

PATTERN OF PRESENTATION AND ORGAN INVOLVEMENT IN DENGUE FEVER AT DHAKA MEDICAL COLLEGE HOSPITAL

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Abstract

Dengue fever first identified as 'Dhaka Fever' in 1964 & became endemic around 2000. The most recent spreading of dengue in 2019 was also notable for change in the presenting features of the patients attributed by some to the fact that causative virus might be of different serotype. Our study aims to assess the current pattern of presentation of dengue virus infection, done in inpatient of Department of Medicine of Dhaka Medical College Hospital Dhaka. This was a cross-sectional, observational, descriptive study conducted between 1st August and 30th September 2019. A total 70 subjects, age >12 years were included in this study. Among them 55 were male & 15 were female, with a mean age of 28.33(±12.15) years. Comorbidities noticed in few cases such as DM (2, 2.90%), HTN (3, 4.35%), IHD (1, 1.45%), CKD & COPD (1, 1.45%). The most common presentation were fever (64, 91.43%), headache (62, 88.57%) anorexia (59, 85.51%), generalised pain (51, 73.91%), nausea (49, 71.01%). Examination findings at admission were temperature was high but not very high, pulse were normal, both systolic & diastolic pressure were somewhat normal, among the warning signs, severe abdominal pain (27.54%), persistent vomiting (21.74%), lethargy /restlessness /sudden behavioural change (21.74%) were most common. The common haematological parameters & routine investigation values were not deviated from expected range. As dengue is likely to continue to constitute a serious public health problem in Bangladesh, this study may help the practitioners to understand the changing pattern & to manage patients accordingly.

Keywords: Dengue, Clinical features, Presenting features, Changes, New Serotype, Dhaka, Bangladesh.

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Introduction

Since its first introduction to the world during 1779-1780 in Asia¹, annually, 100 million cases of dengue fever and half a million cases of DHF occur worldwide.² The word Dengue came from the word "Denga" which was its local name in Zanzibar during 1870 epidemic.³ Although Bangladesh saw the first dengue outbreak in 1964-65,^{1,3} then identified as "Dhaka Fever",

it is not until the epidemic in 2000, dengue really gained the attention of medical community, mass people, media and concerned authorities.^{1,3-5} Since then, dengue has remained endemic in Bangladesh.⁶ Dhaka has always been in the most likely cluster for dengue fever.⁴ In Bangladesh, hospital based prevalence of immunoglobulin M positive dengue cases among febrile patients has been determined to

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be 69% in a cross sectional study.⁷ In 2016, it was reported that dengue incidence began increasing, and alarm has been raised in mainstream media too.^{8,9} But the real panic set in 2019, where the spread of dengue span all over the country in a sudden surge. According to Directorate General of Health Services (DGHS), 14 people had died and 19,513 people had been affected before 1st August 2019, many of whom were children.^{10,11} According to Centre for Disease Control (CDC), DGHS, between January-August of 2019, total number of reported cases was 38,844 and total number of reported deaths was 29.¹² Mutsuddy et.al have suggested that the climate changes after 2014, and other associated factors, such as rapid unplanned urbanization may have caused some ecological imbalances in the environment that leads to occurrence of more dengue cases in the pre-monsoon season and has also led to an explosion of chikungunya for the first time in Bangladesh in 2017.¹³ For a long time, dengue fever has been believed to be caused by four different serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). A fifth serotype DENV-5 has been detected during screening of viral samples taken from a 37 year old farmer admitted in hospital in Sarawak state of Malaysia in the year 2007 and announced in October 2013.¹⁴

Dengue is a painful disease for the patients, and has infamously been called as “break-bone fever”, a name given during the first described epidemic in Philadelphia in 1780,¹⁵ indicating the notoriety and severity of symptoms.¹⁵⁻¹⁷ The clinical features of dengue patients may consist of the following:

1. Symptoms

- a. Fever: Typically lasting for five to seven days, with saddleback or biphasic curve manifested by a second phase fever lasting for one or two days.^{18,19}
- b. Headache
- c. Retro-orbital pain
- d. Muscular pain/myalgia
- e. Joint pain/arthralgia
- f. Marked fatigue lasting for days to weeks
- g. Other symptoms²⁰

- i. Rash
 - ii. Gastrointestinal symptoms including nausea or vomiting
 - iii. Respiratory tract symptoms including cough, sore throat, and nasal congestion
2. Signs: mostly nonspecific²¹
 - a. Fever
 - b. Rash: The rash is typically macular or maculopapular and may be associated with pruritus.
 - c. Conjunctival injection
 - d. Pharyngeal erythema
 - e. Lymphadenopathy
 - f. Hepatomegaly
 - g. Petechial
 - h. Positive tourniquet test
 3. Laboratory findings:
 - a. Leukopenia: Common in both adults and children²¹⁻²³
 - b. Thrombocytopenia is noted in most patients with dengue fever.¹⁷
 - c. Serum aspartate transaminase (AST) levels are frequently elevated in both adults and children with dengue fever.¹⁸

Although, above mentioned clinical features or investigation findings have been known for long to be associated classically with dengue infection, the most recent experience of dengue outbreak in Bangladesh in 2019 is much different from the previous ones. The shift in the known pattern of dengue infection is seen in epidemiological context in terms of mortality and morbidity, and also in the presentation of the disease.¹³ Akram A reported that in 2019, the mostly detected dengue virus was of DEN 3 serotype (predominant) followed by co-detection of DEN2 & DEN3 and DEN1 & DEN3 (few cases), in contrast to the previous years (2013-18).²⁴ This may also explain the fact that clinical presentations are often very much different from the previous experience. This phenomenon is noted by many leading clinicians, including Professor Dr. Md. Muzibur Rahman, Head, Department of Medicine, Dhaka Medical College, as he has pointed out in an interview to Daily Sun,²⁵ but to this date, this phenomenon has not been properly studied or reported in any scientific literature, neither in

Bangladesh or abroad. Thus, this study aims to assess the current pattern of presentation of dengue virus infection.

Materials and methods

General Objective:

Main objective of this study was to compare clinical features and CBC, and other routine investigatory parameters of dengue patients.

Specific Objectives:

1. To find out the clinical features associated with dengue infection.
2. To find out the CBC parameter changes associated with dengue infection.
3. To find out the pattern of organ involvement associated with dengue infection.

Type of study

This was a cross-sectional, observational, descriptive study.

Time of study

The conduction of study was done between 1st August and 30th September 2019.

Place of study

The study was done in the inpatient of Department of Medicine, Dhaka Medical College Hospital, Dhaka, a tertiary level Government run health care facility, acting as the ultimate referral centre. In fact, the hospital provides service to entire Bangladesh, and has to deal with a very high patient load, so a suitable place for conducting such study.

Sampling method

Consecutive, purposive sampling technique was employed. A total of 70 patients were included in this study.

Inclusion Criteria

1. Patient >12 years old, presenting to Department of Medicine with any of the following condition, according to operational definition:
 - a. Probable Dengue infection OR,
 - b. Dengue fever with warning signs OR,
 - c. Severe dengue

AND,
2. Dengue NS1 antigen was positive OR,
3. Dengue IgM was positive.

Exclusion criteria

1. Dengue IgG was positive but without Dengue NS1 antigen or, Dengue IgM positivity.
2. Unwilling to participate.
3. Patients with suspicion of bacterial fever.
4. Patients with suspicion of other virus infection.
5. Patients with significant co-morbidity which might cause fever e.g. malignancy (hepatoma) or endocrine disorders (thyrotoxicosis)

Operational definition

1. Probable dengue:²⁶
 - a. Live in or travel to dengue endemic area (e.g. Dhaka),
 - b. Fever and two of the following criteria:
 - i. Nausea, vomiting
 - ii. Rash
 - iii. Aches and pains
 - iv. Tourniquet test positive
 - v. Leukopenia
 - vi. Any warning sign
2. **Laboratory confirmed dengue:** Dengue IgM or Dengue NS1 antigen was positive.
3. **Dengue with warning sign:**²⁶
 - a. Abdominal pain or tenderness
 - b. Persistent vomiting
 - c. Clinical fluid accumulation
 - d. Mucosal bleed
 - e. Lethargy, restlessness
 - f. Liver enlargement >2 cm
 - g. Increases in hematocrit concurrent with rapid decrease in platelet count.
4. **Severe Dengue:**²⁶
 - a. Severe plasma leakage leading to
 - i. Shock
 - ii. Fluid accumulation causing respiratory distress
 - b. Severe bleeding
 - c. Severe organ involvement
 - i. Liver ALT/AST \geq 1000 U/L
 - ii. CNS: Impaired consciousness
 - iii. Signs of heart or other organ involvement (e.g. raised troponin I)

Data collection process

Data was collected by a structured closed end questionnaire with predefined set of questions. Data collection was done meticulously with detailed interviewing of the respondents.

Ethics, consent and permissions

Written informed consents were taken from all of the participants or in case of minors, consents were taken from the accompanying legal guardians/parents. In all steps of the study, all ethical aspects were strictly observed and the privacy of the data of the patients were strictly maintained.

Ethical approval

Ethical approval was taken from the Ethical Review Committee of Dhaka Medical College, Dhaka.

Data analysis

Data analysis was done in Statistical Package for Social Sciences, (SPSS, IBM Corporation, USA) version 23.0. Mostly descriptive analysis was conducted and presented with figures and tables, suitable with the purpose of this article.

Results

A total of 70 subjects, age > 12 years, who were admitted in the Department of Medicine, Dhaka Medical College Hospital, diagnosed as dengue virus infection, were included in the study to see the pattern of presentation and organ involvement in dengue infection. The results are

presented below in tables and graphs. Among the total 70 patients, 55 (78.57%) were male, and 15 (21.43%) were female (Figure 1, Table 1).

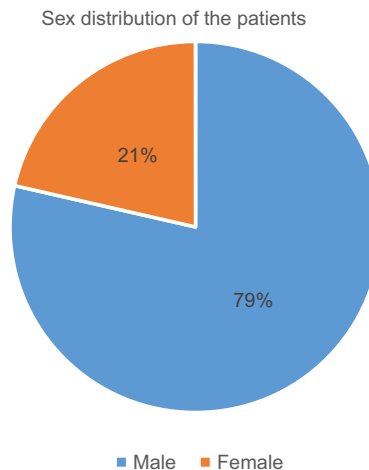


Fig.-1: Sex distribution of the patients

Most of the patients were young, with a mean age of 28.33 (SD, ± 12.15) years and a median age of 23 (IQR, 23-35) years (**Table 1**). Most of the patients lived at home in urban area 59 (86.76%) and lived in brick-built buildings 54 (79.41%), and only a very small number of them suffered from any other significant pre-existent co-morbidity, such as, diabetes mellitus (2, 2.90%), hypertension (3, 4.35%), ischemic heart disease (1, 1.45%), chronic kidney disease (1, 1.45%) chronic obstructive pulmonary disease (1, 1.45%) (**Table 1**).

Table-1
Baseline characteristics of the patients

		Total (N)	Count (n)	%
Age in years (Median, IQR)	23 (23-35)			
Age in years (Mean ± SD)	28.33 ± 12.15			
Sex	Male	70	55	78.57%
	Female		15	21.43%
Location of home	Urban	68	59	86.76%
	Rural		9	13.24%
Type of household	Building	68	54	79.41%
	Slum house		2	2.94%
	Semi paka		12	17.65%
Diabetes mellitus		69	2	2.90%
Hypertension		69	3	4.35%
Ischemic heart disease		69	1	1.45%
Chronic kidney disease		69	1	1.45%
Chronic obstructive pulmonary disease		69	1	1.45%

*IQR= Interquartile range. SD= Standard deviation, N= total valid number of subjects upon which the observation is made, n= number in sub-category

Table-II
Initial presentations of the patients

	Total (N)	Count (n)	%
Fever	70	64	91.43%
Headache	70	62	88.57%
Anorexia	69	59	85.51%
Generalized pain	69	51	73.91%
Nausea	69	49	71.01%
Backache	70	47	67.14%
Vomiting	69	46	66.67%
Arthralgia	70	45	64.29%
Fatigue	69	44	63.77%
Retro orbital pain	70	36	51.43%
Dyspepsia	69	26	37.68%
Break-bone fever	69	14	20.29%
Upper respiratory tract infection (URTI) symptoms	69	14	20.29%
Prostration	68	13	19.12%
Lacrimation	69	11	15.94%
Pharyngitis	67	7	10.45%
Hyperesthesia	68	6	8.82%
Depression	68	6	8.82%
Scleral injection	69	6	8.70%

*N= total valid number of subjects upon which the observation is made, n= number in sub-category

The most common presentation was fever (64, 91.43%), headache (62, 88.57%), anorexia (59, 85.51%), generalized pain (51, 73.91%) and nausea (49, 71.01%), followed by backache, vomiting, arthralgia (Table 2).

Examination findings of the patients at admission are shown in Table 3. Here it can be seen that usually temperature was high, but not very high, mean temperature in degree Fahrenheit (\pm SD): 100.74 \pm 1.70 $^{\circ}$ F, median (IQR):101.00 (99.00-102.00) $^{\circ}$ F. Pulse was almost normal, mean (\pm SD): 80.53 \pm 11.61 beats/min, median (IQR): 80.00 (72.00-89.00) beats/min. both systolic and diastolic BP were somewhat on the lower side of normal range. Rash was the most common examination finding (21, 30.88%) followed by bleeding spots (12, 17.14%).

Among the warning signs (Table 4), severe abdominal pain (27.54%), persistent vomiting (21.74%), lethargy/restlessness/sudden behavioral change (21.74%) were the most common, followed by hematocrit rise > 20%, black stool, pale, cold, clammy hands and feet.

Table-III
Examination findings of the patients

	Total (N)	Count (n)	%
Pulse (beats/min)	Mean (\pm SD): 80.53 \pm 11.61, Median (IQR): 80.00 (72.00-89.00)		
Systolic BP (mm-Hg)	Mean (\pm SD): 98.79 \pm 13.50, Median (IQR):100.00 (90.00-110.0)		
Diastolic BP (mm-Hg)	Mean (\pm SD): 65.57 \pm 9.76, Median (IQR): 70.00 (60.00-70.00)		
Temperature in Fahrenheit	Mean (\pm SD): 100.74 \pm 1.70, Median (IQR):101.00 (99.00-102.00)		
Rash	68	21	30.88%
Bleeding spots	70	12	17.14%
Disorientation	69	1	1.45%
Lymphadenopathy	69	0	0.00%
Hepatomegaly	69	0	0.00%

*IQR= Interquartile range. SD= Standard deviation, N= total valid number of subjects upon which the observation is made, n= number in sub-category

Table-IV
Warning signs of the patients

	Total (N)	Count (n)	%
Severe abdominal pain	69.00	19.00	27.54%
Persistent vomiting	69.00	15.00	21.74%
Lethargy/restlessness/sudden behavioral change	69.00	15.00	21.74%
Hematocrit rise > 20%	68.00	13.00	19.12%
Black stool	69.00	10.00	14.49%
Pale, cold, clammy hands and feet	69.00	8.00	11.59%
Dark colored urine	69.00	6.00	8.70%
Epistaxis	69.00	5.00	7.25%
Clinical worsening during afebrile phase	67.00	4.00	5.97%
Giddiness	68.00	4.00	5.88%
Excessive menstruation/PV bleeding	17.00	1.00	5.88%
Less urine output for 4-6 hours	69.00	4.00	5.80%
Hematemesis	69.00	3.00	4.35%
Hematuria	69.00	1.00	1.45%
Liver enlargement > 2 cm	68.00	0.00	0.00%

*N= total valid number of subjects upon which the observation is made, n= number in sub-category

Table-V
Results obtained from investigation of the patients

	Mean \pm SD	Median (IQR)
Haemoglobin (g/dL)	13.77 \pm 1.72	13.60 (13.15-14.75)
Total count of WBC (per cu. mm)	5448.18 \pm 3313.21	3800.00 (3000.00-9000.00)
Neutrophils (per cu. mm)	5630.00.	5630.00 (5630.00-5630.00)
Lymphocytes (per cu. mm)	4500.00.	4500.00 (4500.00-4500.00)
Eosinophils (per cu. mm)	230.00.	230.00 (230.00-230.00)
Hematocrit (%)	41.96 \pm 11.30	41.00 (35.65-44.05)
ESR (mm at 1st minute)	19.09 \pm 12.69	18.50 (7.00-30.00)
Total count of platelets (per cu. mm)	83879.74 \pm 70207.36	60000.00 (25000.00-121000.00)
Serum creatinine (mg/dL)	1.08 \pm .38	1.01 (.76-1.30)
SGPT/ALT (U/L)	239.17 \pm 645.27	52.00 (30.00-120.00)
SGOT/AST (U/L)	130.00 \pm 125.23	103.00 (27.00-205.00)
Total serum bilirubin (mg/dL)	2.38 \pm 3.00	.70 (.60-5.85)
Direct serum bilirubin (mg/dL)	1.10.	1.10 (1.10-11.10)

* SD= Standard deviation, IQR= Interquartile range

The common haematological parameters and routine investigation values are shown in Table 4. It is evident, that none of the values was much deviated from expected range.

Discussion

In this study, total 70 patients were enrolled, among which 55 (78.57%) were male, and 15 (21.43%) were female (Figure 1, Table 1). Most of the patients were young, with a mean age of 28.33 (SD, \pm 12.15) years and a median age of 23 (IQR, 23-35) years (Table 1). This finding is also similar to that found by Manthalkar and Peerapur, who have also reported that age group of 16–30 years was more affected followed by 31–45 years.²⁷ The sex distribution of the patients are dissimilar to Manthalkar and Peerapur, probably owing to the fact that in this study, random sampling technique was not employed.²⁷

Most of the patients lived at home in urban area 59 (86.76%) and lived in brick-built buildings 54 (79.41%), and only a very small number of them suffered from any other significant pre-existent co-morbidity, such as, diabetes mellitus (2, 2.90%), hypertension (3, 4.35%), ischemic heart disease (1, 1.45%), chronic kidney disease (1, 1.45%) chronic obstructive pulmonary disease (1, 1.45%) (Table 1). This findings are consistent as reported by Cousins S, Akram A and others who have suggested urban areas, and especially Dhaka being at the centre of all dengue infections.^{24,28}

In this study, the most common presentation was fever (64, 91.43%), headache (62, 88.57%), anorexia (59, 85.51%), generalized pain (51, 73.91%) and nausea (49, 71.01%), followed by backache, vomiting, arthralgia (Table 2). These findings are similar to findings by Tsai et.al. and Yung et.al.^{29,30} Tsai et.al. have reported that patients with DENV-3 were more likely to have a malignancy ($p = 0.011$), myalgia ($p = 0.03$), skin rash ($p < 0.001$), ascites ($p = 0.04$), and fever ($p = 0.003$) than patients with DENV-2.²⁹ Yung et.al. have reported headache, eye-ache, muscle pain, joint pain, rash being the most common manifestations, similar to this study.³⁰

In this study, examination findings of the patients at admission are shown in Table 3. Here it can be seen that usually temperature was high, but not very high, mean temperature in degree Fahrenheit (\pm SD): 100.74 \pm 1.70 $^{\circ}$ F, median (IQR):101.00 (99.00-102.00) $^{\circ}$ F. Pulse

was almost normal, mean (\pm SD): 80.53 \pm 11.61 beats/min, median (IQR): 80.00 (72.00-89.00) beats/min. both systolic and diastolic BP were somewhat on the lower side of normal range. Rash was the most common examination finding (21, 30.88%) followed by bleeding spots (12, 17.14%). The systolic BP is much lower than found in study by Yung et.al. who have reported median systolic BP between 112-116 mm-Hg in all serotypes.³⁰ This low level of systolic BP could possibly be attributed to many factors in this study, including, increased proportion of the sample being relatively younger, presentation at the highest referral centre requiring a great deal of journey from remote areas of country which caused pronounced dehydration, or lack of awareness of the patient parties who presented late to the hospital.

In this study, several warning signs (Table 4) such as, severe abdominal pain (27.54%), persistent vomiting (21.74%), lethargy/restlessness/sudden behavioural change (21.74%) were the most common, followed by haematocrit rise $> 20\%$, black stool, pale, cold, clammy hands and feet.

The common haematological parameters and routine investigation values are shown in Table 4. It is evident, that none of the values were much deviated from expected range. Tsai et.al. reported that patients with DENV-3 had their lowest levels of white blood cells and platelets, and peak plasma activated partial thromboplastin time (aPTT) 1 day later than patients with DENV-2.²⁹ DENV-2 infection was associated with a higher monocyte count and more prolonged aPTT early in the clinical course.²⁹ In this study, median platelet count was 60,000 (25,000-1,21000)/mm³ which is much lower than found in the study by Yung et.al. where they have found the lowest platelet count (1,14,000/mm³) in DENV-2 serotype, which is still much higher than our result.³⁰ Haematocrit and other parameters are similar to findings in study by Tsai et.al. and Yung et.al.^{29,30}

According to Akram A, since 2000, Bangladesh has experienced dengue fever in every year. All four serotypes have been detected, with DENV-

3 predominance until 2002.²⁴ Later, during the years 2013 to 2016 a recent report showed that DENV-1 and DENV-2 were the predominantly circulating serotypes in 3 major cities in Bangladesh, including Dhaka.³¹ Akram A has suggested that as DENV-1 and DENV-2 have been in circulation for more than a decade, thus, a large portion of the country's population might be immune to serotypes DENV-1, DENV-2 or both; however, they are at risk of developing severe dengue infection by DENV-3 or DENV-4.²⁴ Thus, the high frequency of severe dengue cases in 2018 and 2019 correlates with the prevalence of serotype DENV-3.³² There have been studies suggesting differences of symptoms, signs, and laboratory findings across different serotypes of dengue, without any significant differences in outcomes.^{29,33} After reviewing the current opinions, and recent findings, it can be deduced that DENV-3 serotype has re-emerged in Bangladesh. Thus, not only the epidemiological traits, also the clinical features have also become largely different from what the clinicians have seen for the last decade or more. Therefore, for the clinicians, a source of reference should be present regarding the currently found clinical features. This study hopefully may function as that source of reference. Moreover, according to different researchers, including Suppiah et.al. and Yung et.al., severity of disease varies among the different serotypes, and so knowing the serotype early in the course of the disease may help in predicting the severity.^{30,34}

Cousins S reported in the 'Lancet Infectious Diseases Journal' that the dengue picture in Bangladesh is being further complicated by management problems such as, understaffed public hospitals in urban areas, as urban health is sorely neglected in Bangladesh, although the country boasts strong rural health system.²⁸ The policymakers must be aware of the true situation. As, dengue is a arthropod borne viral infection, no amount of clinical management, or curative treatment will be enough to save the vast and one of the densest population like ours, without proper preventive measures, and adequate vector control.

Conclusion

To conclude it can be predicted that dengue is likely continue to constitute a serious public health problem for Bangladesh, as Mutsuddy et.al have suggested.¹³ The changing disease pattern should be clearly understood and constant monitoring is needed. From the policy and management level, steps should be taken up to prevent the disease.

Limitations of the study

For time and monetary constraints, only a few number of patients were enrolled in the study. Serotyping of dengue virus could not be done for the same reasons.

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Conflict of interest: None.

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