

# Chikungunya Related Sudden and Unexpected Deaths in Brazil.: Is the Worst yet to Come?

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## Abstract

Brazilian citizens and its public health system have been dealing with *Aedes aegypti* and dengue for more than a decade now. More recently, Zika and Chikungunya (CHIKV) viruses have arisen, sharing the same vector as dengue. Some reports initially suggested that those new arboviruses had a better prognosis, but specially (CHIKV) infection is such a young variation of dengue that researches worldwide still need more time to understand its behaviour. The population previously exposed to the virus together with climatic changes and inadequate sanitary situation were favorable for an outbreak and then a decrease in clinical cases in Brazil. CHIKV infection can present with an acute/subacute phase followed by a chronic condition. The acute phase has shown severe atypical manifestations mainly in people with comorbidities, increasing the risk of death. The objective of this case report is to describe the sudden and unexpected deaths of two young and healthy females presumed caused by CHIKV in a 24-hour period after admission to a Public Health Hospital in Rio de Janeiro, Brazil. On this behalf, this more recent arbovirus infection still represents a great challenge to emergency care physicians and researchers worldwide and it seems too early to determine CHIKV acute and late prognosis. Science should be aware that CHIKV outbreak emerge as lethal as dengue or even worse.

**Keywords:** Dengue virus; Prognosis; Fever

## Introduction

One of the difficulties in fighting CHIKV is its differential diagnosis, since the initial clinical manifestations of the disease are very similar to the main arboviruses, such as dengue and zika as well as the yellow fever [1-7]. These acute febrile illnesses look like the flu and can easily be misdiagnosed in emergency rooms. The disease can cause severe morbidity, but since 2005, fatal cases have been reported in Africa [8,9]. In Brazil, there were 185,854 probable cases of CHIK fever recorded in 2017 and 277,882 in 2016. In 2017, 156 deaths were confirmed, and 58 deaths are still under investigation [6,9]. In 2018, there were 47,791 probable cases of CHIK fever in Brazil, with an incidence of 23 cases/100 thousand inhabitants. Of these, 30,251 (63.3%) were confirmed and another 11,503 suspected cases were discarded. In 2018 eight deaths were serologically confirmed related to CHIKV and there are still 39 deaths to be confirmed or discarded (Figure 1). Therefore, diagnosis in the initial stages of the disease is essential and may influence prognosis of the disease and prevent future outbreaks [3].

Only molecular diagnosis makes it possible to differentiate one case from the other [3,10]. Those include laboratory tests that exclude dengue, such as immunological methods (IgG/IgM detection), molecular methods such as real-time reverse transcriptase-polymerase chain reaction and viral isolation methods - NS1, IgM and RT - PCR),

and IgM serology to confirm CHIKV infection [10]. Synthetic peptide-based isolated from the CHIKV E2 envelope glycoprotein have proven to be an efficient and a more accessible approach in immunodiagnosics, seem to be more specific and do not require high-level sophisticated infrastructures [10].

## Case Reports

**Case 1:** A.M.S, female, 18 years old, previously healthy, started symptoms during the night of October 8th, 2017. She had been struggling with fever, polyarthralgia, periarticular edema, myalgia, headache, chills and diarrhoea. Her family convinced her that probably she had the flu and because of a social history of missing work days, the patient took some aspirin and proceeded to work. On arrival, she collapsed without any warnings and her co-workers rushed her to the nearest hospital facility. She arrived conscious at Medical Triage, her blood pressure was normal, and her worst complaint was a severe headache. Blood samples were analysed and showed moderate thrombocytopenia and slightly elevated transaminases (Table 1). As more serious cases began to arrive at the emergency department, she was taken to the observation unit. One hour after admission she collapsed again and rapidly evolved to respiratory failure and pulmonary congestion leading to death in less than 12 hours after the onset of symptoms. Laboratory tests excluded dengue (NS1, IgM and RT - PCR), and confirmed CHIKV by IgM serology.

**Case 2:** B.M, female, 15-year-old was diagnosed with mild asthma



Figure 1: *Aedes aegypti*.

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during childhood. She started symptoms on the morning of December 2<sup>nd</sup>, complaining of pain in the right deltoid muscle. Her parents took her to patients' case 1 same hospital. She arrived hemodynamically stable and had a normal physical examination except when moving the affected muscle. An x-ray was performed without any evidence of fractures. She was then medicated for the pain and promptly released. No blood samples were collected. Two days later, the patient returned to the same hospital, severely dehydrated and confused. The deltoid muscle pain was so severe that she would not stop crying. At that time edema in the right hand was observed by the attending physician. Blood samples were collected. Rheumatoid factor and Anti-streptolysin were within normal levels. Six hours later, while in the observation unit, receiving serotherapy, the patient evolved with worsening mental status, fatigue, intense polyarthralgia, general exanthema, nausea, vomiting, joint edema, pallor and cyanosis labialis. She was immediately transferred to the Intensive Care Unit (ICU) and blood samples were collected for the second time. Arterial blood analyses showed a high level of lactate and mild metabolic acidosis. Despite this, she recovered conscience and hydration seemed the right approach. There were no R-rays' abnormal findings. When asked by the medical staff she still complained of intense polyarthralgia and back pain despite morphine and glucocorticoids having been administered. She also reported nausea and vomiting with traces of blood. The exanthema seemed more pronounced. After an eight-hour period monitored into the ICU, the patient suddenly had a cardiorespiratory arrest. Resuscitation manoeuvres were unsuccessful, and she was pronounced dead 20 hours after symptoms began. Laboratory tests excluded dengue (NS1, IgM and RT - PCR), and confirmed CHIKV by IgM serology.

### Discussion

The acute phase of CHIKV infection is mostly characterized by generalized or hand localized edema (Figure 2), an exanthema (Figure 3), severe headache and myalgia. All those clinical manifestations are until now reported as benign and with a good prognosis. It is of common knowledge that dengue fever is also accompanied by some unspecific laboratory testing results. Overall, 80% of dengue fever cases show increased values of serum transaminases. The serum glutamic oxaloacetic transaminases (SGOT) and serum glutamic

pyruvic transaminases (SGPT) are sometimes found to be increased 5-10 times in dengue fever due to liver parenchymal damage caused by the virus, reflecting early liver damage [11]. Those early alterations of biochemical markers can help into the initial diagnosis of dengue



Figure 2: Hand edema.



Figure 3: Cutaneous rash (exanthema).

Patients	1		2		1		2		1		2		1		2						
	RBC		WBC		Haemoglobin		Haematocrit <sup>1</sup>		Platelet Count/ ml <sup>(ii)</sup>		AST <sup>(iii)</sup>		ALT <sup>(iii)</sup>		AST <sup>(iv)</sup>		ALT <sup>(iv)</sup>		Arterial Blood Gas <sup>(v)</sup>		IgM CHIKV Serology
Hospital Admission	Normal	4.6	72,000	204,000	26	64					BE= -5			+							
		17,100																			
		13,3																			
		40,3																			
ICU Admission	+	4.8	114,000									Lactate= 26 Ph= 7,30 HCO3= 20 BE=-4			+						
		9,693																			
		13.8																			
		37,9																			

Note: Normal values (11,13,14.)

I) Red cells (RBC): 3,0-5,30 10<sup>12</sup> /L/ Leucocytes (WBC): 4-12 10<sup>9</sup>/L/ Haemoglobin (Female): 12,3-15,7 g/ dl/ Haematocrit (Female): 38-47%.

II) 150,000 to 450,000/ ml.

III) Aspartate aminotransferase: 8-20 U/L.

IV) Alanine-aminotransferase: 7- 56 U/L.

V) pH: 7,36-7,44/ Lactate: 4-16 mg/dl / HCO<sub>3</sub>=22-28 mEq/l Base Excess: -2-0 nml/m;10

Table 1: Laboratory analyses of blood samples collected from both patients.

fever in suspicious cases, at least until serology is performed. The first case reported of CHIKV related death was published in 2010 [12]. Severe systemic infection with cardiovascular collapse was probably the terminal event for that 66-year-old man in Malaysia with no prior illnesses, who managed to survive the infection for six days. Despite that, there were clearly clinical and laboratory evidence of hepatitis on disease presentation [12]. Unfortunately, we were not able to document transaminases levels in patient 2, but patient 1 demonstrated mild laboratory liver function alterations at the onset of the disease, having not lived enough time to monitor daily liver transaminases [13]. Platelet counts do not seem to reflect prognosis and do not correlate to fever duration in dengue and seems to be the same as with CHIKV infection [14]. A decline in platelet function was observed in patient 2, but it could be attributed to the rapidly evolving inflammatory system cascade [8].

After being diagnosed with CHIKV, it is estimated that 30 percent of patients will experience the chronic phase [7]. When clinical manifestation become chronic and the longer they last, more bone damage and destruction are expected [7]. Some victims have developed chronic rheumatic diseases, such as rheumatoid arthritis. This delayed autoimmune response together with an initial inflammatory acute phase may explain the more aggressive behaviour of the CHIKV reported above. Bilateral polyarthralgia characteristic of the chronic phase of CHIKV, has been treated with anti-inflammatories (steroids or not) and immunosuppressants. New cases of autoimmune diseases such as psoriasis, lupus and diabetes have been related to this chronic phase. In one study, this was seen in 5% of patients [7], reemphasizing that initial and late inflammatory responses observed in CHIKV infection are unpredictable so far.

Atypical presentations and severe complications of CHIKV infection have been documented in elderly patients and/or with comorbidities, increasing the risk of death, which is why they are classified as more vulnerable [5]. However, case reports documenting such a sudden decline in all major organ functions that could only be related to a lethal virus behaviour affecting young and until proven healthy women has never been reported.

Some researches also emphasize the overlapping of both diseases, which can worsen prognosis and maybe explain why CHIKV infection has behaved in those two cases so differently from its first clinical presentation and diagnosis [7].

These acute febrile illnesses look like the flu and may be easily misdiagnosed in emergency rooms, which can delay initial treatment and impact on outcome [9]. Based on that and on the fact that it has always been a widely accepted concept that dengue is the one that kills and kills fast, and that molecular diagnosis are nor widely available in brazilian hospitals, emergency clinicians treat all patients like dengue [6], mainly with serotherapy and anti-inflammatories. A great portion of patients are relieved after these procedures. The epidemiological outbreak of these arboviruses between 2015 and 2017 in Brazil [6] served as an alert that will be useful in a new outbreak, but maybe this time the disease may be presenting with a worse prognosis and the health system should be on alert. These two case reports confirm specialists' observations that an inflammatory process plays a very important role in disease mechanism when the body is fighting the virus, such as observed in clinical cases of systemic sepsis [8]. Most septic bacterial scenarios can be managed with fluid resuscitation and broad-spectrum antibiotics but unlike most of these bacterial infections, CHIKV virus has no specific treatment. Physicians fight the symptoms, not the virus. These two case reports may also reinforce the thesis that women are

not only more affected by the disease but also more vulnerable to a worst presentation, although these phenomena have to date only been described during the chronic phases of the disease. This observation has no scientific explanation so far [9].

## Conclusion

It has never been related such an aggressive clinical behavior of CHIKV infection, not only considering the rapid evolution to death but also considering the special subgroup affected of young and healthy women whose immune systems should be more prepared to fight such an inflammatory cascade that resembles the first hours of septic shock or prolonged surgical procedures. Attention must be paid to recognizing the possibility of a rapidly decline in organic functions since diagnostic suspicion of CHIKV infection. This case report is an objective demonstration of this on-going phenomena because once the inflammatory process starts there seems to be no return. Another aspect to be considered and maybe the most important of all is that there is no cure for these arboviruses, even when the infection is correctly and rapidly diagnosed. Without specific treatment, an effective vector control is urgently required. The emergence or resurgence of CHIKV virus and other mosquito-borne diseases may be related to global climate change and deforestation. Nonetheless, they are also conditioned by variables such as the adequacy of sanitation facilities, the availability of piped water and the destination of the waste produced in the communities. In the end, the only effective strategy remains to try to stop mosquitoes from breeding. Controlling *Aedes aegypti* is still a huge challenge not only in Brazil but also in Africa and other underdeveloped regions. Public policies, population engagement and the adoption of various strategies for directly combating the virus, such as insecticides and the introduction of transgenic mosquitoes in Brazil should be started immediately before the true nature of CHIKV emerges as a global and very serious health problem.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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