Zika Virus: A Review to Clinicians

Vírus Zika: Revisão para Clínicos

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ABSTRACT

Zika virus is a flavivirus related to Dengue virus, yellow fever virus and West Nile virus. It is considered an emerging arbovirus transmitted by mosquitos of the genus *Aedes*. Its first description took place in 1947 in the Zika Forest in Uganda, isolated on *Rhesus* monkey used as bait to study the yellow fever virus. Sporadic cases have been detected in African countries and at the end of the 70's in Indonesia. In 2007, epidemics were described in Micronesia and other islands in the Pacific Ocean and more recently in Brazil. Clinical picture is characterized as a 'dengue-like' syndrome, with abrupt onset of fever and an early onset evanescent rash, often pruritic. Occasionally the disease has been associated with Guillain-Barré syndrome. Nevertheless, until now deaths and complications caused by the disease were not reported. The diagnosis can be performed by PCR or by IgG and IgM antibodies detection. The rapid spread of the virus and its epidemic potential are especially problematic in countries where there are the circulation of other arboviruses which imposes difficulties in the differential diagnosis and healthcare burden. Control measures are the same recommended for dengue and chikungunya which are based in health education and vector control.
Keywords: Aedes; Arboviruses; Flavivirus; Flaviviridae Infections.

RESUMO

O vírus Zika é um flavivírus filogeneticamente relacionado com o vírus dengue, vírus da febre-amarela e vírus do Nilo Ocidental. É considerado uma arbovirose emergente transmitida por mosquitos do género *Aedes*. A sua descoberta deu-se em 1947 na floresta Zika no Uganda, isolado em macaco *Rhesus* que servia de isco para estudo do vírus da febre-amarela. Foram detetados casos isolados em países de África e no final da década de 70 na Indonésia. A partir 2007 foram descritas epidemias na Micronésia e outras ilhas do Oceano Pacífico e, mais recentemente, no Brasil. Carateriza-se clinicamente como uma síndrome febril aguda 'tipo-dengue' com aparecimento precoce de exantema evanescente muitas vezes pruriginoso; ocasionalmente a doença tem sido associada à síndrome de Guillain-Barré. No entanto, até ao momento não foram relatadas mortes pela doença e suas complicações. O diagnóstico pode ser realizado por meio de técnica de reação em cadeia da polimerase ou por pesquisa de anticorpos IgG e IgM. A rápida disseminação do vírus e seu potencial epidémico são preocupantes especialmente em territórios com circulação de outras arboviroses pela dificuldade no diagnóstico diferencial e na sobrecarga dos serviços de saúde. As medidas de controlo são as mesmas recomendadas para a dengue e chikungunya, baseadas em educação em saúde e controlo do vetor.
Palavras-chave: Aedes; Arbovirus; Flavivírus; Infecções por Flaviviridae.

Aetiology

Zika virus (ZIKV) is a member of the *Flaviridae* family and the *Flavivirus* genus and therefore evolutionarily related to other mosquito-borne arboviruses such as dengue, yellow-fever (YFV) and West Nile virus. It has a positive sense single-stranded ribonucleic acid (RNA) genome. Although its virion structure has not yet been determined, when compared to the other known flaviviruses, this must be limited by a host-cell endoplasmic reticulum (ER)–derived lipid envelope, surrounding a nucleocapsid with still undefined structure and symmetry, composed of the protein C and the viral genome. The viral envelope should contain the two surface proteins (M and E) and the viral genome additionally encodes several non-structural proteins with enzyme activity (NS3: RNA-helicase and protease and NS5: RNA polymerase, RNA-dependent) or with regulatory functions (replication, transcription, transduction and immune response control) during intracellular replication.[1,2]

ZIKV was isolated for the first time in 1947 at the Zika forest in Uganda, from a serum sample obtained from a *Rhesus* monkey that was a sentinel for a surveillance project on jungle (sylvatic) yellow-fever (YF).[3] Upon phylogenetic analysis of the viral genome, it was found that the virus probably emerged around 1920 at this location and upon two migration stages to West Africa has started the two African lineages. From Uganda, the virus must have migrated to Asia in the 1940s and emerged as the Asian lineage, with outbreaks reported in Indonesia and a major epidemics in Micronesia.[1,4] The Asian lineage was also responsible for the native transmitted cases of the virus that recently occurred in Brazil.[5]

Worldwide distribution

Upon the isolation of the virus in the late 1940s, the first cases of ZIKV infection in humans were identified in Uganda

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in 1952.[6] Cases were also found in Nigeria in 1953[7] and mosquitoes of the species *Aedes aegypti* were laboratory-infected in 1956 resulting in a 60% successful transmission of the virus in mice.[8] ZIKV-positive patients were still found in serological testing made in Nigeria in the 1960s and also in febrile patients during a YF epidemics that emerged in 1970.[9] Serological and virological evidence of ZIKV infection was found in Sierra Leone, Nigeria, Senegal, Gabon, Ivory Coast and in Central African countries in 1975-1977.[10-15]

The first evidence of ZIKV circulation out of the African continent occurred between 1977 and 1978 when acutely febrile patients were admitted to an hospital in Indonesia and ZIKV antibodies were found in sera from 30 patients.[16] Two ZIKV epidemics were reported in the Federated States of Micronesia (in the island of Yap) over the last decade, representing the first outbreak outside Africa and Asia.[17,18] The disease rapidly spread through the islands along the Pacific Ocean and the first cases were detected in the French Polynesia in October 2013, where the situation progressed to an outbreak involving around 19,000 suspected and 284 confirmed cases of ZIKV infection.[19]

Cases of the disease were reported in the Easter Island (Chilean territory in the Pacific Ocean) in February 2014, for the first time in the Americas, probably related to the outbreak that occurred in Micronesia and in French Polynesia.[20] ZIKV circulation was confirmed in 2015 in Northeast Brazil from a viral isolation obtained from suspected cases of dengue.[5] Recently, the Brazilian Ministry of Health has published a report describing several cases of the disease already confirmed in more than eight states within Brazil, involving the Northern, Northeast and Southeast regions.[21] The countries where the presence of the infection in seroepidemiological studies and the disease's native transmission were already reported are shown in Fig. 1.

Transmission

ZIKV transmission is associated to a mosquito bite (from an *Aedes* genus mosquito) and was isolated in 1948 from a macerate of mosquitoes of the *Aedes africanus* species collected at the Zika forest.[6] Seroepidemiological studies based on blood samples obtained from residents in that region of Uganda have shown an anti-ZIKV antibody prevalence of around 6%.[17] In addition, this virus has been repeatedly isolated from mosquitoes collected both in Africa and in Asia, leading to conclude that species such as *Aedes africanus, Aedes aegypti* and *Aedes hensilli* have a role in ZIKV enzootic maintenance (within a sylvatic environment).[22-25]

The *Ae. aegypti* and *Ae. albopictus* competence for the transmission of ZIKV imposes a great public health concern. These arthropods are widely spread in tropical, sub-tropical (*Ae. aegypti*) and temperate (*Ae. albopictus*) areas, affecting a large number of susceptible people.[8,26]

Sexual, perinatal and blood transfusion-transmitted ZIKV infection has been described, although less frequently[27-29] and the magnitude of the epidemiological significance of these mechanisms has not yet been established.

Clinical presentation

Clinical presentation of the ZIKV infection has not yet been fully established and data are restricted to reports of isolated cases or case series within epidemic situations. The incubation period is 3-12 days upon the bite of an infected mosquito, similar to what was described with other arboviruses.[30,31] The clinical presentation may depend on patient's location and a dengue-type syndrome is the most frequent presentation, although asymptomatic infections have been described, based on serological studies.[32-34]

MacNamara[7] has described the first three human

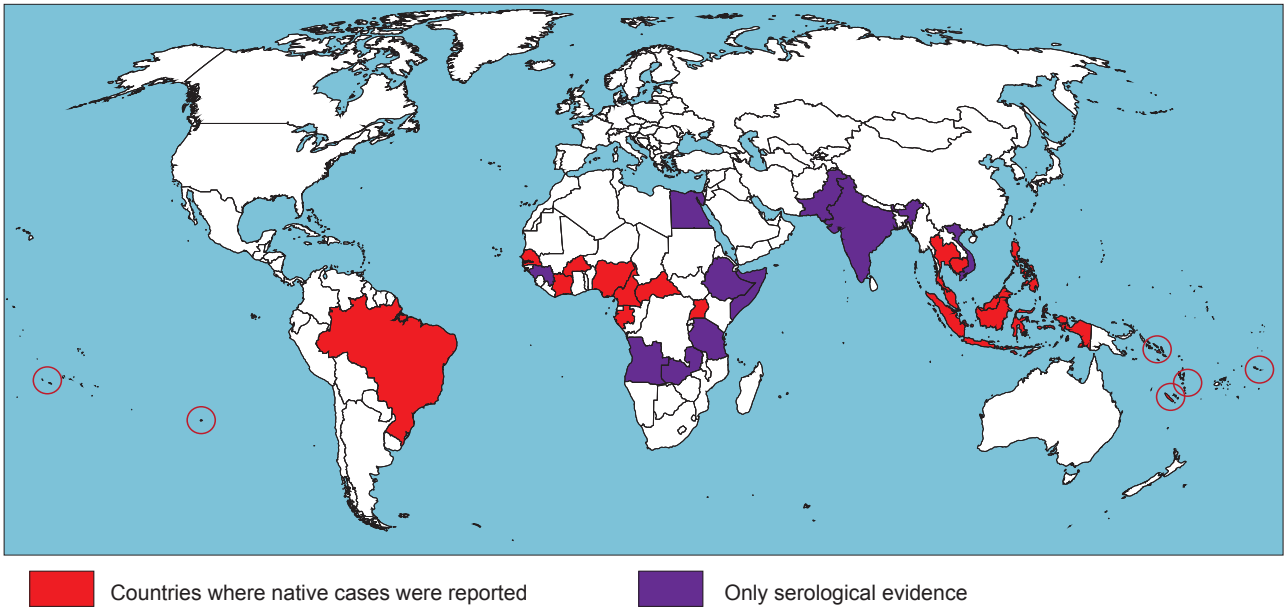

Figure 1 - Countries with an evidence of native transmission or with positive results in seroepidemiological studies.
Source: CDC, May 2015; adapted by Acta Médica Portuguesa, December 2015.

cases of ZIKV infection in Nigeria in 1954, associated to jaundice. Nevertheless, this occurred in a malaria and YF-endemic location and therefore the clinical manifestations of the ZIKV disease were indistinguishable from these other diseases. Bearcroft[35] subsequently induced the infection in one healthy volunteer through exposure to infected females of *Ae. aegypti*; the patient progressed with a nonspecific and self-limited febrile syndrome with no rash, three days upon inoculation; this experimentally-infected patient does not seem to have developed sufficiently intense viraemia that would allow the transmission of ZIKV to the *Ae. Aegypti* that fed on the patient.

Cases described in Africa over the following years have characterised the ZIKV infection as a sudden-onset febrile episode followed by a mild headache and a pruriginous maculopapular rash on the second day involving the face, trunk, limbs, hand palms and feet soles (Fig. 2). Fever usually declines within one or two days upon rash onset, which may persist for 2-14 days (six days, on average).[11,36]

Fever is usually low, although it was higher in some case reports in Brazil and reaching 39º C.[5] Muscle and joint pains and low-grade back pain have been reported although, unlike chikungunya, these are less intense and usually affect hands, knees and ankle joints. These usually decline one week later (3-5 days, on average).[18,19,33] Conjunctivitis has been frequently described and is usually non-purulent (Fig. 3).[37] Other nonspecific manifestations may occur, including anorexia, nausea, vomiting, dizziness and retro-orbital pain.[16]

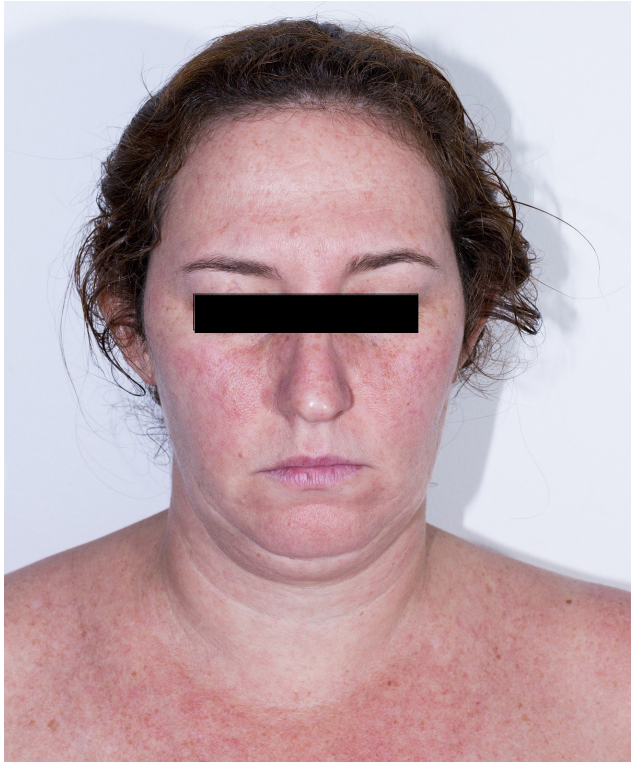

Figure 2 - ZIKV infection-related rash in a 39-year-old woman living in Rio de Janeiro, Brazil. Diagnosis was confirmed by clinical and epidemiological criteria and dengue serology was negative.

The ZIKV infection may be considered as a benign disease although, such as in PA's epidemic, many patients presenting with Guillain-Barré syndrome (GBS) a few days upon clinical onset have been described in Brazil. The triggering mechanisms of this condition are still unknown and an autoimmune process is likely to occur, such as what has been observed in other infections. No deaths have been reported up to now in patients that have developed GBS, although some patients required to be admitted to intensive care units. Nevertheless, the association between ZIKV infection and GBS still needs to be confirmed by laboratory studies.[20,38]

Until now, dengue and ZIKV co-infection has not shown any synergistic effect regarding severity or clinical presentation of both diseases. Two co-infected patients were described in New Caledonia (South Pacific), with good progression and without the need for hospitalisation.[39]

Data regarding blood and biochemical changes in ZIKV disease are scarce and conflicting. Elevated lactic dehydrogenase and C-reactive protein levels were described in some case reports. Low-grade leukopenia and thrombocytopenia may occur.[40]

Differential diagnosis is mainly established with dengue and chikungunya. Differences regarding the clinical presentation of these three diseases are shown in Table 1.[30] Exanthematous diseases caused by viruses such as the *Human parvovirus* B19, *Epstein-Barr*, measles and rubella, among others, should also be looked for, due to their high spread capability in the community.[41] The ZIKV infection should also be considered in cases of post-travel fever in patients returning from tropical regions.[42-44]

No ZIKV re-infection cases were described and it is considered as an infection that confers lifetime immunity.

Laboratory diagnosis

Due to the fact that currently no commercial tests allowing for the serological diagnosis of ZIKV infection are available, ZIKV acute infection may be diagnosed by RT-PCR (reverse transcription polymerase chain reaction)

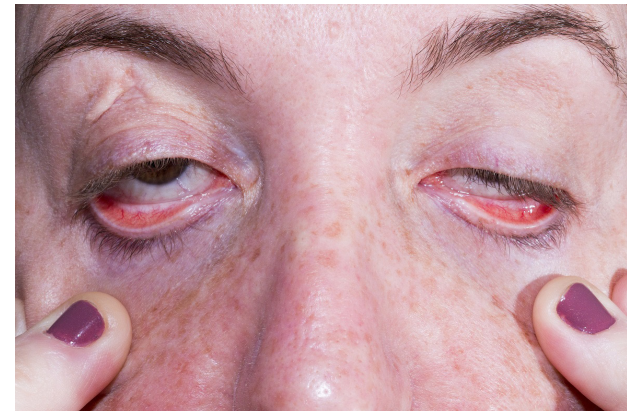

Figure 3 - ZIKV infection-related conjunctival congestion in a 39-year-old woman living in Rio de Janeiro, Brazil. Diagnosis was confirmed by clinical and epidemiological criteria and dengue serology was negative.

Table 1 - Clinical manifestations more frequently associated to dengue, chikungunya and ZIKV infection.

Symptom	Dengue	Chikungunya	Zika
Fever (intensity)	+++	++	+
Mialgia	+++	++	+
Rash	+	++	+++
Arthralgia	+/-	+++	+
Headache	+++	+	+
Conjunctivitis	-	++	+++
Blood dyscrasia	++	+/-	-
Shock	+++	+/-	-
Thrombocytopenia	+++	+/-	+/-
Neutropenia	++	+	ND
Lymphopenia	++	+++	ND

ND: no data available. Adapted from the *Manual de Manejo Clínico do Chikungunya*, Ministry of Health, Brazil, 2014.

directly from virus RNA in patient's serum, preferably obtained up to the sixth day of disease. However, the virus was identified (by virus genomic amplification) at the 11th day upon symptom onset in one patient from the epidemic on the island of Yap.[18,45] The virus may also be detected by using molecular techniques in other body fluids like saliva and in urine.[46,47]

IgM antibodies may be found from the third day of disease onset and IgG antibodies should be looked for in the acute and convalescent serum.[17,48] The possible cross-reactivity related to previous infections with other flaviviruses can be a problem.[17,18,49] The presence of ZIKV epidemics in regions where dengue virus was previously in circulation may represent a diagnostic challenge. Even the use of a plaque reduction neutralization test (PRNT), also used in the epidemic on the island of Yap, is unable to differentiate possible cases of ZIKV infection in patients with previously acquired anti-dengue virus antibodies, even when the anti-ZIKV titres were higher than the heterologous (non-ZIKV).[18]

Nevertheless, different studies have described both qualitative and quantitative assessments regarding the presence of anti-ZIKV antibodies in biological samples where some of the techniques that have been used are non-standardized techniques used in specific laboratory contexts (in-house techniques).

Despite the presence of diagnostic tests, its use is still rather limited as no commercial kits are available on the market. Therefore, diagnosis is restricted to public health, training and research institutions. The detection of viral genome through RT-PCR is the most sensitive and specific method for the diagnosis of the ZIKV infection; however, these are not fail-safe methods. Unlike other viruses, the limited circulation of the virus has reduced the knowledge regarding its real genetic diversity and therefore there is a non-zero probability that the primers used in ZIKV genomic amplification may not allow the required amplifications to be obtained (false-negative results in amplification tests).

Treatment

There are no specific antiviral vaccines or drugs and treatment is symptomatic. Analgesics and antipyretic agents must be carefully used, in order to prevent any adverse effects including hepatopathy, allergy and nephropathy. The use of aspirin should be avoided in order to prevent the induction of bleeding disorders in patients with dengue misdiagnosed with ZIKV infection due to an inconclusive clinical diagnosis and to an unreliable serological analysis.

The severe pruritus that follows the rash has been described by patients as an intense discomfort. The approach to pruritic rash may start with the recommendation that patients should avoid hot baths, the excessive use of soap and use adequate skin moisturisers. When these are not successful, cold baths and the use of refreshing lotions with calamine or menthol is recommended. The pathogenesis of skin manifestations is still unclear and thus the use of older antihistamine agents may benefit the patient due to the sedative action rather than to some direct action on the cause of pruritus.[50, 51] Topic corticosteroids should be avoided as their efficacy on this symptom is unknown.

GBS should be conventionally approached. Diagnosis is established when the patient presents with progressive weakness affecting two or more limbs, areflexia and clinical progression in up to four weeks. Cerebrospinal fluid (CSF) analysis may show protein increase and low cellularity (albuminocytologic dissociation). Patients with suspected GBS should be monitored in intensive care units due to the risk of progression to respiratory muscle paralysis. GBS

therapeutic options include plasmapheresis or hyperimmune IVIG (hyperimmune immunoglobulin): both reduce time to recovery despite being expensive therapies.[52]

Control measures

Ae. aegypti is a highly synanthropic mosquito that takes advantage from peri-domestic environments and may even make its blood meals within human households. Considering that it is one of the ZIKV vectors and that vector control measures based on the use of insecticide agents are difficult due to (i) financial constraints, (ii) logistic issues, (iii) strict regulations regarding the use of insecticide agents and/or (iv) spreading of resistances in vector population, removal of larval breeding sites has a crucial role in the control of this vector. Individual protection measures should also be encouraged, involving the use of insect repellents and window and door screens to keep insects outside. The detection and study of suspected cases, aimed to prevent transmission in more problematic regions should be the priority in health surveillance. Those with an active disease or that recently presented with it are unable to donate blood.[53]

Although no ZIKV-related deaths occurred until now, health professionals should be aware and trained in order to differentiate ZIKV disease from other diseases that simultaneously circulate, namely dengue.[39]

Attention to travellers returning from regions with ZIKV transmission should be a priority in ZIKV-free regions. Early recognition may contribute to take measures aimed to prevent disease spreading, considering the spread of *Ae. albopictus* in temperate regions.[43]

CONCLUSION

ZIKV-related epidemics over the last decade lead to a relevant spreading from Asia and Pacific Ocean to the Americas. It is not yet known whether this flavivirus will establish within these new territories and further studies on its transmission dynamics are needed.

Its presence in areas where the transmission of other flaviviruses has been already observed, such as the different serotypes of dengue virus, brings the possibility of an increase in mortality due to issues related to the differential diagnosis and also to the unavailability of commercial diagnostic kits. Despite the apparently benign characteristics of the disease, potentially lethal complications such as GBS emerged as a new issue in the approach to patients presenting in regions with active transmission.

Vector control measures should be increased, as well as healthcare actions. In ZIKV-free regions and where there is the circulation of *Aedes* mosquitoes, care should be taken with travellers returning mainly from tropical regions.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to the regulations established by the responsible body of the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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