IMAJ • VOL 18 • MARCH-APRIL 2016

Chikungunya Fever Presenting as a Systemic Disease with Fever, Arthritis and Rash: Our Experience in Israel

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ABSTRACT: Chikungunya fever (CHIK-F) has been increasingly documented among Western travelers returning from areas with chikungunya virus transmission, which are also popular tourist sites. We present three Israeli travelers who developed fever, maculopapular rash and long-standing arthralgias while visiting northern Indian states not known to be involved in the chikungunya fever epidemic. We also present an epidemiological review of the chikungunya epidemic over the past decades. Rare systemic manifestations of this disorder, like catastrophic antiphospholipid syndrome (CAPS) and adult-onset Still's syndrome, are discussed. The present era of international travel poses a new diagnostic and epidemiologic challenge that demands increased awareness to the possibility of an exotic tropical infectious disease.

IMAJ 2016; 18: 162–163

KEY WORDS: chikungunya fever (CHIK-F), international travel, mosquitoes, arthritis, rash

Chikungunya fever (CHIK-F) is a systemic viral disease manifesting with fever, acute arthritis and rash. The acute symptoms can last for days but articular symptoms and pain can persist for months and even years [1]. It is endemic in Africa and Southeast Asia where during the past 60 years several outbreaks and epidemics occurred [2,3]. The chikungunya virus (CHIK-V), family Togoviridae, genus *alphavirus*, is a single-stranded RNA virus that is transmitted by mosquitoes in an epizootic cycle between small mammals, large mammals and humans [1]. The global spread of the vectors *Aedes aegypti* (AAe) and *Aedes albopictus* (AA) over the years has a dynamic global distribution pattern allowing for the emergence of CHIK-F outbreaks and epidemics in West Africa and Central America, followed by southern and Southeast Asia [4]. In rural areas the burden of chronic manifestations of the disease was reported in 36% of CHIK-F-affected individuals [5]. International travel contributes to the appearance of CHIK-F among tourists from Western countries returning from popular tourist sites infested by CHIK-V and its vectors [6,7]. The first three Israeli cases who contracted the disease in northern India and were reported earlier will be mentioned briefly [8]. Rare manifestations complicating the course of CHIK-F will be reviewed.

PATIENT DESCRIPTIONS

A married couple (a 58 year old man and his 56 year old wife) visited northwestern India in the fall of 2006. They both became ill one day apart, with high fever, rigors, myalgia and arthralgia, followed by a non-palpable rash of the face and extremities in the wife. Five days later the fever, arthralgias and rash subsided. Both lost 6–9 kg of body weight. They returned to Israel and 3 weeks later a symmetric polyarthritis of small and large joints accompanied by morning stiffness lasting 45–120 minutes ensued and was diagnosed by a rheumatologist. The rest of the physical examination was normal. Laboratory workup for connective tissue disease was negative. CHIK-F was confirmed by indirect immunofluorescence assay (IFA) with immunoglobulin (Ig) G antibody titers > 1:640. IgM antibody was also positive. Other relevant viral serologies were negative in both patients. Non-steroidal anti-inflammatory drugs (NSAIDs) were effective and joint symptoms subsided over a period of 4 weeks. The patients remained well, asymptomatic and functional during a 1 year follow-up.

The other case was a 22 year old woman who had stayed in northern India from July until October. Two days after returning to Israel she suffered a high fever as well as maculopapular rash and headache lasting 4 days. At the same time she experienced severe arthralgias of the hands and feet with marked functional disability. Chikungunya serology was positive for IgM and IgG by both enzyme-linked immunosorbent assay (ELISA) and IFA. Her symptoms lasted for 2 months with some amelioration. A month later she was free of symptoms [8].

DISCUSSION

CHIK-F, endemic in forested Africa, emerged and spread beyond Africa as early as the 18th century by way of sea travel between Africa and Asia, into the Indian Ocean region, India and Southeast Asia, causing outbreaks that still occur in these regions even today [9]. The exponential rise in air travel introduced a new mode of CHIK-F spread introduced by CHIC-V-

infected Western travelers returning to Europe, the Americas and Asia, posing a diagnostic challenge on the one hand and local transmission of CHIK-F in Italy, France and South East Asia on the other [10,11]. In addition to the AAe, a new Asian vector, AA, was identified as a CHIC-V vector spreading in global proportions [4]. Early in 2015, 1,253,400 probable and 23,400 confirmed cases of CHIK-F were reported in the Americas and the Caribbean [12]. The reported attack rate is 35–60% when newly introduced in naïve populations where the vector is spread widely, favoring the emergence and evolution of large outbreaks [12]. The diagnosis is mainly clinically based especially when fever, arthritis and rash coincide in areas where CHIK-F is endemic. In the acute phase, virus detection is facilitated by RT-PCR (reverse transcriptase-polymerase chain reaction) where available. Serologically, serum IgM is present from day 5 after onset of the disease for several months. Seroconversion to IgG with a rise in titer is diagnostic and practical. Methods used include commercial IFA and ELISA kits.

The pathogenesis of CHIK-F has been studied mainly in animal models. Type I interferon response occurs primarily in the infected sites, especially skeletal muscles, enthesis and articular capsules. Monocyte and macrophage interaction with CHIK-V contributes to the inflammatory response with pro-inflammatory cytokines and to the clearance of the infected cells [13,14]. Rarely, severe forms of CHIK-F can manifest as myocarditis, hepatitis, encephalitis and even as multi-organ failure.

Recently published were two cases of Still's disease and catastrophic antiphospholipid syndrome (CAPS) triggered by chikungunya infection (two hyperferitinemic syndromes) [15]. This underlines the significance of the inflammatory response in a viral infection that in susceptible individuals may initiate a pro-inflammatory cytokine storm. The treatment of CHIK-F is limited to supportive care and anti-inflammatory drugs. NSAIDs and low dose corticosteroid in the acute phase are usually sufficient. Most patients are free of symptoms after a few weeks but some may still be symptomatic for months and, rarely, years. In the latter, chronic more severe course is dependent on co-morbidities and socioeconomic conditions [9]. Disease-modifying anti-rheumatic drugs (methotrexate, azathioprine) may be required in these cases. A recent article from southern India discusses the burden of disability associated with persistent pain following an epidemic of CHIK-F. The authors reported that 36.28% of affected individuals had persistence of pain and 16.3% had moderate to severe disability [16].

There is still no specific therapy or vaccine against CHIC-V. Passive immunotherapy can be given to neonates of infected viremic mothers. The main efforts to control the spread of the disease are aimed at vector reduction and limiting the contact between human populations and mosquitoes [9]. Future research priorities will have to concentrate on molecular mechanisms of adaptation of the virus to mosquito vectors, which might lead to new targets for control strategies. Given the present era of international travel which poses a new diagnostic and epidemiologic challenge, our awareness of the possibility of an exotic tropical infectious disease must be higher.

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"If there must be trouble, let it be in my day, that my child may have peace"

Thomas Paine (1737-1809), American political activist, philosopher, political theorist, and revolutionary