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Short communication

Fatal encephalitis associated with Zika virus infection in an adult

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ABSTRACT

Background: Zika virus (ZIKV) was first identified in the Americas in 2015, when an outbreak of an exanthematous illness occurred in Brazil. Subsequentely, there was an increase of microcephaly cases, suggesting an association between ZIKV and this neurological complication. Currently, ZIKV has been recognised as causing a wide range of neurological complications including Guillain Barré syndrome, and myelitis.
Objectives: In this report, we describe the first fatal case of encephalitis in a 47 years old non pregnant woman, infected during the Brazilian zika epidemic of 2016.
Study design: The diagnosis of encephalitis was determined by the presence of a disturbed level of consciousness and focal neurological signs during an exanthemous viral infection.
Results: CSF analysis supported the diagnosis of viral encephalitis, revealing lymphocytic pleocytosis, a high protein concentration, and the presence of IgM zika antibodies. RT-PCR analysis for ZIKV was positive in the urine. A brain computed tomography showed massive brain swelling. Our case differs from previous reports, because her neurological picture developed rapidly and in a very aggressive manner leading to brain death after eleven days of admission.
Conclusion: In endemic areas, ZIKV should be considered as an aetiological agent in cases of encephalitis, and clinicians should be aware of its potential severity.

1. Background

ZIKV was first isolated in Zika Forest, Uganda, in 1947, and in recent years has caused outbreaks in Yap Island, Micronesia, and in French Polynesia [1–3]. However, since 2015 it has spread rapidly through South and Central America and has reached epidemic proportions [4]. The associated increase in the incidence of both Guillain–Barré syndrome and fetal microcephaly led the World Health Organization (WHO) to declare a Public Health Emergency of International Concern on February 1, 2016. Before this association, zika virus infection used to be described as a mild febrile illnesss with other common symptoms like macular or papular rash, arthritis or arthralgia, nonpurulent conjunctivitis, myalgia, headache, retro-orbital pain, edema, and vomiting [5].

2. Objectives

In this report, the first fatal case of encephalitis in a 47 years old woman, infected by ZIKV is described. The spread of ZIKV towards new regions is eminent and a rapid diagnosis and treatment of severe cases is required.

3. Study design

A 47-year-old Brazilian woman, with an unremarkable medical history, presented with a cutaneous itchy rash and arthralgias, on 6th January 2016. She did not have fever or conjunctivitis, and there was no past history of dengue. There was no history of similar infection in her family or partner. Four days later, she devel-

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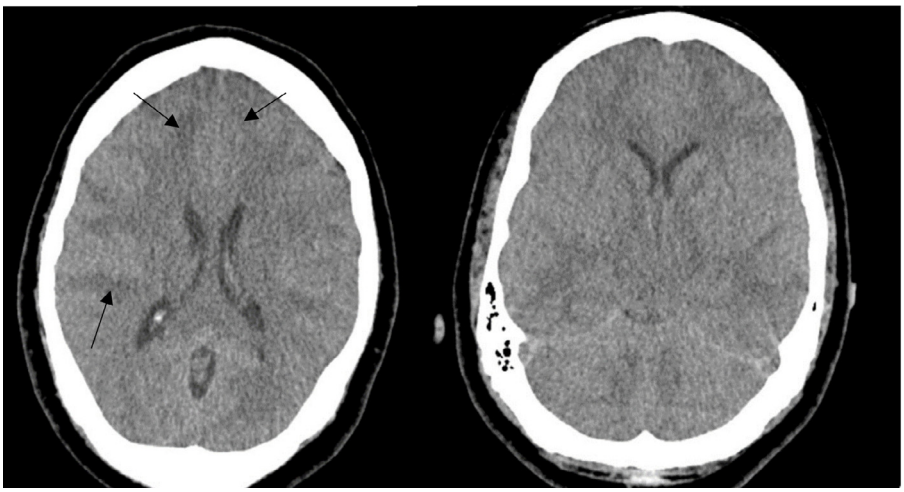

Fig. 1. Computerized Tomography (CT) head showing diffuse cerebral edema with effacement of basal cisterns and sulcal markings. Observe diffuse subcortical hypodensities, mainly on frontal regions (arrows).

oped weakness on her lower limbs, dysarthria and confusion. She was admitted to a private hospital on 11th January, with a Glasgow coma score 13 and symmetrical reflexes (3+/4+). Her pupils were isocoric and with a normal light reaction. On the same day her clinical picture deteriorated rapidly, requiring intubation and mechanical ventilation.

4. Results

Laboratory investigations showed she had mild anaemia (Ht:35.5%, Hb 10.5 g/dl), but had normal platelet and leucocyte count. Dengue serology (IgM and IgG) and HIV testing were negatives. Reverse transcription polymerase chain reaction (RT-PCR) analysis for Zika virus (ZIKV) was positive in the urine and negative in the serum. RNA was extracted from 140 μl of urine sample and eluted in 50 μl using the Qiamp Mini Elute Virus Spin Kit from Qiagen (Brasil).

Cerebrospinal fluid (CSF) examination on the second day of hospitalization showed 10 cells/mm^3 (80% of lymphocytes), glucose of 48 mg/dl (plasma glucose: 70 mg/dl), and total protein of 111 mg/dl. Microscopy and culture on CSF were negatives as were PCR for ZIKV, herpes simplex virus 1 and 2.

A computed tomography (CT) brain scan, performed on 17th January, showed massive brain swelling (Fig. 1). Despite treatment of mannitol for elevated intracranial pressure, two days later the patient deteriorated further, losing all responses to painful stimuli and becoming areflexic with fixed dilated pupils. Brain stem reflexes became negative within hours, and brain death was declared. Unfortunately, a brain magnetic resonance image and autopsy could not be done. An electroencephalogram showed electrical silence. At this stage another CSF sample was collected (on 21th January), which confirmed the lymphocytic pleocytosis (15cells/mm^3) and elevated protein (272 mg/dl). In this second CSF and serum samples, CSF albumin to serum albumin ratio was 41.7×10^3 (normal $< 8 \times 10^3$) and the immunoglobulin index was 1.02 (normal < 0.7). Both values indicate respectively that a blood—CSF barrier dysfunction and intrathecal antibody synthesis had occurred.

The Enzyme-linked immunosorbent assay (ELISA) for detection of IgM and IgG zika antibodies was performed in both serum and CSF samples. The presence of IgM zika antibodies was detected in all of them. IgG zika antibody was positive only in her second serum sample. It is known that IgG zika antibody achieves a significant rise in a pair of samples taken at least two weeks apart, and it is also an evidence of an acute infection. IgM and IgG antibodies to Zika virus NS1 antigen were measured using commercial ELISAs (Euroimmun, Luebeck, Germany), according to the manufacturer's protocol.

5. Discussion

ZIKV was found to be neurotropic in animal experiments conducted in the 1950s [2]. However, evidence of central nervous system (CNS) infection by this virus has gained strength after its detection in amniotic fluid, placental, or brain tissue of babies with nervous system malformations, including those stillborn or with fetal microcephaly [6–8].

A wide range of neurological complications are now being recognised, including myelitis and a recent case of meningoencephalitis in an adult following a cruise in the area of New Caledonia, Vanuatu, the Solomon Islands, and New Zealand [9,10].

These neurological phenotypes may simply be rare complications of ZIKV infection, which is normally asymptomatic or causes a mild illness, but which have become evident due to the infection of a much larger population. Alternatively, there may be unknown host factors which increase the risk of developing serious neurological illness [11].

Our case is the first description of fatal encephalitis associated with ZIKV infection, in a 47 years old non pregnant woman infected during the Brazilian epidemic of 2016. Our patient presented with mild infectious symptoms, consisting of rash and arthralgia. However, our case differs from previous reports because her neurological symptoms and signs developed rapidly and in a very aggressive manner leading to death. The diagnosis of encephalitis was determined clinically, by the presence of a disturbed level of consciousness and focal neurological signs during an exanthemous viral infection. Brain CT showed nonspecific findings, suggestive of encephalitis, but not specific to Zika. Similarly, CSF analysis supported the same diagnosis. It revealed active inflammation, characterized by lymphocytic pleocytosis and a high protein concentration, with normal CSF glucose. Although ZIKV was not detected in the CSF by RT-PCR, its presence in the urine confirmed the diagnosis. A low concentration of the virus in the CSF may not have been detected, since the first CSF sample was collected seven days after the onset of clinical illness. The sensitivity and specificity of RT-PCR for ZIKV in CSF has yet to be established.

In addition, the existence of blood-CSF barrier dysfunction and intrathecal antibody synthesis provides indirect evidence of viral invasion involving the central nervous system. Although this find-

ing is not specific of ZIKV infection, it has been described also in other viral infections including dengue, an important differential diagnosis. Dengue virus has been associated with intrathecal antibody synthesis in cases of myelitis but not in encephalitis [12]. Less likely, an immunopathological hypothesis causing cerebral damage should be considered as zika pathogenesis is still not fully understood. This is the first description of an encephalitis case in an adult associated with ZIKV detected by PCR in urine, with intrathecal antibody synthesis and specific IgM antibody against ZIKV. IgM was detected in both serum and CSF after seven and fifteen days of the beginning of the febrile illness. However, how earlier this antibody appears in these severe neurological cases it is still not known.

In endemic regions, ZIKV should be considered as a potential aetiological agent in cases of encephalitis. As ZIKV infection can be oligosymptomatic, the number of cases with neurological manifestations in association with the disease may be underestimated, and a high index of suspicion should be maintained.

Consent

This work was approved by the IPEC-FIOCRUZ Ethics Committee No. 0026.0.009.000-07. Written informed consent was obtained from the family patient for publication of this Case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

Cristiane Soares and Patricia Brasil coordinated the study, followed the patient, and drafted the manuscript. Fernando Teophilo and Vitor Borges managed the patient. Tom Solomon and Mark Ellul, drafted and revised the manuscript. Raquel Medialdea Carrera, Patricia Carvalho Sequeira and Ana Maria Bispo de Filippis carried out the molecular and immunological studies, participated in the sequence alignment and helped draft the manuscript. All authors contributed to the management through discussing the case and implications of the results. All authors read and approved the final manuscript.

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