Mini Review

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Journal of MPE Molecular Pathological Epidemiology

2017
Vol.2 No.S1:01

A Review of the Evidence Linking Zika Virus to the Developmental Abnormalities that Lead to Microcephaly in View of Recent Cases of Birth Defects in Africa

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Received date: Oct 03, 2016; **Accepted date**: Oct 25, 2016; **Published Date**: Oct 28, 2016

Citation: Icheku V. A review of the evidence linking Zika virus to the developmental abnormalities that lead to microcephaly in view of recent cases of birth defects in Africa. J Mol Pathol Epidemiol. 2017, 2:S1.

Abstract

The World Health Organization (WHO) in May 2016 confirmed an outbreak of the Zika virus on the African island chain of Cape Verde, linking it to cases of the brain disease, microcephaly. This finding is of concern because Zika was first discovered in East Africa in 1947 with no known link to brain or birth disorders until the WHO reported findings. The question, therefore, is: if the Zika virus has been in Africa for 69 years, why wasn't any association to microcephaly detected before the recent WHO findings in Brazil (see below) and Cape Verde? This study reviews the evidence linking Zika to microcephaly in view of recent cases of birth defects in Africa, with the aim of providing vital clues as to why there was no documented case of such birth defects in Africa, where the Zika virus originated.

The literature for this review was gathered through internet searches, including the websites of the European Centre for Disease Prevention and Control (ECDC), the United States Centre for Disease Control and Prevention (CDC), the World Health Organization (WHO) and Public Health England (PHE).

Materials from these sources were reviewed on the link between the Zika virus and microcephaly in relation to the recent cases of birth defects in Africa. Two possible explanations emerged from the review. The first explanation suggests that the phenomenon called herd immunity may have taken place in Africa. The Zika virus cannot infect the same person twice because it reaches a stage where there are too few people left to be infected for transmission to be sustained. The second explanation suggests that microcephaly linked to birth defects is caused by other conditions.

In conclusion, the findings of this review opens up the debate on the connection between the Zika virus and the birth defect attributed to mosquito-borne microcephaly, given that there is no documented case of birth defect in Africa 69 years after the discovery of the Zika virus. Large-scale research is recommended on the Zika virus and pregnancy in Africa for better understanding of the ecology and epidemiology of the virus in the continent.

Keywords: *Aedes aegypti* mosquito; Africa; Birth defect; Microcephaly; Pregnancy; Zika virus

Introduction

The Zika virus is a Flavivirus from the family Flaviviridae, which has emerged as a global mosquito-borne pathogen of growing public health concern [1]. The Aedes *aegypti* mosquito was implicated in a study by Boorman and Porterfield as the main vector transmitting the Zika virus. This finding was confirmed by a later experimental study that demonstrated the competence of the Aedes *aegypti* mosquito to transmit the Zika virus [2]. The Aedes aegypti mosquito is one of the two mosquitoes (Aedes *aegypti* and Aedes *albopictus*) that spread the dengue and chikungunya viruses. The virus is mostly transmitted to individuals through bites from infected *Aedes aegypti* mosquitos. The mosquito becomes infected when it feeds on a person already infected with the virus; it cannot be caught from merely coming into contact with the infected person. The symptoms of an infected person include fever, headache, myalgia, joint pains, maculopapular rash, eye pain, itching, arthralgia, muscle pain, and conjunctivitis or "red eye" [1,3].

Serological evidence and virus isolations have demonstrated widespread distribution of the Zika virus in Africa, the Indian subcontinent, Southeast Asia, Micronesia and French Polynesia, and most recently the American continent. For example, the latest Global Situation Report on Zika by WHO shows that 72 countries and territories have reported evidence of Zika virus transmission since 2007. The report further shows that since February 2016, 20 countries or territories have reported microcephaly potentially associated with Zika virus infection. Four of the 20 countries reported microcephalic babies born from mothers in countries with no endemic Zika virus transmission but who reported recent travel history to Zika-affected countries [4]. Thus, having considered the evidence presented at the fourth meeting of the WHO Emergency Committee on Zika held on 1 September 2016, the Committee agreed that, due to continuing geographic expansion and considerable gaps in understanding of the virus and its consequences, the Zika virus infection continues to be a Public Health Emergency of International Concern (WHO, 2016), as originally notified in February 2016 [5].

In May 2016, WHO tests confirmed 200 cases of Zika virus with 7,557 suspected cases in the African island chain of Cape Verde [6]. Cape Verde is an Atlantic archipelago that is about 350 miles (570 km) west of Senegal and which has historic ties to Brazil [7]. The virus was first isolated in 1947 from a febrile sentinel rhesus monkey in the Zika forest in Uganda, where it got its name [1]. The forest at the time was the hub of scientific research in East Africa and, while carrying out tests on wild African monkeys in the Zika forest, scientists, whose research had been funded by the Rockefeller Foundation, unexpectedly discovered a previously unknown microorganism, which they later named Zika [8].

According to CDC, Zika showed up in Brazil in 2014 with only 150 cases, which is a very small number for its population, compared to the outbreak in 2015. The outbreak in Brazil, beginning in May 2015, was unprecedented and is reported to have resulted in in more than 1 million cases, with 4,000 suspected cases of microcephaly, and 270 confirmed cases that health officials believe are linked to the Zika virus [9]. Microcephaly is a condition that makes a baby's head smaller than expected when compared to other babies of the same sex and age. The babies often have smaller brains apparently lacking in normal development. Other complications of microcephaly include seizures, hearing loss, vision problems, intellectual disability such as decreased ability to learn and function in daily life, developmental delay such as problems with speech or other developmental milestones, including sitting, standing and walking. These problems can range from mild to severe, are often life-long and, in some cases, can be life-threatening [1].

One study shows that the association of Zika virus infection with pregnancy began during the outbreak of the disease in north-east Brazil in early 2015. The test carried out by the Brazilian Ministry of Health identified Zika virus RNA (ribonucleic acid) in the amniotic fluid of two women whose foetuses had been found by prenatal ultrasound to have microcephaly [10]. This finding prompted the Brazilian Ministry of Health to report on its website a possible association of microcephaly with Zika virus infection during pregnancy. Subsequently, the Pan American Health Organization (PAHO) reported the identification of Zika virus RNA by reverse transcription-polymerase chain reaction (RT-PCR) in in the tests on the two pregnant women, and the identification of Zika virus RNA from multiple body tissues, including the brain, of an infant with microcephaly who died in the immediate neonatal period [11]. The report of these findings prompted both the ECDC and CDC to publish reports concerning the possible association of microcephaly with the Zika virus outbreak [12]. The WHO Global Situation Report on Zika in 2016 reported that Zika virus infection during pregnancy causes microcephaly [13].

In May 2016, the WHO tests confirmed two hundred cases of Zika virus with 7,557 suspected cases in the African island chain of Cape Verde. The Zika virus, linked in Brazil to the birth defect microcephaly, was first identified in the Ugandan Zika forest in 1947. Until this recent WHO finding, there was no documented evidence of Zika-associated microcephaly in any part of Africa, where the virus originated [7]. This once more raises the question as to what is the connection between Zika virus and microcephaly. In other words, is mosquito-borne infection actually the cause of the defects in babies born to Zika-virus-infected mothers?

Aim and Objective

The aim of this study is to review the evidence linking Zika virus to the developmental abnormalities that lead to microcephaly in view of recent cases of birth defects in Africa. The objective is to provide vital clues as to why there was no documented case in Africa of such birth defects linked to the virus during the 69 years since its discovery in East Africa.

Method

The literature for this review was gathered through searches on Google Scholar and the Google search browser. The European Centre for Disease Prevention and Control (ECDC), United States Centre for Disease Control and Prevention (CDC), World Health Organization (WHO) and Public Health England (PHE) websites were also searched.

Result

The Zika virus, which has been linked in Brazil to the birth defect called microcephaly, was first identified in the Ugandan Zika forest in 1947 [1]. Until the recent WHO finding in Cape Verde, there was no documented evidence of Zika-associated microcephaly in any part of Africa, the continent where the virus originated [7]. This once more raises the question as to what is the connection between Zika virus and microcephaly. The review found evidence suggesting that the phenomenon called herd immunity may have taken place in Africa. The Zika virus cannot infect the same person twice when it reaches a stage where there are too few people left to be infected for transmission to be sustained [13-15]. The review also found evidence suggesting that microcephaly linked to birth defects is caused by other conditions [12]. This suggestion re-opens the debate on the connection between the Zika virus found in pregnant women and the birth defects attributed to mosquito-borne microcephaly infections.

Discussion

Until this recent WHO's finding, there was no documented evidence of Zika-associated microcephaly in any part of Africa where the virus originated [7]. The question, therefore, is: although the Zika virus has been in Africa for 69 years, why was no association to microcephaly detected before the recent WHO findings? Two possible explanations emerged from this review:

The first possible explanation is due to a phenomenon called herd immunity. According to Fine et al. (2011) the term herd immunity, referring to an entire population's immunity, was used to describe a naturally occurring phenomenon in the 1930s when it was observed that, after a large group of children had become immune to measles infection, new infections decreased in the short term [13]. In other words, herd immunity becomes a type of indirect protection from infectious disease, occurring when a significant percentage of a population has become immune to an infection, thereby providing a measure of protection for individuals who are not immune and thus decreasing the number of new infections [14].

As indicated above, the virus was discovered in the Zika forest in Uganda 69 years ago. It is common in Africa but it did not begin spreading widely in the Western Hemisphere until May 2015 when the outbreak occurred in Brazil [16]. Herd immunity may have been the reason why there was no scientific evidence linking microcephaly to the Zika virus earlier. The greater the proportion of individuals in the herd community who are immune to the virus, the lesser the probability that those who are not immune will come into contact with an infected individual [13]. It is not surprising therefore that a new study by scientists at Imperial College London predicted that “once the current epidemic is over, herd immunity will lead to a delay of at least a decade before large epidemics may recur” [15].

The second possible explanation opens up the debate on the connection between the Zika virus found in pregnant women and the birth defects attributed to mosquito-borne microcephaly [17,18]. The WHO Global Situation Report on Zika virus in 2016 reported that Zika virus infection during pregnancy is a cause of microcephaly. The conclusion was based on a systematic review of the literature up to 30 May 2016. However, the findings, which emerge from a causality framework that WHO, developed in February 2016 to appraise the strengths and weaknesses of available evidence, identify gaps in research [4].

The association between viral infections and pregnancy has long been recognized. For example, one study on viral infections and pregnancy shows that pregnant women suffer worse outcomes during viral epidemics and pandemics than the general population and non-pregnant women. A study explains that women go through an immunological transformation during pregnancy. Adverse pregnancy outcomes may result when the immune system required for promoting and supporting the pregnancy and growing foetus is compromised due to infection [19].

In a review of literature, Icheku and Icheku (2016) found no conclusive evidence that Zika virus infection caused any of the abnormalities found in the babies with microcephaly. The study could also not find any conclusive scientific evidence of the full spectrum of outcomes that might be associated with Zika virus infection during pregnancy or the factors that might increase risk of the disease infection to the fetus [1]. However, a subsequent systematic review panel on Zika virus infection and neurological disorders found epidemiological studies, which suggested a marked increase in the risk of brain abnormalities in fetuses and new-borns when a woman acquires Zika virus infection during pregnancy [20].

CDC recently reported that the causes of microcephaly in babies are mostly inconclusive. Some babies have microcephaly because of other abnormalities. Other causes of microcephaly, including severe microcephaly, can include exposures during pregnancy to certain infections such a s rubella, toxoplasmosis or cytomegalovirus; also to lack of nutrients or not getting enough food, exposure to harmful substances, such as alcohol, certain drugs, or toxic chemicals, and interruption of the blood supply to the baby’s brain during development. Finally, this calls for large-scale studies to produce conclusive evidence of other causes of abnormalities in babies born to mothers infected with Zika virus during pregnancy [12].

Conclusion

The likelihood that herd immunity occurred may explain why the Zika virus has been in Africa for almost seven decades without any documented link to microcephaly. Herd immunity may have provided protection against the Zika virus in Africa when a significant percentage of the population has become immune to the disease, thereby providing a measure of protection for individuals who are not immune and thus decreasing the number of new infections [14]. In addition, the absence of large scale studies that produce robust scientific evidence linking microcephaly to other causes seem to offer additional clues as to why there had been no known cases of microcephaly in Africa [12].

Finally, the findings of this review opens up the debate on the connection between the Zika virus and the birth defect attributed to mosquito-borne microcephaly, given that until recently, there is no documented case of birth defect in Africa where the virus originated. Large-scale research is recommended on the Zika virus and pregnancy in Africa for better understanding of the ecology and epidemiology of the virus in the continent.

References

1. Icheku V, Icheku C (2016) Exploration of Zika Virus Travel-related Transmission and a Review of Travel Advice to Minimise Health Risks to UK Travellers. Universal Journal of Public Health 4: 203-211.
2. Cornet M, Robin Y, Adam C, Valade M, Calvo MA (1979) Transmission expérimentale comparée du virus amaril et du virus Zika chez Aedes aegypti L. Cah ORSTOM ser Ent med et Parasitol 17: 47-53.
3. Centers for Disease Control and Prevention (2016) Recognizing, managing, and reporting Zika virus infections in travelers returning from Central America, South America, the Caribbean, and Mexico. CDC Health Advisory. Atlanta.
4. WHO (2016) Latest Global Situation Report on Zika: Zika virus, Microcephaly and Guillain-Barré syndrome.
5. WHO (2016) WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome.
6. WHO (2016) Zika situation report.
7. Davis N (2016) Brazilian strain of Zika virus confirmed in Africa, says WHO.
8. BBC news (2016) Zika virus: Inside Uganda's forest where the disease originates.

9. CDC2 (2016) Facts about Microcephaly.
10. Campos GS, Bandeira AC, Sardi SI (2015) Zika virus outbreak, Bahia, Brazil. Emerging infectious diseases 21: 1885-1886.
11. PAHO (2015) Neurological syndrome, congenital malformations, and Zika virus infection: Implications for public health in the Americas—epidemiological alert. Washington DC: World Health Organization, Pan American Health Organization.
12. CDC (2016) Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015.
13. Fine P, Eames K, Heymann DL (2011) "Herd immunity": a rough guide. Clinical infectious diseases 52: 911-916.
14. Orenstein WA, Hinman AR, Papania MJ (2004) Evolution of measles elimination strategies in the United States. Journal of Infectious Diseases 189: S17-S22.
15. Ferguson NM, Cucunuba ZM, Dorigatti I, Nedjati-Gilani GL, Donnelly CA, et al. (2016) Countering Zika in Latin America. Science 353: 353-354.
16. McNeil D, Louis CS, St Fleur N 2016 Short answers to hard questions about Zika virus. The New York times.
17. CDC (2016) Pregnancy, Centers for Disease Control and Prevention.
18. CDC (2016) Transmission through mosquito bites, Centers for Disease Control and Prevention.
19. Silasi M, Cardenas I, Kwon JY, Racicot K, Aldo P, et al. (2015) Viral infections during pregnancy. Am J Reprod Immunol 73: 199-213.
20. WHO (2016) Zika causality statement, Update of WHO Statement published on 31 March 2016.

This article was originally published in a special issue, entitled: **"Zika virus epidemiology and recent Epidemics",** Edited by Dr Suzane Ramos da Silva