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A review of Zika virus: Pathogenesis, Clinical presentation and Development in research

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ABSTRACT

Zika virus was isolated from a rhesus monkey placed by British scientists working at the Yellow fever, maculopapular rash, arthralgia and conjunctivitis. Additionally, in pregnant women, fetal neurological cFever Research Laboratory located in the Zika forest area of Uganda, hence its name, and is transmitted chiefly by the mosquito vector, Aedes aegypti. Moreover, the three-fourth population of Yap was infected by this virus in 2007 and afterwards, it spreads in French Polynesia in 2013. Furthermore, its symptoms are mild consisting, complications include brain damage and microcephaly. However, virus associated Guillian-barre syndrome is common in adults. Initially, it was a belief that this virus can only be transmitted through mosquitoes but when the semen of a patient in Texas was isolated then it reveals that it can be transmitted sexually too. There are no as such remedies available for the treatment of Zika Virus infection, only preventative measure is available. In the present article we aimed to review the pathogenesis, clinical manifestations, current progress in research and prevention and treatment of Zika virus.

KEY WORDS: Zika virus, Mosquito vector, Microcephaly, Prevention and treatment.

1. INTRODUCTION

Zika virus (ZIKV) is a member of Flaviviridae family. The virus carries the name of the forest where it was first identified (Dick, 1952), a name that means "overgrown" in the Luganda language (Emerg Infect Dis, 2014). Apart from ZIKV, the genus flavivirus contains 52 more viral species which includes yellow fever, dengue, Saint Louis encephalitis and West Nile viruses. Moreover, this infection occurs in the apparent absence of any environmental or inherited cause in Africa and Asia. It has been suggested that ZIKV infection is spread within these continents. Besides Aedes aegypti, other Aedes species such as culex species (Vogel, 2016; Franchini, 2016) has promoted Zika Viral infection (Prada P, 2016). Zika virus was firstly isolated in African in 1947 from rhesus macaque monkey when some American scientists were working on yellow fever syndrome in Zika forest of Uganda in Africa. Soon after the discovery, ZIKV was observed to infect humans (Macnamara, 1954). More recently, introduction of ZIKV into Human Population has yielded rapidly spreading outbreaks in umpteen pacific island clusters such as French Polynesia, Easter Island, Cook Island, Micronesia and thereafter, it reaches the Haiti (Americas) (Malone, 2016) has spread subsequently to Brazil, the Caribbean, and worldwide via travellers visiting affected regions. The Phylogenetic analyses discovered that ZIKV has two main virus lineages i.e African and Asian. The research by (Nicolas, 2014) suggested that a different ZIKV subtype of the West African circulated in the Aedes species in Central Africa. Moreover, molecular evolution studies unconcealed that ZIKV might have undergone umpteen natural recombination events, which is a distinct feature with respect to other members of genus flavivirus. It was observed in the genetic material of the mosquito cell that it adopt, a genetic change which includes the recurrent loss and profit of N-linked Glycosylation site in the E-protein which has been suggested that this genetic change could be related to mosquito-cell infection tendency (Faye, 2014). A growing number of ZIKV genome sequence are determined and their phylogenic link with respect to other members of the flavivirus genus revisited in the recent epidemics in the Americas (Freire, 2015; Calvet 2016).

Transmission cycle: The virus transmitted through Mosquitoes to Monkeys or vice verse and this type of transmission is known as Epizootics. In the beginning, mild responses such as fever and fatigue were associated with Zika virus infection, later on; pregnant women especially Brazillian women were tested positive for the Zika virus infection and had foetuses born with brain defects. Additionally, Zika virus infection is associated with Guillain-barre syndrome (Lednicky, 2016). Experts reckon that the virus was stuck into Brazil during the World Cup soccer competition in 2014, during which four Pacific countries viz., New Caledonia, French Polynesia, Easter Island, and Cook Islands in which ZKV spread in 2014 had teams participating in this competition (Bogoch, 2016). With more than 2.7 Million arrivals from Brazil to the United States Furthermore, an abrupt upliftment in the counts of infants born with microcephaly and the amniotic fluid of affected infants contain single-stranded Positive RNA virus during detection. The Symptom of Primary microencephaly is a significant degree of decrease in the head circumference of the newborn and is associated with different levels of impairment in the motor, sensory and cognitive functions. Microcephaly includes the reduction in the production of neurones during the development of the brain in the uterus which further results in impaired proliferation of cortical progenitor cells or decrease in its count of cell divisions. Moreover, flavivirus genus contains members which are neurotrophic in nature and could cause an exceptional case of brain infection in infants. Apart from it, nearly about 2500 babies have infected with Zika virus-induced microcephaly in Brazil. This rare, devastating, and

incurable complication of the fetus was declared a public health emergency of international concern (Musso, 2015; Oliveira, 2016; Ventura, 2016). The neurotropism of the virus was recognized early and this has been evident in the recent rise in microcephaly incidence in Brazil (Petersen E, 2016). ZIKV can be transmitted via infected female mosquito during its blood sucking. Moreover, ZIKV is also detected in breast milk of the infected mother (Besnard M, 2014). Appropriate caution should be taken regarding the risk of contamination by the blood transfusion for ZIKV and arboviruses that co-circulate in the American continents such as DENV and CHIKV (Aubry M, 2015). ZIKV was isolated from the semen of a patient several weeks after the acute phase of the disease (Musso, 2015), and a case of sexual transmission has been reported (Foy, 2011). Due to the risk of sexual transmission of ZIKV, men are recommended to use a condom during sexual intercourse with his partner, especially if his partner is a pregnant woman (Oster, 2015). ZIKV RNA and/or protein have also been detected in urine (Gourinat, 2016), saliva (Musso, 2015), amniotic fluid (Oliveira, 2016) and placental tissues (Martines, 2016), highlighting the possibility of other modes of transmission.

Diagnosis: The Zika virus infection's diagnosis has been a herculean task. The Zika virus disease infection symptoms can easily be confused with those of another arbovirus induced diseases due to its non-specificity. Therefore, the differential diagnosis is important. In vitro detection of ZKIV can be done by detection of virus, viral nucleic acid, viral antigen, or antibody or by a collaboration of these techniques. However, the method of detection is decided on the basis of detection required such as clinical, epidemiological study, or vaccine development. Moreover, the type of laboratory facilities and expertise available is also a matter of concern prior to initialization detection. A test for the detection of viral or nucleic acid was done after collecting the sample from the patient in the initial days after the onset of symptoms. The virus detection is based on isolation from cell culture (using mosquito or mammalian cell lines), directly from mosquitoes, or intracerebrally from newborn mice (Dick, 1952; Buathong, 2015; Fonseca, 2014; Berthet, 2014). However, virus isolation is restricted to specialised laboratories and is rarely successful. The low levels of viremia may explain this difficulty with the isolation (Lanciotti, 2008). For the detection of viral RNA, molecular techniques, such as conventional or real-time RT-PCR, have been developed (Lanciotti, 2008; Balm, 2012; Faye, 2008; Faye, 2013). Additionally, serological testing is done to detect the Anti-ZIKV IgM and IgG antibodies. Usually, ELISA or immunofluorescence can be used for the detection of IgM antibodies from day five to six after the onset of symptoms. However, it can be detected as early as the third day of symptoms produced (Lanciotti, 2008; ECDC, 2015). RT-PCR technique for the early and rapid detection and identification of flaviviruses, including Zika virus, were established as early as 1994 (Pierre, 1994). Originally primers were originated from the NS5 gene's nucleotide sequences or from the 3'non-coding region. In 2008, an RT-PCR protocol utilising sequences encoding the envelope protein region was developed. However, 7.7pfu per reaction was detected and it is determined that the methodology was 100% sensitive in serum. However, it is found to be specific when it was failed to amplify genomes of nineteen other flaviviruses (Faye, 2008). The NS5 gene region displays a high degree of conservation among flaviviruses and therefore, chosen for primer development, whereas envelope protein genes may differ within a mono flavivirus and thus present false negative data (Balm, 2012). The real-time reverse transcriptase PCR (RT-PCR) shows a quick and quantitative method to detect and evaluate the existence of Zika virus in mosquitoes. It is now recommended that RT-PCR testing must be done within the first 6 days of the onset of illness. It is also reckoned that in the initial phases of the infection, the virus is present in its peak concentrations in the saliva, but that existence can be more persistent in the urine, thus detection should be done from one of these two specimens (Gourinat, 2015). The concentration of IgG and IgM obtained from titration to Zika virus claims inaccurate results rates in higher quantity in patients live in the regions containing flaviviruses such as dengue, chikungunya, yellow fever virus etc. However, plaque reduction neutralisation testing (PRNT) is useful to differentiate between cross-reacting antibodies. A study from the investigators in France and french Polynesia discovered the prevalence of seropositivity to different related arboviruses over the tenure of three years from 2011 to 2013 in which overall seropositivity rates for the Zika virus came out to be 0.87%, 1.5% for West Nile virus, 1.3% for Japanese encephalitis and 80.3% for at least one of the four dengue virus serotypes (Aubry, 2015).

Pathogenesis: Zika virus belongs to the family Flaviviridae and the genus Flavivirus. Flaviviruses categorised to viruses labelled as "arboviruses", which is a descriptive term that pertains to a century of RNA viruses which rely upon arthropods like mosquitoes or ticks for transmission (Tetro, 2016; Choumet, 2015). Arboviruses (arthropod-borne viruses) are the cause of umpteen fatal diseases in Homo sapiens and fauna worldwide. Additionally, the families of RNA arboviruses contain Bunyaviridae, Flaviviridae, Reoviridae, Rhabdoviridae, and Togaviridae. The arboviruses are acquired orally by their hematogenous vectors in the shape of a blood meal of an infected vertebrate host. These viruses are non-pathogenic to the vector but have to be able to live on in a live form in the vector which then transmits via saliva deposition into a new vertebrate host. The tendency of the vector to induce infection incorporating the Zika virus depends upon the cycle through which it infect the host cells and this is inevitable to be taken into consideration in order to know that whether the virus replicates with the vector host and even prior to that it is required to know that how do virus survives in the vector host, and if replicated, then it is important to know the kind of cells are infected with the vector. Moreover, it is essential to find out that whether the virus manipulates its structure through any means into any kind like

glycosylation of its envelope (Faye, 2014).There is a total of seven groups of mosquito-borne flaviviruses, according to the International Committee on Taxonomy of Viruses. The genus flavivirus consists of 39 different mosquito-borne viruses (Thiel, 2005).

Structure: Zika virus is made up of a positive-sense, single strand RNA genome. The Zika virus is a positive polarity RNA virus with a genomic size of about 11 kb (Marano, 2016). Moreover, the single open reading frame sequence of its RNA genome encodes a polyprotein (Weissenbock, 2010) that contains 3 components, including a capsid (105 aa), a premembrane portion (187 aa) and membrane termed C, P and M respectively. Additionally, there are additional 7 divisions that are non-structural (NS) and an envelope protein (E, 505 aa). These seven proteins are designated NS1 (352 aa), NS2a (217 aa), ND2b (139aa), NS3 (619 aa), NS4a (127 aa), NS4b (255 aa) and NS5 904 aa) (Baronti, 2014), which plays an important role in viral genome replication, counteraction of host innate antiviral response and polyprotein processing. However, the envelope protein is the primary flavivirus antigenic part which brings down adherence of the virion and entrance into the host cell. Moreover, folding of the E protein is regulated by the premembrane protein, which is cleaved by furin to synthesise the membrane protein before to mature virion discharged from the cell (Lindenbach, 2003).

Genome: There is two known pedigree of the Zika virus, an African lineage and an Asian lineage (Duffy, 2009). These are differentiated by intense genetic investigation of the RNA sequence (Haddow, 2012). Primary variability, when comparing strains appears to be related to the dispute in the availability of potential glycosylation sites. However, three Zika viruses were isolated from Sylvatic mosquitoes in the Central African Republic which represented 99.9% and 100% nucleic acid sequence and amino acid sequence homology with each other respectively, but were different from other Zika strains. In pithy, it was concluded by the authors of this study that while these virus strains belong to an African lineage, there exists a contrary West African Zika virus subtype in Central Africa from the African strains found in other countries such as Gabon (Berthet, 2014).

Clinical manifestations: About two weeks are required by the symptoms of ZIKV infection to be exposed after the host has been bitten by the mosquito. However, the requirement of the hospitalisation is not common in the case of ZIKV infection though the symptoms of ZIKV are very similar to the dengue-like disease but in a mild form. Apart from this, more than seventy cases of Guillian-barre syndrome and other problems related with neurones have been admitted in French Polynesia which is linked with ZIKV infection (Fauci, 2016). Due to 20-times upliftment in the cases of microcephaly over the tenure of one year between 2014 and 2015 in Brazil epidemic of ZIKV led the public health officials to conclude that this practice is happening because of ZIKV in the pregnant women. There is no indication which can straightaway connect the nexus between microcephaly and pregnant women. Nevertheless, health officials suggest all expecting women take cautiousness in preventing mosquito bites and even to hold up pregnancy. It has been reported by the Brazilian research ministry that the highest risk of ZIKV induced microcephaly and malformations has occurred over the first trimester of pregnancy (Dick, 1952).

Complications:

Pregnancy, Microcephaly and the Zika virus infection: In 1952, Dick introduced the Zika virus genome into the mice intraperitoneally which results in increment the virus concentration and thus the pathological properties of Zika virus were firstly observed (Bell, 1971). It was depicted by this research that Zika virus could penetrate the blood-brain barrier. However, the research findings were complemented by bell and colleagues in 1972 when they observed the progression of the disease in the infected mouse brain (Dreux, 2010). According to their findings, intracytoplasmic inclusions were produced by the infected neurones and ganglia and these inclusions were named as “Virus factories”. Moreover, these factories were originated from the endoplasmic reticulum and associated with other organelles including the nucleus and the mitochondria.Those microscopic observations describe what we now know as autophagy. This was discussed by travassos and Carneiro in this issue and they demonstrated that this cellular process is made to ensure cell homoeostasis through entrapment and eventual degradation of the unwanted cellular material. However, viral infection was combat with this mechanism although the efficiency is varied as a result of viral regulatory mechanisms (Blazquez, 2014). In the case of flavivirus infection, interactions between the virus and the Endoplasmic Reticulum induce autophagy (Jheng, 2014). The process of autophagy is prevented by these viruses and a state of flux is created which provides an appropriate environment to viruses to establish a viral factory and to uplift the viral replication up to the zenith and then amplification (Dreux, 2010). Although, Zika virus infected neural cells did not possess autophagy whereas experimentally induced infect fibroblasts have shown autophagy and the biological process is hijacked by the virus for replication (Thornton, 2009). Some evidence has been provided by this study that supports the involvement of zika virus in the other cell lineages as seen by Bell (1971), in neural cells (Dreux, 2010). Defective function of centrosomes is one of the reasons behind microcephaly (Marthiens, 2013). It has been unconcealed that amplification of centrosome number is one of the reasons which causes this situation (Liang, 2008). It is involved in the initiation and maturation of auto phagosomes as well as centrosome and chromosome stability (Zhao, 2012; Mathew, 2007). Another is Beclin-1, which plays an integral role in autophagy and is known to contribute to chromosomal stability in cancer cells (ECDC, 2016). In the reference to neural brain development, a delay in mitosis, an upliftment

in apoptosis, defective neural stem cell orientation, immature neuronal differentiation, and a decrement in progenitor cells are the results of increment in centrosome number in mice (Zhao, 2012). The overall consequences of all above lead to the reduction in the formation of brain content leading to the depleted brain size which indicates microcephaly. In spite of all above, there is no as such evidence to prove that whether the microcephaly is induced by zika virus infection or not and thus future studies need to be performed so that a solid link can be established.

Guillian-barre syndrome and other neurological complications: Umpteen countries in the Americas have delineated unexpected increment in victims of Guillian-barre syndrome (GBS) in collateral with the ongoing Zika virus outbreak (Dirlikov, 2016; Pan American Health Organization, 2016). The increases in the pace of GBS in union with Zika virus infection has also been observed in other surveys (ECDP, 2016; Pan American Health Organization, 2016; Oehler, 2014; Cao-Lormeau, 2016; Paploski, 2016; Karimi, 2016). A case-control study in French Polynesia assess the connection between GBS and Zika virus infection for a time period of one year viz., 2013 to 2014 epidemic which involve cases with 42 patients investigated with GBS; one control batch involved 98 patients with nonpyrogenic illness which were matched for age, sex and residence and another control group held with 70 Zika virus infected patients which did not show neurological problems (Brasil, 2016). Moreover, 93 percent of GBS patients were detected positive with Zika Immunoglobin (Ig) M versus 17 percent of patients in the first control batch; serologic evidence obtained from former dengue infection was identical among all three batches. Less than 50 percent of GBS cases were accommodated with Anti-glycolipid IgG antibodies. 88 percents of GBS patients were detected with Zika virus infection; the time period between the viral syndrome and onset of neurological symptoms was six days. Intravenous immunoglobin was given to all GBS cases and intensive care was provided to 38 percent of cases whereas 29 percent of cases were facilitated with respiratory care as per their need; all survived. The occurrence of GBS throughout the ZIKV outbreak was projected to be 2.4 cases/10,000 ZIKV infections.

Haemorrhagic complications: Moderate haemorrhagic symptoms such as petechiae, minor mucosal bleeding was reported in 21% of 119 ZIKV infection cases that reported in Rio de Janeiro, Brazil, January–June 2015. Haematospermia was detected in men with ZIKV infection (Burke, 2016). Moreover, laboratory tests are usually in the normal range, considering blood cell and platelet counts and liver and kidney function tests. Umpteen cases which involve severe bleeding disorders are linked with leucopenia, mild thrombocytopenia and incremented transaminases are reported with reference to Zika virus infection; required hospitalisation (Foy, 2011).

Prevention and Treatment: In order to prevent the further transmission of Zika virus infection, health specialists advised pregnant women to avoid travelling to that area where Zika virus infection has occurred, already going on or are prone to the same. However, in case if the travelling to such areas is unavoidable due to certain circumstances then they have provided some guidelines to follow strictly such as usage of mosquito repellent creams, wear long-sleeved shirts and trousers, permethrin-treated clothes and avoid exposing the body to surrounding as much as possible (Petersen, 2016; Brasil, 2016). Moreover, men are advised to use condoms during intercourse and women to avoid pregnancy in prone areas and for 28 days even after returning to United Kingdom. Additionally, any pregnant woman who has been entered into the nation of UK after travelling from Zika virus-Infected region is advised to have a checkup from the obstetrician or from a general physician (Petersen, 2016). Apart from all above, if a pregnant woman who has been detected positive with RT-PCR Zika virus infection then she has to consider proper Ultrasound check up of her body as well as her foetus for about one month followed by amniocentesis for the detection of viral bodies in amniotic fluid and other neonatal infection (CDCP, 2016; Thomas, 2016). Some guidelines have been revealed by the Centre for Disease Prevention and Control to cure Zika virus infection such as taking appropriate rest, incrementation of fluid uptake to prevent dehydration, fever and pain relief medicines and NSAIDs are avoided to be administered. Surprisingly, a study illustrated that the ZIKV inactivation in Fresh-frozen plasma is possible using Ultraviolet an illumination and amotosalen (Aubry, 2016; Fauci, 2016).

2. CONCLUSION

In nutshell, it can be said that, there is no as such remedies available for the treatment of Zika Virus infection yet, only preventative measure are available and therefore, thorough research is required in this area. However, it can be expected that suitable drugs and vaccination to cure the same will be available in the near future.

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