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1

Arthritis after infection with Chikungunya virus

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Chikungunya virus (CHIKV) is an emerging alphavirus responsible for several infectious outbreaks in the world. After an acute stage of illness characterised by a fever–arthralgia syndrome and rash, joint disorders due to CHIKV infection can sometimes persist for several months or years. Chronic arthritis after this emerging disease is well documented, and similarities to rheumatoid arthritis have been described. Knowledge of the geographical epidemiology of CHIKV infection is crucial for better control of the disease. Thus, recent outbreaks have led to several studies, which have highlighted the need for a better understanding of the clinical features of Chikungunya (CHIK) and beginning knowledge of the pathophysiogenesis, which can lead to further research.

Recent epidemics have revealed Chikungunya virus (CHIKV) as a dangerous, important, emerging arbovirus. The virus is one of 29 distinct species in the family Togaviridae, genus Alphavirus. It is transmitted by haematophagous arthropod vectors, particularly *Aedes aegypti* or *Aedes albopictus* mosquitoes. The virus was discovered in the mid-1950s from the serum of a febrile patient during a dengue fever-like epidemic in Tanzania [1]. The word 'chikungunya' in the Makonde language translates to 'that which bends up' in reference to the stooped posture associated with the chronic and incapacitating arthralgia of infected patients [2]. Indeed, CHIKV causes an acute fever–arthralgia syndrome that can evolve into chronic arthritis. Most infected individuals show symptoms; only about 5% of cases of asymptomatic CHIKV infection have been reported [3]. The resurgence and global spread of CHIKV infection in recent years have provided opportunities for greater knowledge of its clinical features [4].

In this article, we describe the epidemiological data for CHIKV infection and discuss clinical manifestations, particularly rheumatic symptoms, and some aspects of resistance and susceptibility of

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CHIKV infection. A better understanding of the clinical features of CHIK and beginning knowledge of the pathophysiogenesis can lead to further research.

Geographic epidemiology

Since its discovery, CHIKV has been somewhat ignored by scientists, except when it has caused large human outbreaks of infection. Historically, the disease may be older than expected; an episode of epidemic fever–arthralgia symptoms in 1779 was widely but mistakenly cited as the first documentation of dengue fever and is now believed to be an outbreak of CHIKV infection fever. CHIKV infection was reported as an epidemic febrile disease in Batavia (now Jakarta, Indonesia) [5,6].

After the first report of confirmed CHIKV infection fever outbreak in 1952, in Makonde Plateau in Tanzania, East Africa [1,7], CHIKV infection was frequently reported in numerous African countries [8], in Central and Southern Africa [9,10] including Sudan [11], Uganda [12], Malawi, Zimbabwe, Democratic Republic of Congo [13,14], the Central African Republic [15], South Africa and Kenya. CHIKV has also been isolated in West African countries, including Senegal [16], Benin, the Republic of Guinea [17], Ivory Coast and Nigeria [18,19].

CHIKV infection outbreaks were reported in Asia since 1958, when the virus was first isolated in Bangkok [20]. CHIKV infection has been documented in many parts of Southern and Southeast Asia. India reported its first confirmed epidemic in 1963, in Calcutta [21], and subsequently in Madras, affecting more than 3 million people [22]. Frequent outbreaks have been observed in Malaysia, Indonesia, the Philippines, Cambodia, Vietnam, Myanmar, Pakistan, Singapore and Thailand [8].

The virus was considered an important emerging arbovirus after two major epidemics. The first apparently began on the coast of Kenya in 2004, before reaching the Comoros in 2005. The virus rapidly disseminated to other islands in the Indian Ocean, most notably Reunion Island, where about 270 000 cases were reported, with an attack rate of about 35% [23].

In Europe, cases of CHIKV infection were reported in several countries, including Italy, UK, Belgium, Germany, Czech Republic, Norway, Poland, Spain and France [24]. These cases were directly associated with the return of tourists from India and affected islands in the Indian Ocean. However, imported cases could be a risk for local outbreak, as was illustrated in Emilia-Romagna, Italy, where an infected man came back from India and local transmission involved 205 cases [25,26].

Other cases associated with travellers were reported in some Asian countries, such as Taiwan [27], Hong Kong [28], Sri Lanka [29], Japan [30] and China [31]. Cases of CHIKV infection have rarely been reported among international travellers in Canada, the United States and Australia [32,33].

Mode of transmission

Typically, CHIKV has two distinct transmission cycles: sylvatic and human–mosquito–human. Sylvatic transmission involves wild primates, such as monkeys and forest-dwelling *Aedes* species of mosquitoes, primarily *Aedes furcifer*, *Aedes taylori*, *Aedes luteocephalus*, *Aedes africanus* and *Aedes Neoafricanus* [34]. This cycle is confined to Africa (Senegal, Ivory Coast, Central African Republic and South Africa) and is responsible for sporadic human cases and small outbreaks. The human–mosquito–human transmission cycle maintains CHIKV infection in urban areas. It involves primarily a vector, the *Aedes aegypti* mosquito, which is an extremely efficient urban vector because it preferentially feeds on humans, often bites several people during a single blood meal and is adapted to live and breed peridomestically; the mosquito is therefore the most likely initiator of the large regional and global outbreaks of the disease [35].

In recent years, *A. albopictus* has emerged as the second vector to efficiently transmit CHIKV; this mosquito has shown importance in areas where *A. aegypti* is absent [35]. The distribution of *A. albopictus* is more northern than that of *A. aegypti* because the former is better adapted to cold weather. Thus, globalisation of *A. albopictus* has created new risk areas for outbreak of CHIKV infection [36].

Thus, in the event of epidemics, humans have served as the CHIKV reservoir, and outside of epidemic periods, monkeys, birds, rodents and other vertebrate species are the vectors [37].

Recently, authors suspected that CHIKV could be transmitted by blood transfusion. The CHIKV transfusion risk was assessed for Reunion Island and northern Italian outbreaks, although the

relatively short duration of viraemia and high proportion of symptomatic infections that could identify and exclude potential donors from donating are factors limiting the risk of CHIKV transmission by transfusion [38].

Risk factors for epidemics

Massive urbanisation has facilitated the spread of contagious diseases in human populations as has increased fast travel over greater distances and worldwide trade. In light of this, CHIKV transmission is closely associated with travel [39]. Furthermore, the risk of emerging or re-emerging CHIKV disease epidemics is associated with the worldwide distribution of well-adapted vectors and the pronounced viraemia in acutely infected humans [40]. The high-titre viraemia in humans is sufficient to infect mosquitoes, which permits an urban transmission cycle between humans and mosquitoes.

Climate change is also considered a risk factor. Studies have shown that an increase of 1–2 °C in temperature results in augmented virus replication [41]. Further, CHIKV outbreaks heavily depend on mosquito density, which increases after a period of heavy rainfall [42]. However, other factors such as virus evolution, especially emergence of CHIKV strains better adapted to mosquitoes, are important [43]. Several studies of viral isolates and infectious clones have elegantly shown that a single mutation can result in high viral replication and dissemination rates in *A. albopictus* and thereby shorten the extrinsic incubation period. The length of the extrinsic incubation period determines the infective life span of a vector and therefore has a great influence on the epidemic potential of the virus–vector partnership. Absence of herd immunity [44] and the lack of vector controls have been associated with the re-emergence of CHIKV infection.

Clinical manifestations

Most infected individuals show symptoms [4]. CHIKV infection has two consecutive phases. After an incubation period typically ranging from 3 to 7 days [4], the initial phase is characterised by three classic symptoms: abrupt febrile illness (temperature often exceeding 38.9 °C); maculopapular rash, which typically involves the trunk and extremities but sometimes the palms, soles and face; and the most characteristic symptom, joint pain responsible for a stooped walk. Other common, nonspecific symptoms include headache, fatigue, nausea, diarrhoea, vomiting, abdominal pain, chills, conjunctivitis, neuritis, pharyngitis and myalgias. The acute signs and symptoms usually resolve in <2 weeks; then the disease progresses to a second stage, with chronic rheumatic manifestations as a major feature [45,46].

Severe forms of CHIKV infection with complications have been described (Table 1). During the 2005–2006 outbreak in Reunion Island, of 610 cases reported, 222 were severe; the overall mortality was 10.6% and increased with age. Hypertension and underlying respiratory or cardiological conditions were independent risk factors for disease severity [47]. CHIKV disease is more severe and is accompanied by more joint disorders in adults than in children.

Table 1
Complications of Chikungunya virus (CHIKV) infection.

- Vasculitis
- Fulminant hepatitis
- Neurological complications
  - encephalitis (CHIKV-infected neonates)
  - facial paralysis
- Heart failure, myocarditis
- Pneumonia
- Mild haemorrhage
- Pre-renal failure
- Death

Rheumatic manifestations

Historically, the epidemic febrile disease in Batavia (now Jakarta, Indonesia) in 1779 is now believed to be an outbreak of CHIKV infection. An infected person, David Bylon, described his disease: "It was last May 25, in the afternoon at 5:00 when I noted while talking with two good friends of mine, a gnawing pain in my right hand, and in the joints of the hand and arm, which gradually increased, extending to the shoulder and then over my whole body, so that at 9:00 that evening I was in my bed with high fever … it's now been three weeks since I… was stricken by the illness, and because of that had to stay home for 5 days: but even until today I have continuously pain and stiffness in the joint[s] of both feet, with swelling of both ankles; so much so, that when I get up in the morning, or have sat up for a while and start to move again, I cannot do so very well and going up and down stairs is very painful." [6,46].

Polyarthralgia has been described in more than 90% of patients; typically, it ensues within a few minutes or several hours of fever onset and results in a characteristic stooped walking position, the hallmark of the disease [7].

In the acute stage, joint pain is usually symmetric, involving large and small joints of the upper and lower limbs. Joint pain occurs commonly in wrists, elbows, fingers, knees and ankles; nevertheless, the knee is the most commonly involved joint, and the proximal joints, hip and shoulder, are less affected [45,48]. A swollen joint is frequently reported, and often in the acute stage of the illness, the arthritis is symmetrical.

The chronic stage is characterised by chronic rheumatic manifestations. Up to 64% of patients with CHIKV fever report joint stiffness and/or pains more than a year after the initial infections [49,50]. Persistent and/or recurring joint stiffness and/or pain lasting more than 1 year after the initial infection affected more than half of all CHIKV-infected patients in La Reunion Island during the 2005–2006 outbreak [50]. Likewise, chronic arthritis after CHIKV infection has been well documented [49]. Rheumatic manifestations fluctuate; symmetrical arthritis has been described, but it can be asymmetrical and even present as oligoarthritis or monoarthritis. This arthritis mimics rheumatoid arthritis (RA); indeed, 21 cases fulfilling the American College of Rheumatology (ACR) criteria for RA after CHIKV infection were reported in Reunion Island outbreak.[51–53]Furthermore, some deformity and limitations in joint mobility have been described, but redness of joints was never seen [45].

Apart from arthralgia, other rheumatic manifestations have been reported. Pain in the sacroiliac joint and lumbosacral and cervical vertebral joints was found in some patients [45]. Pain within or around tendons is a common trait and evolves to tenosynovitis or enthesopathy. Back pain was described in some reports of CHIKV infection [54].

Chronic CHIKV infection-related arthritis is highly debilitating and results in high economic cost and human suffering. During the 2006 epidemic in India, the disability-adjusted life year (DALY), which is a measure of the loss of healthy days in a society, was used to estimate the burden due to CHIKV infection. It exceeded 265 per million in some states, which accounted for up to 69% of the total DALYs [55]. In a recent longitudinal follow-up study of 203 patients with serologically confirmed CHIKV infection, fatigue accompanied joint pain when the disease entered the second month and added to the morbidity [45].

Radiographic abnormalities

In the previously described cohort in India [45], radiographs showed lesions that suggested bony erosion; on magnetic resonance imaging (MRI), the inflammatory findings were joint effusion, bone-marrow oedema or erosion and synovial thickening, tendinitis and tenosynovitis.

Manimunda et al. showed with relative certainty that chronic CHIKV infection-related arthritis is an inflammatory erosive arthritis [45]; this finding is in agreement with previous studies finding bony erosion in several cases [51,52,56,57] as well as tenosynovitis and enthesopathy seen on ultrasonography [56,57].

Biological abnormalities

By analogy to infection with other alphaviruses, in CHIKV infection, laboratory values remain largely within the normal range; nevertheless, the acute infectious phase of CHIKV disease is characterised by pronounced lymphopaenia and moderate thrombocytopaenia [58].

According to several previous studies [4,58–61], the common haematological and biochemical abnormalities described in CHIKV infection include leucopaenia, neutropaenia, lymphopaenia, thrombocytopaenia and elevated transaminase, creatinine and creatinine kinase levels. In a recent study describing the daily haematological values, lymphopaenia was most prominent during days 2–3 of the illness, whereas leucopaenia reached its nadir from days 3–5. Interestingly, mild thrombocytopaenia persisted from days 3–9, with a corresponding increase in haematocrit value [62]. Win et al. noted that lymphopaenia preceded the decrease in total leucocyte count. The erythrocyte sedimentation rate was elevated in most patients during the 10th month of illness in the study in India [45].

Furthermore, Chopra et al. found a high level of C-reactive protein (CRP) in more than 70% of the studied cohort [56]. However, Borgherini et al. suggested that elevated levels of CRP and transaminases and reduced calcium level and polymorphonuclear neutrophil count were associated with more severe illness [58].

Two main methods of laboratory diagnosis are available, namely real-time polymerase chain reaction (RT-PCR) and serology for antibodies to CHIKV (immunoglobulin M (IgM) or IgG). During the initial viraemic phase, RT-PCR is very useful, although classic serological methods are simpler; hence, IgM antibodies are detectable after 2 days, on average, by enzyme-linked immunosorbent assay (ELISA) and persist for several weeks to 3 months [63]. IgG antibodies are detected in convalescent samples and persist for years.

Factors associated with persistence of arthralgia after infection

Identifying factors associated with persistent arthralgia after CHIKV infection is of special interest. Independent markers for persistent joint pain include age $\geq$45 years, initial severity of joint pain and underlying osteoarthritis [64]. However, a recent study in Singapore found age not associated with persistent arthralgia [62], and the only significant marker associated with persistent joint pain in this study was low creatinine level; however, women were more likely to have persistent arthralgia and tended to have lower creatinine levels. Furthermore, thrombocytopaenia and elevated liver enzyme levels were suggested as associated with slow recovery from joint pain [58]. The occurrence of a new viral mutation was suspected to be related to the more aggressive clinical burden of the disease and a higher risk of chronic arthralgia [65]. As well, previously injured joints were especially susceptible [58].

Similar epidemics

In recent years, the number of outbreaks of arboviral-induced arthralgia and severe and long-lasting arthritis has increased in frequency. Apart from CHIKV, six viruses of the alphavirus group (comprising 29 viruses) can cause arthralgia evolving to arthritis; these include O'nyong nyong virus (ONNV), Semliki Forest virus (SFV), Ross River virus (RRV), Sindbis virus (SINV), Mayaro virus (MAYV) and Barmah Forest virus (BFV) [66,67].

SINV is the most widely distributed of all known arbovirus. Antibodies to SINV are detected in humans in various geographical areas, but clinical infections are reported mostly from Finland, where the SINV infection is associated with fever, rash and arthritis, known as Pogosta disease. A major Pogosta disease outbreak has occurred every 7 years in Finland since 1974, involving hundreds or even thousands of patients [68,69].

RRV is a mosquito-borne alphavirus endemic to Australia and New Guinea and is the aetiological agent of epidemic polyarthritis (EPA), an explosive epidemic that also swept through several islands of the South Pacific and resulted in tens of thousands of cases; the principal symptoms of EPA are arthritis or arthralgia, which is often severe and usually lasts 30–40 weeks, with about 25% of patients experiencing symptoms for a year or more [70,71].

ONNV (family Togaviridae, genus *Alphavirus*) was first isolated from human blood and anopheline mosquitoes in Gulu, Uganda, in 1959, and has been responsible for several outbreaks in humans that occurred in East Africa (Kenya, Uganda, Tanzania, Malawi and Mozambique). Between 1959 and 1962, an epidemic of O'nyong nyong (ONN) fever in Africa affected at least 2 million people [72].

MAYV has been isolated only in northern South America and in French Guyana and is responsible for acute illness with rash, fever and severe arthralgia. The last-named lasts for several weeks and affects principally the ankles, wrists and toes but also can affect major joints. The most recent outbreak occurred in a settlement in Santa Barbara, northern Brazil [73].

SFV has been described only in Africa. Its clinical manifestations include fever, severe persistent headache, myalgia, arthralgia and a long convalescence marked by asthenia. This virus was responsible for an outbreak of febrile illnesses in Bangui, Central African Republic, during October–December 1987 [74].

BFV is currently found only in Australia. This virus can cause arthritis, myalgia and fatigue for 6 months or longer, which result in substantial morbidity and economic impact. During the summers of 2005 and 2006, the largest BFV epidemic on record occurred in Australia, with 1895 notifications [71].

Other viruses can cause major outbreaks and joint disorders, particularly dengue virus, which is a member of the Flaviviridae family, genus *Flavivirus*. The dengue virus shares many characteristics with CHIKV, including some of the factors associated with its emergence. In addition, dengue virus and CHIK infection are the two most important arboviral infections of global significance. An estimated 50–100 million cases of dengue fever and about 250 000–500 000 cases of dengue haemorrhagic fever occur every year [75]. Haemorrhage and shock syndrome distinguish dengue virus infection from CHIKV infection. Despite the similarities in clinical presentations of the infections, the differential diagnosis is still difficult [76].

Pathophysiology of arthritis after CHIKV infection and its relationship with RA

The pathogenesis of the rheumatic manifestations of CHIKV infection is still poorly understood. Macrophages are considered an important source of synovial pro-inflammatory cytokines that act as effector molecules in RA pathogenesis, but the precise mechanisms in viral arthritides caused by alphaviruses are still unclear. The role of macrophages in perpetuating chronic arthralgia or arthritis is unknown. Recent evidence identifies the importance of persistent organisms in synovial macrophages in the pathogenesis of viral arthritis [57]. Furthermore, the degradation of extracellular matrix is an important process in arthritis. Migration inhibitory factor (MIF), tumour necrosis factor-alpha and interleukin 1-beta are believed to participate in this process by stimulating the production of matrix metalloproteinases (MMPs).

A recent study has shown that SINV can replicate in human macrophages, and stimulate production of several cytokines and activate the expression of two important MMPs involved in joint damage. The same study demonstrated the involvement of macrophage MIF in the secretion of other inflammatory cytokines and in the expression of MMPs in SINV-infected macrophages. These results may contribute to the understanding of the mechanisms involved in the development of viral arthritides [77], and may be extrapolated to CHIKV infection. The authors found that CHIKV has profound cytotoxic effects and can induce apoptosis *in vitro* and in synovial tissues, as assessed by the presence of numerous cleaved poly adenosine diphosphate (ADP)-ribose polymerase-positive cells, whereas a high expression of MMP2 may contribute to chronic tissue lesions [57].

The aetiology of RA still not fully understood; multiple factors interact to initiate RA or to increase susceptibility to the disease. Actually, infections are suspected to contribute to the maturation of the immune system from the innate to adaptive phases and therefore may take part in the induction of auto-immune conditions [78]. The role of viruses in the pathogenesis of RA and other auto-immune diseases has been suggested, but never clearly demonstrated [78]. Recently, serologic evidence of the association of RA and exposure to specific infections has been shown with the herpes-related Epstein–Barr virus and cytomegalovirus, which suggests a role of these viruses in the pathogenesis of RA [79].

The incidence of RA is reported to be high in populations with previous CHIKV infection, as compared with the general population. Indeed, 21 cases of RA after CHIKV infection were reported in The Reunion Island; 12 patients (57.1%) were positive for rheumatoid factor, but anti-cyclic citrullinated peptide-2 (anti-CCP-2) antibodies were detected in only six (28.6%) [51,52]. In the cohort in India, about 36% of the patients met the ACR criteria for RA [45,53]. One patient tested positive for anti-CCP antibodies [45], despite the absence of radiographic signs of abnormalities. Chopra et al. did not find any major classic bone erosions typical for RA after CHIKV infection, and hence arthritis after CHIKV infection, despite common features, can be differentiated from RA [56].

According to several recent data, positivity for anti-CCP antibodies ranged from 0% to 37% during infectious diseases. Furthermore, these diseases may involve symptoms from the locomotor system, and if in addition, they show anti-CCP antibody positivity, these features can lead to a false diagnosis of RA [80].

How to treat CHIKV infection-associated arthritis

To date, no specific treatments exist for CHIKV infection in the acute stage of the disease; treatment is limited to supportive care, including rest, antipyretics and analgesics. For chronic arthralgia or arthritis, non-steroidal anti-inflammatory drugs or corticosteroids can be used. Nevertheless, in severe forms, disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, hydroxychloroquine or sulphasalazine has been proposed. In parallel, high levels of CRP in the study in India (more than 70% of the cohort) suggested some inflammatory processes, which prompted aggressive treatment regimens with DMARDs or corticosteroids for up to 6 months [56].

The role of pro-inflammatory cytokines and chemokines in the pathogenesis of RA is well established and has led to the development of effective targeted therapies in this disease. Remarkable similarities were observed in the macrophage response induced by SINV infection and RA, which suggested the use of some therapies used in RA to treat viral arthritis [77].

Control of infection

Considering the lack of a vaccine or specific treatment, the control of CHIKV infection is based primarily on interfering with virus transmission. First and foremost, preventive measures consist in individual protection against mosquito transmission by wearing long-sleeved clothing, use of mosquito nets and efforts to eliminate potential mosquito breeding sites, such as water-containing reservoirs, tyres and roof gutters. Furthermore, the best method for preventing CHIKV infection is mosquito control, particularly by use of insecticides to treat breeding sites [81]. However, with global warming, vector control has become more challenging. Recent data have shown mosquito resistance to insecticides.

Resistance and susceptibility to infection

In the age of genomics, it is realised that common disease such as RA are genetically complex and that disease susceptibility as well as clinical features are influenced by a combination of genetic and environmental factors. Similar interactions with genetic and environmental factors could also apply to viral arthritis. Such factors are still unexplored, but hinted at by a recent study. An outbreak of CHIKV infection in southern India, particularly in the Anantapur District of Andhra Pradesh, led Sudarsanareddy et al. to study genetic predisposition to CHIKV infection in affected families to identify susceptible or resistant blood groups [82]. The authors concluded that subjects with Rh-positive blood were susceptible. Particularly, subjects with O-positive blood were more susceptible to infection than those with other blood groups. No individual with Rh-negative blood was infected with CHIKV, which suggested that Rh-negativity is associated with resistance to CHIKV infection.

Conclusions

CHIKV infection outbreaks continue to pose a significant threat in many regions of the world and cause debilitating chronic arthritis with a large impact in humans. In the absence of effective treatment and the challenging task of *Aedes* mosquito control, developing successful approaches to immunoprophylaxis and vaccine-mediated protection against CHIKV infection is paramount. A better understanding of the pathophysiology of chronic arthritis due to CHIKV infection may lead to the development of improved therapeutic strategies.

Practice points

- Chikungunya virus (CHIKV) infection is an emerging disease that is responsible for several epidemics in several new locations around the world.
- Chronic arthritis after CHIKV infection is well documented.
- CHIKV infection 'in its chronic locomotor manifestations may mimic RA but is a distinct non-erosive entity'.
- At present, no vaccine or efficient treatment exists for CHIKV infection. Preventive measures are imperative.
- CHIKV infection epidemics have identified Rh-negativity as protective.

Research agenda

- Understand the molecular pathophysiology of arthritis after CHIKV infection.
- Develop an specific treatment for controlling CHIKV infection, e.g., a vaccine for CHIKV infection.
- Long-term follow-up of individuals developing true RA after CHIKV infection to better understand the relationship between these two diseases.

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