Original Research Paper

Volume - 7 | Issue - 6 | June - 2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Medical Science

PROFILE OF THE ZIKA VIRUS EPIDEMIC IN BRAZIL AND WORLDWIDE

Eleomar V. Moraes	Doctorate student in Health Sciences / Faculdade de Medicina / Federal University of Goiás-Brazil
Olegário R. Toledo	Institute of Biological Sciences and Health / Federal University of Mato Grosso-Brazil
Flávia L. David	Institute of Biological Sciences and Health / Federal University of Mato Grosso-Brazil
Mariza M. Avelino	Department of Pediatrics and Child Care / Faculty of Medicine / Federal University of Goiás-Brazil

ABSTRACT The Zika Virus (ZIKV) is the responsible agent for the latest epidemic to affect the Americas. According to the World Health Organization (WHO), the world population exposed is 1,357,605,792 individuals, 207,713,686,176 (15.3%) of them are in Brazil. Objective: To evaluate ZIKV peculiarities, such as diagnosis, clinical status, treatment and prevention. Methodology: It was an integrative review, which had 204 articles analyzed. Results: Studies indicate that the offspring can be infected in any trimester of gestation. Sexual transmission is confirmed and pregnant women with partners at risk should use condoms on all types of sexual relations. In addition to these factors, there are uncertainties in the determination of the dimension of this pathology because, after the certainty of the existence of a new strain of the virus in Brazil, doubts about the true percentage of asymptomatic ones regarding this lineage were found. In this perspective, the cephalic perimeter varied according to the intensity of exposure to ZIKV, hindering the diagnosis. In addition, adult individuals infected with ZIKV with severe thrombocytopenia were found. As consequence, it is recommended to avoid prescribing acetylsalicylic acid (ASA) and derivatives to these patients, preventing hemorrhagic complications. Conclusion: There are advances in diagnosis, treatment, clinical status and prevention. Despite this, we are far from understanding the pathophysiology of this infection, so further studies are needed.

KEYWORDS : Flaviviruses, Fetal Malformation, Cephalic Perimeter.

INTRODUCTION

Zika virus (ZIKV) is transmitted by *Aedes aegypti* mosquito species (vector shared with yellow fever, chikungunya fever and dengue fever, among others)[1]. Isolated in the year of 1947 in Uganda[2], it was, initially, limited to sporadic infections in a small number of countries. For this reason, little clinical importance was associated with Zika's disease at that time, especially for mild symptoms and for being asymptomatic in 80% of the cases[3,4]. In 2007, 60 years after its onset, ZIKV stopped showing sporadic infections and spread to other continents.

In 2007 and 2013, outbreaks on the Pacific islands for the first time appeared. To date, some 73 countries and territories have been hit; most of them located in the Americas. The world population exposed to the ZIKV is 1,357,605,792 individuals, 15.3% of them are in Brazil[5].

The size of the epidemic in Brazil began to be understood after October 2015 when malformations of 26 newborns were associated with ZIKV and, subsequently, by reports of increased microcephaly in the Northeast region. With the events, the Emergency Operations Center for Public Health on Microcephaly (COES) claimed the situation was "Emergency in Public Health"[6]. Subsequently, WHO stated that the set of microcephaly cases and other neurological disorders that occurred in Brazil represented a "Public Health Emergency of International Importance"[7].

According to COES, despite the authorities' efforts, ZIKV has reached 27 states of the federation. According to the geographical distribution, the 9.953 reported cases are distributed in 1.726 (31%) of the 5,570 Brazilian cities[8].

With this situation, the country faces an unusual challenge, with the circulation of different arboviruses such as dengue (DENV), chikungunya (CHIKV) and ZIKAV. There have already been simultaneous outbreaks of Zika and Dengue[9], which allows more severe coinfections and complications.

In this context, some scholars argue that pre-immunity to Dengue would increase the risk of complications during Zika infection[10]. It was also suggested that vaccination against dengue could increase the risk of hemorrhagic dengue in children aged two to five years old, and could generate a disastrous scenario in relation to ZIKV[11,12].

It is important to mention that, the moment presents other aggravating factors. One of them is the heterogeneity of determinants of intrauterine infections present in the Brazilian population, such as toxoplasmosis, cytomegalovirus, herpes, rubella and syphilis, which may confuse clinical diagnosis. Similarly, laboratory testing for viral RNA called PCR (Polymerase Chain Reaction) only provides a reliable result in the narrow viraemia period, whereas serological tests show extensive cross-reaction with flavivirus of vaccination or of contact[13].

Facing the situation of Public Health Emergency of International Importance with the increase in the number of confirmed cases in Brazil, the objective was to evaluate some aspects of ZIKV such as forms of transmission, diagnosis, clinical picture, treatment and prevention.

METHODOLOGY

This study was an integrative review that included 204 full-text articles published in the year of 2016, and analyzed in relation to their importance for the study. From this amount, 31 articles were chosen among observational, experimental, review, original and editorial reports. The searches were carried out in the Google Scholar, BioMed Central, PubMed and Scielo databases, and they occurred between October and November 2016. The following descriptors were used together: "Complications associated with the Zika virus", "Zika virus", "Pregnancy", "microcephaly" and "fetal malformation". Articles with full texts available in English and Portuguese were included for analysis. The study was guided by the following questions: What are the forms of ZIKV transmission and diagnosis? What are the clinical manifestations of ZIKV in the general population, and especially in pregnant women? And, finally, what are the forms of treatment and prevention of ZIKV?

RESULTS E DISCUSSION

Forms of Transmission

The scientific community differs over the period of transmission of Zika during pregnancy. For example, according to Noronha and collaborators (2016),[14] viremia in the early embryonic period appears to be more related to congenital anomalies. It also suggests that, pregnant women infected after placental maturation would be better protected against possible fetal contagion. In fact, another study found indicative of vertical transmission of a pregnant woman who had symptoms at the end of the first trimester of pregnancy. In this case, ZIKV was detected in brain and placenta tissues of the fetus born with

neurological defects[15]. On the other hand, in fetuses of pregnant women at the end of the third trimester, brain abnormalities associated with maternal skin eruptions were found; a specific clinical characteristic of ZIKV, but with cephalic perimeters within the parameters of normality[16]. Information on congenital Zika virus syndrome changes rapidly, but studies indicate a consensus that the offspring can be infected in any trimester of pregnancy.

The transfer of ZIKV through sexual relation is possible, but the biggest concern is with the occurrence during the gestational period. Literature points to several cases that prove this type of transmission[17] and, recently, 14 new events of possible contamination by this route have been found[18]. Therefore, pregnant women with partners who live or travel to areas with ZIKV transmission should avoid sexual activity or always use condoms in all relationships, regarding whether they are vaginal, anal and oral[19].

In addition, it is important to mention that there are two major strains for ZIKAV. An African strain, divided into two groups (eastern and western) and another grouping Asian and American strains[20]. These strains differ significantly from the African ones, since they have adapted to the human defense system, which facilitated their infectivity[21]. Studies indicate that, the infection by this strain is difficult to diagnose, since 80% of the infected population can remain asymptomatic and never seek medical attention. From the American strain, in Bahia, a new strain of ZIKV (129 C class) has emerged, of which, there are no studies confirming the percentage of asymptomatic individuals yet. In addition, there is the possibility of multiple co-circulating strains in state[22].

Diagnosis of ZIKV:

World Health Organization (WHO) warns that, most of the diagnosis tests available on the market have not been regulated. However, efforts are being made to establish a regulatory support and accelerate the evaluation and approval of future clinical trials for ZIKAV vaccines and treatments[23].

The diagnosis of ZIKV infection by ELISA serological method, has been hampered by the cross-reactivity between anti-flavivirus antibodies, and aggravated by the widespread distribution of immunity against these infections in tropical regions[24], especially by Dengue Fever. In addition, it has limited availability in developing countries, particularly in Brazil. On the other hand, the use of the molecular PCR method with modified sensitivity for the detection of ZIKV, is considered gold standard, although it detects the agent only in the period in which the signs and symptoms are evident[25].

ZIKV virus can be detected by PCR from different organic samples: fetal tissues, saliva, blood (plasma, serum) and urine[25,26,27]. In urine samples, besides being considered a non-invasive procedure, it has a wider collection range, and can reach up to 15 days after the end of the viremia[26,28]. Regarding ZIKV detection by saliva[27], it should be considered that, the viral quantity and ideal volume for the sample is still unknown. Furthermore, the time for the appearance of viral particles in this type of sample is unknown. Thus, the PCR technique seems to be more suitable for the urine examination. However, it is possible to confirm the ZIKV infection with combined tests of blood, urine and saliva, and it is up to the health professional to evaluate the cost-benefit of this indication. However, a serological method of consensus, which meets the diagnostic demand for ZIKV infection, is awaited.

Clinical Manifestations of ZIKV:

Epidemiological studies characterize Zika disease as an acute, nonspecific, and self-limiting infection. In most cases, it does not require hospitalization or specialized medical treatment and the individual commonly improves in a week.

The classic clinical picture of this infection, in some aspects, is similar to that of Dengue Fever and Chikungunya Fever, which makes differential diagnosis difficult. The infected person may present low fever, myalgia, polyarthralgy, rashes, head and eye pain, bilateral non-purulent conjunctivitis, maculopapular rash, edema[29,30] and Guillain-Barré syndrome[31].

There is strong evidence that, ZIKV infection is associated with congenital malformations such as microcephaly, intrauterine growth restriction[32,33,34,15,35] and neurological syndromes[36]. Regarding microcephaly, it was found that the size of the newborn's head might vary according to the intensity of exposure to the virus[16]. Thus, it is advisable not to target the clinical criteria only for microcephaly in order not to underestimate the true size of this epidemic.

With recent advances in knowledge on the subject, it has been possible to relate ZIKV infection with a number of additional effects for infected individuals such as severe thrombocytopenia[37]. For the arthrogryposes concept[38], spontaneous abortions and bilateral neuro retinal atrophy[39]. Surely, no other microorganism has affected the human reproductive process to such a large extent.

Treatment and prevention of ZIKV

Despite the efforts of the global scientific community, there is still no vaccine against ZIKV[40,41]. However, although knowledge about the biology of the Zika virus is scarce, there has recently been confirmation of the possibility of manufacturing a vaccine[42].

In the absence of vaccination, control of the disease is limited to the spraying of any insecticide and to the destruction of larval breeding sites. However, there is difficulty in eliminating and identifying foci, since the mosquito is resistant to insecticides in general[43]. Therefore, it is possible to assume that the control of *Aedes aegypti* has become a challenge for the affected countries.

Regarding pharmacological treatment, as the studies progressed, there was evidence that, there is an association between ZIKA infection and severe thrombocytopenia. Thus, it would be prudent to advise against the prescription of ASA and its derivatives to patients suspected of this pathology, to prevent possible hemorrhagic complications.

In the treatment of support, analgesics, and antipyretics and, for cutaneous symptoms, antihistamines should be used[44]. It is also indicated rest and ingestion of liquids.

On the other hand, there are prophylactic strategies that must be followed to avoid mosquito bites such as wearing appropriate clothing (pants and long-sleeved clothing, shoes, socks), treatment of clothes and equipment with permethrin and use of insect repellents. It is worth mentioning that repellents containing picaridin, DEET, eucalyptus citriodora oil (OLE), or IR3535[40], are recommended for pregnant women with more than two months of gestation or infants. Still regarding the repellent, it is recommended to place it after the sunscreen. Finally, the creation of a mechanical barrier of screens on windows and doors, as well as the use of mosquito nets, are strategies that may contribute to non-disease. Before, however, it is necessary that the population understands the need to modify their own behavior that will facilitate the adherence to this prophylactic system.

CONCLUSION

There are advances in diagnosis, treatment, clinical status and prevention. Despite this, we are far from understanding the pathophysiology of this infection, so further studies are needed.

ACKNOWLEDGEMENTS

The study was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

There is no conflict of interest

REFERENCES

[1]. Ioos S, Mallet HP, Goffart IL, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. Medecine et maladies infectieuses. 2014; 44(7):302-307.
[2]. Dick GW, Cozinha SF, Haddow AJ. Vírus Zika I. Os isolamentos e especificidade sorológica. Trans R Soc Trop Med Hyg 1952; 46: 509-520. Disponível em: http ://w ww .ncbi. nlm.n ih.g ov/ pub med/ 12995440, doi: 10,1016 / 0035-9203 (52) 90042-4.
[3]. Simpson DIH. Zika virus infection in man. Trans R Soc Trop Med Hyg. 58:335–8, 1964. DOI: 10.1016/0035-9203(64)90201-9.
[4]. Fagbami AH. Zika virus infections in Nigeria: Virological and seroepidemiological investigations in Oyo State. J Hyg (Lond),1979;83:213–9.
[5]. World Health Organization (WHOa). [Internet]. Situation report: Zika virus, microcephaly, Guillain-Barré syndrome http: // apps .who .int/iris /bitstream/ 10665/ 246112/1/zikasitrep-23Jun2016-eng .pdf? ua=1 (June 23, 2016) (accessed December 16, 2016).
[6]. Centro de Operações de Emergências em Saúde Pública sobre Microcefalias (COES). [Internet]. Monitoramento dos casos de microcefalias no Brasil informe Epidemiológico N0 01 - Brasil 2015. Disponível em http:/www .saude.gov.br/svs.
[7]. World Health Organization (WHOb). [Internet]. Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome http://www.who.int/ media centre/news/statements/2016/emergency-committee-zika-microcephaly/en/# (Feb 1, 2016) (accessed December 16, 2016).
[8]. Centro de Operações de Emergências em Saúde Pública sobre Microcefalias (COES). [Internet]. Monitoramento dos casos de microcefalias no Brasil informe

Epidemiológico 49 - Brasil 2016. Disponível em http:/www .saude .gov. br/svs (acessado em 15 dezembro 2016).
[9]. Campos GS, Bandeira AC, Sardi SI. Zika virus outbreak, Bahia, Brazil. Emerging infectious diseases, 2015; 21: (10) 1885.
[10]. Dejnirattisai W, Supasa P, Wongwiwat W, Rouvinski A, Barba-Spaeth G, Duangchinda T et al. Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. Nat Immunol. 2016; 17(9): 1102–8.
[11]. Capeding M R, Tran NH, Hadinegoro SRS, Ismail HIHM, Chotpitayasunondh T, Chua MN et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet. 2014; 384(9951): 1358–65.
[12]. Villar L, Dayan GH, Arredondo-García JL, Rivera DM, Cunha R, Deseda C. et al.: Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med. 2015; 372(2): 113–23.
[13]. Waggoner JJ, Pinsky BA. Zika Virus: Diagnostics for an Emerging Pandemic Threat. J Clin Microbiol, 2016.
[14]. Noronha LD, Zanluca C, Azevedo MLV, Luz KG, Santos CNDD. Zika virus damages the human placental barrier and presents marked fetal neurotropism. Mem Inst Oswaldo Cruz, Rio de Janeiro: 1-7, 2016.
[15]. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, Vizjak, A. Zika virus associated with microcephaly. New England Journal of Medicine. 2016; 374(10), 951-958 1.
[16]. França GV, Schuler-Faccini L, Oliveira WK, Henriques CM, Carmo EH, Pedi VD, Barros FC. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. The Lancet. 2016; 388(10047), 891-897.
[17]. Foy BD, Kobylinski KC, Chilson Foy JL, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. 2011;17:880-2.
[18]. Duhaime-Ross A. Zika ligada a defeitos de nascimento mais do que apenas microcefalia. À beira de 2016.[Online] Disponível a partir de:http://www.the verge.com /2016/3 /8/11181088/zika-birth-defects-fetal-death-growth-retarda tion-who.
[19]. Oduyebo T, Petersen EE, Rasmussen SA, et al. Update: interim guidelines for health care providers caring for pregnant women and women of reproductive age with possible Zika virus exposure-United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65.
[20]. Saiz JC, Vázquez-Calvo A, Blázquez AB, Merino-Ramos T, Escribano-Romero E, Martín Acebes-MA. Virus Zika: as últimas Iniciante. Frente Microbiol. 2016; 7: 496.
[21]. Andersen KG, Shapiro BJ, Matranga CB, Sealfon R, Lin AE, Moses LM, Folarin OA, Goba A, Odia I, Ehiane PE. Sequencing clínica descobre origens e evolução do vírus de Lassa. Celular. 2015; 162: 738-750.
[22]. NACCACHE, Samia et al. Discovery of a persistent Zika virus lineage in Bahia, Brazil. bioRxiv. 2016; p. 049916.
[23]. World Health Organization (WHO). [Internet]. Statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations . http://www.who.int/ mediacentre/news/statements/2016/1st-emergency-commi tt ee - zika/en/; Feb 1, 2016. (accessed Dez 7, 2016).
[24]. Hayes EB et al. Zika virus outside Africa. Emerg Infect Dis, v. 15, n. 9, p. 1347-50, 2009.
[25]. Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, Lambert AJ, Johnson AJ et al.Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007 Emerg Infect Dis, 14. (2008), pp. 1232–1239.
[26]. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine Emerg Infect Dis, 21 (2015), pp. 84–86.
[27]. Musso D, Roche C, Nhan TX, Robin E, Teissier A, Cao-Lormeau VM. Detection of Zika virus in saliva J Clin Virol, 68 (2015), pp. 53–55.
[28]. Campos MR, Cirne-Santos C, Meira GL, Santos LL, Meneses MD, Friedrich J, et al. Prolonged detection of Zika virus RNA in urine samples during the ongoing Zika virus epidemic in Brazil. J Clin Virol 2016; 77: 69-70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26921737, doi: 10.10 16/ j.jcv.2016.02.009.
[29]. Heang V, Yasuda CY, Sovann L, Haddow AD, Travassos da Rosa AP, Tesh RB, Kasper MR. Infecção Zika vírus, Camboja de 2010 Emerg Infect Dis. 2012; 18349-351.
[30]. Aubry M, Finke J, Teissier A, Roche C, Broult J, Paulous S, Despres P, Cao-Lormeau VM, Musso D. Soroprevalência de arboviroses entre doadores de sangue na Polinésia Francesa, 2011-2013 Int J Infect Dis. 41 (2015), 11-12.
[31]. Cao-Lormeau VM, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, Vial AL. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. The Lancet, 387(10027), 1531-1539, 2016.
[32]. ECDC. Microcefalia no Brasil potencialmente decorrente da epidemia do vírus Zika. Centro Europeu de Prevenção e Controlo das Doenças de Estocolmo; 2015.
[33]. Calvet G, Aguiar RS, Melo AS, Sampaio SA, Filippis I, Fabri A, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect. Dis. 16, 653–660 (2016)
[34]. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. The Lancet. 2016; 387(10033), 2125-2132.
[35]. Vogel, G. (2016). Emerging diseases. A race to explain Brazil's spike in birth defects. Science 351, 110–111.
[36]. Pan American Health Organization. (OPAS). Update Neurological syndrome, congenitall anomalies, and Zika virus infection. 2016 (http://www. paho. org/hq /index. php? option= com_ docman &task=doc_download& Itemid=&gid=32879&lang=en Epiidemiiollogiicall). (accessed December 16, 2016).
[37]. Sharp TM, Muñoz-Jordán, J, Perez-Padilla J, Bello-Pagán MI, Rivera A, Pastula DM, et al. Zika virus infection associated with severe thrombocytopenia. Clinical Infectious Diseases. 2016; ciw476.
[38]. Martines RB, Bhatnagar J, Oliveira Ramos AM, Davi HPF, Iglezias SDA, Kanamura CT, Ritter J. Pathology of congenital Zika syndrome in Brazil: a case series. The Lancet. 2016; 388(10047), 898-904.
[39]. Ventura CV, Maia M, Bravo-Filho V, Góis AL, Belfort R. Zika virus in Brazil and macular atrophy in a child with microcephaly. Lancet. 2016; 387, 228.
[40]. Fauci AS, Morens DM. Zika virus in the Americas – Yet another Arbovirus threat N Engl J Med, 374 (7) (2016), pp. 601–604 Ministry of Health. Zika virus. [Online]. Available from: http://www.health.govt.nz/our-work/ diseases-and-conditions/zika-virus. [Accessed on 30 March 2016].
[41]. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N. Engl. J. Med.374, 1552–1563 (2016).
[42]. Larocca RA, Abbink P, Peron JPS, Paolo MDA, Iampietro MJ, Badamchi-Zadeh A, et al. Vaccine protection against Zika virus from Brazil. Nature. 2016; 536(7617), 474-478.
[43]. Lima PE, Paiva MH, Araujo AP, et al Resistência a inseticidas em Aedes aegypti populações do Ceará, Brasil. Parasitas vetores. 2011; 4:5
[44]. Simmons CP, McPherson K, Chau NVV, Tam DH, Young P, Mackenzie J, Wills B. Os avanços recentes na patogênese da dengue e manejo clínico.Vaccine. 2015; 33,7061-7068.