

Chikungunya encephalitis: report of a fatal case in Northeastern Brazil

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ABSTRACT

Chikungunya, a viral infection that presents with fever, rash and polyarthritides, is usually an acute febrile illness. Uncommon neurological manifestations include meningoencephalitis, encephalitis, myelitis, Guillain-Barre syndrome, myelopathy and neuropathy. During an outbreak of the disease in La Reunion Island, abnormalities were observed in the magnetic resonance imaging (MRI) of patients with encephalitis and acute disseminated encephalomyelitis, showing bilateral, frontoparietal, white matter lesions with restricted diffusion, similar to our case. We report a 57-year-old male patient with comorbidities, admitted with high fever, arthralgia, asthenia, vomiting, psychomotor agitation, behavioral changes and seizures. Cerebrospinal fluid (CSF) values revealed pleocytosis (98 cells/mm³ with 68% lymphocytes and 12% monocytes) and high levels of protein (161 mg%). Brain MRI showed hyperintense lesions in the temporal and frontal lobes and bilaterally in the posterior thalamus. CSF serology was positive for IgM antibodies to Chikungunya virus. Encephalitis due to an acute viral infection by Chikungunya was diagnosed. The patient's clinical condition worsened and he died on the twenty-fourth day of admission to our hospital.

KEYWORDS: Chikungunya encephalitis. Neurological manifestations. Magnetic resonance imaging. Fatal cases.

INTRODUCTION

Chikungunya virus (CHIKV) belongs to the *Alphavirus* genus, which is a member of the *Togaviridae* family. Although neuro-chikungunya is relatively infrequent, there has been a recent increase in reports of such complications, due to a number of people infected across three continents during the 2004–2009 outbreaks. CHIKV seems to target ependymal cells, progenitor and stem cells in the subventricular zone. This impairs neurogenesis and neuronal migration, and is a hypothesis for the neuropathogenesis of encephalomyelitis related to CHIKV¹. The literature presents many reports of dengue and Zika cases, which seek to explain the association between neurological and arboviral findings, clinical aspects, laboratory diagnosis and patients' evolution. However, few studies have addressed the association with neurological deficit using the detection of antibodies raised to the virus in cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI)^{2,3}. In the literature review, we found case reports in several different locations. In India, two cases were reported with clinical and neuroimaging findings and one case with brain autopsy findings of encephalomyeloradiculitis from CHIKV, a relatively unknown and rare complication of the infection. The neuroimaging findings were bilateral

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Received: 13 April 2020

Accepted: 16 May 2020

frontoparietal white matter lesions with restricted diffusion, which are described as early signs of viral encephalitis. These patients were infected during an epidemic in an endemic zone of Eastern Maharashtra, India¹. In a study by Chandak *et al.*⁴ on neurological complications, encephalitis was the most common syndrome presented in 55% of patients. In this series, the neuropathy was a predominantly demyelination. Magnetic Resonance Imaging (MRI) presented signal changes in the spinal cord suggestive of a demyelination pathology in only three of the 14 patients with myelopathy/myeloneuropathy. In a case series study conducted in Brazil, one significant finding was that four patients with evidence of Zika virus (ZIKV) infection also presented with central nervous system infection caused by CHIKV. Ten further patients, who were negative for Zika virus, tested positive for chikungunya virus. In South America, reports of neurological disease associated with CHIKV are scarce, which may reflect a lack of awareness amongst clinicians regarding the potential of the virus to affect the nervous system, or the relatively recent arrival of the virus. It is interesting that, in our patient, the virus was detected 30 days after the onset of the neurological disease, suggesting a persistent infection or a late coincidental infection³. In summary, these studies have demonstrated the growing evidence that a broad spectrum of neurological diseases is associated with arboviruses infections. One important finding is that some patients suspected of having a neurological disorder associated with Zika virus were infected by CHIKV, and many were infected with more than one arbovirus.

CASE REPORT

A 57-year-old male agricultural worker with a history of type 2 diabetes and arterial hypertension, presented with high-grade fever, arthralgia, asthenia and vomiting during the eight days prior to admission to our hospital. On the 8th day, he presented with psychomotor agitation, behavioral changes and seizures. A computed tomography (CT) brain scan without contrast was performed and had no abnormalities. CSF analysis presented neutrophilia (72%) pleocytosis (240 cells/mm³) with normal glucose and high protein levels. Because of the neurological deterioration, the patient was admitted to our hospital. On admission, hypotension, bradycardia and a reduced level of conscience was observed (Glasgow coma scale 11). On the same day, the patient presented severe dyspnea and was promptly intubated. He received mechanical ventilation and continuous sedation. One-gram ceftriaxone and antiepileptic drugs were initiated. Laboratory tests revealed renal dysfunction, but conservative treatment (no hemodialysis)

was maintained. On the second day, the antimicrobial therapy was modified to include one-gram of ampicillin and 250 mg of acyclovir. A brain MRI revealed frontal, parietal and mesial bilateral temporal cortical and subcortical altered signals with restricted diffusion and similar abnormalities in the posterior thalamus, midbrain and cerebellar vermis, and no enhancement was noted. These findings were compatible with a diffuse encephalitis. Further CSF analysis (day 12 of the disease) revealed pleocytosis (98 cells/mm³ with 68% of lymphocytes and 12% of monocytes), high protein (161 mg%), normal glucose (81 mg%) and high adenosine deaminase level (47.9 international units (UI)/L, normal < 4.5 UI/L). Negative results were obtained for syphilis and the human immunodeficiency virus (HIV) antibodies and polymerase chain reaction for *Mycobacterium tuberculosis*, herpes virus types 1 and 2 were carried out. CSF and serum were positive for IgM antibodies to CHIKV (using the IgM antibody capture ELISA [MAC-ELISA]⁵ and commercial ELISA [Euroimmun, Lübeck, Schleswig-Holstein, Germany], respectively). A clinical deterioration of the patient was identified and despite the absence of sedative drugs, he remained in a coma and died on day 24 after onset of the illness.

DISCUSSION

In most cases, the damage caused by CHIKV has a self-limiting course with nonspecific symptoms, similar to dengue fever and including headache, joint pain and weakness. The characteristic clinical manifestations of CHIKV are intense joint pain and arthritis⁶. Fatality usually occurs in patients with associated comorbidities and aging, as in the case of our patient. The involvement of the nervous system is not uncommon in arboviral infections, and CHIKV belongs to the alphavirus genera, of which some members are known to be neurotropic⁷. This study reports a fatal case of CHIKV associated with encephalitis using the findings from both, CSF analysis and brain MRI. There were similar clinical characteristics and neuroimaging features of encephalitis and acute disseminated encephalomyelitis, with bilateral frontoparietal white matter lesions with restricted diffusion, as previously described during an outbreak of the disease on La Reunion Island^{6,8}. Another case report of encephalitis associated with CHIKV described two patients from Thailand with neurological manifestations: seizures, behavioral changes and motor dysfunction as in our patient. However, there was no fatal outcome⁹. As presented in [Figure 1](#), our patient presented notable hyperintense lesions in the temporal and frontal lobes and bilaterally in the posterior thalamus in the diffusion weighted imaging (DWI) sequences. This MRI appearance

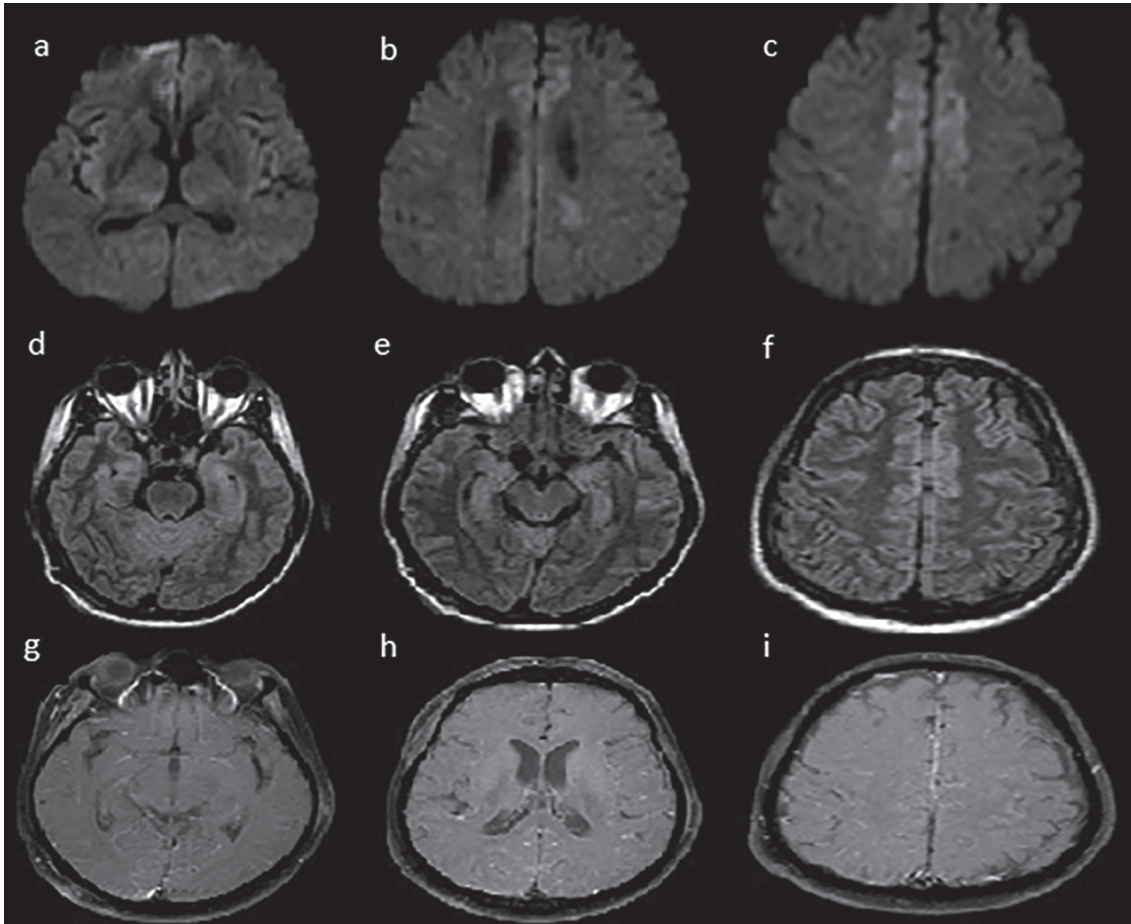


Figure 1 - Magnetic resonance imaging showing lesions in the temporal and frontal lobes of the patient. Axial diffusion-weighted images (a, b, c), FLAIR (d, e, f) and T1 with gadolinium (g, h, i) demonstrate bilateral hyperintensities in the medial temporal and frontal lobes and the posterior thalami with similar but less intense abnormalities in the FLAIR sequences and no enhancement after gadolinium administration.

using DWI is closely related to the pathologic changes (cytotoxic edema) that occur following a viral invasion. The most important differential diagnosis of these lesions (Figure 1) in our patient is the epileptic status, which probably occurred during the first days of hospitalization. In the epileptic status, neuronal injury results primarily from an excitotoxic mechanism mediated by the intrinsic neuronal seizure activity. During the epileptic status, the neuronal seizure activity increases the release of glutamate from the presynaptic terminals of neuronal axons. Excessive glutamate crosses the synaptic cleft to bind with N-methyl-D-aspartate (NMDA) and non-NMDA receptors, which causes cytotoxic edema in the neurons and glial cells, leading to apoptosis or selective neuronal necrosis. Astrocytes play an important role in cellular and tissue repair by detoxifying excessive glutamate. It is presumed that the cytotoxic edema of reactive astrocytes in the acute phase is responsible for the reversible abnormalities of the signal intensity. Encephalopathy with epileptic status often involves the hippocampus, other parts of the limbic

system, the thalamus, and the cerebellum. This distribution of lesions in DWI seems to be related to the distribution of NMDA-type glutamate receptors, which are concentrated in the hippocampus and in other parts of the limbic system⁷. Our patient presented with a different pattern of lesion distribution, raising the possibility of encephalitis-related abnormalities. In acute viral encephalitis, concentrations of glutamate and glycine in the CSF are significantly increased. This observation suggests that an excitotoxic mechanism plays a role in neuronal damage. Excessive glutamate release, due to free radicals generated during the immune response to infections, might initiate the excitotoxicity. The areas usually affected are the medial temporal lobes, the inferior frontal lobes and the insula⁷. In our patient, it does not determine the origin of the IgM detected in the CSF, whether synthesized in the CSF itself or derived from blood, reaching the CSF through the damaged blood-brain barrier. However, the systemic, epidemiological, and serological conditions support the diagnosis of acute CHIK infection and the neurological condition, secondary to its

complication. There are no definitive studies on the origin of IgM antibodies against CHIK detected in the CSF^{10,11}, but the detection of viral RNA and the alteration found in the CSF suggest a neurotropic action of CHIKV^{12,13}. A case report demonstrated the intrathecal synthesis of antibodies to CHIK in a patient with encephalitis, using the specific index of IgG antibodies in the CSF. The authors suggested that this finding associated with the clinical situation is the basis for diagnosing encephalitis caused by CHIKV¹⁴.

ACKNOWLEDGEMENTS

To the Correia Picanço Hospital and to the Organ of Development, Foundation of Science and Technology Support of Pernambuco (FACEPE), for funding the research.

AUTHORS' CONTRIBUTIONS

Elaine Cristina Bomfim de Lima: elaborated, wrote, analyzed and interpreted the results; Alexandre Medeiros Sampaio Januário: technical support in the clinical and neurological aspects of the patient; Eliane Guimarães Fortuna e Maria Eulália de Corte Real: support in the acquisition of medical records and review of the manuscript; Heloísa Ramos Lacerda: revision of the manuscript and approval of the final version to be published.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

CONSENT FOR PUBLICATION

Our case report has the consent of the patient's family described, according to the form required by the journal. Ethics Committee of the Health Sciences Center of the Federal University of Pernambuco (UFPE) - CAAE N° 55508216.0.0000.5208.

ETHICAL APPROVAL

This research was approved by the Ethics Committee of the Health Sciences Center of the Federal University of Pernambuco (UFPE) - CAAE N° 55508216.0.0000.5208. Patient-identifying data were anonymised.

FUNDING

Funded by the Foundation of Support for Science

and Technology (FACEPE), financial feasibility for data collection and processing.

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