

Changes in the Clinical and Laboratory Parameters in Children with Dengue Syndrome: Experience during Dengue Outbreak in 2019 of Bangladesh

Sayeeda Anwar^{1*}, Habiba Khatun², Fatema Farzana³, Mohammad Shafiqul⁴, Alam Chowdhury⁵

¹Professor and Head, Department of Pediatrics, Dhaka Medical College Hospital, Dhaka, Bangladesh. Email: anwar_sayeeda@yahoo.com

*Corresponding author

³MD student, Department of Pediatrics, Dhaka Medical College, Dhaka, Bangladesh.

⁴Consultant, Department of Pediatrics, MAbdur Rahim Medical College Hospital, Dinajpur, Bangladesh.

⁵Assistant Professor, Department of Paediatrics, Dhaka Medical College Hospital, Dhaka, Bangladesh.

Received: March 2021

Accepted: April 2021

Abstract

Background: Dengue is an acute febrile disease caused by a flavi virus with four known serotypes (DENV-1, DENV-2, DENV-3 and DENV-4). The infection is transmitted by the bite of female mosquitoes of the genus *Aedes* *aegypti* and *Aedes* *albopictus*. Dengue was first reported in Bangladesh in 1964 when it was known as “Dacca Fever”; since then, it has remained endemic. Aim of the study: To assess changes in the clinical and laboratory parameters in children with dengue syndrome in Bangladesh. **Methods:** This cross-sectional analytical study was conducted at the Department of Paediatrics, Dhaka Medical College and Hospital (DMCH) during the period from April, 2019 to March, 2020. Total 384 admitted children of both gender between the ages of one month to 12 years and with clinical manifestations of suspected dengue and positive NS1 antigen and/or dengue antibody with serology IgM or IgG or both. Statistical analysis was done by using the statistical package for social science (SPSS-21) program. Every precaution was taken so that study does not cause any harm or delay for treatment of cases. No incentive was given to the participants. **Results:** Mean age was 7.5±3.2 years with a range of 1 month to 12 years. Males were predominant to females. Fever was present in all patients 384 (100%). All patients were positive with NS1 antigen, however higher number of patients were positive with IgM antibody. IgG was mostly positive in DSS patients. Significantly highest number of patients in DF had haemoglobin level between 10-15 gm/dl. Maximum patients of DF, DHF, DSS and EDS had haematocrit (%) between (35-45) percent. Significantly highest number of patients in DHF had raised SGPT (45-200U/L) & SGOT value (60-200U/L). Half of the patients of EDS had SGPT & SGOT >1000U/L. Low random blood sugar and raised serum creatinine was present in one fourth of the EDS patients. **Conclusion:** In this study, majority of the cases were DSS. Most common clinical presentation was vomiting, shock, abdominal pain and bleeding manifestations along with fever. Raised HCT, leucopenia and neutropenia were observed in small number of patients.

Keywords: Dengue, Children, Fever, Febrile, Mosquitoes.



INTRODUCTION

Dengue made its debut as early as 1780, when Benjamin Rush described the condition as a “break bone fever”. Since its first recognition during the last quarter of eighteenth century, outbreaks have been reported from both developed and developing countries with Asia always remaining the area of highest endemicity.^[1]

Dengue is an acute febrile disease caused by a flavivirus with four known serotypes (DENV-1, DENV-2, DENV-3 and DENV-4).^[2] The infection is transmitted by the bite of female mosquitoes of the genus *Aedes aegypti* and *Aedes albopictus*. Human are the main reservoir for the dengue virus. Infection with one dengue serotype confers lifelong homotypic immunity to that serotype and a very brief period of partial heterotypic immunity to other serotypes, but a person can eventually be infected by all 4 serotypes. Several serotypes can be in circulation during an epidemic.^[3] Secondary infection with another serotype or multiple infections with different serotypes enhance the chances of severe form of disease.^[4] Bangladesh is situated in tropical and sub-tropical regions like other South-East Asian (SE) countries and like them has become a suitable habitat for the dengue vector and its increased transmission.^[5] Dengue was first reported in Bangladesh in 1964 when it was known as “Dacca Fever”; since then, it has remained endemic. In 2018 Bangladesh experienced an unusual outbreak of Dengue with highest incidence of recorded cases.⁶ In the year 2019 there was significant

increase in number of cases of dengue throughout the country and even from the rural areas.^[4] Dengue fever (DF) and its severe form -dengue haemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS) have emerged as a notable public health problem in recent decades in terms of mortality and morbidity associated with it. Many patients infected with dengue virus remain asymptomatic. Others, after an incubation period of 4-7 (range 3-14) days, develop a febrile illness the manifestations of which are similar and overlapping in nature grouped into 'Dengue Syndromes' which encompass the following: Undifferentiated fever, DF, DHF, DSS & expanded dengue syndrome (rare).^[4] The new classification also encompasses a set of 'warning signs' intended to help clinicians identify patients likely to develop complications during the critical phase of the illness.^[7] The next 24-48 hours of the critical stage can be lethal; proper medical care is needed to avoid complications and risk of death.⁸ The incidence and severity of dengue in children is changing every year in Bangladesh, but the outbreak of this year is different from previous years, creating a significant public health concern. Although children are the most vulnerable group affected by the dengue syndromes, little published data regarding the recent trends are available in Bangladesh. So this study can be used to find out the changes in the clinical, hematological and biochemical parameters and their frequency in the outbreak of 2019 and that will help in the management of

subsequent outbreak especially in children.

MATERIALS AND METHODS

This cross-sectional analytical study was conducted at the Department of Paediatrics, Dhaka Medical College and Hospital (DMCH) during the period from April, 2019 to March, 2020. Total 384 admitted children of both gender between the ages of one month to 12 years and with clinical manifestations of suspected dengue and positive NS1 antigen and/or dengue antibody with serology IgM or IgG or both. Patients were divided into undifferentiated fever (UDF), dengue fever (DF), dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS) and expanded dengue syndrome (EDS) group. Clinical parameters such as fever, skin rash, bleeding, vomiting, abdominal pain, convulsion, signs of shock, positive tourniquet test, hepatomegaly, ascites and pleural effusion; hematological parameters such as haemoglobin (Hb), haematocrit (HCT),

total leucocyte count, neutrophil, lymphocyte value and total platelet count and biochemical parameters such as SGPT, SGOT, PT, aPTT and serum albumin value of all subjects were recorded and analyzed. Statistical analysis was done by using the statistical package for social science (SPSS-21) program. Informed written consent from the parents/attendant was taken prior to include the child in the study. Every precaution was taken so that study does not cause any harm or delay for treatment of cases. No incentive was given to the participants.

RESULTS

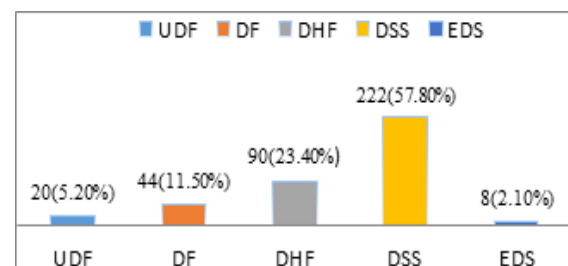


Figure 1: Types of dengue syndromes (N=384)

Table 1: Demographic and epidemiological parameters of subjects (N= 384)

Parameters	Frequency (n)	Percentage (%)
Age		
1month-1year	11	3
1-4 year	68	17
4-9 year	137	36
9-12 year	168	44
Mean ± SD (min-max)7.5±3.2 (0.45-12)		
Gender		
Male	226	59
Female	158	41

Table 2: Distribution of symptoms in children with Dengue Syndrome (N=384)

Parameters	Frequency (n)	Percentage (%)
Fever		
Low-grade	27	7



High-grade	357	93
Duration		
<5days	186	48
≥5days	198	52
Skin rash		
Maculopapular	37	9.6
Rubelliform	29	7.6
Flushing	3	0.8
Bleeding	5	1.3
Vomiting	132	34.4
Abdominal pain	303	78.9
Convulsion	166	43.2
	4	1.0

Table 3: Distribution of the subjects according to signs (N=384)

Parameters	Frequency (n)	Percentage (%)
Signs of shock	227	59.0
Tourniquet test (+ve)	110	28.6
Hepatomegaly	42	10.9
Ascites	52	13.5
Pleural effusion	84	21.9

Table 4: Dengue serology in subjects with dengue syndromes (N=384)

Parameters	UDF (n=20) N (%)	DF (n=44) N (%)	DHF (n=90) N (%)	DSS (n=222) N (%)	EDS (n=24) N (%)	Total (n=384) N (%)
NS1	18(90)	40(91)	77(86)	190(86)	6(75)	331(86)
IgM only	2(10)	3(7)	8(10)	19(9)	2(25)	34(9)
IgG only	0(0)	0(0)	1(1)	9(4)	0(0)	10(3)
IgM+IgG	0(0)	1(2)	4(3)	4(1)	0(0)	9(2)

Table 5: Haemoglobin (Hb) and haematocrit (HCT) % among groups (N=384)

Parameters	UDF (n=20) N (%)	DF (n=44) N (%)	DHF (n=90) N (%)	DSS (n=222) N (%)	EDS (n=8) N (%)	p value
Hb(gm/ dl)						
<10	5(25)	2(5)	14(15)	26(12)	2(25)	0.031a
10-15	15(75)	42(95)	70(78)	164(74)	5(63)	
>15	0(0)	0(0)	6(7)	32(14)	1(12)	
HCT (%)						
<25	0(0)	0(0)	2(7)	6(3)	0(0)	0.122a
25-35	14(70)	16(36)	35(33)	68(30)	4(50)	
35-45	6(30)	28(64)	50(52)	124(53)	4(50)	
>45	0(0)	0(0)	3(8)	24(14)	0(0)	

Table 6: TLC (cells/mm³), neutrophil (%) and lymphocyte (%) among groups (N=384)

Parameters	UDF(n=20) N (%)	DF(n=44) N (%)	DHF(n=90) N (%)	DSS(n=222) N (%)	EDS(n=8) N (%)	p value
TLC (cells/mm ³)						
<4000	0(0.0)	12(27.3)	18(20.0)	49(22.1)	2(25.0)	0.07a
4000-11000	18(90.0)	29(65.9)	62(68.9)	147(66.2)	2(25.0)	
>11000	2(10.0)	3(6.8)	10(11.1)	26(11.7)	4(50.0)	



Neutrophil (%)						
<40	2(10.0)	18(40.9)	37(41.1)	89(40.1)	1(12.5)	0.113a
40-60	13(65.0)	13(29.5)	35(38.9)	86(38.7)	4(50.0)	
>60	5(25.0)	13(29.5)	18(20.0)	47(21.2)	3(37.5)	
Lymphocyte (%)						
<20	3(15.0)	7(15.9)	5(5.6)	19(8.6)	1(12.5)	0.465a
20-40	5(25.0)	12(27.3)	23(25.6)	62(27.9)	4(50.0)	
>40	12(60.0)	25(56.8)	62(68.9)	141(63.5)	3(37.5)	

Table 7: Total platelet count/TPC (cells/mm³) of the subjects among groups (N=384)

Parameters	UDF(n=20) N (%)	DF(n=44) N (%)	DHF(n=90) N (%)	DSS(n=222) N (%)	EDS(n=8) N (%)	p value
<20000	0(0.0)	0(0.0)	11(11.1)	33(14.9)	1(12.5)	<0.001a
20000-50000	0(0.0)	7(15.9)	32(35.5)	74(33.3)	0(0.0)	
50000-100000	0(0.0)	20(45.5)	23(28.9)	65(28.8)	0(0.0)	
100000 - 1500000	0(0.0)	17(38.6)	16(17.8)	27(12.2)	2(25.0)	
1500000- 450000	18(90.0)	0(0.0)	8(8.1)	23(10.8)	5(62.5)	
>4500000	2(10.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	

Table 8: SGPT and SGOT level (U/L) among study groups (N=384)

Parameters	UDF(n=20) N (%)	DF(n=44) N (%)	DHF(n=90) N (%)	DSS(n=222) N (%)	EDS(n=8) N (%)	p value
SGPT (U/L)						0.001a
≤45(Normal)	19(95)	36(82)	25(28)	98(44)	3(38)	
45-200	1(5)	8(18)	54(60)	117(53)	1(12)	
200-1000	0(0)	0(0)	11(12)	7(3)	0(0)	
>1000	0(0)	0(0)	0(0)	0(0)	4(50)	
SGOT (U/L)						0.001a
≤60 (Normal)	19(95)	38(86)	22(25)	82(37)	4(50)	
60-200	1(5)	6(14)	47(52)	115(52)	0(0)	
200-1000	0(0)	0(0)	21(23)	25(11)	0(0)	
>1000	0(0)	0(0)	0(0)	0(0)	4(50)	

Table 9: PT (sec), aPTT (sec) and S. Albumin (gm/dl) level among study groups (N=384)

Parameters	UDF(n=20) N (%)	DF(n=44) N (%)	DHF(n=90) N (%)	DSS(n=222) N (%)	EDS(n=8) N (%)	p value
PT (sec)						<0.001a
>16	0(0)	0(0)	3(29)	1(8)	4(50)	
≤16	20(100)	44(100)	87(71)	221(92)	4(50)	
APTT (sec)						<0.001a
>36	0(0)	1(2)	13(14)	29(13)	3(37)	
≤36	20(100)	43(98)	77(86)	193(87)	5(63)	
Albumin(gm/ dl)						<0.001a
<3.0	0(0)	0(0)	17(19)	79(35)	1(12)	
≥3.0	20(100)	44(100)	73(81)	143(65)	7(88)	

Table 10: Random blood sugar, s. calcium and s. creatinine of EDS subjects (n=8)

Parameters	Frequency (%)
Random blood sugar (m mol/l)	
Low (<3.3)	2 (25.0)
Mean \pm SD (Range)	4.1 \pm 0.7 (3.0-5.2)
S. Calcium (mg/dl)	
Low (<8.8)	5 (62.5%)
Mean \pm SD (Range)	8.11 \pm 0.84 (6.76-9.0)
S. Creatinine (mg/dl)	
Raised (\geq 1.0)	2 (25.0%)
Mean \pm SD (Range)	0.95 \pm 0.68 (0.4-2.5)

[Table 1] showed maximum patients were in the age group of 9-12 years and lowest number of cases was in age group of 1month-1 year. Mean age was 7.5 \pm 3.2 years with a range of 1 month to 12 years. Males were predominant to females. [Figure 1] showed maximum patients belonged to DSS followed by DHF, DF, UDF and EDS. [Table 2] showed fever was present in all patients 384 (100%), majority of them had high grade fever and higher fever duration (\geq 5 days). Next common symptoms were vomiting, abdominal pain, bleeding, skin rash and convulsion. Most common skin rash was maculopapular rash. [Table 3] showed majority of patients had signs of shock followed by positive tourniquet test, pleural effusion, ascites and hepatomegaly. [Table 4] showed almost all patients were positive with NS1 antigen, however higher number of patients were positive with IgM antibody. IgG was mostly positive in DSS patients. [Table 5] showed that significantly highest number of patients in DF had haemoglobin level between 10-15 gm/dl. Maximum patients of DF, DHF, DSS and EDS had haematocrit (%) between (35-45) percent. Table VI showed maximum patients of UDF,

DHF and DSS had normal total leucocyte count; however maximum patients of EDS had leukocytosis. Majority of the patients of DF, DHF and DSS had neutropenia and majority of UDF & EDS had normal neutrophil (%). Maximum patients of UDF, DF, and DHF & DSS had lymphocytosis. Majority of EDS had normal lymphocyte (%). [Table 7] showed association of total platelet count with dengue syndromes. Among UDF maximum had TPC within 150000 to 450000 cells/mm³, among DF maximum had 50000-100000; among DHF maximum 20000-50000; among DSS maximum 20000-50000 and among EDS maximum had TPC 1500000 to 4500000 cells/mm³. [Table 8] showed significantly highest number of patients in UDF had normal SGPT & SGOT value. Significantly highest number of patients in DHF had raised SGPT (45-200U/L) & SGOT value (60-200U/L). Half of the patients of EDS had SGPT & SGOT >1000U/L. Table IX showed all the patients of UDF and DF had significantly normal PT & aPTT. All patients of UDF had significantly normal serum albumin level. Half of EDS patients had prolonged PT. Table X showed low random blood sugar and raised serum creatinine was present in one fourth of the EDS patients. However, low serum calcium was present in more than half of them.

DISCUSSION

In this study, the frequency of dengue syndromes was higher in the age group of 9-12 years. Mean age was 7.5 \pm 3.2 years. Males predominated to females

giving a male to female ratio of 1.4:1 which was similar to Sharma et al & Afroze et al.^[6,9] Among 384 patients maximum patients belonged to dengue shock syndrome (DSS) which was (57.8%) followed by dengue haemorrhagic fever (DHF) (23.4%) which was completely different from that of Sharma et al,^[9] where UDF cases were 8.5%, DF with 80% and severe dengue (DHF and DSS) were 11.5%. Afroze et al,^[6] reported 3% mortality due to expanded dengue syndrome. Fever was noted in all patients, among them almost all had high grade fever and mean duration of fever was 4.5 ± 1.6 days that is similar to Afroze et al,^[6] Next common symptoms were vomiting (78.9%), abdominal pain (43.2%), bleeding (34.4%) and skin rash (9.6%). These findings were completely different from that of Shah et al,^[1] where they reported vomiting (98%), abdominal pain (96%), myalgia (95%) and bleeding manifestations (68%). In this study maculopapular rash was most common skin rash. In dengue infection cutaneous manifestations can vary from maculopapular or rubelliform rash, skin bleeds and flushing. Thrombocytopenia is one of the important causes of developing petechial rash but other mechanism like immunologic cause may be involved for causing these rashes. In this study, convulsion was present in 1% which was half (4 patients) of the expanded dengue syndrome (EDS). In a study by Shultana et al,^[7] reported convulsion in 25% patients. Among 384 patients, signs of shock were present among more than half of the cases, two third of EDS patients had features of shock.

Hepatomegaly was seen in 10.9% patients. Signs of shock and hepatomegaly findings were opposite to Alam et al,^[10] where shock was 11.1% and hepatomegaly 31.5%. In this study positive tourniquet test, pleural effusion and ascites were present in 28.6%, 21.9% and 13.5% cases respectively which were similar to Alam et al.^[10] Among the 384 patients, (86%) were found NS1 positive, (9%) with IgM, (3%) with IgG and (2%) patients were both IgM and IgG antibodies positive. This finding was similar to a study by Afroze et al.^[6] Less frequency of positive IgM and IgG may be due to the test done during window period (4th – 5th day) of fever. Among 384 patients, small number of patients had haemoglobin value <10.0 gm/dl and >15.0 gm/dl. Raised HCT of $>45\%$ was noted in 7% patients which was opposite to Gupta et al,^[8] with raised HCT in 23.33% and mean \pm SD of HCT was 40.8 ± 7.6 . A 20% rise of HCT from the baseline is indicative of significant plasma leakage⁴. In this study, few patients had leucopenia of <4000 cells/ mm^3 and leukocytosis (>11000 cells/ mm^3) which was similar to Sastry and Padmavathi.^[2] Leucopenia is caused by bone marrow suppression by virus and is an early marker of dengue infection Joshi et al.^[11] In this study, about one third patients had neutropenia ($<40\%$) and maximum patients had lymphocytosis ($>40.0\%$). Bone marrow suppression causes a decrease in polymorphs with increase in lymphocytes especially atypical lymphocytes due to stimulation by nonspecific or specific viral antigens. The differential count (especially

lymphocytosis) helps in differential diagnosis & prognostication in dengue Joshi et al.^[11] In this study, severe thrombocytopenia ($<100000/\text{mm}^3$) was present in more than two third of patients which was similar to Alam et al.^[10] Thrombocytopenia in dengue may be due to decreased platelets production owing to bone marrow suppression and increased platelets destruction in DHF. This is caused by the direct infection of the megakaryocytes by the virus itself and presence of antibodies against platelets Hamed.^[12] In this study, SGOT was raised in more patients than SGPT that was similar to Mishra et al.^[13] SGPT and SGOT value >1000 (U/L) was present in half of the patients of EDS. Mechanisms of liver injury in dengue may be due to direct effects of the virus or host immune response on liver cells, circulatory compromise, metabolic acidosis and/or hypoxia caused by hypotension or localized vascular leakage inside the liver Jagadishkumar et al¹⁴ Prolonged PT and aPTT were observed in 2% and 12% cases respectively which were opposite to Sastry and Padmavathi² where prolonged PT and aPTT were seen in 20.9% and 33.3% respectively. Among 384 patients, low albumin level (<3.0 gm/dl) was noticed in 25%, all of them were DHF, DSS and EDS cases which was different to Jagadishkumar et al,^[14] where they found reduced serum albumin in 66%. Random blood sugar, serum calcium and serum creatinine were done patients of EDS. Of them one fourth had hypoglycaemia. One fourth patients had raised serum creatinine. Two third patients of EDS

had hypocalcaemia that was quite similar to Manjunath, Balla & Kumar.^[15]

Limitations of the study:

Sample size was small and follow-up period were short in comparison to other studies. So, the result of the study may not reflect the exact scenario of the whole country.

CONCLUSION

In this study, majority of the cases were DSS. Most common clinical presentation was vomiting, shock, abdominal pain and bleeding manifestations along with fever. Raised HCT, leucopenia and neutropenia were observed in small number of patients. Lymphocytosis and severe thrombocytopenia were experienced in about two third of patients. Majority of the patients had raised SGPT and SGOT level and normal PT, aPTT and serum albumin level. Two third patients of EDS had hypocalcaemia and one fourth had hypoglycemia & raised serum creatinine. This study result will help in management of subsequent outbreak especially in children.

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Source of Support: Nil, Conflict of Interest: None declared