ZIKV [34]. Reverse genetic strategies, either in vitro or in vivo, may constitute a valuable approach through which research will gain a more thorough understanding as to ZIKV's biology and pathogenesis. The creation of recombinant viruses with specific mutations through the manipulation of the ZIKV genome has enabled researchers to shed a light on the function of viral proteins, the interactions involved between ZIKV and its host, and associated disease [35]. Research strategies harnessing reverse genetics have also proven valuable in the development of new effective prevention and control measures [36][37]. The bioengineering of replicating-competent recombinant ZIKV, which can be used to modify the ZIKV genomic RNA at the DNA level and express reporter genes, has, in fact, shown remarkable potential for the development of anti-viral therapeutic options to treat ZIKV infection [38][39], provided that the instability commonly linked to the construction of full-length cDNA clones can be overcome [40][41]. New research avenues are currently being pursued, relying on novel methods for more efficient and easier infectious clone construction, for instance, through the use of homologous recombination clones during plasmid construction [42].

## 5. Prenatal Diagnosis

The gold standard for prenatal diagnosis of ZIKV infection is the polymerase chain reaction essay (PCR) on amniotic fluid. Virus-specific IgM antibodies may be detected 3 days after the onset of symptoms. The serology findings can determine false positives due to cross-reaction with other flaviviruses (like West Nile virus, Dengue and yellow fever). After birth, the viral genome is detectable in saliva, breast milk, urine, and serum within several days after delivery; these data support the possible perinatal transmission of the infection [1].

Another limitation for prenatal diagnosis of the infection is persistent viremia and viruria in pregnancy, even weeks and months after primary exposure [43]. In the case of microcephaly, defined head circumference <2SDS is detectable by ultrasound starting from the second trimester, whereas ZIKV infection occurs typically in the first trimester. Other ultrasound signs suggestive of infection include ventriculomegaly, brain calcifications and posterior fossa destructive lesions; these findings are not found in other congenital infections [44]. According to some studies, another typical sign is disproportion in fetal growth, such as an unusual femur sparing growth restriction [45].

## 6. Clinical Signs

The distinctive features of the congenital ZIKV syndrome in the new-born are the following: severe microcephaly with partially collapsed skull, redundant scalp skin, early closure of the fontanelles, macular scarring and focal pigmentary retinal mottling, congenital contractures of one or more joints (similar to arthrogryposis, very rare in other congenital infections) and extrapyramidal motor symptoms with marked hypertonia. According to some authors, microcephaly may develop in new-borns with a normal head circumference at birth [1][46]. In severe cases, placental insufficiency caused by infection can lead to fetal growth restriction and, sometimes, even to fetal demise [6][47].

## 7. Neuroimaging

Neuroimaging with computed tomography (CT) or magnetic resonance (MRI) has found calcifications of the cortico-medullary junction with band distribution, more frequently in the basal ganglia and less commonly in the thalamus. Other alterations include cysts, mainly in the occipital area, delayed myelination and ventriculomegaly (**Table 1**). The latter, if severe, may require ventricular-peritoneal shunt surgery. Some of the alterations mentioned above may be present even in children with normal head circumference [1].

**Table 1.** MRI findings in congenital ZIKV infection.

| CT [1] and MRI [2] Findings in Congenital Zika Syndrome |
| --- |
| Punctate calcifications (basal ganglia > thalami) |
| Severe ventriculomegaly |
| Global delayed or hypo-myelination |
| Pachygyria or polymicrogyria (mostly in the frontal lobes) |
| Hypoplasia of the cerebellum and the brainstem. |
| Enlarged cisterna magna |
| Abnormalities of corpus callosum (hypoplasia/hypogenesis) |
| Cysts/Pseudocysts (mainly in the occipital area) |

[1] CT: computed tomography; [2] MRI: magnetic resonance.

In congenital ZIKV infection, the whole development of the brain is compromised, with a reduction in cortical gyrification, cerebellar hypoplasia, and hypo/dysmyelination of the white matter in almost all affected subjects. These pathologic alterations are visible both with CT performed after birth and with fetal MRI [48].

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