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Research Update (Minireview)

Outbreak of Zika Virus

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Zika virus (ZIKV) is a vector-borne flavivirus. It was initially identified in Uganda in 1947, and the first human infection was reported in Nigeria in 1953. Since 2015, ZIKV has been spreading rapidly in Brazil and the Americas. Given its general symptoms, ZIKV is considered to be a mild, febrile illness, although it is associated with severe neurologic complications. On February 1, 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC). We conducted a review of the literature on the epidemiology and transmission, clinical manifestations, and diagnosis of ZIKV. Additionally, we introduce original literature on the current ZIKV outbreak in this review.

Key Words: Zika virus, Epidemiology, Transmission, Clinical manifestation, Diagnosis

I. INTRODUCTION

Zika virus (ZIKV) is a mosquito-borne flavivirus that is in the Flaviviridae family and is related to dengue fever, Japanese encephalitis, West Nile, and yellow fever viruses. It was initially identified in Uganda in 1947 in the blood of a sentinel rhesus macaque that had been placed in the Zika Forest of Uganda and was first identified in humans in Nigeria in 1952 (1). Outbreaks of ZIKV disease have been reported in Africa, the Americas, Asia and the Pacific. From the 1960s to the 1980s, human ZIKV infections were found from Africa to Asia (1).

In 2007, in the Island of Yap in the Federated States of Micronesia, a large outbreak of ZIKV infection was first reported. Since September 2015, ZIKV has been spreading rapidly in Brazil and the South American Continent (2, 3). ZIKV commonly causes mild infection in humans, although it is associated with serious neurologic complications such as microcephaly and Guillain-Barré syndrome (GBS) (4, 5). On February 1, 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC, http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/). We present a review of the literature on the epidemiology and transmission, clinical manifestations, and diagnosis of ZIKV infection as well as introduce original literature on the current ZIKV outbreak.

II. Epidemiology of ZIKV

ZIKV was first introduced into northeastern Brazil in March 2015 from the Pacific Islands and spread rapidly throughout the Americas (1). It became the first major com-

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municable disease that was associated with serious neurologic complications such as microcephaly in infants (1).

ZIKV is a flavivirus and was first isolated in *Aedes africanus* mosquitoes in 1947 (6). Human infection with ZIKV was first observed in Nigeria in 1953 (7).

ZIKV infection, a mild, febrile disease, was reported over the next 57 years (1). However, a 2007 outbreak of ZIKV infection that resulted in an estimated 5000 infections among the total population of 6700 residents on several islands in the State of Yap in the Federated States of Micronesia was a great surprise (8). Subsequently, in 2013 and 2014, outbreaks of ZIKV infection occurred on other Pacific islands, including New Caledonia (in 2014), Easter Island (in 2014), Cook Islands (in 2014), Samoa (in 2015), and American Samoa (in 2016) (1).

In March 2015, ZIKV infection was first noted in the South American Continent (9). The outbreak began in February and extended to June 2015 in Salvador, the capital of Bahia. As many as 1.3 million suspected cases had occurred by December 2015 (10, 11). Colombia reported the first indigenous transmission of ZIKV in October 2015 (12), and ZIKV had spread to at least 33 countries of the South American Continent by March 2016 according to situation report by world Health Organization (Zika virus microcephaly and Guillain-Barré syndrome, 31 Mar 2016).

III. Transmission of ZIKV

ZIKV is transmitted to humans, mainly through the bite of an infected *Aedes* mosquito, mainly *A. aegypti* in tropical regions (13). *Aedes* mosquitoes, the same mosquitoes that transmit chikungunya, dengue and yellow fever viruses, generally bite during the day, peaking during the early morning and late afternoon or evening (1, 13). ZIKV is also transmitted from person to person through sexual contact all around world (14). Other pattern of transmission such as blood transfusion have also been reported (15).

Aedes mosquito-borne transmission

In Africa, ZIKV is maintained in a sylvatic transmission cycle involving primates such as monkeys and *Aedes* mosquitoes, although a sylvatic transmission cycle has not yet been identified in Asia (16). In (sub)urban environments, ZIKV is transmitted in a human-*Aedes* mosquito-human transmission cycle. *A. aegypti* and *A. albopictus* are major vectors of ZIKV (17). They are widely distributed throughout subtropical and tropical regions, and *A. albopictus* can exist in a more temperate region than *A. aegypti*, which extends the potential range within which outbreaks may occur (1).

Non-*Aedes* mosquito-borne transmission

The nucleic acid of ZIKV was discovered in the amniotic fluid of mothers whose foetuses had cerebral abnormalities as detected by ultrasonography (18, 19). Moreover, the antigen and nucleic acid of ZIKV were detected in the brain tissue and placentas of infants who had microcephaly and died soon after birth (20) as well as in the tissue of miscarried foetuses (20). Therefore, ZIKV can be transmitted from the mother to the foetus during pregnancy (21).

ZIKV reportedly can also be transmitted via sexual intercourse (22). Sexual transmission occurs both before the onset of symptoms and during the development of symptoms and shortly thereafter. Although the risk factors have not yet been identified, replicative viral particles and high viral RNA copy numbers have been detected in sperm, and viral nucleic acid has been identified up to 62 days after the onset of symptoms (22).

The transmission of ZIKV through a blood transfusion has also been reported (15).

IV. Clinical Manifestations of ZIKV Infection

The incubation period of ZIKV infection has not yet been defined. However, it appears to be less than 1 week (lasts for 2~7 days), and the manifestations of ZIKV infection are mild and similar to those of chikungunya and dengue infections. Nevertheless, ZIKV infection has been associated with serious neurologic complications such as microcephaly and GBS in French Polynesia, Brazil, and Colombia (1).

Congenital microcephaly is a neurological abnormality that is present at birth. It is defined as a head circumference at least 2 standard deviations (SD) smaller than the mean

for individuals of the same sex, age, and ethnicity, with a head circumference at least 3 SDs smaller being deemed as serious (23). Simon Cauchemez *et al*. presented retrospectively reported data showing an increase in the number of foetuses with microcephaly after the ZIKV outbreak in French Polynesia (23). Victora *et al*. also reported an increase in the number of infants born with microcephaly, and more than 4300 cases of microcephaly were reported after ZIKV transmission occurred in Brazil, America (24).

GBS is characterized by acute areflexic paralysis with albuminocytologic dissociation (25), and several studies have shown that ZIKV infection is linked to GBS (5, 27).

In the outbreak in French Polynesia, 38 cases of GBS occurred among an estimated 28,000 patients, and Van-Mai Cao-Lormeau *et al*. found a strong association between GBS and ZIKV infection (5).

Beatriz Parra *et al*. characterized the clinical features of patients with GBS following ZIKV infection in Colombia. In their study, 97% (66/68) of patients had symptoms that were compatible with ZIKV infection before the onset of GBS. The median period between the onset of symptoms of ZIKV infection and symptoms of GBS was 7 days. Additionally, 50% of the 68 patients with GBS had bilateral facial paralysis upon examination. Furthermore, 78% (36/68) of the patients had symptoms that were consistent with the acute inflammatory demyelinating polyneuropathy subtype of GBS. The authors also found a correlation between GBS in association with ZIKV infection and previous exposure to dengue virus infection (27).

ZIKV is also associated with meningoencephalitis (28) and acute myelitis (29) in infected adults.

V. ZIKV Diagnosis and Drug

The diagnosis of ZIKV infection involves the detection of ZIKV RNA via reverse transcriptase-PCR (RT-PCR) and IgM antibodies via enzyme-linked immunosorbent assay (ELISA). Viral RNA has been successfully detected in serum using RT-PCR within 1 week after the onset of clinical symptoms due to generally low-level or transient viremia (1). However, in the case of an infected pregnant woman, ZIKV RNA was detected in serum approximately 10 weeks after ZIKV infection (1). IgM maybe appear within the first week after symptom onset and persist for several months, and the cross-reactivity of dengue virus antibodies is possible (1). The plaque reduction neutralization test (PRNT) can be used to verify ELISA results (1).

The nucleic acid of ZIKV is detected for a longer period in urine than in serum, and RT-PCR has greater sensitivity in saliva than in serum (1). RT-PCR and immunohistochemical testing are useful in detecting ZIKV infection in the tissue of miscarried foetuses and infants who died after birth (1).

No drug has been approved to treat or prevent ZIKV infection until now (29). Miao Xu *et al*. performed a drug repurposing screen and identified compounds that either inhibited ZIKV infection or suppressed infection-induced caspase-3 activity in different neural cells. A pan-caspase inhibitor, emricasan, inhibited ZIKV-induced increases in caspase-3 activity and protected human cortical neural progenitors in both monolayer and three-dimensional organoid cultures. Niclosamide, a category B anthelmintic drug, inhibited ZIKV replication (30).

VI. Closing Remarks

This review summarises the literature on the epidemiology and transmission, clinical manifestations, diagnosis, and drug of ZIKV for understanding of outbreak of ZIKV the South American Continent.

ZIKV was initially identified in Uganda in 1947 in rhesus macaque and was first identified in humans in Nigeria in 1952 (1). Since September 2015, ZIKV has been spreading rapidly in Brazil and the South American Continent (2, 3).

Aedes mosquitoes are primary vector of chikungunya, dengue, and Zika virus, which are recent international increases in the spread or emergence. Lyle R. Petersen *et al*. suggested internationalization and deforestation such as urbanization are general mechanisms of transmission and viral mutations, which are affected virulence or transmission, are also contributed increase and appearance of vector borne diseases (1).

Therefore, future research is crucial to elucidate the interaction between vector and vector borne pathogens in relation to understanding the ecological transmission dynamics and geographic distribution of vector, which are related vector borne disease such as chikungunya, dengue, and Zika virus (31).

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