

ZIKV: What do we know about this Virus?

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Abstract

The emergence of Zika virus alerts clinicians about the existence of an unknown before viral infection which if undiagnosed timely can result in unwanted and even catastrophic consequences for the public health system and the individuals. Currently, there are six hundred sixty one cases of the virus detected in the United States and US Territories. This virus is one of the causes of a birth defect-microcephaly, is especially dangerous for pregnant women and women who are planning to get pregnant, can be transmitted through mosquito bites, sexually, perinatally, and through blood transfusions, and recently found to be an additional cause of a debilitating neurological disease Guillain-Barre syndrome.

Keywords: Zika virus; Aedes mosquitoes; Microcephaly

Introduction

What is Zika virus? It is a single-stranded RNA arbovirus from Flaviridae family and Flavivirus genus containing ten thousands seven hundred and ninety four nucleotides encoding three thousands four hundred and nineteen amino acids. It is related to dengue, Yellow fever, West Nile, Spondweni viruses, and the next siblings are Ilheus, Rocío, and St. Louis encephalitis [1,2]. Its virion structure is limited by a host-cell endoplasmic reticulum-derived lipid envelope, surrounding a nucleocapsid with still undefined structure and symmetry, composed of the protein C and viral genome. The viral envelope contains the two surface proteins (M and E) and the viral genome additionally encodes several non-structural proteins with enzyme activity (NS3: RNA-helicase and protease and NS5: RNA polymerase, RNA-dependent) or with regulatory functions (replication, transcription, transduction and immune response control) during intracellular replication [2].

Discussion

The very first isolation happened in western Uganda in April, 1947 in the Zika Forest located on Lake Victoria, about 15.5 miles east of the Uganda capital, Kampala during sentinel rhesus monkey exploratory program started in 1946 by East African Virus Research Institute in the Bwanba County to study yellow fever virus immunity in rhesus monkeys in the forest. One of the yellow fever study rhesus monkey 766 who was kept on a wooden platform and observed daily, had a spike of fever on 04/18/1947 and 04/19/1947. The serum sample taken from monkey was injected into mice intra cerebrally and intraperitoneally; mice had

shown signs of sickness on the tens day of the inoculation. Another Rhesus monkey 771 who also was injected with the same serum remained healthy. The agent isolated in the Entebbe laboratory from sick mice was named Zika virus (strain 766) and, lately, was neutralized by the serum antibodies of the same Rhesus 766 monkey [3].

The second isolation was done utilizing eighty six Aedes (Stegomyia) Africanus (Theobald) mosquitoes caught in January, 1948 in the same Zika Forest for the purpose of isolation of yellow fever virus; the catch was transferred to the Entebbe laboratory where mice and Rhesus 758 monkey were injected with a solution which mosquitoes were centrifuged in. The monkey stayed healthy again displaying just insignificant temperature changes while some mice died and some became significantly sick but survived. This second strain incidentally isolated in a place of yellow fever virus became known as Zika virus (758 strain) and was neutralized by the serum antibodies of Rhesus 758 monkey [3].

Later on, in 1958 in the Lunyo Forest and in 1962-1963 in the Zika Forest Zika was isolated from other mosquito species such as Aedes apicoargenteus, Aedes luteocephalus, Aedes aegypti, Aedes vittatus, and Aedes furcifer, Aedes albopictus, and Aedes hensilli, and suggested that some species play role in ZIKV enzootic maintenance within the sylvatic cycle (in which mosquito becomes infected by biting one monkey and then reinjects the virus into another monkey) [2,3]. In general, most authors agree that modes of transmission in monkeys are a sylvatic cycle, and in humans are primary-through Aedes mosquito's bites.

It is established that virus can be transmitted sexually, perinatally, and through blood transfusion according to Centers of Disease Control recent publications. Two confirmed cases of sexual transmission were reported to CDC during February 2016. In the first case a man who returned from a ten-days trip to the Caribbean developed Zika-associated symptoms, had unprotected vaginal intercourse with his female partner on a second day of the disease; his female partner who had no history of travel or mosquito bites developed a febrile illness thirteen-fourteen days after the intercourse; RT-PCT assay detected Zika virus RNA in woman's serum. The similar case was reported when a man after returning from four-weeks trip to Central America developed conjunctivitis, fever, rash, and arthralgia; had unprotected sex with his female partner on the eighth day of disease, and the woman developed febrile illness displaying symptoms characteristic for ZIKV infection [4].

Another CDC publication has a description of study performed in French Polynesia from November 2013 to February 2014 for the purpose of developing specific nucleic acid testing (NAT) to detect the virus in blood donors, confirmation of the possibility of transmission of ZIKV through blood transfusions, and to alert the healthcare authorities about this fact [5]. The French Polynesia has experienced the largest reported outbreak of ZIKV infection started in October 2013 with estimated twenty eight thousands cases (11% of the population) concomitantly with circulating dengue virus of serotypes 1 and 3. Since it was established that other arboviruses such as dengue, chikungunya, and West Nile can be transmitted through blood transfusions, the attention was directed to implement precautions to prevent similar mode of transmission of ZIKV. The study reports the detection of ZIKV in forty two of one thousand five hundred and five blood donors who were asymptomatic at the time of blood donation. Blood donor samples were tested in mini-pools with no more than three blood donors including in each pool. ZIKV NAT was implemented routinely starting January 13, 2014. RNA was extracted from 200 ml of mini-pooled sera using the French-manufactured the Easymag extraction system. ZIKV RT-PCR real-time was performed on a CFX Biorad PCR analyzer using two real-time primers/probe amplification sets specific for Zika.

The sensitivity of the assay was controlled by amplifying serial dilutions of an RNA synthetic transcript that covers the region targeted by the 2 primers/probe sets. A sample was considered positive when amplification showed a cycle threshold (Ct) value <38.5 and, at least on prime/probe set was controlled by individual RT-PCR to avoid false negative results due to pooling. From five hundred and thirty five mini-pools tested, sixty one were found positive with, at least, one Ct value <40. Asymptomatic on the moment of blood donation Zika-positive donors were contacted, and eleven out of forty two declared that they had Zika-like syndrome from three to ten days after they gave blood. The findings of this study suggest that ZIKV NAT should be used to prevent blood transfusion-transmitted ZIKV. In area endemic for Aedes mosquitoes a preparedness plan to respond to future

outbreaks of ZIKV infection should include emergency plans to sustain blood supply [5].

Two cases of perinatal transmission were reported in French Polynesia in December 2013 and February 2014: in a first case, mother had illness on a moment of labor and delivery, the newborn displayed no signs of sickness later, but both were tested positive for ZIKV. In second case, mother developed symptoms of ZIKV infection on a 3rd day after labor and delivery, the baby displayed insignificant diffuse rash, they also were tested positive for ZIKV. It was suggested that the possible routes of transmission are transplacental, during delivery, during breastfeeding, and by close contact between mother and a newborn [6].

One of the most recent and comprehensive study of microcephaly in babies written by the faculty members of the University Medical Center, Ljubljana, Slovenia and published on February 10, 2016 at NEJM presents a case of vertical transmission of ZIKV in a 25-years old woman from Brazil who became infected with Zika at her first trimester of pregnancy and presented to the Department of Perinatology at the University Medical Center in Ljubljana, Slovenia at her thirteen week of pregnancy. The study states that pregnancy was electively terminated at thirty two weeks of gestation after the fetus was given a poor prognosis for neonatal health due to severe brain disease and microcephaly discovered on series of ultrasounds; fetal tests were performed analyzing fetal blood, cerebrospinal fluid, body and brain tissues. On fetal autopsy the most prominent histopathological features were multifocal collections of filamentous, granular, and neuron-shaped calcifications in the cortex and subcortical white matter with focal involvement of the whole cortical ribbon. A complete ZIKV genome sequence (ten thousands eight hundred and eight nucleotides) was recovered from brain tissue, similar to how it was isolated in 1947 from intracerebrally injected mice.

Phylogenetic analysis showed the highest identity (99.7) with the ZIKV strain isolated from a patient from French Polynesia in 2013 and ZIKV detected in San Paolo, Brazil, in 2015, followed by a strain isolated in Cambodia in 2010 (98.3% identity) and with strain from the outbreak in Micronesia (with 98% identity). Electron microscopy analysis detected spherical virus particles in the brain with morphologic characteristics consistent with viruses of the Flaviridae family. Prenatal ultrasounds demonstrated intrauterine growth retardation (estimated third percentile of fetal weight) with normal amniotic fluid, placenta with normal size in thickness with numerous calcifications, microcephaly, moderate ventriculomegaly, and transverse cerebellar diameter below the second percentile along with blurry brain structures [7].

The case-control study performed in the hospital in Tahiti, French Polynesia during the outbreak of Zika between October, 2013 and April, 2014 on forty two patients diagnosed with Guillain-Barre syndrome to exclude the possible connection between Zika virus and GBS. Forty one patients (98%) had anti-Zika virus IgM or IgG and all (100%) had neutralizing antibodies against Zika. 39(93%) with GBS had Zika virus IgM and thirty

seven(88%) had experienced a transient illness before the onset of the neurological symptoms (about six days) suggesting recent Zika infection. The most unusual presentation of GBS in this case was a rapid progression (four to six days) of the disease comparing to GBS of autoimmune etiology (two to four weeks). The antiglycolipid antibodies hypothetically involved in the pathogenesis of GBS were found only in 31% of patients which pointed out to the possibility of Zika-associated GBS triggered directly by viral infection rather than autoimmune reaction. The interpretation of this first study providing evidence for Zika virus infection causing GBS supports the need for health facilities of at risk countries to be prepared to manage patients with GBS by creating adequate intensive care units with sufficient number of beds and equipment [8].

Conclusion

There are no commercially available tests for the serological diagnosis of Zika virus infection. Zika virus infection may be diagnosed by reverse transcription polymerase chain reaction (RT-PCR) directly from virus RNA in patient's serum, it is the most sensitive and specific method for the diagnosis and preferably has to be obtained up to the six day of the disease. IgM antibodies may be found from the third day of the disease onset; IgG antibodies should be looked for in the acute and convalescent serum. ZIKV RNA has been detected in saliva, nasopharyngeal swabs, urine and semen [9]. The cross-reactivity related to dengue and chikungunya viruses may represent the diagnostic challenge, even the use of a plaque reduction neutralization test (PRNT) is unable to differentiate possible causes of Zika infection in patients with previously acquired anti-dengue or anti-chikungunya antibodies.

Elevated lactic dehydrogenase and C-reactive protein levels were reported in some cases. Low-grade leukopenia and thrombocytopenia may occur. The differential diagnosis is mainly established with dengue and chikungunya viruses, and, even though the Centers for Disease Control and Prevention list arthralgia, myalgia, rash and conjunctivitis as symptoms of predominantly Zika infection, arthralgia was observed more frequently during chikungunya virus', and myalgia during dengue virus infections rather than Zika's [2]. For the Americas the alphaviruses Mayaro virus, Oropouche virus and equine encephalitis virus as well as West Nile virus and La Crosse encephalitis virus may be considered. Malaria and rickettsioses may be taken into account. Other acute viral infections including influenza, rubella and measles should be considered as well [9].

Physical exam is limited to maculopapular generalized rash, low-grade fever, bilateral conjunctivitis; patient might also complain of anorexia, vomiting, dizziness, and periorbital pain [2]. If suspected, specimens of blood work, cerebrospinal fluid, or fresh-frozen tissue, according to CDC guidelines for handling specimens, are be forwarded to DVBD Arbovirus Diagnostic Laboratory in Fort Collins, CO, and results usually are available in three weeks after specimen gets received. CDC requires all result to be reported to the appropriate state health department [10].

There is no specific treatment of ZIKV virus infection at present, and it is mostly symptomatic with avoidance of aspirin until dengue infection is ruled out to prevent the risk of hemorrhage. Bothersome pruritic rash can be managed with menthol lotions, calamine, and cold bath. Topical corticosteroids should be avoided because of unclear efficacy. The most serious and dreadful complication of ZIKV such as Guillain-Barre syndrome should be approached conventionally, patient has to be monitored in intensive care unit because of risk of respiratory muscles paralysis, and plasmapheresis and IVIG remain treatments of choice to shorten time to recovery [2].

Prevention of this virus from spreading initially is based on a common sense and familiarity with modes of transmission. The removal of larval breeding sites of vector mosquitoes is extremely important if use of insecticides is limited by any financial, logistic, regulatory, religious, or other constraints. Individual protection measures are encouraged involving the use of insect repellents, window and doors screens to keep mosquitos outside [2], use of condoms for men having sex with someone who travels to or lives in the area infected with ZIKV, treating clothing with permethrin or permethrin-containing solution, wearing of long-sleeves clothing while being in areas endemic for mosquitoes, and avoidance of travel to the epidemic areas by pregnant women or women who are trying to get pregnant. The governmental role in prevention of this virus as well as other infectious diseases from spreading traditionally belonged to Centers for Disease Control and Prevention, but presently the Obama administration supported by the House of Representatives is planning to join the fight with ZIKV by investing \$1.9B starting in September 2016 in prevention measures and researches. Currently, in March and April 2016 new alerts and notices were issued for travelers to Aruba, Puerto-Rico and Fiji Islands, and the new guidelines recommended for health agencies in the USA and around the globe.

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