# Rheumatic Manifestations in Patients with Chikungunya Infection

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**Chikungunya virus (CHIKV) infection is a common cause of febrile arthritis. The most common manifestations of acute infection are fever, symmetrical polyarthralgias or polyarthritis, myalgias, and maculopapular rash. Up to 80% of patients may develop musculoskeletal manifestations that persist longer than 3 months, causing impairment in their quality of life. The most common chronic manifestations are persistent or relapsing-remitting polyarthralgias, polyarthritis, and myalgias. Fingers, wrists, knees, ankles, and toes are the most frequently involved, but proximal joints and axial involvement can occur in the chronic stage. Chronic manifestations of CHIKV infection may resemble those of some autoimmune connective tissue diseases. Furthermore, CHIKV infection can cause cryoglobulinemia and may induce rheumatoid arthritis and seronegative spondyloarthropathies in genetically susceptible individuals. The Centers for Disease Control and Prevention recommend acetaminophen and non steroidal anti-inflammatory drugs for the acute rheumatic manifestations of CHIKV infection. However, some studies suggest that low-dose corticosteroids for about 1-2 months (depending on clinical course) are beneficial in relieving acute rheumatic symptoms. Conversely, hydroxychloroquine in combination with corticosteroids or other disease modifying anti-rheumatic drugs (DMARDs) has been successful in treating chronic rheumatic manifestations. Methotrexate and sulfasalazine (alone or in combination) have also been effective for chronic CHIKV arthritis. Patients with CHIKV infection should be closely monitored to identify those with chronic arthritis who would benefit from a rheumatologic evaluation and early treatment with DMARDs. [*P R Health Sci J 2015;34:71-77*]**

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Chikungunya virus (CHIKV) is a single-stranded RNA alphavirus transmitted to humans by the Aedes mosquitoes (1). It causes an acute febrile illness with polyarthralgias which are often severe and debilitating (2-5). After its discovery in 1952 in Tanzania, few sporadic outbreaks were described in Africa and Asia (2). In 2005, the virus underwent a mutation that enabled transmission through Aedes albopticus, a widely distributed mosquito (2, 4, 5). Since then, numerous CHIKV epidemics have been reported in Africa, South East Asia, the Indian Ocean islands, and Europe. More recently, in 2013, CHIKV transmission was described for the first time in the Caribbean. Since then, CHIKV has spread through the Antilles and is currently causing an epidemic in the Caribbean islands of Saint Martin, US Virgin Islands, Puerto Rico, and Dominican Republic, among others (6, 7).

## Clinical features

### Acute manifestations

Acute CHIKV infection is characterized by high fever and severe polyarthralgias, after an incubation period that lasts from 2 to 7 days (2, 3, 8-11). A retrospective cohort study in La Réunion reported that 96% of patients with acute CHIKV infection presented with arthralgias involving more than one joint, 73% had symmetrical joint involvement, and 32% had associated joint swelling (3). Distal joints such as fingers, wrists, knees, ankles and, toes are the most frequently involved (3, 10-13). Although some reports have described involvement of temporomandibular joints, elbows, shoulders, neck, lower back and hips, this appears to occur less frequently (11, 13, 14). Muscle manifestations are also common in CHIKV infection. Myalgias have been reported in up to 81% of patients (8). Although uncommon, myositis with elevation of creatinine phosphokinase has been described in one

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series and animal experimental models (15, 16). Additional reported symptoms include fatigue/general malaise (43-45%), gastrointestinal symptoms (nausea, vomiting, diarrhea; 47%), and rash (17-40%) (2, 3, 8, 9, 11). The most common skin lesion is a maculopapular eruption involving the face, trunk, and limbs occurring during the first week of illness. Pruritus is reported in 4% to 20% of patients and bullous skin lesions in 3% of patients with skin manifestations (2, 3, 11, 17).

### Chronic musculoskeletal manifestations

Patients with CHIKV infection may continue to experience musculoskeletal symptoms that persist for a long period of time causing severe impairment in their quality of life. Studies report that 40 to 80% of patients with CHIKV infection develop chronic rheumatic symptoms (8-10, 12, 18-21). A prospective cohort study of 203 CHIKV infected patients in India found that 46% experienced persistent joint pain 10 months after the acute infection (10). Similarly, Schilte et al. prospectively studied 76 patients with acute CHIKV infection in La Réunion and reported that 69% had persistent arthralgias after 36 months of follow-up (18). Of these patients, 45% reported continuous arthralgias and 24% had partial recovery with relapsing symptoms. Most of these patients (90%) reported symmetrical joint involvement, 63% had associated local joint swelling and 39% also had chronic myalgias (18).

The most frequently affected joints during the chronic stages are the knees, ankles, and small joints of the upper and lower extremities (10, 12, 18, 19). However, some authors have noted greater involvement of proximal (elbows, shoulders, and hips) and axial joints (neck and sacroiliac joints) during the chronic stage of CHIKV infection compared to the predominant distal joint involvement in the acute stage (10, 14). Although arthralgia is the most common musculoskeletal manifestation, many authors have described the presence of inflammatory polyarthritis, tenosynovitis, enthesopathies, and bone erosions (10, 11, 14). Morning stiffness, myalgias and edema of upper and lower extremities have also been described several months after the acute infection (12, 18). Table 1 summarizes the most common musculoskeletal manifestations of CHIKV infection.

### Other rheumatic disorders

Similar to other viral illnesses such as hepatitis C virus, CHIKV infection has been associated with a high prevalence of mixed cryoglobulinemia (22). A study by Oliver et al. found that 94% of travelers returning from the Indian Ocean islands with confirmed CHIKV infection had cryoglobulinemia at least once during a 14-month follow-up (22). Fifty-five percent of patients tested after one year of disease onset had persistent cryoglobulinemia. Authors noted that the presence of cryoglobulins coincided with persistent arthralgias. Interestingly, in this study, those with mixed cryoglobulinemia did not present with palpable purpura or other clinical manifestations of small vessel vasculitis.

**Table 1**. Musculoskeletal manifestations of chikungunya infection.

| Features | Comments |
|---|---|
| *Acute manifestations* | |
| Polyarthralgias/arthritis | Fingers, wrists, knees, ankles and toes are the most frequently involved. Symmetrical pattern is common (3, 10-13). |
| Myalgias | Very common (8) |
| Myositis | Uncommon, rhabdomyolysis is rare (15, 16). |
| Cryoglobulinemia | Common but manifestations of vasculitis are rare (22). |
| *Chronic manifestations* | |
| Polyarthralgias/arthritis | Fingers, wrists, knees, ankles and toes are the most frequently involved. Occasionally, elbows, shoulders, neck, sacroiliacs and hips are affected (10, 12, 14, 18, 19). Symptoms may be persistent or remitting-relapsing (17). |
| Myalgias | Very common (12, 18) |
| Tenosynovitis/enthesopathies | Rare (10, 11, 14) |
| Bone erosions | Rare (10, 14, 25) |
| Cryoglobulinemia | Common but manifestations of vasculitis are rare (22). |

### Nonrheumatic manifestations

While fever and arthralgia/arthritis are the most common symptoms of CHIKV infection, other clinical features have been reported. In a cohort study from La Réunion of 610 hospitalized patients with extraarticular CHIKV manifestations, 11% presented with encephalitis, 2% with meningoencephalitis, 2% with seizures, 1% with Guillain-Barré syndrome, 7% with hepatitis or hepatic insufficiency, and 6% with myocarditis (2). In addition, ophthalmologic involvement manifested as optic neuritis, retinitis, episcleritis, and iridocyclitis has been documented in few case series (23, 24). Other nonrheumatic manifestations that have a significant impact in the quality of life such as sleeping disorders (56%), depression (50%), memory impairment (44%), and cognitive disorders (39%) have been reported several months after infection (18).

### Laboratory abnormalities

Laboratory findings during acute CHIKV infection are non-specific. In a retrospective cohort study of 157 patients with CHIKV infection, lymphopenia (<1000 $10^9$/L) was the most common laboratory abnormality; this was observed in 79% of patients (3). Severe lymphopenia (<500 $10^9$/L) was seen in 39%. Forty-four percent of patients had thrombocytopenia (<150 $10^9$/L), 55% had hypocalcemia, and 10% had a two-fold increase in transaminases. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are frequently elevated during the acute infection and may remain elevated in patients with chronic musculoskeletal symptoms (8, 10, 14, 25).

### Diagnosis

A definitive diagnosis of CHIKV infection is made by detection of viral RNA in serum by reverse transcription-polymerase chain reaction (RT-PCR) or the detection of serum IgM and/or IgG antibodies by enzyme-linked immunosorbent assay (26, 27). CHIKV RNA may be detected in a patient's serum during the first 7 days of infection while serum antibodies usually appear by the end of the first week (26, 27). Panning et al. prospectively studied 63 patients with confirmed CHIKV infection and found 100% of patients evaluated during the first 4 days of illness had a positive RT-PCR and all had IgM antibodies after the first 5 days of illness (26). IgM antibodies may persist up to 36 months post infection (18, 28).

### Differential diagnosis

The differential diagnosis of CHIKV infection is dependent on the geographical area and the patient's travel and exposure history. Dengue virus, transmitted by the Aedes mosquitoes and thus prevalent in similar geographical areas as CHIKV, should be considered. While dengue shares several clinical manifestations with CHIKV, other features including retroorbital pain, petechiae, hemorrhage and severe thrombocytopenia are more common in dengue (27). Parvovirus B19, transmitted by respiratory aerosol secretions, also causes fever with symmetrical polyarthritis in adults; however outbreaks tend to occur in a seasonal pattern (late winter) and patients have a history of exposure to an infected individual (usually infants and children) (29). Other causes of acute febrile illness such as leptospirosis, adenovirus, enterovirus, measles, and rubella should also be considered. Moreover, patients with persistent arthralgias, and particularly those with arthritis, should be followed closely and examined for other serious causes of chronic arthritis including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), spondyloarthritis, and vasculitis, among others.

### Chikungunya and autoimmune connective tissue diseases

The clinical manifestations in acute and chronic CHIKV infection, such as arthralgias, arthritis, myalgias, and rash, may resemble those of some autoimmune connective tissue diseases such as RA, seronegative arthritis and SLE (10, 20). In fact, a longitudinal cohort of CHIKV-infected patients in India, reported that 36% of patients with persistent arthralgias met the American College of Rheumatology (ACR) classification for RA 10 months post-infection (10, 30). Moreover, several authors have reported the development of RA after CHIKV infection (10, 14, 25, 31). Rheumatoid factor (RF) and anti-citrullinated protein (CCP) antibodies were documented in many of these patients as well as radiographic findings common to RA such as joint space narrowing, effusions, and bone erosions (10, 14, 25, 28, 31). However, other authors have not noted any structural joint damage in patients with post-CHIKV RA (14, 31). Interestingly, Boquillard et al. described that 14 of 21 (66%) patients with post-CHIKV RA were HLA DRB1*01 or DRB1*04 positive, alleles known to be associated with RA (25). In addition, seronegative spondyloarthropathies (psoriatic arthritis and ankylosing spondylitis), have also been reported after CHIKV infection, particularly in those with positive HLA B27 (14, 28, 31). These findings suggest CHIKV infection may induce autoimmunity in susceptible individuals, a concept that has been well established for autoimmune rheumatic conditions (32, 33).

The clinical course of CHIKV infection in patients with pre-existing autoimmune rheumatic diseases has not been thoroughly examined. Chopra et al. described 2 patients with psoriatic arthritis and one with reactive arthritis, previously in clinical remission, who experienced a relapse of their disease after CHIKV infection (14). Reactivation and worsening of psoriatic skin disease has also been reported (17).

### Pathophysiology of articular involvement

The exact pathophysiology for CHIKV-induced joint disease remains uncertain. Most data are based on several animal (mouse and macaque) model studies and few human studies (34-40). It is not entirely clear whether joint damage is caused by direct viral effect or by viral activation of the immune system and its associated inflammatory reactions. Viral RNA was found in muscles, lymph nodes, spleen, liver, and joints of CHIKV inoculated mice and macaques (34-36). In addition, viral RNA has been found in synovial biopsies of patients with acute and chronic CHIKV infection along with cellular infiltrates consisting of activated macrophages, natural killer cells and T cells (35). Several studies have shown that macrophages seem to have a major role in joint injury (34, 36, 37). Experimental mouse models with depleted macrophages do not develop joint disease when inoculated with CHIKV (34, 36, 37). In addition, the most commonly described cytokines in animal experimental models and few human studies of CHIKV infection are IL-1β, IL-6, IL-8, IL-12, INF-α, and MCP-1; all of which are associated with macrophage activity (34, 35, 37-40).

The mechanism behind the development of persistent CHIKV arthralgia/arthritis has not been clearly established. Scant data suggest viral persistence in joint tissues and thus perpetuation of chronic inflammation (35, 40). A rapid humoral response seems to be important in eliminating the virus and protecting from chronic disease. Kam et al. noted a higher viremia was associated with more severe illness, early CHIKV IgG production, and complete clinical recovery in a cohort of 30 CHIKV-infected patients (41). Conversely, some authors have noted a higher viral load during the acute phase creates stronger cellular and molecular innate immune activity, and higher cytokine levels; thus, causing greater joint damage (35, 38). High levels of IL-1β, IL-6, IL-12, and IL-17 have been described in patients with persistent CHIKV symptoms (8, 35, 38). Most of these cytokines are produced by activated macrophages in response to antigenic stimuli, further denoting the pathological role of macrophages in CHIKV infection.

## Risk factors for chronic musculoskeletal involvement

Risk factors for developing chronic rheumatic symptoms after CHIKV infection have not been clearly established and reports have yielded inconsistent data. Few small prospective studies have depicted associations between development of chronic symptoms and female gender, older age, comorbid conditions and severity of symptoms at onset of infection (9, 12, 14, 18, 20, 42). Arterial hypertension, diabetes mellitus, osteoarthritis and dyslipidemia have been associated with the development of chronic arthralgias in several longitudinal studies (12, 18, 42). Gérardin et al. noted that patients with two or more comorbid conditions were more likely to experience long-lasting musculoskeletal symptoms after CHIKV infection (42). These findings are not surprising as these comorbid conditions are linked to increased morbidity in other infectious disorders. In addition, severe rheumatic involvement and joint pain during the acute phase of CHIKV infection have been associated with chronic rheumatic symptoms (42). However, other authors have not found associations between indicators of disease severity such as number of joints affected, viral load, hospitalizations and the development of persistent symptoms (9, 18, 21).

## Treatment

### Anti-inflammatory drugs

There are no established evidence–based treatment guidelines for acute CHIKV infection, causing uncertainty among clinicians and heterogeneity of treatment in the community. The Centers for Disease Control and Prevention (CDC) recommends supportive treatment that includes rest, adequate hydration with fluids, and acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) for fever and joint pains (7).

Data regarding the role of corticosteroids are controversial. In a small randomized control trial, Padmakumar et al. found that patients treated with aceclofenac (a diclofenac analog [200 mg/day]), hydroxychloroquine (400 mg/day) and prednisone (10 mg/day) and those treated with aceclofenac and prednisone (same doses) during the first 6 weeks of CHIKV infection had a greater reduction in the perception of pain (using a visual analog scale) and improvement in activities of daily living scores compared to patients receiving aceclofenac and hydroxychloroquine or aceclofenac alone (43). Symptoms returned in all groups after discontinuation of therapy 6 weeks later. Simon et al. observed dramatic improvement of acute and chronic rheumatic symptoms in CHIKV infected travelers treated with corticosteroids (44). However, corticosteroid doses were not described in detail. These data suggest that a low-dose corticosteroid treatment can be beneficial in relieving the acute rheumatic symptoms of CHIKV infection and in improving quality of life. However, a prolonged course (1-2 months) with slow tapering may be required to prevent rebound symptoms (22, 43, 44). Sissoko et al. noted that 76% of patients who received treatment with corticosteroids reported being satisfied with their therapy compared to 35% of patients who received NSAIDs and acetaminophen alone (12).

Corticosteroids have also been used successfully to treat other uncommon but serious complications of CHIKV infection such as optic neuritis and encephalitis (24, 45). Rose et al. reported that 9 out of 10 patients who developed acute optic neuritis during CHIKV infection experienced an improvement in visual acuity after treatment with pulse doses of intravenous methylprednisolone followed by oral prednisone tapper over one month (24). In addition, Gauri et al. reported a patient with demyelinating encephalitis presenting with vertigo, dysarthria, and ataxia who improved with intravenous steroid therapy (45).

### Disease modifying anti-rheumatic drugs

Data are also limited regarding the appropriate treatment for CHIKV-induced chronic arthritis. Because of the pathophysiological and clinical resemblance to inflammatory arthritides, several disease modifying anti-rheumatic drugs (DMARDs) have been studied. A small randomized-control trial comparing chloroquine to meloxicam found no statistical difference in symptom improvement between treatment groups (46). Evidence with hydroxychloroquine treatment in combination with NSAIDs has not been favorable (43). However, when used in combination with other DMARDs (methotrexate [MTX] and sulfasalazine) or steroids, the efficacy seems to increase (43, 47). Many authors have reported chronic CHIKV arthritis effectively treated with methotrexate, alone or in combination with sulfasalazine (25, 28, 47, 48). Pandya et al. reported that 49% of patients who were treated with MTX (15-20 mg/weekly) and hydroxychloroquine (400 mg/day) achieved ACR 20 clinical response, 20% achieved ACR 50 response, and 5% ACR 70 response after 16 weeks of therapy (47). Ganu et al. also noted that treatment with MTX and sulfasalazine was beneficial in 71% of patients with persistent arthritis 3 months post CHIKV infection and 13% of patients responded to MTX alone (48). Tumor necrosis factor blockers were successful in 6 patients with RA diagnosed post-CHIKV infection who failed MTX therapy (25). However, caution should be exerted if considering biologic agents as etanercept was shown to aggravate articular disease in a mouse model inoculated with Ross River virus (an alphavirus similar to CHIKV) (49).

It is not clear when it is appropriate to initiate DMARD therapy for CHIKV-induced arthritis. However, immunosuppressive agents should be reserved for the chronic stages of CHIKV infection. Mouse models show early treatment with MTX may cause a more severe illness (49, 50). Ribéra et al. found that patients with rheumatic symptoms persisting longer than 3 weeks were at increased risk for developing inflammatory polyarthritis and recommended rheumatologic evaluation at no longer than 3 months of symptoms persistence (51). Table 2 depicts treatment options for acute and chronic arthritis induced by CHIKV.

**Table 2**. Treatment of acute and chronic arthritis induced by chikungunya infection.

| Drug | Comments |
|---|---|
| *Acute treatment* | |
| Acetaminophen<br>NSAIDs | For relief of fever and pain per CDC recommendations (7) |
| Corticosteroids | Combination therapy with prednisone 10 mg/day (or equivalent) and NSAIDs with/without hydroxychloroquine was superior to other combinations without prednisone (43). |
| *Chronic treatment (> 3 months)* | |
| NSAIDs<br>Chloroquine | No differences between meloxicam and chloroquine treatment groups (46) |
| Hydroxychloroquine | Effective in combination with corticosteroids or other DMARDs (methotrexate/sulfasalazine) (43, 47). No studies have been conducted with hydroxychloroquine alone. |
| Methotrexate | Methotrexate (15-20 mg/weekly) in combination with hydroxychloroquine (400 mg/daily) was effective after 16 weeks of therapy (47). Not recommended during early CHIKV infection (49, 50). |
| Sulfasalazine | Beneficial in combination with methotrexate in 71% of patients with persistent CHIKV arthritis > 3 months (48). Monotherapy has been successful in few case reports (25). |
| TNF-α blockers | Successful in 6 patients (etanercept = 4, adalimubab = 2) who failed methotrexate therapy in one case series (25). |

NSAIDs: nonsteroidal anti-inflammatory drugs; CDC: Centers for Disease Control and Prevention; DMARDs: disease modifying anti-rheumatic drugs; TNF: tumor necrosis factor

## Conclusion

In summary, CHIKV infection can lead to chronic musculoskeletal manifestations. The most frequent are symmetrical polyarthralgias and polyarthritis. Myalgias may also persist several months following acute infection. The chronic manifestations of CHIKV may resemble those of an autoimmune inflammatory arthritis with or without associated joint damage. The CDC currently recommends treatment of acute CHIKV symptoms with acetaminophen and NSAIDs (7). However, some studies suggest that an extended course (1-2 months) of low-dose corticosteroids, started at the onset of disease, is successful in relieving the acute rheumatic symptoms of CHIKV and thus improving the patient's quality of life (22, 43, 44). Nonetheless, prospective longitudinal studies are needed to ascertain the duration of therapy and their role in preventing CHIKV-induced chronic arthritis. In addition, close follow-up of these patients is essential to evaluate chronic CHIKV manifestations and to screen those who would benefit from an evaluation by a rheumatologist and further treatment with DMARDs. Monitoring inflammatory markers (ESR, CRP) and examining autoantibodies (RF, anti-CCP, and antinuclear antibodies) should be considered in patients with chronic arthritis. Also, imaging studies such as plain radiographs, sonograms, or magnetic resonance should be performed when deemed appropriate to evaluate for erosive or inflammatory changes.

## Resumen

La infección por el virus del chikungunya (CHIKV) es una causa común de artritis febril. Las manifestaciones más comunes de la infección aguda son fiebre, poliartralgias o poliartritis simétrica, mialgias y erupción maculopapular en la piel. Hasta un 80% de los pacientes desarrollan manifestaciones musculoesqueléticas que persisten por más de 3 meses, afectando la calidad de vida. Las manifestaciones crónicas más comunes son poliartralgias, poliartritis y mialgias las cuales pueden ser persistentes o fluctuantes. Los dedos de las manos y los pies, las muñecas, las rodillas y los tobillos son los más afectados pero envolvimiento de las articulaciones proximales y axiales puede ocurrir en la etapa crónica. Las manifestaciones crónicas de CHIKV pueden parecerse a algunas enfermedades reumáticas de tejido conectivo. En adición, CHIKV puede causar crioglobulinemia y podría inducir artritis reumatoide y espondiloartropatía seronegativa en pacientes con predisposición genética. Los Centros para el Control y Prevención de Enfermedades recomiendan acetaminofén y antiinflamatorios no esteroideos para tratar las manifestaciones reumáticas agudas del CHIKV. Sin embargo, algunos estudios demuestran que el tratamiento por 1-2 meses con dosis bajas de corticosteroides es efectivo para aliviar los síntomas reumáticos agudos. Por otro lado, la hidroxicloroquina combinada con corticosteroides o con otros antirreumáticos modificadores de la enfermedad (DMARDs, por sus siglas en inglés) ha sido efectiva para el tratamiento de las manifestaciones reumáticas crónicas de CHIKV. Metotrexato y sulfasalazina (por si solos o en combinación) también han sido beneficiosos para tratar la artritis crónica. Los pacientes afectados con CHIKV deben ser vigilados continuamente para identificar aquellos con artritis crónica que podrían beneficiarse de una evaluación reumatológica y de tratamiento temprano con DMARDs.

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