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Chapter 1

Introductory Chapter: Clinical and Epidemiological Implications of Zika Virus Infection - The Experience of RECOLZIKA in Colombia

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1. Introduction

1.1. Overview and general aspects of Zika

Zika virus (ZIKV) is a mosquito-borne flavivirus discovered in rhesus monkeys in the Zika close to Kampala, Uganda in 1947, but it was not until February 2016 that the World Health Organization (WHO) declared Zika a public health emergency [1–5]. The introduction and spread of ZIKV throughout Latin America embodies a convergence of ecologic, social and environmental factors that foster the emergence of new infectious threats in susceptible populations. Although ZIKV infection is typically asymptomatic or causes a mild flu-like, birth defects indicate a wide clinical spectrum that includes severe manifestations that underlie global concern [4–7]. These, along with evidence of non-vector-borne transmission routes such as vertical transmission, blood transfusion and sexual contact [8–11], highlight the need for augmented research in the area [12]. Currently, research efforts have been increasingly focusing on disease prevention through vaccine design and understanding of the role of antibody disease enhancement (ADE) on the immunopathogenesis of severe cases and fetal outcomes. New diagnostic tools are required in order to bypass cross reactivity with other flaviviruses

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like dengue or yellow fever, and there is a gap for implementation research in order to develop effective strategies for vector control and awareness programs among people [10–18].

2. Epidemiology

It is difficult to exaggerate the medical importance and burden of vector-borne infectious diseases as a series of emerging and re-emerging arboviruses epidemics are propagated in recent decades in previously unexposed geographic areas in Latin America and the Caribbean [9]. ZIKV has caused epidemics during 2015–2017 in different countries of the Americas, with more than 50 countries/territories affected in this region, and 148 globally affected in any form (including imported cases). After Brazil, probably Colombia is the second most affected country in the region, with over 100,000 cases having been reported from this northern South American country, reflecting overall incidence rates above 150 cases/100,000 [18]. During the years 2015–2017, the circulation of ZIKV was confirmed in 560 municipalities and four districts of Colombia. Suspected cases of ZIKV disease have been reported in 245 municipalities, adding a total of 809 municipalities with reported cases between confirmed and suspected cases. Thirty-five territorial entities of the departmental and district order have notified the surveillance system of ZIKV [19].

Although Colombia is not currently (November 2017) at epidemic status for ZIKV, it has become endemic with continued transmission. The main territories affected are those with previous circulation of dengue and chikungunya. In this sense, the departments (at the first administrative level) of Valle del Cauca, Santander, Tolima, Cundinamarca and Meta account with more than the 60% of the cases reported during 2017. On the other hand, 238 cases of symptomatic ZIKV infection had been documented in pregnant women (37 confirmed cases), and 20 cases charted in municipalities with no previously known ZIKV transmission. By territorial entity of residence, the one that has reported the largest proportion of cases is Santander with 46 pregnant women in the northeastern region, border with Venezuela [19].

3. Clinical aspects

It is estimated that 80% of people infected by ZIKV are asymptomatic, but they can still develop complications that lead the patient to death or generate severe chronic conditions such as Guillain-Barré syndrome. Asymptomatic individuals may be important for sustaining ZIKV transmission within a population despite being undiagnosed as a ZIKV case [6, 20].

Individuals with acute, symptomatic cases (25%) experience fever (elevation of axillary body temperature greater than 37.2°C), nonpurulent conjunctivitis, headache, myalgia, arthralgia, asthenia, maculopapular rash (usually in extremities and trunk) **(Figure 1)**, lower limb edema and less frequently, retro-orbital pain, and gastrointestinal disturbance such as abdominal pain, nausea, and diarrhea. Notwithstanding, afebrile patients with rash should also be assessed for ZIKV infection [3, 11, 12]. These relatively mild symptoms last a few days (4–7 days), uncommonly result in hospitalization and are hardly distinguishable from other, better-known disease caused by other arboviruses [7, 16, 21]. Some neurological manifestations including Guillain-Barré syndrome,

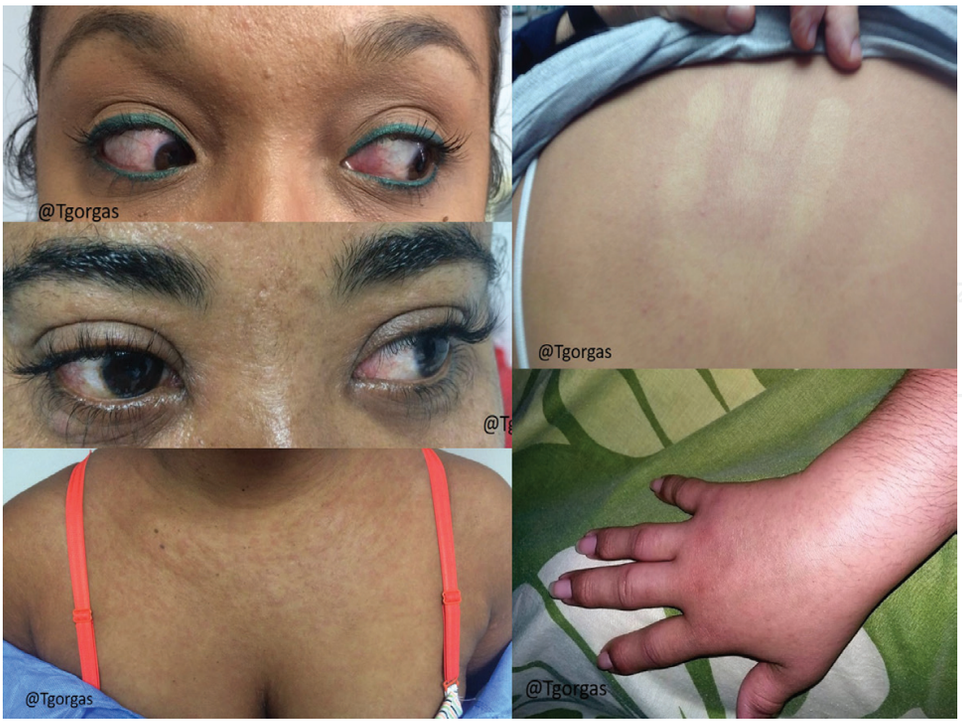

Figure 1. Clinical aspects of patients with Zika virus infection (confirmed by PCR) (pictures took and provided with patient authorization, by co-author Jose Antonio Suarez, Instituto Gorgas, Panama): conjunctivitis, rash, arthralgia.

acute myelitis, and meningoencephalitis are associated with detection of ZIKV in the cerebrospinal fluid [2, 16, 22]. Interestingly, this virus can cross the fetoplacental barrier to affect the fetus and cause microcephaly, microcephaly-related intellectual disabilities to neonates, ophthalmological alterations, loss hearing and epilepsy. Evidence has suggested that ZIKV could also invade cardiac cells, which could explain a described association between congenital heart disease in an infant born to a ZIKV-infected mother [13, 23, 24]. Differentiation on clinical grounds alone is often a very difficult task. The biological and clinical behaviors exhibit not only different characteristics but also great similarities; thus, ZIKV could be easily confused with other arboviruses. The clinical picture may be further complicated by coinfections with various combinations of arboviruses [9, 12, 18].

4. Diagnostics

The transmission of the diseases through mosquito bite is the most common scenario in ZIKV infection, which was described in 1966 in Malaysia. However, few cases of nonvector-borne infections have been reported, and the existence of ZIKV in the pharynx and saliva of infected patients represents a potential but unproven route of transmission. ZIKV also has been detected in semen, cervicovaginal fluid and urine, consistent with several well-documented cases of sexual transmission [3, 14, 16, 25].

The diagnosis of ZIKV infection is established through detection of ZIKV RNA by reverse transcription polymerase chain reaction (RT-PCR) typically performed on serum, plasma or urine within 2 weeks of symptom onset. ZIKV can also be diagnosed by serology (IgM

antibodies). Serum RT-PCR is positive if done in the acute phase of the viremia, in blood on the first 3–7 days of the onset of illness, and for up to 10–14 days in urine. Enzyme-linked immunosorbent assay (ELISA) is used to detect IgM, but unfortunately, there are only a few laboratories able to perform an ELISA for ZIKV. Fewer laboratories still are able to perform neutralization assays, which may be more specific than ELISA, but require greater resources and biosafety containment. Although the specific antibodies against ZIKV in serum (IgM antibodies) are detectable after 4 days of symptom onset, its diagnostic value is limited due to cross-reactivity with other flaviviruses. Comparing relative titers of binding or neutralizing antibodies may be helpful in discriminating ZIKV from related flaviviruses like dengue in research settings, this is not yet standardized to aid in clinical diagnosis [16, 21].

The probable modes of perinatal transmission are transplacental or may occur during delivery. Concern has raised about the possibility of breastfeeding transmission. Prenatal fetal evaluation of pregnant women suspected or confirmed to have a ZIKV infection is done by regular fetal ultrasound examination, which can detect abnormalities as early as 18–20 weeks of gestation. The main ultrasound findings associated with fetal ZIKV infection are microcephaly, intracranial calcifications, hydranencephaly, ventricular dilatation, brain atrophy, anhydramnios, *hydrops fetalis*, and intrauterine growth retardation. Amniotic fluid obtained by amniocentesis after 15 weeks of gestation can be tested for the presence of viral RNA by RT-PCR, but the sensitivity and specificity is unknown during gestation [13, 21, 26].

It is important in the differential diagnosis of dengue and chikungunya, among other conditions such as malaria, leptospirosis, measles, and also to consider the possibility of coinfections, especially in endemic areas where all these pathogens can cocirculate simultaneously. During the symptomatic period of infection, various laboratory parameters provide information on ZIKV infection. Various laboratory parameters such as leucopenia, thrombocytopenia, serum lactate dehydrogenase, gamma glutamyl transferase and elevated protein markers may be suggestive of ZIKV infection, but these findings are nonspecific [4, 13, 26]. Also, the virus can be detected in semen up to 81 days after infection.

5. Treatment

Currently, there is no ZIKV vaccine available, but the WHO has made ZIKV vaccine development a top priority. Thus, more than 50 ZIKV vaccine candidates are now in various stages of research and development, mainly, in phase I/II clinical trials that include inactivated whole viruses, recombinant measles viral vector-based vaccines, DNA and mRNA vaccines, and a mosquito salivary peptide vaccine [17, 27].

The treatment for ZIKV infection is entirely supportive, no antiviral. No drugs have yet been approved for a specific ZIKV treatment, although numerous nucleoside analogs have some antiviral activities in cell cultures such as ribavirin, sofosbuvir or favipiravir. Acetaminophen is used to control fever and pain, avoiding aspirin or nonsteroidal anti-inflammatory drugs, because of their risk of hemorrhage (in case of DENV infection), and fluids are generously administered to prevent dehydration [24, 26, 28].

6. Control and prevention

During the last few decades, Latin America has been threatened by an unprecedented explosion of emerging arboviral outbreaks. These epidemics of emerging and re-emerging arboviruses are due to a number of factors such as climate change, levels of urbanization, increasing international travel, foreign trade, poor socioeconomic conditions, susceptible geographical areas (tropical and subtropical regions) among other factors. The presence of *Aedes* mosquitos enables ZIKV to invade new areas and poses a worldwide risk as there are no preventive approaches or vaccines for ZIKV [9, 12, 16, 26].

In countries where ZIKV epidemics are reported, cost-effectiveness studies may be important to determine the feasibility of systematic screening of blood components in donated samples. Unfortunately, at the moment, no specific data are available on the rate of reduction of blood-borne transmission due to such practices. Because the prevalence of viremia in blood donations is high in endemic areas, mainly asymptomatic donors, donor selection professionals should carefully evaluate the appropriateness of the donation based on the patient's background, likewise, follow up on donors with the aim of identifying the onset of symptoms [16, 26].

The most challenging aspect of ZIKV is preventing congenital infection. Recommendations to avoid mosquito exposure or avoid pregnancy altogether are not practical for most women living in ZIKV-endemic areas. Women who are or are planning to become pregnant are discouraged from visiting areas of ZIKV transmission by travel restrictions issued by the US Center for Disease Control and other public health institutions. For preventing the sexual transmission of ZIKV for couples in which a man has traveled to or resides in an area with active ZIKV transmission, safe sexual practices for 6 months after the exposure regardless of the appearance of symptoms are recommended. What constitutes totally safe sexual practice is unclear, and some studies suggest that transmission of the small ZIKV (40 nm) may not be fully prevented by condoms [1, 2, 26, 29].

Much work remains before effective antiviral drugs and vaccines are available for ZIKV. For the time being, recognizing the importance of epidemiological control of emerging viral diseases and taking preventive measures such as the increase in *Aedes* vector control and containment strategies guided by the scientific literature is a priority to achieve control of tropical viruses with epidemic potential [2, 3, 9]. In general, in countries with sporadic imported cases of ZIKV infection or in ZIKV-free countries, the only precaution that must be taken is to notify the cases. However, for epidemic areas, the main way to combat ZIKV is to cover skin by cloths, use mosquito repellents, reside in air-conditioned or screened rooms, and avoid being near water containers like stagnant water ponds, old automobile tire or plants containing water [16, 17, 26].

Finally, it is important to note that because only symptomatic individuals are diagnosed with ZIKV, robust epidemiologic data required for optimal control programs are lacking. Additionally, only a few reported cases have received laboratory confirmation; thus, conditions such as dengue, chikungunya, malaria, leptospirosis, measles, among others may be incorrectly identified as ZIKV (or vice versa).

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