ISSN 3007-2433 (Print), 3007-2441 (Online)

ORIGINAL ARTICLE

Neuropathic Pain Associated with Chikungunya: A Cross-Sectional Study

Md Mostafa Kamal[1], Shahara Afroz[2], Md Zunaid[3], Md Shafiqul Islam[4], Md Sayedur Rahman Khan[5], AKM Akhtaruzzaman[6]

DOI:https://doi.org/10.62848/bjpain.v1i1.3562

Received 15 January, 2021
Accepted 12 April, 2021

1 Anaesthesiologist, Department of Anaesthesia, Intensive Care and Pain Medicine, SSMC Dhaka, Bangladesh

2 Post Graduate Student Department of Anaesthesia, Intensive Care and Pain Medicine, SSMC Dhaka, Bangladesh

3 Registrar, Department of Anaesthesia, Analgesia, Intensive Care and Pain Medicine, DMCH Dhaka, Bangladesh

4 Associate Professor, Department of Anaesthesia, Analgesia and Intensive Care and Pain Medicine, BSMMU Dhaka, Bangladesh

5 Assistant Professor Anaesthesia, OSD on Lien JDWNRH Hospital, Thimpu Bhutan

6 Professor, Department of Anaesthesia, Analgesia and Intensive Care Medicine BSMMU Dhaka Bangladesh

Correspondence
AKM Akhtaruzzaman
akm.akhtaruzzaman@bsmmu.edu.bd
ORCID: 0000-0002-2427-1863

Abstract

Background: Chikungunya is a tropical arboviral disease affecting millions of people around the world. It is characterized by fever and debilitating pain which frequently turns into chronic pain as a long-term complication of the infection. Neuropathic pain after acute infection lasting for months to years has been reported, but very few studies have evaluated this aspect of the disease. Hence, this study was aimed to evaluate neuropathic pain in post chikungunya infection.

Methods: A six months long cross-sectional study was conducted in the pain clinic of a tertiary care hospital of Bangladesh. One hundred and thirty-six serologically confirmed patients of chikungunya suffering from chronic pain were enrolled and assessed by visual analogue scale (VAS) and Questionnaire Douleur Neuropathique 4 (DN4) to evaluate the pain intensity and presence of neuropathic component, respectively. Patients with causes of chronic pain other than chikungunya were excluded. All statistical tests were performed using SPSS version 23.

Results: A total of 26 patients had post-chikungunya neuropathic pain accounting foran overall estimated prevalence of 19.1% (95% Confidence Interval [CI]: 12.5 – 25.7). The prevalence of male and female were 17.54% (95% CI: 7.67 – 27.42) and 20.25% (95% CI: 11.39 – 29.12), respectively. The mean intensity of chronic pain on the visual analogue scale was 5.54 ± 0.81 and the mean duration was 5.25±1.47 months. There were no significant differencs in intensity and duration of pain between patients with or without neuropathic pain ($p > 0.05$). The most common affected location was lower (96%) and upper limbs (91%) respectively and the most commonly affected joints were ankle/foot (80%), knee (76%), and hand/wrist (64%).

Conclusion: A significant proportion of chronic pain patients develop neuropathicpain after acute chikungunya virus infection which requires particular attention during management.

Keywords: Chikungunya, Neuropathic pain, Prevalence, DN4, VAS

Citation: Kamal MM, Afroz S, Zunaid M, Islam MS, Khan MSR, Akhtaruzzaman AKM. Neuropathic Pain Associated with Chikungunya: A Cross-Sectional StudyBangladesh J. Pain. 2021;1(1):16-21. doi:10.62848/bjpain.v1i1.3562

Introduction

Chikungunya is a viral disease caused by the arthropod-borne chikungunya virus that belongs to the Alphavirus genus of the family Togaviridae[1]. The disease is transmitted by Aedes mosquitoes[2]. Aedes aegypti and Aedes albopictus are the main vectors of chikungunya in Asia and the Indian Ocean islands[3]. Chikungunya was first identified in a patient in Tanzania[2] and was first described by Robinson and Lumsden[4,5]. The first epidemic of Chikungunya occurred in Makunde Plateau of Southern Tanzania in 1952[4]. Since then it has spread globally to affect millions of people around the world[6]. In 2008, the first recognized outbreak of Chikungunya occurred in the northwestern part of Bangladesh[7]. Since then two rural outbreaks were reported[8,9] till the massive outbreak in Bangladesh in 2017[10]. During the last outbreak more than 13000 clinically confirmed cases were reported from Dhaka city alone[8]. Chikungunya causes a self-limiting acute febrile illness characterized by intense and diffuse joint and muscular pain. The name 'chikungunya' is derived from the Makonde (an ethnic group in southeast Tanzania and northern Mozambique) word meaning "that which bends up" about the stooped posture developed as a result of the arthritic symptoms of the disease[1]. Other symptoms like headache, photophobia, nausea, vomiting, diarrhea and a maculopapular or morbilliform skin rash may also occur[3,9]. Approximately 90% of individuals infected with the chikungunya virus present with symptomatic infection. The disease may evolve in three phases which include acute or febrile (lasting up to 10 days), sub-acute (11-90 days), and chronic (> 90 days)[14, 15]. Although the clinical features of acute infection have already been described in many reports, little is known about the long-term outcomes the disease, particularly, in the context of Bangladesh. Chronic pain due to persistent arthralgia after resolution of acute chikungunya infection is evident from several studies[11]. Patients aged >40 and female are more likely to develop the long-term sequel[12]. Nearly half of the patients suffering from acute infection may develop chronic joint pain that can last months to years. On Reunion Island, it was reported that 80-93% of patients had the chronic disease after 3 months, 57% after 15 months, and 47% after 2 years of acute infection[11,13]. The neurotropism of chikungunya virus is well established with wide spectrum of neurological features and complications developing in patients[14]. However, a few studies described an association of peripheral neuropathy with chikungunya[12,15], with fewer evaluating neuropathic pain[12]. After the massive outbreak of chikungunya in 2017 in Bangladesh, one study found that 19% of their participants have been suffering from long-term arthralgia after 9-12 months of acute infection[8]. However, the prevalence of post-chikungunya neuropathic pain is yet to be studied. Hence, this study aimed to assess the prevalence of post-chikungunya neuropathic pain which would help physicians to decide on the management of pain in this group of patients.

Methods

Study place, participants and design

This cross-sectional study was conducted at Pain Medicine Outpatient Unit and Specialized Pain Outpatient Department (Kosaka Pain Clinic) in Department of Anesthesia, Analgesia and Intensive Care Medicine of Bangabandhu Sheikh Mujib Medical University, from September 2019 to February 2020. Adult patients (age >18 years) with a history of positive serology for chikungunya IgG and/or IgM, and complaints of chronic pain (pain persisting > 3 months) were included. Patients having pain due to causes other than chikungunya were excluded from the study. This included patients having rheumatologic, diabetic polyneuropathy, lumbar or cervical radiculopathies), cancer pain, and patients with a diagnosis of any psychiatric disease, receiving antipsychotic drugs, and those who had a history of drug abuse.

Study measures

A pretested structured questionnaire was use for data collection. The questionnaire consisted of two parts-demographic characteristics of patients and assessment of pain. Pain intensity was assessed using Visual Analogue Scale (VAS), location was asked using a body diagram, and presence of neuropathic pain was evaluated using Questionnaire Douleur Neuropathique 4 (DN4)[16].

Visual Analogue Scale (VAS)
VAS is widely used in studies evaluating pain. It consists of a linear scale measuring 10 cm (100mm) and marked from 0-10 cm (0-100mm). The most common VAS consists of 10 horizontal or vertical line with its two endpoints '0' and '10' representing 'no pain' and 'worst pain ever' (or similar verbal descriptions), respectively[17].

Questionnaire Douleur Neuropathique 4 (DN4)
The DN4 questionnaire was used to diagnose neuropathic pain. It is a clinician-administered questionnaire consisting of ten items. Out of ten items, seven are related to pain quality (i.e. sensory and pain descriptors) which are based on an interview with the patient and three items based on the clinical examination. It has been widely used since 2005 because of its simplicity and well validation in several studies. It is an easy-to-use screening tool that is reliable for discriminating between neuropathic and nociceptive pain conditions in daily practice to diagnose neuropathic pain and also for clinical research. The DN4 questionnaire is valid for a cut-off value of ≥ 4 points[16].

Statistical analysis
Quantitative variables were expressed as mean ± standard deviation (age, duration of pain, DN4 score, and VAS score). Qualitative variables were expressed as proportion and percentages (sex, presence of neuropathic pain, and location of pain). Analysis was conducted using Chi-square test, Fisher's exact test for categorical variables and independent sample t-test for quantitative variables. The results were presented using tables and/or figures. A p-value of <0.05 was considered statistically significant. SPSS (Statistical Package for Social Sciences)-for Windows (version 23) was used to perform statistical analysis.

Results

A total of one hundred and thirty-six patients with a serological evidence of chikungunya infection were included in this study. Out of them, 26 patients (19.1%, 95% Confidence Interval [CI]: 12.5 – 25.7) had neuropathic pain. The prevalence in male and female were 17.54% (95% CI: 7.67 – 27.42) and 20.25% (95% CI: 11.39 – 29.12), respectively **(Figure 1)**.

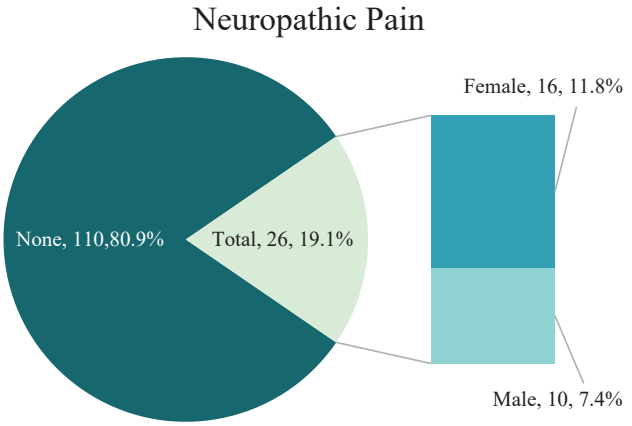

Fig. 1: Prevalence of neuropathic pain among study participants (n=136)

The mean age (± SD) of the patients of 37.05± 9.28 years. Of all, 58.1% patients (n=57) were male and 41.9% were female (n=79) with a male-to-female ratio of 1.0:1.38. There was no significant difference in age distribution between patients with or without neuropathic pain (36.07 ± 8.012 v 37.15 ± 9.38; p = 0.514). The mean duration of pain was 5.26± 1.41 months. The average duration of pain was similar between patients with or without neuropathic pain (5.25 ± 1.4 v 5.22 ± 1.41; p = 0.623). The intensity of pain of all patients measured by VAS score was 5.53 ± 0.78 with no difference between patients with or without neuropathic pain (5.54 ± 0.81 v 5.56 ± 0.78; p = 0.949). The mean DN4 score of the patients with neuropathic pain was 4.23±0.42. **(Table I)**

Table I: Demographic and clinical characteristics of the studied patients (n=136)

Variable	Total	Patients with neuropathic pain (n=26)	Patients without neuropathic pain (n=110)	P value*
Age (years)	37.05±9.28	36.07±8.12	37.15±9.38	0.514
Sex				
Female	79 (58%)	16 (62%)	63 (57%)	0.314
Male	57 (42%)	10 (38%)	47 (43%)	
Duration of pain (months)	5.26±1.41	5.25±1.47	5.22±1.41	0.623
Intensity of pain (VAS score)	5.53±0.78	5.54±0.81	5.56±0.78	0.949
Neuropathic pain intensity (DN4 score)		4.23±0.42	1.5±1.02	0.001

Values are expressed as mean±SD or absolute number, within parenthesis are percentage.
*p-value determined by independent samples t test and Chi-square test where appropriate

The characteristics of neuropathic pain is shown in **Table II.** The pain sensation was described as burning by 24 patients (92.3%), tingling by 23 (88.5%), pins and needles by 20 (76.9%), numbness by 19 (73.1%).

Table II: Distribution of neuropathic pain characteristics determined by DN4 (n=26)

Characteristics	Frequency*	Percentage (%)
Burning	24	92.3
Tingling	23	88.5
Pins and needles	20	76.9
Numbness	19	73.1
Itching	11	42.3
Cold	10	38.5
Electric shock	9	34.6
Hypoesthesia to touch	7	26.9
Hypoesthesia to pinprick	6	23.1
Pain on brushing	5	19.2

*Multiple response considered

The participants aged 30 – 49.9 years suffered the most from chronic pain with or without neuropathic pain across both sexes. Overall, 71.3% (n=97) patients were aged 30 – 49.9 years, among male 75.4% patients (n=43) and among female 68.4% patients (n=54) were of the same age group. The prevalence of neuropathic pain was 19.6% (95%CI 11.7 – 27.5) among patients aged 30 – 49.9 years. It was 18.6% (95%CI 7.0 – 30.2) and 20.4% (95%CI 9.6 – 31.1) in male and female, respectively, of the same age group **(Table III).**

Table III: Age and gender distribution of pain

Variable	Patients with chronic pain n (%)	Patients with neuropathic pain n (%)	Values (95% CI)
Age			
< 30 years	22 (16.2)	3 (11.5)	13.6 (0.0, 28.0)
30 - 49.9 years	97 (71.3)	19 (73.1)	19.6 (11.7, 27.5)
> 50 years	17 (12.5)	4 (15.4)	23.5 (3.4, 43.7)
Gender			
Male			
< 30 years	7 (12.3)	1 (10.0)	14.3 (0.0, 40.2)
30 - 49.9 years	43 (75.4)	8 (80.0)	18.6 (7.0, 30.2)
> 50 years	7 (12.3)	1 (10.0)	14.3 (0.0, 40.2)
Female			
< 30 years	15 (19.0)	2 (12.5)	13.3 (0.0, 30.5)
30 - 49.9 years	54 (68.4)	11 (68.8)	20.4 (9.6, 31.1)
> 50 years	10 (12.7)	3 (18.7)	30.0 (1.6, 58.4)

Values are expressed as absolute number and within parenthesis are percentage. CI = confidence interval

All patients reported pain at different locations of the body (Figure 2). Upper limb (91%) and lower limb (96%) were the two most common locations affected. And ankle/foot joints were most frequently involved (80%). In addition to joint pain, some patients also reported non articular pain.

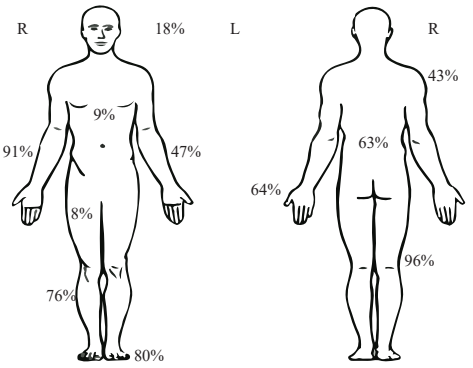

Fig. 2: Distribution of pain reported by patients.

Body areas: Head/neck 18%, Thorax/abdomen 9%, Back 63%, and Upper Limbs 91%, Lower Limbs 96%. Joints: Shoulder 43%, Elbow 47%, Hand/wrist 64%, Hip 8%, Knee 76%, and Ankle/foot 80%.

Discussion

Several outbreaks in different regions of the world have drawn attention to chikungunya virus infection, a long-neglected disease. The major outbreak of 2017 in Bangladesh appeared as an epidemic with 23 of 65 districts of the country getting infected[8].

Although pain is one of the hallmarks of chikungunya infection, only a few studies attempted to explore the association between neuropathic pain and chikungunya[12]. This is the first study that provides estimates on the prevalence of post-chikungunya neuropathic pain in Bangladesh. Chikungunya virus was found to infect all ages and both sexes. In this study, the mean age of patients was 37.05 ± 9.28 years which is consistent with the age distribution of chikungunya patients irrespective of pain[8,9]. But compared to patients with chronic pain after chikungunya in Reunion Island our study noted a lower average age of the patients[11,12]. However, this could be explained by the higher average age during the original outbreak of chikungunya in Reunion Island[18]. Hence an age-related increase in pain intensity couldn't be hypothesized without further study. Moreover, we didn't

notice any significant difference in age between patients with neuropathic pain and without neuropathic pain. Previous evidence[12] suggests that age is not a significant determinant of pain-associated deterioration in quality of life indicating that age doesn't impact on pain perception in patients with chronic chikungunya infection. Nonetheless a meta-analysis of risk factors for long term disabilities associated with chikungunya found that older patients were more likely to develop chronic complications than their younger counterpart[19]. We found a higher proportion of female among our participants. This might indicate a higher percentage of female attending the outdoors with chronic pain after chikungunya infection. The study by de Andrade et al. also supports the observation[12]. The pooled analysis by Farha et al. also supports this finding[19]. However, we noted that the prevalence of neuropathic pain in patients were statistically unrelated with their sex. Our findings suggest that many chikungunya patients were suffering from pain for a duration longer than found in other relevant studies[12]. We also noted that duration of pain was unrelated with presence of neuropathy among the patients. Patients in average reported a moderate pain intensity in the VAS scale and the intensity didn't differ significantly in relation to neuropathy. The study by de Andrade et al. in Reunion island among chronic chikungunya patients with pain also supports our findings[12]. In this current study, patients reported pain at multiple sites. The ankle/foot, knee, and hand/wrist joints were found to be most affected. Besides this, patients also reported pain in the upper and lower limbs. This finding remain consistent with other studies[7,20]. The current study demonstrated that the overall prevalence of post-chikungunya neuropathic pain was 19.11%. Interestingly this is similar to that found among general population where nearly one-third patients were found to have chronic pain and 19.9% had neuropathic pain[20]. Similar to these findings, we found a higher prevalence of neuropathic pain among female chronic chikungunya patients than male. The limitation of this study was that it was based on evaluation of painful patients seeking medical attention only. To estimate actual prevalence of post-chikungunya neuropathic pain in the general population, prospective studies involving large number of patients in the communities are needed.

Conclusion

This study documented neuropathic pain amongpatients suffering from chronic pain after chikungunya infection. These findings could facilitate comprehension of neuropathic pain related to chikungunya virus infection. Although the mechanism remains unclear, identification of neuropathic pain will help to develop efficient management and therapeutic strategies.

Declaration

Ethics approval:

The study was approved by the Ethical Review Committee of BSMMU. Informed written consent was taken from the participants before inclusion.

Author Contributions:

Conception and development of the idea: AKMA, MMK
Data collection: MMK, SA, MZ
Data analysis: MMK, MSI, MSRK
Writing - Original Draft Preparation:MMK, SA
Review & Editing: AKMA, MMK, MSRK

Funding: This study was funded by a Research Grant from Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka-1000, Bangladesh.

Conflict of Interests: None

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