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Short Communication

Severe manifestations of chikungunya virus in critically ill patients during the 2013–2014 Caribbean outbreak

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SUMMARY

Objectives: A chikungunya epidemic occurred in 2013–2014 in the Caribbean and Americas. Although the disease is usually benign, some patients required admission to the intensive care unit (ICU). The characteristics and outcomes of patients with chikungunya virus (CHIKV) infection admitted to an ICU during this epidemic are reported.

Methods: An observational study of consecutive patients with confirmed CHIKV infection admitted to ICUs in Martinique and Guadeloupe, French West Indies, between January and November 2014, was performed. In addition, patients with CHIKV-related manifestations were compared with those whose manifestations were not specifically related to CHIKV infection.

Results: Sixty-five patients were admitted to the ICU with CHIKV infection. Fifty-four (83%) had a pre-existing underlying disease and 27 (41.5%) were admitted due to exacerbation of a comorbidity. Thirty-seven (57%) patients were mechanically ventilated. ICU and hospital mortality rates were 26% and 27%, respectively. CHIKV-related manifestations were observed in 28 (18%) patients and were mainly encephalitis, Guillain–Barré syndrome, and severe sepsis. These patients less frequently had chronic arterial hypertension and diabetes and more frequently had autoimmune diseases compared with patients without CHIKV-related manifestations.

Conclusions: Most patients admitted to the ICU with CHIKV infection had a pre-existing comorbidity. However, severe manifestations such as Guillain–Barré syndrome, encephalitis, and severe sepsis could be specifically related to CHIKV.

1. Introduction

Chikungunya fever (CHIKF) is an arboviral disease that was first identified in 1953.[1] The causal agent, chikungunya virus (CHIKV), is transmitted to humans by mosquitoes of the *Aedes* genus.[1] Epidemics of CHIKF have occurred mainly in Africa and Southeast Asia. In October 2013, CHIKV was detected in Saint Martin and thereafter spread rapidly throughout the Caribbean and the Americas,[2] affecting more than a million patients in 42 territories.[3] In the French West Indies, 159 623 suspected cases have been reported, representing more than 17% of the total population.[2,3] Although CHIKF is usually benign, severe forms of the disease have been described,[4] and the need for admission to the intensive care unit (ICU) was reported for the first time during the epidemics in Reunion Island in 2006.[5,6]

2. Methods

This study aimed to describe the critically ill patients with CHIKV infection admitted to ICUs of the university hospitals in Guadeloupe and Martinique during the 2013–2014 Caribbean

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outbreak. These university hospitals are the main hospitals in the French West Indies. From January to November 2014, at the height of the outbreak, clinical and laboratory data were collected from each consecutive patient with CHIKV infection confirmed by either a positive real-time PCR (RT-PCR) or positive IgM serology. RT-PCR (RealStar Chikungunya RT-PCR Kit 1.0; Altona Diagnostics) was performed on the serum and cerebrospinal fluid (CSF), when available, between days 1 and 10 of symptoms. IgM testing was performed from day 5 after the first symptoms. Organ failure was assessed during the first 48 h after admission and was defined as a Sequential Organ Failure Assessment (SOFA) score of 3 or 4. Encephalitis was defined based on the diagnostic criteria of the Consensus Statement of the International Encephalitis Consortium.[7] Severe sepsis and septic shock were defined according to the International Sepsis Definitions Conference.[8] Patients with CHIKV-related manifestations were defined as those lacking any other acute cause or predisposing medical condition identified to explain the acute illness; these patients were compared to patients whose manifestations were not directly related to CHIKV infection.

3. Results

During the study period CHIKF was confirmed in 65 patients. Baseline characteristics for CHIKF patients are shown in Table 1. Fifty-four patients (83%) had a pre-existing disease, predominantly chronic hypertension, diabetes mellitus, chronic heart failure, and chronic renal failure. Thirty-seven (57%) patients required invasive mechanical ventilation, 30 (46%) had shock and needed vasoactive drugs, and 20 (31%) required renal replacement therapy. ICU and hospital crude mortality rates were 26% and 27%, respectively, and were similar to the global mortality rate in each ICU.

CHIKV-related manifestations, such as a central or peripheral neurological disorder and severe sepsis or septic shock, were observed in 18 (28%) patients. Five patients (8%) demonstrated disorders of the central nervous system (CNS), including three who met criteria for encephalitis and two who had diffuse brain ischemia leading to brain death. In addition, six patients (9%) had Guillain–Barré syndrome. Six patients (9%) had severe sepsis ($n = 3$) and septic shock ($n = 3$) that was neither clinically nor microbiologically documented and for whom the only infectious agent identified was CHIKV. CHIKV-related myocarditis was diagnosed in one patient.

Patients with CHIKV-specific manifestation and those without did not differ in terms of organ failure, Simplified Acute Physiology Score (SAPS II), or laboratory findings, as reported in Table 2. More patients with CHIKV-related manifestations had autoimmune diseases. In addition, they less frequently required renal replacement therapy and had a shorter length of stay in the ICU. There was no difference in crude mortality rate between the two groups.

Table 1
Clinical and laboratory features and outcomes of 65 patients with chikungunya virus infection admitted to the ICU

Characteristic	$N = 65$
Age, years, median (IQR)	63 (52–70)
Sex, male, *n* (%)	41 (63)
Pre-existing disease, *n* (%)	
Hypertension	36 (55)
Diabetes mellitus	21 (32)
Chronic renal failure	13 (20)
Chronic heart failure	13 (20)
Autoimmune disease	5 (8)
Including lupus	3 (5)
Sickle cell disease	4 (6)
No pre-existing disease	11 (17)
Diagnosis of chikungunya, *n* (%)	
PCR	38 (58)
IgM	34 (52)
Both PCR and IgM	7 (11)
Laboratory findings on admission	
WBC count, $\times 10^9$/l, median (IQR)[a]	10.2 (6.7–14.0)
Lymphocyte count, $\times 10^9$/l, median (IQR)	0.86 (0.45–1.25)
Lymphopenia $<1 \times 10^9$/l, *n* (%)	42 (65)
Platelet count, $\times 10^9$/l, median (IQR)	150 (101–220)
Platelet count $<150 \times 10^9$/l, *n* (%)	33 (51)
Creatinine level, μmol/l, median (IQR)	142 (85–371)
CK level, mmol/l, median (IQR)[b]	699 (344–3799)
CK level >1000 mmol/l, *n* (%)	21 (32.3)
ALT levels, IU/l, median (IQR)[c]	37 (22–108)
CRP levels, mmol/l, median (IQR)	66 (27–235)
Lactate level, mmol/l, median (IQR)[c]	2.2 (1.4–5.2)
Organ failure on admission[d], *n* (%)	
Haemodynamic	29 (45)
Renal	27 (41)
Neurological	18 (28)
Respiratory	17 (26)
Hepatic	17 (26)
Haematological	13 (20)
ICU management-associated variables	
SAPS II, median (IQR)	39 (28–54)
Vasopressor support[e], *n* (%)	30 (46)
Mechanical ventilation[e], *n* (%)	37 (57)
Renal replacement therapy[f], *n* (%)	20 (31)
Outcome variables	
ICU length of stay, days, median (IQR)	6 (4–11)
Hospital length of stay, days, median (IQR)	16 (8–24)
Crude ICU mortality, *n* (%)	17 (26)
Crude hospital mortality, *n* (%)	18 (27)

ICU, intensive care unit; IQR, interquartile range; PCR, polymerase chain reaction; WBC, white blood cell; CK, creatinine kinase; ALT, alanine aminotransferase; CRP, C-reactive protein; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

[a] Data missing for two patients.
[b] Data missing for 13 patients.
[c] Data missing for five patients.
[d] Organ failure was defined as a SOFA score of ≥3 for each organ.
[e] During the first 48 h.
[f] At any time during the ICU stay.

4. Discussion

This study reports a large cohort of patients with CHIKV infection admitted to the ICU. As reported previously during the Reunion Island epidemic, severe manifestations affect only a small number of patients in the total infected population,[6] and are predominantly seen in patients with debilitating conditions, in whom CHIKV infection often triggers an exacerbation of a pre-existing disease.

It is well documented that CHIKV infection can affect the nervous system.[9] In this study, 10 out of 65 (17%) patients presented with an acute neurological disease possibly related to CHIKV infection. Encephalopathy has so far appeared to represent the most common neurological manifestation; this was reported in 19 out of 33 patients hospitalized in the ICU during the Reunion Island epidemics.[6] However, only three patients in the present series had criteria for encephalitis. This difference may be explained by the strict criteria for encephalitis used in the present study.[7] The high incidence of Guillain–Barré syndrome is consistent with reports from previous epidemics.[6,10] It is also consistent with the probable link between Guillain–Barré syndrome and other arboviral diseases, such as Zika virus infection and dengue fever.

CHIKV-related severe sepsis or septic shock was present in six patients. This complication has not been observed in previous outbreaks, but has been reported since the beginning of the current epidemic in some patients in Colombia and Venezuela, including some cases of multiple organ failure with fatal outcome.[11,12] Hemodynamic failure is also observed in other arboviral diseases,

Table 2
Comparison of characteristics and outcomes of patients with chikungunya virus-related manifestations and patients without chikungunya virus-related manifestations

	Patients with CHIKV-related manifestations[a] *n* (%) (*n* = 18)	Patients without CHIKV-related manifestations *n* (%) (*n* = 47)	*p*-Value[b]
Sex, male	13 (72)	28 (60)	0.89
Age, years, median (IQR)	60 (52–65)	65 (48–72)	0.97
Pre-existing disease			
Hypertension	4 (22)	32 (68)	0.002
Diabetes mellitus	1 (5)	20 (43)	0.01
Chronic renal failure	2 (11)	11 (23)	0.45
Chronic heart failure	1 (5)	12 (26)	0.15
Autoimmune disease	4 (22)	1 (2)	0.03
Organ failure on admission			
Haemodynamic	6 (33)	22 (47)	0.33
Renal	4 (22)	23 (49)	0.09
Neurological	6 (33)	12 (25)	0.53
Respiratory	3 (17)	13 (28)	0.56
Hepatic	4 (22)	13 (28)	0.9
Haematological	5 (28)	8 (17)	0.53
ICU management-associated variables			
SAPS II, median (IQR)	38 (25–52)	40 (29–54)	0.34
Vasopressor support	7 (39)	22 (47)	0.56
Mechanical ventilation	12 (66)	25 (53)	0.33
Renal replacement therapy	1 (6)	19 (40)	0.01
Laboratory findings on admission			
Lymphocyte count, $\times 10^9$/l, median (IQR)[c]	0.85 (0.38–1.2)	0.86 (0.54–1.41)	0.49
Lymphopenia $<1 \times 10^9$/l	13 (72)	28 (68)	0.53
Platelet count, $\times 10^9$/l, median (IQR)	143 (84–240)	153 (104–219)	0.52
Platelet count $<150 \times 10^9$/l	9 (50)	23 (49)	0.94
Lactate level, mmol/l, median (IQR)[d]	2.6 (1.9–3.7)	2 (1.2–5.4)	0.45
Lactate level >4 mmol/l	6 (33)	20 (43)	0.5
LOS ICU, days, median (IQR)	8 (5–20)	6 (3–11)	0.05
Crude ICU mortality	4 (22)	13 (28)	0.76

CHIKV, chikungunya virus; IQR, interquartile range; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; LOS, length of stay.
[a] Patients with CHIKV-specific manifestations had encephalitis (*n* = 3), brain ischemia (*n* = 2), Guillain–Barré syndrome (*n* = 6), severe sepsis or septic shock (*n* = 6), and myocarditis (*n* = 1).
[b] Categorical variables were compared using the Khi 2 test or Fisher's exact test, as appropriate, and continuous variables were compared using the non-parametric Mann–Whitney test. *p*-Values of less than 0.05 were considered statistically significant.
[c] Data missing for two patients.
[d] Data missing for five patients.

such as dengue fever. Although the pathophysiology is unclear, a cytokine storm induced by the virus similar to that observed in sepsis has been suggested.

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