Chioma M. Okeoma *Editor*

Chikungunya Virus

Advances in Biology, Pathogenesis, and Treatment

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Preface

Chikungunya virus (CHIKV) is a mosquito-transmitted virus associated with increased morbidity and causes a debilitating chronic musculoskeletal disease in infected humans. The mosquito genus *Aedes* is responsible for CHIKV transmission. *Aedes* mosquitoes were previously restricted to the tropical and subtropical countries of the world, but increased globalization has resulted in worldwide spread of CHIKV-transmitting *Aedes* mosquitoes, including the species *Aedes aegypti* and *Aedes albopictus*. Despite precautions being taken to contain the spread of CHIKV, the number of cases of traveler-associated and locally transmitted CHIKV keep increasing in many countries. In some countries, including the United States, CHIKV infection is a nationally notifiable condition reportable to government health protection agencies, such as the US Centers for Disease Control and Prevention. Sadly, there are no vaccines or effective therapies for CHIKV infection, leaving infected people to rely on their immune systems to fight the disease. Since the re-emergence of CHIKV in 1941, exciting discoveries have been made in various aspects of CHIKV research. We have done our best to report the current state of knowledge of CHIKV; however, much work remains to be done to understand fully the fundamentals of CHIKV interaction with the environment, the vector, and the hosts.

Chikungunya Virus is the first book of its kind and consists of 12 chapters written by leading experts in the broad areas of CHIKV epidemiology, CHIKV biology, mechanisms of infection and pathogenesis, host response to infection, and clinical syndromes. These chapters are independent but interrelated. The chapter on clinical syndromes highlights the complexity of CHIKV infection in patients and the current approach to managing CHIKV disease in the absence of definitive therapy. Therefore, *Chikungunya Virus* will be of great interest to a wide audience and is intended for researchers, educators, postdoctoral and medical fellows, graduate and undergraduate students, health practitioners, and other public health officials.

Iowa City, IA, USA — Chioma M. Okeoma

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Clinical Syndrome and Therapy

Sylvie Abel and André Cabié

Introduction

Chikungunya virus (CHIKV), "that which bends up" in the Makonde dialect is an emerging alphavirus transmitted to humans by *Aedes* mosquitoes (*Ae. aegypti*, *Ae. albopictus*). CHIKV emergence in all the tropical zones at the beginning of the twenty-first century allowed experts to discover the polymorphism of its clinical manifestations (Weaver and Lecuit 2015).

The female mosquito becomes infected after feeding on blood of a viremic person (viremia for 5–7 days after onset of clinical signs). The virus replicates in the mosquito for a few days, and then the mosquito can transmit the virus to another person, throughout its life (Fig. 1; Schwartz and Albert 2010). Mother-to-child transmission can occur during childbirth when the mother is viremic (Gérardin et al. 2008). Although direct person-to-person transmission has not been reported, nosocomial transmission most probably occurs following blood transfusion or needlestick injury (Gallian et al. 2014; Parola et al. 2006).

CHIKV infection is most often symptomatic (≈80 % of cases); the symptoms last from a few days to several years depending on the case. In France, experts have defined three clinical stages (Simon et al. 2015): acute stage (from the first day on which the first symptoms appear (D1) up to day 21 (D21)); post-acute stage (from D21 to the end of the third month); and chronic stage (after 3 months; Fig. 1). This time staging takes into account the pathogenic, clinical, and therapeutic variations over time. The post-acute stage and a fortiori the chronic stage are not observed in all patients. The mortality rate of CHIKV is comparable to that of seasonal influenza (≈0.01 to 0.1 %), and is mainly related to the patient's age (increased over 75 years) and/or to chronic comorbidities (Schwartz and Albert 2010).

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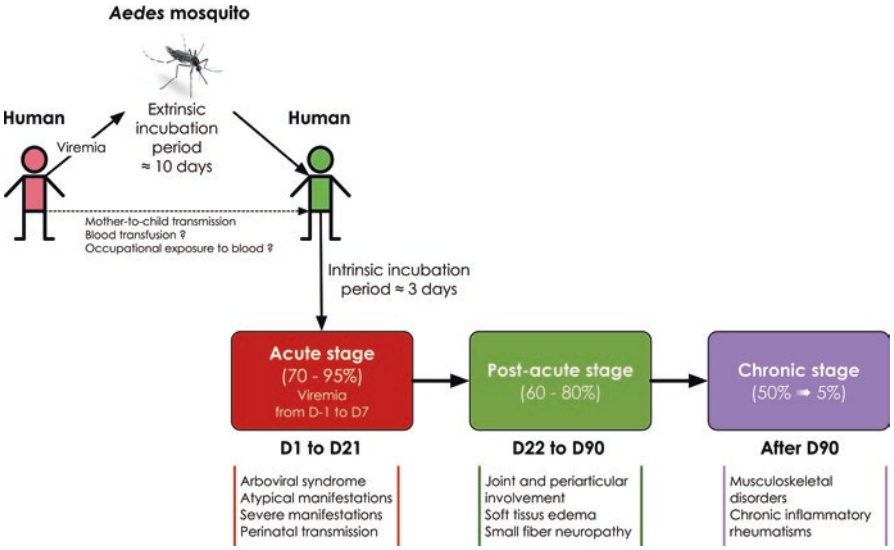

Fig. 1 Transmission cycle and natural history of chikungunya. D1 defined as the day of symptom onset

Acute Stage

Clinical Manifestations and Symptoms

Arboviral Syndrome

In contrast to other arboviral diseases, CHIKV infection is symptomatic in more than 70 % of cases, and ranges from 72 to 96 % (Appassakij et al. 2013). In symptomatic patients the mean incubation period is 3 days, range 1–12 days (Burt et al. 2012). In the common presentation, chikungunya is a rapid-onset febrile disease with no prodromal phase (Thiberville et al. 2013). High-grade fever occurs suddenly, along with inflammatory arthralgia and arthritis with periarticular edema and sometimes severe pain (Fig. 2). Joint pain is mostly polyarticular, bilateral, symmetrical, and occurs mainly in peripheral joints (wrists, ankles, and phalanges) and some large joints (shoulders, elbows, and knees). Sometimes arthralgia appears a few hours before the onset of fever. Other typical symptoms are: myalgia, headache, backache, macular to maculopapular rash, frequently associated with cutaneous pruritus (palms and soles) and edema of the face, lymphadenopathy. The rash appears after fever onset and is typically maculopapular involving the trunk and extremities but can also involve palms, soles, and the face (Fig. 3). External ear redness has been observed, and this may reflect chondritis and is evocative of CHIKV infection (Fig. 4) (Javelle et al. 2014). Fever and cutaneous

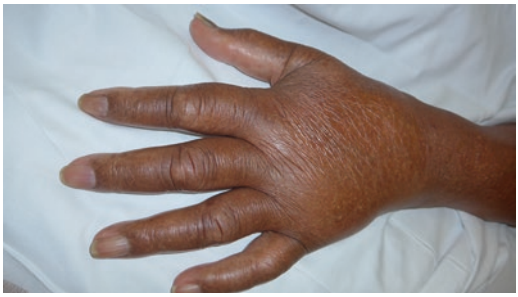

Fig. 2 Acute chikungunya: arthritis and distal edema

Fig. 3 Acute chikungunya: maculopapular rash and palm erythema

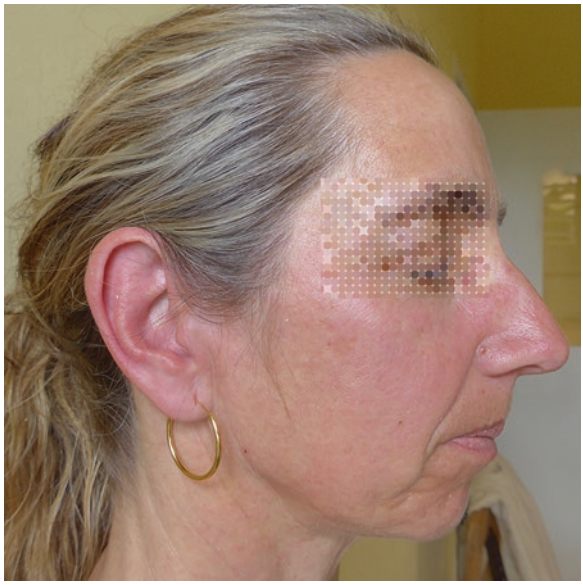

Fig. 4 Acute chikungunya: rash of the face and external ear redness

Table 1 Comparison of clinical and biological manifestations of dengue, chikungunya, and Zika virus infection

	Chikungunya	Dengue	Zika virus infection
Fever	+++	+++	++
Myalgia	+	+++	++
Arthralgia	+++	++	++
Retro-orbital pain	+	+++	+
Skin rash	+++	++	+++
Nonpurulent conjunctivitis	+	0	+++
Arthritis/edema	+++	0	++
Hypotension	+	+++	+
Minor bleeding	±	++	±
Lymphadenopathy	++	++	+
Thrombocytopenia	+	+++	±
Lymphopenia	+++	+++	±

rash last 3–5 days (viremic period), but articular manifestations may last 2–3 weeks in some patients (Thiberville et al. 2013). Asthenia and anorexia are common after regression of fever. The main laboratory finding is lymphopenia, which is closely associated with viremia when the lymphocyte count is less than 1000 per cubic millimeter. Other laboratory abnormalities include moderate thrombocytopenia, increased levels of aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase, and mild increase in C-reactive protein levels (about 50–60 mg/L). The clinical presentation is similar to that of other arboviruses (dengue, Zika virus infection) and may pose diagnostic difficulties (Table 1; Ioos et al. 2014; Simon et al. 2011; Staples et al. 2009).

Atypical Manifestations

Atypical presentations are observed in 0.5 % of cases, mainly in vulnerable patients (young children, elderly patients, chronic alcohol abusers, patients presenting with chronic medical conditions including systemic lupus; Economopoulou et al. 2009; Rajapakse et al. 2010). Atypical presentations include hyperalgic symptoms, gastrointestinal symptoms (diarrhea, vomiting, abdominal pain), and neurological symptoms (confusion, optic neuritis), damage to mucous membranes (oral or genital ulceration, conjunctivitis), and malaise (hypotension, dysautonomia). CHIKV can directly induce severe atypical presentations (rhabdomyolysis, bullous dermatosis, fulminant hepatitis, encephalitis or encephalopathy, Guillain-Barré syndrome, polyneuropathy, myocarditis, multiple organ failure; Betancur et al. 2016; Das et al. 2010; Farnon et al. 2008; Lemant et al. 2008; Simon et al. 2008). More frequently, it causes decompensation of chronic cardiac, respiratory, renal, systemic (lupus), and metabolic (diabetes) diseases, or various complications (dehydration, thromboembolism, loss of autonomy). The risk of drug toxicity by overdose

(self-medication) or drug interaction is high for acetaminophen as well as for other analgesics, anti-inflammatory drugs, long-term treatments, and traditional medicines used for self-medication.

Neonatal Chikungunya

CHIKV infection has not been linked to increased risk of miscarriage, fetal death in utero, or birth defects. However maternal–neonatal transmission can occur in viremic women during childbirth. Fifty percent of neonates are infected when they are born the day before or 5 days after the mother's first symptoms (Ramful et al. 2007). Neonatal chikungunya can either be congenital or neonatal (by mosquito bite after birth). Infected neonates exhibit atypical clinical presentation (fever, difficulty to breast-feed, and pain) occurring after a median incubation period of 4 days (3–7 days; Gérardin et al. 2008; Ramful et al. 2007). The main laboratory findings are thrombocytopenia, lymphopenia, and moderate increased levels of aspartate aminotransferase and alanine aminotransferase in blood. Severe manifestations occur in 50 % of cases, which include encephalopathy with progressive cerebral edema, hemodynamic disorders inducing severe sepsis, hemorrhagic complications due to intravascular coagulation, and cardiomyopathy. The mortality rate of severe presentations is 50 % and the risk of post-encephalopathy psychomotor sequelae is important (Gérardin et al. 2014).

The disease presentation in infants and children is often similar to that of adults. Nevertheless, some atypical or complicated presentations have been reported including hyperalgesia resistant to analgesic treatment, extensive bullous rash, hemodynamic disorders, dehydration, food intolerance, seizures, and meningeal syndrome.

Clinical Assessment

The first step is to discuss CHIKV infection in a patient with an acute onset presentation. A suspected case of acute chikungunya is defined by the combination of fever >38.5 °C and sudden onset of debilitating joint pain without any infectious focus. However, less symptomatic or atypical presentations have been reported. Physicians should be aware of other possible diagnoses in tropical areas: dengue, Zika virus infections, meningitis, malaria, and leptospirosis. The absence of joint involvement, predominance of myalgia, a hypotensive or bleeding trend, abdominal pain, and fever for more than 5 days may justify search for other diagnoses.

The clinical step allows identifying proven clinical signs of severity, atypical and/or complicated presentations (intense pain, organ failure, bleeding, dehydration, decompensation of comorbidity, thrombosis), pregnant women, patients at risk of severe presentations (neonates, children with a history of febrile convulsion, elderly patients, chronic disease treatment, social isolation), and guiding the patient triage (hospital admission or consultation, outpatient management; Fig. 5).

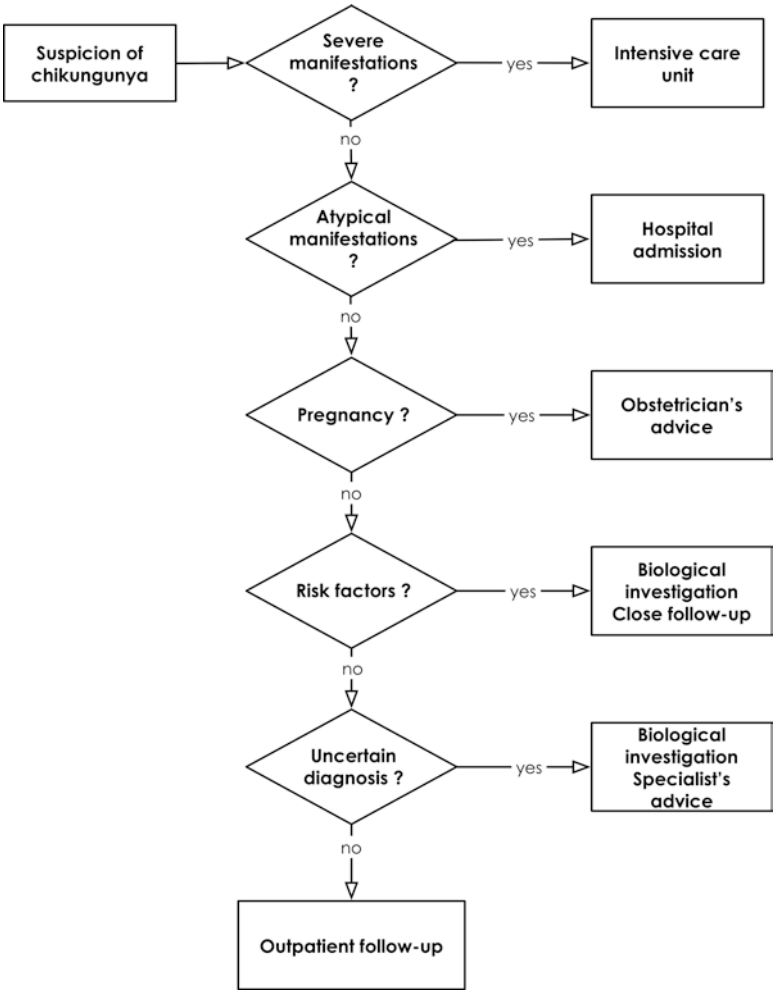

Fig. 5 Acute chikungunya: management of a suspected acute chikungunya

Some pediatric presentations may be atypical or complicated (hyperalgesia despite analgesic treatment, extensive bullous rash, hemodynamic disorders, dehydration, food intolerance, seizures, and meningeal syndrome) and should be referred to the emergency unit (Economopoulou et al. 2009; Ramful et al. 2007).

The suspicion of CHIKV infection in pregnant patients requires screening for signs of severity including fever >39 °C, neurological disorders, bleeding, uterine contractions, inability to eat, poor global health status, and/or alteration of the fetal heart rate pattern (FHRP) after 28 weeks. Any sign of severity requires emergency hospitalization, at best in obstetrics and neonatal resuscitation. A hospital consultation is recommended for any case of suspected chikungunya in the last 3 months of pregnancy. CHIKV infection suspected on the basis of a common presentation should be confirmed by ruling out other causes of potentially severe fever, according to the

clinical presentation, e.g., listeria, pyelonephritis, toxoplasmosis, rubella, malaria, dengue, Zika virus infection, and by recording the FHRP in the case of contractions, in order to define an obstetrical strategy. Furthermore, during epidemics, all patients in labor should be questioned about symptoms in the delivery room to identify any risk of CHIKV transmission for the unborn child.

Social isolation should also be taken into account to organize care, because of the great risk of rapid loss of autonomy among the weakest patients.

The clinical evaluation, in the acute stage, is sufficient to assess the impact of musculoskeletal lesions by identifying the site and the intensity of inflammatory manifestations. There is no indication for X-rays or ultrasound of the joints at this stage, except for another diagnosis.

Diagnosis of Acute CHIKV Infection

In contrast to dengue, routine biological tests are not essential for typical uncomplicated presentations in patients without any chronic disease or risk. The assessment of complete blood count, kidney and liver function, blood glucose, fluid and electrolyte level, and level of inflammation should be decided on a case-by-case basis. Screening for a differential diagnosis may justify implementing additional laboratory tests in the case of atypical clinical presentation, and complicated or abnormal outcome. Main differential diagnoses are dengue or Zika virus infection (possible coinfection), acute HIV infection, malaria, leptospirosis, sepsis, post-streptococcal immune reactions, and other acute viral infections.

The need for virological CHIKV infection confirmation depends on clinical manifestations and on the epidemic context. CHIKV infection confirmation is needed in cases of atypical or severe manifestations, in patients at risk of severe presentations (chronic diseases, extreme ages, pregnancy), in sporadic suspected cases, or in the first weeks of CHIKV emergence in a naïve population, as well as for other public health issues (study of strains, suspicion of a new focus, suspected post-epidemic cases). Conversely, in epidemic regions, diagnostic confirmation in the acute stage is not recommended during epidemics for typical cases without risk of severe presentation.

The confirmed diagnosis relies on virus detection through reverse transcriptase–polymerase chain reaction (RT-PCR) testing during the first week (Fig. 6; Simon et al. 2011). Specific antibodies detection is facilitated by the limited antigenic diversity of CHIKV and extensive cross-reactivity of the antibodies induced by different strains. Serum IgM is detectable from day 5 (and even earlier) to several months after the onset of illness and is also considered as a diagnostic parameter. Seroconversion can also be detected by an increase in IgG by a factor or 4 or more between the acute phase and convalescent phases. The tests are usually performed as follows: RT-PCR between Day 1 and Day 5, RT-PCR and serology between Day 5 and Day 7, serology alone after Day 7; viral culture is not routinely performed. The interpretation of the tests is based on the epidemiological context and clinical information provided by the clinician (time of onset of symptoms is mandatory).

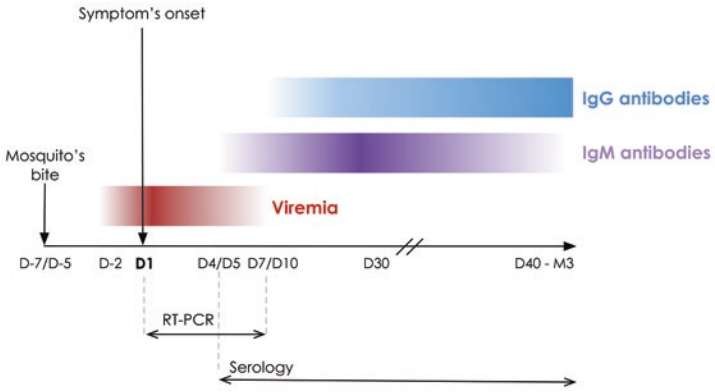

Fig. 6 Biological diagnosis of chikungunya

Therapeutic Management

General Principles

Thus far, no specific therapeutic agent is available for the treatment of infected persons. Treatment is symptomatic and should be adapted to the clinical context and medical status (risk groups). The purpose of treatment is to control fever, pain, dehydration, and to prevent organ failure, iatrogenic risk, and functional impairment. Preventing viral spread to relatives completes the management plan for CHIKV.

The analgesic treatment is based on acetaminophen (stage 1) in first intention. The risk of hepatitis, sometimes fulminant, is increased in the acute stage of chikungunya by the conjunction of viremia and supra-therapeutic doses (maximum dose in healthy adult 60 mg/kg/day and not more to 4 g/day), of interactions (drugs, alcohol, traditional medicines), and comorbidities (liver disease, malnutrition, etc.). The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates is not recommended within the 14 days after onset of the disease because of the risk of bleeding complications related to a possible dengue fever and Reye's syndrome induced by aspirin. The use of stage 2 analgesics (weak opioids) is required if acetaminophen is not effective, either as tramadol alone or in combination with acetaminophen. Morphine administered per os or subcutaneously should be discussed case by case, usually at the hospital and after a strict assessment of the risk–benefit ratio because of possible respiratory, digestive, neurological, and urinary complications.

Prescribing corticosteroids is not recommended, regardless of the route of administration, because it brings no benefit in the medium to long term, and because it promotes a severe rebound of arthritis and tenosynovitis (Fig. 7). This treatment should be discussed by specialists in the case of encephalopathy or neuritis.

It is recommended to prevent dehydration in every case (oral or parenteral fluid intake, stopping diuretics, etc.). The management of CHIKV infection includes screening for new chikungunya-related pathological events (pyrexia, bullous skin lesions, and organ involvement) and increased monitoring of cardiac, hepatic, renal,

Fig. 7 Post-acute chikungunya: severe rebound of arthritis (*black arrow*) and tenosynovitis (*white arrow*) after corticosteroid discontinuation

metabolic, and systemic comorbidities. Iatrogenic risk prevention should also be implemented by monitoring long-term treatments (including antihypertensive drugs), by complying with the prescribed maximum doses and combinations to be avoided, as well as by informing the patient about the dangers of self-medication (interactions, toxicity), including herbal medicines.

Physical measures complete the management, which include sick leave or any occupational adjustment to prevent exhaustion and hypersolicitation of inflammatory joints, removing rings and other tourniquet-acting devices in the case of edema, icing and/or partial immobilization in the case of arthritis (night orthosis), and prevention of decubitus-related complications as appropriate. Prescribing physiotherapy (active–passive mobilization) should be discussed in the case of adverse outcome after 1 week if there is a risk of functional loss, as well as analgesic physiotherapy for pain resistant to analgesics. Social care may be required (housekeeper, frequent visits of a nurse or close relatives) for fragile patients at risk of aggravating or losing their autonomy.

Severe Manifestations

Severe manifestations must be managed in a hospital with an appropriate intensive care unit. Using immunoglobulins is indicated in cases of chikungunya-related Guillain-Barré syndrome.

Pregnant Women

The recommended symptomatic treatment is acetaminophen, with a maximum dose of 1 g×4/day. All NSAIDs (including aspirin and topical presentations) are contraindicated after 24 weeks of amenorrhea (risk of fetal renal failure and closure of the ductus arteriosus, eventually leading to fetal death in utero). The mother and relatives should be informed about the risks of self-medication and aromatherapy (hepatic enzyme induction).

The advice of an obstetrics specialist is required for the diagnosis when a woman is infected at the end of her pregnancy in order to assess the impact on the unborn child as well as for a possible obstetrical decision. Cesarean section has no proven protection against CHIKV transmission to the child (Ramful et al. 2007). Cesarean section is indicated in case of FHRP alteration, as with any threatening fetal distress. Effective tocolysis can delay delivery beyond the viremic phase, and decrease the risk of neonatal transmission. The ongoing CHIKIVIG-01 clinical trial in the French Caribbean territories and in French Guyana aims to evaluate the safety and effectiveness of intravenous hyperimmune anti-CHIKV immunoglobulins to prevent neonatal CHIKV infection in neonates of viremic mothers (No. ClinicalTrial.gov NCT02230163).

Neonates and Children

Sustained 7-day monitoring of neonates is implemented when the mother delivers and is suspected to be infected. If the mother is confirmed to be infected, and the neonate is born with an undetectable viral load, he or she must be monitored for at least 5 days in the maternity unit. Clinical surveillance includes body temperature, quality of breast-feeding, pain, skin condition (rash, edema of the extremities), and hydration level. The typical pediatric presentations are treated symptomatically as for adults.

Prevention

Applying individual antivectorial protection measures (mosquito nets, repellents adapted to the patient, air conditioning) is recommended for suspected cases of chikungunya in the acute stage in areas with *Aedes* circulation. This practice in addition to actions implemented to eradicate mosquito breeding sites will help to break the chain of transmission. CHIKV infection may be acquired by accidental exposure to the blood of a viremic patient. Standard precautions are recommended for prevention.

Post-Acute Stage (From D22 to D90)

The post-acute stage of CHIKV infection is mainly characterized by persistent joint pain in about 60 % of patients. Higher incidence is observed after 40 years of age and in female patients (Simon et al. 2011). The other parameters associated with

persistent joint symptoms are mainly: severity of the acute stage (high-grade fever, arthritis ≥6 joints, depression, high level of viremia), lack of rest in the acute stage, and previous musculoskeletal comorbidities.

Clinical Symptoms

The main characteristic of the post-acute stage is the persistence or the occurrence of multiple and polymorphic manifestations dominated by inflammatory manifestations: inflammatory arthralgia, arthritis (synovitis with or without effusion), tenosynovitis, bursitis, tendinitis with risk for tendon rupture, enthesitis, bursitis capsulitis, or periostitis. The trend is a continuous mode or inflammatory attacks frequently promoted by cold and associated with decompensation of pre-existing degenerative or traumatic arthropathy, and local events such as edema of extremities, tunnel syndromes, joint stiffness, or neuropathic pain (Fig. 8). The absence of anti-inflammatory treatment, untimely excessive physical stress, and even a complete and prolonged joint rest, can have a deleterious effect on clinical recovery. This post-acute stage may also include severe asthenia and neuropsychological disorders, particularly if pain is not controlled.

Clinical Assessment

An accurate semiotic analysis allows defining the diagnostic workup that determines the optimization of treatment. It should particularly discriminate between pain and functional impairment due to a persistent inflammatory process, and

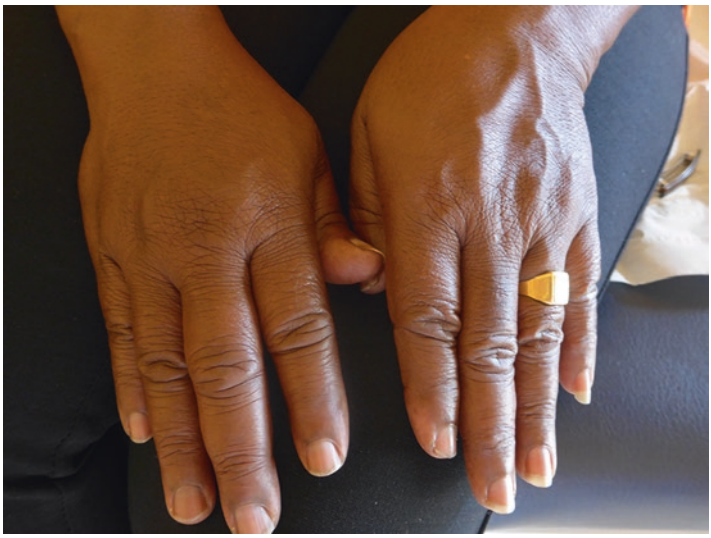

Fig. 8 Post-acute chikungunya: edema of extremities

symptoms related to decompensation of joints already altered by osteoarthritis or other processes. Indeed, treatment choices and effectiveness depend on the accurate assessment of lesions.

Biological Tests and Imaging

At this stage, it is essential to confirm serologically the diagnosis of CHIKV infection. Other laboratory tests are used to determine the level of inflammation and, as appropriate, to carry out a pretherapeutic assessment and screen for sources of comorbidities, such as rheumatic disease.

Imaging is not systematically performed at this stage, unless in case of diagnostic doubt or a severe disease lasting more than 6 weeks, as it may modify therapeutic choices (suspected pre-existing arthritis, tendon rupture, etc.). Plain radiographs and ultrasound of symptomatic joints should be used when clinical examination is not definitive enough. Consultation with rheumatologists is required in the case of inflammatory disease with painful and debilitating arthritis persisting beyond 6 weeks or if bone erosion is observed.

Therapeutic Management

The objective of treatment is to relieve the patient of pain and inflammation and to limit the consequences of the inflammatory process: joint stiffness, loss of muscle tone, and loss of physical fitness. The treatment is implemented by the general practitioner (GP) who takes into account the patient's clinical presentation, comorbidities, and socioeconomic status.

The therapeutic approach is primarily based on analgesics (stage 1 and 2, antineuropathic drugs) and NSAIDs. Analgesia should be optimized by combining a stage 1 or 2 analgesic agent, depending on the pain, with an agent targeting the painful neuropathic component (e.g., nefopam, pregabalin, gabapentin) if necessary, and active physical therapy on the persistently painful areas. Stage 3 agents may be used when stage 2 analgesics combined with an appropriate anti-inflammatory treatment have failed. Consulting a pain specialist is advised. No NSAID class has demonstrated superiority of effectiveness on post-acute chikungunya symptoms. This treatment is prescribed at full dose unless contraindicated, in taking care to cover the night by taking an evening and/or extended-release formulation. The effectiveness of NSAIDs should be reassessed (dose, schedule) during the first week; an inadequate response on the 10th day imposes a switch to another class of NSAIDs. It is important to continue NSAID treatment for several weeks; if well tolerated, gradually wean the patient.

Systemic corticosteroids should only be used for highly inflammatory polyarticular presentations, especially when associated with tenosynovitis, active synovitis, or in the case of resistance or contraindication to NSAIDs. The dose of 10 mg/day of prednisone for 5 days with de-escalation within 10 days is usually sufficient for refractory to moderate NSAIDs. A 0.5 mg/kg/day dose of prednisone for 5 days, with gradual weaning for 10 days is used for the most severe presentations.