Original Article

Sub-acute and chronic musculoskeletal manifestations in chikungunya fever: experience in a tertiary care hospital of Bangladesh

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ABSTRACT

Background: *Chikungunya is a mosquito-borne viral disease and presentation usually follows 3 phases: acute, sub-acute and chronic. Erratic, relapsing and incapacitating arthritis is the hallmark of chikungunya and many patients go on to develop post-chikungunya arthritis. Bangladesh experienced a major outbreak of chikungunya since April-May of 2017 which created a mass panic among people. The present study aimed to evaluate the course and pattern of musculoskeletal manifestations of patients who had been diagnosed as a case of chikungunya fever.*

Methods: *It was a prospective observational study, conducted in Department of Internal Medicine, BIRDEM General Hospital from October, 2017 to August, 2018. Total 100 patients suffering from chikungunya were selected and data were collected by interview using a semi-structured questionnaire and medical records analysis. These patients were followed up after 3 weeks and 3-months of symptom onset and musculoskeletal features were recorded.*

Results: *A total 100 patients were studied and among them female patients were 54%. Mean age of the patients was 49.7 years. Eighty-three patients were managed from outpatient department. All of the patients had history of fever and joint pain at the onset. Among 100 patients, musculoskeletal symptoms resolved in 23 patients within the acute phase and 77% went through sub-acute phase. Twenty six percent patients entered into chronic phase.*

Conclusion: *Study revealed that for one-fourth patients, musculoskeletal manifestations resolved in acute phase, three-fourth patients entered in sub-acute phase and one-fourth patients entered in chronic phase.*

Key words: *chikungunya virus, chronic, post-chikungunya rheumatism, sub-acute.*

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INTRODUCTION

Chikungunya virus infection was first identified in the mid-1950s in Tanzania, later spread to sub-Saharan Africa.[1,2] In Asia, outbreaks have been reported since 1958.[3] Several outbreaks have since been reported in South Asia and Southeast Asia, particularly in Malaysia, Indonesia, Cambodia, Vietnam, Myanmar, Pakistan, Singapore, Thailand and the Philippines.[4] Bangladesh, in 2017, swayed with a severe outbreak of chikungunya, thousands of cases presented in different hospitals and clinics and it emerged as an important public health issue in Bangladesh.[5-7]

Chikungunya is characterized by fever, polyarthralgia and sometimes associated with rash. In the acute phase, the axial spine is often affected and results in a characteristic stooped walking position.[8] Polyarthralgia

is often symmetric and involves the large and small joints of the extremities. The wrists, hands, ankles and toes are commonly affected[9] but some report the knee as the most commonly affected joint. The articular symptoms, often debilitating, usually resolve within weeks but have been reported to last for months, even though the natural history of this infection has not been precisely studied in prospective studies.[8,10,11]

Chronic arthralgia is considered incapacitating for daily life tasks and impacted professional activities and quality of life.[12,13] Persistent arthralgia, arthritis, alopecia and depression were most frequently mentioned features impacting the quality of life. A follow-up study of patients described the most prevalent symptoms;[14] joint pain was reported in 32% of cases, musculoskeletal pain also in 32% of patients and 26% had joint edema 9 months after the acute condition. Some studies showed up to 64% of patients with chikungunya fever, report joint stiffness and/or pain more than a year after the initial infection.[8,9] Persistent and/or recurring joint stiffness and/or pain lasting more than 1 year after the initial infection, affected more than half of all chikungunya virus infected patients in La Reunion Island of France during the 2005–2006 outbreak.[9] Bangladesh faced, for the first time, such a huge outbreak of chikungunya and as we did not have statistics on prevalence of post-chikungunya rheumatism, we evaluated the course and pattern of sub-acute and chronic musculoskeletal manifestations in chikungunya fever.

METHODS

This prospective observational study was done at the Department of Internal Medicine, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital in Dhaka, Bangladesh from October, 2017 to August, 2018. Adult patients (>18 years), with a confirmed diagnosis[15] of chikungunya were included in this study and were followed up clinically whether they enter into sub-acute (more than 3 weeks) and chronic phase (more than 3 months). Patients with known acute or chronic inflammatory arthropathy and those lost to follow-up were excluded.

The study protocol was approved by Institutional Review Board (IRB) of BIRDEM Academy and Research and Training Monitoring Department (RTMD) of Bangladesh College of Physicians and Surgeons (BCPS). In all cases, informed written consent of the patients was taken.

Statistical Package for Social Sciences (SPSS) version 23 for windows was used to analyze the data. Tables and graphs were constructed according to the findings by using Microsoft Excel.

RESULTS

Total 100 patients were enrolled with female predominance (54%) and 91% were from urban area. Mean age of the patients was 49.7 ± 13.6 (range 18 – 77) years. Almost half of the female patients (26/54, 48.1%) were housewives while nearly half of the males (20/44, 45.5%) were service holders. All had history of fever and arthralgia at the onset and other features are shown in Table I. Sixty three patients came to hospital during 3-7 days of illness, 28 patients came after 6 days and only 9 patients came in first two days of illness.

Table I Clinical presentation of patients with chikungunya (N = 100)

Clinical features	Frequency	Percentage
Fever	100	100
Joint pain	100	100
Headache	53	53
Rash	77	77
Oral Ulcer	27	27
Diarrhoea	22	22
Others	16	16

Knee, ankle, wrist and small hand joint involvements were common (Table II) and most had involvement of multiple joints. Other articular features are shown in Table II.

Diagnosis was confirmed by RT-PCR in 2 cases, IgM in 62 and both IgM and IgG in 36 cases. Most (83%) cases were treated as outpatient, whereas 17% patients were admitted in hospital. Among 100 patients, 15% had anemia, 37% had leukopenia, 8% had thrombocytopenia, 74% had raised erythrocyte sedimentation rate (ESR) and 53% had raised C-reactive protein (CRP).

Patients took paracetamol in variable doses and duration during the course of illness, with or without prescription and other drug received by patients in acute phase are shown in Table II.

Table II Disease course, patterns of joint involvements and treatment received by patients

Parameters	Acute phase (100) Frequency (%)	Sub-acute phase (77) Frequency (%)	Chronic phase (26) Frequency (%)
Joints involved			
Knee	73 (73)	55 (71.4)	20 (76.9)
Ankle	71 (71)	54 (70.1)	21 (80.8)
Hip	6 (6)	4 (5.2)	2 (7.7)
Wrist	59 (59)	47 (61.0%)	14 (53.8)
Hand joints	64 (64)	52 (64.5)	9 (34.6)
Foot joints	30 (30)	22 (28.6)	7 (26.9)
Elbow	40 (40)	31 (40.3)	6 (23.0)
Shoulder	42 (42)	34 (44.2)	8 (30.8)
Temporomandibular	7 (7)	-	-
Sacroiliac	3 (3)	2 (2.6)	1 (3.8)
Features other than joint pain			
Swelling	83 (83)	53 (68.8)	11 (42.3)
Redness	31 (31)	-	-
Stiffness	79 (79)	51 (66.2)	12 (46.2)
Warmth	76 (76)	17 (22.0)	-
Restricted movement	92 (92)	65 (84.4)	21 (80.8)
Tenderness	84 (84)	58 (75.3)	9 (34.6)
Patterns of joint involvement			
Polyarticular	62 (62)	55 (71.4)	9 (34.6)
Oligoarticular	33 (33)	20 (26.0)	15 (57.7)
Monoarticular	5 (5)	2 (2.6)	2 (7.7)
Treatment given			
Paracetamol	100 (100)	77 (100)	26 (100)
Steroids (prednisolone)	7 (7)	67 (87.0)	11 (42.3)
Hydroxy-chloroquine	-	32 (41.6)	17 (65.4)
NSAIDs	3 (3)	17 (22.1)	-

NSAIDs = non-steroidal anti-inflammatory drugs

Among 100 patients, 23% resolved within the acute phase and 77% went through sub-acute phase. Among them (sub-acute group, n = 77) 51 patients resolved in this phase and 26 patients further progressed into chronic phase of post-chikungunya arthralgia/arthritis (Table II). Patterns of joint involvements, numbers of joint involvements, inflammatory features and treatment given are presented in Table II. Most patients had polyarticular involvement and corticosteroids and hydroxychloroquine were the two commonly prescribed medications in chronic phase.

DISCUSSION

In this prospective observational study of cases of chikungunya fever, which was done on a small number of patients in a selected tertiary care hospital of Dhaka, Bangladesh revealed, 77% of the patients progressed to have sub-acute joint symptoms and 26% to chronic joint symptoms. In studies of patients of chikungunya,

there appear a wide range of patients had developed sub-acute and chronic stage of the disease ranging from 25 to 75 percent of patients.[16-18] In a 2016 meta-analysis including approximately 5700 patients in 18 studies, chronic inflammatory rheumatism occurred in approximately 40% of individuals with chikungunya virus infection; symptoms persisted beyond 18 months in 56% of these patients.[19] The present study also revealed that a large number of patients tend to have persistent joint symptoms.

There was slight female predominance in our study similar to the study done by Mathew et al.[20] in south India. Rahim AA et al.[21] found that 62.3% of patients with post-chikungunya arthritis were females. Ivan et al.[22] reported that female sex and smoking were associated with post-chikungunya arthritis.

Mean age of our study participants were just below 50 years, which was consistent with findings of Mathew et al. from south India.[20] On the other hand, Larrieu et al.[22] found that mean age of French patients with post-chikungunya arthritis was over 50 years. Claire[23] reported that, patients with post-chikungunya arthritis were of increasing age in West Indies, which was also true in two other reports.[16,24] Over 90% of study subjects of the present study were from urban areas, indicating that chikungunya outbreaks are facilitated by the *Aedes* mosquitoes, which breed in stored fresh waters.

The clinical manifestation of acute chikungunya fever of recent study was not different from other concurrent reports; fever and arthralgia/arthritis were the two most common features, though there may be variation in their percentages in different series, within or outside the country.[6,7,25-31] Almost all the patients in current series were diagnosed by the presence of IgM against chikungunya. One-third had leukopenia and one in every 11 patients had thrombocytopaenia. A study by Borgherini et al.[32] found that the acute infectious phase of chikungunya disease is characterised by pronounced lymphopenia and moderate thrombocytopaenia. However, Chopra et al.[33] did not find any cases with anaemia, leukopenia or thrombocytopenia.

Post-chikungunya rheumatism is an established sequel. In the current study, over three-fourths had entered subacute phase and one-fourth in chronic phase. In a 2018 meta-analysis of studies in the Americas, approximately half of patients with chikungunya virus infection developed chronic disease.[34] Among 47 patients with acute chikungunya fever followed in one study in Marseilles, France, 82 percent had persistent joint symptoms. At one, three and six months following acute illness, symptoms persisted in 88, 86, and 48 percent of patients, respectively; at 15 months, 4 percent remained symptomatic.[35] This phenomenon is supported by the observation of Chopra et al.[33] which revealed 31% had persistent joint pain at 6-8 months. It is also supported by many other studies such as Moro et al.[12], Schilte et al.[16], Larrieu et al.[23] among others. A recent case series from Bangladesh revealed that 25% of patients with pre-existing rheumatic diseases had post-chikungunya rheumatism.[36]

About three-fourths of the patients came with involvement of knee and ankle joints followed by small joints of the hand, wrist and shoulder during first presentation in the present series of chikungunya patients. Similar fact was observed in both sub-acute and chronic phase of the disease, though involvement of small joints of hands was much lower in chronic phase. Mathew et al.[20] also found a higher percentage of involvement of knee (83.3%) and ankle (63.2%) joints in acute phase of chikungunya fever, which was also supported by reports of Chopra et al.[33] The same study[33] demonstrated that chronic patients had less involvement in shoulder, elbow, foot, hip, joint involvement in comparison to acute cases, though ankle involvement remained almost equal. It has been observed that most of the patients had polyarthralgia/arthritis in all three phases of chikungunya fever.

Our study had some limitation; small numbers of patients were studied in a single center. A larger sample from multiple centers would provide a more representative results.

A significantly large proportion of patients (three-fourths) entered in sub-acute phase and one-fourth patients entered in chronic phase of post chikungunya arthritis. The clinical presentation of chikungunya virus infection in an adult population indicated that fever and arthralgia were the dominant acute phase symptoms. Among the joints that involved, knee, ankle, hand, wrist, elbow, shoulder and joints of feet are affected frequently in acute phase. Patients in sub-acute phase had a predominant involvement of small joints of hands in comparison to chronic phase, while patients in chronic

phase had more involvement of ankle and knee joints than sub-acute phase. It also revealed that predominantly patients were suffering from multiple joints involvement. We need to quantify the impact of chikungunya fever on quality of life, functional status, disability-adjusted life years and economic consequences because it is causing sub-acute and chronic arthritis in a large number of patients.

Authors' contribution: TSUH, MAR and AKMM designed the research, TSUH and MAR collected data, TSUH and RFA analyzed data and drafted the manuscript; MAR revised the manuscript critically and modified it. All authors read and approved the manuscript for submission.

Conflicts of interest: Nothing to declare.

REFERENCES

1. Burt FJ, Rolph MS, Rulli NE, Mahalingam S, Heise MT. Chikungunya: a re-emerging virus. Lancet 2012; 379:662–71.
2. Sudeep AB, Parashar D. Chikungunya: an overview. J Biosci 2008; 33:443–9.
3. Hammon WM, Sather GE. Virological finding in the 1960 hemorrhagic fever epidemic (dengue) in Thailand. Am J Trop Med and Hyg 1964; 13:629–41.
4. Powers AM, Logue CH. Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus. J Gen Virol 2007; 88:2363–77.
5. Kabir I, Dhimal M, Müller R, Banik S, Haque U. The 2017 Dhaka chikungunya outbreak. Lancet Infect Dis 2017;17: 1118.
6. Rahman MM, Sayed SJB, Moniruzzaman M, Kabir AKMH, Mallik MU, Hasan MR, et al. Clinical and Laboratory Characteristics of an Acute Chikungunya Outbreak in Bangladesh in 2017. Am J Trop Med Hyg 2019 Feb; 100(2): 405–10.
7. Rahim MA, Uddin KN. Chikungunya: an emerging viral infection with varied clinical presentations in Bangladesh: Reports of seven cases. BMC Res Notes 2017;15; 10(1):410.
8. Brighton SW, Prozesky OW, De La Harpe AL. Chikungunya virus infection: A retrospective study of 107 cases. S Afr Med J 1983; 63:313–5.
9. Borgherini G, Poubeau P, Jossaume A, Gouix A, Cotte L, Michault A, et al. Persistant arthralgia associated with chikungunya virus: a study of 88 adult patients on Reunion Island. Clin Infect Dis 2008; 47:469–75.
10. Calabrese LH. Emerging viral infections and arthritis: the role of the rheumatologist. Nature Clin Pract Rheumatol 2008; 4:2–3.
11. Dupuis-Maguiraga L, Noret M, Brun S, Le Grand R, Gras G, Roques P. Chikungunya disease: infection-associated markers from the acute to the chronic phase of arbovirus-induced arthralgia. PLoS Negl Trop Dis 2012; 6: e1446.
12. Moro ML, Grilli E, Corvetta A, Silvi G, Angelini R, Mascella F, et al. The Study Group Infezioni da Chikungunya in Emilia-Romagna: Long-term chikungunya infection clinical manifestations after an outbreak in Italy: A prognostic cohort study. The J Infec 2012; 65: 165–72.
13. Couturier E, Guillemin F, Mura M, Leon L, Virion JM, Letort MJ, et al. Impaired quality of life after chikungunya virus infection: a 2-year follow-up study. Rheumatology (Oxford) 2012; 51:1315–22.
14. Zeana C, Kelly P, Heredia W. Post-chikungunya rheumatic disorders in travelers after return from the Caribbean. Travel Med Infect Dis 2016; 14(1): 21–5.
15. Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare. Government of People's Republic of Bangladesh. Bangladesh National Guideline on Clinical Management of Chikungunya Fever; 2017.
16. Schilte C, Staikowsky F, Couderc T, Madec Y, Carpentier F, Kassab S, et al. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. PLoS Negl Trop Dis 2013; 7 (3): e2137.
17. Couzigou B, Criquet-Hayot A, Javelle E, Tignac S, Mota E, Rigaud F, et al. Occurrence of Chronic Stage Chikungunya in the General Population of Martinique during the First 2014 Epidemic: A Prospective Epidemiological Study. Am J Trop Med Hyg 2018; 99(1):182.
18. Sissoko D, Malvy D, Ezzedine K, Renault P, Moscetti F, Ledrans M, et al. Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. PLoS Negl Trop Dis 2009; 3(3):e389.
19. Rodríguez-Morales AJ, Cardona-Ospina JA, Urbano-Garzón SF, Hurtado-Zapata SJ. Prevalence of Post-Chikungunya Infection Chronic Inflammatory Arthritis: A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken) 2016; 68:1849.
20. Mathew AJ, Goyal V, George E, Thekkemuriyil DV, Jayakumar B, Chopra A. Rheumatic-musculoskeletal pain and disorders in a naïve group of individuals 15 months following a Chikungunya viral epidemic in south India: a population based observational study. Int J Clin Pract 2011; 65:1306e12.
21. Rahim AA, Thekkekara RJ, Bina T, Paul BJ. Disability with persistent pain following an epidemic of chikungunya in rural south India. J Rheumatol 2016; 43:440e4.
22. Ivan D, Brenda P, Valery M, Jose G, Francisco E, Alejandro D, et al. Smoking and female sex as key risk factors associated with severe arthralgia in acute and chronic

phases of Chikungunya virus infection. Exp Ther Med 2018 Mar; 15(3): 2634–42.

23. Larrieu S, Pouderoux N, Pistone T, Filleul L, Receveur MC, Sissoko D, et al. Factors associated with persistence of arthralgia among Chikungunya virus-infected travellers: report of 42 French cases. J ClinVirol 2010 Jan; 47(1): 85–8.

24. Claire J, Jason L, Trevor P, Idis M, Derek B, George M, et al. The Identification of Risk Factors for Chronic Chikungunya Arthralgia in Grenada, West Indies: A Cross-Sectional Cohort Study. Open Forum Infect Dis 2018 Jan; 5(1): ofx234.

25. Essackjee K, Goorah S, Ramchurn SK, Cheeneebash J, Walker-Bone k. Prevalence of and risk factors for chronic arthralgia and rheumatoid-like polyarthritis more than 2 years after infection with Chikungunya virus. Postgrad Med J 2013; 89: 440–7.

26. Mohan A. Chikungunya fever: clinical manifestations and management. Indian J Med Res 2006; 124:471–4.

27. Bandyopadhyay D, Ghosh SK. Mucocutaneous features of Chikungunya fever: a study from an outbreak in West Bengal, India. Int J Dermatol 2008; 47:1148–52.

28. Kannan M, Rajendran R, Sunish IP, Balasubramaniam R, Arunachalam N, Paramsivan R, et al. A study on chikungunya outbreak during 2007 in Kerala, south India. Indian J Med Res 2009; 129:311–5.

29. Hossain MS, Hasan MM, Islam MS, Islam S, Mozaffor M, Khan MAS, et al. Chikungunya outbreak (2017) in Bangladesh: Clinical profile, economic impact and quality of life during the acute phase of the disease. PLoS Negl Trop Dis 2018 Jun 6; 12(6): e0006561.

30. Rahim MA, Ananna MA, Zaman S, Jahan I, Habib SH, Chowdhury TA, et al. Socio-demographic, Clinical and Laboratory Characteristics of a Chikungunya Cohort from the 2017 Dhaka Outbreak of Bangladesh. BIRDEM Medical Journal 2019; 9(2): 106–10.

31. Arroyo-Ávila M, Cabán A, García-Rivera EJ, Irizarry-Pérez M, Torres H, Gorbea H, et al. Clinical Manifestations Associated with Peripheral Joint Involvement in Patients with Acute Chikungunya Virus Infection. Am J Trop Med Hyg 2017 Apr; 96(4): 916–21.

32. Borgherini G, Poubeau P, Staikowsky F, Lory M, Le Moullec N, Becquart JP, et al. Outbreak of chikungunya on Reunion Island: early clinical and laboratory features in 157 adult patients. Clin Infect Dis 2007; 44: 1401.

33. Chopra A, Anuradha V, Ghorpade R, Saluja M. Acute Chikungunya and persistent musculoskeletal pain following the 2006 Indian epidemic: a 2-year prospective rural community study. Epidemiol Infect 2012; 140: 842–50.

34. Edington F, Varjão D, Melo P. Incidence of articular pain and arthritis after chikungunya fever in the Americas: A systematic review of the literature and meta-analysis. Joint Bone Spine 2018; 85(6): 669.

35. Simon F, Parola P, Grandadam M, Fourcade S, Oliver M, Brouqui P, et al. Chikungunya infection: an emerging rheumatism among travellers returned from Indian Ocean islands. Report of 47 cases. Medicine 2007; 86:123–37.

36. Rahim MA, Zaman S, Uddin KN. Chikungunya among patients with pre-existing rheumatological diseases: a case series and review of literature. Ethiop Med J 2021; 59(3): 257–9.