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Neurotropism and Birth Defect Induced by ZIKV

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Abbreviations: NPCs: Neuroprogenitor cells; ZIKV: Zika virus; CNs: Cerebral neurons; GBS: Guillain Barré Syndrome; MCPH: Microcephaly

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"The current paradigm is that an important factor in ZIKV-induced neurological disorder by apoptosis of infected fetal cortical neural stem/progenitor cells (NSCs) that results in depletion of neurons from the cortex and consequent malformation of the cerebral cortex leading to microcephaly and birth defect [1-2]".

A human outbreak of Zika virus (ZIKV) that started in 2015 in Brazil has now spread to over 30 countries in the Americas with hundreds of thousands of confirmed or suspected cases. Nearly five hundred cases of travel-associated ZIKV infection have also been reported in the United States. ZIKV is primarily transmitted by mosquitos of the genus Aedes that are widely distributed throughout the world including much of the Southern United States. Additionally, the virus can also be transmitted from males to females by sexual contact. The epidemiological investigations during the current outbreak found a causal link between infection in pregnant women and development of microcephaly in their unborn babies.

This finding is a cause for grave concern since microcephaly is a serious neural developmental disorder that can lead to significant postnatal developmental abnormalities and disabilities. Currently, it is not known how ZIKV causes microcephaly, but in vitro and in vivo data indicate that ZIKV causes apoptosis of fetal neural progenitor cells (NPCs) and/or cerebral neurons (CNs) that results in malformation of cerebral cortex leading to microcephaly [5,6]. To have a deeper understanding of the pathogenesis of ZIKV-induced microcephaly and birth defect, it is critical to decipher the molecular mechanisms by which ZIKV causes apoptosis of NPCs/CNs.

The phylogeny of ZIKV suggests two important lineages known as African and Asian, evaluating from one ancestry, mostly apparent in Uganda [3]. Probably the vectors are Aedes polynesiensis and Aedes aegypti, a species of Aedes found in French Polynesia, reported in Yap [4-6]. Aedes species found in various parts of USA [2,5]. The viral RNAs has 3419 amino acids and host and viral proteases help in the translation and cleavage of polyprotein into structural and non-structural proteins [7,8]. Initially, the ZIKV attached with host endosomal membrane by endocytosis and then ssRNA is released into host cytoplasm followed by translation and cleavage of protein and finally resulted in formation of viral proteins.

In the next step, the dsRNA produced after replication in endoplasmic reticulum followed by production of additional ssRNAs to form new virus progeny. The newly emerged virus particles move into Golgi complex and finally released into the intracellular spaces to infect the neighboring cells [8]. There is a very close link between flaviviruses such as Zika, Chikungunya and Dengue, which have common symptoms like a headache, rash, myalgia, arthralgia fever, and maculopapular. The published information provided a convincing evidence about the development of neurological symptoms like Dementia in South America and Polynesia [9]. Based on published data the ZIKV infection to pregnant women will lead to the development of MCPH in the developing fetuses [1,2].

ZIKV infection and the risk of Dementia

Zika virus infection in adults has been reported with symptoms. However, given its neurotrophic ability and tendency to infect neural progenitor cells, Zika virus could also infect the brain cells and results in neurological disorders in adults. Brain infection and neurological symptoms have been found in Zika virus infection of mice lacking type I and type II interferon response [13]. Acute myelitis with the detection of the viral RNA in the cerebrospinal fluid has been recently reported in a 15-year-old patient. It is therefore accountable that Zika virus infections that might induced in unusually widespread systemic infection or prolonged viremia in immune-compromised adult individual, could culminate in cerebrospinal fluid infection. A previous reported data has shown that TLR-3 stimulation in West Nile virus infections could compromise the blood–brain barrier (BBB) and enhance CNS infection in mice [14]. Given that TLR-3 is also specifically elevated in ZIKV infection [15], it is again accountable that weakening of the BBB could lead to Dementia in adult.

Microcephaly and birth defect induced by ZIKV

Microcephaly is a brain disorder defined as the measurement of head occiptofrontal circumference being more than two standard deviations below the mean for age and gender [1,2]. It is known that the brain of microcephalic patients is proportionally smaller , thus about 90% of the cases are linked with some degree of intellectual disability [10]. It is very urgent to remind that microcephaly is not a diagnosis but a clinical finding, hence further investigation is necessary when facing this situation [5,10]. Microcephaly can be classified as primary (congenital) or secondary (postnatal). Post-natal microcephaly can be diagnosed before 36 weeks of gestation. This may occur by inhibition of neurogenesis, by destructive pre-natal insults or by very early degenerative processes. The congenital microcephaly can be caused in any region during the development and function of the central nervous system. It is commonly associated with neurological disorders [12].

The origin of microcephaly is extensive, as this can be caused by many genetic, environmental, and maternal factors [11]. Genetic microcephaly progresses with dysmorphic features or concomitantly with other congenital abnormalities and it is very common the association with Down Syndrome [11,12,]. As for environmental and maternal factors, there are hypoxic ischemic insults, placental insufficiency, systemic and metabolic disorders, exposure to teratogens during pregnancy, pregnant women with severe malnutrition, maternal phenylketonuria, and central nervous system infections (such as rubella, con-genital toxoplasmosis, cytomegalovirus infection, herpes, and HIV) [11,12]. However, in some cases, the etiology of microcephaly cannot be defined [12]. Consequently, with the increase in cases of microcephaly notified in Brazil and worldwide, there was an outbreak of ZIKV infection, which was listed as a possible cause of that neuronal malformation and early birth defect.

Zika virus infection and decay of function of these cells would axiomatically affect human fetal corticogenesis. Excitingly, AXL is also noticed to be expressed in the outer margin of human neural retina, simultaneously its adjacent ciliary marginal zone [1,14], which could be potentially explain the occurrence of macular atrophy reported in ZIKV-associated microcephalus infants.

Conclusion

In this article, we have provided an update of recent reports demonstrating causality between ZIKV infection and microcephaly to risk of dementia. Based on the published information provided, it is clear that transplacental infection of the neural progenitor cells in the developing fetus, mainly in the first trimester, is the most likely cause for the ZIKV infection associated congenital malformation. ZIKV efficiently infects human fetal brain cells and organoids *in vitro*. Mouse models have also recapitulated critical aspects of human ZIKV pathology pertaining to fetal demise, fetal brain infection and cortical development *in vivo.*

It is apparent that the macular atrophy observed with some of the microcephalic newborns is also a result of ZIKV infection of the developing fetal retinal structures, as this was also seen in infected mice newborns. ZIKV deregulate Akt-mTOR signaling, one of the key cellular pathways essential for brain development in human. There is some evidence for the capability of ZIKV to target the adult human central nervous system and gives dementia like symptom, but any confirmation of such neurotropism would require the analysis of a larger number of cases. Based on current published reports, there is an urgent need to conduct more research to gather more information so that an effective disease management strategy can be design and developed to protect the spread of Zika virus infection.

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