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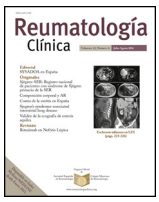

Review Article

Tropical Arthritogenic Alphaviruses☆

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ABSTRACT

Tropical alphaviruses have special tropism for bone and joint tissue. Patients can develop chronic rheumatic disorders similar to rheumatoid arthritis and ankylosing spondylitis. The prototype is *Chikungunya* virus, although other lesser known viruses in our environment such as *Sindbis*, *Ross River*, *Mayaro*, *O'nyong nyong* and *Barmah Forest* viruses have the potential to be sped through vectors and cause chronic rheumatic disease.

International population movements have increased the numbers of patients diagnosed with these tropical viruses in areas in which they are not endemic. Since they can leave persistent symptoms and affect the quality of life of the patients, it is important that we be aware of them. Changes in ecosystems have favored the expansion of competent mosquitoes, making fears of local transmission in southern Europe a reality.

The objective of this review is to provide a clinical approach to the different arthritogenic tropical alphaviruses, especially those in which chronic rheumatic disease is more frequent.

Alfavirus tropicales artritogénicos

Palabras clave:
Artritis infecciosa
Artritis crónica
Alfavirus

RESUMEN

Los alfavirus tropicales tienen especial tropismo por el tejido osteoarticular. Los pacientes desarrollan cuadros crónicos reumatológicos similares a la artritis reumatoide y la espondilitis anquilosante. El prototipo es el virus *Chikungunya*, aunque otros virus menos conocidos en nuestro medio como *Sindbis, Ross River, Mayaro, O'nyong nyong y Barmah Forest* tienen un potencial para propagarse a través de vectores y causar cuadros reumatológicos crónicos.

Los movimientos poblacionales internacionales han aumentado el número de pacientes diagnosticados por estos virus tropicales en zonas no endémicas. Dado que pueden dejar secuelas y afectar la calidad de vida, es importante conocerlos. Los cambios en los ecosistemas han favorecido la expansión de mosquitos competentes, haciendo realidad el temor de transmisión local en el sur de Europa.

El objetivo de esta revisión es dar una aproximación clínica de los distintos alfavirus tropicales artritogénicos, especialmente de aquellos en los que la patología reumática crónica es más frecuente.

Introduction

Although there is little data on the prevalence of rheumatic diseases in tropical regions, it seems that the number of cases of rheumatoid arthritis (RA), spondyloarthritis and connective tissue diseases is increasing worldwide.[1]

Infectious diseases are an important cause of the involvement of bone and joint tissue. Table 1 shows the viruses responsible for these manifestations and their geographic distribution.

Parvovirus B19, the rubella virus, hepatitis A virus and certain arboviruses often result in joint involvement, whereas respiratory viruses, enteroviruses, herpes family viruses and mumps virus are rarely the cause of arthritis. Arthralgia is common in other infections produced by tropical flaviviruses such as dengue virus or Zika

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Table 1
Viruses That Cause Musculoskeletal Manifestations and Their Geographic Distribution.

Virus	Geographic distribution
Adenovirus	Worldwide
Influenza	Worldwide
Parainfluenza	Worldwide
Hepatitis A, B, C	Worldwide
Parvovirus B19	Worldwide
CMV, EBV	Worldwide
Varicella zoster	Worldwide
HSV type 2	Worldwide
Rubella virus	Worldwide
Mumps virus	Worldwide
HIV	Worldwide
HTLV type 1	Worldwide
Enterovirus	Worldwide
Yellow fever virus	Africa, South America
Dengue virus	Africa, Asia, Central America-Caribbean and South America
Chikungunya virus	Africa, Asia, Central and South America
Barmah Forest virus	Australia
Mayaro virus	South America
O'nyong nyong virus	Africa
Ross River virus	Australia
Semliki Forest virus	Africa
Sindbis virus	Northern Europe

CMV, cytomegalovirus; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T lymphotropic virus.

virus. During the acute febrile phase in Zika virus, up to 65% of the patients have arthralgia or arthritis and, occasionally, swelling of hands and ankles. These manifestations occur during a short period of time and the severity is generally limited. There are a number of bacteria and fungi capable of producing reactive arthritis, which can even be severe and prolonged.[2]

Tropical alphaviruses have a special tropism for musculoskeletal tissue. They are arboviruses that belong to the *Togaviridae* family, and are classified among those associated with New World meningoencephalitis and those associated with polyarthritis (Table 2). The reservoirs of these viruses are generally wild animals and, although a human can become a reservoir, mosquitos are responsible for their transmission and nonvectorial transmission from one person to another is unusual.[3]

The confluence of a number of factors in recent years has enabled the spread of several tropical viruses that had previously been confined to certain specific geographic regions.[3] The main causes may have been the growth in the population and the increase in international travel, global trade and climate change. We are facing a globalization of tropical diseases, especially those transmitted by mosquitos and, as paradigmatic examples, we have dengue and Chikungunya virus (CHIKV) and, recently, Zika virus. Between 2009 and November 2014, the Spanish network for the study of infections imported by way of travelers and immigrants received reports on 136 cases of imported arboviruses. By July 2015, the number had increased to 228 cases, led by dengue virus, followed by CHIKV.[4]

The great potential for the spread of these diseases from their tropical niche to temperate regions lies in the fact that there are competent alternative vectors widely distributed all over the world. *Aedes albopictus* was detected in Europe (Albania) in 1979 and in Spain (San Cugat del Vallés in Catalonia, in the northeast of the country) in 2004. Since then, it has expanded throughout southern Europe. Fig. 1 shows the risk of transmission due to the establishment of *A. albopictus* in temperate areas such as southern Europe.

The clinical manifestations provoked by these viral agents can, in some cases, be confused with classical rheumatic diseases because of their prolonged, fluctuating and disabling course. The objective of this review is to offer a clinical approach to the different tropical arthritogenic alphaviruses, especially those that are most often associated with chronic rheumatic manifestations.

Pathophysiology

After inoculation via the vector bite, the virus is hematogenously disseminated through infected monocytes toward the spleen, the lymphatic system and the liver. In contrast to other viruses, they infect bone, skeletal muscle, myotendinous insertions and joint capsules. It was recently observed that Ross River virus (RRV) can affect osteoblasts, producing bone resorption, and that Sindbis virus (SINV) is capable of replication in the periosteum and the tendons of the long bones. Dissemination to the central nervous system (choroid plexuses, meninges, ependymal cells) has been observed in animals, but it is not known whether it infects neurons or brain endothelium. It does not infect trophoblasts, a fact that explains that vertical transmission occurs only during delivery. The infected target tissues undergo an extensive infiltration of lymphocytes, natural killer cells, neutrophils and macrophages.[5] The pathogenesis of chronic disease is due to the conjunction of an autoimmune response to persistent viral antigens and to the chronic presence of the virus (or of its products) in the target cells, with the resulting local accumulation of inflammatory mediators.[6] The virus replicates and persists in the macrophages, even if the viral burden is undetectable in peripheral blood. In macaques, that

Table 2
Vector, Reservoir and Geographic Distribution of Alphaviruses.

Etiological agent	- Vector - Wild reservoir	Geographic distribution
Barmah Forest virus (BFV)	- Aedes, Culex - Foxes	Australia and New Zealand
Chikungunya virus (CHIKV)	- Aedes - Monkeys	East Africa, Central Africa (Gabon, Cameroon, Angola) and South Africa, Southern Europe, Central-South Asia, Southeast Asia, Central America
Mayaro virus (MAYV)	- Haemagogus - Monkeys	South America
O'nyong nyong virus (ONNV)	- Anopheles - ?	East Africa
Ross River virus (RRV)	- Aedes, Culex - Marsupials	Oceania
Semliki Forest virus (SFV)	- Culex - Several animals	Central, South, East Africa
Sindbis virus (SINV)	- Culex, Culiseta - Birds	East Africa, South Africa, Europe, Australia