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Persistent Arthralgia and Related Risks Factors: A Cohort Study at 12 Months from Laboratory-Confirmed Chikungunya Infection

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Aim of the study. To assess the cumulative incidence and clinical markers associated with persistent arthralgia (PA) at 12 months from acute chikungunya virus (CHIKV) infection.

Methods. A multicenter retrospective cohort study was conducted in the state of Colima, Mexico, and 217 serologically confirmed cases of CHIKV infection were enrolled. Participants aged 15 years and older were interviewed on 6 months basis from acute illness onset and the main binary outcome was self-reported PA at 12 months. To assess clinical markers associated with PA we used a generalized linear model. The 2-item Patient Health Questionnaire (PHQ-2) was used to screen for depressive symptoms among PA-positive individuals.

Results. The cumulative incidence of PA was 31.8%. In the generalized linear model, individuals ≥40 years of age (risk ratio (RR) = 1.68; 95% confidence interval (CI), 1.10−2.55) and those with 8 or more arthralgia sites (RR = 2.91, 95% CI 1.87−4.53) at acute disease had a significantly increased risk of PA at 12 months from CHIKV infection. Self-reported arthralgia (any site) at 3 months post-infection, a sub-chronic clinical marker, was also associated with a significantly increased risk of long-term articular manifestations (RR = 7.06, 95% CI 2.97−16.81). Depressive symptoms (PHQ-2 score ≥3) were reported by 33.3% of PA-positive participants.

Conclusions. Our findings suggest that chronic CHKV-related articular manifestations were a frequent event in the study sample and the impact on functional status was potential. These results may be useful in health care settings in the risk-stratification of PA after CHIKV infection.

Key Words: Chikungunya fever, Cohort studies, Risk, Arthralgia, Chronic pain, Mexico.

Introduction

Chikungunya virus (CHIKV), an arbovirus of the genus *Alphavirus*, is transmitted to humans through the bite of infected *Aedes (Ae.) aegypti* and *Ae. albopictus* mosquitoes (1). The virus is responsible for explosive outbreaks reported in most tropical and subtropical areas of the world

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(2−4). Due to the fact that there is no effective vaccine or specific pharmacological treatment, the CHIKV represents a major global challenge for health systems (5,6).

In Mexico, the first autochthonous case of CHIKV infection was reported in the last trimester of 2014 in the state of Chiapas, located in the southeastern region of the country (7). Several disease outbreaks were then reported nationally in most of the areas where the arthropod vectors are found. The CHIKV was isolated in nearly 80% of blood samples from febrile patients between 2014 and 2015 (Chiapas, Mexico) (8).

The state of Colima (pop 711,200 inhabitants) is located in the western part of the country and the permanent presence of *Ae. aegypti* has been documented (9,10). Public medical units of the Mexican Institute of Social Security (from the Spanish Instituto Mexicano del Seguro Social, IMSS) registered nearly 7,500 cases of CHIKV infection within the time frame of March 2015 (when the first autochthonous case was identified) and December 2016. The unadjusted incidence rates were 2,083 and 132 cases per 100,000 affiliated in 2015 and 2016 respectively (Figure 1).

Acute infection is symptomatic in more than 75% of infected individuals and it is characterized by abrupt peripheral arthralgia and impaired ambulation (11). It is frequently self-limited and resolves within 7−10 d, but a subset of patients experience persisting arthralgia (PA) lasting from months to years (12). The current scientific knowledge regarding the factors associated with increased risk of PA is limited and the impact on the functional status of the patient is potential (13). Most of the published studies have been conducted in the Réunion Island, in the Indian Ocean (14−18), and ethnic differences in chronic pain perception are plausible (19).

The present study aimed to estimate the cumulative incidence of PA at 12 months from acute laboratory-confirmed CHIKV infection among adults and to evaluate the association of several clinical markers with the risk of chronic articular manifestations. In addition, we screened for depressive symptoms among PA-positive individuals.

Material and Methods

Study Design

A multicenter retrospective cohort study was conducted in the state of Colima, Mexico, from December 2015−January 2017. The database from the National System for Epidemiological Surveillance (from the Spanish Sistema Nacional de Vigilancia Epidemiológica, SINAVE) was used to identify the eligible individuals. The SINAVE uses a web-based platform to report suspected cases identified at public and private health facilities according to governmental standards (20). The study was conducted at primary care medical units of the IMSS.

Participants

Subjects aged 15 years and older, with laboratory-positive (reverse transcription quantitative-polymerase chain reaction, RT-qPCR) CHIKV infection and acute disease onset occurring between June and December 2015 were included. Individuals with a self-reported history of any systemic rheumatologic disease (rheumatoid arthritis, multiple sclerosis or systemic lupus erythematous) were excluded. A complete description of the eligibility criteria analyzing the outcome of interest at 6 months from acute infection in a subset of participants (n = 136) was previously published (21).

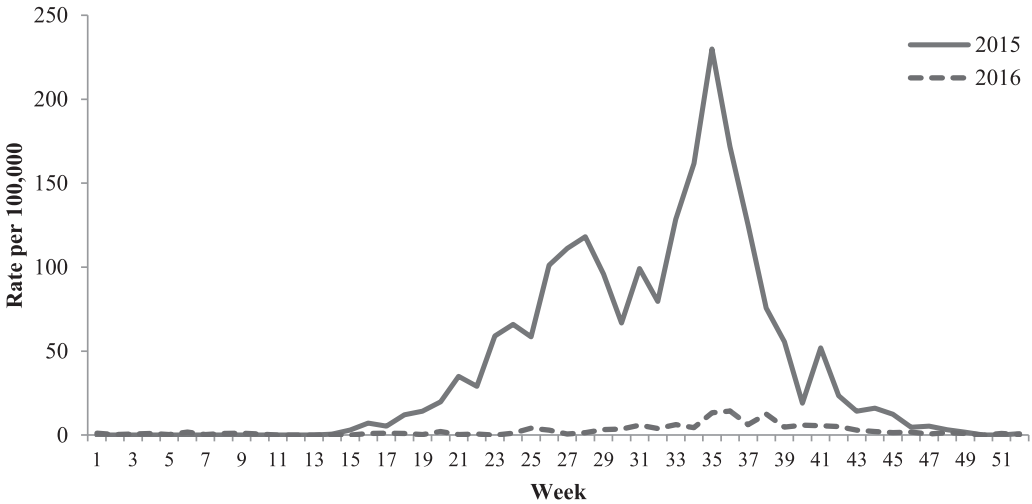

Figure 1. Weekly incidence rate of suspected cases chikungunya virus infection in the Mexican Institute of Social Security from the state of Colima, Mexico, 2015−2016. Notes. The total number of individuals (n = 337,000) affiliated to the Mexican Institute of Social Security in the state of Colima, Mexico was used to estimate unadjusted incidence rates per 100,000 inhabitants. The definition of suspected cases of CHIKV infection included the abrupt onset of severe polyarthralgia or arthritis. Data source: National System for Epidemiological Surveillance.