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Congenital Zika syndrome: etiology, transmission, clinical features, treatment, and prevention

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ABSTRACT:

Zika virus (ZIKV), belonging to the Flavivirus family, has been documented to primarily circulate within the Latin American and Caribbean countries, with small clusters reported in Asia recently. It is transmitted to humans primarily by arthropods, but can also spread *via* sexual intercourse, blood transfusions, and from an infected mother to a child. This vertical transmission of the virus can give rise to a severe clinical entity, called congenital Zika syndrome, which encompasses mild to severe birth defects. As the number of reported cases of congenital anomalies associated with the Zika virus progressively increased, the emphasis of research into this syndrome became important within the scientific community. Since the declaration of the public health emergency in 2015, several studies have documented the sequelae of antenatal exposure to the Zika virus. While this is similar to other arthropod-borne viruses, a unique feature of ZIKV is the positive tropism towards the central nervous system. Congenital Zika syndrome is characterized by a spectrum of anomalies that can affect the hearing, vision, neurological, and thus, the development of a child. This article aims to highlight the unique nature of this arthropod-borne virus, with emphasis on the etiology, transmission, clinical features, treatment, and prevention of congenital Zika syndrome.

Keywords: Zika virus, Congenital Zika syndrome, Flavivirus, Fetal anomalies.

INTRODUCTION

Zika virus (ZIKV) is an arthropod-borne virus within the family Flavivirus, similar to those causing dengue, yellow fever, and Japanese encephalitis. ZIKV was first isolated from the blood of a sentinel rhesus monkey in 1947[1]. The first human infection was documented in 1954, in a 10-year-old female[2]. In this case, along with ZIKV, malaria parasites were also detected, which made the diagnosis a challenge. In the same year, two other cases were reported, which were confirmed by the presence of serum antibodies against the viral antigen.

The first outbreak of ZIKV was reported in the Western Pacific in 2007[3]. In subsequent years, the virus spread throughout Brazil and the Americas, with the World Health Organization (WHO) estimating a possibility of 4 million cases in 2016. By 2017, ZIKV was reported to circulate across Latin American and Caribbean countries[4]. A recent publication[5] in the year 2025 reported that several Zika case clusters have been found in countries such as India, the Maldives, Thailand, and Singapore.

The exact global burden of the Zika virus may not be accurate, as those with mild disease often may not seek medical care. Additionally, due to its

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similar presentation to other illnesses such as dengue fever and chikungunya, the number of misdiagnosed cases may be on the higher side[6].

VIROLOGY AND TRANSMISSION OF THE ZIKA VIRUS

The Zika virus is primarily transmitted *via* infected *Aedes* mosquitoes, such as *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes hensilii*. The surface of ZIKV contains an envelope protein that is involved in attaching the virus to the host cell membrane to promote endocytosis. The viral genome is then translated into the host, resulting in the formation of polyproteins. Once the parts of the virion are assembled, it is transported out of the cell. The Zika virus increases in number and eventually takes over the host's immune defense system[7].

Non-vector transmission can occur vertically, sexually, and *via* transfusion of infected blood or organ transplantation[8]. Although vertical transmission, from mother to child during pregnancy, has been observed, the transmission through breastfeeding has not been established yet (Figure 1). Hence, the WHO recommends mothers continue breastfeeding regardless of infection.

Sexual transmission of Zika virus infection was first reported in 2008. Since then, several cases have been observed among sexual partners of infected individuals arriving from endemic areas. Furthermore, the ZIKV has been observed to have a positive tropism towards testicular tissues and has been noted to be excreted in semen for months after infection[9].

CLINICAL FEATURES

Similar to arthropod-borne flavivirus, the incubation period of the Zika virus is expected to be around 1 week. The most common symptoms observed among those affected were macular papular rash, arthritis, arthralgia, low-grade fever, conjunctivitis, myalgia, headache, retro-orbital pain, edema, and vomiting. Along with this, neurological complications, such as Guillain–Barré syndrome, meningoencephalitis, and acute myelitis, have been reported as well (Table 1).

ZIKA FEVER

The fever observed in the Zika virus infection is typically low-grade and self-limiting. It resolves within 2 to 3 days of a pruritic generalized maculopapular rash, which spreads in a cephalocaudal direction. Along with this, infected individuals often report retro-orbital pain, non-purulent conjunctivitis, myalgia, arthralgia, and periarticular edema of small joints[10].

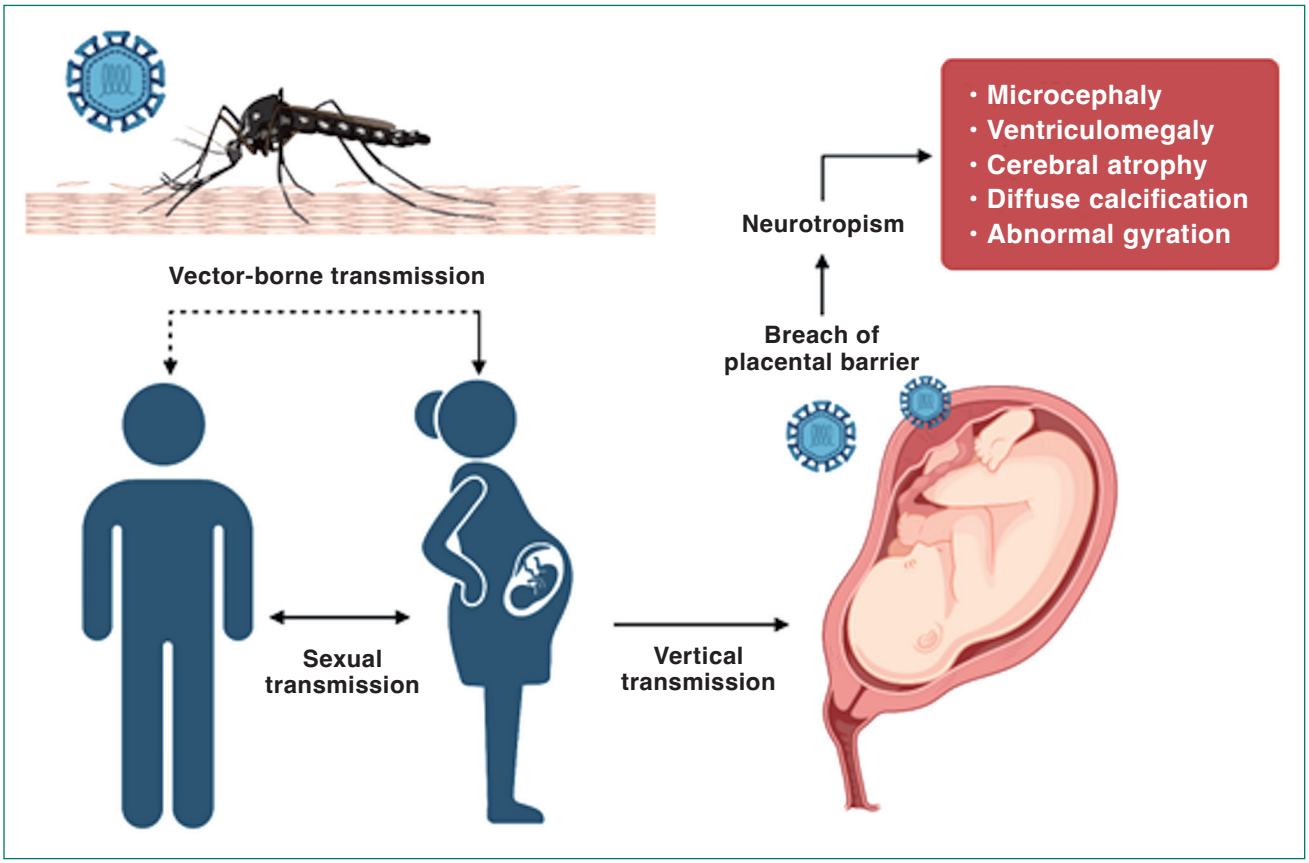

Figure 1. Routes of transmission and complications of congenital Zika syndrome.

Table 1. Clinical features of Zika fever and congenital Zika syndrome.

Clinical features of Zika fever	
Mild cases	Self-limiting fever Rash Retro-orbital pain Conjunctivitis Myalgia Arthralgia Periarticular edema
Severe cases	High-grade fever Lymphadenopathy Vomiting Diarrhea Hematospermia Hematuria
Clinical features of congenital Zika syndrome	
Neurological manifestations	Microcephaly Hypertonia Hyperreflexia Hypotonia Seizures
Ocular involvement	Chorioretinal atrophy Retinitis pigmentosa Cataract Glaucoma Astigmatism
Other systemic involvement	Congenital heart disease Coronal hypospadias Cryptorchidism Hearing abnormalities Hip dysplasia Club foot Polydactyly Camptodactyly

In severe cases, there may be high-grade fever, with chills and rigors. Additionally, more prominent systemic symptoms such as lymphadenopathy, vomiting, diarrhea, hematospermia, and hematuria may be observed. Although the clinical presentation of Zika virus is similar to other arthropod-borne viruses, studies[10] have observed a difference in the prominence of symptoms in ZIKV infection, such as headache and malaise.

CONGENITAL ZIKA SYNDROME

The earliest known case of Zika virus-related CNS anomalies was first described in French Polynesia in 2014[11]. In 2015, among the 69 countries reported by the WHO to have had cases of ZIKV infection, 29 of them reported cases of Zika virus-associated central nervous system (CNS) malformation. The WHO declared a public health emergency of international concern in response to an increased number of severe congenital malformations observed among newborns with ZIKV infection. Following this, the WHO registered a total of 2,656 congenital syndromes associated with the Zika virus, out of which the majority were reported in Brazil[12].

Congenital Zika syndrome encompasses a pattern of fetal anomalies resulting from ZIKV infection. The Pan American Health Organization defines a suspected case of congenital syndrome associated with the Zika virus as a newborn with microcephaly or another congenital malformation of the central nervous system, whose mother had possible exposure to the virus through travel or sexual intercourse during pregnancy. Confirmed cases require the virus to be detected in the specimens of the newborns, in addition to meeting the criteria for suspicious cases[13].

While the clinical presentation varies from mild to severe disease, the association between the phenotype and the timing of the infection is not well established. A case of two infants with confirmed ZIKV infection, born with brain abnormalities, was reported to have been exposed to the virus during the third trimester[14]. In contrast, a study[15] conducted in Colombia did not observe any anomalies among newborns who were exposed to ZIKV in the third trimester. Other studies[16] also report that maternal infection that occurred between 6 and 32 weeks resulted in early fetal loss and fetal death, with the highest risk of microcephaly being observed between 7 and 13 weeks. Newborns with congenital Zika syndrome were found to have an 11 times higher mortality rate in comparison to newborns without the syndrome. While this risk is the highest during the first year of life, the risk persists throughout the first three years of life[17].

SPECTRUM OF CONGENITAL ZIKA SYNDROME

Predominantly, the clinical features of congenital Zika virus are observed to be a consequence of neurological involvement of the virus, resulting in structural and functional impairment. Among the structural abnormalities most commonly affected are the cranial, ocular, and congenital contractures. Additionally, neurological manifestations such as hypertonia, hypotonia, and seizures have been reported as well. Viral RNA was also detected in ocular structures, with features of chorioretinal atrophy and retinitis pigmentosa. Congenital contractures were observed in one or multiple joints, and the clinical picture depended on the location of the contracture. Along with this, ZIKV has been observed to affect the reproductive system of infants as well, such as spermatogonia damage in males[18].

DEVELOPMENT OF INFANTS WITH CONGENITAL ZIKA SYNDROME

The severity of congenital Zika syndrome can vary from mild to severe. However, fetal infection can

have a significant impact on the development of infants. Within the spectrum of congenital anomalies, microcephaly is the most prominent and commonly reported feature. This is defined as a head circumference ≥2 standard deviations below the mean for gestational age and sex. Even among the 20% of newborns with normal head circumference, a delay in head growth was observed. Additionally, among infected newborns with no microcephaly or other birth defects, neurodevelopment differences were observed to manifest as the child got older[19].

PATHOLOGY OF CONGENITAL ZIKA SYNDROME

The unique feature of ZIKV is its ability to replicate efficiently in the fetal and reproductive tissues. New research suggests that the ubiquitin system of the host cell plays an important role in promoting viral persistence and tissue tropism[20]. During the replication of ZIKV, the virions that are released contain a ubiquinated envelope. This has the capacity to determine the tissue tropism and attach to receptors more efficiently. Thus, increasing the viral load in specific tissues, such as fetal and reproductive tissues[21].

Histopathological assessment of confirmed cases showed the presence of the Zika virus antigen within the cytoplasm of neurons and glial cells. Additionally, microcalcifications, cell degeneration, and necrosis were reported as well. Unlike other viruses that result in similar congenital malformations, there was a lack of inflammatory response noted in the brain[22].

The exact mechanism for the deformities associated with Zika congenital syndrome is not well established yet. However, several studies[3,5,6] report that the virus has a positive tropism towards fetal CNS tissue, resulting in subsequent damage to the brain. Viral antigen was also observed in chorionic villi, with an edematous placenta[23]. However, further research is required to establish if this is a direct result of viral infection or if it is due to an immune response.

TREATMENT

The treatment for ZIKV infection remains primarily symptomatic management, as no specific antiviral drugs are currently available for the Zika virus. Paracetamol is recommended for symptoms such as fever, myalgia, and headache. However, non-steroidal anti-inflammatory drugs are to be avoided due to the risk of hemorrhagic complications[22].

PREVENTION AND CONTROL

As ZIKV is an arthropod-borne virus, primary prevention includes vector-control strategies and prevention of mosquito bites. This includes the use of insect repellents, wearing long-sleeved shirts and pants, use of bed-nets, screens covering windows and doors, and staying indoors during periods when mosquitoes are most active. Emptying and cleaning any containers that can be a breeding ground for mosquitoes can significantly reduce the vector population as well[24].

Furthermore, the WHO recommends the use of contraceptives for the prevention of sexual transmission and counselling to avoid possible adverse outcomes during pregnancy.

Currently, there is no vaccination available for the prevention of Zika virus infection; however, it remains an area of active research[23].

CONCLUSIONS

With a high percentage of maternal-fetal transmission and elevated risk of congenital anomalies, screening for ZIKV among pregnant women, especially in endemic areas, is vital, as most of the infected individuals are asymptomatic. The current literature on ZIKV is based on a brief period of 10 years. However, as approximately 3.6 billion people are living in high-risk areas, continued research is essential.

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