Encephalitis associated with the chikungunya epidemic outbreak in Brazil: report of 2 cases with neuroimaging findings


INTRODUCTION

Chikungunya fever (CF) is caused by an arthropod-borne alphavirus that belongs to the Togaviridae family and is transmitted by Aedes mosquitoes1. Chikungunya virus (CHIKV) was first isolated in 1952-1953, during an epidemic in East Africa. The term chikungunya is derived from the Makonde language (spoken in some areas of Mozambique and Tanzania), which means that which bends up, referring to the stooped posture due to the severe arthralgias it causes1. Other symptoms such as high fever, headaches, nausea, and vomiting may also occur1. An increase in the frequency of outbreaks caused by this arbovirus has been observed since 2005, when more than 240,000 people were infected and 203 deaths occurred in the French island of Reunion1, followed by a worldwide spread. Since its first description, the virus has been identified in 60 countries2.

The first report of local transmission in Brazil occurred in 2014 in the City of Oiapoque, Amapá and in 2016, it was estimated that the CHIKV is circulating in almost half of Brazilian cities2. Only in the first half of this year, Brazil recorded 170,000 cases of CHIKV disease — 10 times the number seen in the same period in 20154 — and the country now accounts for 94% of confirmed cases of the disease in the Americas5. In Brazil, CHIKV is transmitted by Aedes aegypti, the same mosquito that carries the Zika virus (ZIKV), which has been declared a public health emergency in Brazil, as well as dengue fever.

According to a recent meta-analysis, up to 40% of patients may have chronic complications, mainly arthritis2,6, and severe or fatal forms of the disease with CNS involvement have been observed, in both adults and neonates2,7. Herein we describe two adult cases of CHIKV-associated central nervous system (CNS) disease during the Brazilian outbreak with emphasis on imaging findings. To the best of our knowledge, these are the first CNS imaging reports since the arrival of CHIKV into the country.

CASE REPORTS

Case 1

A 55-year-old man, previously healthy, presented with a 4-day history of fever, polyarthralgia, diffuse skin rash, adynamia, mild conjunctivitis, and dry cough. He was a native of Fortaleza, Northeastern Brazil, and had no history of recent travels. He had no previous cognitive impairment and was independent for activities of daily living. Upon physical examination, he was alert, afebrile and had an altered respiratory pattern
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FIGURE 1 - Multiple supratentorial FLAIR (A) and DWI (B) hyperintense foci (arrowheads) distributed randomly in the white matter. Diffuse FLAIR hyperintense white matter was also noted on the centrum semiovale (arrows in A). FLAIR: Fluid-attenuated inversion recovery; DWI: Diffusion weighted imaging.

(with moments of apnea). Lung auscultation was normal. His abdomen was flaccid, not tender and without organomegaly. There was no evidence of arthropathy. The neurological examination showed inattention and disorientation in time and space. No focal deficits or pathological reflexes were found, and he had no cranial nerve abnormalities. Cerebrospinal fluid (CSF) analysis showed an increase in white cells with a predominance of lymphocytes [white blood cell count of 61 cells/mm³ (lymphocytes 71%)], no red blood cells, CSF glucose of 62mg/dL, and CSF protein of 98mg/dL. CSF gram and fungal stains, as well as bacterial cultures, were negative. Immunoglobulin M (IgM) for dengue, cytomegalovirus, Epstein-Barr virus, and toxoplasmosis, as well as blood cultures, yielded negative results. Seroconversion to CHIKV was confirmed on enzyme-linked immunosorbent assay (ELISA) by the presence of IgM antibodies [reactivity = 3.9 (reference > 1.1)]. Magnetic resonance imaging (MRI) with contrast showed bilateral supratentorial white matter fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) hyperintensities (Figure 1), with some of the cortical and subcortical foci showing restricted water diffusion on the apparent diffusion coefficient (ADC) map (Figure 2). There was no specific predominance, and no leptomeningeal or parenchymal enhancement was noticed. There was also mild cortical atrophy (global cortical atrophy scale - 1). There were no signs of cranial nerve involvement. An MRI scan with contrast of the spinal cord was normal. His CSF was tested via reverse transcription-polymerase chain reaction (RT-PCR) for CHIKV ribonucleic acid (RNA) and yielded negative results. On the 5th day of hospitalization, he experienced disorientation in time and space and urinary retention, but with no signs of meningeal irritation. Because of the abnormal CSF results, we decided to start intravenous corticosteroid (dexamethasone, 40mg, every 6h). The patient responded well to symptomatic treatment with resolution of the fever, normalization of platelets, and improvement of neurological symptoms two days after the initiation of corticotherapy; he was discharged ten days later.
Case 2

A 74-year-old male patient, a native of Morada Nova, Northeastern Brazil, previously healthy and with no cognitive deficits, presented with a 4-day history of fever, maculopapular rash, and severe arthralgia. Four days after the onset of symptoms he presented with confusion and fluctuating level of consciousness, leading to hospitalization. On admission, the patient was somnolent, however responsive, with temporal and spatial disorientation. The CSF study showed an increase in white cells with a predominance of lymphocytes (leukocytes: 90/mm³; 91% lymphocytes) and increased protein (179mg/dL). The patient developed progressive lower limb weakness (an initial grade 3 power in the lower limbs, progressing rapidly to grade 0 after 5 days) and diffuse areflexia. There was no clear sensory level or bladder dysfunction and there were also no signs of cranial nerve or cerebellar lesions. Anti-chikungunya IgM was found in serum. The electroencephalogram showed disorganized electrical brain activity with the presence of triphasic waves, and the nerve conduction study (NCS)/electromyography (EMG) displayed sensorimotor axonal neuropathy. Sequential brain MRI exams showed the appearance of multiple bilateral FLAIR and DWI hyperintense foci with restricted water diffusion in the supratentorial white matter (Figure 3). An MRI scan with contrast of the spinal cord was normal. After receiving intravenous immunoglobulin (400mg/kg/day) for 5 days, she recovered quickly. Brain MRI four months later demonstrated persistent, but reduced hyperintense foci on FLAIR, which were absent on DWI.
DISCUSSION

The diagnosis of encephalitis was based on the clinical presentation, laboratory CSF results, and MRI findings. CSF examinations showed elevated protein with mild pleocytosis and lymphocyte predominance, typically seen in viral encephalitis.

Both patients tested positive for anti-chikungunya IgM in their serum. Although genomic products in CSF were negative in case 1, this was not surprising, given the brief period (4-5 days) of viremia. Both patients were infected during a recent epidemic in an endemic zone in the Northeast region of Brazil.

Our findings are consistent with earlier reports of CNS complications of CHIKV infection, ranging from mild neurocognitive or behavioral disorders to severe neurologic syndromes including acute encephalitis/encephalopathy, acute disseminated encephalomyelitis (ADEM) and Guillain-Barré syndrome. Our patients had different clinical presentations, the first case being a mild encephalopathy with a good response to steroids. On the other hand, the second patient had a more severe neurological disease involving signs of encephalitis and an acute flaccid weakness with an axonal pattern in EMG and NCS and CSF pleocytosis with high protein content. This second pattern has been described previously in some arbovirus, particularly the one caused by West Nile virus. These findings underscore the varied presentations of neurological symptoms in chikungunya fever.

The neuroimaging findings were bilateral predominantly frontoparietal white matter lesions with increased signal on DWI, which is described as an early sign of viral encephalitis. These findings are similar to the cases of CHIKV-associated encephalitis reported by Ganesan et al. in India. However, these authors reported nodular enhancement in some of the lesions with restricted diffusion in one of the cases, which was not seen here. Moreover, Case 2, presented with clinical signs of polyradiculitis. Myeloradiculitis was reported by Ganesan et al., depicted on spine MRI scan as a cauda equina nerve root enhancement – also not present here.

Bilateral white matter lesions with restricted diffusion due to cytotoxic edema may be secondary to plasma leakage from capillaries and venules, which can occur in vasculitis and acute demyelination induced by sensitization to viral antigen and microglial activation. Restricted diffusion precedes signal abnormalities seen on FLAIR images and is also known to resolve earlier than the FLAIR signal abnormalities during the recovery period, as seen in Case 2. In the cases reported here, given the MR-DWI abnormalities, cerebral vasculitis and autoimmune encephalitis were differential diagnoses. However, the acute clinical presentation and the benign course did not support either of these diagnoses. In addition, the resolution of the DWI lesions and radiologic lack of disease activity at 3 months rarely occurs in either of these diseases.

This report highlights the clinicoradiologic findings in patients with encephalitis following chikungunya infection in the recent Brazilian epidemic. From an imaging perspective, a careful analysis of DWI is essential for the diagnosis of CHIKV-associated encephalitis since it can easily be interpreted as unspecific findings on FLAIR images, such as age-related white matter changes, and clinical correlation is necessary.

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Conflict of interest
The authors declare that have no conflicts of interest.

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