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Zika Virus, Microcephaly and its Possible Global Spread

Syed Lal Badshah, Yahia Nasser Mabkhot, Nasir Ahmad, Shazia Syed and Abdul Naeem

Abstract
Zika virus is an arbovirus that is spreading at an alarming state in the American continents and now in Asian countries. The Aedes mosquitoes are the vectors for the spread of this virus beside other ways of transmission. Currently, there are no vaccines or drugs available for its treatment. The Zika virus–related microcephaly cases are reported in fetuses of pregnant women who got this viral infection. However, the exact mechanism of Zika virus and microcephaly is still not established. Here we review Zika virus epidemiology, its unusual relationship with microcephaly in fetuses and current scientific research progress on it.

Keywords: Zika virus, microcephaly, Aedes mosquitoes, epidemic, vaccines

1. Introduction and background

Zika virus (ZIKV) of the family Flaviviridae was on the list of neglected diseases, and like all neglected diseases, it is now an epidemic causing microcephaly in new-born and Guillain-Barré syndrome in adults [1]. The Aedes aegypti mosquitoes are the main vectors for it beside other reported species like Aedes hensilli [2]. Historically, it was identified back in 1947, and recently, Chang et al. have thoroughly discussed its full history [3] and several authors have reviewed the literature [4–9], but still there is a need for updated information. In the past 70 years, different strains of Zika virus have been isolated from time to time in different parts of Africa [10–15]. It is generally believed that the current progress in human travel technology and its frequent use by people and the spread of Aedes due to its invasive nature cause the global spread of Zika virus [6]. Zika virus infection was also reported in a few returning travelers in the Netherland and Switzerland, so its possible spread to the Europe is also difficult to avoid [16–18]. It was recently reported that another vector mosquito called Aedes albopictus has the capacity to spread Zika virus in North America and Europe [19].
The threat of Zika virus to the United States population was not given importance initially, but several reports from Puerto Rico, Texas, and other parts alarm bells in the scientific community and a wake-up call to National Institute of Health [20, 21]. Zika virus is now on the door step of Asia with cases reported from Manila (Philippines), and parts of Singapore, Thailand, India, etc., which have favorable environmental conditions for Aedes mosquitos, and in the past, minor outbreaks were also recorded [14, 22–24]. This is an alarming situation and there is no preparation on the emergency basis. In the past, several cases of Zika virus were reported in Asian countries like Cambodia [25] and Senegal in Africa [26, 27], but it was not that widespread. Before 2007, few cases were reported at different places in different times, but it is suggested that increase in mosquito breeding and environmental changes due to human activities may cause mutation in the RNA genome of Zika virus and it becomes more adaptable to the mosquitos [28, 29]. In 2014–2015, Zika virus infection spread in South and Central America and Caribbean regions and is now spreading to other parts of the world [20, 30]. The spread of Zika virus in northeastern parts of Brazil occurred in the beginning of 2015 when it was observed that some patients had mild fever, rash, conjunctivitis and arthralgia and their tests were negative for dengue virus [31]. Later on, the reverse transcription-polymerase chain reaction from the sera showed the presence of Zika virus and its classification showed that it belonged to the Asian group [31]. The human skin fibroblasts cells are permissive to Zika virus entry. The viral replication in infected cells causes activation of an antiviral innate immune response with the production of type I interferons [32].

2. Transmission

The common possible ways of spreading beside the mosquito bites and transplacental transmission are blood transfusion, transplantation of organs, sexual activities, breastfeeding [33], respiratory along with sweat and tear droplets and animal bite [28, 34]. In North America and European countries, the spread through sexual contacts are more as these regions are not favorable for Aedes mosquitos [35]. In such areas, blood and semen donations should be properly checked for the presence of Zika virus, and further, people coming from affected areas should take care when they donate blood and semen in unaffected areas [36].

3. Relation between Zika virus and microcephaly

Microcephaly is one of the associated medical effects of Zika virus infection in mothers with their new born babies [36–40]. In the past, cases of Zika virus with microcephaly were not that common, but in Brazil, it was observed that the rate of microcephaly is twenty times more, which is quite alarming and new cases are still emerging [41]. Zika virus has the capacity to cross the placental barrier and infect the fetus [42, 43]. The infected mothers of these babies have rashes in the first and second trimesters [44]. Beside microcephaly, brain calcifications, cataracts and intraocular calcifications of eyes in fetuses are also reported [45]. In other cases, agyria, hydrocephalus and associated cortical displacement and mild focal inflammation are also present [46–48]. Similarly in another case in addition to the above-mentioned symptoms,
ultrasound of the infected fetus showed damaged lesions of posterior fossa and ascites along with subcutaneous edema [49]. Recent studies also suggested that the brain tissue and cells are favorable places for Zika virus growth as it targets the brain tissues in the neonate very easily [50, 51]. Zika virus decreases the viability and growth of neurospheres and brain organoids, and in that way, it targets the brain to cause microcephaly [52, 53]. Bullerdiek et al. hypothesized that the virus proteins affect the mitotic spindle proteins and their apparatus and this could be the possible way through which Zika virus causes teratogenic effects like microcephaly [54].

There are also ambiguities about the role of Zika virus and microcephaly, as in the past microcephaly was not linked with Zika virus infection, and the cases of microcephaly were very low and it is possible that other factors may be involved in it [55, 56]. Evans et al. suggested that the insecticide pyriproxyfen that is used for the control of mosquito populations in drinking water is the possible agent for microcephaly in Brazil [57]. The insecticide pyriproxyfen has shown to act as juvenile hormone and has cross-reactivity with most of the fat soluble molecules like retinoic acid (a metabolite of vitamin A) and a ligand for RXR receptor [57]. The RXR receptor is a type of nuclear receptor and this cross-reactivity of two agents results into abnormal activity of RXR receptors with the ultimate abnormality of microcephaly [57]. However, experiments on zebra fish models showed that pyriproxyfen did not cause any deformities in the central nervous system [58]. To counter such ambiguities, different groups are studying the effect of Zika virus on mouse models, and in one of the recent reports, the researchers showed that when a mouse is infected with a Brazilian Zika virus strain, it causes intrauterine growth restriction and signs of microcephaly were also observed [59]. They also showed that Zika virus attacks the human cortical progenitor cells and destroys them, and further the viral infection also damages the human brain organoids with a decrease in proliferative zones and damages the cortical layers [59]. In different brain and neural cells infected with Zika virus, it has been observed that the viruses halt the process of mitoses and damage the centrosome and the structural organization of the dividing cell with ultimate result of cell death [60]. It has been observed that a single point mutation of serine to asparagine (S139 N) in the ZIKV polyprotein resulted in high virulence ability in human progenitor cells [61]. This mutation occurred before the 2013 French Polynesia and was maintained during the later spread of ZIKV in the Brazil and its neighbors [61]. ZIKV has the capacity to infect the placental barrier cells and thus damage the fetus [62]. ZIKV has the sole capacity to interact with anexelekto, meaning uncontrolled (AXL) receptor, which is a tyrosine kinase receptor on the placental barrier cells while other Flaviviridae viruses cannot link with these receptors [62]. The other important arboviruses that damage the nervous system include the Japanese encephalitis virus (JEV) from the family Flaviviridae [63]. The vector for JEV is Culex mosquito species that feeds mostly on birds and livestock blood while humans are the accidental host of the virus [63, 64]. JEV causes birth defects and certain neurological complications [63]. A number of vaccines are available, but it is still endemic in South East Asian countries [63, 65]. Beside its effects on nervous system, Zika virus also damages the kidneys, eyes and genital organs [66–69].

4. Current scientific progress

For understanding the pathobiology and development of vaccines and drugs, it is important to sequence the genome and crystallize the important proteins of Zika virus. Recently, a Zika
virus strain named ZikaSPH2015 genome has been fully sequenced that contained all the structural and nonstructural proteins. This strain was isolated from a patient in São Paulo, Brazil [70]. In the past, a Zika virus strain from French Polynesia was also sequenced and the results showed its Asian background [71]. It is important to compare the genome of different strains and observe the differences in them for the possible mutations. Previous phylogenetic studies showed that there are basically two strains, one Asian and the other African, with some modifications due to glycosylation of amino acid sequence [72]. Recently, Kostyuchenko et al. have resolved a 3.7 Å resolution structure of Zika virus through cryoelectron microscopy [1], while Sirohi et al. have resolved a 3.8 Å resolution structure of mature particles [73]. As compared to other flaviviruses, Zika virus is stable even at 40°C. They also showed that its envelope (E) protein is similar in structure and function to that of West Nile and Japanese encephalitis viruses and dengue virus [1].

The isolation, purification and crystallization of different Zika virus proteins are also in progress and they will be helpful in designing vaccines and chemotherapeutic agents (Figure 1) [74]. The nonstructural protein (NS1) crystal structure showed unique electrostatic properties at the host interaction site and it is possible in different modes of action as compared to other NS1 proteins of flaviviruses [75]. It was also observed that the NS1 codons are helping more in adaptation to humans, as in the past Zika virus was more restricted to the zoonotic cycle [76]. Tian et al. resolved the crystal structure of helicase of Zika virus and they observed that

![Figure 1](sketch.png)

**Figure 1.** Sketch of the 11 kb genome of ZIKV and its important proteins. (A) The polyprotein and its cleavage products. (B) Topology of the polyprotein inside the membrane [85].
structurally it is similar to that of dengue virus but there are some differences in the motor domain [77]. That is why, Zika helicase binds to RNA differently and certain conformational changes can be seen in the motor domain [77]. Jain et al. resolved a 1.6 Å resolution structure of nonstructural (NS3) protein that acts as an RNA helicase of Zika virus, which was a French Polynesia strain [78]. This NS3 has similarity with that of dengue NS3 but there are some variations in its binding loops of ATP and RNA. This NS3 structure might be helpful in making necessary drugs to control Zika virus [78]. Rossi et al. studied Zika virus in murine models and this study could be helpful in the development of vaccines and drugs [79]. Shan et al. made an infectious cDNA clone of Zika virus using the clinical isolated strain of Zika virus of Asian origin [80]. This cDNA clone can infect the brain cells in mice and it can also infect the Aedes mosquito; thus, it is a useful tool to study the virus transmission, related diseases and research suitable therapeutics [80]. Like dengue virus, model studies suggested that there are chances that it will spread throughout the world [81, 82] and it may be possible to spread along with other flaviviruses like dengue, West Nile virus, chikungunya and Stratford virus due to the common vector Aedes [83, 84].

5. Vaccine and drugs

Some scientific groups have suggested releasing the Wolbachia-harboring mosquitoes in the environment as competitors for Aedes mosquitoes because they are resistant and they do not carry Zika virus; in this way, we can control the spread of Zika virus [86]. There is no vaccine or medicine available for the treatment of Zika virus, so it is important to be safe from mosquito bite and sexual contacts in Zika virus-affected places, which is the only solution [34, 87]. The health departments of USA are giving guidelines from time to time for prevention and control of Zika virus [88, 89]. Currently, different research institutes are working in developing a vaccine against this virus, but it will certainly take time in preparing it [90–93]. It has been observed that the polyphenol epigallocatechin 3-gallate (EGCG) inhibits the entry of Zika virus into the cell [94]. This polyphenol is present in green tea and is also part of many dietary supplements. Such observations were also recorded previously for other viruses, especially hepatitis C and herpes simplex, but how efficient this compound exactly is and its mechanism of action are still not clear [95–99]. Larocca et al. made DNA vaccines that express the premembrane and envelope protein of Zika and offer protection against the Brazilian virus challenge in murine models [100]. This initial vaccine development is a positive sign of a more effective vaccine development and its marketing in the near future for the control of Zika virus. It is also reported that those parts of Brazil where yellow fever vaccination was done have lower level of microcephaly cases due to Zika virus [101]. Thus, there is a possibility that the yellow fever vaccine may be helpful for the treatment of Zika virus infection. An opposite case to this was reported where a male American traveler had yellow fever vaccination record but still he developed symptoms of Zika virus infection like rash, fever, extreme fatigue, back pain and conjunctivitis [102]. There are also suggestions to develop better mouse and other ani-
mal models that can be used to study the pathogenesis and vaccine development of Zika virus; further, the already present neuroteratogenic problem–causing virus models can also be utilized for Zika virus infection [103–106]. Computational studies predicted that the antibodies are produced in humans during Zika virus and the infection causes an autoimmune response that results in rash, microcephaly and other symptoms [107]. Therefore, remedy for such autoimmune proteins should also be considered for treatment during development of vaccines and drugs. On the drug and development side, it was noted that the 7-deaza-2′-C-methyladenosine (7DMA) has the potency to inhibit the replication of Zika virus in mice, and further trials should be performed to check its efficiency against different strains of Zika virus [108]. Eyer et al. tested a series of substituted nucleoside bases to inhibit the replication of Zika virus and they observed that the 2′-C-methylated nucleosides are promising drug candidates [109]. For research purposes, it has been suggested that the famous adenosine analog NITD008 that has been used in the past against other viruses [110–112] also has the antiviral activity both \textit{in vitro} and \textit{in vivo} against Zika virus [113]. Now, the sequences and in some cases the crystal structure of different important Zika virus proteins are available and they can be targeted through computational drug designing techniques [114–117]. Similarly, the already available data on the closely related viruses like dengue virus enzymes can be exploited for novel drug design [118]. In mouse model, it was noted that 25-hydroxycholesterol prevents the entry of virus particles inside the cell and is the first line of defense molecule [119]. One of the positive aspects of ZIKV is that it can be utilized for brain cancer treatment. It was observed that the ZIKV possesses oncolytic properties and it can destroy brain cancer cells called glioblastoma with high specificity [120].

6. Conclusions

The way Zika virus is spreading silently first in South America and now in Asian countries is quite alarming. If the spread continues and microcephaly cases increase, then a whole generation born might be a patient of microcephaly. Zika virus has already affected the tourism economy of different countries, and if this spread persists in Asia, then the loss will be too large. There is a need to figure out how exactly Zika virus causes microcephaly. The current research progress in terms of vaccine and drug development is at a snail pace and collaborative efforts are required to control this viral disease. Further, the spread of Aedes mosquitoes is also alarming as they are the source of other viruses too, and controlling the vector means control on ZIKV, dengue and chikungunya.

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