Manifestations of Atypical Symptoms of Chikungunya during the Dhaka Outbreak (2017) in Bangladesh

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Abstract. Chikungunya (CHIK) has emerged as a major public health concern worldwide. Recently, atypical manifestations are drawing special attention because these might be associated with various complications. Information on atypical manifestations of CHIK is still limited. Here, we analyzed a dataset of 1,326 cases from our recent Dhaka outbreak study to explore the demographics and distributions of atypical manifestations. About 80% of cases reported at least one atypical symptom. Among all atypical symptoms, the most common and unique atypical symptom was joint pain before fever (90.2%), occurred predominantly in female respondents. Other common symptoms included red eye (68.2%), oral ulcer (37.7%), and dermatological manifestations (27.1%). More than two-thirds of patients reported multiple atypical symptoms. Atypical manifestations were not significantly different across age groups, except ocular complications. This study would be an important resource for clinicians and epidemiologists to understand the diversity of Chikungunya infection and, thus, help in better patient management.

INTRODUCTION

Chikungunya (CHIK) is a reemerging viral disease that has been causing widespread public health concerns affecting millions in different parts of the world in recent years. Since its origin in Africa in 1953, CHIK has caused over 72 epidemics in several countries across the world between 1959 and 2017.¹ India, the neighboring country of Bangladesh, has suffered from 12 epidemics, among which seven of them occurred after 2000.¹ Bangladesh also experienced a massive CHIK outbreak in 2017 after its first emergence in 2008 and subsequent two small-scale outbreaks in 2011–2012.^{2,3}

Clinical features of CHIK range from asymptomatic or mild infections to potentially fatal manifestations.^{4,5} However, Chikungunya virus (CHIKV) infection typically presents with an abrupt onset of high fever followed by incapacitating polyarthralgia, sometimes associated with macular or maculopapular rash.⁶ Other common symptoms include headache, fatigue, muscle pain, joint swelling, nausea, and vomiting.⁷ All the acute symptoms usually resolve within 7–10 days, although arthralgia may persist for years.⁸

Generally, CHIKV infection is considered to be a benign condition in terms of mortality because severe forms of infections are rare. With the recent rise in CHIKV outbreaks worldwide, atypical manifestations are drawing special attention of clinicians and epidemiologists because of their major and sometimes fatal complications.⁵ Information on the atypical manifestations of CHIKV infection is scarce apart from a few sporadic case reports and hospital-based studies.^{6,9,10} Careful assessment of the atypical symptoms is crucial in understanding the true characteristics of CHIKV infection and its effect on infected patients. The objectives of our study were to 1) investigate the occurrence and frequency

of atypical forms of manifestations among the patients and 2) identify demographic factors and comorbid conditions associated with an increased risk of atypical forms of CHIKV infection.

MATERIALS AND METHODS

There is no general consensus over the definition of atypical manifestations of CHIK infection. However, a panel of experts from the WHO proposed a formal definition of atypical cases.¹¹ In line with that, we recorded any manifestation other than fever and joint pain as an atypical symptom and grouped them according to the organ system involved. The onset of joint pain before fever was also taken into consideration as an atypical symptom. Atypical clinical manifestations were classified into neurological, skin, cardiac, and ocular based on the system involved. All other symptoms were kept under “others”. However, because nausea, vomiting, loss of appetite, and myalgia are common nonspecific symptoms for viral infection, they were left out of consideration for atypical manifestations.⁵

During the peak of CHIK outbreak (2017) in Dhaka city, the Biomedical Research Foundation (BRF) conducted a cross-sectional study to investigate the clinical profiles, economic burden, and quality of life of CHIK patients.² The study was conducted using a structured questionnaire with a face-to-face interview of the affected individuals within the first 2 weeks of the infection. The demographic and clinical profile dataset of the original study ($N = 1,326$) was retrieved from the Research Electronic Data Capture (REDCap) system hosted at the BRF.² A dataset of 1,098 cases was created having at least one atypical symptom as described earlier. Descriptive and inferential statistics were applied to analyze the dataset using IBM SPSS Statistics for Windows (SPSS Inc., Chicago, IL), version 25.0. Categorical variables were presented using counts and percentages, and continuous variables were summarized using means and standard deviations. For testing the association between categorical variables, Pearson's χ^2 test with continuity correction was used when necessary. A P -value smaller than

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0.05 was considered significant. To show the distribution of shared atypical symptoms among patients, a Venn diagram was constructed using InteractiVenn.¹² To create sets of patients, unique REDCap record identification numbers were used. The original study was approved by the Institutional Review Board of the Bangladesh University of Health Sciences (memo no.: BUHS/BIO/EA/17/077).

RESULT

Of 1,326 enrolled CHIKV cases in the original dataset, 1,098 cases (82.8%) had at least one atypical clinical manifestation. Nearly 6.4% of cases were children (aged < 15 years), whereas 6.9% were elderly (more than 60 years); the proportions of adolescents and young adults (15–29 years) and adults (30–59 years) were almost equal (over 40%). The male-to-female ratio was 1.26. A total of 336 (30.6%) patients had comorbidity, with the most common being hypertension (12.6%), diabetes (9.4%), and ischemic heart disease (3%).

Table 1 reports the frequency of atypical symptoms in the Dhaka (2017) outbreak. Joint pain preceding fever was the most frequently (90.2%) encountered atypical manifestation in our study followed by ocular symptoms, reported by more than two-thirds of the cases (74.4%). Other recorded symptoms included dermatological (27.1%) and neurological (9.7%) manifestations, particularly memory loss. In addition, about 38% of patients developed oral ulcer and 16% had chest pain during the acute phase of CHIKV infection. Interestingly, 21 patients (1.9%) experienced a fall in blood pressure from the baseline that returned to normal once the acute phase subsided.

Among patients with different atypical manifestations, there was a strong negative association between age and development of ocular symptoms ($\chi^2 = 8.471$, $P < 0.037$) (Figure 1).

TABLE 1

The classification of atypical symptoms manifested during the Chikungunya Dhaka outbreak, 2017

Atypical clinical manifestations	Number	%
Joint pain before fever	990	90.2
Neurological	106	9.7
Memory loss	103	9.4
Vertigo	2	0.2
Hallucination	1	0.1
Cutaneous	298	27.1
Pigmentation	229	20.9
Ulcerated lesion	54	4.9
Erythema	1	0.1
Maculopapular eruption	87	7.9
Cardiovascular	21	1.9
Drop in blood pressure	21	1.9
Ocular	817	74.4
Blurred vision	230	20.9
Red eye	749	68.2
Others	531	48.4
Oral ulcer	414	37.7
Bleeding manifestations	40	3.6
Chest pain	170	15.5
Alopecia	3	0.3
Hearing difficulty	1	0.1
Lymphadenopathy	2	0.2
Excessive thirst	1	0.1
Irritability	1	0.1
Total	1,098	100.0

The frequency of atypical symptoms varied significantly depending on gender. Female respondents experienced more neurological ($P = 0.038$), skin ($P = 0.007$), and joint pain before fever ($P = 0.003$) symptoms, whereas male respondents complained more about ocular symptoms ($P < 0.001$). Patients with preexisting chronic medical conditions were more likely to suffer from neurological symptoms ($P < 0.0001$) and less likely to develop ocular symptoms ($P < 0.0001$) than patients without comorbidity (Supplemental Table 1). More than 70% of patients reported more than one atypical symptom during the acute phase (Figure 2); 18 patients manifested symptoms involving all systems analyzed.

DISCUSSION

The purpose of this study was to report the atypical clinical presentation of CHIK in the Dhaka outbreak. Overall, atypical symptoms were noted in a higher frequency in our study than previous reports and showed significant association with age, gender, and comorbidity. Joint pain is the commonest reported symptom of CHIKV infection, typically appearing minutes to hours after the onset of fever in 87–99% cases.^{13,14} By contrast, in our study, more than 90% of the patients declared joint pain before the onset of fever. This unique finding was observed predominantly in female respondents compared with male respondents, with no differences across the age groups. Joint pain as the initial symptom was also reported in the Kerala outbreak (2007); however, the overall frequency was only 17% and it was highly prevalent among elderly (77%) compared with younger age groups.¹⁵ This might indicate a notable change in the pattern of CHIKV infection and, thus, could be an active area of future research.

In the present study, the proportion of patients developing eye redness (68.2%) and oral ulcer (37.7%) was much higher than that in outbreaks in India and Singapore.^{13,15} In contrast to the findings from the Reunion Island outbreak, the prevalence of blurred vision (20.9%) was lower, whereas the frequency of chest pain (15.5%) was higher.^{6,16} Fall in blood pressure during the acute phase of CHIKV infection was observed in a smaller fraction of patients (1.6%) than that in the epidemic in Reunion Island.⁶ Although this atypical symptom is frequently reported to occur in patients with dengue fever, it was rarely reported for CHIKV infection. In contrast to other outbreaks, cutaneous manifestations (27.1%) were not so frequent in the Dhaka outbreak.^{5,16,17} Although mostly observed as a long-term sequel of CHIKV infection in different outbreaks, we found that alopecia could also complicate the acute phase of CHIK fever in a few cases (0.3%) in our study.¹⁸

Our study suggests that women had a significantly higher risk of developing atypical manifestations during the acute phase, except for ocular complications, than men. The probability of developing atypical symptoms was not significantly different among age groups in the present study, except ocular manifestations, which occurred more frequently in children. In addition, we found that patients with comorbidity had a significantly higher chance of experiencing neurological symptoms. A similar observation has been reported in some other outbreaks.¹⁹

This study has some limitations. The findings were based on patient-reported outcomes of a nonrandom survey conducted when the outbreak was ongoing. This outbreak was widely

FIGURE 1. Distribution of atypical symptom manifestation over age and gender in the Chikungunya Dhaka outbreak, 2017 (N = 1,098).

covered in the media, which may have influenced patients' responses in some way. Also, patients were asked about their clinical symptoms retrospectively within the past 2 weeks of the survey, which is subject to some recall bias. Nevertheless, because of the scarcity of existing studies of similar nature, we could not validate the findings of this study using past studies. However, Bangladesh is a country with a homogenous population in terms of food, lifestyle, living conditions, and culture. As such, we hypothesize that similar outcomes would be observed for other regions within Bangladesh and other parts of the Indian subcontinent that share the common socio-environmental characteristics of its population.

A substantial amount of scientific literature in the last two decades suggests that CHIK should not be considered as a benign disease because it can inflict significant morbidity and mortality.⁶ A better understanding of this disease is critical for updating management strategies. This study, for the first time, has documented a comprehensive atypical clinical profile of the Dhaka outbreak based on a large sample. Information presented here would be invariably helpful, especially for clinicians and policymakers of Bangladesh, in improving the outcome of future outbreaks.

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Note: Supplemental table appears at www.ajtmh.org.

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FIGURE 2. Distribution of different atypical symptoms in the Chikungunya Dhaka outbreak, 2017 ($N = 1,098$). As the pain before fever manifested among 90.2% of patients suffering with atypical symptoms, this is excluded from the Venn diagram to make it readable. This figure appears in color at www.ajtmh.org.

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