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Editorial

Chikungunya virus (CHIKV): What can be expected after the acute phase?☆

La enfermedad producida por el virus chikungunya. ¿Qué esperar luego del estadio agudo?

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Chikungunya virus (CHIKV) was identified for the first time in Tanzania in 1952, when it was isolated in humans and in *Aedes* mosquitos during an epidemic that had features compatible with dengue.[1] It is classified as an arbovirus of the *Togaviridae* family, genus *Alphavirus*, a group that also includes other viruses such as Ross River, O'nyong-nyong, Barmah Forest and Mayaro, which have been associated with the development of arthritis in humans. It is considered to be endemic in large areas of Africa, the Middle East, India and Southeast Asia.[2] Although the ecology of these agents differs, morphologically and antigenically, they are closely related; moreover, the diseases they cause are practically indistinguishable.[3]

The term "chikungunya" is derived from the expression in the Makonde language for "that which bends up" or "bent over with pain".[4] The disease is a zoonosis transmitted by mosquitos of the *Aedes albopictus* and *Aedes aegypti* species.[5] It is important to point out that the *Aedes* mosquito is the vector of several arboviruses, including dengue (a flavivirus). In countries in which both Aedes vectors are present and where the diagnostic facilities may be limited, it would be difficult to distinguish between CHIKV and dengue, especially in children, since the symptoms and signs overlap.[6] Comparative studies have shown that characteristics like myalgia, arthralgia and rash are particularly associated with CHIKV, whereas thrombocytopenia is more is more frequently found in dengue.[7,8]

It is important to point out that the A226V mutation made it possible for the virus to adapt itself better to *Aedes albopictus*, the only competent vector on Reunion Island, a circumstance that also explains its unusual virulence in the last outbreak in 2005.[9] Chikungunya infection is thought to generate antibodies that protect individuals for life.[10]

With regard to the clinical signs, more than 85% of the patients had the typical symptoms of CHIKV infection: sudden high fever (>38.9 °C), chills, headache, photophobia and an itchy petechial or maculopapular rash. Most infected individuals complain of severe joint pain, which is often disabling, and edema in extremities; there have also been cases of painful inguinal lymphadenopathy,[11–13] ocular involvement, most frequently anterior uveitis,[14] and gastrointestinal manifestations (diarrhea and vomiting). Reportedly, 5–18% of the infected patients are asymptomatic.[15]

The acute phase typically has a duration of a few days to a couple of weeks, although arthralgia and/or myalgia can persist from weeks to months, or even years.[16] Some patients develop an authentic chronic arthritic syndrome,[17] which is usually symmetrical, polyarticular and migratory, predominantly affecting small joints of the hands, wrists, ankles and feet. The large joints are less frequently involved. Periarticular inflammation, pain, redness and limited mobility may be observed.[4] Persistent polyarthritis occurs in 30–40% of the patients affected by the alphavirus, and proinflammatory mediators, such as interleukin 6 (IL-6), have been proposed as the cause.[18] Joint damage fluctuates over time, but is always found in the same parts of the body, mainly the extremities (hands, ankles and knuckles).[15]

The percentage of affected individuals gradually decreases, with recurrent joint pain persisting in at least 10% to 20% of the patients 1 year after acute infection, and in up to 12% at 3 and 5 years.[19] The mortality rate is low (0.4%), although it is higher among infants under 1 year of age (2.8%) and increases in older individuals with

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concurrent diseases (cardiovascular, neurological and respiratory tract disorders).[20]

On the other hand, there have been reports of patients with a post-CHIKV rheumatoid arthritis (RA)-like disorder,[21] possibly due to the presence of the HLA-DRB1 gene, which is associated with the development of RA, a disease that would be triggered by the CHIKV infection. The presence of progressive erosive arthritis has been reported. However, in contrast to what is known about RA, high levels of rheumatoid factor and anti-cyclic citrullinated peptide were not detected.[22]

On 9 December 2013, the Pan American Health Organization issued a regional alert on indigenous CHIKV transmission in the Americas for the first time. This alert was released after the health authorities of the island of Saint Martin (a French territory in the Caribbean) confirmed 2 autochthonous cases in laboratory tests on 6 December 2013.[23]

Up to 4 December 2013, 1,724,759 suspected cases had been reported to the Pan American Health Organization, as well as 59,932 confirmed cases and 271 deaths related to the disease, spread over 44 countries or territories in the Americas and the Caribbean, including the United States and Brazil.[24] The real figures are much higher, since the majority of the cases are not reported. It was estimated that more than 60% of the population of the Dominican Republic was affected, out of a total of around 10 million inhabitants.

The phase of greatest transmission of CHIKV may be exponential and progress in very little time (from 3 to 6 months), as could be observed in the Dominican Republic.

When documents on CHIKV epidemics are reviewed, the high attack rate constitutes the major concern. This rate is estimated to be between 30% and 68% of the population, and is reached within short periods of time. In the Dominican Republic, it was predicted that the activity of that epidemic would be widespread, as the scenario was a tropical, densely populated country, with a highly mobile population and the presence of the vector responsible for the transmission of the virus.[25]

The infection is diagnosed on the basis of clinical, epidemiological and laboratory criteria, although it should be pointed out that there are no laboratory findings that are pathognomonic for the disease. Signs like thrombocytopenia, leukopenia, abnormal liver function test results, and elevated erythrocyte sedimentation rate and C-reactive protein have been observed. To date, a number of diagnostic tests have been developed to detect CHIKV infection in both the acute phase and late stage of the disease. The majority of the epidemiological studies in the literature are based on IgM and IgG enzyme-linked immunosorbent assay (ELISA), a fact that demonstrates the importance of assays of this type.[26,27]

There is no specific treatment for CHIKV and, moreover, at the present time, there is no available vaccine. The disease is usually self-limiting and resolves over time. Rest is indicated during the acute phase, while there are joint symptoms. Infected individuals should avoid exposing themselves to mosquitos (remain indoors and/or under a mosquito net) during the first days of the disease so as not to contribute to the transmission cycle of the virus.[28]

The main concern over the next few years could be that larger epidemics arise in recently affected regions, like the Americas, Europe and Oceania.[29,30] These regions comprise countries with naïve populations and well established *Aedes* vectors, added to the fact that some have a relatively poor public health and diagnostic infrastructures.[31]

At this time, it is not possible to determine whether CHIKV will become endemic in the Dominican Republic. First, the behavior of the epidemic should be observed over the next few years, and systems of biosurveillance need to be implemented. More than a year after the acute outbreak, the patients continue to have musculoskeletal complaints of variable intensity that can be confused with the diagnosis of RA and spondyloarthritis.

Chikungunya virus has been added to the group of infectious diseases that are shared with Haiti, a country with which the Dominican Republic will join forces to persevere in the efforts to control and eradicate these diseases, with the same determination that has been, and continues to be, devoted to malaria, cholera and lymphatic filariasis.[32]

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