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Introduction

Zika virus belongs to *Flaviviridae* family which is spread via *Aedes* mosquitoes namely *A. aegypticus* and *A. albopictus*. It was originally discovered in 1940s in a monkey in the Zika forest of Uganda. Since then till 2007, about 14 cases of Zika virus have been reported globally. (Reynolds, 2017). Due to similar symptoms as compared to other diseases, Zika has been potentially thought to be underreported. However, in 2016, Zika virus was declared a public health emergency due to the increased incidence of Gullian Barre Syndrome (GBS) and microcephaly in the Americas (Broutet et.al, 2016; Johansson et. al, 2016; dos Santos et. al, 2016).

As per CDC, what makes Zika infection very dangerous is the inability of clinicians to detect infections early on due to the lack of symptoms or presence of nonspecific symptoms like fever, maculopapular rash, arthralgias and ocular symptoms including conjunctivitis. These symptoms are found in other closely related viral infections including dengue fever and Chikungunya. In addition, most patients have no or only mild to moderate symptoms initially; thus, they don’t usually get sick enough seek medical care. In addition, many cases have been documented in which women affected with ZIKV have presented with spontaneous abortions or miscarriages (Burnett, 2016; van der Eijk et. al, 2016). The most important information in terms of clinical diagnosis is a thorough history which includes travel to endemic areas of Africa, Central or South America or exposure to individuals who have travelled to these areas where Zika has higher incidence & prevalence.

Finally, the most important point for Zika Virus is its high perinatal and antenatal morbidity and mortality rate secondary to microcephaly and its associated neurological damage. In terms of pathogenesis, previous research has demonstrated the following possible mechanism: transmission through infected mosquito via bite, sexual contact from mother to baby à followed by invasion of viral particles through dermal cellsà crossing of placental barrierà placental macrophages that enable viral entry leading to fetal infection and consequences such as microcephaly (Olagnier et.al, 2016; Musso et. al, 2016; Furtado et. al, 2016; Faizan et. al, 2017). Molecular pathogenesis include various intracellular phenomena: transcriptional dysregulation, impaired neurogenesis secondary to high TLR3 mediated innate response and change in intracellular pH status post infection of the virus. (Faizan et. al, 2017).

Prior to October 2015, the number of babies born with microcephaly secondary to Zika virus infection has increased almost 70 fold, from 156 per year to 4000 per year along with increased incidence in US (Goodman et.al, 2016). Consequently, preventative strategies and vector control needs to be incorporated in endemic areas along with physician education in order to keep a high index of suspicion for a possible Zika infection in their daily patient care (Kline et.al, 2016).

Correspondence: Smit Shah, MS-3, Rutgers Robert Wood Johnson Medical School, NJ, USA
Email: spshah1991@gmail.com
Methods

We performed a literature review of case reports, public health articles, newspaper trade publications, academic journals, review papers, case reports and CDC data from 2001 to 2017 in order to gather adequate information to fulfill the above-mentioned goals. We specifically focused on articles: (1) that describe different hypothesis of ZIKV pathogenesis, (2) various mice models used to study ZIKV susceptibility that could be extrapolated to human models, (3) various therapeutic methods and targets that could be used to either prevent the progression or infection of cells from ZIKV and (4) statistics based on latest prevalence and incidence of ZIKV across different countries including US.

Discussion

Based on our literature review, we found many interesting points about the pathogenesis and presentation of Zika virus infections. Research by Weger-Lucarelli et.al demonstrated three strains of Zika virus, taken from different parts of world, can replicate independently in the A. aegypti mosquitoes (Weger-Lucarelli et. al, 2016; Li et. al, 2016). Of these, two strains from Africa demonstrated high rate of infectivity as compared to the currently present American strain (Weger-Lucarelli et.al, 2016). In addition, many closely related species to Zika virus have been found. For instance, Haddow et. al. found Spondweni virus strains which are closely related to Zika virus (Haddow et.al, 2016). Spondweni viruses are another member of Flavivirus family but were found to be separate species as compared to Zika virus (Haddow et.al. 2016). However, Spondweni viruses have limited potential to cause infection in urban environment unlike Zika, yellow fever and dengue viruses most likely due to differences in vector transmission and ecological survival (Haddow et.al. 2016). Further insight into pathogenesis was gained by Donald C. et al who found sub-genomic Flavivirus RNA inhibits Type I IFN which possibly plays an extremely important role (Donald et. al, 2016).

Clinical presentation of Zika virus infection can be similar to symptoms of dengue and chikungunya viruses (Donald et. al., 2016). In addition, Zika virus infection is associated with GBS and microcephaly (Donald et. al., 2016; Parra et. al., 2016; Frieden et.al. 2016). Recent studies have demonstrated significant incidence of microcephaly in pediatric patients whose mothers were exposed to Zika virus between the 14th to 17th weeks of pregnancy (Jaenisch et. al., 2016). Based on Johannsson et.al., the estimated risk of microcephaly was found to be 0.95 percent (Confidence internal 0.34 to 0.91) between 2013 and 2014 during the first trimester of pregnancy secondary to 8 major microcephaly cases documented in French Polynesia amongst the population of 270,000 people with an overall estimated Zika virus infection of sixty six percent (Jaenisch et. al., 2016; Cauchemez et. al. 2016). In addition, they also found a delay between the Zika outbreak and incidence of microcephaly most likely secondary to 1st trimester exposure in pregnant women who were full term during their time of diagnosis (Jaenisch et. al., 2016). Microcephaly in cases of Zika virus infection is defined as head circumference 2 to 3 standard deviations below the mean and it varies based on age, gender and ethnicity of pediatric patients (Trier, 2016).

From a clinical standpoint interesting case reports have documented the presence of uveitis in patients with Zika virus infection (Kodati et. al, 2017; Furtado et. al, 2016). For instance, patients infected with ZIKV were found to have high ZIKV titers in the anterior chamber specifically aqueous humor in the infected eye which had conjunctival hyperemia along with keratotic precipitates that resolved with 1 week of treatment with glucocorticoids (Kodati et. al, 2017; Furtado et. al, 2016). These case reports could potentially point to the role ZIKV medial chorioretinal damage that could contribute to visual impairment in affected patients. (Kodati et. al, 2017; Furtado et. al, 2016).

In addition, various animal models have been proposed to explore the potential role of cross placental transfer of Zika virus during pregnancy (Tripathi et. al, 2017; Becker, 2016). By using mice deficient in anti-cytokine responses i.e. transgenic AG 129 mice, researchers are currently trying to find various birth defects that Zika virus can potentially cause in addition to microcephaly (Becker, 2016). From a preventative standpoint, the lag time and time to diagnosis varies amongst various regions of the world. For instance, from a study by Zhang et. al. the minimal incubation period for 9 imported Zika virus cases in China was 5.2 days along with 2.6 days of time to diagnosis from urine, saliva and serum sample (Zhang et. al., 2016).

From a therapeutic standpoint various targets have been developed from basic science research (Eboigbodin et.al, 2016) because of increased cross reactivity of ZIKV antibodies to various other environmental triggers (Stettler et. al, 2016). For instance, Zhao H., et al designed various monoclonal antibodies that could potentially serve as therapeutic means to counteract ZIKV infection during pregnancy (Zha et.al, 2016). One of them is an antibody against the lateral ridge of D3 region of envelope protein on the surface of ZIKV that could neutralize the virus during its infective stages more specifically in the first trimester of pregnancy (Zha et.al, 2016). In addition, various replicons have been developed that aid in drug delivery for ZIKV (Xie et.al, 2016). Replicon systems are convenient since they allow researcher to analyze various intracellular viral events like viral transcription and translation in absence of viral entry (Xie et.al, 2016). This can potentially help researchers analyze various intra-viral events in infected patients and potentially develop various antiviral or viral replication inhibitors.

Globally, many countries and states of the US (Walker et. al, 2016) are specifically struggling to cope with ZIKV infection. The biggest examples are countries like Brazil (Hennigan, 2016; Franca et. al, 2016; Septfons et.
al, 2016; Barreto et al., 2016), states like Florida, Texas, Hawaii and many other nations (Lessler et al., 2016) like Korea which have transmission of ZIKV via immigration despite of being geographically far as compared to South America (Jang et al., 2016). In Brazil, as of early 2016, “…4107 cases of microcephaly had been reported for investigation, with 583 cases already confirmed as associated with Zika virus and 950 discarded, […] The federal government is fighting hard against the Aedes aegypti mosquito, deploying the military to help communities eliminate its breeding grounds. But a severe financial crisis meant that the public health system was already under severe stress before the Zika epidemic hit it” (Hennigan, 2016). In Hawaii about 50 percent of patients who had babies with microcephaly had detectable ZIKV based on serum sample (Kumar et al., 2016). Also male to female transmission has also been documented secondary to ZIKV positive semen samples (Gaskell et al., 2017). The prolonged shedding of ZIKV post infection and exposure to travelers can expedite the spread of ZIKV at a drastic pace (Oliveira et al., 2016). In addition, strict ZIKV screening guidelines for blood collection should be implemented in arbovirus prevalent countries (Dyer, 2016; Marano, 2016; Demir et al., 2016; Swaminathan et al., 2016). Preventative measures that specifically include travel restriction to ZIKV endemic areas can play most important role in controlling ZIKV, a global pandemic (Honein, 2016).

Finally, in terms of vaccination many strategies have been designed. Strategies include: (1) identifying communities with high infection rates to serve as trial sites in order to acquire sufficient infection end points; (2) using incidence of confirmed symptomatic infection as a primary end point, relying on report of symptoms and diagnostic confirmation and also capturing both asymptomatic and symptomatic infections (Marston et al., 2016). Many different models have been proposed currently to develop successful vaccines. Proposed approaches include “…using the inactivated virus, using the live attenuated virus, using virus-like particles, using a recombinant subunit vaccine, using viral vectored vaccines, and using peptide, DNA, and RNA vaccines” (Hsiao-Han et al., 2017). By developing different modalities hopefully, we will be able to see a cure and prevention of Zika virus in the near future.

Conclusion

We present current data from literature review on pathogenesis, transmission, prevention and treatment of Zika virus. In addition, we shed light on the latest research in terms of pathogenesis, potential new therapeutic treatment options for children and mother infected with Zika virus, and vaccine options.

Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References


