

Rheumatic Manifestations in Patients with Chikungunya Infection: Comment on the Article by Arroyo-Ávila and Vilá

To the Editor:

We read with interest the recent review of Arroyo-Ávila and Vilá about rheumatic manifestations in patients with Chikungunya virus (CHIKV) (1). However, based on our experience in Colombia (2, 3), country which has been significantly affected by more than a quarter million cases, we would like to discuss some aspects of that review that deserve some comments and even corrections.

CHIKV is an arthropod-borne virus (arbovirus) transmitted to humans primarily by *Aedes aegypti* (2, 3). CHIKV has become very important due to the increase of cases all over the world, in Africa, Asia, Europe and more recently (ending 2013) in the Americas (2). In Latin American nations, CHIKV has emerged in 2014 as one of the most significant tropical infectious diseases, where other arbovirus such as dengue, and now zika, are also transmitted by *A. aegypti* (4). Its clinical knowledge among healthcare workers is utmost importance in order to avoid its misdiagnosis as dengue fever, due to their clinical similarities (5). Until today, unfortunately no effective licensed vaccine is yet available and vector control measures rely as the most important in prevention of disease (3, 4).

Clinical manifestations of CHIKV infection are acute and chronic. Chronic stage is characterized by chronic rheumatic manifestations (6, 7), particularly the so-called post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR) (6, 7). Is important to highlight that its relative frequency is highly variable according to some reports, ranging from 14.4% to 87.2% (6). Even more, pCHIK-CIR can persist even after several years (follow up studies now even indicate more than 5 years) (6). This is a highly debilitating condition and results in high economic cost and human suffering. Recent estimates indicates that 47.57% (95%CI 45.08–50.13) of patients in a median time of 20.12 months will develop pCHIK-CIR. In the case of Puerto Rico, assuming the official number of cases reported by the Pan-American Health Organization for 2014, this would imply that between 12,901 and 14,347 patients would develop pCHIK-CIR there (356.9 to 396.9 cases/100,000 pop) (6). This has clear epidemiological implications but also for rheumatologists in the country (1, 6, 8).

Regard diagnosis, until today two main methods of laboratory are available. Real-time polymerase chain reaction (RT-PCR) and serology for antibodies to CHIKV (IgM or IgG) are the recommended methods (2, 3, 7). During the initial viremic phase, RT-PCR is very useful. Although classic serological methods are simpler, after five days, IgM antibodies are detectable by enzyme-linked immunosorbent assay (ELISA) but these not persist after three months. IgG antibodies, also

raised after 5 days, but these persist for years. This is another aspect to corrected in the review of Arroyo-Ávila and Vilá that wrongly stated that IgM antibodies may persist up to 36 months post infection (1, 8).

Regard the cellular and molecular mechanisms of chikungunya pathogenesis, there are still many aspects to be defined (9). When transmitted by mosquito bite, CHIKV is delivered intradermally, where local replication occurs in endothelial cells, fibroblast cells and macrophages. After, CHIKV rapidly enters the circulatory system which use to access to the lymphoid organs and a variety of other cell and tissue including dendritic cells, muscles and osteoblast cells. Macrophages are considered as particularly important during CHIKV-induced rheumatic disease demonstrating that there are a primary cellular target during CHIKV infection. This may assist in virus dissemination, and source of synovial pro-inflammatory cytokines, because it take the role in perpetuating chronic arthralgia or arthritis, with the help of migration due to inhibitory factors, tumor necrosis factor (TNF- α) and interleukin 1-beta, which ones stimulating the production of matrix metalloproteinases (6, 8, 9).

During the ongoing epidemics of CHIKV, we consider of utmost importance the proper dissemination of knowledge of acute but also chronic manifestations of this viral disease. Then, we would like to call on the limitations of the discussed reviews. Nevertheless, there are still many gaps in the treatment of CHIKV infection, where no effective treatment has been really recommended. No clinical trials and systematic review are still available. Even more there is no clear information available regard the evolution of CHIKV infection in patients with former diagnosis of rheumatologic diseases like rheumatoid arthritis, systemic lupus erythematosus or multiple sclerosis (7). Absence of studies for proper management of pCHIK-CIR in those populations remains as a concern (1, 6, 8).

Jorge A. Sánchez-Duque, Juan Pablo Orozco-Hernández, Alfonso J. Rodríguez-Morales, MD, MSc, DTM&H, FFTM RCPSPG; Public Health and Infection Research Incubator and Group, Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Risaralda, Colombia

References

1. Arroyo-Ávila M, Vilá LM. Rheumatic Manifestations in Patients with Chikungunya Infection. *P R Health Sci J* 2015;34:71-7.
2. Alfaro-Tolosa P, Clouet-Huerta DE, Rodríguez-Morales AJ. Chikungunya, the emerging migratory rheumatism. *Lancet Infect Dis* 2015;15:510-2.
3. Rodríguez-Morales AJ. La amenaza de Chikungunya y otros virus emergentes en las Américas. *Revista Hispanoamericana de Ciencias de la Salud* 2015;1:9-12.

4. Rodríguez-Morales AJ, Paniz-Mondolfi AE. Venezuela: far from the path to dengue and chikungunya control. *J Clin Virol* 2015;66:60-1.
5. Bedoya-Arias JE, Murillo-García DR, Bolanos-Munoz E, Hurtado-Hurtado N, Ramirez-Jaramillo V, Granados-Alvarez S, et al. Healthcare students and workers' knowledge about epidemiology and symptoms of chikungunya fever in two cities of Colombia. *J Infect Dev Ctries* 2015;9:330-2.
6. Rodríguez-Morales A, Cardona-Ospina J, Villamil-Gómez W, Paniz-Mondolfi A. How many patients with post-chikungunya chronic inflammatory rheumatism can we expect in the new endemic areas of Latin America? *Rheumatol Int* 2015 June.
7. Cardona-Ospina JA, Vera-Polania F, Rodríguez-Morales AJ. Chikungunya or not, differential diagnosis and the importance of laboratory confirmation for clinical and epidemiological research: comment on the article by Rosario et al. *Clin Rheumatol* 2015 Jun 19 [Epub ahead of print].
8. Alla SAO, Combe B. Arthritis after infection with Chikungunya virus. *Best Practice & Research Clinical Rheumatology* 2011;25:337-46.
9. Schwartz O, Albert ML. Biology and pathogenesis of chikungunya virus. *Nature reviews Microbiology* 2010;8:491-500.

Reply

To the Editor,

We appreciate Sánchez-Duque et al. for their interest in our review (1). While we agree with some of their comments related to the epidemiological implications concerning the development of post-chikungunya (CHIKV) chronic rheumatism, there are some clarifications that we would like to bring to their attention.

First, Sánchez-Duque et al. incorrectly state that serum CHIKV IgM antibodies do not persist after three months following acute CHIKV infection. Several authors have reported the presence of CHIKV IgM antibodies in patients' serum after 12 months of acute infection (2, 3, 4). Persistence of IgM antibodies in serum could be related to viral persistence in the hosts' tissues; however, this notion has not been extensively studied (4).

Regarding the authors' comments on CHIKV pathogenesis, we want to clarify that the purpose of our manuscript was to describe the rheumatic manifestations of CHIKV infection and not to provide an extensive review on the biomolecular and cellular pathophysiology of CHIKV infection. Clearly, there are many aspects of CHIKV infection pathogenesis that are yet to be elucidated and this topic on its own would be worthy of a full-length review (5).

Finally, as we clearly stated in our review, currently there are no established treatment guidelines for CHIKV arthritis. However, there are published randomized trials evaluating the treatment of non-steroidal anti-inflammatory drugs, corticosteroids and hydroxychloroquine in acute CHIKV arthritis (6, 7). In addition, successful treatment of CHIKV chronic arthritis with disease-modifying antirheumatic drugs (DMARDs) and tumor necrosis factor- α inhibitors has been documented in observational studies and case reports (8, 9). While we are not suggesting that all patients with CHIKV arthritis should be treated with corticosteroid or DMARD therapy, we do encourage the evaluation of such patients by a rheumatologist, especially those with persistent chronic symptoms, in order to ascertain the need for more aggressive but closely observed therapy.

Mariangeli Arroyo-Ávila, MD and Luis M. Vilá, MD

Division of Rheumatology, Department of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, PR

References

1. Arroyo-Ávila M, Vilá LM. Rheumatic manifestations in patients with chikungunya infection. *P R Health Sci J* 2015;34:71-77.
2. Borgherini G, Poubeau P, Jossaume A, et al. Persistent arthralgia associated with chikungunya virus: a study of 88 adult patients on Réunion Island. *Clin Infect Dis* 2008;47:469-475.
3. Grivard P, Le Roux K, Laurent P, et al. Molecular and serological diagnosis of Chikungunya virus infection. *Pathol Biol (Paris)* 2007;55:490-4.
4. Malvy D, Ezzedine K, Mamani-Matsuda M, et al. Destructive arthritis in a patient with chikungunya virus infection with persistent specific IgM antibodies. *BMC Infect Dis* 2009;9:200.
5. Schwartz O, Albert ML. Biology and pathogenesis of chikungunya virus. *Nature reviews Microbiology* 2010;8:491-500.
6. Chopra A, Saluja M, Venugopalan A. Effectiveness of chloroquine and inflammatory cytokine response in patients with early persistent musculoskeletal pain and arthritis following chikungunya virus infection. *Arthritis Rheumatol* 2014;66:319-326.
7. Padmakumar B, Jayan JB, Menon RMR, Krishnankutty B, Payippallil R, Nisha RS. Comparative evaluation of four therapeutic regimes in chikungunya arthritis: a prospective randomized parallel-group study. *Indian J Rheumatol* 2009;4:94-101.
8. Pandya S. Methotrexate and hydroxychloroquine combination therapy in chronic chikungunya arthritis: a 16 week study. *Indian J Rheumatol* 2008;3:93-97.
9. Bouquillard E, Combe B. A report of 21 cases of rheumatoid arthritis following Chikungunya fever. A mean follow-up of two years. *Joint Bone Spine* 2009;76:654-657.