Virology Journal

REVIEW

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Zika virus tropism and pathogenesis: understanding clinical impacts and transmission dynamics

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Abstract

The Zika virus (ZIKV) is classified within the Flavivirus genus of the *Flaviviridae* family and is categorized as an arbovirus. The virus was initially identified in a rhesus monkey in Uganda in 1947 and later in a human in Nigeria in 1952. Since 2007, the prevalence of the virus has been on the rise, culminating in a major outbreak in the United States (US) in 2015. During this outbreak, the adult population was severely impacted, experiencing a range of symptoms, including organ failure, microcephaly, fetal death, and Guillain-Barré syndrome (GBS). Additionally, skin rash, limb swelling, fever, headache, and heightened sensitivity are found in most adults with Zika syndrome. Although the virus can be transmitted through blood, vertical transmission from mother to child, and sexual contact, the primary way of transmission of the virus is through the Aedes mosquito. Cells such as neurons, macrophages, peripheral dendritic cells, and placental cells are among the target cells that the virus can infect. The TAM AXL receptor plays a crucial role in infection. After the virus enters the body through the bloodstream, it spreads in the body with a latent period of 3 to 12 days. Currently, there is no specific treatment or publicly available vaccine for the ZIKV. Limited laboratory testing has been conducted, and existing drugs originally designed for other pathogens have been repurposed for treatment. Given the Aedes mosquito's role as a vector and the wide geographical impact of the virus, this study aims to comprehensively investigate Zika's pathogenesis and clinical symptoms based on existing knowledge and research. By doing so, we seek to enhance our understanding of the virus and inform future prevention and treatment strategies.

Keywords Zika virus (ZIKV), Pathogenesis, Clinical manifestations, Neurological complications, Congenital Zika syndrome

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Introduction

The Zika virus (ZIKV) is a member of the *Flaviviridae* family and falls under the Flavivirus genus. Within this genus, other viruses like yellow fever (YFV), tick-borne encephalitis (TBEV), dengue hemorrhagic fever (DENV), and West Nile fever (WNV) viruses are also included [1]. This virus is one of the arboviruses and is transmitted by mosquitoes [2]. Structurally, it is an 11 kilobases (kb) long positive-sense single-stranded RNA virus. The genome of this virus initially encodes a polyprotein, which is finally converted into three structural proteins and seven non-structural proteins by viral and cellular proteases. The structural protein C forms the icosahedral capsid of the virus and finally, the virus is enclosed by a lipid envelope that comes from the host cell [3–5]. The virus was primarily separated from a rhesus monkey in Uganda in 1947 [6], its first isolation from humans occurred in 1954 in Nigeria [7]. Although ZIKV prevalence has increased since 2007, it was initially discovered according to the evidence in the American continent in 2015 as an epidemic in adults, with symptoms including Guillain-Barré syndrome (GBS), multiple organ failure, and birth defects, such as the birth of babies with neurological disorders, microcephaly, and the death of the fetus [8–10].

Based on phylogenetic analysis, the virus is divided into two lineages: Asian and African. According to the research, Asian lineages exhibit more genetic diversity and a greater number of single nucleotide variants in the viral genome compared to African lineages [11]. Although transmission by the Aedes mosquito is the main route of ZIKV transmission, the virus can also be transmitted through blood, vertical mother-to-child, and sexual contact [12–16]. Furthermore, according to studies, this virus also exists in biological body fluids such as breast milk, saliva, urine, and semen [17–20]. Different cells including peripheral dendritic cells, macrophages, various types of neurons, and placental cells are considered as ZIKV target cells [9]. After entering the body, the virus is disseminated to other parts of the body through the bloodstream [21]. According to studies, the latent period of the virus is between 3 and 12 days. However, in pregnant women, the infection may persist longer, leading to viral multiplication in the brain due to its teratogenic effects [22]. A maculopapular rash accompanied by limb edema, headache, and fever has been seen in most adults infected with the ZIKV. Also, symptoms such as thrombocytopenia, encephalitis, and meningitis are rarely seen in adults with severe disease. In addition, the ZIKV can be associated with neurological complications such as GBS [23–26]. According to the studies, no vaccine has been developed to be used by the general public. It is crucial to emphasize that, based on previous studies, no new drug has been specifically created for this virus. Instead, the treatments used have mainly been repurposed from medications originally designed for other pathogens. In addition to these drugs, antibodies are also employed as part of the treatment [27].

This study seeks to conduct an in-depth examination of ZIKV pathogenesis and its clinical manifestations by drawing on current knowledge and existing research. The objective is to not only provide a thorough understanding of the mechanisms through which ZIKV causes disease but also to analyze the range of symptoms associated with infection. By consolidating and expanding on this information, we aim to contribute valuable insights that can guide the development of more effective prevention measures and treatment strategies, ultimately improving public health responses to future ZIKV outbreaks.

Genome structure and tropism

The ZIKV is characterized as an enveloped, single-stranded RNA virus. Its genetic material contains an ORF encoding a polyprotein, which is subsequently cleaved into ten distinct proteins by both cellular and viral proteases. Among these proteins, three function as structural components: envelope (E), membrane precursor (prM), and capsid (C) proteins. The remaining seven proteins, known as nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5), play essential roles in the replication and assembly of the virus [3–5, 28]. Figure 1 provides a complete illustration of the virus genome and its associated proteins.

Moreover, several well-established ZIKV receptor candidates include receptors typically linked to other flaviviruses, such as Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN). Two other receptors, T-cell immunoglobulin and mucin domain 1 (TIM-1) and the Tyro3, Axl, and Mer receptors (TAM family), are also involved. These receptors belong to the phosphatidylserine receptor family [29]. Among these receptors, TAM receptor AXL plays a major role [30]. The presence of Nonstructural protein 1 (NS1) antigenemia is instrumental in the ingestion of flaviviruses by mosquitoes [31]. Based on the findings of Yang Liu et al., the existence of NS1 in the bloodstream of the infected host affects ZIKV infection in *Aedes aegypti* mosquitoes. They found that an alanine-to-valine amino acid substitution at residue 188 in NS1 increased NS1 antigenicity, which in turn increased ZIKV's ability to be transmitted from hosts to vectors, which could facilitate ZIKV transmission [32].

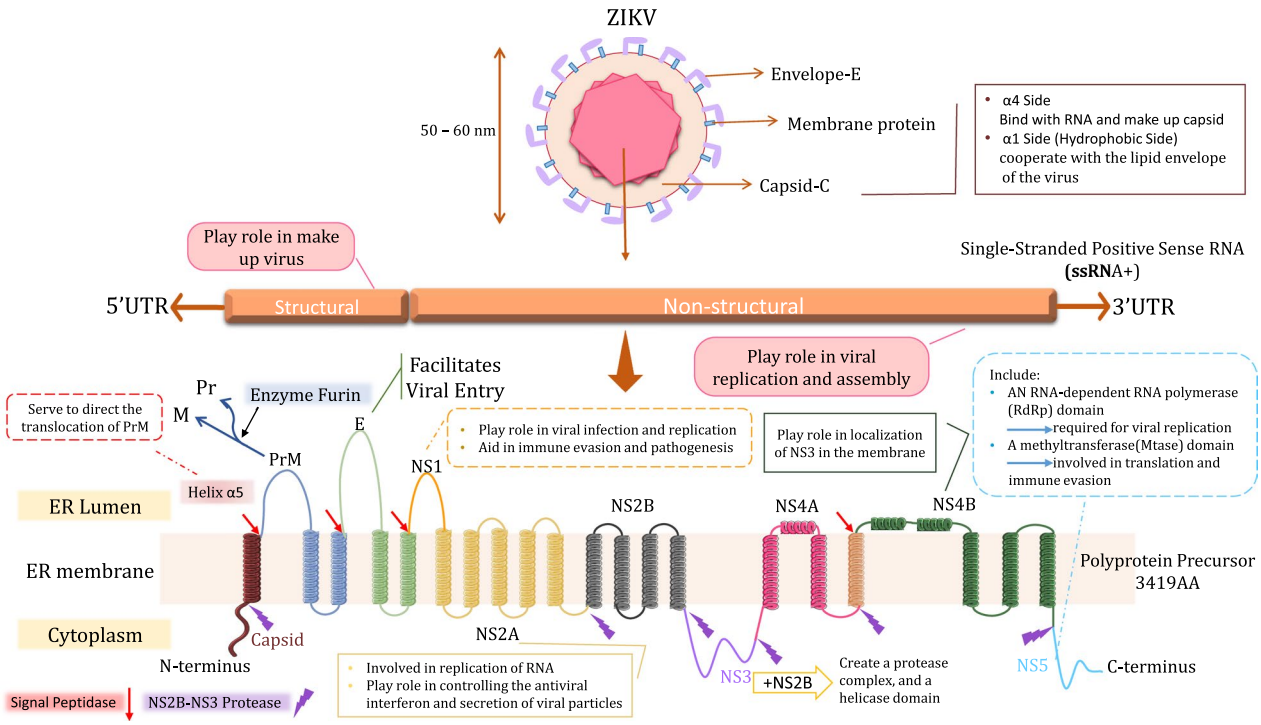

Fig. 1 ZIKV has a single-strand positive sense RNA genome, as well as an icosahedral capsid. The figure shows the polyprotein structure which is encoded by the ZIKV genome, in Endoplasmic Reticulum (ER) membrane [14, 118, 119]

Transmission routes

Vector-borne transmission

The ZIKV can be transmitted through various ways (Fig. 2). This virus is primarily spread by mosquitoes, especially those belonging to the Aedes genus [33–35]. Various species of Aedes mosquitoes have been identified as potential carriers, including *Aedes africanus*, *Aedes albopictus*, *Aedes hensilli*, and *Aedes aegypti* [36]. However, *Aedes aegypti* and *Aedes albopictus* are regarded as significant transmitters of ZIKV [37]. ZIKV circulates in an enzootic cycle among non-human primates through mosquitoes in sylvatic environments. These infected mosquitoes can then transmit the virus to humans, creating an epidemic cycle. Additionally, the virus may enter human populations via bites from infected Aedes mosquitoes that come from regions experiencing ZIKV outbreaks or spillover from sylvatic habitats [38]. Aedes africanus is believed to be the sylvatic vector of ZIKV, while Aedes henselli has been associated with the outbreak on Yap Island. However, Aedes aegypti is considered the primary vector for outbreaks in the Americas, the Pacific, and Asia [39].

Non-vector-borne transmission

There are several non-vector modes of transmission for ZIKV, such as through sexual intercourse [40–43], and from a mother to her fetus during pregnancy [44–50]. ZIKV might infect children through several ways, including intrauterine, intrapartum, and postnatal routes [46, 51, 52]. Instances of perinatal transmission of the ZIKV from mothers infected during childbirth have been documented, with two such cases identified. In one case, the infant showed no symptoms, while in the other case, the infant presented with a maculopapular rash and thrombocytopenia [44]. The clinical manifestations of the illness in children are strikingly like to those seen in infected adults [53]. Identifying arthralgia in newborns and young children can be challenging. Symptoms may include limping (among ambulatory children), trouble moving or reluctance to move an extremity, discomfort when moving the affected joint actively or passively, irritability, or ache upon palpation [53].

As well, the presence of ZIKV in semen and its potential for transmission through sexual contact have raised questions about its ability to breach the blood-testis barrier (BTB) or the Sertoli cell barrier (SCB). The E protein, a key antigenic component of ZIKV, is significant for its crucial role in receptor binding and membrane fusion. Numerous investigations have highlighted the significance of the E protein in the virulence and pathogenicity of ZIKV. Investigations have revealed that ZIKV infection leads to a rearrangement of actin filaments, a process in

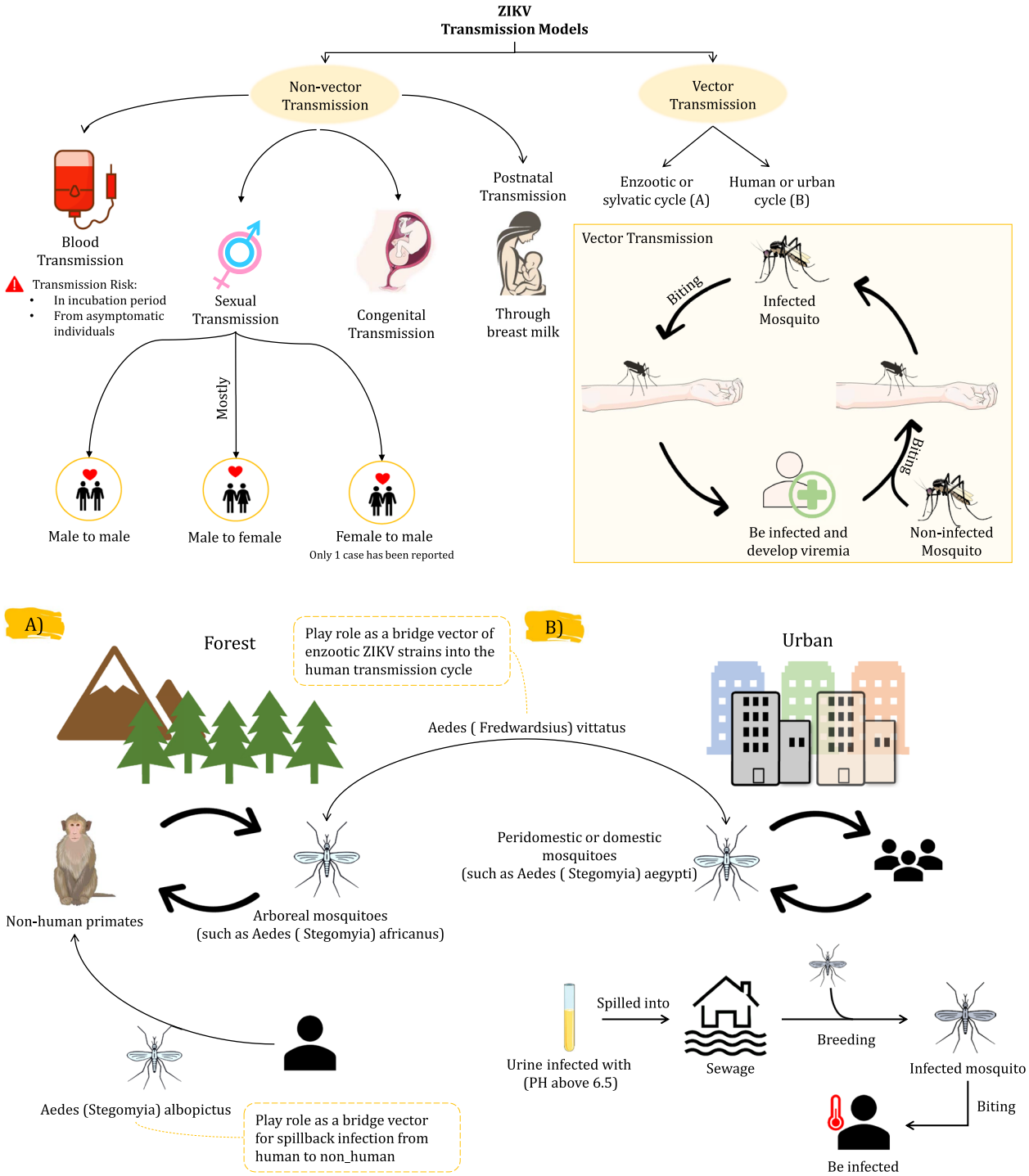

Fig. 2 ZIKV is an arthropod-born (arbovirus) that can be transmitted through other patterns such as sexual transmission, blood transmission, etc. The vector transmission consists of two cycles: **A** Enzootic or sylvatic cycle; and **B** Human or urban cycle. ZIKV can remain stable in urine for a long time. Therefore, urine can play a role in the urban cycle [12, 38, 120–123]

which the E protein is believed to be involved. This disruption of actin filament dynamics is a contributing factor to the ZIKV infection. In summary, the interplay between the ZIKV E protein and F-actin results in a rearrangement of the F-actin network, ultimately compromising the integrity of the BTB [54]. During the gestation

period in mammals, the placenta mainly performs as a barrier, offering both physical and immunological protection between the mother and the developing fetus. Within the placenta, primary human trophoblasts (PHTs), comprising cytotrophoblasts and syncytiotrophoblasts, play a crucial role as barrier cells. Syncytiotrophoblasts are particularly significant as they are in straight interaction with maternal blood. In cases involving full-term placentas, PHTs are generally resistant to ZIKV infection because they continually release antiviral interferon lambda 1 (IFNλ1). Additionally, it was noted that the medium derived from uninfected PHT cells exhibited a protective influence against ZIKV infection in non-placental cells. PHT cells themselves displayed elevated levels of interferon-stimulated genes (ISGs), signifying that IFNλ1 operates both in a paracrine manner (protecting neighboring cells) and an autocrine manner (protecting trophoblast and non-trophoblast cells) to safeguard against ZIKV infection [55]. It has also been shown that trophoblast cell lines obtained from choriocarcinoma explants and early human villous explants were found to be susceptible to ZIKV infection [56]. However, placentas from later stages of pregnancy, which possess a more mature placental barrier, showed heightened resilience against infection. For ZIKV to effectively infect syncytiotrophoblasts, it likely needs to evade the protective mechanisms established by IFNλ1 produced by trophoblasts, along with other antiviral factors that are specific to trophoblasts. Alternatively, the virus may need to find alternative routes to enter the fetal compartment by breaching the placental barrier. This scenario is particularly relevant during the second half of pregnancy, which corresponds to the stage when PHT cells are most abundant. These alternative pathways might involve non-trophoblast infection routes, for instance infecting immune cells or using transcytosis to transport virions complex with maternal antibodies through the neonatal Fc receptor (FcRn) [57]. Recently, it has been observed that human placental macrophages, identified as Hofbauer cells (HCs), are susceptible to the virus infection [58–60].

In the context of immune cells, innate immune cells are probably to be targeted by ZIKV once they breach the trophoblast layer in the placenta. Upon infection, HCs manufactured IFN-α, pro-inflammatory cytokines, and also stimulated genes that are associated with antiviral responses, although it did not significantly induce cell death. ZIKV replication was also observed in human placental cytotrophoblasts, albeit with deferred kinetics and ISG expression. This suggests that ZIKV may replicate within cytotrophoblasts and HCs, potentially facilitating vertical transmission. However, syncytiotrophoblasts are resistant to ZIKV infection, leaving us with the question of how the virus penetrates the cytotrophoblast layer and HCs. Considering that significant morphological changes occur in the human placenta during the first and second half of pregnancy, including the absence of maternal blood interaction with the syncytiotrophoblast layer in the earliest trimester of pregnancy and a substantial reduction in the cytotrophoblast cell layer during pregnancy, the methods for vertical transmission of ZIKV are likely to differ in any stages of pregnancy [57]. Also, The ZIKV may be transmitted via blood transfusions and organ transplants, although the associated risks are not completely understood [61, 62].

Pathogenesis in rhesus monkey (RM)

The ZIKV was initially isolated from a febrile rhesus monkey (RM) [63], indicating that studying virus replication, immune responses, and certain characteristics of disease progression can be effectively modeled in RMs. In one particular experiment, RMs were inoculated subcutaneously to simulate a mosquito bite, which induced transient viremia and fever [64]. Moreover, another study expanded its scope by examining the tissue tropism throughout the infection. Groups of RMs were necropsied on days 7, 28, or 35 post-inoculations. Seven days following inoculation, viral RNA was found in various tissues. This included lymphoid tissues such as widely distributed lymph nodes and the spleen, joints (especially those proximal to the inoculation site, but also in some distal joint tissues), and peripheral nervous tissues, exclusively the brachial plexus, trigeminal ganglion, and sciatic nerve. Concurrently, the RNA of the virus was linked to the spinal cord (cervical, lumbar, and thoracic regions), although it was not present in the brain and cerebrospinal fluid (CSF). This could suggest a predilection for nervous tissues but a limitation in the retrograde transportation of the infectious virus into the central nervous system (CNS), or it might imply that CNS infection requires a longer incubation period. RNA from the ZIKV was also identified in the kidneys and bladder of the male RM, but not in the testes or prostate. Collectively, these observations signify that ZIKV spreads rapidly to various tissues in the body, containing lymph nodes, spleen, peripheral nerves, skin, and the genital and urinary tracts. Furthermore, in the female RM, the presence of viral RNA was identified in reproductive organs for example the uterus and vagina. This indicates that these tissues can be infected by the virus and maintain the infection for a minimum of four weeks. This finding could have profound consequences for the transmission of ZIKV and the potential for fetal infections during pregnancy. Additionally, the seeding of the virus into semen via the urethra could represent another possible route of transmission [65].

Clinical observations and laboratory findings

Clinical manifestations

The ZIKV is the causative agent of Zika fever, a syndrome characterized by fever, rash, and joint pain that bears a striking resemblance to dengue fever [66]. A significant portion of individuals infected with ZIKV, especially in the period from the 1960s to the 1980s, have exhibited either no symptoms or only mild clinical signs [38]. Notably, severe illness and case fatality rates associated with ZIKV infection are remarkably low, and the symptoms of the illness typically abate within a relatively short timeframe of 2–7 days [67]. The incubation period of ZIKV infection in humans is estimated to span from 3 to 14 days [68]. Furthermore, the viremic period, characterized by the virus's existence in the bloodstream, is generally observed within 3 to 4 days after symptoms onset [69].

Evidence has indicated a connection between ZIKV infection and optical/neurological disorders, including optic nerve pallor, chorioretinal scarring, increased intraocular pressure, and corneal clouding at birth [70, 71]. It is estimated that 20–25% of people infected with ZIKV exhibit noticeable symptoms [38]. They exhibit the following symptoms: fatigue [72], arthralgia [73–75], temporary and moderate fever [75], accompanied by maculopapular, itchy rashes (that typically progress descendingly from the face to the extremities) [76], non-purulent conjunctivitis [77–80], and in some cases, redness of the eyes, loss of appetite, vomiting and edema [23, 38], as well as, sore throat, and cough [72, 81]. Clinical signs frequently associated with acute ZIKV infection encompass transient hearing loss [66], subcutaneous haematomas [82], myalgia, asthenia [83], headache, retro-orbital pain [23, 83, 84], and hematospermia [15, 85]. Other uncommon manifestations of ZIKV infection include mucous membrane ulceration, abdominal pain, diarrhea, nausea, and thrombocytopenia [86]. Figure 3 provides a detailed overview of the clinical manifestations of ZIKV and their associated neurological complications.

Neurological complications

ZIKV is also linked to neurological complications, including GBS, microcephaly [38], and neurological complications such as acute myelitis [87], and meningoencephalitis [88]. Microcephaly is a prenatal condition characterized by underdeveloped brain growth, leading to reduced head size in affected infants, while GBS manifests as muscle weakness stemming from immune-mediated harm to the peripheral nervous system [89]. During a ZIKV outbreak in Bangladesh, patients with ZIKV-associated GBS exhibited involvement of cranial, autonomic, and sensory nerves. Although electrophysiological studies predominantly confirmed most cases

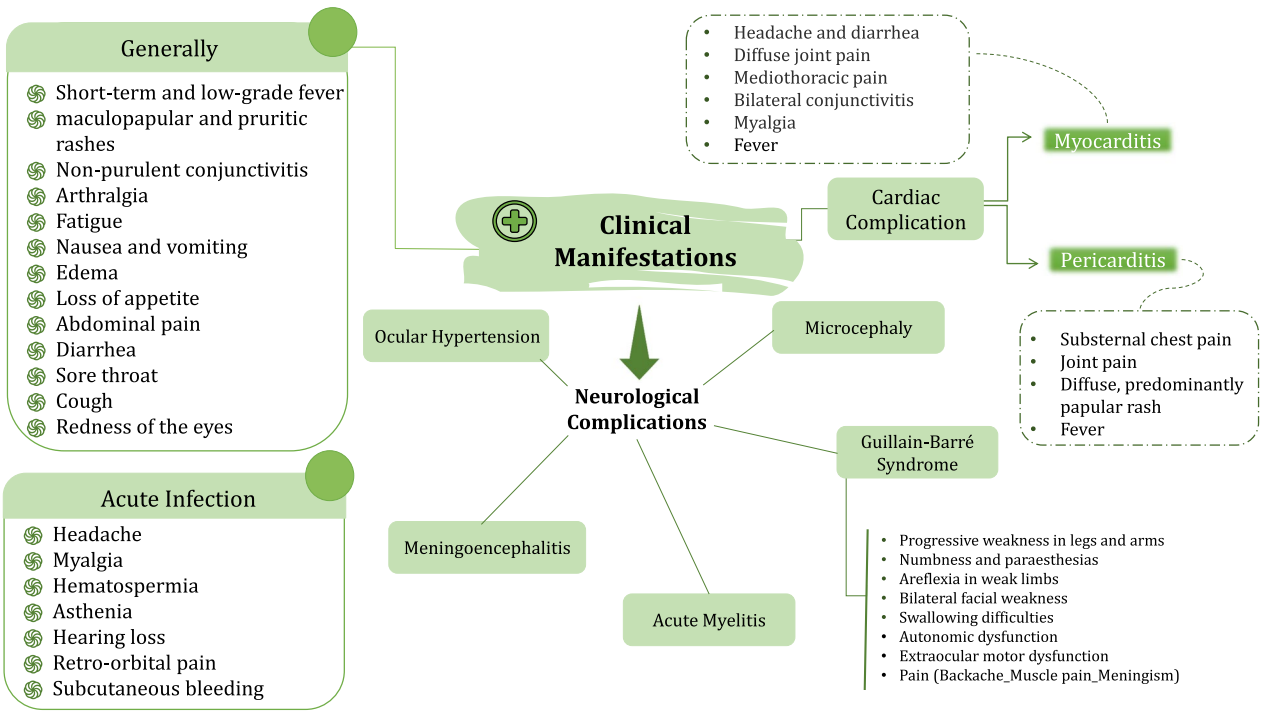

Fig. 3 Clinical symptoms of ZIKV and their neurological complications include acute myelitis, ocular hypertension, microcephaly, meningoencephalitis, and Guillain–Barré syndrome [15, 38, 66, 73, 75, 76, 80, 82, 87, 88, 93, 96, 97, 110, 124, 125]

as acute inflammatory demyelinating polyneuropathy (AIDP) [90]. In Brazil, ZIKV contributed to nearly equivalent incidences of acute motor axonal neuropathy (AMAN) and AIDP [91]. ZIKV-associated GBS is correlated with increased morbidity in the acute phase, frequently presenting with prevalent deficits in cranial nerves and acute neuropathy [92]. Research on fetuses exposed to the ZIKV has revealed occurrences of microcephaly, retardation of intrauterine growth, and CNS damage [46, 47] **(**Fig. 3**)**.

Laboratory findings

During ZIKV infection, laboratory values regarding biochemistry and hematology typically remain within normal limits. Nevertheless, during the viremic phase, a subset of patients may exhibit temporary and moderate lymphopenia, leucopenia, or activated lymphocytes. They may also experience monocytosis, thrombocytopenia, neutropenia, and increased serum levels of aspartate aminotransferase, C-reactive protein, lactate dehydrogenase, gamma-glutamyl transferase, fibrinogen, and ferritin [83, 84, 93–95]. Cases of cardiac complications related to ZIKV infection include myocarditis, pericarditis, Arrhythmias, and heart failure [96–98]. Additionally, incidence rates of ZIKV infection are observed to be higher in females than males, and it is more common in older individuals than in younger ones [23, 99]. Due to the overlapping signs, the clinical diagnosis of Zika persists challenging in tropical settings, especially in regions with concurrent transmission of dengue and chikungunya viruses [100]. Unlike Chikungunya and Dengue fever, ZIKV is characterized by more noticeable edema of the extremities and conjunctivitis and the ZIKV does not exhibit thrombocytopenia and leukopenia as seen in Chikungunya and Dengue cases [23, 76]. Additionally, malaise and headache in ZIKV fever tend to be less severe, while the maculopapular rash is more pronounced [23]. Table 1 provides a comparison of the clinical symptoms associated with Zika, Dengue, and Chikungunya infections.

Table 1 Comparison of Zika, Dengue, and Chikungunya clinical symptoms [76]

Symptoms	Zika	Dengue	Chikungunya
Fever	+++	++++	+++
Maculopapular rash	+++	++	++
Hepatomegaly	–	–	+++
Conjunctivitis	+++	–	+
Arthralgia/Myalgia	++	+++	++++
Edema of extremities	++	–	–
Retro-orbital pain	++	++	+

* –Don't have/ +Have

Neural dysfunction

The ZIKV disrupts the natural cell cycle and transcription processes in human neural progenitor cells (hNPC) [101]. Experimental studies have indicated that ZIKV infection leads to significant alterations in neuronal proliferation and migration. Specifically, Asian ZIKV isolates have been found to impede the growth and movement of hNP cells with less cell death. The cerebral cortex's structural development largely relies on the growth and movement of hNP cells. Subsequently, neurons in the cerebral cortex mature by extending neurites and forming synaptic connections. The cohesion of the neurite structure is crucial for the proper operation of the central nervous system (CNS). However, ZIKV infection can disrupt this process, affecting the cytoskeletal organization, microtubule dynamics, and neurite outgrowth. To assess the effect of ZIKV on neurons, researchers measured the rate of neurite growth and ramification. The High multiplicity of infections of the Asian SPH isolate of ZIKV significantly reduces neurite numbers, neurite length, and the number of branch points. Based on medical documentation of congenital ZIKV infection, ocular abnormalities, and seizures have also been documented. The observed impairment in neurite proliferation and migration is associated with seizures and cognitive deficits [102].

As well, distinct interactions between ZIKV and human proteins related to brain development contribute to the virus's influence on the nervous system. One of these interactions involves NS4A binding with Ankyrin Repeat and LEM Domain-Containing Protein 2 (ANKLE2), which is particularly intriguing [103]. Notably, mutations in *ANKLE2* have been linked to autosomal recessive microcephaly in humans, as documented in previous studies [104]. These discoveries collectively imply that the expression of NS4A may hinder critical functions of ANKLE2 during brain development [103]. Although the ANKLE2 pathway plays a role in ZIKV-induced microcephaly, several developmental pathways likely collaborate to promote this condition following ZIKV infection. As an example, ZIKV RNA binds to MSI1 (Musashi-1), an RNA-binding protein responsible for regulating the microcephaly gene *MCPH1*, thus aiding virus replication in neural stem cells [105]. Moreover, ZIKV NS2A can impede brain development in mice by breaking down adheren junction proteins disorders in the ZIKV capsid-mediated decay pathway may also affect brain growth. Additionally, as a result of the studies that have demonstrated ZIKV NS4A and NS4B's inhibition of neural stem cells (NSC) division through the Akt-mTOR pathway, it's plausible that NS4A contributes to neuropathogenesis via several mechanisms [106].

GBS is one of the common reasons for acute neuromuscular paralysis worldwide [107]. This syndrome is an acute polyradiculoneuropathy with an immune-mediated origin and usually appears due to a preceding infection, particularly an infection caused by *Campylobacter jejuni*. The disease often involves sensory and cranial nerves. Respiratory failure can occur in 20–30% of GBS cases, which have severe and general manifestations [108]. The incidence of GBS varies between 0.81 and 1.89 cases per 100,000 people per year [109]. The classic form of GBS is characterized by rapid and progressive symmetric weakness in the limbs, accompanied by sensory symptoms and hyporeflexia or areflexia [110]. Various subtypes of GBS have been identified through electrophysiological studies, including Acute Motor Axonal Neuropathy (AMAN), Acute Motor and Sensory Axonal Neuropathy (AMSAN), and Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) [111]. In 2014, the first report of a link between GBS and ZIKV was published, concerning a female patient with GBS in French Polynesia. Initial symptoms included distal limb paresthesia, which progressed dominant tetraparesis in the lower limbs. Other clinical symptoms included bilateral facial palsy, diffuse myalgia, and sustained ventricular tachycardia [112]. Further studies investigating ZIKV-associated GBS revealed common neurological findings such as any limb paresis (97%), areflexia or hyporeflexia (96%), tetraparesis (64%), facial palsy (51%), sensory deficits (49%), and bulbar palsy (25%) [113]. Several hypotheses exist regarding ZIKV-associated GBS. One hypothesis suggests molecular mimicry as a potential pathogenic mechanism. According to this hypothesis, the ZIKV polyprotein resembles human proteins involved in axon function, myelination, and neurodevelopment. Consequently, neutralizing antibodies induced by ZIKV may cross-react with peripheral nerve proteins, leading to immune-mediated damage [114]. Another hypothesis involves T cell responses stimulated by ZIKV, which may target neural, axonal, myelin, or Schwann cell antigens. This hypothesis is supported by the observation of perineural T-cell infiltration in nerve tissues from autopsies of GBS cases associated with other pathogens [115].

Moreover, human astrocytes, pivotal in providing support and protection to neurons, are vulnerable to ZIKV infection. Following infection, a gradual demise of human astrocytes is evident. Notably, there is an absence of indications of apoptosis or pyroptosis, effectively excluding these pathways of cell demise. Nevertheless, heightened levels of serine/threonine-protein kinase-1 (RIPK1), RIPK3, and receptor-phosphorylated protein lineage kinase-like domain (MLKL) signal the onset of planned necrosis or necroptosis in infected astrocytes [116]. Recent findings indicate that elements of the necroptosis cell death pathway might serve to constrain ZIKV neuroinfection. In particular, the activation of Z-DNA-binding protein 1 (ZBP1) and RIPK1/RIPK3 in cortical neurons can initiate a series of reactions that regulate the expression of the immune response gene 1 (IRG1) and the metabolite itaconate. Itaconate exerts a suppressive effect on viral genome replication by impeding the formation of succinate dehydrogenase (SDH) [117].

Author contributions
S.T, A.L: Review and Editing, Supervision. A.V. F, O.S.A, S.S, M.K, F.A, T.M, R.S: writing original draft, tables and figures, investigation, methodology. Z.T: Review and Editing. M.KH: Figures.

Funding
No Funding.

Data Availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests:
The authors declare no competing interests.

Received: 2 June 2024 Accepted: 17 October 2024
Published online: 29 October 2024

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