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Chikungunya, a Global Threat Currently Circulating in Latin America

Alfonso J. Rodriguez-Morales, Jaime Andrés Cardona-Ospina and Wilmer E. Villamil-Gómez

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Abstract

Chikungunya fever (CHIK) is a highly important arbovirosis currently established in Latin America and the Caribbean (LAC); its acute and chronic burden is an overlooked issue for policy makers. Disease spread control and proper management of chronic-derived sequelae do not seem like a realistic goal in short- and mid-term. The CHIKV circulating in the Western Hemisphere is closely related to strains from Philippines, China, and Yap (Federated States of Micronesia), and vertical and horizontal transmission of infection has been reported. Pathogenesis is still not well understood, and vaccines are under development yet. Here, we provide a summary of information regarding LAC spread of the disease from a public health, clinical and molecular perspective, particularly from the experience in Colombia.

Keywords: Chikungunya, Latin America, public health, molecular epidemiology, clinical manifestations

1. Introduction

Chikungunya fever (CHIK) is a highly important arbovirosis to Latin America and the Caribbean (LAC) because it is an infectious disease that have evolved from a simple threat to an established disease with acute and chronic burden to almost all the American continent, both mainland and overseas territories. Moreover, the presence of suitable ecological conditions in nontropical areas and our highly interconnected world have led to the report of cases in at least four continents in the world. CHIK is an arthritogenic fever that has arrived to stay in the Americas. After its introduction in 2013 to the island of Saint-Marteen (two autochthonous cases confirmed on December 6, 2013), it quickly spread through overseas Caribbean

territories with autochthonous transmission (Martinique and Saint Marteen, December 19, 2013; Guadeloupe, December 24, 2013; Saint Berthelemy, December 31, 2013; and British Virgin Islands, January 15, 2014). Next, on February 21, the World Health Organization (WHO) confirmed the arriving of CHIK to mainland South America in French Guiana with seven confirmed cases (two autochthonous). Since then, the disease has spread over the entire continent. Until today, it continues accounting for important acute and chronic burden to the healthcare systems of the region [1–7]. For example, in Colombia, until June 2016, more than 16,000 new cases of CHIK have been reported.

Currently, almost every country in LAC has reported autochthonous transmission of CHIK, some of them in confined territories, but others such as Colombia, Venezuela, and Ecuador with a more generalized and intense disease transmission. Non-LAC territories have suffered the impact of travel and suitable ecological conditions with vector availability (*Aedes aegypti and Aedes albopictus*). The United States of America presently report mainland autochthonous disease transmission in Florida, and in Europe the vector is widely spread through Italy, the southern coast of Spain and France, and some areas of Switzerland, Croatia, Montenegro, Slovenia, Albania, Greece, and Romania [8]. Additionally, although previous CHIK cases have been reported in Europe, alongside the LAC outbreak, there were mainland reported cases in France and Spain in 2014 and 2015, respectively. On October 21, 2014, the National IHR Focal Point for France notified the WHO of four laboratory confirmed and locally acquired CHIK cases in Montpellier. The four cases occurred within a same family who did not have any history of traveling outside France or their district of residence, but who lived near to an imported case from Cameroon. This was the first time that locally acquired transmission of CHIK has been detected in France since 2010 [9]. On the other hand, on August 3, 2015, the WHO was notified by the National IHR Focal Point for Spain of a case of CHIK in the city of Gandia, Valencian Community. The patient, a 60-year-old man, had no history of travel outside the European Region. A regional laboratory identified him with the detection by ELISA of IgM titers and subsequent IgG seroconversion. However, the National Reference Laboratory failed to confirm these results and it apparently was a false positive [10]. Likewise on September 9, 2015, the Ministry of Health and Social Affairs of Senegal notified the WHO of the beginning of active circulation of chikungunya virus (CHIKV) on August 27 in the region of Kédougou, where the latest active circulation was reported between 2009 and 2010 [11].

As showed, CHIKV can easily be spread into areas where suitable ecological conditions are done. In 2016, 16,653 CHIK cases in LAC have been newly diagnosed, both suspected and confirmed (epidemiological week 7) [12]. By the same time, in 2014, there were 1980 cases, but the current data are only about 17% of the reported cases in the same epidemiological week in 2015. Although it is possible that CHIK cases this year would be importantly lower than the previous, attention must be paid because probably it is going to have an epidemiological behavior that resembles dengue with episodes of seasonal epidemic outbreaks. Moreover, after the arriving of Zika to the region, efforts must be oriented not only to vector control programs but to develop proper diagnosis, treatment, and follow-up strategies in order to grant management and assessment of acute and chronic symptoms. Chikungunya, dengue, and Zika are

three arbovirosis that already pose an important burden to LAC healthcare systems. They have showed our weaknesses in managing infectious disease spread and taught us that viral emerging infectious diseases are more than febrile illnesses. The latent threat of introduction of other *Aedes* sp. transmitted arbovirosis, like Mayaro or other viral hemorrhagic fevers transmitted for arthropods, call our attention to learn lesson and to take planed actions.

2. Virology and molecular epidemiology

CHIKV is a member of the genus *Alphavirus*, family *Togaviridae*, that was first isolated from the serum of a febrile human in Tanganyika (Tanzania) in 1952–1953 [13,14]. However, reported cases from India and Japan have suggested that CHIKV epidemics could have occurred as early as 1779 [15]. Besides, after its isolation, the virus was found repeatedly in numerous countries in Central, Southern, and Western Africa, as well as in many areas of Asia, and it has caused multiple outbreaks and epidemics in Africa, Southeast Asia, and Southern Europe [16–18].

The CHIKV is an enveloped, spherical virus with a diameter of 60–70 nm. It has a RNA, positive sense, linear genome of 11.8 kb that resembles eukaryotic mRNAs; given that at the 5′ end, it has a methyl guanylate cap, which is a nonstructural poly-protein precursor, and at the 3′ end, it has a poly(A) tail [17]. The 5′ precursor is cleaved into nsP1, nsP2, nsP3, and nsP4, which are involved in the virus replication and have functions and structures that are shared by other alphaviruses [17,19–21]. The nsP1 protein functions as cytoplasmic RNA capping enzyme, the nsP2 protein is a cysteine protease with a partially constricted substrate-binding site and two separate domains with helicase and protease activity [20], the nsP3 protein is essential for negative strand RNA synthesis, and the nsP4 protein works as an RNA-dependent RNA polymerase [17–19,21]. The 3′ poly(A) tail consists of 26S mRNA whose products include the structural proteins: the surface glycoproteins (E1 and E2), the capsid protein, and small peptides (E3 and 6K). The surface glycoprotein E2 has a role in viral attachment, and the surface glycoprotein E1 is the fusion protein that facilitates the viral entry [18,19,22].

Currently, there are three CHIKV-identified genotypes based on the E1 gene and the full genome sequence: East/Central/South African (ECSA), West African, and Asian. Phylogenetic analyses suggest that CHIKV spread from Africa to Asia episodically [23,24] and that the CHIKV strains circulating in the Caribbean came from the >2005 Southeast Asian clade, which previously moved into Western and South Pacific (American Samoa and Yap) and then to the Western Hemisphere. The CHIKV circulating in the Western Hemisphere is closely related to strains from Philippines, China, and Yap (Federated States of Micronesia) [25–30]. By contrast, the circulation of the ECSA genotype has been confirmed in Brazil apparently imported from Angola [31]. During the current LAC epidemics, the virus has showed mutation rates that are in accordance with previous evolutionary rate model, which predicted approximately 10 nucleotide mutations over the entire genome during the course of a 1-year epidemic [23,26,30]. The LAC CHIKV possess two unique amino acid differences and a 12-nucleotide deletion that could be useful in future for tracking of this strain [26].

3. Pathogenesis and disease transmission

Conventionally, CHIKV transmission is considered to be through flying arthropods of the *A. aegypti* o *A. albopictus* species. However, evidence suggested that viable infective virus is excreted in the saliva of monkeys, mice, and humans, and it could be a source of infection particularly in immunocompromised patients [32,33]. Vertical transmission has also been reported [34,35]. Despite some studies failed to show effect of CHKV infection during pregnancy on major obstetrical outcomes or congenital anomalies, long-term follow-up studies have reported poor neurocognitive outcomes of newborns and even poorer results in patients with neonatal CHIKV encephalopathy [36,37].

After its entry to the human host, the CHIKV first replicates in the skin fibroblasts [38,39], next it enters to the circulatory system, and triggers an early type I interferon response [40]. Apparently, alterations in this response are associated with more severe disease and death [41]. Next, it disseminates from blood to various tissues, it lodges in immune-privileged niches, and it replicates in the joints and skeletal muscles that are associated with extensive inflammatory cell recruitment [38,40,42–45]. CHIKV infection can persist in mononuclear cells and macrophages that are another primary cellular target and help in virus dissemination and chronic articular symptoms [38,46,47]. It has been proposed that viral persistence is associated with expression of interferon (IFN)-α, interleukin (IL)-10, and monocyte chemotactic protein 1 (MCP-1 or CCL2) [40]. Chikungunya infection causes high levels of IFN-α, suggesting strong innate immunity, along with the production of IL-4, IL-10, and IFN-γ, suggesting the engagement of the adaptive immunity. Notably, circulating T lymphocytes showed a CD8+ T lymphocyte response in the early stages of the disease and a CD4+ T lymphocyte-mediated response in the later stages, and IFN-γ and IL-12 levels have been observed to rise dramatically during the acute phase of chikungunya fever. The level of IL-12 returns to normalcy in patients who recover. In contrast, patients who develop chronic arthritis show persistently high IL-12 levels. Histologic examination of synovia from patients with chronic arthritis following chikungunya fever has revealed joint inflammation due to macrophages containing viral material. Elevated expression of MCP-1, MCP-2, and MCP-3 has been associated with bone reabsorption and bone lose, and CHIKV seems to favor a pro-osteoclastic microenvironment disrupting the receptor activator of nuclear factor-κB ligand/osteoprotegerin (RANKL/OPG) ratio [43,48].

Support cells of the central nervous system, such as astrocytes and oligodendrocytes, have shown to be infected with CHIKV in human, primate, and mice models [49,50]. Apparently, the astrocytes play an important role in replicating the virus and are susceptible to die because of the infection, whereas the microglia seems to be infection-resistant [50]. The infected cells are induced to express high levels of cytokines and chemokines related to an upregulation on innate immune response [50,51]. The adaptive immune response apparently occurs early in the infection. Higher and early increase of IgG3 titers has been correlated with efficient viral clearance and long-term viral protection [52], whereas higher level of C-reactive protein is related to lymphopenia, lower monocyte level, neutrophilia, and high viral load [19,53].

4. Clinical manifestations and chronic sequelae

It was previously believed that asymptomatic seroconversion was a rare event. However, results point that the subclinical: symptomatic proportion is at least of 4.6:1 patients [54]. The clinical course of CHIK could be divided into three phases: acute, subacute, and chronic. The acute phase has usually been considered from the start of the symptoms (day 0) until the day 10. The most frequent symptoms are arthralgia, fever, and rash [28,55,56]. Other symptoms that could be present are headache, myalgia, pruritus, dizziness, nausea, vomiting, diarrhea, asthenia, red eyes, and although unusual, hemorrhagic symptoms could be present too [28]. The arthralgia usually is a bilateral and symmetric polyarthralgia of large joints that involves the appendicular skeleton; it is more severe in viremic patients, and the joints more frequently affected are of the lower limbs particularly, knees and ankles. Impairment of the finger joints is more frequent in women like the periarticular swelling too. Some patients can feel pain in previous bone fractures or ligament injuries as well as pain along ligament insertions and talalgia [57,58]. Likewise, skin involvement is important, although some studies reporting cutaneous manifestations are limited by the lack of confirmation of infection through serological test. Dermatological lesions comprise a wide spectrum. It could be morbilliform eruption, the most common type of lesion, scaling, confluent macular erythema, intertrigo, hypermelanosis, xerosis, excoriated papules, urticaria, petechial spots, and bullae, among others [58,59]. The macular erythematous rash could appear at fourth day of fever, while dengue rash appears between days 5 and 6, and in Zika fever it could appear on the first symptomatic day. Mucosal involvement has been reported, with aphthous ulcers in mouth, conjunctival injection, and nasal ulceration with nasal skin necrosis [60,61]. Similarly, CHIK cases could manifest with vasculitis in legs or nose with complications that could lead to amputation. Laboratory findings are often unremarkable; lymphopenia and thrombocytopenia could be present but are rare and slight elevation of hepatic aminotransferases could be observed [58]. During this time, there is a lot of overlap between symptoms caused by CHIK, dengue, and Zika, and for this reason differential diagnosis must be made through specific laboratory assessment (Specific IgM titers or RT-PCR) [62,63]. However, some features could help to guide clinical probability in field work. For instance, acute reactants such as C-reactive protein and sedimentation rate could be high, in contrast with dengue and Zika [64–103]. Cardiovascular assessment through electrocardiographic and echocardiographic imaging must be strongly considered. Ventricular and supraventricular arrhythmias and signs of myocarditis or acute effusive pericarditis could be present [104].

During the acute phase of the disease, some patients evolve to some clinical presentations that, because it is apparent rare occurrence, have been called "atypical manifestations" that include severe disease manifestations. These clinical manifestations include comprises in neurological, respiratory, cardiovascular, and cutaneous systems, among others that could evolve to death [3,61,64–68]. Older age and comorbidities are associated with the appearance of severe cases, death, and evolution to chronic forms of the disease [64]. Ocular manifestations are important too, being the anterior uveitis the most frequent, although retinitis and optic neuritis have also been reported [69]. During the outbreak of 2006 in Reunion Island, mortality attributable to CHIK was recorded, and during the LAC outbreak, fatalities have been noted with an

estimated case fatality rate of 0.012% [3,64,65]. It is important to highlight that co-infection could be an issue where co-circulation of CHIK, dengue, and Zika has been reported since mixed clinical pictures could be present.

After 10 days of infection, the majority of patients will improve and symptoms will disappear, but there is a proportion of patients that will evolve to the subacute and chronic phase of the disease. The chronic phase is usually defined as the presence of symptoms at least for 2 or 3 months. The symptoms present during this phase affect quality of life and they can be derived from different involving systems [70]. According with previous estimates, 41.57% of CHIK-infected people would develop chronic inflammatory rheumatism (pCHIK-CIR), both arthritis and arthralgia, at 12 months [71]. Estimates derived from a systematic review and meta-analysis [105] showed, in the most conservative scenario, about 25% of CHIK would develop pCHIK-CIR, 34% considering the most representative studies, and 14% would develop chronic arthritis. Retrospective studies from cohorts in Colombia support these findings [72,73], but prospective studies are needed in order to establish the real risk of progression in LAC since geographical variation has been reported. When pCHIK-CIR appears, it usually involves ankles, knees, shoulder, and elbow [74]. And sometimes, it can mimic seronegative rheumatoid arthritis [75–77]. Although it is unknown if pCHIK-CIR is a lifetime condition, follow-up studies have found persistence of bone erosions and articular symptoms even after 6 years [78]. The risk of articular symptoms' persistence is apparently increased with older age, severity of initial joint pain, underlying osteoarthritis, gender (i.e. women), and number of comorbidities [64,70,79–81].

Although less well documented, there are other chronic worrisome sequelae that could be derived from CHIK. For example, chronic sequelae derived from post-CHIK Guillain-Barré or post-CHIK neuropsychiatric disorders such as anxiety or depression [66,67,82,83], vision defects from ocular involvement [69], or congestive heart failure from dilated cardiomyopathy associated with myocarditis [84]. Hence, although CHIK-burden is already worrisome, derived costs, both direct and indirect, are probably underestimations of the real problem. Healthcare systems of the affected areas must be aware of the possible chronic consequences of CHIK infection and efforts for prevention of infection must be done and proper follow-up of infected patients must be granted. The real scope of the problem is still unknown and more research is needed.

5. Treatment and antiviral development

Until today, CHIKV infection during the acute phase is treated with hydration, non–anti-inflammatory antipyretics (acetaminophen), and symptomatic relief through the use of antihistaminic drugs or lotions for pruritus control. When pain does not relief with usual analgesia, general measures such as alternating cycles of 10 minutes of cold and 20 minutes of warm each 8 hours could be used avoiding the prescription of corticoids or nonsteroidal anti-inflammatory drugs. Currently, there are no approved antivirals to treat the infection, but research in the field has been increasing. Some antiviral molecules, which act by blocking virus

proteins important for virus replication, have been reported [85]. Polymerase inhibitors, mainly nucleotide, have been tested with difficulty because the core polymerase subunit nsP4, which is shared by other alphaviruses, is inactive on its own [21,85]. However, Faviparir (6-fluoro-3-hydroxy-2-pyrazinecarbox-amide), a nucleotide RNA-base analog inhibitor, is promising because it reduces CHIKV replication, as well as in other alphaviruses, in mice [86]. Likewise, efforts have been made in order to identify pharmacophore features of protease (nsP2) inhibitors [87]. Molecular modeling has been used in the identification of novel and selective inhibitors with one of them having encouraging features [88]. Other drugs, such as ribavirin, interferon, mycophenolic acid, or arbidol, with known antiviral activity against other pathogens have been proved in CHIKV infection and could potentially be used in treatment [85,89]. Equally, other drugs without conventional antiviral activity have been proposed for treatment. For instance, chloroquine has been suggested as a drug with prophylactic and therapeutic effects apparently by impairing endosomal-mediated virus entry during early stages of virus replication [90]. Other anti-parasite agents, such as ivermectin and a benzimi-dazole-derived drug, have showed effects on replication at early and late stages of infection [91,92]. Doxycycline combined with ribavirin effectively inhibited CHIKV replication and attenuated its infectivity in vivo in animal models [93]. Besides, some plant-derived products, such as green tea components, flavonoids, diterpene esters, and complex plant alkaloids, have showed antiviral activity against CHIKV [85,94–96].

For the chronic phase of the disease, particularly for articular symptoms, there is little high-quality evidence to guide treatment. Recommendations worldwide have suggested treating inflammatory articular symptoms in an early fashion as rheumatoid arthritis, and some disease-modifying antirheumatic drugs, such as hydroxychloroquine and methotrexate, have been proved in pCHIK-CIR appa rently with good results [77,97]. Glucosamine and chondroi-tin sulfate could be used to treat pain in patients with previous arthrosis, and those patients with neuropathic pain pregabalin could be prescribed. Treatment of other nonarticular pCHIK chronic sequelae have been poorly studied and reported, and there is no a clinical studied and approved drug for pCHIK-CIR risk reduction. Although studies suggest that passive immunization with monoclonal antibodies may help in CHIKV-infected patients who are at risk of severe disease or in neonates born from viremic mothers [85].

6. Vaccines, disease prevention and control

Although efforts have increased up to this moment, there is no an approved vaccine for CHIK prevention. There are several vaccine strategies proven in CHIK that comprises live attenuated virus, chimeric virus, DNA vaccines, viral vector vaccines, viral subunits, inactivated virus, and virus-like particles. All of them in preclinical phase trials are used in animal models, mainly mice [85,98]. As for other virus diseases, apparently the best choice for anti-CHIKV vaccination is a strategy using an attenuated live virus vaccine, and there are developed candidates. For instance, two mutant virus strains, with large deletions in either the nsP3 gene or in the entire 6K gene, proved to be genetically stable, attenuated, highly immunogenic, and able to confer durable immunity after a single immunization in mice [99]. Neutralizing

antibodies recognize the epitopes in the E2 glycoprotein and therefore E2 is another vaccine candidate [100].

Besides, efforts have been made in order to improve vector control strategies. Implementation research has been conducted in LAC in order to find ways to improve use of prevention tools such as insecticide-treated nets and covers, education, social mobilization, and water storage cleaning [101,102]. The potential to prevent and control not only CHIK, but to dengue and Zika too, encourages to direct efforts in order to grant vector control. Likewise, recent studies have shown that vector co-infection with the bacterium *Wolbachia pipientis* impedes virus infection. This bacterium is maternally inherited and is a promising technology to control disease spread [103].

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