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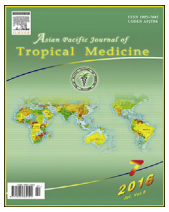

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Zika virus infections: An overview of current scenario

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ABSTRACT

Zika virus (ZIKV) was discovered more than half a century ago, recently it has gained unprecedented attention by the global health community. Until 2007, only 14 cases of human ZIKV infections were reported around the globe, while during the current outbreak, estimated cases mounted to approximately 1.5 million in Brazil alone, the virus was disseminated to wider South-American territories and travel-associated ZIKV infections were reported in USA, Europe and recently in China. ZIKV infections remain asymptomatic in approximately 80% of the individuals, and no anti-viral treatments were recommended. Yet, neurological complications associated with the infections, such as infant microcephaly and Guillain–Barré syndrome are major cause of the concern. Although, based on small numbers of cases, existing evidence strongly supports an exclusive link of viral infection and observed neurological complications. However, much work remains to assign exact numbers of complications caused by ZIKV. Regarding its structural attributes ZIKV shows remarkable resemblance with dengue virus and West-Nile virus. Despite, genomes of different ZIKV strains have already been decoded; role of the viral components in infection process and particularly pathogenesis of the disease remain widely unclear. In vulnerable areas, most viable strategy to ensure public health safety is vector control and enhanced public awareness about the transmission of the disease.

1. Introduction

In year 1881, Carlos Juan Finlay, world renowned Spanish-Cuban physician, presented the concept of yellow fever transmission by mosquito bite [1]. Later on, in the year 1901, it was proven by Walter Reed and colleagues. Yellow fever virus was the first to be identified among Arboviruses in year 1907 and the dengue fever virus was identified as second such virus. Transmission of dengue fever was explained by John Burton Cleland and Joseph Franklin Siler [2]. Among arboviruses, except, African-Swine fever virus that belongs to *Asfarviridae*, all clinically important viruses are classified into four families: *Bunyaviridaes*, *Flaviviridae*, *Reoviridae* and *Togaviridae* [3].

Zika virus (ZIKV) is an Arbovirus which belongs to the family *Flaviviridae* and phylogenetically, it relates to *Spondweni* virus, originally found in sub-Saharan Africa, and Papua New Guinea. The name 'ZIKA' originates from Zika forest located near the Lake Victoria in Uganda. First scientific report about ZIKV was published in 1947 [4]. A year later virus was isolated from *Aedes africanus*, a mosquito species indigenous to that region [4]. Subsequently, several reports confirmed prevalence of ZIKV in Nigeria, Sierra Leone, Gabon, Uganda, Central African Republic and Côte d'Ivoire [5–12]. Presence was confirmed in several Asian-countries including Cambodia, Indonesia, Malaysia, Micronesia and Pakistan [13–17]. Despite these earlier published reports, virus gained significant attention only in year 2007, after an outbreak on Yap Island [15,18,19]. Prior to this outbreak, only 14 cases of human infections were reported. In year 2013, an outbreak of ZIKV occurred in French Polynesia, which was accompanied by dengue epidemic and during this outbreak, for the first time malformations such as Guillain–Barré Syndrome (GBS) and microcephaly were reported in the patients [20]. Another unique aspect of this outbreak was dissemination of virus outside the African and Asian regions. In 2016, ZIKV was reported in more than 28 countries with highest numbers of infections in Brazil. The current outbreak in Brazil started during the month of April, in year 2015. The city named 'Natal' located in the state of Rio Grande do Norte in

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Northeast of Brazil, reported first case of ZIKV infection [21]. Soon after, virus disseminated across the country and frequent reports of microcephaly coincided with ZIKV infections [20,22]. Moreover, several cases of miscarriages and stillbirths were also reported. According to the recent estimates, total numbers of ZIKV cases during this outbreak may surpass 1.5 million. It was the largest outbreak recorded in human history and became a reason for public health emergency in Brazil [21].

2. Structure and genome

The ZIKV virion shows icosahedral symmetry of its nucleocapsid which is approximately (50–60) nm in size [23–26]. Recently, cryoelectron microscopic structure of the mature ZIKV was elucidated, that reflects structural similarities with other members of the *Flaviviridae*, including dengue virus (DENV) and West-Nile virus [26]. Virus carries a positive-sensed RNA of approximately, 11 kb in size with an estimated mutation rate up to 12 to 25 bases per year [27–29]. The architecture of the genome reveals two flanking regions, which are non-coding and are known as 5′ and 3′ NCR regions [29]. Apart from these two regions, rest of the genome is translated as a single open-reading frame encoding a polyprotein that is processed to make C-protein, encoding capsid, prM-protein, a precursor of membrane, E-protein, encoding envelop and seven other non-structural molecules known as NS-proteins [29]. A 53 kDa, E-protein of the virus plays a key role in binding and membrane fusion process [30,31]. The largest protein encoded by ZIKV is NS5 (≈103 kDa), a multifunctional molecule, its C-terminal confers, RNA-dependent RNA polymerase activity, while N-terminus carries methyl transferase activity that mediates RNA capping [29]. Function of the remaining NS-proteins remains unknown. The role of 3′ NCR region of the ZIKV genome has been postulated in recognition of cellular and viral factors, translation process, genome stabilization and RNA packaging [29]. First full genome sequence of ZIKV has been reported in 2007 [30]. Till to date, other than few studies, not much is known about the evolutionary dimensions of ZIKV strains [32]. Based on 43 viral strains collected over the period of 60 years (from 1947 to 2007) revealed three major clusters of strains which were spread across African and Asian regions, all originated from common ancestral lineage [32]. Moreover, a recent phylogenetic study, in Brazil, endorses origin of all isolates to common ancestor, identified as ZIKV strain of French Polynesia. In addition, it was also confirmed that viral spread occurred from Pacific island to Brazil during second half of the year 2013.

3. Vectors and transmission

Both *Aedes* and *Culex*, mosquito species are common inhabitant of Zika forest [33]. *Aedes aegypti (A. aegypti)*, is known as predominant vector for the transmission of both DENV [34] and ZIKV. It originated in African region and was descended from a zoophilic tree hole mosquito species known as *A. aegypti formosus*. Hypothetically described, *A. aegypti* was introduced to the new world by slave trade and later it disseminated to distant the geographical regions including tropical and sub-tropical areas [35]. Unlike *A. aegypti*, second important vector of ZIKV, *Aedes albopictus* is a zoophilic forest mosquito which originated from Asia. Over the time, it was also spread across different islands in Indian and Pacific Ocean [36] and further disseminated across Europe, the United States and Brazil [37,38]. Currently, both mosquito species are persistent across wider Asian and American territories [39]. Obviously, dissemination of these mosquito species has a great influence on public health around the globe [40–42]. For example, DENV alone is estimated to cause 100 million symptomatic infections each year, while every second person in the world is at the risk of developing DENV infection [40,41]. Epidemiological patterns of these two important arboviruses suggest that in the future, ZIKV may cause other outbreaks, particularly in the areas of high vector concentration. Before the recent outbreak of ZIKV in Brazil, distribution of *A. aegypti* and *Aedes albopictus* was predicted across different continents [43] and based on the available entomological data, it was shown that American region particularly Brazil has the highest reported occurrence rates for both ZIKV vectors [43]. Thus, higher concentration of these vector species in Brazil might be one reason for the current outbreak of this magnitude and as well for the rapid dissemination of ZIKV infection across the country. Other potential vectors for ZIKV include *Aedes furcifer*, *Aedes vittatus*, *Aedes dalzieli*, *Aedes metallicus*, *Aedes hirsutus*, *Aedes unilinaetus*, *Aedes africanus*, *Aedes taylori*, *Aedes hensillican* and *Aedes luteocephalus*.

Other than mosquito-borne transmission perinatal and sexual transmissions of the virus were also reported [44,45]. First incidence of sexual transmission was recorded in year 2008, while during the current outbreak multiple cases of sexual transmission were witnessed, latest in France [46]. In year 2013, in French Polynesia, presence of ZIKV nucleic acid was confirmed among 2.8% of the asymptomatic blood donors and transfusion transmitted infection was reported recently [47].

4. General clinical manifestations and laboratory diagnostic

Majority of the ZIKV infections remain asymptomatic and less than 20% of the infected individuals show symptoms which include but are not limited to fever, maculopapular rash, conjunctivitis and arthralgia. Hence, asymptomatic infections may remain unnoticed. Incubation period for the virus is suggested to be (3–12) d while the course of infection may extend up to (2–7) d, which is mostly self-limiting. However, persons exposed to secondary infections of dengue fever virus may experience severe form of the infection. During symptomatic episode of the infection, several laboratory parameters and symptoms may help to indicate ZIKV infection, as for example, leukopenia, thrombocytopenia, serum lactate dehydrogenase, gamma-glutamyl transferase and elevated protein markers (including C-reactive protein, fibrinogen and ferritin) are noticed. One of the most important challenges regarding detection of the virus in patient's samples is lack of sensitive and specific laboratory test. Unfortunately, previously reported tests show serious cross-reactivity and are difficult to perform [48–50]. Although, PCR based testing of saliva, blood and urine is highly recommended, availability of the desired amount of nucleic acid in different body fluids remains as significant hindrance (50). To date, for the detection of this virus no commercially available laboratory test is reported.

5. Clinical complications

Infant microcephaly and GBS are the major clinical complications associated with ZIKV infections.

5.1. Microcephaly

Microcephaly as a complication of ZKIAV infection was noticed in year 2013 [20]. During the recent outbreak in Brazil, microcephaly cases attained unprecedented attention [51]. That was mainly because, within the few months of first ZIKV case, a remarkable increase in the infant microcephaly cases was recorded. Yet, general perception about the magnitude of this problem could be misleading. In fact, till the month of February, health officials in Brazil scrutinized more than 1 113 cases of suspected microcephaly, out of which 404 were confirmed as microcephaly, and based on concrete evidence just 17 cases were linked to ZIKV infection. Overall, after the first report of ZIKV infection in Brazil, total numbers of suspected microcephaly cases were 3 670 till the month of January 2016 [51]. Hence, it seems plausible, that due to the stringent scrutiny of microcephaly cases in the country otherwise unreported cases were also reported. Notably, RNA of ZIKV has been detected in the samples of brain tissues, placenta and amniotic fluid. However, assigning exact number of microcephaly cases to ZIKV infection at this time point remains quite trivial. In this regard, Ministry of Health in Brazil has recently mounted its efforts by setting large control studies. Despite these efforts, epidemiological data alone may not suffice a strong evidence for the clinical association of microcephaly with ZIKV infection. Thus quest for the concrete scientific evidence to solve this issue requires scientific investigations based on relevant infection models. Yet, the toughest part of the riddle is the vast majority of the mothers infected with ZIKV gave birth to healthy babies.

5.2. Guillain–Barré syndrome

GBS is characterized as a rapid-onset of muscle weakness that occurs due to the damage to peripheral nerves caused by the immune system. During the last outbreak in French Polynesia, total 8 000 cases of suspected ZIKV infections were reported, out of which 396 were confirmed by PCR. Neurological complications were reported in 70 cases and 38 were confirmed as GBS. Other, 25 cases of neurological complications were characterized as encephalitis, meningoencephalitis, paresthesias, facial paralysis and myelitis [52]. In Brazil, similar to increase in microcephaly cases during the episode of ZIKV infection, sharp increase in GBS cases was also recorded [53]. Yet again, exact numbers of GBS cases caused by ZIKV during this outbreak remains to be established, however, available data strongly endorses a link between GBS and ZIKV infections.

6. Treatment of ZIKV infection

Supportive therapy is recommended for the patients who may develop symptomatic disease and it relies solely on severity of the symptoms. Patient care includes proper hydration, monitoring for possible coagulopathy and multiple organ failure. Intensive care is recommended for the patients depicting serious conditions, like showing signs of coagulopathy, tachycardia, hypotension and renal dysfunction. Patients with neurological complications such as GBS, require hospitalization. In-case of suspected patients in pregnancy phase, sonography is recommended to monitor the proper fetal growth and particularly to avoid complications of infant microcephaly. Non-steroidal anti-inflammatory drugs and aspirin can be recommended for the treatment, such medications should be avoided in case of concomitant infection with dengue fever virus. No antiviral treatments are suggested for ZIKV infection.

7. Prevention and control

In order to combat ZIKV infection, public awareness should remain the top priority, particularly information about breeding grounds of the mosquitoes, such as stagnant water ponds, unattended furniture, polythene bags in rain, old automobile tires, risk factors, associated with gardening and plants containing water. Moreover, use of mosquito nets should be highly encouraged. At the governmental level, policy makers should address emerging threats of vector-borne infections particularly in vulnerable societies. Current scenario of global climate change must be given serious considerations. Planning in advance and infrastructure developments, prior to the occurrence of the outbreaks are key measures which are mostly ignored in the developing countries. In order to effectively counter ZIKV or other mosquito-borne diseases, a collective sense of responsibility must prevail in societies, both at public and governmental level. Recent studies endorsed transmission of ZIKV via sexual contact which demands more efforts regarding public awareness. Effective vector control strategies and quarantine measures are necessary to minimize geographical spread of the virus.

8. Conclusions

Recent episodes of the infections caused by ZIKV in South-American territory highlighted epidemiological importance of this virus, which now demands a new level of vigilance and resource allocation to minimize the risk of future outbreaks. In terms of its magnitude, current outbreak was unprecedented that stresses the need for preparedness and development of effective strategies for the vector control. In addition, appropriate diagnostic tools for ZIKV identification are urgently needed, efforts related to scientific research should be mounted to establish a clear link between ZIKV infections and suspected clinical complications. Current evidence regarding sexual transmission and transfusion transmitted infections of ZIKV needs enhanced public awareness. To avoid the risk of transfusion transmitted infections blood screening protocols must be updated particularly in high risk areas. In short, a collaborative approach at the global level should be given high priority to minimize the spread of the vector-borne viral diseases like ZIKV infection. Developing countries should be encouraged to combine efforts for the vigilant and well-structured national surveillance programs for monitoring infectious diseases on regular basis.

Conflict of interest statement

We declare that we have no conflict of interest.

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