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Zika Virus: A Recent Emerging Threat to Global Health

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Review Article

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ABSTRACT

Zika virus (ZIKV) is a mosquito-borne virus that belongs to the virus family *Flaviviridae* and the genus *Flavivirus*. It was first isolated from a rhesus monkey in Uganda in 1947, and caused sporadic human infections in some African and Asian countries, with usually mild symptoms of fever, rash, and arthralgia. It is also related to the Dengue, Yellow fever, Japanese encephalitis, and West Nile viruses. It has been known to occur within a narrow equatorial belt from Africa to Asia, since 1950s. Zika virus is an emerging pathogen and is the focus of an ongoing pandemic and public health emergency. Most often people get Zika through the bite of an infected Aedes Aegypti mosquito; this is the same mosquito that spreads dengue and Chikungunya. All these viruses cause similar symptoms, but there are some certain symptoms that suggest one disease or another. Most Zika patients have skin rashes in the whole body. No specific treatment like vaccine or preventive drug has been discovered yet for this infection. Possible treatment includes taking rest, drinking fluids to prevent dehydration and taking medicines such as acetaminophen or paracetamol to relieve fever and pain. This review summarizes the current understanding of ZIKV biology and epidemiology, as well as possible interventions to understand the role of the virus and the pathogenesis of these disorders to prevent contagion and transmission.

INTRODUCTION

Zika virus is a mosquito-borne Flavivirus that was first discovered in Uganda in 1947 through a colony of monkeys suffering from Yellow fever. It was then later detected in humans in 1952 in Uganda and the United Republic of Tanzania. Outbreaks of Zika virus sickness had been recorded in Africa, the Americas, Asia and the Pacific. From the 1960s to 1980s, human infections had been determined across Africa and Asia, creating a major health problem around the world. The enormous outbreak of sickness caused through Zika infections that are explored from the Island of Yap (Federated States of Micronesia) in 2007 [1]. In July 2015, Brazil stated that there exist some

similarities between Zika virus illness and Guillain-Barré syndrome. In October 2015, Brazil again mentioned that ZIKV infection resembles microcephaly [2]. In spite of growing knowledge about this virus, there are some factors like virus's vectors and reservoirs, pathogenesis, genetic variety, and potential synergistic effects of co-contamination with different circulating viruses need to be discovered [3].

HISTORY

Virus in Monkeys and Mosquitoes, 1947

The virus was first isolated in April 1947 from a rhesus macaque monkey that had been placed in a cage within the Zika woodland of Uganda, close Lake Victoria, through the scientists of the Yellow Fever research Institute. A second isolation from the mosquito *A. africanus* followed on the same site in January 1948 [4]. When the monkey developed a fever, researchers isolated a "filterable transmissible agent" from its serum that was named Zika in 1948.

Evidence of virus in Humans, 1952

Zika had been recognized to contaminate humans from the result of serological surveys in Uganda and Nigeria, released in 1952: amongst 84 humans, 50 contributors had antibodies to Zika, and all above 40 years of age had been immune. A 1952 study performed in India had proven a particular number of Indians had exhibited an immune response to the virus, suggesting it had been prevalent inside human populations [5,6].

Extent in Equatorial Africa and Asia, 1951-1983

From 1951 to 1983, proof of human illness with Zika was reported from other African nations, like Central African Republic, Egypt, Gabon, Sierra Leone, Tanzania, and Uganda, countries of Asia including India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam and Pakistan. From its discovery until 2007, 14 human instances of Zika contamination had been found from Africa and Southeast Asia [7].

Outside of Asia and Africa, 2007

The very first occurrence in the external of Africa and Asia came about on the island of Yap in the Federated States of Micronesia in April 2007, characterized with the aid of making use of rash, conjunctivitis, and arthralgia, which was recommended to be Dengue in the beginning, Chikungunya, or Ross River ailment [8]. RNA of Zika had been detected in the serum samples of the people suffering from illness. There had been 49 confirmed instances, 59 unconfirmed events with no hospitalizations, and no deaths [9].

2015-present

In the beginning of 2016, a modern outbreak of Zika was on-going, mainly inside the Americas. The outbreak commenced in April 2015 in Brazil, and has spread to specific locations of South America, Central America, Mexico, and the Caribbean. In January 2016, the WHO said the virus can be spread to many parts of America within a year, and in February 2016, the WHO declared the cluster of microcephaly and Guillain-Barré syndrome instances

mentioned in Brazil was strongly suspected to be related to the Zika outbreak, a Public Health Emergency of International Concern. It is estimated that 1.5 million individuals have been infected by Zika in Brazil, with over 3500 cases of microcephaly was reported between October 2015 and January 2016 [10].

VIROLOGY AND PATHOGENESIS

Zika virus is a single-stranded RNA virus in the family Flaviviridae, which includes a variety of mosquito-borne viruses of scientific significance (e.g. Dengue virus and Yellow fever virus). Its closest relative is Spondweni virus, the only different member of its clade. The Zika virus genome comprises 10,794 nucleotides encoding 3,419 amino acids. Like other Flaviviruses, Zika virus is composed of two noncoding regions (5′ and 3′) that flank an open reading frame, which encodes a polyprotein cleaved into the capsid, precursor of membrane, envelope, and 7 non-structural proteins.

Phylogenetic analysis indicates that Zika virus can be classified into specified African and Asian lineages; each one of them emerged from East Africa in late 1800s or early 1900s. The Asian lineage originated during the virus's migration from Africa to Southeast Asia, the place it was once first detected in Malaysia. From there, Zika virus spread to the Pacific Islands, individually to Yap and French Polynesia, and then to New Caledonia, Cook Islands, Easter Island, and the Americas [11].

A study was conducted from 1947 to 2007 on Zika virus's molecular evolution based on viral lines gathered from four countries in West Africa revealed that Zika contains several sites that were under negative selection pressure. This discovery suggests purging of deleterious polymorphisms in functionally primary genes and the probability of recombination, which occurs amongst Flaviviruses in very few cases. The implications of this discovery require further analysis with respect to viral spread, zoonotic maintenance, and epidemiologic knowledge.

After mosquito inoculation of a human host, cellular entry probably resembles that of other Flaviviruses, whereby the virus enters skin cells by means of cellular receptors, enabling migration to the lymph nodes and bloodstream. Few reviews have investigated the pathogenesis of Zika virus contamination. One has confirmed that human skin fibroblasts, keratinocytes, and immature dendritic cells allow entry of Zika virus [12]. Infection is caused by several entries and adhesion factors, and cellular autophagy, needed for Flaviviral replication, enhances Zika virus replication in epidermis fibroblasts. After entry, Flaviviruses usually replicate within endoplasmic reticulum derived vesicles. Also, Zika virus antigens have been discovered solely in the nuclei of contaminated cells; this invention suggests a location for replication that differs from that of different Flaviviruses and merits further investigation [13].

CLINICAL MANIFESTATIONS

In humans, the incubation interval from mosquito bite to symptom development is approximately 3-12 days. Infection is probably going asymptomatic in approximately 80% of circumstances. All ages are susceptible (4 days-76 years) to this virus, with a slight preponderance of situations in women. When signs arise, they are regularly mild, self-limiting, and nonspecific; similar to other arbovirus infections e.g. Dengue and Chikungunya virus may just confound the analysis [14]. Maximum reported signs include rash, fever, arthralgia, myalgia, fatigue, headache, and conjunctivitis. Rash, a distinguished function, is maculopapular and pruritic frequently; it starts proximally and

spreads to the extremities with spontaneous resolution within 1-4 days of onset. Fever is generally low grade (37.4°C-38°C). Symptoms develop within 2 weeks; accounts of longer persistence are rare. Infrequent deaths were described in sufferers infected with Zika virus. Besides 1 boy or girl death, 3 other fatalities were mentioned (2 from Brazil and 1 from Colombia); 1 man with lupus erythematosus, persistent corticosteroid use, rheumatoid arthritis, and alcoholism; and 2 ladies sixteen years of age, 1 with sickle cell disease and medical historical past was not mentioned for the other lady [15].

TRANSMISSION

Zika virus, like different Flaviviruses, is transmitted by mosquitoes, mainly of the Aedes (Stegomyia) genus. A couple of Aedes sp. had been implicated, including *Ae. Aegypti, Ae. Africanus, Ae. Hensilli,* and *Ae. Albopictus*. The *Ae. Aegypti* mosquito seems to be the most important vector in Asia and was once suspected to be the principal vector for the French Polynesia outbreak. Zika virus has been detected in the forest of Uganda in *Ae. Aegypti* mosquitoes, Laboratory experiments in *Ae. Aegypti* have been proven to transmit Zika virus, *Ae. Hensilli* mosquitoes have been implicated in the Yap outbreak, yet Zika virus has never been isolated from these mosquitoes [16].

Other non-vector modes of Zika virus transmission comprises congenital, perinatal, and sexual. Transmission by blood transfusion, animal bite, and laboratory exposure has been described; nevertheless, confounding by way of contemporaneous vector borne transmission in these instances cannot be excluded [17]. For example, a person infected with Zika virus after a monkey bite had concomitant exposure to mosquitoes, a possible route of acquisition. Similarly, one of the two patients with probably laboratory-obtained contamination reported recent exposure to mosquitoes; no definitive mechanism for transmission was described for both the sufferers.

Intrauterine transmission is supported with the aid of the finding of Zika virus RNA by means of Reverse Transcription Polymerase Chain Reaction (RT-PCR) in amniotic fluid of two mothers with signs of Zika virus contamination in the course of pregnancy; both delivered babies with microcephaly. Zika virus RNA has additionally been identified in tissue of foetuses from women infected throughout pregnancy and in brains of two recently born babies with microcephaly who died within twenty hours after start. Probable intrapartum transmission has also been described: two new-borns had been determined to be viremic with Zika virus in a time span of less than four days after taking birth from two infected mothers. Viral RNA has been detected in breast milk, but transmission via breast-feeding has not been reported yet [18].

Two cases of possible transmission of Zika virus via transfusion were reported in Brazil. Furthermore, during the French Polynesia outbreak, a study found that 42 (2.8%) of 1,505 asymptomatic blood donors were positive for Zika virus by RT-PCR; 11 donors described a Zika fever-like syndrome 3-10 days after donation.

DIAGNOSIS

Clinical evaluation alone is unreliable for a diagnosis of Zika virus illness. Diagnosis depends on laboratory testing because of scientific overlap with different arboviruses. Evaluation for Zika virus, Chikungunya virus, and Dengue virus will have to be undertaken concurrently for all patients who have acute fever, rash, myalgia, or arthralgia after recent (previous 2 weeks) travel to a place of on-going Zika virus transmission [19]. Commercial assays had been

developed, including a PCR-headquartered assay that has been approved by using the Communauté Européenne (RealStar Zika Virus RT-PCR kit 1.0, altona Diagnostics, Hamburg, Germany) and a serologic assay that has been authorized by the US food and Drug Administration for limited use in emergency occasions. Testing has frequently been carried out by using large reference laboratories (e.g. US CDC and US state laboratories) and universities. CDC's normal turnaround time is 4-14 days. On the basis of clinical information provided by the requesting healthcare supplier, laboratory selects proper tests for them. To coordinate sample assortment, providers should contact public health agencies in the neighbourhood before testing [20].

The sort of sample may affect the probability of detection. Although diagnostic checking out is carried out mainly on serum or cerebrospinal fluid, the diagnostic utility of alternative specimen types (e.g. urine, saliva, amniotic fluid, and tissue) is being evaluated [21]. Urine and saliva may offer alternatives, especially when blood collection is problematic (e.g. in children or remote locations). Viruria may persist longer than viremia. One of the study reported that Zika virus RNA was once detected in urine as much as 20 days after viremia had come to be undetectable; for this reason, RT-PCR testing of urine should be considered when Zika virus is clinically suspected, regardless of terrible serum checking out. In a similar way, RT-PCR carried out with saliva has been proven to increase the detection expense throughout the acute segment of infection but does not lengthen the window of detection of Zika virus RNA; as a result, blood remains the preferred sample [22-24].

MANAGEMENT AND PREVENTION

No targeted medication or vaccine is still discovered for Zika virus illness. Management is supportive and includes rest, fluids, antipyretics, and analgesics. Aspirin and other non-steroidal anti-inflammatory medications should be avoided until dengue is excluded due to the fact of the risk for hemorrhage amongst dengue patients.

Different measures has been taken for the prevention of mosquito bites, together with individual defense (e.g. long pants, light-colored apparel, insect repellants, bed nets), especially when Ae. Aegypti are more in number (early morning and late afternoon). Community-level methods aim to remove egg-laying sites (e.g. potted plant saucers, water storage items, used tires) by means of drying wet environments or utilizing insecticide treatment. Pregnant females dwelling in nations that are not Zika virus-endemic are told to avoid travel in affected international locations. Testing will be provided to all pregnant women who have travelled to areas with on-going Zika virus transmission. Serial foetal ultrasounds should be done to observe foetal anatomy and development every 3-4 weeks in pregnant ladies with positive or inconclusive Zika virus test reports, and the infant should be verified at birth. Men who live in or have travelled to a field of lively Zika virus transmission should abstain from sexual exercise or use proper precautions for the period of intercourse as sexual transmission of Zika virus is also possible [25].

ZIKA VIRUS EVOLUTION

From the genetic studies, it has been discovered that Zika virus has developed into 3 targeted genotypes: West African (Nigerian cluster), East African (MR766 prototype cluster), and Asian. Also, it has been suggested that the virus originated in East Africa after which spread into both West Africa and Asia in approximately 50-100 years. In early 2015, instances of Zika virus infection have been detected in Rio Grande State, Northern Brazil, and

restrained sequence analyses concluded that the virus was similar to a 2013 isolate from French Polynesia, within the Asian clade [26].

The phylogenetic evaluation has revealed numerous sequence variations in Zika virus genomes between the African and Asian lineages, even in different strains within Asian lineage, as the clinical disease induced by Zika virus has now transformed from causing a simple benign health problem to now including severe neuropathology [27]. The modeling analyses proposed that these sequences could mediate particular alterations in the prM protein, that are proved to be significant in virulence or improved fitness. Moreover, these variations limited to a reasonable number of amino acid or nucleotide changes that can be examined for their effects on Zika virus infectivity. Future experiments will be needed to investigate which amino acid or nucleotide substitutions are dependent for the feasible elevated neurotropism directly, heightened viral health, and enhanced transmissibility and infectivity from the mosquito vector to the human host [28,29].

In agreement with the preliminary sequencing of samples from Brazil, it was revealed that the 3 newly sequenced Zika viruses from Guatemala and Puerto Rico are all inside the Asian genotype and most closely related to strains isolated from Brazil (2015) and French Polynesia (2013). The tree topology confirms previous findings and suggests that Asian genotype viruses were constantly evolving and spreading geographically throughout Asia and the Pacific Islands since 1966. The percentage nucleotide identity among the entire Western Hemisphere Zika viruses is greater than 99%, and as a group, these Western Hemisphere viruses are approximately 89% equal to viruses of the East African and West African genotypes [30].

The phylogeny and action of Zika and Chikungunya viruses are strikingly identical. Each virus is grouped into three genotypes of very identical geographic distribution: East Africa, West Africa, and Asia. It also seems that both the viruses from East Africa migrate into Asia approximately fifty to hundred years ago and evolved into a particular Asian genotype. Moreover, similarity with respect to the recent movement of these viruses from Asia into the Pacific Islands and then into the new world is significant. It appears that identical ecological or human social reasons are accountable for the transmission of Chikungunya and Zika viruses into the new world in approximately the equal time. Further reviews would elucidate the detailed mechanism of this transcontinental action, leading to effective preventive measures [31,32].

CONCLUSION

Zika virus has been declared a public health emergency, as many as 1.3 million people had been affected in Brazil alone, and 20 countries or territories have pronounced neighbourhood transmission of the virus during 2016. Considering of the convenience of air travel and global exchange, further spread into regions where the virus is not endemic is probably going, and transmission is possible in places with capable mosquito vectors. An effective, multifaceted response is underway that entails public wellness authorities, government agencies, the biomedical industry, medical practitioners, and researchers. However, uncertainty remains regarding points of the virus's vectors, epidemiology, and pathogenesis. As the epidemic unfolds, evaluating incoming knowledge analytically will be necessary to separate reality from speculation.

Transfusion-transmitted Zika virus can easily enter into the blood stream and spread into the body. The US Food and Drug Administration arrange a 28-day deferral for blood donors with demonstrated or suspected Zika virus illness. Donor screening through nucleic acid testing can be done but is difficult to put in force due to the high costs and regulatory issues. Pathogen reduction science has shown efficacy as a remedy for the treatment of plasma. However, licensed pathogen reduction technology can be used in red cells, excessive incremental rates, and technical limitations render such technology an unlikely brief-time solution.

The most important matter of concern is diagnosis remains suboptimal. Diagnostic instructions are contingent on laboratory testing that is not commonly available. Despite the fact that commercial check-ups for Zika virus are restricted in number and availability, and most of them are under development, together with prototype multiplex molecular assays that at the same time test for Zika virus, Dengue and Chikungunya virus.

Preventive measures (most significantly, vector manipulation) are a current precedence, pending advances in diagnostics; the World Health Organization and the Pan American Health Organization have issued recommendations. In the United States, a couple of reasons safeguard towards the explosive epidemic occurring throughout Central and South America. Particularly, lower rates of human crowding in city areas, wider access to air conditioning and mosquito repellents, and waste administration restrict mosquito-borne transmission, which has been the case for dengue virus. Nonetheless, additional entomologic study is required to define the range of Zika virus vectors and identify new areas where autochthonous transmission might take position to allow early intervention. Investment is also wanted in durable control measures equivalent to adaptable vaccine systems for arboviruses; as no Zika virus vaccines are in advanced development for the management, and prevention of this emerging pathogen.

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