

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

**Licia Pacheco Pereira<sup>[1],[2]</sup>, Rafaela Villas-Bôas<sup>[2]</sup>, Stephanie Suzanne de Oliveira Scott<sup>[3]</sup>, Paulo Ribeiro Nóbrega<sup>[3]</sup>, Manoel Alves Sobreira-Neto<sup>[3]</sup>, José Daniel Vieira de Castro<sup>[1]</sup>, Bruno Cavalcante<sup>[4]</sup> and Pedro Braga-Neto<sup>[3]</sup>**

[1]. Divisão de Neurorradiologia, Departamento de Radiologia, Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, Fortaleza, CE, Brasil.

[2]. Departamento de Radiologia, Hospital Geral de Fortaleza, Fortaleza, CE, Brasil.

[3]. Divisão de Neurologia, Departamento de Medicina Clínica, Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, Fortaleza, CE, Brazil. [4]. Departamento de Medicina Clínica, Hospital Monte Klinikum, Fortaleza, CE, Brasil.

## Abstract

Chikungunya, an alphavirus infection presenting with fever, rash, and polyarthritis, is most often an acute febrile illness. Neurologic complications of chikungunya infection have been reported. Here we report the clinical and neuroimaging data of 2 patients with chikungunya-associated encephalitis during the recent Brazilian epidemic.

**Keywords:** Chikungunya virus. Encephalitis. MRI.

## INTRODUCTION

Chikungunya fever (CF) is caused by an arthropod-borne alphavirus that belongs to the *Togaviridae* family and is transmitted by *Aedes* mosquitoes<sup>1</sup>. 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 causes<sup>1</sup>. Other symptoms such as high fever, headaches, nausea, and vomiting may also occur<sup>1</sup>. 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 Reunion<sup>1</sup>, followed by a worldwide spread. Since its first description, the virus has been identified in 60 countries<sup>2</sup>.

The first report of local transmission in Brazil occurred in 2014 in the City of Oiapoque, Amapá<sup>3</sup> and in 2016, it was estimated that the CHIKV is circulating in almost half of Brazilian cities<sup>2</sup>. 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 2015<sup>4</sup> – and the country now accounts for 94% of confirmed cases of the disease in the Americas<sup>5</sup>. 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 arthritis<sup>2,6</sup>, and severe or fatal forms of the disease with CNS involvement have been observed, in both adults and neonates<sup>2,7</sup>.

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

**Corresponding author:** Dra. Licia Pacheco Pereira.

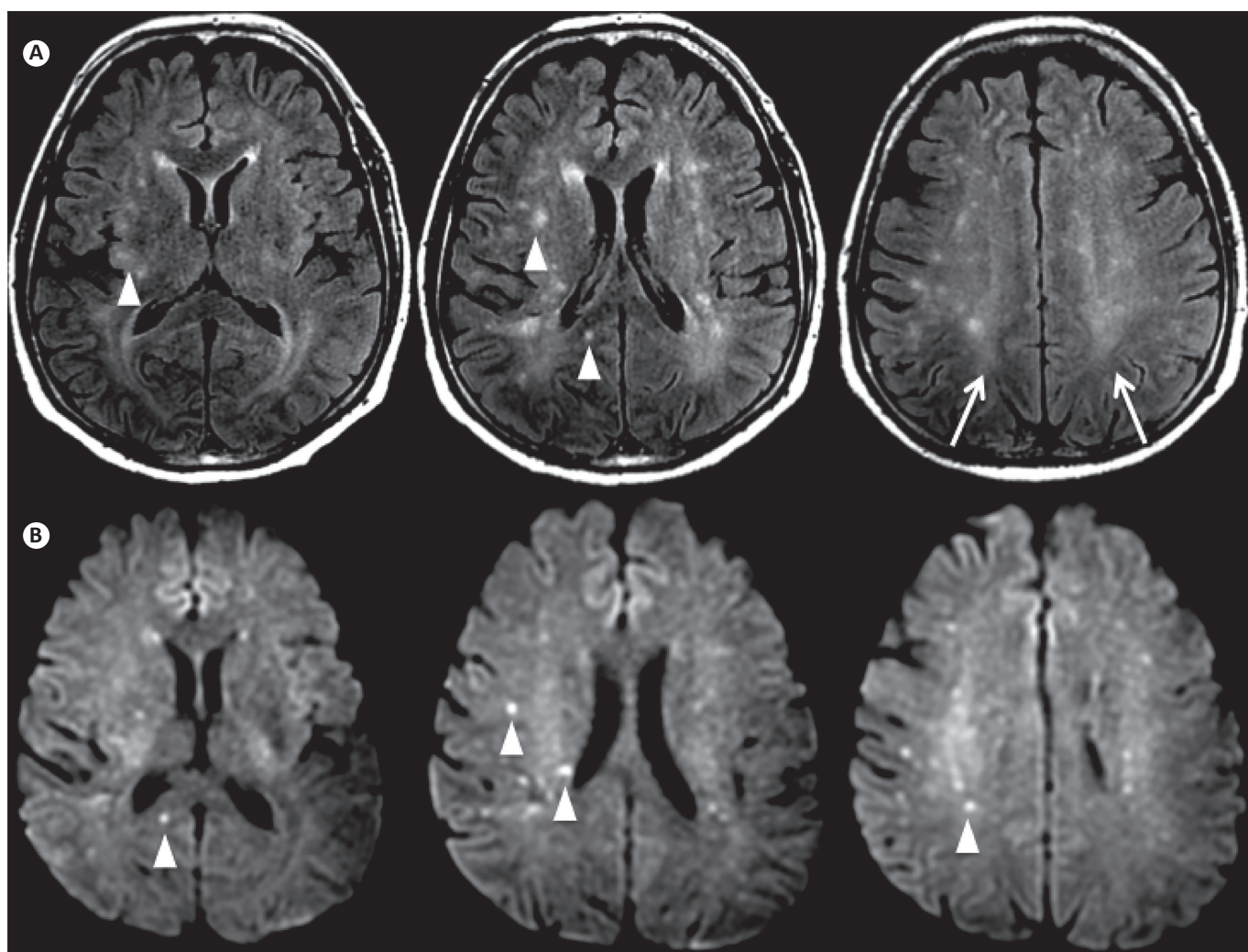
**e-mail:** liciap.luna@gmail.com

**Received** 31 October 2016

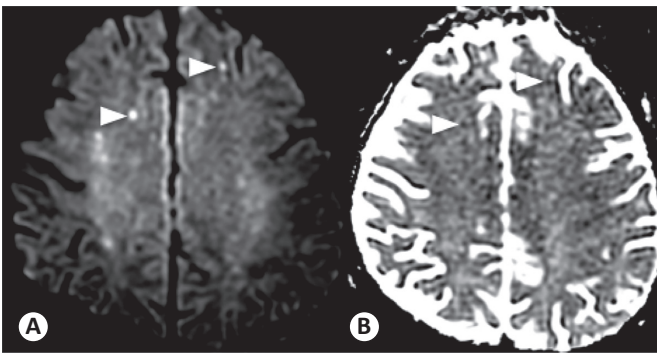
**Accepted** 25 January 2017

(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/mm<sup>3</sup> (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 5<sup>th</sup> 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.



**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.**

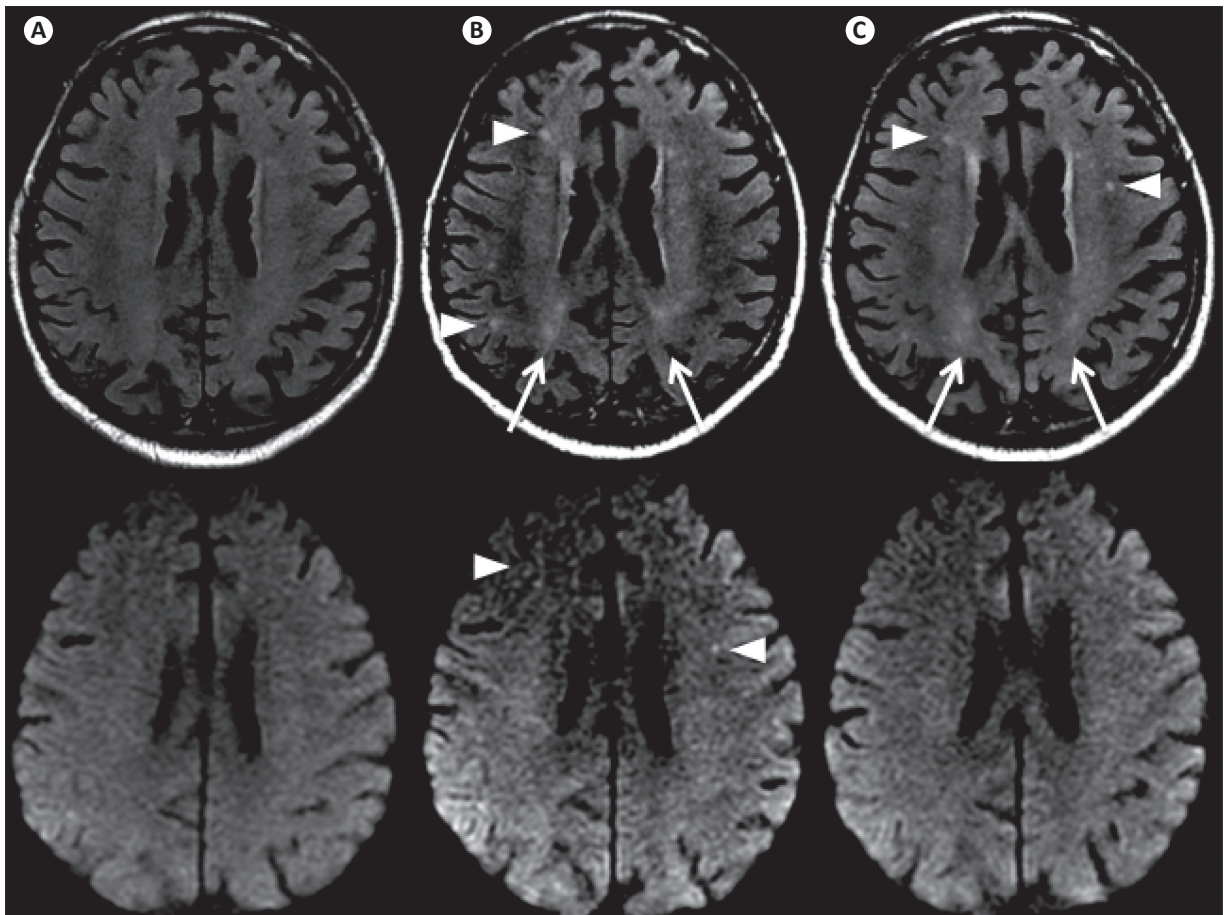


**FIGURE 2** - The cortical and subcortical hyperintense foci (arrowheads) in DWI (A) show restricted water diffusion seen as hypointense areas on the ADC map (B). DWI: Diffusion weighted imaging; ADC: Apparent diffusion coefficient.

**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/mm<sup>3</sup>; 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.



**FIGURE 3** - (A): Normal brain MRI (2nd day of hospitalization). (B): Appearance of multiple FLAIR and DWI hyperintense foci (arrowheads) on the supratentorial white matter 5 days after the 1st MRI. The DWI hyperintensities are very subtle. (C): Brain MRI done 4 months later showing the persistence of some of the FLAIR hyperintensities (arrowheads), no longer noticed on DWI. FLAIR hyperintense regions on the parietal white matter were also noted, which partially disappeared on control MRI (arrows on B and C). MRI: Magnetic resonance imaging; FLAIR: Fluid-attenuated inversion recovery; DWI: Diffusion weighted imaging.



## 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<sup>8</sup>. 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<sup>7,9</sup>. 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 arbovirolosis, 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<sup>10</sup>. These findings are similar to the cases of CHIKV-associated encephalitis reported by Ganesan et al. in India<sup>11</sup>. 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 or acute demyelination induced by sensitization to viral antigen and microglial activation<sup>11</sup>. 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.

### Acknowledgments

We offer our deepest thanks to Dr. Francisco Ronald Pedrosa de Oliveira Junior for his important support and help in providing the clinical information about one of the patients reported here.

### Conflict of interest

The authors declare that have no conflicts of interest.

## REFERENCES

1. Kucharz EJ, Cebula-Byrska I. Chikungunya fever. *Eur J Intern Med.* 2012;23(4):325-9.
2. Collucci C. Brazil sees sharp rise in chikungunya cases. *BMJ.* 2016;354:i4560.
3. Lima-Camara TN. Emerging arboviruses and public health challenges in Brazil. *Rev Saude Publica.* 2016;50:36. doi: 10.1590/S1518-8787.2016050006791
4. Ministério da Saúde (MS). 2016. Boletim epidemiológico. Brasília: Secretaria de Vigilância em Saúde; 2016.
5. Pan American Health Organization. World Health Organization (PAHO WHO). Chikungunya: PAHO/WHO Data, Maps and Statistics. 2016.
6. Rodriguez-Morales AJ, Cardona-Ospina JA, Urbano-Garzon SF, Hurtado-Zapata JS. Prevalence of post-Chikungunya infection chronic inflammatory arthritis: a systematic review and meta-analysis. *Arthritis Care Res.* 2016;68(12):1849-58.
7. Gérardin P, Couderc T, Bintner M, Tournebise P, Renouil M, Lémant J, et al. Chikungunya virus-associated encephalitis: a cohort study on La Réunion Island, 2005-2009. *Neurology.* 2016;86(1):94-102.
8. DeBiasi RL, Tyler KL. Molecular methods for diagnosis of viral encephalitis. *Clin Microbiol Rev.* 2004;17(4):903-25.
9. Lebrun G, Chadda K, Reboux AH, Martinet O, Gaüzère BA. Guillain-Barré syndrome after Chikungunya infection. *Emerg Infect Dis.* 2009;15(3):495-6.
10. Nouranifar RK, Ali M, Nath J. The earliest manifestation of focal encephalitis on diffusion-weighted MRI. *Clin Imaging.* 2003;27(5):316-20.
11. Ganesan K, Diwan A, Shankar SK, Desai SB, Sainani GS, Katrak SM. Chikungunya encephalomyeloradiculitis: report of 2 cases with neuroimaging and 1 case with autopsy findings. *AJNR Am J Neuroradiol.* 2008;29(9):1636-7.