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Review Article

Chikungunya Fever. Rheumatic Manifestations of an Emerging Disease in Europe☆

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ABSTRACT

Chikungunya fever is a viral disease caused by an alphavirus belonging to the Togaviridae family, transmitted by several species of *Aedes* mosquitoes: *Aedes aegypti* and *Aedes albopictus (A. albopictus)*. It is endemic in Africa and Asia with recurrent outbreaks. It is an emerging disease and cases in Europe transmitted by *A. albopictus* have been established in Mediterranean areas. The first autochthonous cases detected on the Caribbean islands suppose a serious threat of spreading disease to America, which so far has been disease free.

Clinical symptoms begin abruptly with fever, skin rash and polyarthritis. Although mortality is low, a high percentage of patients develop a chronic phase defined by persistent arthritis for months or even years. A severe immune response is responsible for joint inflammation. The absence of specific treatment and lack of vaccine requires detailed studies about its immunopathogenesis in order to determine the most appropriate target.

Fiebre chikungunya. Manifestaciones reumáticas de una infección emergente en Europa

Palabras clave:
Fiebre chikungunya
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Alerta internacional

RESUMEN

La fiebre chikungunya es una enfermedad producida por un alfavirus perteneciente a la familia *Togaviridae*, transmitida por miembros de diferentes especies del género *Aedes*: *Aedes aegypti y Aedes albopictus (A. albopictus)*. Es endémica en África y Asia, ocasionando brotes epidémicos recurrentes. En 2007, surge de forma emergente en Europa transmitida por *A. albopictus*, asentado en el área mediterránea. Los primeros casos autóctonos detectados recientemente en las islas caribeñas suponen una seria amenaza de propagación al continente americano, libre hasta el momento de la enfermedad.

Se manifiesta de forma aguda con fiebre, rash cutáneo y poliartritis. La mortalidad es baja, pero un porcentaje elevado de enfermos desarrollan una fase crónica definida por poliartritis persistente durante meses e incluso años.

Una severa reacción inmunitaria de defensa con incremento de citocinas proinflamatorias es la responsable de la inflamación articular. El tratamiento es sintomático. No disponemos de terapia antiviral específica ni vacuna preventiva. Por ello, debemos profundizar en el estudio de la inmunopatogénesis, con el fin encontrar dianas terapéuticas más apropiadas.

Introduction

Chikungunya fever is a viral infection caused by a single-stranded RNA alphavirus belonging to the *Togaviridae family*. It is transmitted to humans by *Aedes* mosquitoes: *Aedes aegypti (A. aegypti)* and *Aedes albopictus (A. albopictus)*. It is endemic in

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Africa and Asia, causing recurrent outbreaks. The spread of the disease through imported cases has caused outbreaks in indigenous regions of the Indian Ocean and Europe, as happened in northern Italy in 2007.[1]

The notification, in December 2013, of the first indigenous cases in the territories of the Caribbean islands has alerted international authorities on the possibility of spread of the disease to the Americas, a continent so far free from the disease. Since then, the number of reported cases has progressively increased. The spread of the disease in a globalized world is causing alarm among global epidemiological health authorities. Multiple European travelers come each year to the region of the Caribbean islands, the current focus of the disease and may act as a vehicle to spread the disease to the European continent. Suitable climatic conditions for the development of the *A. albopictus* mosquito occur in the Mediterranean region of Europe favoring the colonization of this vector. Their presence has been detected in various regions of Spain. Therefore, Chikungunya fever could become, from imported cases, an emerging disease in our territory.

Clinically, the disease manifests itself as acute and abrupt fever, rash, joint pain/arthritis and fatigue that causes significant functional disability. The response to symptomatic treatment is slow, showing a high incidence of recurrence and chronicity at the joint level.[2]

A severe immune response to the viral infection is responsible for rheumatic manifestations. Current therapeutic resources are scarce. We have no effective antiviral treatment or vaccine, and response to symptomatic treatment is moderate. The study of the immunopathogenesis will lead us to more appropriate therapeutic targets.

Epidemiology and Natural History

Chikungunya virus (CHIKV) is a single-stranded RNA alphavirus belonging the *Togaviridae family*. Alphaviruses are small, spherical and encapsulated viruses, measuring 60–70 nm in diameter. Their replicative cycle is very fast, about 4 h.[2]

The reservoir of CHIKV in its urban endemic/epidemic cycle is infected human beings, and transmission occurs primarily through the bite of mosquitoes of the *Aedes* genus: *A. aegypti* and *A. albopictus*. *A. aegypti* is widely distributed in the urban areas of the tropics and subtropics and is responsible for human transmission in endemic areas. *A. albopictus, known in Spain as "Asian tiger mosquito", is a more aggressive mosquito, active throughout the day and with longer lifetime. The use of plastic containers and climate change in developing countries have facilitated the spread of this vector, expanding to other geographical areas through transport containers and tires from Asia.*[3] *Environmental changes have also led to a suitable habitat for vector development in recipient countries.*[4] *Moreover, in the course of the epidemic in the Indian Ocean, there was a mutation in the E1 protein (A226V)* of CHIKV, conferring an evolutionary advantage in replication to the *A. albopictus mosquito, the main* vector involved in the epidemic.[5] In Spain, the *A. albopictus* vector is present at least since 2004, when it was first detected in Sant Cugat del Vallès (Barcelona). In late 2012, the vector had established in many cities of the Mediterranean coast (Girona to Murcia, with the exception of Valencia) and Mallorca, making it impossible to rule out its circulation to areas of the Ebro Valley.[6]

CHIKV was first isolated in Tanzania in 1952. Initially, it remained limited to East Africa and Southeast Asia, causing massive epidemics, such as the one that occurred between 1999 and 2000 in the Democratic Republic of Congo, which affected some 50 000 people, and the one that in 2000–2003 occurred in Indonesia. In 2004 it began a process of global expansion, characterized by various epidemics affecting 5–10 million people.[7] In 2004 propagation was produced, from Kenya, of a new virus variant (A226V) adapted to the *A. albopictus vector*, to the islands of the Indian Ocean.[5] The epidemic in Réunion island (2006–2007) attracted worldwide interest in this disease as a result of the significant economic and social impact produced in a zone with an elevated sociosanitary development.[8] From the beginning of the epidemic, more than 1000 cases of imported CHIKV have been detected in European and American travelers arriving from affected areas.[4] Between July and September 2007, 205 indigenous cases of Chikungunya fever were detected in Italy, 175 confirmed, constituting the first autoctonous epidemic in Europe. The cases disappeared after a drop in temperature, and no new cases have been recorded so far.[9] In 2010, 2 new cases of local transmission occurred on the southwestern coast of France.[10] As for Spain, since 2006, several imported cases have been notified. Seco Sanchez et al. analyzed[11] the presence of the infection in 308 travelers with clinical manifestations of the disease who came from endemic areas.PCR and culture were used for detection. 29 cases were diagnosed in total, 9 in travelers from the western islands of the Indian Ocean and 20 in India. These cases occurred between 2006 and 2007, coinciding with epidemic outbreaks in these geographical areas. Confirmation of Chikungunya fever imported into Spain has promoted the adoption, in 2013, of a monitoring protocol designed to avoid the occurrence of cases and preventing vector settlement.[12]

Today, a new outbreak is emerging in the region of the Caribbean islands. In December 2013, the publication of the first indigenous cases of Chikungunya reported in America, covering the territories of the Caribbean islands: British Virgin Islands, Guadeloupe, Martinique, St. Barthelemy, St. Maarten (Dutch) St. Martin (French), French Guiana, Dominica, Anguilla and Aruba, Santo Domingo and Haiti, with 130,941 suspected cases and 4486 confirmed cases (June 6, 2014, last updated by WHO).[13] The disease spreads quickly and progressively. The emergence of Chikungunya fever as an emerging disease in the Americas has led to the publication by the WHO (24 January 2014) of a series of recommendations to prevent the progression of indigenous transmission of this disease.[14,15]

Clinical Manifestations

The bite of an infected mosquito in humans produces manifestations of the disease in 95% of cases. After CHIKV infection, a silent incubation period occurs lasting 2–4 days. After this short period, the acute period of the disease occurs abruptly, coinciding with maximum viremia. It occurs with high fever, followed within hours by myalgia, joint pain and generalized, severe and disabling arthritis, accompanied by headache, backache and[1] maculopapular rash, predominantly on the thorax. Sometimes, facial edema and bullous dermatitis can also appear, specially in children.[16,17] The acute phase reactants are normal or moderately elevated. There may be leucopenia, lymphopenia and thrombocytopenia. Among the ophthalmologic manifestations described, we found anterior uveitis, retinal vasculitis with a subsequently benign course, with resolution in 6–8 weeks.[18,19] Less common manifestations are myopericarditis, massive toxic hepatitis and meningoencephalitis. After this acute episode of 7–10 days, a high percentage of patients start the chronic phase of the disease. This is manifested in the form of persistent polyarthritis/polyarthralgia, accompanied by morning stiffness and fatigue, which remains even after 3 years.[20]

Fetal-maternal transmission of the virus is possible. Out of 35 pregnant women with confirmed disease at the time of delivery, 30 transmitted the disease to infants, constituting the first cases of fetomaternal transmission documented.[21] Subsequently, other cases have been published by various authors. Likewise, transmission may occur through blood transfusion. This caused considerable problems for the Italian health authorities during the epidemic that

affected its territory in 2007; the application of the precautionary measures taken by the blood banks led to a considerable drop in blood products.[22]

Chikungunya fever cannot be considered a serious disease in terms of mortality refers.[23] Its incidence is low and, for the most part, occurs in patients over 65. Its severity lies in the massive involvement of numerous individuals, as well as the chronicity of their rheumatic manifestations, which can have an important work, social and economic impact on the population.

Rheumatic Manifestations of the Disease

Although joint pain is the most typical rheumatic manifestation, both in the acute and the chronic phase, arthritis with marked synovitis can be objectified in both phases of the disease. It presents a distal, symmetrical, polyarticular pattern, affecting hands, wrists and ankles. It less commonly affects elbows, knees, shoulders, hips and temporomandicular joints. Entheseal disease, heel pain and chondrosternal pain occur less frequently. The prevalence of rheumatoid factor positivity in the chronic phase of the disease varies between 25 and 43%, with less anti-cyclic citrullinated peptide antibody positivity.[24] Another manifestation described is tenosynovitis of the fingers, wrists and ankles, which can be severe, contributing to the onset of carpal and tarsal and ulnar tunnel syndromes.[25]

Chronic polyarthritis is persistent or intermittent, with or without an ongoing migratory pattern and sometimes with recurrence after resolution of the initial manifestations.[25] The affected rate decreases over time, being 88 to 100% in the first 6 weeks, reaching 12% at 3–5 years. As can be seen, patients with chronic polyarthritis may meet criteria for rheumatoid arthritis

Other symptoms that may occur in both phases of the disease, and described by various working groups, are axial pain, present in up to 28–32% of chronic phase patients,[26] Raynaud's phenomenon and asthenia.

Immunopathogenesis

After inoculation, the CHIKV penetrates directly into subcutaneous capillaries, starting immediately replication in skin cells and macrophages, fibroblasts and endothelial cells. After this short phase, the virus is transported to nearby lymph nodes at the site of inoculation, which massively infect monocytes and macrophages. Thus, the virus carried by these cells quickly reaches the circulatory system, to spread to different locations, such as muscle, joints, liver and brain. We consider, therefore, monocytes/macrophages as genuine Trojan horses that help spread the virus. This fact explains the persistence of the disease despite the short duration of viremia. The resolution of the infection involves a vigorous immune response from the host. Failure of the regulatory mechanisms of this response could be due to the persistence of inflammation in synovial tissue, manifested as joint pain/chronic arthritis. As an expression of the inflammatory activity, interleukin-6 levels remain elevated in the chronic phase of the disease.[27] The theory of the persistence of CHIKV in synovial tissue used as a reservoir is consistent with findings in animal experimental model. The CHIKV is detected in the joint tissue of primates 90 days after infection, with obvious signs of chronic inflammation.[28,29]

Knowing the immunopathogenesis during disease development is instrumental in understanding its clinical course. The defense against CHIKV involves both innate immunity, via the action of IFN α as well as adaptive immunity, through various proinflammatory mediators.[30,31] It is possible that the A226V mutation detected in recent epidemics confers resistance to the antiviral activity of INF α·This has not yet been demonstrated in experimental studies of inhibition of viral replication. Currently, knowledge of the immunobiology of l CHIKV is still in its infancy. Understanding the virus/host interplay helps researchers develop the right conditions for disease control strategies.

Diagnosis and Monitoring

The diagnosis is established, first, on the basis of clinical characteristics and the epidemiology of the disease. Confirmation is absolutely necessary to establish the differential diagnosis with other *Aedes* mosquito borne *diseases* such as dengue, endemic in the same geographic areas. The microbiology laboratory must assume the responsibility to notify any finding of an imported virus in a patient who may have started a cycle of autoctonous transmission reside in an area colonized by the vector. The confirmation of the results by the National Reference Laboratory is also mandatory, and of crucial importance to the efforts for national and international surveillance.

The direct demonstration of the presence of the virus in blood through the determination of viral RNA by RT-PCR or culture isolation in cell lines must be performed as early as 5–10 days from disease onset, the viremia peak time. CHIKV isolation, in addition to its diagnostic value, is useful in biological, antigenic and molecular genetics research to identify and characterize new viruses.

After the acute episode, indirect serological determinations should be made. Immunofluorescence and ELISA are the most rapid and sensitive techniques for the detection of specific antibodies and allow us to distinguish between IgM and IgG. IgM appears within 2–3 days after infection and is maintained over 3 months, rarely more than a year. IgG appears soon after IgM and persists for[32] years.

Treatment

There is currently no specific antiviral treatment or vaccine for Chikungunya fever. Symptomatic treatment is our only recourse in the acute phase of the disease, although the response to nonsteroidal anti-inflammatory drugs is moderate. We must be cautious with the use of steroids because of the risk of reactivation of the rheumatic manifestations after tapering. The use of aspirin must be avoided due to the risk of Reye syndrome.

It has been suggested that chloroquine, being capable of reducing viral replication, could be effective in the prophylaxis and treatment of early stage disease, although no efficacy has been demonstrated[33,34] in the chronic phase. Moreover, methotrexate has been used successfully in a group of patients with chronic destructive polyarthritis (ACPA+) after[35,36] CHIKV infection.

The maintenance of inflammatory activity with elevated proinflammatory cytokines is a fact in the chronic phase. This opens the door to further studies of efficacy with disease modifying drugs and even biological therapy.

A continuing lack of vaccines, preventive pest control measures and protection against mosquito bites, as well as early diagnosis and notification of imported cases, are measures to be taken to prevent the occurrence of an outbreak.

Conclusions

Chikungunya fever may become an emerging disease in Spain, where the suitable climatic conditions for *A. albopictus* development, the vector of the disease, are present. At present, we have already detected the presence of this mosquito in various areas of the Mediterranean basin, affecting the resident population in the form of multiple stings. Potentially, a massive epidemic of indigenous cases with significant morbidity may be imported.

Its expansion to America in a globalized world is causing alarm among global epidemiological health authorities. Multiple European tourists travel each year to the region of the Caribbean islands, the current focus of the disease, and may act as a vehicle of spread to Europe.

Rheumatic manifestations should be known to Spanish rheumatologists, which will help us to get involved with epidemiologists, microbiologists and immunologists in the management and control of the disease.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of Interest

The authors have no conflict of interest to state.

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