MYSTERY SOLVED

Virus that causes chikungunya provokes inflammation in several organs, including the brain, and can lead to death

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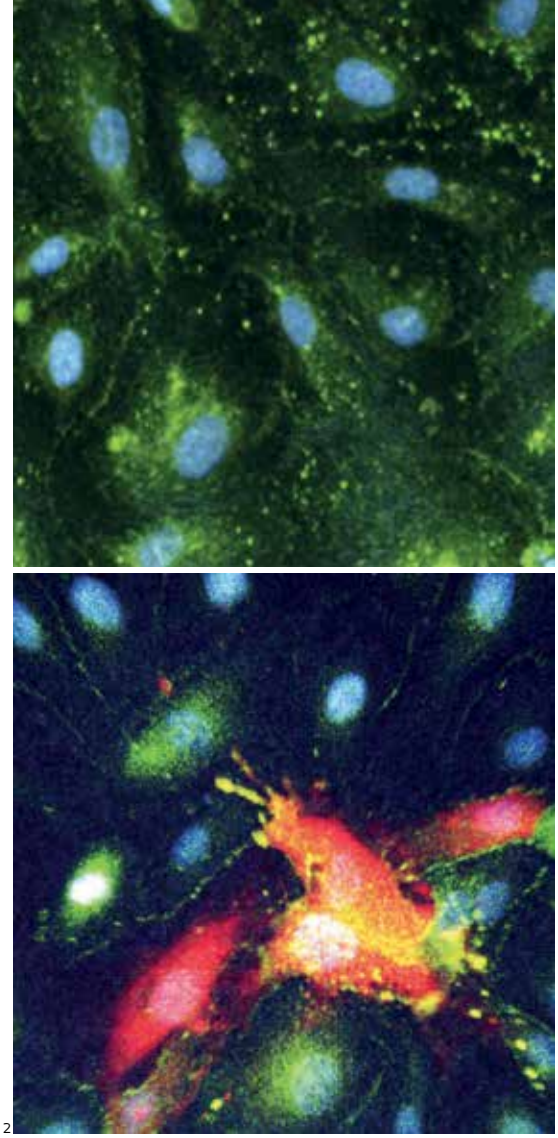
Chikungunya is a highly debilitating disease caused by a virus transmitted by the bite of female mosquitoes of the genus Aedes. Chikungunya is characterized by high fever, red rashes across the body, and most notably, swelling and severe pain in the joints that can last for months and cause people to remain hunched over while walking or standing. However, few studies mention the risk of death, which is low but possible. In certain regions, the proportion of deaths from chikungunya can surpass the national average of deaths from dengue (one case in every thousand patients).

Since its arrival in Brazil in 2014, the chikungunya virus has been proven to have infected 254,000 people—the number of suspected cases of the desease has reached 1.2 million–and killed at least 909 people. Ceará, the most affected state over the 10-year period, accounted for 31% of the deaths. "We know that chikungunya can kill, but we always wondered: why do the people die?" says Brazilian virologist William Marciel de Souza of the University of Kentucky in the USA.

To solve this mystery, Souza and researchers from several institutions in Brazil, the USA, and the UK analyzed blood and tissue samples from 32 people who died because of acute chikungunya infection in 2017 in Ceará. The results were subsequently compared with those of 39 individuals who developed milder forms of the disease and survived and those of 15 healthy blood donors. The study received funding from FAPESP, and the results were published in April in the journal *Cell Host & Microbe*. The conclusion of the study was that chikungunya kills because the virus, known as CHIKV, spreads across different tissues, including the brain, and causes intense inflammation that damages the organs, preventing them from functioning properly.

An examination of the samples revealed that, in general, patients who died exhibited an increased amount of blood and an accumulation of liquid in the lungs, heart, liver, spleen, kidneys, and brain, although they did not have a greater concentration of the virus than the survivors did, nor had they been infected with a more aggressive strain of CHIKV.

The blood from patients who died also contained significantly higher levels of two types of chemical communicators than in patients from the other groups: proinflammatory cytokines, proteins that coordinate the immune defense, and chemokines, a class of cytokines responsible for attracting cells from the immune system to the sites of inflam-



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Intact cells from the lining of blood vessels of the brain (*top*), compared with CHIKV-infected cells that have been destroyed (*left, in red*)

mation. Associated with symptoms of hyperinflammation, these molecules alter the permeability of the internal wall of the blood vessels, allowing the liquid portion of the blood to escape and accumulate within the tissues. These molecules also facilitate the penetration of defense cells in tissues; while attempting to eliminate the virus, defense cells can sometimes destroy healthy cells.

Among the patients who died, the presence of defense cells was observed in the heart, liver, kidneys, and, most intriguingly to researchers, the brain. The blood vessels that supply the central nervous system have a unique and highly selective lining called the blood-brain barrier. This barrier allows the passage of oxygen, nutrients, and some rare defense cells from the blood to the brain but usually prevents the entry of pathogens. Souza and colleagues reported that the virus was detected in the cerebrospinal fluid, the liquid that surrounds the brain and other organs of the central nervous system, in all patients who died, which indicated that CHIKV had crossed the blood-brain barrier. The virus was detected in 13% of the brain samples, 20% of the heart and kidney samples, 28% of the liver samples, 44% of the lung samples, and 52% of the spleen samples from patients who died.

All of the infected people exhibited metabolic dysregulation, which was more intense in patients who died than in the survivors. This dysregulation affects the integrity and permeability of the blood-brain barrier, potentially facilitating the invasion of the brain by pathogens.

However, metabolic dysregulation was not the only mechanism involved. Laboratory tests performed by the group revealed that the virus was also capable of infecting monocytes, which are defense cells that naturally cross the blood–brain barrier, using them as a type of Trojan horse. "It hides inside the monocytes and, therefore, reaches the brain," explains pharmacist Shirlene de Lima of the Central Laboratory of Public Health of the State of Ceará (LACEN/CE), one of the lead authors of the study.

By analyzing the affected organs and tissues, researchers identified extensive damage in the brain, including bleeding and cell death. They still do not know which of the factors–hemodynamic imbalance, exacerbated inflammation, or infection of the central nervous system–is the most important factor indicating a fatal outcome. "We need more studies to understand the contribution of each of these problems and why they affect some people more than others," says Lima. "This knowledge is fundamental for developing better treatment approaches." Currently, therapy consists of the administration of analgesics, antipyretics, and anti-inflammatories to alleviate symptoms.

"The study provides relevant information mainly about the behavior of the chemokines and about molecular signatures associated with the patients who died," states infectologist Julio Croda of the Oswaldo Cruz Foundation in Mato Grosso do Sul (FIOCRUZ-MS), who did not take part in the study. "The infiltration of the infected monocytes in the brain and its effect is a new finding. Now we need larger studies, with people of different ethnicities, ages, and genders, to validate these conclusions."

Until a more effective treatment is found, hope rests on the development of a vaccine. In November 2023, the Food and Drug Administration (FDA), the agency that regulates food and drugs in the USA, approved the use of Ixchiq, a vaccine based on the weakened virus developed by the Franco-Austrian pharmaceutical company Valneva, for adults. In Brazil, the company has a partnership with the Butantan Institute, which is currently testing the composition in phase 3 clinical trials in adolescents before submitting a request for approval by the Brazilian Health Regulatory Agency (ANVISA). ■

The research projects and scientific articles consulted for this report are listed in the online version.

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