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Case Report

Encephalitis associated with inappropriate antidiuretic hormone secretion due to chikungunya infection in Recife, State of Pernambuco, Brazil

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Abstract

The symptoms of chikungunya virus (CHIKV) infection include fever, headache, muscle aches, skin rash, and polyarthralgia, characterized by intense pain, edema, and temporary functional impairment. This is the first report of encephalitis caused by CHIKV infection associated with an atypical presentation of syndrome of inappropriate antidiuretic hormone secretion, evolving to cognitive impairment and apraxia of speech.

Keywords: CHIKV. Encephalitis. Syndrome of inappropriate antidiuretic hormone hypersecretion.

INTRODUCTION

The first cases of chikungunya virus (CHIKV) infection in Brazil were reported in 2014[1], continuing through 2015 during the epidemic of newborns with microcephaly and adults with Guillain-Barré syndrome caused by Zika virus infection. The clinical symptoms of arbovirus infections include high fever, headache, muscle aches, vomiting, and skin rash. CHIKV infection also causes polyarthralgia, characterized by intense pain, edema, and temporary functional impairment, with recurrent episodes of arthralgia that may occur months after disease onset. This is the first report of central nervous system involvement caused by CHIKV infection associated with syndrome of inappropriate antidiuretic hormone secretion.

CASE REPORT

On February 24, 2016, a 48-year-old woman was admitted to the emergency unit of a private hospital in Recife, State of Pernambuco, Brazil, with asthenia, edema, erythema, arthralgia involving the wrists, knees and ankles, and blisters on the wrists and palate that had developed over 24 hours prior to hospitalization (**Figure 1**). There was no fever, headache, nausea, vomiting, or diarrhea. The laboratory test results showed discrete lymphopenia and increased C-reactive protein levels of 6.11mg/dL (reference <0.30mg/dL). The patient was discharged following a diagnosis of Chikungunya infection based on awareness of the outbreak affecting the city and on the clinical symptoms. On February 27, 2016, the patient attended the emergency unit with dehydration and poor general condition. These symptoms were attributed to hyponatremia (sodium=121mEq/L, reference 136-145mEq/L). There were no complaints of vomiting or diarrhea. Hypertonic saline were administered over 24 hours, and following clinical improvement, the patient was discharged. Two days later, the patient was readmitted with poor general condition and behavioral changes, initially attributed to anxiety disorder, as there was a previous history of this condition associated with clonazepam and diphenhydramine self-medication. On admission, the laboratory tests showed persistent hyponatremia with a plasma osmolality below 275mOsm/kg H_2O, preserved renal function (urea=7mg/dL, creatinine=0.3mg/dL), normal thyroid hormone levels (TSH=0.9mcIU/mL, T4 free=1.46ng/dL), and no hypocortisolemia; high urine sodium and potassium concentration was also observed despite correction of the fluid balance (**Table 1**), meeting the criteria for a diagnosis of syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH). Appropriate therapeutic support and clinical investigations were commenced.

After 24 hours of hospitalization, the patient's condition deteriorated, with temporo-spatial disorientation, decreased level of consciousness, and worsening hyponatremia (sodium=103mEq/L) despite intravenous fluid replacement,

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TABLE 1

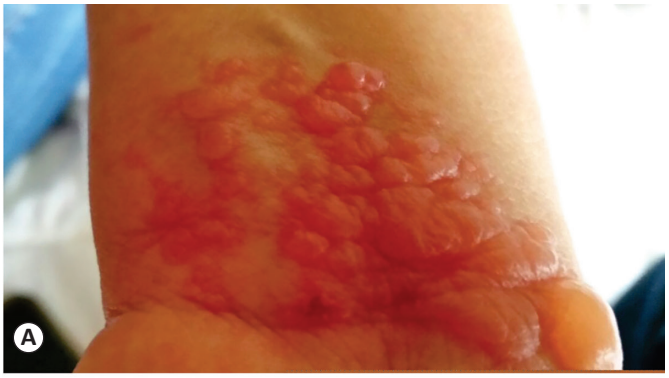
Laboratory test results of the adult patient during the acute phase of chikungunya infection.

	February 24th	February 27th	February 29th	March 1st	March 3rd, 4th	March 6th, 7th	March 9th
Clinical	**blisters**	**dehydration**	**hyponatremia**	**coma**	**conscious**	**cognitive deficit**	**discharged from ICU**
Blood cell count (*ref)							
erythrocytes (3.9-5.4 million/µL)	3.29	4.03	3.65	3.93	3.27	3.54	3.57
hematocrit (35-47%)	28.5	34	31.1	34.5	28	30.1	30
hemoglobin (12-16g/dL)	9.8	11.5	10.6	11.7	9.8	10.3	10.1
leukocytes (4,000-11,000/ µL)	3,900	3,000	3,800	8,100	7,500	7,300	5,500
platelets (140,000-450,000/ µL)	225,000	260,000	282,000	303,000	332,000	334,000	386,000
Hydroelectrolytic balance (*ref)							
sodium (136-145mEq/L)		121	119	103	133	132	137
chloride (98-107mEq/L)		86	82	69	105	95	99
bicarbonate (21-32mmol/L)		25	21	16	19	24	25
potassium (3.5-5.1mEq/L)		3.8	4	3.1	4.1	3.9	3.7
calcium (8.6-10.0mg/dL)			8.2	7.4	8	8.5	8.7
phosphorus (2.5-4.8mg/dL)				2.1	5.8	3.7	3.8
magnesium (1.2-2.6mg/dL)				1.5		1.7	1.7
Liver function and other tests (*ref)							
albumin (3.4-4.8g/dL)		4	4		2.7		3.3
aspartate aminotransferase (15-37UI/L)	31	77	92	131	64	96	60
alanine aminotransferase (6-45UI/L)	44	76	162	274	168	116	107
lactate dehydrogenase (81-234U/L)			306				
gamma-glutamyl transpeptidase (5-55UI/L)			**77**				
direct bilirubin (up to 0.2mg/mL)		0.1	0.1	0.2		0.1	0.1
indirect bilirubin (0.1-1.0mg/mL)		0.1	0.4	0.4		0.3	0.2
amylase (25-115UI/L)	55						
lipase (73-393UI/L)	138						
Inflammation markers/others (*ref)							
C-reactive protein (< 0.30mg/dL)	6.11	0.64	0.35	0.22	7.39	1.72	2.18
creatine phosphokinase (26-192U/L)				323		2,272	249
erythrocyte sedimentation rate (0-15mm)		14	14				
ferritin (4.6-204ng/mL)				230.6			
cortisol (4-22mcg/dL)				37.1			
thyroid-stimulating hormone, TSH (0.3-5.0mcIU/mL)				0.9			
thyroxine, T4 free (0.7-1.8ng/dL)				1.46			
glucose (60-99mg/dL)					97		99
Arterial blood gas analysis							
pH (7.35-7.45)				7.3	7.40	7.53	
PCO_2 (35-45mmHg)				35	30	30	
PO_2 (80-105mmHg)				171	158	178	

Continue...

SO_2 (94-100%)			99	99	100	
HCO_3 (22-26mmol/L)			17.2	18.6	25.1	
Base excess (-2 a +2mmol/L)			-9.2	-6.2	2.4	
Renal function (*ref)						
urea (15-50mg/dL)	5	7	7	8	10	11
creatinine (0.5-1.3mg/dL)	0.4	0.4	0.3	0.6	0.3	0.3
plasmatic osmolality (275-295mOsm/Kg H_2O)	268	264.5	232.5	292.7	291	301
Urine test, 10mL random sample						
aspect			Clear			
glucose (mg/dL)			250			
bilirubin			Negative			
ketone			Negative			
density (1,000-1,030)			1010			
Hemoglobin			Positive			
pH (5.0-9.0)			5.0			
protein (mg/dL)			100			
urobilinogen			Normal			
Nitrites			Negative			
sodium (20mEq/L)			64			
potassium (15mEq/L)			43			
creatinine (20-230mg/dL)			82.4			
urea (350-1,000mg/dL)			364			
urine osmolality (50-1,200 mOsm/Kg H_2O)			280.11			
Cerebrospinal fluid						
cells (0-4/mm^3)			7,0			
proteins (10-28mg/dL)			24			
relation albumin/globulin			1.61			
glucose (40-70mg/dL)			68			
chlorate (680-750mg/dL)			700			
reactions of Pandy, Nonne and Takata-Ara			Negatives			
direct examination – China Ink			Negative			
reaction of VDRL			Non-reagent			
fungal antigens testing (CRYTO-LA-TEST)			Non-reagent			
Serology						
neurosyphilis (Wasserman, FTA-ABS, Hemagglutination)			Non-reagent			
cisticercose (Weinberg test; Immunofluorescence, ELISA)			Non-reagent			
toxoplasmosis (Immunofluorescence)			Non-reagent			
toxoplasmosis (Hemagglutination)			Reagent (1/4)			
cytomegalovirus (IgM and IgG, ELISA)			Non-reagent			
herpes simplex 1 and 2 (IgM and IgG, ELISA)			Non-reagent			
herpes zoster (IgM and IgG, ELISA)			Non-reagent			
human T- lymphotropic virus type 1 and 2 (ELISA)			Non-reagent			
human immunodeficiency virus type 1 and 2 (ELISA)			Non-reagent			
dengue (IgM ELISA)			Non-reagent			

ICU: intensive care unit; ***ref:** reference values; **VDRL:** Venereal Disease Research Laboratory nontreponemal test; **FTA-ABS:** Fluorescent Treponemal Antibody Absorption; **ELISA:** enzyme-linked immunosorbent assay; **IgM:** Immunoglobulin M; **IgG:** Immunoglobulin G. On March 1, the thromboplastin and prothrombin time and fibrinogen were normal; blood and urine cultures were negative, anti-*Treponema pallidum* specific antibodies were non-reagent.



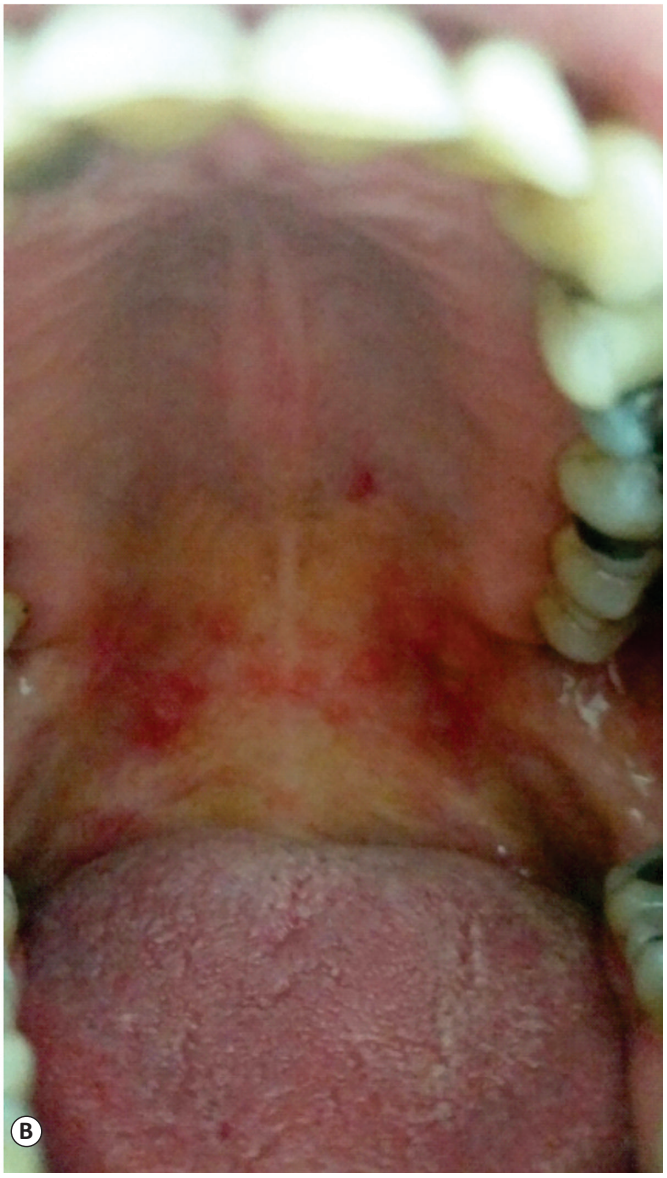


FIGURE 1 - Atypical presentation of chikungunya virus infection. (A): The top panel shows blisters on the wrists. (B): The bottom panel shows an erythematous lesion on the palate due to the rupture of blisters.

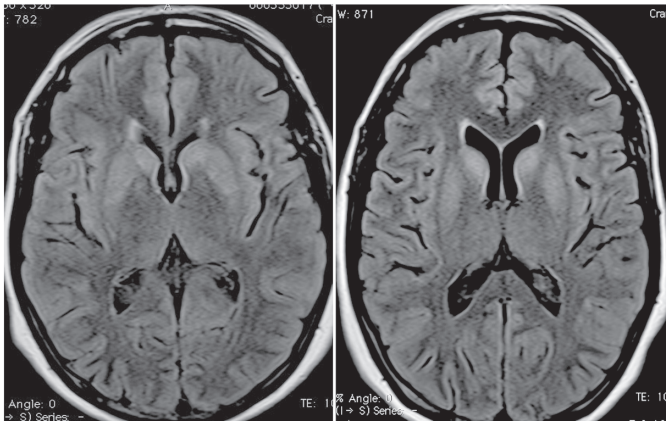


FIGURE 2 - Brain MRI. The patient with encephalitis caused by chikungunya infection underwent three MRI scans (24 hours, 7 days, and 14 days after ICU admission) using 1.5-T Magnetom Espree (Siemens, Erlangen, Germany), with head coil (eight channels). Axial T2 FLAIR showed a bilateral and symmetrical increased signal in the putamen and caudate nucleus, with no mass effect. There was a mild increased signal in the thalamus bilateral. **MRI:** magnetic resonance imaging; **ICU:** intensive care unit**; T2 FLAIR:** T2-weighted fluid attenuated inversion recovery.

culminating in an episode of generalized tonic-clonic seizures and the need for mechanical ventilation. The patient was sedated for 24 hours for clinical stabilization and clinical investigations focused on the involvement of the central nervous system (CNS), with neuroimaging studies, cerebrospinal fluid analysis (**Table 1**), and electroencephalogram (EEG) studies. Initially, these tests did not show any significant changes.

Following the uneventful reversion of sedation and extubation, there was no evidence of neurological motor disorders. However, important cognitive-behavioral changes were observed, including affective disorders, infantile behavior, as well as different types of apraxia, particularly regarding personal care activities and writing. Laboratory tests indicated an increased natremia (30mEq/L) over 24 hours. A further brain magnetic resonance imaging (MRI) study showed bilateral and symmetric high signal intensity on T2-weighted fluid attenuated inversion recovery (T2 FLAIR) in the caudate and putamen nucleus, which was interpreted as osmotic demyelination syndrome (**Figure 2**). There was no diffusion restriction or enhancement following intravenous contrast.

Serological investigations for neurosyphilis, toxoplasmosis, cysticercosis, and viral infection showed negative results (**Table 1**). Urine and blood cultures were also negative.

Serum and CSF were tested by reverse transcription-polymerase chain reaction (RT-PCR) and/or real-time RT-PCR (qRT-PCR) for the detection of Zika virus, dengue virus, and CHIKV. Chikungunya virus infection was confirmed by virus isolation in Vero cells from serum samples collected on March 1 and confirmed by qRT-PCR. The viral genome was also detected by qRT-PCR in the CSF sample, confirming encephalitis caused by CHIKV. The serum sample collected 14 days after the onset of symptoms was positive for chikungunya immunoglobulin M (IgM) serology.

The patient was diagnosed with encephalitis and SIADH secondary to CHIKV infection and discharged after 16 days of hospitalization with cognitive behavioral rehabilitation. The patient had no systemic complaints and serum sodium levels were normal. After seven months of rehabilitation with a speech and language therapist, a physiotherapist, and psychologist care, improvements in memory and speech were observed.

DISCUSSION

Atypical symptoms of CHIKV infection include neurological, cardiovascular, renal, ocular, and skin manifestations[2]. This is the first report of neuropathy and encephalitis caused by CHIKV infection associated with a rare and serious presentation of SIADH, occurring in a patient from Recife, state of Pernambuco, Brazil. CHIKV infection was confirmed by viral isolation and RT-PCR of serum and CSF samples. This is an atypical case because there was no associated high fever. The only complaints were intense joint pain, blisters on the wrists, and occurrence of blisters on the palate. There are no previous reports of CHIKV infection causing lesions on the palate; however, bullous dermatosis has been described in children infected by CHIKV[3,4]. A further atypical symptom was the development of SIADH with severe hyponatremia, which preceded the neurological manifestations and may have contributed to the delay in associating the neurological manifestations with arbovirus infection. The onset of neurological symptoms occurred 6 days after the onset of arthralgia and edema, and within a few hours, these progressed to mental confusion, convulsions, and coma, requiring mechanical ventilation. The lowest plasma sodium level was recorded on the day of the onset of coma. The onset of neurological symptoms has been reported to occur early within 2-3 days[5] or after weeks of the onset of the disease[6].

A common finding in patients with CHIKV infection is the increase in creatine phosphokinase (CPK) levels (CPK=2,272U/L; reference 26 - 192U/L), due to intense myositis caused by the infection[6]. Liver enzymes levels were also increased in this case.

Patients with encephalitis may have normal CSF or, more frequently, increased protein levels, and increased cellularity in a few cases[5,6]. Chandak et al. reported increased protein levels in 14 out of 20 patients with encephalitis, low glucose levels in 3, and increased cellularity in 6 cases[6]. The CSF in the present case was collected a few hours after the onset of coma and showed a discrete increase in cellularity that was not taken into account at the time.

The EEG revealed no specific changes and the presence of slow waves, observed in the present study, has also been reported by previous authors in patients with neurological manifestations of CHIKV infection[3,7].

The hyperintense signal on T2 FLAIR MRI scans of the basal ganglia was a non-specific finding. These changes can occur in different situations, mainly hypoxic-ischemic encephalopathy, neurofibromatosis type 1, acute diffuse encephalomyelitis, carbon monoxide intoxication, and infectious vasculitis. Less common causes are drug abuse, cerebral gliomatosis, osmotic demyelination syndrome, and encephalitis. Rare causes are Creutzfeldt-Jacob disease, acute hypertensive encephalopathy, metabolic inherited disease, and Huntington's disease. The first differential diagnosis for the patient in the present study was acute demyelination syndrome; however, this is commonly associated with white matter damage and brain stem injury, particularly involving the pons, and these were not observed here. A further potential diagnosis was viral encephalitis, because CHIKV infection had already been confirmed by the detection of viral genome in the CSF. Viral encephalitis is associated with nonspecific neuroimaging findings, such as involvement of the basal ganglia and the thalamus, characterized by bilateral and symmetric high signal intensity on T2 FLAIR[8].

Retrospective studies of the CHIKV epidemic in 2006 in Reunion Island[4] and in the state of Maharashatra[6], western India, reported the presence of neurological complications in 16-24% of the studied cases, and encephalitis was the most common manifestation (55-69% of cases). Neurological manifestations occur in adults[8,9] and children[3,10] and may progress to partial or complete recovery or result in permanent dysfunction[8]. Mortality is related to the presence of co-morbidities in adults[6] and is associated with the severity of neurological manifestations and patient age in children[3].

Until 2006, CHIKV infection was restricted to the African continent and Southeast Asia, spreading to the Caribbean and Brazil in 2013[11] and 2014, respectively.[1] In Brazil, although cases of CHIKV infection are frequently under reported, in the first four months of 2016, there were 122,762 cases of chikungunya fever (incidence rate of 60 cases/100 million inhabitants), most of them in the Northeast region. In the State of Pernambuco, there were 40,627 cases, 26 confirmed deaths, and 238 deaths under investigation[12]. However, there is no official record of the number of cases with neurological involvement, which may reflect the lack of knowledge regarding this complication or difficulties in performing the specific diagnostic tests in public reference laboratories. The spread of CHIKV across Brazil, as with dengue, can lead to a significant increase in neurological complications. Therefore, it is crucial that clinicians are aware of the risks associated with infection, emphasizing the need for further research and notification of atypical forms.

Conflict of Interest

The authors declare that there is no conflict of interest.

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