

# CLINICAL PROFILE OF CHIKUNGUNYA SEQUELAE, ASSOCIATION WITH OBESITY AND REST DURING ACUTE PHASE

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**Abstract.** The scarcity of literature regarding chikungunya infection sequelae makes it an unexplored area of medicine. We analyzed 1,111 patients with confirmed chikungunya sequelae and found a female predominance in those with sequelae which increased with age up to 40-50 years old, then decreased with further increase in age. In males age >60 years old was the predominant age group affected. The symptoms were mainly symmetrical polyarthralgia of the proximal and distal interphalangeal joints. Dermatological manifestations were mainly hyper pigmented patches, generalized pruritus, and a maculopapular rash. Insomnia, fatigability and headache may indicate neurological involvement. Obesity gave an odds ratio of 2.07 for risk of arthritis. There was no significant benefit from rest during the acute phase ( $p < 0.001$ ) of chikungunya in preventing chronicity of sequelae. Obesity as an independent risk factor for chronicity of chikungunya infection sequelae is a new finding.

**Key words:** chikungunya sequelae, obesity, rest, acute phase

## INTRODUCTION

Chikungunya (CHIKV) infection had slipped into oblivion until recently. The disease has made a strong resurgence in the islands of Indian Ocean and in India (Yergolkar *et al*, 2006; Anonymous, 2008). This reemergence is postulated to be due to an alteration in the genetic sequence which allows it to multiply more easily in mosquito cells and utilize the Asian tiger mosquito as a vector in addition to *Aedes aegypti* mosquitoes (Powers and Logue, 2007; Arankalle *et al*, 2007).

CHIKV is an acute febrile illness caused by an Alphavirus which is transmitted by infective *Aedes* mosquitoes. The vi-

rus was first isolated in 1953 in Tanzania (Lumsden, 1955; Robinson, 1955). CHIKV virus is a member of the genus *Alphavirus* and the family *Togaviridae*. The disease typically consists of an acute illness characterized by fever, rash, and incapacitating arthralgia. CHIKV is a tropical disease; it is geographically restricted and outbreaks are relatively uncommon. The name is derived from the Makonde word meaning "that which bends up" in reference to the stooped posture developed as a result of the arthritic symptoms of the disease (Lumsden, 1955; Robinson, 1955).

Curiously, it was the sheer magnitude of the 2005-2007 CHIKV outbreak that brought this virus to the awareness of both the scientific community and the general public. We had a lot of clinical experience as well as a significant financial impact due to CHIKV outbreak affecting the economy

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and daily wage earning population, local businesses affected by absenteeism due to incapacitating symptoms, and individual families whose members were unable to work for weeks or months due to the post-infection sequelae of the “crippling” disease.

A major problem regarding CHIKV persons is the possibility of developing various types of sequelae which may persist for years after acute infection. The manifestations include musculo skeletal, dermatological and psychological problems. One study (Abraham and Sridharan, 2007) found that most patients recover from arthralgia within 2-3 weeks but a few may persist for more than 3-4 months. More severe and unusual forms of arthralgia have been observed following a recent epidemic (Brighton and Simson, 1984).

The primary objective of this study was to determine the common clinical sequelae of CHIKV infection, so as to help differentiate them from systemic arthritis and other arthritic conditions. We also assessed the association between obesity and chronic CHIKV sequelae. The association between rest during the acute phase of CHIKV infection and chronic sequelae was also assessed. Our goal was to provide data to the international medical community to make the medical care of CHIKV patients easier.

#### MATERIALS AND METHODS

The study was begun in November 2007 at Kerala State Institute of Virology and Infectious Diseases (KSIVID) as a part of FEEPOKS (Fever Epidemic Evaluation Project of Kerala State) 2007 and our study concluded in June 2008. We informed the community through medias to attend this special CHIKV clinic at KSVID Alappuzha. The public were informed through the me-

dia and through posters there was a CHIKV clinic evaluating patients suffering from CHIKV infection and its sequelae, specifically for those infected during the 2006-2007 epidemic or who developed fever and arthralgia with or without joint swelling or who had other manifestations consistent with CHIKV infection. The ethics committee of TD Medical College Alappuzha approved the study protocol and all subjects gave written informed consent before participating in the study.

We were equipped with medical personnel specializing internal medicine, dermatology, rehabilitation medicine, community medicine as well as physiotherapists, medico-social workers and pharmacists. Patients reported to the CHIKV clinic were evaluated using a fixed performa containing basic details of the patient, major symptoms and their details, past medical history, general examination and systemic examination of relevant systems involved. Subjects were mainly from Kottayam, Alappuzha and Pathanamthitta Districts, Kerala state, where the outbreak mainly occurred.

Patients were confirmed as having CHIKV infection using the National Institute of Communicable Disease (NICD) criteria (NICD, 2006) and were included in the study. Patients were screened to rule out other causes of joint symptoms which could have been present prior to CHIKV infection. After evaluation we offered the patients therapy for obtaining pain relief and to improve their quality of life using a multidisciplinary approach.

We saw 1,206 cases with CHIKV infection sequelae. Due to a lack of confirmation of the diagnosis we limited the number to 1,111 confirmed cases with CHIKV sequelae. We categorized the subjects according to their major symptoms.

Table 1  
Age-sex frequency of 1,111 patients with chikungunya sequelae.

Age in years	Male		Female		Total	
	No.	%	No.	%	No.	%
0-10	0	0.0	7	1.0	7	0.6
11-20	1	0.3	25	3.5	26	2.3
21-30	10	2.6	55	7.6	65	5.9
31-40	44	11.3	115	15.9	159	14.3
41-50	90	23.2	243	33.6	333	30.0
51-60	93	24.0	178	24.6	271	24.4
>60	150	38.7	100	13.8	250	22.5
Total	388	100.0	723	100.0	1,111	100.0

The subjects were also categorized by Body Mass Index (BMI) based on WHO criteria (WHO, 2000) into the following groups: <18.5 as underweight; 18.5-24.9 as normal, 25.0-29.9 as overweight and  $\geq 30$  as obese. We assessed the association between CHIKV sequelae and overweight and obese patients evaluating the odds ratio for each. We questioned each patient regarding their activity during the acute phase to assess the association of rest during the acute and CHIKV sequelae.

After evaluating of patient we filled out a case report form and data entry was done in Microsoft Excel version 2003. Descriptive analysis and tables were drawn using both Microsoft Excel and SPSS version 11. Graphs were prepared using Microsoft Word 2007 version.

## RESULTS

Of the 1,111 patients confirmed in the study 91.2% were above age 30 years old (Table 1), 723 (65.1%) were females and 388 were males, the difference was significant. Females >40 years old were more likely to have chronic CHIKV sequelae (72.1%) than females <40. Males predominated

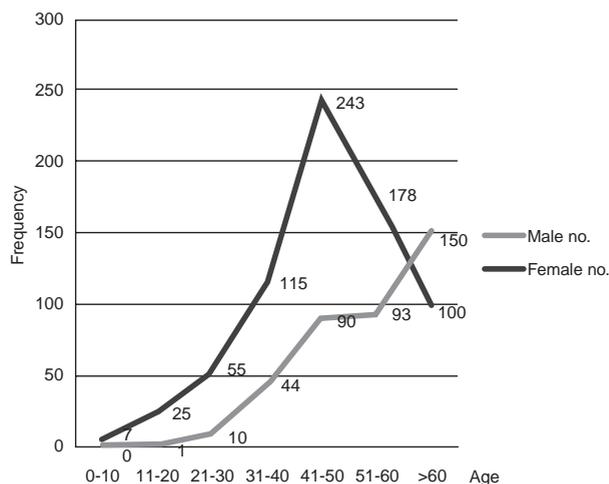


Fig 1—Age and sex distribution.

150/1,111 in the >60 year old age group (females, 100/1,111).

There was an increase in incidence of CHIKV sequelae with increasing age up to 50 years old. In females over age of 50 years there was a lower incidence of CHIKV sequelae. The peak incidence of CHIKV sequelae in females was between ages 40 and 50, in males it was above age 60 (Fig 1).

Table 2  
Major chikungunya sequelae.

Symptoms	Male		Female		Total	
	No.	%	No.	%	No.	%
Arthralgia and arthritis	293	57.0	532	66.0	825	74.3
Skin lesions	26	6.7	51	7.1	77	6.9
Headache	23	5.9	48	6.6	71	6.4
Fatigability	13	3.4	21	2.9	34	3.1
Alopecia	17	4.4	11	1.5	28	2.5
Insomnia	15	3.9	58	8.0	73	6.6
Oral ulcers	1	0.25	2	0.3	3	0.3
	388	100.0	723	100.0	1,111	100.0

Table 3  
BMI descriptive statistics.

	N	Minimum	Maximum	Mean	Std deviation
BMI	1,052	13.21964	47.33382	24.91247	4.098446

The major CHIKV sequelae (Table 2) were arthritis and arthralgia. Out of 1,111 total patients, 698 (62.8%) had arthralgia, 127(11.4%) had arthritis and 77 (6.9%) had persistent skin lesions. Other symptoms included alopecia, fatigability and oral ulcers.

#### Joint symptoms

CHIKV sequelae had no significant association with sex except for arthritis. Joint symptoms were polyarticular in 92% of cases and involved the proximal and distal interphalangeal joints. The symptoms were symmetrical in 82.1%.

#### Skin lesions

Dermatological lesions included hyperpigmented patches of the face and especially the nose (36 cases), generalized pruritus (19 cases), maculopapular rash (20 cases) and scrotal ulcers (2 cases). Dermatological manifestations were the second most common group of symptoms.

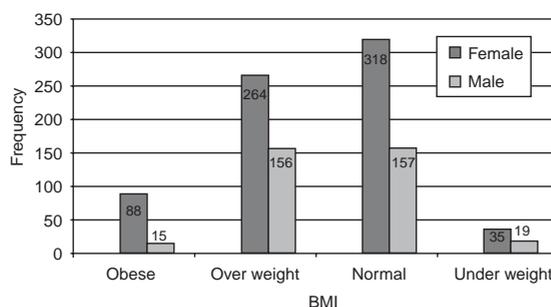


Fig 2-BMI-sex distribution.

#### Other symptoms

Other symptoms included alopecia (28 cases), insomnia (73 cases), headache (71 cases), stomatitis (3 cases) and fatigability (34 cases).

#### BMI and CHIKV sequelae

A significant number of cases had a BMI greater than normal (over weight and obese) using WHO criteria (WHO, 2000). Of 1,052 cases for which data was avail-

Table 4  
Relationship between rest during acute infection and chikungunya sequelae.

Rest during acute phase	Males	Females	Total No.
Yes	315	616	931
No	73	107	180
Total	388	723	1,111

able to calculate BMI, 420 were over weight, 103 were obese, 475 had a normal BMI and 54 were under weight.

Overweight and obesity were significantly associated with CHIKV sequelae. Overweight gave an odds ratio of 1.3 (95% CI 1.2-1.4). Of 103 obese patients 89 were females. Obesity was an independent risk factor for arthritis as a sequelae of CHIKV with an odds ratio of 2.07 (95% CI 1.9-2.1) which gives more than twice the risk. There was no sex difference in the overweight and obese patients since overweight females (52.5%) and males (52.1%) were equally affected.

Regarding the relationship between rest during acute infection and chronic CHIKV sequelae 931/1,111 ( $p < 0.001$ ) of affected subjects rested during the acute and convalescent phases. This shows rest during the acute phase does not seem to reduce the incidence of sequelae.

## DISCUSSION

The results and age-sex distribution of the population suffering the sequelae of CHIKV infection match the risk factors for being bitten by the vector (*Aedes aegypti* mosquito). Females age 40-50 had the greatest incidence. In males, the age group at most risk were those above 60. In Kerala these people form the group who spend the majority of their time at home in and around the premises where

they are susceptible to the *Ae. aegypti* mosquito bites. *Ae. aegypti*, a day biter, has its breeding places in small water collections (Mangiafico, 1971). Home oriented populations are more prone to become infected. Other factors may play a role in the female preponderance of chronic CHIKV sequelae but their identification is not within the scope of this study.

Our study shows the arthritogenic nature of the virus along with the significant lesions seen on the skin. There may be nervous system involvement as suggested by the incidence of headache, fatigability and insomnia. Some of our subjects presented with chronic fatigue syndrome like presentations. Chronic fatigue syndrome can occur following viral infections and is well established following Epstein Barr virus infection (Buchwald *et al*, 1987). In case of CHIKV it requires further follow-up and confirmation of the diagnosis.

The joint symptoms of CHIKV infection have a lot of similarities with rheumatoid arthritis in the site involved, age-sex predominance, and nature of presentation. It is mainly a symmetrical polyarthritis with predominant involvement of distal joints of the hand in females age 40 -50 years old. This similarity was previously studied by Fourie and Morrison in 1979. Physicians should keep this in mind when evaluating, and following up these patients. After our study some of our physicians had concerns CHIKV infection

could precipitate the onset of rheumatoid arthritis in genetically predisposed individuals; this question requires further study. A case report in 1984 claimed CHIKV arthritis could progress to joint destruction before ultimately regressing after 15 years, leaving sequelae of destroyed metatarsal heads and late osteoarthritis changes (Brighton *et al*, 1983; Brighton and Simson, 1984). We are continuing to follow our subjects to detect early any of these type of changes.

We also studied the association between BMI and the incidence of arthritis due to CHIKV infection. Obesity and overweight have been shown to be independent risk factors for self reported arthritis in adults (Mehrotra *et al*, 2004). Our study found a greater than 2 times risk for arthritis in obese individuals compared to normal weight subjects. We found an association between chronic CHIKV arthritis and overweight, although the team was unable to find any literary support for this.

Recent studies regarding the pathological changes in obesity consider it as a chronic inflammatory state with increased levels of cytokines, especially TNF- $\alpha$  and IL-6 (Yudkin *et al*, 1999; Engstrom *et al*, 2004; Nguyen *et al*, 2009). Inflammation in the presence of obesity is thought to arise primarily in adipose tissue as a result of chronic disruption of metabolic homeostasis, which leads to increased cytokine production and the activation of inflammatory signaling pathways in the body (Yudkin *et al*, 1999; Engstrom *et al*, 2004; Hotamisligil, 2006; Fauci and Harrison, 2008). These inflammatory changes already present in obese population can exacerbate the inflammatory changes due to CHIKV infection, especially the musculoskeletal manifestations. We think this may be one mechanism which could lead to the increased incidence

of CHIKV inflammatory arthritis in the obese population.

The association between rest during the acute phase and developing CHIKV sequelae was assessed. We relied entirely on clinical history for this. The assessment revealed no significant benefit for rest during the acute phase in preventing the incidence of sequelae.

Our study concludes chronic CHIKV sequelae mainly affect females age 40 to 50 years old, especially house wives. As age increases, the incidence of CHIKV sequelae increases, and peaks at 50 years in females and 60 years in males, after that a gradual decline occurs. The major CHIKV sequelae include polyarthralgia and arthritis, involving mainly the proximal and distal interphalangeal joints. Dermatological involvement is the next most common sequelae. Central nervous system involvement is indicated by the presence of insomnia, fatigability and headache. Obesity was an independent risk factor for the development of arthralgia and arthritis. One possible mechanism is the inflammatory changes that occur and the increased levels of cytokines already present in the obese population may accelerate the inflammatory changes due to CHIKV infection, especially the musculoskeletal manifestations. There was no significant advantage of rest during the acute stage in reducing the incidence sequelae. Further studies with good cohorts are needed to evaluate the association between obesity and rest during acute phase and joint symptoms and the possibility of central nervous system involvement.

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