

Absence of Zika Virus Associated Congenital Syndrome despite Prolonged Maternal Viremia until the 27th Week of Gestation

Silvia García-Bujalance¹, Elena Trigo², Alonso L¹, Milagros García-Hortelano³ and María de la Calle⁴

¹Microbiology and Parasitology, University Hospital La Paz-Carlos III, Spain

²National Referral Unit for Tropical and Travel Medicine, Internal Medicine, University Hospital La Paz-Carlos III, Spain

³Pediatrics, Infectious Diseases Unit, University Hospital La Paz-Carlos III, Spain

⁴Department of Gynecology and Obstetrics, Maternal-Fetal Medicine Unit, University Hospital La Paz-Carlos III, Spain

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ABSTRACT

Background: Vertical transmission of Zika virus has been previously reported in several studies. The percentages of fetuses or infants with possible Zika-associated birth defects among completed pregnancy rising to 11% in those infected at first-trimester. **Case report:** We describe a case of symptomatic Zika virus infection during pregnancy in a 37-years-old Mexican woman with maternal viremia for 133 days that resulted in delivery of normal infant. In addition, sexual contact can be excluded because her husband was not infected. Urine, endocervix, vaginal secretions, saliva and amniotic fluid were negative for Zika virus by real time-PCR. **Conclusion:** The etiology of persistent viremia in pregnant women is unclear. Identify the mechanism of prolonged maternal Zika virus RNA detection to reduce the risk of fetal infection is needed. Recommendations of the Center for Disease Control and Prevention (CDC) 2017 for diagnosis of Zika virus infection of pregnancies must be taken under consideration.

Introduction

Zika virus (ZIKV) is an arthropod-borne virus in the genus of Flavivirus. The virus has spread through the Americas since 2015. ZIKV infection in northeastern Brazil has been implicated in a nearly 20-fold increase in the incidence of microcephaly and other severe brain defects in the fetus and newborn. In non-endemic countries such as Spain, cases of vertical transmission from pregnant woman with imported ZIKV infection might happen. Viremia dynamics for ZIKV in infected pregnant women must be monitored. That may last different time spans in asymptomatic adults, infants, pregnant women among others. Persistent maternal viremia may occur as a consequence of viral replication in the fetus or placenta. An appropriate clinical management of pregnancies has been facilitated; the Center for Disease Control and Prevention (CDC) currently recommends a nucleic acid testing of symptomatic pregnant women within 12 weeks of illness onset [1].

Case Report

We describe a case of Zika virus infection during pregnancy in a 37-years-old Mexican woman who visited Mexico in 2016 for three months. Some days before arriving to Spain, she started with fever, non-pruritic maculopapular

Correspondence:

Silvia García-Bujalance,
Paseo de la Castellana 261,
University Hospital La Paz-Carlos
III, 28046 Madrid, Spain,
Tel: +34-91-2071364; Email:
sgbujalance@salud.madrid.org

rash, arthralgia, myalgia and a conjunctival injection (Figure 1).



Figure 1: Maculopapular rash during Zika virus infection

One week later, all symptoms had disappeared. Testing for dengue (Dengue ELISA, Viracell® Microbiologist) and Chikungunya virus (anti-Chikungunya virus ELISA, Euroimmun®) were negative. Testing for ZIKV infection (Anti-Zika Virus ELISA, Euroimmun®) showed a positive IgG and a negative IgM, a positive plaque-reduction neutralization test (CNM, Majadahonda, Spain) and a positive viremia in serum on day 14 since the onset of the symptoms. Thereby, she was started with symptoms in the 8th gestational week. Her Spanish husband was not infected (Anti-Zika Virus ELISA, Euroimmun®). Protected sex during pregnancy was recommended. Laboratory findings showed a haemoglobin concentration of 11.6 gr/dL, normal cell count and leukocyte formula (8.39 x 10⁹ cells/L, N 69.7%, L 22.4 % M 4.7%), normal platelet count (258 x 10³ cells/μL) and a bit elevated C-reactive protein concentration of 11.2 mg/L. A real time RT-PCR assay, RealStarZika® virus RT-PCR kit 1.0, Altona Diagnostics, Germany [2] was performed to follow-up during the pregnancy. She continued viremic at least 131 days after the onset of illness. The viral load was 6.8 x 10³ copies per milliliter (day 45), 1.09 x 10³ copies per milliliter (day 80), 15.7 x 10³ copies per milliliter (only performed in plasma sample, not in serum) (day 101) and 203 copies per milliliter on day 131. On the same dates, urine samples were always negative for ZIKV. On day 168 and day 224, ZIKV RNA was no longer detected. Thus, she presented a prolonged ZIKV maternal viremia between the 8th and 27th week of gestation. Sequencing of the partial genome of ZIKV

described by Oliveira et al. [3] was performed in two consecutive maternal serum samples (GeneBank-Accession numbers MG912101, MG912102). Phylogenetic analysis is showed (Figure 2). Serology screening was negative for *Toxoplasma gondii*, HIV, HCV, HBV, syphilis, cytomegalovirus and positive for Rubella. The amniotic fluid was negative for ZIKV at the 20 weeks plus 6 days of gestation. Fetal neurosonography during pregnancy showed no evidence of brain abnormalities and fetal growth was normal. Vaginal, endocervix and saliva samples were negative for ZIKV by RT-PCR. The baby was delivered at 41 weeks' gestation. There were no abnormal results on neurologic examinations: hypertonicity, hyperreflexia, spasticity or abnormal hearing deficits. Postnatal echography was also normal. ZIKV RT-PCR of urine and serum at birth, in the first and third month were negative, within IgM antibodies negative for ZIKV.

Discussion

ZIKV viremia usually lasts up to 5-7 days since the onset of the illness in symptomatic adults. Viremia could persist for 28 days after infection in whole-blood specimens [4]. However, the pregnant woman described here maintained viremia for 133 days. In previous reports, authors explained that a prolonged maternal viremia may be associated to fetal infection [5-7]. Persistent viremia, they suggested, may occur as a consequence of viral replication in the fetus or placenta. A Finnish woman infected at the first trimester of gestation remained positive for ZIKV RNA for 8 weeks in blood samples. Ultrasonography (US) displayed substantial brain abnormalities and she elected termination of pregnancy. Other of the cited cases above describes a Colombian woman infected at 9 weeks' gestation. ZIKV RT-PCR testing remained positive for 89 days in blood samples. Postnatal ultrasonography at delivery confirmed the presence of microcephaly. Bhatnagar and colleagues demonstrated ZIKV in fetal brains and placentas [8]. In the recent months, two case series have described prolonged viremia in pregnant women that resulted in delivery of normal infants [9,10]. Our case also suggests an absence of viral replication in fetal

brain. Despite a prolonged persistence of ZIKV in maternal serum, the baby was born uninfected and healthy. Nine months later, the infant presents a normal psychomotor development and remains without central nervous system dysfunction or any ocular abnormalities. We highlight the importance about this issue because a time-sensitivity decision about elected termination of pregnancy could be contemplated. In this case report, we obtained a negative ZIKV RNA detection in amniotic fluid at the 20 weeks' gestation. Obstetricians decided to avoid a second amniocentesis despite the persistent viremia because there were not brain injuries in the fetal US. Moreover, fetal weight was normal for the gestational aging.

Vertical transmission of ZIKV has been previously reported in several studies [11,12]. The percentages of fetuses or infants with possible ZIKA-associated birth defects among completed pregnancies and laboratory evidence of recent ZIKV infection were 6%, rising to 11% in those infected at first-trimester of pregnancy [13]. The etiology of prolonged viremia in pregnant women is unclear. Placentas as temporary reservoirs of viral replication could explain the prolonged persistence of ZIKV in the maternal serum. In our case, ZIKV RT-PCR performed in placenta, membranes and umbilical cord returned negative. An effective maternal or fetal immune response could be also occurring, even these are difficult to ascertain.

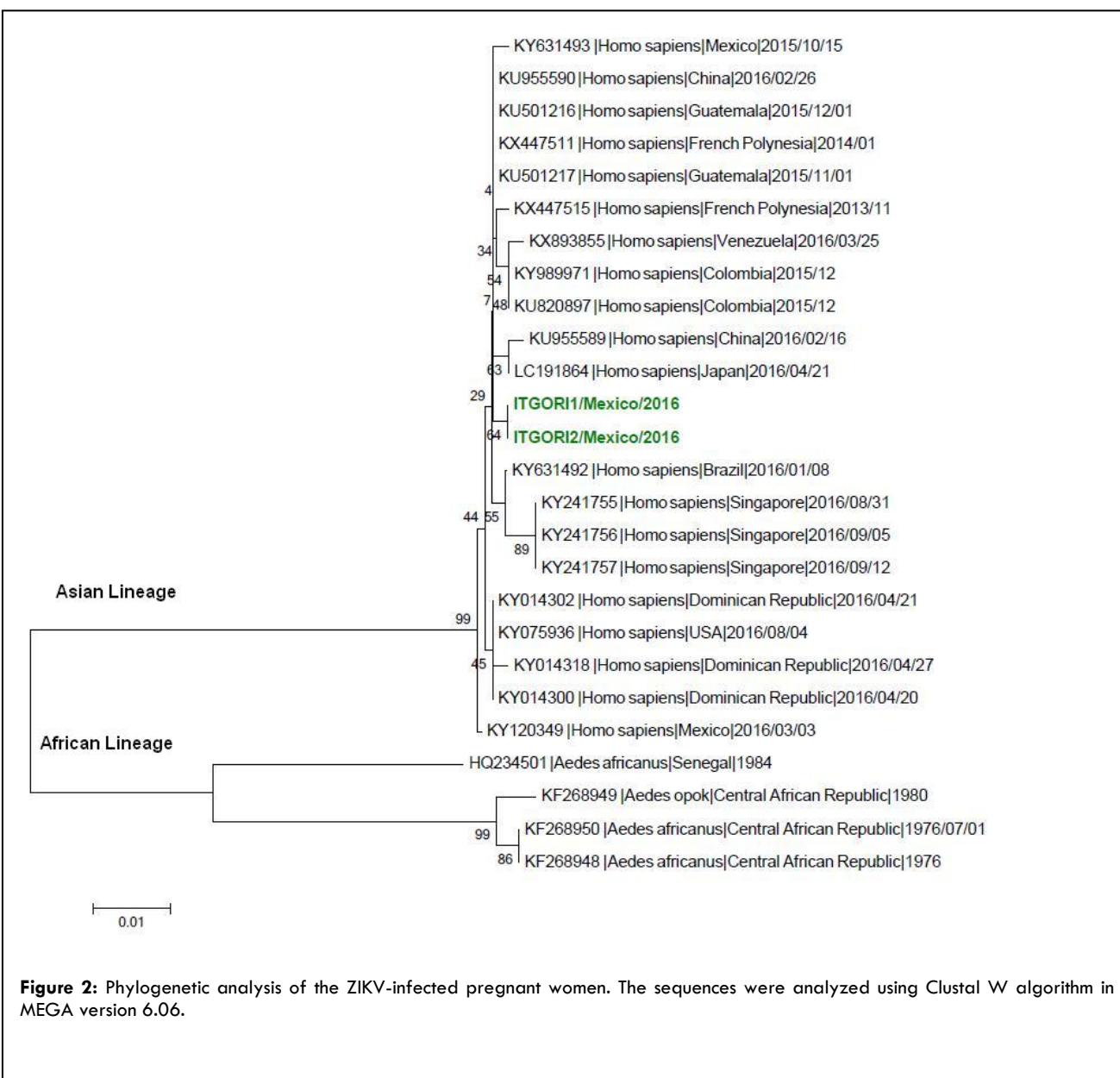


Figure 2: Phylogenetic analysis of the ZIKV-infected pregnant women. The sequences were analyzed using Clustal W algorithm in MEGA version 6.06.

We hypothesize that the placental barrier protected the fetus while the embryogenesis was completed. In addition, we know the vertical transmission of other virus such as cytomegalovirus or chickenpox is lower in the first trimester, although it might have fatal pregnancy outcome if virus infection had occurred at first-trimester of pregnancy.

Conclusion

Presented here is a case of symptomatic infection for ZIKV during first trimester of gestation in a woman with prolonged maternal viremia for 133 days that resulted in delivery of normal infant. Further research is needed to identify the mechanism of prolonged maternal ZIKV RNA detection and to reduce the risk of fetal infection.

Contributors

SGB: drafting of manuscript and revision of microbiological assays; ET: revision for intellectual content and collection of clinical data; LA: revision of manuscript; MGH: critical inputs in manuscript; MC: critical revision and study supervision.

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