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Rev Inves Clin. 2015;67:329-32 PERSPECTIVES

Zika Virus: A New Epidemic on Our Doorstep

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ABSTRACT

Zika virus, a flavivirus transmitted to humans by mosquitoes of the genus *Aedes,* was first described in humans as isolated cases in Africa. Outbreaks have been reported outside that region since 2007, followed by its gradual introduction to different geographical areas. In 2015, Zika virus was detected in Brazil, from where it is rapidly expanding in the continent; the first case in Mexico was detected in October 2015. Initially deemed as a cause of mild illness, confirmation of microcephaly cases associated with this infection in Brazil have resulted in the World Health Organization declaration of Zika virus infection as a Public Health Emergency of International Concern. The US Centers for Disease Control and Prevention issued travel alerts for countries with declared cases. The vector is widely distributed in Mexico and control measures are the most effective means for prevention, not only of Zika virus, but also dengue and chikungunya. (REV INVES CLIN. 2015;67:329-32)

Key words: Zika. Microcephaly. Aedes albopictus. Mexico.

INTRODUCTION

Zika virus (ZIKV), an arbovirus of the genus *Flavivirus,* was first described in 1947 in Kampala (Uganda) in a Rhesus monkey, during studies of yellow fever in the Zika forest. The first human cases were described in 1952 in Uganda and Tanzania; subsequently, only isolated cases in Africa were reported. The first major outbreak outside Africa occurred in Yap Island, Micronesia, in 2007. In 2013, an outbreak in French Polynesia affected 11% of inhabitants. Zika virus has a single positive-strand RNA genome; there are several clades from two different lineages: African and Asian[1].

TRANSMISSION

Zika virus is mostly transmitted by *Aedes aegypti* mosquitoes, as other flaviviruses; the mosquito is widely spread in the Pacific, Gulf of Mexico, and the Caribbean

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Received for publication: 03-11-2015
Accepted for publication: 10-12-2015

coasts. *Aedes albopictus*, a cause of worldwide distribution of dengue, was associated with recent ZIKV outbreaks, including in Gabon in 2007. This is particularly relevant in urban areas where *A. albopictus* has been found. In Mexico, it was first described in Tamaulipas in 1992, probably related with trade by land with the USA. In the past two decades, *A. albopictus* spread to coastal regions and the Neovolcanic Belt, potentially exposing large populations in 12 states (Chiapas, Coahuila, Hidalgo, Morelos, Nuevo León, Oaxaca, Puebla, Querétaro, Quintana Roo, San Luis Potosí, Tamaulipas, Veracruz)[2].

Person-to-person, possibly sexual, transmission is suggested in two cases of women whose partners were infected in Senegal and Venezuela, respectively[3]. Replication-competent ZIKV was isolated from semen in a patient with hematospermia, recovering from a Zika-like illness[4].

Regarding blood transmission, during the French Polynesia outbreak, ZIKV was detected by polymerase-chain reaction (PCR) in 2.8% of 1,505 asymptomatic volunteer blood donors, and replicating virus was cultured in some samples[5].

CLINICAL MANIFESTATIONS

The ratio of symptomatic to asymptomatic infection is unknown, although the latter appears to be high. The incubation period has not been established; symptoms start few days after infection, lasting 3-12 days. Clinically it resembles dengue (arthralgia, peripheral edema, fever, headache, retro-ocular pain, non-purulent conjunctivitis, and centrifugal, pruritic, maculopapular rash). Myalgia, dizziness, and gastrointestinal manifestations (vomiting, diarrhea or constipation) are less frequent. Table 1 compares the clinical manifestations of dengue, chikungunya, and Zika. Urinary tract manifestations (hematospermia and prostatism) have been reported[6].

Treatment is nonspecific, based on symptom control (antihistamines, acetaminophen), hydration, and rest.

DIAGNOSIS

The standard for diagnosis is the identification of ZIKV by RT-PCR in blood or tissue; it can also be detected in saliva or urine. Due to short viremia, blood RT-PCR sensitivity decreases 3-5 days after symptom onset. Serology may be used, although cross-reactivity with other flaviviruses (dengue, yellow fever, Japanese encephalitis) has been described. Serologic techniques (plaque reduction neutralization) are required in regions with active transmission.

Table 1. Comparison of the main clinical manifestations of dengue, chikungunya, and Zika

Symptom	Dengue fever	Chikungunya	Zika
Fever	+++	+++	++
Myalgia	+++	++	+
Arthralgia	+/-	+++	+
Arthritis	+	+++	+
Headache	+++	+	+
Edema in extremities	+	-	+
Maculopapular rash	+	++	+++
Retroocular pain	++	+	++
Non-purulent conjunctivitis	-	+	+++
Lymphadenopathy	++	++	+
Hepatomegaly	+	++	-
Hemorrhage	++	-	-
Shock	+	+/-	-
Thrombocytopenia	+++	+/-	+/-
Neutropenia	+++	+	+
Lymphopenia	++	+++	+

Adapted from Ioos, et al.[3]

ZIKA VIRUS OUTBREAKS

The ZIKV pathway around the world could be followed according to phylogenetic studies[7]. It possibly appeared in eastern Africa in 1920 (confidence range 1892-1947), spreading to Southeast Asia around 1945 (1920-1960), where it was described in Malaysia for the first time. The ZIKV continued eastward, causing the Yap Island outbreak in 2007. This virus is of Asian lineage, and the moment of its introduction is undefined, given the coexistence with dengue and chikungunya. The following outbreak, in 2013, occurred in French Polynesia. Since this virus is closely related to the one from Southeast Asia but not to the Yap Island virus, an independent introduction has been postulated. Subsequently, it spread to the Pacific Islands (New Caledonia in 2014, Cook Islands in 2014, Easter Island in 2015), which apparently are the source of the outbreak in America. On February 15, 2015, the

first case was reported in Salvador, Brazil; by year's end, 18 Brazilian states were affected. The 2014 Soccer World Cup was suspected as the cause of ZIKV introduction, although phylogenetic analyses show similarity between strains from Brazil and Pacific Islands. Zika virus was likely introduced in America during the Va'a World Sprint Championship Cup canoe race held in Rio de Janeiro in 2014, attended by countries from the Pacific Islands. On May 7, 2015 the Pan American Health Organization (PAHO) released an epidemiological alert for the Americas; in October, Mexico detected its first case[8].

ASSOCIATION WITH MICROCEPHALY AND OTHER NEUROLOGICAL COMPLICATIONS

Zika virus infections were considered as of a benign course, even less severe than dengue or chikungunya. In the French Polynesia outbreak (approximately 10,000 cases), 70 patients presented a more severe disease, including neurological (Guillain-Barré Syndrome or meningoencephalitis) or autoimmune (thrombocytopenic purpura or leukopenia) complications. The first report of perinatal transmission was documented.

In October 2015, Brazilian authorities declared a national public health emergency due to a significant increase (20-fold) of reported microcephaly in ZIKV-affected areas; three deaths were reported. The PAHO issued a new epidemiological alert, and investigations are underway. Although this marked increase in microcephaly may be an overestimation of surveillance and reporting systems[9], the temporal association of the rise of ZIKV infection and microcephaly cases, the plausibility of in-utero transmission, and the virus's ability to affect neural tissue are well established. In December 2015, the PAHO reported the identification of ZIKV by RT-PCR in amniotic fluid of two cases of antepartum-diagnosed microcephaly; additionally, in brain and other tissues of an infant with microcephaly who died in the perinatal period, and of a fetus with 29 weeks of gestation, with consistent findings on electron microscopy. The complete genome of ZIKV was recovered from the fetal brain[10].

The careful description of 35 cases of microcephaly, where genetic or other infectious causes of malformation were discarded, is strong evidence for causality. In this group, 74% of mothers reported a rash in the first or second trimester of pregnancy, and infants presented severe microcephaly (> 3 standard deviations below average for gestational age). Imaging studies (computed tomography and transfontanellar ultrasound) repeatedly revealed a pattern of scattered calcifications, mainly in basal ganglia, thalamus, and periventricular areas. In 30%, cell migration alterations (lissencephaly and pachygyria) were observed. Ventriculomegaly (secondary to cortical/subcortical atrophy) was frequent[11].

The CDC recommended the restriction of travel to affected countries (including Mexico), as well as testing pregnant women with a febrile illness and a history of travel to those areas. Additionally, ultrasound is recommended to rule out fetus malformations in asymptomatic pregnant travelers.

PREVENTION

Individual prevention relies on avoiding contact with the vector: using mosquito nets in windows and beds, staying in air-conditioned areas, avoiding outdoor activities at dusk and dawn, avoiding exposed skin, and using repellent (products containing ≥ 20% of DEET [N,N-Diethyl-m-toluamide] appear more effective).

Given the possibility of sexual transmission, people who have visited an endemic area or developed the disease are recommended to abstain from sexual intercourse or use barrier methods (condoms). Recommendations should be followed throughout pregnancy. Partners should discuss the potential risk of exposure by this route.

Regarding public health measures, fumigation must be continuous and public education should be aimed at elimination of potential mosquito breeding sources.

CONCLUSIONS

Once again, the world faces a global epidemic, whose characteristics will unfortunately be defined along its course. Currently, Mexico is confronting two other infections that share the vector and have similar clinical manifestations. Even though adherence to known control measures is essential, some of them begin to

show less effectiveness, presenting an opportunity for innovation. Education is needed to avoid exposure in vulnerable groups.

Many questions start to emerge on ZIKV. There is evidence of *in utero* infection, although there is no scientific cause-effect confirmation for microcephaly. The possibility of vertical transmission should be further explored since there are data suggesting sexual transmission and the presence of isolated cases without evidence of vector involvement. Zika virus neurotropism should be studied in depth, considering its association with isolated cases of Guillain-Barré syndrome and the confirmation of retinal lesions in fetuses and children with microcephaly. In general, unknown aspects of the infection are the magnitude of central nervous system damage and the existence of autoimmune responses; therefore, studies on the natural history of Zika infection should be started without delay. Routes of international collaboration to accelerate basic and clinical research on ZIKV must be established.

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