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A Glance on Zika Virus Infection

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ABSTRACT

Zika virus is mainly transmitted through its vector Aedes aegyti are now a days affecting the world population, this infection has also affected to the pregnant women, which causes microcephaly in their newborns. Zika virus infection also causes Guillain BarreÂ syndrome GBS. Till date, there was no specific medication available for treatment of Zika virus infection. Some preventive measurements will be applicable. The Scientists are trying to investigate the vaccine which will be useful in future.

Keywords: Zika Virus, Treatment, ZIKA.

I. INTRODUCTION

Zika virus was first isolated in the Zika Forest near Lake Victoria, Uganda in April 1947 from a sentinel rhesus monkey placed; in January 1948 a second isolation from the mosquito *Aedes africanus* followed at the same site .[1]

Zika virus (ZIKV) infection has been a source of concern in the recent few months due to increase in the number of patients being affected by it with epidemic proportions in Brazil and its potential of spread to other countries. The association of microcephaly in newborns due to the Zika virus has further created panic and worry among the people. It is thus essential to clarify the doubts and confusion in the minds of physicians and people at large. This article is designed to reflect the best information regarding the Zika virus in depth.

Background

Zika virus (ZIKV) belongs to the family flavivirus is a mosquito-transmitted found in both Africa and Asia. Infection of this to human may result in a febrile illness similar to dengue fever and many other tropical infections found in these regions.

World Health Organization (WHO) report that some neurological disorder such as Guillain BarreÂ syndrome (GBS) and of microcephaly also caused by Zika virus infection.

II. METHODS AND MATERIAL

Epidemiology

In 1947, Zika virus first found in rhesus monkeys in the Zika forest of Uganda.[2] It was later identified in humans in 1968 for the first time in Nigeria.

There were only about 14 or 15 cases documented until 2007. In 2007, sudden spontaneous occurrence of Zika was reported, in the Island[3]. Currently Zika virus has spread to other countries in America, Brazil, and the Colombia.WHO has reported 23 countries and territories in Americas from where local transmission of Zika virus has been reported.[4].

Out Of 76-suspected deaths from microcephaly and congenital central nervous system malformations, 15 were investigated and confirmed to have microcephaly and/or central nervous system malformations.

Structure of the Zika virus

Zika virus, has a positive-sense, single-stranded RNA genome approximately 11 kilobases in length. The RNA contains strands of 5′ and 3′ that encodes a polyprotein and was cleaved into three structural proteins, namely a) the capsid (C), b) premembrane/membrane (perm), and c) envelope (E), and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, 2K, NS4B, and NS5) [5].

The Zika virus particle has the same general structure as other Flavivirus species [6]. It is spherical, 42-52nm in diameter [7]. Its envelope is formed by a lipid bilayer embedded in 180 units of glycoproteins E and M for binding to a variety of cell receptors [8]. Glycoprotein E has a typical three-domain structure, but differs from that of dengue-2 virus because it has only one glycosylation site (Asn154) that appears as a small protrusion on the viral surface. Glycosylation at this specific site has been linked to neurotropism of the West Nile virus [9]. Notably, loss of glycosylation sites has been noticed in Zika virus strains from Africa that are not commonly reported to cause neurological damage. Glycosylation has been reported in Asian strains causing Guillain-Barre syndrome (GBS) and microcephaly, as seen in Brazil [10]. In another study, the loss and gain of glycosylation sites detected in African strains were associated with viral capacity to infect specific mosquito species [11].

Zika virus nucleocapsid is formed by protein C associated with a positive-sense, single-stranded viral RNA molecule that has a genomic organization characteristic of the Flaviviridae family, encoding three structural and seven non-structural proteins [12]. A complete genome sequencing of the Brazilian strain verified that it shared 97-100% similarity with the French Polynesian strain, with a 51.2 % GC ratio [13]. In contrast to what was initially hypothesized, no recombination events were detected that would explain its enhanced neuroinvasion or neuropathogenesis. Similar results were obtained for Zika virus isolate that infected a Slovenian woman in Brazil . The long viral persistence in the mother and fetus, from 13th to 32nd week of pregnancy, deserves attention and has been reported in other Zika microcephaly cases [14]. The virus replicates in the rough endoplasmic reticulum membranes, as demonstrated in brain cells in vivo and in neurospheres in vitro [15].

Modes of Transmission:

Transmission of Zika virus carried by mosquitoes of genus Aedes, such as *A. aegypti*. This is the same mosquito which also transmits Dengue and Chikungunya
infections. Also transmitted by arboreal mosquitoes such as *A. africanus, A. apicoargenteus, A. furcifer, A. hensilli, A. luteocephalus,* and *A. vitattus* which are daytime-active mosquitoes. Zika virus can transmit by sexual contact (16,17) and during pregnancy, it can cross the placenta and affect on an unborn fetus. Another mode of transmission of Zika is through blood **(18).** The reproduction period of Zika virus has been reported to be around in between 7-10 days.

The monkeys and human beings were the prominent host of the Zika virus.

Symptoms:

After the mosquito bite, it usually takes around two to seven days for the symptoms to appear.
The most common symptoms of Zika virus are acute onset of fever with cutaneous rash, anguish of small joints of hands and feet, with possible swollen joints, conjunctivitis. Other commonly reported symptoms include myodynia, headache, retro-ocular headaches and post-infection astheny which seems to be frequent.

Deaths are rare and severe disease requiring hospitalization is uncommon. Guillain-Barre syndrome (GBS) and of microcephaly also reported as a cause of Zika virus infection.

Zika virus and microcephaly:

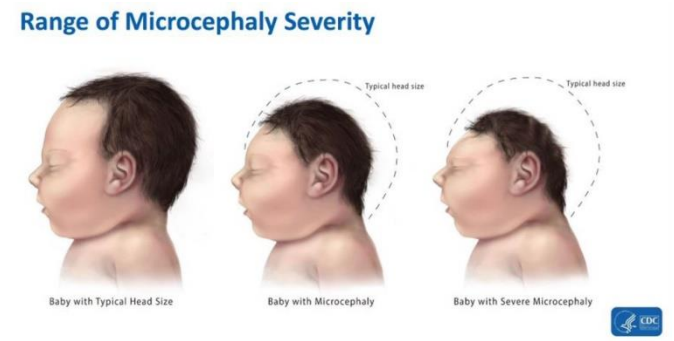
After study of literature it was concluded that, there was a causal relationship between Zika virus infection in pregnant women and microcephaly [19].
Microcephaly means smallheadedness

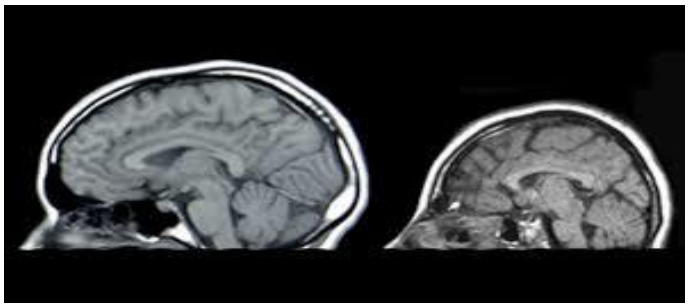
Microcephaly generally is due to the smaller size of the largest part of the human brain, the cerebral cortex, and the condition can arise during embryonic and fetal development due to insufficient neural stem cell proliferation, impaired or premature neurogenesis, the death of neural stem cells or neurons, or a combination of these factors. [20]

Microcephaly is the irreversible neurological complication caused by Zika virus infection [21]. It is characterized by a reduction in the cephalic perimeter, usually caused by an inappropriate development and/or destruction of the neural cells. The greatest risk of microcephaly is in the first trimester. It can be detected

by ultrasound, tomography, or by cephalic perimeter measurements. According to WHO, newborns with a head circumference >2 standard deviations below the expected mean should be considered as having microcephaly, and those with >3 standard deviations below the expected mean should be considered as having severe microcephaly [22].

Ocular lesions have been observed in 34.5% of microcephalic newborns [23] and can be extensive, with macular atrophy, optical nerve alterations, optic disc hypoplasia, gross macular pigment mottling, and juxtafoveal chorioretinal atrophic lesions [24].
Most of the reports, however, have been published at the beginning of the Brazilian outbreak and additional detailed studies are needed to establish a link between Zika virus and ocular lesions.





Left : normal brain; right: brain with microceplalies

Zika virus, GBS, and other neurological disorders in adults

Guillain-Barre syndrome is an acute auto-immune neuropathy that may be caused by infections, many of which involve *Flavivirus* [25] and other arboviruses such as Chikungunya [26]. It is characterized by superior/ inferior limb extremity paresthesia, ascending muscular weakness, and paralysis that can evolve into respiratory and deglutition disorders, and death [27]. The sensory motor deficits are symmetrical and bilateral. GBS immunopathogenesis is complex, involving Toll-like receptors, the production of pro-inflammatory cytokines with toxic activity, cell mediated immune responses with cytotoxic T cell activation, production of auto-antibodies, and complement activation [28].

The first association between Zika virus infection and GBS was reported in French Polynesia in 2013 in a woman who had fever, rash, and conjunctivitis 7 days before hospitalization when diffuse demyelinating disorder was confirmed. Viral antigens were not detected, but neutralizing antibodies [immunoglobulin M (IgM) and immunoglobulin G (IgG)] against dengue and Zika viruses were present, which can be one of the causes of this syndrome [29].

III. RESULTS AND DISCUSSION

Treatment

Till date, there is no specific medicine or vaccine for Zika virus.

To treat the symptoms following instructions were followed:

- Get plenty of rest.
- Drink fluids to prevent dehydration.
- To reduce fever and pain take medicine such as Paracetamol.
- Do not administered non-steroidal anti-inflammatory drugs (NSAIDS) like ibuprofen until dengue can be ruled out to reduce the risk of bleeding.
- If you are taking medicine for another medical condition or if you are pregnant, talk to your doctor or other healthcare provider before taking additional medication.

Diagnostic testing for Zika virus

- Real time reverse transcriptase-polymerase chain reaction (rRT-PCR) for viral RNA in clinical specimens collected less than7 days for serum or less thsn 14 days for urine after illness onset.
- Serology for IgM and neutralizing antibodies in serum collected up to 12 weeks after illness onset.

- Plaque reduction neutralization test (PRNT) for presence of virus-specific neutralizing antibodies in paired serum samples.
- Immunohistochemical (IHC) staining for viral antigens or RT-PCR on fixed tissues.

The presumptive diagnosis of ZIKV is typically clinical with confirmatory laboratory tests performed using serum, saliva and/or urine samples. If samples are collected within 1–3 days of fever onset, NS1 antigen may be detected in serum and reverse transcription PCR (RT-PCR) can be used to detect a specific region of the viral genome that includes NS5. ZIKV RNA can also be detected in both urine and saliva samples collected within the first 3–5 days of fever onset.[30,31,32]. Current testing recommendations are to obtain RT-PCR results from urine or saliva within the first 5 or 6 days of illness.[33] Serological tests, such as enzyme-linked immunosorbent assays and immunofluorescence assays can be performed to detect anti-ZIKV IgM and IgG antibodies.[34,35]. For confirmation of enzyme-linked immunosorbent assay-positive and RT-PCR-negative samples, a plaque reduction neutralization test5 can be performed at reference laboratories. Nevertheless, secondary flavivirus infections potentially complicate plaque reduction neutralization test-based diagnostics because of the induction of broadly cross-reactive antiflavivirus antibody responses [36] (e.g., including ZIKV there at least 10 flaviviruses in Brazil).

Current Vaccine Development Efforts:

Although there are no licensed vaccines for ZIKV many vaccine platforms/approaches that have bee utilized for vaccine research for other flaviviruses a being applied to ZIKV. Table 1 show platforms/technologies being used in the nonclinic development of flavivirus vaccines, [37] and mar groups are investigating the same technologies for a ZIKV vaccine.

Technological approach	***Antigen***[a]
Recombinant subunit	EDIII-p64k fusion proteins and EDIII-capsid fusion proteins
vaccines	expressed in *Escherichia coli*
	Bivalent 80E-STF2 fusion proteins expressed in baculovirus/insect cells
	E protein
	80 E protein
	EDIII protein expressed in *E. coli*
DNA vaccines	prM/E expressed from plasmid vector
VLP vaccines	prM/E
	EDIII-HBsAg VLPs or ectoE-based VLPs expressed in *Pichia pastoris*
	MVA-VLP
Recombinant chimeric live vaccines	YF 17D backbone
	DENV-2 backbone
	JE SA14-14-2 backbone
	Host range mutations
	Targeted mutation (2′-*O*-Methyltransferase mutant)
	DENV-4 backbone
	EDIII expressed from live-attenuated measles virus vector
Single round replicating viruses	E85 expressed from single-cycle VEE virus vector
	RepliVax
Virus-vectored vaccines	Live adenovirus 4/7 oral vector
Purified inactivated virus vaccines	Purified inactivated
	Purified inactivated virus (+Venezuelan equine encephalitis −particle adjuvant)

1.
2. Abbreviations: DENV, dengue virus; MVA-VLP, modified vaccinia ankara-virus like particle; VEE, Venezuelan equine encephalitis; ZIKV, Zika virus.
3. 80E and E85 refer to the N-terminal 80% and 85% of the E protein, respectively, which is the ectodomain of the E protein (also termed ectoE by some). EDIII is domain III of the ectodomain. prM/E is premembrane and envelope protein genes.

Development and testing Zika virus Vaccine-Challenges:

There are more than 60 research institutes and companies working on products to combat the spread of ZIKV.[38]. The pathway to a ZIKV vaccine is still in the nonclinical stage.[39]. To date, there is only one

published paper [40] on ZIKV vaccine candidates, and very little information is available regarding induction of immunity against ZIKV in humans or animals. However, the related flavivirus, DENV, has been the topic of intensive vaccine research with a recently licensed product and several vaccine candidates in clinical and preclinical development. Several of these vaccine platforms could potentially be applied to ZIKV vaccine development. Notably, ChimeriVax yellow fever-Japanese encephalitis vaccine has been licensed since 2010 (under the trade name IMOJEV) and the ChimeriVax-yellow fever, dengue LAV vaccine from Sanofi Pasteur (trade name DENGVAXIA) containing DENV structural genes in a YFV backbone has completed phase III clinical trials and been licensed in several countries.[41]. Additional recombinant or chimeric LAV DENV vaccines have entered phase II or III trials, and purified, inactivated, recombinant subunit and DNA vaccines have entered phase I trials.Suitability of these approaches for the target population(s) needs to be considered. Using one of these platforms utilizing ZIKV antigens should be technically feasible and would potentially result in faster vaccine development because of the use of regulatory pathways established for these platforms during JEV and DENV vaccine development. Before these platforms enter clinical evaluation, nonclinical evaluation must be conducted, which is hampered by the lack of a validated animal model.

Discussion

Zika virus has been declared a public health emergency. As many as 1.3 million persons have been affected in Brazil alone and 20 countries or territories have reported local transmission of the virus during 2016. Prevention measures (specifically, vector control) are a current priority, pending advances in diagnostics; the World Health Organization and the Pan American Health Organization have issued recommendations.

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