Article published online: 2023-09-06

DOI: 10.1590/0004-282X20160035

VIEW

Guillain-Barré syndrome associated with the Zika virus outbreak in Brazil

Síndrome de Guillain-Barré associada ao surto de infecção por vírus Zika no Brasil

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ABSTRACT

Zika virus (ZIKV) is now considered an emerging flavivirosis, with a first large outbreak registered in the Yap Islands in 2007. In 2013, a new outbreak was reported in the French Polynesia, with associated cases of neurological complications including Guillain-Barré syndrome (GBS). The incidence of GBS has increased in Brazil since 2015, what is speculated to be secondary to the ZIKV infection outbreak. The gold-standard test for detection of acute ZIKV infection is the polymerase-chain reaction technique, an essay largely unavailable in Brazil. The diagnosis of GBS is feasible even in resource-limited areas using the criteria proposed by the GBS Classification Group, which is based solely on clinical grounds. Further understanding on the relationship of ZIKV with neurological complications is a research urgency.

Keywords: Guillain-Barre syndrome, GBS, Zika virus, Zika virus infection outbreak, neurological complications.

RESUMO

O vírus Zika (VZIK) é agora considerado uma flavivirose emergente, com um primeiro grande surto registrado nas ilhas Yap, em 2007. Em 2013, novo surto foi registado na Polinésia francesa, com complicações neurológicas, incluindo a síndrome de Guillain-Barré (SGB). A incidência de SGB experimentou um aumento durante o ano de 2015, o que se especula ser secundário ao surto de infecção pelo ZIKV. A técnica em reação em cadeia de polimerase é considerado o teste padrão-ouro, mas é pouco disponível no Brasil. O diagnóstico da SGB é possível mesmo em áreas com recursos limitados usando os critérios propostos pelo *GBS Classification Group*, os quais são baseados exclusivamente em achados clínicos. Um maior entendimento da relação entre a infecção pelo ZIKV e complicações neurológicas é uma urgência de pesquisa.

Palavras-chave: Síndrome de Guillain-Barré, SGB, vírus Zika, complicações neurológicas.

The Zika virus (ZIKV) was named after the Zika forest, located in Uganda. It was first isolated in April 1947 from specimens collected from a sentinel rhesus monkey. Since this pivotal event, the virus has progressively spread outbounds, being detected in the sub-Saharan region, and later on in India and Southeast Asia, although only small limited outbreaks and sparse cases were reported in the following decades[1]. In 2007, the first large outbreak of ZIKV occurred in the Yap Islands, an archipelago located within the Federated States of Micronesia. Forty-nine cases of ZIKV infection were confirmed, with roughly 73% of the islanders aged 3 years or older being potentially infected with ZIKV according to a household survey[2]. A larger outbreak occurred in the end of 2013 in the French Polynesia[3]. It is still unclear how ZIKV was introduced in Brazil. The lineage identified in serum samples from the first cases in the State of Bahia resembles a previously identified Asian lineage[4].

The infection outbreak has been recognized as a major public health issue in Brazil since the beginning of 2015. The ZIKV belongs to the ***Flaviviridae*** family, the same family of Dengue, hepatitis C, and yellow fever virus[5]. ZIKV is an arbovirosis transmitted by ***Aedes aegypti*** mosquitoes which are found widespread in Brazil[6]. Currently, there is scant but worrisome evidence suggesting it might also be transmitted via sexual intercourse[7,8], through blood transfusion, as well as by vertical transmission[9,10,11]. ZIKV disease often presents with mild or non-specific symptoms, similar to other prevalent viral diseases in Brazil, such as dengue and chikungunya, hampering attempts to perform an accurate diagnosis based solely on clinical grounds. The disease is usually characterized by an acute onset of fever, non-purulent conjunctivitis, headache, arthralgia, myalgia, asthenia and a maculo-papular rash. The disease course is self-limited, normally lasting 4-7 days. In the minority of cases, it might be

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Conflict of interest: There is no conflict of interest to declare.

Received 30 December 2015; Received in final form 24 February 2016; Accepted 02 March 2016.

observed retro-orbital pain, anorexia, vomiting, diarrhea and abdominal pain. Until a recent Brazilian report, the disease was not considered potentially fatal. The hospitalization ratio is believed to be low and the prognosis after an acute infection is considered good, usually with full recovery[2,3]. Therapy is based only in symptom relief. Mainly due to a possible similarity to other flavivirus with associated hemorrhagic complications, the use of non-steroidal anti-inflammatory drugs (NSAID) has been contraindicated for the treatment of pain and fever. Antihistaminic drugs are recommended for the pruritic rash. Currently, no vaccine is available[3,12].

In the Polynesian outbreak of ZIKV in 2013/2014, 396 cases were confirmed by PCR. Another 8262 cases were suspected, presenting with symptoms suggestive of ZIKV infection. However, differently from the Yap Island outbreak, during which no significant complications were observed, a higher incidence of severe events was reported in Polynesia. The association of ZIKV and neurological complications was noticed for the first time, including 70 cases of neurological or autoimmune events in suspected cases. Among these, there were 38 cases of Guillain-Barre syndrome (GBS) and 25 cases of different neurological complications (encephalitis, meningoencephalitis, paresthesias, facial paralysis and myelitis). Seven other cases developed immune thrombocytopenic purpura, ophthalmologic and cardiac complications. No deaths were reported. Unfortunately, most patients did not have their diagnosis confirmed by PCR technique[3]. A recent study showed that ZIKV portends similar cellular targets as dengue virus (DENV). Fibroblasts and keratinocytes seem to play a major role in the pathogenesis of the disease, likely serving as a gateway to infection. Another noticeable finding is that ZIKV promotes apoptosis, leading to decreased immune response, the same strategy used by DENV. Finally, dendritic cells seem to be more susceptible to ZIKV infection[13]. A German study using a mice model observed active replication in neurons, confirming an active role of ZIKV in the destruction of nervous tissue. In addition, it was observed that the host´s immune response also contributes to the damage to the central nervous system[14].

The ZIKV has a single-strand positive RNA composed of 10 794 nucleotides with the open reading frame of 3 419 amino acids, which encodes several structural genes and 5 non-structural genes[5]. The sequencing of the virus allows its classification into two main lineages: African and Asian. The African lineage is further subdivided into Eastern and Western[15,16] . Currently, the most accurate diagnostic essay for ZIKV is the isolation of viral RNA. Even though its viremic period is not well described, the initial 3-5 days from the onset of symptoms is most likely the ideal timeframe to detect the virus. Serologic tests for specific IgM/IgG are available, but the cross-reactivity with other flaviviruses, such as dengue and West Nile virus, remains a challenge. As a consequence, PCR techniques to detect viral RNA remain the gold-standard for diagnosis[3]. The limited availability of PCR for the diagnosis of ZIKV in Brazil has been a limiting factor to better delineate and understand the current outbreak.

After the first case of ZIKV infection in Brazil, an alarming number of cases have been reported, further characterizing a large outbreak[17]. It has spread from the Brazilian Northeast to several other states. As described in the French Polynesia outbreak, the relation between ZIKV infection and GBS was again observed. In May 23rd 2015, neurologist Mario Emilio Dourado, in a personal communication, was the first to call attention for an increased incidence of GBS cases in the State of Rio Grande do Norte, Natal City, Northeast Brazil. Dourado reported 7 GBS cases preceded by symptoms suggestive of ZIKV infection. In July 2015, in the State of Pernambuco, Northeast Brazil, 6 other cases with neurological complications associated with ZIKV were described, 4 cases of GBS and 2 of acute disseminated encephalomyelitis (ADEM), with 1 case confirmed by serum analysis and 5 cases using cerebrospinal fluid[12]. The incidence of GBS in Brazil has been clearly increasing after the ZIKV outbreak, however it is not clear to this moment the real impact of ZIKV in the occurrence of new cases of GBS, as this syndrome can be secondary to other infectious or immune events, as well as to other endemic arbovirosis, such as Dengue[18]. As a personal communication, a research network on GBS in Brazil estimates that the incidence of GBS has likely increased by 5 times since 2015, even tough more accurate data is awaited to support this hypothesis.

Although the relation between ZIKV and GBS still remains unclear, a previous case from the Polinesian outbreak associated these two conditions[19]. Nevertheless, in resource-limited settings, both ZIKV and GBS can be suspected on clinical basis and careful documentation may provide valuable information for scientists and public health agencies.

GBS is a potentially treatable condition, requiring prompt suspicion on clinical grounds to allow early treatment. Extensive investigation based on ancillary tests (nerve conduction studies and cerebrospinal fluid examination) to further document this syndrome might be unavailable in some regions. In 2014, the GBS Classification Group proposed a diagnostic classification for GBS and its variants, such as Miller Fischer syndrome (MFS), based exclusively on clinical grounds[20]. This classification is very simple to apply and useful for the prompt recognition of GBS and MFS, especially in a possible context of a widespread epidemic.

We have recently observed in the State of Rio de Janeiro (Southeastern Brazil), several cases of GBS associated to preceding symptoms suggestive of ZIKV infection, a phenomenon also observed by other neurologists in different States. During this past year, the expected number of GBS cases in Brazil apparently increased during the ZIKV infection outbreak, a hypothesis currently under study. In addition to GBS, we might expect an increased incidence of other neurological complications, due to the likely higher

neurotropism of ZIKV, when compared to other endemic tropical illnesses.

It is imperative that our medical societies and agencies of public health urgently develop training programs for health personnel on clinical suspicion and treatment of GBS and other neurological complications. In addition, the creation of collaborative networks among neurological centers and referral hospitals would be advisable. Finally, it is an obligation and an opportunity for Brazilian neurologists to have make precedence and thoroughly study the current outbreak, producing invaluable scientific knowledge that could aid in further understanding of the pathophysiology, clinical course and therapy response of GBS.

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