REVIEWS

Arthritogenic alphaviruses—an overview

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Abstract | Mosquito-transmitted alphaviruses causing human rheumatic disease are globally distributed and include chikungunya virus, Ross River virus, Barmah Forest virus, Sindbis virus, o'nyong-nyong virus and Mayaro virus. These viruses cause endemic disease and, occasionally, large epidemics; for instance, the 2004–2011 chikungunya epidemic resulted in 1.4–6.5 million cases, with imported cases reported in nearly 40 countries. The disease is usually self-limiting and characterized by acute and chronic symmetrical peripheral polyarthralgia–polyarthritis, with acute disease usually including fever, myalgia and/or rash. Arthropathy can be debilitating, usually lasts weeks to months and can be protracted; although adequate attention to differential diagnoses is recommended. The latest chikungunya virus epidemic was also associated with some severe disease manifestations and mortality, primarily in elderly patients with comorbidities and the young. Chronic alphaviral rheumatic disease probably arises from inflammatory responses stimulated by the virus persisting in joint tissues, despite robust antiviral immune responses. Serodiagnosis by ELISA is the standard; although international standardization is often lacking. Treatment usually involves simple analgesics and/or NSAIDs, which can provide relief, but better drug treatments are clearly needed. However, the small market size and/or the unpredictable and rapid nature of epidemics present major hurdles for development and deployment of new alphavirus-specific interventions.

Introduction

Alphaviruses are a genus of enveloped, positive sense, single-stranded RNA viruses, which are usually transmitted by mosquitoes, and together with the genus *Rubivirus* belong to the *Togaviridae* family. Alphaviruses are commonly referred to as 'Old World' and 'New World' viruses, with Old World viruses (Table 1, Figure 1) generally associated with rheumatic disease in humans and 'New World' viruses (which include Venezuelan, Eastern and Western Equine Encephalitis viruses) primarily associated with potentially fatal encephalitic disease in the Americas. The arthritogenic alphaviruses comprise chikungunya virus (CHIKV), Ross River virus (RRV), Barmah Forest virus (BFV), o'nyong-nyong virus (also known as Igbo Ora), the Sindbis group of viruses and Mayaro virus[1,2] (Table 1, Figure 1). Symptomatic infection of adults with these alphaviruses is nearly always associated with rheumatic disease, primarily polyarthralgia and/or polyarthritis, which can be chronic and debilitating. The global distribution of these viruses, increased international travel, economic development, changes in mosquito vectors and the potentially explosive nature of epidemics can all contribute to these diseases being seen more frequently by doctors and rheumatologists globally. In this Review, we describe the epidemiology, pathogenesis, disease, diagnosis and interventions for arthritogenic alphaviruses, with particular focus on information pertinent to health-care professionals.

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Competing interests
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Alphavirus epidemiology
Chikungunya virus

CHIKV was first isolated in 1952 in Tanganyika (present day Tanzania); however, the first description of the disease might have been by David Bylon in 1779 during an epidemic in Jakarta.[3] Regular epidemics have occurred since then, primarily in Africa and Asia, with early outbreaks (including one in the USA and Caribbean) potentially confused with epidemic dengue fever.[3,4] The largest epidemic of CHIKV disease ever recorded took place in 2004–2011 and was associated with the emergence of a clade of viruses that were efficiently transmitted by *Aedes albopictus*,[5–7] a mosquito vector that has seen a dramatic global expansion in its geographic distribution in the past 30 years.[8] The epidemic began in Kenya, spread across the Indian Ocean Islands to India (where an estimated 1.4–6.5 million cases have occurred[6]) and South East Asia, reaching Myanmar (formerly known as Burma) in 2010.[7] A number of cases were reported in New Caledonia in the Pacific Ocean in 2011.[9] The attack rate for CHIKV disease can be very high; a survey on Grande Comore Island in 2005 suggested an attack rate of ~50%[10] and, in Reunion Island (French Indian Ocean territory), 266,000 cases of CHIKV disease were reported (38% of the population) during 2005–2006. The first autochthonous (endogenously transmitted) infections in Europe occurred in Italy in 2007 (>200 cases)[5,6] and in France in 2010.[11] Due to international travel, imported CHIKV cases have now been reported in nearly 40 countries including USA, Japan and several European countries.[6,9,12–14]

CHIKV is a biosafety level 3 pathogen in most countries and is listed as a US National Institute of Allergy and Infectious Diseases category C priority pathogen.[15] The US Army recognizes CHIKV as a potential biological weapon, and CHIKV is considered a possible agent for bioterrorism owing to the potential for infection via aerosol.[16]

Ross River virus and Barmah Forest virus

RRV was first isolated in 1959 from mosquitoes trapped beside the Ross River in Queensland, Australia. BFV was first isolated in 1974 from mosquitoes collected in the Barmah Forest, Victoria, Australia. The viruses are endemic and enzootic in Australia (with RRV also found in Papua New Guinea; Figure 1), with most cases occurring in northern Australia during the wet season —usually December to February—when mosquito populations are at their peak.[17] RRV and BFV infection are notifiable to public health authorities in Australia.[17–19] Australian-based analyses suggest changing land practices and climate change are likely to increase the range and activity of these and other mosquito-borne infectious diseases in the future.[17,20]

The Sindbis virus group

Sindbis virus was first isolated from mosquitoes in 1952 in Egypt and is the most widely distributed arbovirus found in Eurasia, Africa and Oceania.[2,21,22] However, Sindbis viral diseases in humans are largely restricted to Northern Europe (Table 1, Figure 1), where this organism is endemic, with intermittent outbreaks typically seen in late summer or early autumn.[2,21,22] Cases are also occasionally reported in Australia, China and South Africa.[2,21,22]

O'nyong-nyong virus

O'nyong-nyong virus first emerged as disease-causing entity in Uganda in 1959[2] and so far has caused at least three outbreaks in Africa, one of which involved >2 million cases (Table 1, Figure 1). Although o'nyong-nyong virus is more closely related to CHIKV than the other arthritogenic alphaviruses, it is a genetically distinct virus.[23] As with CHIKV, the attack rate for o'nyong-nyong virus can be very high (45–68%).[2]

Mayaro virus

Mayaro virus was first isolated in 1954 and is enzootic in northern South America. The virus causes sporadic human cases and recurrent small outbreaks, usually associated with residence in, or travel to, humid tropical forests.[2,24,25]

Mosquito transmission

Arthritogenic alphaviruses (Table 1) are maintained in the wild by continuous cycles of transmission between mosquitoes and vertebrate hosts: primates for CHIKV,[26] primarily macropods (kangaroos and wallabies) for RRV and BFV,[16,17] forest birds for Sindbis virus,[2] unknown for o'nyong-nyong virus, and possibly various mammals for Mayaro virus.[27] These reservoirs, on various occasions,

Key points

- Alphaviruses that cause rheumatic disease are globally distributed and cause endemic disease in various locations and, occasionally, large unpredictable epidemics
- The 2004–2011 outbreak of chikungunya virus was the largest ever recorded, involving 1.4–6.5 million cases, with imported cases reported in nearly 40 countries
- Alphaviral disease is characterized by fever, rash, and/or myalgia, and generally symmetrical and peripheral, often debilitating, polyarthralgia and/or polyarthritis, which usually lasts weeks to months
- The arthropathy is rarely destructive and is usually treated with simple analgesics and/or NSAIDs, although relief of symptoms is often inadequate, with better treatments needed
- The pathogenesis of chronic arthralgia and/or arthritis probably arises from inflammatory immune responses induced by the virus persisting in joint macrophages, despite robust antiviral immune responses
- Adequate attention to differential diagnoses in patients with long-term chronic disease is recommended as other rheumatic conditions might be responsible for symptoms

Table 1 | Alphaviruses associated with rheumatic disease

Virus	Occurrence
Chikungunya virus	Large sporadic epidemics
Ross River virus	Mean of ≈4,000 cases per annum in Australia[17] An epidemic occurred in 1979–1980 >60,000 cases in some of the Pacific Islands[18]
Barmah Forest virus	Mean of ≈1,000 cases per annum in Australia[18]
O'nyong-nyong virus	Rare epidemics, >2 million cases in 1959–1961[30,104]
Mayaro virus	Occasional small outbreaks (30–100 cases)[24,122]
Sindbis virus[2,21,22]	
Karelian fever	Rare (Karelia, West Russia)
Ockelbo virus	Mean ≈30 cases per annum (Sweden)
Pogosta virus	Mean ≈140 (range 1–1,282) cases per annum (Finland)

For geographical distribution of these disease outbreaks see Figure 1.

can lead to human infections via mosquito bite, with large epidemics usually associated with subsequent urban transmission cycles (human–mosquito–human).[18] For instance, for CHIKV in Africa, the sylvatic cycle (primate–mosquito–primate) involves various forest dwelling *Aedes* species that occasionally seed human infections, with subsequent urban transmission cycles involving *A. albopictus* and/or *A. aegypti* vectors that cause human outbreaks.[26] Whether a sylvatic cycle provides a reservoir of CHIKV in Asia is less clear,[26] although CHIKV isolates have been recovered from long-tailed macaques in Malaysia.[28]

Pathogenesis

Infection with alphaviruses results in a brief, usually 5–7 days long, viraemia,[6,29,30] which is controlled primarily by IFN-α/β and antibodies.[1,31–34] A wide range of cell types and tissues have been shown to be infected by arthritogenic alphaviruses, including monocytes and/or macrophages,[1,29,35–37] dendritic cells,[29,38] synovial and dermal fibroblasts,[29,31,35,39] endothelial cells,[29,31,35,39] muscle cells,[35,40,41] periosteum,[42] and perhaps keratinocytes.[43] Widespread infection of these cells and the
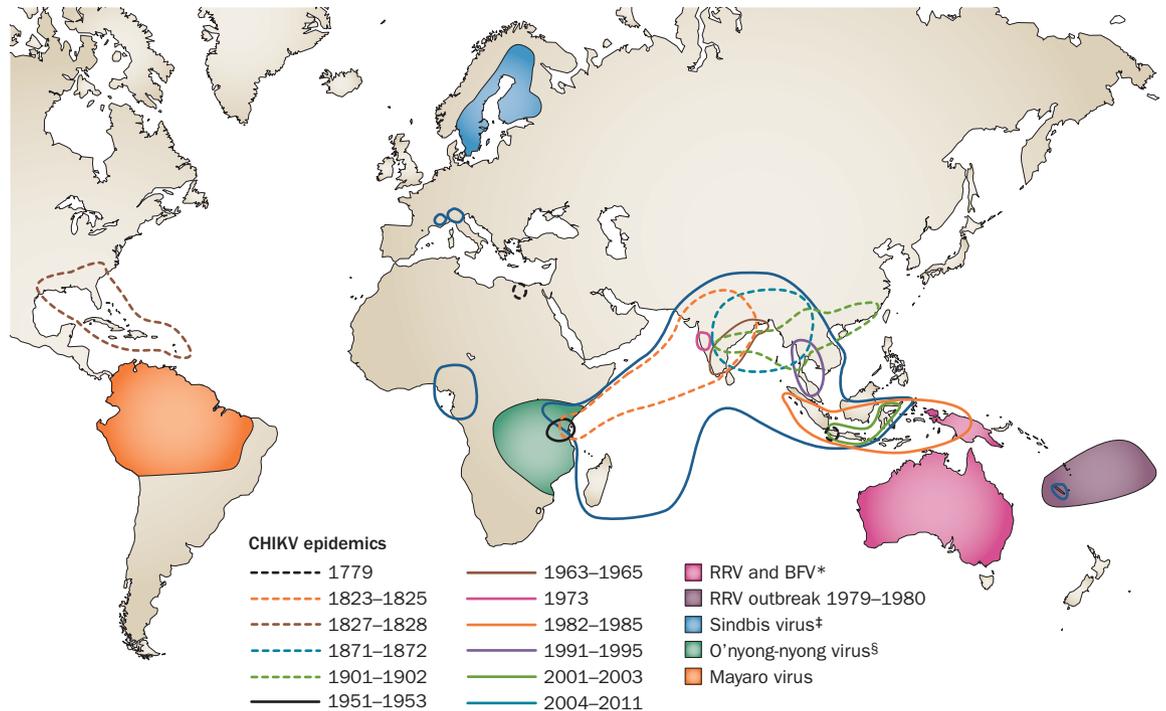
Figure 1 | Approximate geographical locations of diseases associated with arthritogenic alphaviruses. For CHIKV disease, locations of documented large outbreaks are shown;[3,4,7,9,26,112] epidemics prior to 1902 are shown in dashed lines and were initially classified as outbreaks of dengue, but were likely to have been due to CHIKV.[3] *Geographical locations of RRV and BFV diseases overlap, with BFV restricted to the Australian mainland.[17,74] ‡Main location of diseases caused by the Sindbis virus family.[22] §O'nyong-nyong virus disease outbreaks in 1959–1961 (East Africa), 1996–1997 (Uganda) and 2003 (West Africa).[30,104] Mayaro virus disease outbreak regions.[17,25,74] Abbreviations: BFV, Barmah Forest virus; CHIKV, chikungunya virus; RRV, Ross River virus.

associated inflammatory immune responses[6] probably account for the acute symptoms caused by these viruses —primarily fever, polyarthralgia–polyarthritis, rash and myalgia (Table 2).

The central feature of adult disease caused by arthritogenic alphaviruses is the often debilitating polyarthralgia and/or polyarthritis that lasts from weeks to months (Table 2).[2,5,6,26,44,45] No strong evidence exists that autoimmune responses (that might be induced by viral infections) are important for, or substantially contribute to, viral arthropathies. For multiple arthritogenic viruses, evidence indicates that arthropathies are due to inflammatory responses induced by viruses and/or their products residing and/or replicating within joint tissues.[46] Consistent with this view, CHIKV has been shown to persist in various tissues for up to 44 days post-infection in monkeys, with CHIKV antigen and RNA detected in macrophages for 90 days and 55 days after infection, respectively.[29] In one patient with CHIKV infection, CHIKV RNA and protein was found in synovial macrophages 18 months after infection.[47] In addition, RRV RNA has been detected in synovial tissue from those infected with RRV 5 weeks after the onset of symptoms.[1] How these ordinarily cytopathic (apoptosis-inducing) viruses can persist for extended periods in the face of robust neutralizing antibody, T-cell and IFN-α/β responses[29,48] remains unclear. The virus might evade neutralization by antibodies by hiding in apoptotic blebs and maintain infection in macrophages through continuous rounds of infection, apoptosis and phagocytosis, with the phagocyte being infected via the phagosome.[1,39] Evasion of T-cell responses might occur via the rapid shutdown of host-cell protein synthesis (a characteristic of alphaviral infections of mammalian cells[38]), which could limit the number of cell surface major histocompatibility molecules that can present viral antigens to T cells.[49] Some evidence suggests that alphaviral RNA might be reverse transcribed by endogenous reverse transcriptases and integrate into host DNA.[50]

Cells infected with alphaviruses have also been shown to be less responsive to IFN-α/β,[38] with nonstructural viral proteins able to inhibit IFNα/β receptor signalling.[51] Engagement of Fc receptors by alphavirus–antibody complexes might also suppress antiviral responses in macrophages.[52,53] The inflammatory infiltrate in the synovial fluid of patients with RRV disease is primarily monocytic, with macrophages showing an inflammatory phenotype and large phagocytic inclusions.[1] Elevated levels of CC-chemokine ligand 2 (CCL2, also known as MCP-1), TNF and IFN-γ were found in the synovial fluids from such patients.[54] The synovial fluid of a patient with chronic CHIKV disease at 18 months showed monocytes and macrophages with large inclusions, natural killer (NK) cells and CD4+ T cells, with polymorphonuclear cells largely absent, and elevated levels of CCL2, IL-6 and IL-8.[47] Monkey and mouse

Table 2 | Symptoms of disease in adults caused by arthritogenic alphaviruses

Virus	Usual incubation period (range)	% Asymptomatic	Frequency of main symptoms (%)	Other symptoms noted (% frequency)	References
CHIKV	2–6 days (2–12)	≈5–18	Fever: 90 Rash: 40–50 Myalgia: 90 Arthralgia or arthritis: >95	Fatigue, tenosynovitis, headache, nausea, oedema, vomiting, conjunctivitis, occasional bleeding gums and epistaxis*	Toivanen (2008)[2] Jaffar-Bandjee et al. (2010)[5] Staikowsky et al. (2009)[64] Vijayakumar et al. (2011)[65] Simon et al. (2011)[66] Queyriaux et al. (2008)[67] Moro et al. (2010)[123]
RRV	7–9 days (3–21)	55–75	Fever: 20–60 Rash: 40–60 Myalgia: 40–80 Arthralgia or arthritis: 80–100 (3–6 months)	Fatigue (>50), headache, photophobia, lymphadenopathy, sore throat and rarely encephalitis*	Harley & Suhrbier (2012)[17] Harley et al. (2001)[19] Mylonas et al. (2002)[44] Flexman et al. (1998)[74]
BFV	7–9 days	Unknown	Fever: 50 Rash: 40–60 Myalgia: 50–80 Arthralgia or arthritis: 70–95	Lethargy (90) and headache 60	Flexman et al. (1998)[74] Passmore et al. (2002)[124]
Sindbis virus	2–10 days	Very common*	Fever: 15–40 Rash: 90 Myalgia: 50 Arthralgia or arthritis: 95	Fatigue (60), headache (40) nausea (13) and dizziness (16)	Brummer-Korvenkontio et al. (2002)[21] Laine et al. (2004)[22] Kurkela et al. (2005)[45]
O'nyong-nyong virus	Unknown	Unknown	Fever: 80–100 Rash: 70–90 Myalgia: 70 Arthralgia or arthritis: 60–100	Headache (83), pruritis (71), lymphadenopathy (45%), red eyes (45) and bleeding gums (3)	Kiwanuka et al. (1999)[30] Posey et al. (2005)[104]
Mayaro virus	Unknown	8	Fever:100 Rash: 30–50 Myalgia: 75 Arthralgia or arthritis: 50–90	Headache (60–100), oedema (58), retroocular pain (40–60), dizziness (25), anorexia (22), nausea (18), sore throat (18), swollen lymph nodes (17%), vomiting (4–14), diarrhoea (9), bleeding gums (4.5)	Azevedo et al. (2009)[24] Tesh et al. (1999)[125]

Percentages for key symptoms have been rounded up; generally percentages should be viewed as approximate as cohort numbers were often small. The rash associated with arthritogenic alphavirus infection is usually maculopapular and often itchy. No major differences between sexes have been reported. *Percentages not researched. Abbreviations: BFV, Barmah Forest virus; CHIKV, chikungunya virus; RRV, Ross River virus

CHIKV disease models also show pronounced mononuclear infiltrates, primarily monocytes, macrophages and NK cells.[29,33]

Analysis of serum cytokines and chemokines associated with CHIKV infection in humans has not produced a coherent picture.[47,48,55–58] Taken together with animal studies,[29,33] serum IL-6, IFN-α/β, IFN-γ and CCL2 were upregulated in most studies. Granulocyte colony-stimulating factor, granulocyte monocyte colony-stimulating factor, IL-7, IL-12, IL-13, IL-17, and CXC-ligand 10 (CXCL10, also known as IP-10) were upregulated in human studies;[47,48,55–58] whilst TNF was upregulated in some human[47,48,55–58] and animal studies.[29,33] CCL2, TNF, IFN-γ, IL-6 and IL-1β have been found to be induced by a number of arthritogenic viruses, with these inflammatory mediators also prominent in rheumatoid arthritis.[46] Mouse models of RRV disease have also implicated macrophage migration inhibitory factor[59] and complement[60] as important factors in the development of alphaviral rheumatic disease.

A large body of literature exists detailing the molecular aspects of host–virus interactions for alphavirus infections. As this literature is outside the clinical focus of this article, we refer readers to some excellent reviews in the area.[6,38,61] Many of these studies have used Sindbis virus, which in mice behaves like an encephalitic virus rather than an arthritogenic virus.

Clinical features

Acute phase

The main symptoms of disease caused by arthritogenic alphaviruses are summarised in Table 2. The normal time course, based on CHIKV disease, is summarized in Figure 2. For CHIKV infection, viral loads usually range from 1×10^5 to 1×10^9 viral RNA copies per ml of blood,[62] with the viraemia usually lasting 5–7 days (Figure 2).[5,13] CHIKV disease is characterized by an abrupt onset of fever coincident with the viraemia, reaching 39–40 °C in some cases, and resulting in chills and rigors.[63–65] Fever can be treated with antipyretic agents,[63] although such treatment might not be particularly effective (although the exact reasons why are unknown).[66] Aspirin is best avoided for CHIKV disease owing to the risk of bleeding.[63,66] Polyarthralgia and/or polyarthritis usually begins around the time of fever onset and is usually symmetrical. Peripheral joints (interphalangeal joints, wrists and ankles) and large joints (such as shoulders, knees and spine) are often affected.[64,65,67] Joint effusions can be seen in most cases[63,67]—joint symptoms can fluctuate, but do not usually change anatomical location. In our experience, treatment usually involves NSAIDs and/ or simple analgesics. Skin manifestation can appear 2–4 days after onset of fever, usually a maculopapular rash (often pruritic), although a series of other skin conditions have been reported.[63,68–70] The rash usually occurs
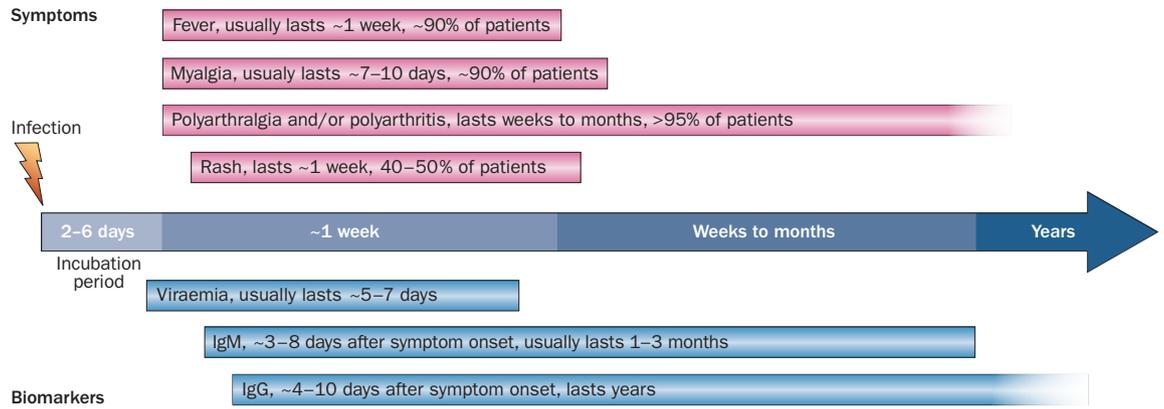
Figure 2 | Usual course of CHIKV disease in adults. The figure shows a schematic representation of the typical course of CHIKV disease, showing typical symptoms and biomarkers (including usual durations) in boxes. The viraemia is usually followed by fever, myalgia, polyarthralgia and/or polyarthritis. A rash can appear 2–4 days after symptom onset. Polyarthralgia and/or polyarthritis and IgG levels can persist. Other symptoms can occur (see main text). Virus-specific IgM and IgG can be detected as early as 3 or 4 days after symptom onset, respectively. The information present in the figure is based on ELISA data reported for CHIKV and Sindbis virus, and will vary with the test used.[13,45,106] IgG generally persists, and IgM can persist in some patients.*Skin depigmentation can take up to 4 weeks to resolve. Abbreviation: CHIKV, chikungunya virus.

on the trunk and limbs and only rarely on the face.[63,68–70] This rash has been reported to occur in as few as 20%[70] and >80% of cases,[71] but usually occurs in 40–50% of patients.[72,73] A series of additional symptoms have also been noted, including fatigue and headache (Table 2). Haematological findings include leukopaenia with lymphocyte predominance, occasionally thrombocytopenia, and elevated erythrocyte sedimentation rate and C-reactive protein levels.[55,63]

The disease course for other alphaviral arthritides represent variations on the theme described above for CHIKV (Table 2). For RRV, the rash has been reported to occur before, after, or at the same time as arthropathy (with purpura occasionally found).[18,19,44,74] Polyarthralgia and/or polyarthritis can be severe, with joint effusions often present, although usually small in size. Raised erythrocyte sedimentation rates can occur, but decrease within a few weeks. Serum C-reactive protein levels are rarely increased.[18,19,44,74] BFV disease cannot reliably be distinguished from RRV disease by symptoms alone, although the rash is more common and florid (vesicular in ~10% of cases), with arthritic symptoms also less pronounced.[74] For Sindbis virus, joint swelling is seen in ~50% of patients.[22,45] No haemorrhagic manifestations have been reported for RRV, BFV or Sindbis virus diseases, and aspirin is sometimes used for treatment.[44,74] Mayaro virus and o'nyong-nyong virus infections largely follow similar patterns (to each other and to CHIKV), and resemble CHIKV disease by showing occasional haemorrhagic manifestations (Table 2).

Differential diagnoses for acute symptomatic infections with arthritogenic alphaviruses, include other infectious arthritides (for example, dengue fever, parvovirus B19, infectious mononucleosis, Lyme disease, measles, varicella, measles, rubella, human herpesvirus 6, hepatitis B, HIV[46]), autoimmune arthritides (for example, rheumatoid arthritis, systemic lupus erythematosus), Still's disease, malaria, yellow fever, meningitis, rheumatic fever, leptospirosis and drug reactions.[19,24,45,63,70,74,75] Persistent, distinct monoarticular arthritis is not consistent with alphaviral disease. Comorbidities (see below) and co-infections might also need to be considered in the diagnosis.[76,77]

Chronic phase
The defining feature of most alphaviral arthritides is chronic, episodic, often debilitating, polyarthralgia and/or polyarthritis, which is often associated with fatigue (Table 2). Although most patients progressively recover within several weeks, in some the disease can last for months.[44,45,55,66,78] NSAIDs and/or simple analgesics can provide relief, but this therapeutic approach is often inadequate.[4,10,44,74] The period of chronic joint pain seems to be somewhat reduced for BFV infection compared with RRV.[74]

Protracted disease—primarily arthralgia—is well documented for Sindbis virus,[45] RRV[44] and CHIKV disease.[78–84] For instance, CHIKV arthritic disease is reported to remain unresolved after 6 months to 3 years in 1.6–57% of patients (depending on the study).[78–84] Notably, these studies did not seek and account for differential diagnoses, did not use validated questionnaires (such as Short Form 36 or the Clinical Health Assessment Questionnaire) and/or did not include a control group. With application of validated questionnaires and a control group, a much more benign picture for chronic CHIKV disease emerges.[85] A prospective survey of patients with RRV disease, which used validated questionnaires and actively sought differential diagnoses, found that the patients with symptoms lasting >3–6 months could nearly all be diagnosed with other conditions that accounted for their long-term disease —primarily osteoarthritis, autoimmune arthritides and depression.[44] Patients who had a confirmed diagnosis

of only RRV disease, progressively recovered within 3–6 months. The presence of individuals with such conditions as osteoarthritis or autoimmune arthritides in cohorts of patients with CHIKV disease[66,73,79,85,86] highlights the need to seek differential diagnoses in patients seeming to suffer from long-term alphaviral arthropathies. It should be noted that the prevalence of self-reported musculoskeletal pain lasting more than week in the past month was 47% in an otherwise healthy UK population,[87] highlighting the need for appropriate diagnosis, prospective studies and validated tools in such rheumatic disease research.

Studies suggesting that viral or alphaviral diseases can trigger autoimmune arthritides such as rheumatoid arthritis[81,88] might be confusing contemporaneous conditions with causation. Currently, no strong evidence exists that viral arthritides lead to autoimmune disease.[46] Presence of rheumatoid factor, anti-cyclic citrullinated peptide antibodies and radiography-detectable joint erosions would suggest rheumatoid arthritis rather than alphaviral arthropathies.[83,89] Nevertheless, in Reunion Island there do seem to be a small group of elderly patients in whom CHIKV disease seems to be protracted and in whom methotrexate (a DMARD used to treat rheumatoid arthritis) seems to be effective.[47] Whether the 2004–2011 CHIKV epidemic ultimately leads to an increased prevalence of rheumatoid arthritis in the affected regions remains to be established. Any such studies would have to account for the general increase in awareness and clinical attention to rheumatic disease that would probably follow a CHIKV epidemic.

Disease in children and infants

RRV and BFV infections in children are usually asymptomatic.[19,74] Sindbis virus infections in children also seem to be asymptomatic or mild, with a rash and no arthropathy.[21,22] Apart from the severe manifestations listed below, CHIKV infection of children usually results in fever, mild arthralgia and rash in >50% of patients, with the remainder presenting with one or two of these symptoms.[5] Fever usually lasts a few days and shows a single spike, with less than one-third showing a second spike in temperature.[4,90,91] Towards the end of the febrile period, a maculopapular rash appears and usually lasts for a few days, with pigmentary changes also reported.[4,90,91] Symptoms in infants involve fever, seizures, loose stools, peripheral cyanosis and maculopaplar rash, vesicobullous lesions and skin peeling.[92,93] Arthralgia and/or arthritis is mild in infants and does not persist.[4,90,92] Exactly why the infection manifests differently in adults and children is currently unknown, but the immature immune system in infants could be a factor.

Severe manifestations of alphaviral disease

Disease caused by arthritogenic alphaviruses can be incapacitating and protracted, but the diseases are generally self-limiting and nonfatal. However, during the 2004–2011 CHIKV epidemic a number of deaths were reported in India, and a case fatality rate of ~0.1% was reported in Reunion Island.[94] Mortality was generally associated with comorbidities and/or old age.[5,94] In addition, in Reunion Island a neonate died from necrotizing enterocolitis with gastrointestinal haemorrhage and *Klebsiella pneumoniae* septicaemia, and two children died from encephalitis.[95,96] Two deaths in newborns were also reported in Mayotte.[97] Some atypical and severe clinical forms of CHIKV disease were also reported in adults including encephalitis, Guillain–Barré syndrome, severe liver damage, heart failure and cases of other organ failures (cerebral, renal, multiple organ, respiratory, and/or acute myocardial infarction).[98–100] Most of these cases had underlying medical conditions. In Reunion Island, the atypical cases aged 40–60 years were 2.5 times more likely to develop severe disease than those aged under 40 years.[5]

Mother-to-child transmission of CHIKV was also seen during the 2004–2011 epidemic. A study in Reunion Island reported 19 children born to viraemic mothers in a total of 7,504 pregnancies; 739 mothers were infected with CHIKV antenatal, prenatal, or intrapartum.[101] About half the neonates born to viraemic mothers became infected, probably shortly before delivery.[101] Symptoms in neonates included pain, prostration and fever in all cases and thrombocytopenia in 89%.[101] About half the infected neonates developed serious forms of CHIKV disease characterized by haemorrhage, disseminated intravascular coagulation, and/or cardiac and neurological manifestations; the latter often leading to permanent disabilities.[5,95,100,101] Severe skin manifestations involving confluent vesiculobullous lesions leading to blistering of 10–30% of total surface body area was also described for some hospitalised CHIKV-infected infants.[93] Severe manifestations are usually rare in children and primarily involve encephalitis, with CHIKV also detected in the central nervous system of some patients.[96,102]

Severe disease manifestations have not been documented for other arthritogenic alphaviruses. Whether this less severe disease is due to the low number of overall cases (compared with CHIKV disease), limited investigations and/or an assumption that these diseases are benign is unclear. Postinfection chronic fatigue syndrome has been documented for several pathogens including RRV.[103]

Diagnostic tests

Serodiagnosis by IgM and IgG ELISA tests are used as standard for laboratory-based diagnoses of arthritogenic alphavirus disease.[18,24,45,74,104] Australia has a long history of use of commercial BFV and RRV ELISA kits (PanBio, acquired by Alere, Stockport, UK). This RRV kit has high sensitivity (98%) and specificity (84.6%) for IgM.[18] Paired tests at least 10–14 days apart are recommended, with acute phase changes confirming the serodiagnosis (a positive result for example includes: 1st test IgM+, IgG−, 2nd test IgM−, IgG+; or IgM−, IgG−/IgM+, IgG−; or IgM+, IgG+/IgM−, IgG+). A fourfold increase in IgG titres has also been used as a serodiagnostic criterion.[18,74]

In-house CHIKV IgM ELISAs have been developed in a number of countries using different protocols and antigens.[13,83,105,106] A commercial ELISA test is being developed by Standard Diagnostics (Kyonggi-do, Korea)[105]

and a point-of-care lateral flow immunoassay is being developed by CTK Biotech (San Diego, USA).[106] Alphavirus-specific IgM persisting for many months to years has been reported;[83] however, its diagnostic value is unclear[45] and could simply reflect where the cut-off point is set for that particular IgM ELISA. International standardization and validation for CHIKV ELISAs is currently limited.

PCR-based diagnosis using serum samples have been used for laboratory-based diagnosis of arthritogenic alphavirus infection.[13,24,45,104] However, these tests are useful only if blood samples are taken during the short viraemic period. Virus can also be cultured from viraemic blood using C6/36 (mosquito cell line) or Vero (monkey kidney cell line) cells.[24,33,45]

Public health response measures

Surveillance is clearly important for early identification of arthritogenic alphavirus outbreaks, with recognition of the disease by health-care providers and public health officials essential. Once an outbreak has been identified, rapid and aggressive control of mosquito vectors (both adult and larvae) by local authorities might be warranted.[107,108] The population should be advised to avoid mosquito bites by wearing protective clothing, to use repellents and (if appropriate) use mosquito nets impregnated with insect repellent.[5] Owing to the potential severity of neonatal infections (particularly for CHIKV), extra care should be taken for pregnant women and neonates. DEET (*N,N*-Diethyl-meta-toluamide, the active ingredient in insect repellents) is not recommended for children under 2 months of age.[5] In Australia, early warning systems are also being developed that might predict arbovirus epidemics.[108] Isolating viraemic individuals to prevent transmission to local mosquitoes might also be appropriate for disease-free countries in which competent mosquito vectors exist.[8]

New interventions

Vaccines

Simple inactivated whole-virus alphaviral vaccines without adjuvant seem entirely capable of efficiently inducing protective neutralizing antibodies. Baxter Bioscience (Deerfield, IL, USA) is currently undertaking phase I human trials of a formalin-inactivated and UV-inactivated RRV vaccine,[34] and formalin-inactivated and UV-inactivated whole virus CHIKV vaccines have been shown to be immunogenic in monkeys.[109] Vaccines against RRV and CHIKV are likely to crossprotect, as anti-RRV sera protects against CHIKV in mice.[33] A live attenuated CHIKV vaccine has also been tested in humans, but was associated with arthralgia.[110] India's Bharat Biotech (Hyderabad, India) is developing a virus-like particle CHIKV vaccine, which has been shown to be immunogenic in monkeys.[111] A range of other approaches for CHIKV vaccine development have also been tested in mice.[16] However, several major hurdles for the commercial development and ultimate deployment of vaccines against arthritogenic alphaviruses do exist. The market size is generally small (Table 1), and disease

is usually self-limiting. In addition, outbreaks are usually sporadic and unpredictable, often with long periods between epidemics (Figure 1). Experience with RRV[18] and CHIKV also illustrates the rapid nature of outbreaks; for instance, in Reunion Island, CHIKV disease case numbers began to escalate in December 2005 and the epidemic on the island was largely over by May 2006.[112]

Drugs and biologic agents

Analgesics and/or NSAIDs remain the main treatment options for the symptoms of arthritogenic alphaviral disease.[1,2,5,44] Steroid treatment combined with NSAIDs has been tested for CHIKV disease, and might improve treatment outcomes,[113] although such combinations increase the risk of gastrointestinal bleeding. Steroid treatment also seemed to improve outcomes for a small cohort of patients with RRV disease; however, the risks of steroid treatment (such as osteonecrosis), should be considered.[114] Chloroquine has been shown to be ineffective against CHIKV disease.[115] Treatment of rheumatoid arthritis with TNF blockers in patients who had CHIKV disease, and who were anti-CHIKV antibody positive, successfully ameliorated the rheumatic symptoms.[88] However, in a young mouse model of acute RRV disease, etanercept treatment given prior to the development of antiviral antibodies resulted in mortality, suggesting that anti-TNF agents are not suitable during the acute phase.[116] A new drug, bindarit, being developed by Angelini (Rome, Italy), inhibits CCL2 production and was effective in young mouse models of RRV and CHIKV disease.[117] Phase II clinical trials of bindarit in patients with lupus nephritis and diabetic nephropathy are underway.[118] The large range of anti-rheumatic drugs being developed for rheumatoid arthritis might ultimately find utility in the off-label treatment of alphaviral arthritides; however, drugs that compromise antiviral immunity should probably be avoided during the acute phase of disease.

Adoptive transfer of neutralizing antibodies (either polyclonal or monoclonal) were able to protect mice against alphaviral viraemia and disease in mouse models.[32,33,119] However, the therapeutic utility of such antibodies might be limited, as patients with a serodiagnosis of an alphaviral disease clearly already have antibodies and administration of antibodies before endogenous antibody production is likely to be impractical. Nevertheless, such antibodies might find utility in preventing mother-to-child infections. Conceivably, neutralizing antibodies could be used prophylactically during an epidemic. However, parenterally administered antibodies (such as tocilizumab and infliximab) have serum half lives of only 8–14 days, so repeated dosing would be envisaged in an extended epidemic.

Mosquito control

Traditional mosquito control measures are costly and labour intensive, with insecticide resistance also emerging.[120] A novel biological control method was reported in 2009 and involves the infection of *A. aegypti* mosquitoes with the intracellular bacterium *Wolbachia*.[120] Such mosquitoes are more resistant to infection with malaria,

dengue virus and CHIKV, presumably by stimulating the mosquito's innate immune system.[120] *Wolbachia*-infected *A. aegypti* have also been successfully introduced into two natural *A. aegypti* populations in Australia, with the hope that such interventions will suppress dengue virus transmission.[121] If widely adopted in dengue affected areas, this strategy could also have an influence on CHIKV transmission as the geographical distributions of these two viruses overlap substantially.

Conclusions

A number of factors—such as climate change, increased development and international travel—combined with changes in vector biology and containment, and viral adaptation, might result in an increase in the prevalence and detection of alphaviral rheumatic diseases. These factors, combined with the explosive and unpredictable nature of epidemics, means a more widespread understanding of these diseases and potential differential diagnoses is needed. Currently, the treatment options for alphaviral arthritides are limited and often inadequate. Hopefully, new drugs being developed for other rheumatic conditions might also be effective for alphaviral arthropathies.

Review criteria

PubMed and Google Scholar were searched for papers using the search terms "chikungunya", "Ross River virus", "Barmah Forest virus", "Sindbis virus", "o'nyong-nyong", "Mayaro virus". All articles identified were peer-reviewed, full-text papers, with the review largely focusing on articles considered relevant to health-care professionals.

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