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Original Research Article

STUDY OF DENGUE FEVER AND ITS VARIANTS IN CHILDREN ADMITTED TO A TERTIARY CARE HOSPITAL IN EASTERN INDIA

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ABSTRACT

Background: Dengue inflicts a significant health, economic and social burden on the populations of endemic areas. Globally the estimated number of disability-adjusted life years (DALYs) lost to dengue in 2001 was 528·
Objective: To study the clinical presentation, management and outcome in children admitted with dengue fever in a tertiary care centre in eastern India and to study the extent of liver dysfunction in dengue and its effect on the outcome of the child.
Materials and Methods: This prospective study was undertaken in Pediatric inpatient department at Apollo Gleneagles Hospitals, Kolkata from September 2012 - October 2013. The study group consisted of 50 children (23 females and 27 males), aged 1-18 years.
Results: Majority of patients falling in the age group of less than 10 years. Fever was present in all patients and was the most common chief complaint with abdominal pain and vomiting as the most common associated symptoms. Bleeding manifestation was most commonly seen as petechiae, followed by epistaxis then hematemesis. Mean duration of stay in the hospital in our study was 7.3 (±3.7) days. Majority of the patients with dengue infection have hepatitis. Severe hepatitis in dengue infection has got worse outcome in terms of length of stay, mortality and complications as compared to mild to moderate hepatitis. Therefore severe hepatitis can be considered as a bad prognostic indicator of outcome in dengue infection. Urinary tract infections and enteric fever were the co morbidities associated with dengue fever in a few cases in our study.
Conclusion: The outcome was 100% as all the patients in the study survived and are on regular follow up with no disability. The revised WHO classification is more effective than the traditional classification for identifying severe cases of dengue. The revised classification exhibits greater practical applicability in developing countries such as India because it is less dependent on complementary exams.
Keywords: Outcome, Children, Dengue fever.

INTRODUCTION

Dengue is the most important arthropod-borne viral disease of public health significance. Compared to nine reporting countries in the 1950s, today the geographic distribution includes more than 100 countries worldwide. Many of these had not reported dengue for 20 or more years and several have no known history of the disease. The World Health Organization (WHO) estimates that more than 2.5 billion people are at risk of dengue infection. Most will have asymptomatic infections.[1] Dengue has a wide spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. While most patients recover following a self-limiting non-severe clinical course,

a small proportion progress to severe disease, mostly characterized by plasma leakage with or without haemorrhage.

Intravenous rehydration is the therapy of choice; this intervention can reduce the case fatality rate to less than 1% of severe cases. The group progressing from non-severe to severe disease is difficult to define, but this is an important concern since appropriate treatment may prevent these patients from developing more severe clinical conditions.[2]

Triage, appropriate treatment, and the decision as to where this treatment should be given (in a health care facility or at home) are influenced by the case classification for dengue. This is even more the case during the frequent dengue outbreaks worldwide, where health services need to be adapted to cope with the sudden surge in demand.

Changes in the epidemiology of dengue, as described in the previous sections, lead to problems with the use of the existing WHO classification. Symptomatic dengue virus infections were grouped into three categories earlier: undifferentiated fever, dengue fever (DF) and dengue haemorrhagic fever (DHF). DHF was further classified into four severity grades, with grades III and IV being defined as dengue shock syndrome (DSS).[2]

There have been many reports of difficulties in the use of this classification,[1,3,4] which were summarized in a systematic literature review.[5] Difficulties in applying the criteria for DHF in the clinical situation, together with the increase in clinically severe dengue cases which did not fulfil the strict criteria of DHF, led to the request for the classification to be reconsidered. Currently the classification into DF/DHF/DSS continues to be widely used.[2] A WHO/TDR-supported prospective clinical multicentre study across dengue-endemic regions was set up to collect evidence about criteria for classifying dengue into levels of severity. The study findings confirmed that, by using a set of clinical and/or laboratory parameters, one sees a clear-cut difference between patients with severe dengue and those with non-severe dengue. However, for practical reasons it was desirable to split the large group of patients with non-severe dengue into two subgroups -- patients with warning signs and those without them.

The increase in dengue mortality is considered to be a reflection of the increase in the proportion of DF patients who develop DHF/DSS. The pathogenesis of DHF/DSS is widely considered to be antibody-dependent enhancement in secondary infection with a virus of different serotype6. Evidence in support of this comes from many studies including from the Cuban epidemics of 1981 and 1997,[6,7] and a five-year study of Yangon (Myanmar).[12] However, absence of a significant association between secondary infection or co-circulation of different serotypes and DHF/DSS has also been noted.[9,10] The disease is widely considered to be associated with secondary infection and co-circulation of several serotypes.

Hence this study was conducted to study the clinical presentation, management and outcome in children admitted with dengue fever in a tertiary care centre in eastern India and to study the extent of liver dysfunction in dengue and its effect on the outcome of the child.

MATERIALS AND METHODS

This prospective study was undertaken in Pediatric inpatient department at Apollo Gleneagles Hospitals, Kolkata from September 2012 - October 2013. The study group consisted of 50 children (23 females and 27 males), aged 1-18 years.

Inclusion Criteria

(A)Clinical criteria of

(1) Probable Dengue which includes fever and 2 of the following (i)Nausea, vomiting (ii)Rash (iii)Aches and pains (iv)Tourniquet test positive (v)Leucopoenia (vi)Any warning signs

(2) Dengue with warning signs which includes (i)Abdominal pain or tenderness (ii)Persistent vomiting (iii)Clinical fluid accumulation (iv)Mucosal bleed (v)Lethargy, restlessness (vi)Liver enlargement >2cm (vii)Increase in HCT with rapid decrease in platelet count

(3) Severe Dengue which includes (i)Severe plasma leakage (ii)Severe bleeding (iii)Severe organ involvement

(B)Confirmatory Serology

Written informed consent was obtained from parents or guardians of all the patients who were offered the study. I myself performed complete physical examination. BP was measured in each subject three times, using a mercury-gravity manometer with proper cuff size under standard conditions. BP measurements were compared with reference values prepared according to age, sex and height.

Anthropometry: Body weight was measured to the nearest 0.1 kg with a balance scale, and height was measured to the nearest 0.1 cm with stadiometer, with subjects lightly dressed and without shoes.

Investigations: Liver Function Tests, Sr. Proteins, were determined from blood samples taken after admission. The tests were run in the Beckman Coulter AU 680.

Glucose was measured by the hexokinase method at 340nm.

Chemical reaction:

$$\text{Glucose+ATP} \xrightarrow{\text{Hexokinase}} \text{Glucose 6-Phosphate+ADP}$$

$$\text{Glucose-6-Phosphate + NAD} \xrightarrow{\text{Glucose-6-PO4 Dehydrogenase}} \text{6-Phosphogluconate +NADH+H}^{+}$$

ALT, ALP is measured by kinetic rate method at 340nm.

$$\text{L-Arginine+}\alpha\text{Ketoglutarate} \xrightarrow{\text{ALT}} \text{Pyruvate+L-Glutamate}$$

$$\text{Pyruvate+NADH+H}^{+} \xrightarrow{\text{LDH}} \text{Lactate+NAD}$$

Sr. Proteins were measured by Biuret method.

Sr. Hemoglobin, Total Leucocyte Count and Platelet levels were run by Coulter Method in SIEMENS ADIVA 2120i Machine.

Coagulation Profile was tested in ELITE PRO Machine.

Serology. The samples were screened for the presence of dengue-specific IgM antibodies by IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA): using a kit prepared by the National Institute of Virology, Pune, India (as an integral part of the National Vector Borne Disease Control Programme), strictly following the manufacturer's protocol.[15]

For detection of the presence of dengue NS1 antigen in the acute sera, Pan Bio (Australia) NS1 ELISA kit was used.

All these tests were considered high or low when they fell above or below the recommended values:

USG Abdomen was performed on all the subjects and evidence of ascites, pleural effusion and organomegaly was noted.

Statistical Analysis: It was done by using descriptive and inferential statistics using chi square test. Software used in analysis was SPSS version 17.0 and graph pad prism 5.0 and $p<0.05$ was considered as level of significance.

RESULTS

Of the 50 children suffering from dengue fever, 26% of children were in the age group of <5 years while 36% were in the age group of 5-9 years. 54% patients in our study were males and 46% were females.

Table 1: Duration of Stay in the Hospital

DAYS	No of patients	Percentage(%)
<5 days	8	16
5-9 days	33	66
10-14 days	6	12
≥15 days	3	6
Total	50	100
Mean ± SD	7.26 ± 3.67	
Range	3-21 days	

Of the 50 children, 66 % of them were discharged within 5-9 days from the institute. Mean duration of stay in the hospital was 7.3(±3.7) days.

All the patients presented with fever followed with vomiting and abdominal pain.

Of the 50 children, 32% required Pediatric Intensive Care Support.

According to the revised WHO classification of Dengue, 32% of cases in our study presented with severe dengue, while 34% presented with dengue with warning signs and similar number of patients presented with probable dengue.

Table 2: Laboratory Parameters

PARAMETERS (n=50)	Number(%)	
	Normal	Deranged
Platelets	13 (26)	37 (74)
Total Leucocyte Count	29 (58)	21 (42)
Liver Function Test	18 (36)	32 (64)

Laboratory parameters showed that 74% of the cases presented with thrombocytopenia and 64% of cases presented with raised liver enzymes.

Table 3: According to Dengue Serology (n=50)

SEROLOGY TEST	No of patients	Percentage(%)
DENGUE NS 1 ANTIGEN	35	70
DENGUE IgM ANTIBODY	37	74
DENGUE IgG ANTIBODY	12	24

70% of cases had NS 1 Antigen positive, while 74% had Dengue IgM Antibody positive.

Table 4: Ultrasonography Findings (n=50)

FINDINGS	NUMBER	Percentage (%)
ASCITES	15	30
PLEURAL EFFUSION	17	34
HEPATOMEGALY	11	22
SPLENOMEGALY	7	14
OTHERS	4	8

**Multiple features were present*

30% of cases had some degree of ascites, while 34% had unilateral or bilateral pleural effusion.

Duration of stay vary significantly among the different age groups

- χ^2-value=14.88, p-value=0.001, Significant

Occurrence of hypotension vary significantly among the different age groups
2ꭥ-value=20.66, p-value=0.0001, Significant

Severity of Dengue vary significantly among the different age groups
2ꭥ-value=18.25, p-value=0.005, Significant

Table 5: Comparison of type of severity and hypotension

TYPE OF SEVERITY	HYPOTENSION (%)
PROBABLE (n=17)	-
DENGUE WITH WARNING SIGNS (n= 17)	3 (18)
SEVERE (n=16)	16 (100)

All the patients who were classified under severe dengue had hypotension

Table 6: Comorbidities seen along with dengue fever (n=11)

FEATURES	No of patients	Percentage(%)
URINARY TRACT INFECTION	6	55
ENTERIC FEVER	2	18
CARDIAC DEFECTS	1	9
THALASSEMIA TRAIT	1	9
ANTI NUCLEAR ANTIBODY POSITIVE	1	9

Comment: 22% of the sample size had co morbidities. Out of that, 55% presented with urinary tract infection.

Association was statistically significant between presence of co-morbidities and severity of Dengue
- **2**-value=10.44, p-value=0.005, Significant

Table 7: Adjunctive management stratergieS (n=50)

THEARPY	No of patients	Percentage
VITAMIN K	10	20
BLOOD PRODUCTS	9	18
INOTROPES	1	2
VENTILATOR	3	6

Multiple features were present

18% of our cases required blood products while only 6% required ventilator support.

DISCUSSION

In the present study, out of 50 cases sampled, 31 (62%) were below 10 years. Sarkar et al,[11] also reported maximum cases in the age group 0–10 years. Gupta et al,[12] and Chakravarti and Kumaria,[13] reported maximum cases in the age group more than 10 years. Our data was similar to a study on dengue fever among hospitalized children in Bandung, Indonesia,[14] in which most of the patients were between 7 to 10 years of age. Similar findings were noted in studies made by Imlan15 and by Sriprom,[16] in Thailand, in which most patients were between 5-to-12 years of age. Said age group may be vulnerable to dengue infection because they are the ones who attend school and leave the house to play in the fields and backyards; thus, they are more exposed to the mosquito vector.

Infants were the least affected sub group with only 1 case of 11 months.

In the present study, 54% children were males and 46% were females. Gupta et al,[12] and Chakravarti and Kumaria44 also reported maximum cases with male preponderance. Sarkar et al,[11] however, reported maximum cases with female preponderance.

82% of patients in our study were discharged within 9 days of admission with mean duration of stay being 7.3 (± 3.7) days. Jonathan G. Lim et al,[17] reported length of stay in hospital to be 5 (±4) days. Fabio Rocha Lima et al,[18] in their study reported the length of stay to be 8.8(±10.2) days.

In the present study, all the patients presented with fever. Rash was present in 40% of patients at the time of admission. Sanjay Kumar Mandal et al,[19] also reported fever in 100% patients and rash in 37.84% cases. In a study of 300 patients by Nadia A et al,[20] flushing was present in 28.7% and 44.9% had maculopapular variety of rash. In a study of 62 patients in Japan, by Itoda et al,[21] rash was more frequent in 82% cases. In a north Indian study by Karoli R et al,[22] rash was present in 26% cases while 16% had cutaneous hypersensitivity. Rahim MA et al,[23] also found rash in high frequency of 78.5% in a Bangladesh based study.

Also 40% of cases had complaints of headache in our study. Headache mostly from systemic inflammatory mediators, are well known features in dengue fever. Sanjay Kumar Mandal et al. found 62.16% patients presented with headache. Similar findings (61.6%) were seen in study by Singh NP et al.[24] But in some studies like by Itoda et al,[21] in Japan, headache was present in 90% cases. On the other hand the north Indian study by Seema A et al,[25] reported headache in only 9% of cases.

In our study 48% patients had abdominal pain which is more or less corroborating with the study by Sharma et al,[26] which reported 38% patients with abdominal pain in their study. This symptom was predominantly noted in the early leak phase and is

attributed to hepatomegaly and serosal inflammation.

38% of children presented with hypotension in our study. Fabio Rocha Lima et al,[18] reported 10% of patients with hypotension.

32% of cases required admission in Pediatric Intensive Care Unit in our study. All of these cases were classified as severe dengue as per the new WHO classification of dengue.

34% of our patients were classified as having dengue with warning signs. This group is comparable to dengue hemorrhagic fever group in the previous classification. In a study by Ratageri et al., dengue fever was present in 18%, DHF in 60% and DSS in 22% of cases.[27] In a study of 134 cases by Anju et al 67% of cases were of DHF whereas remaining 33% were of DSS.[28]

The criteria for DHF were very rigid in the traditional 1997 WHO classification. Patients could be classified as DHF if they presented with all of the following signs,[29] fever for two to seven days, thrombocytopenia (#100,000/ mm3), hemorrhagic manifestations (positive tourniquet test, hemorrhagic skin, and mucosal bleeding), and plasma leakage due to increased capillary permeability (a 20% increase in hematocrit values over the baseline at admission, a 20% decrease in hematocrit values after the appropriate treatment, and the presence of pleural effusion, ascites, or hypoproteinemia). The requirement of meeting all of the criteria caused difficulty in detecting severe cases. Several authors reported difficulties in determining the criteria and classifying patients as DHF.[29,30] In many situations, it is difficult to demonstrate hemoconcentration based on a 20% increase in hematocrit values; intravenous fluid replacement may alter hematocrit levels and hamper the use of this criterion. Many countries do not have a normal hematocrit value for their population, making it difficult to determine the 20% limit. Some researchers use hematocrit values to evaluate hemoconcentration during convalescence. This evaluation involves a retrospective diagnosis, which is not intended to predict the risk of developing severe disease.[31]

Bleeding diathesis is a known feature of DF because of low platelet count and leakage from blood vessels. Bone marrow suppression, Immune mediated clearance, spontaneous aggregation of platelets to virus infected endothelium-all may be responsible for such thrombocytopenia. In the present study, out of the 50 cases evaluated, 74% had thrombocytopenia. In a Delhi based study by Tripathy BK et al,[32] hematemesis, melena and epistaxis were found in 28.28%, 26.78% and 14.28% respectively but only 12.85% cases had platelet count < 70,000/cmm. But in a Hyderabad based study by Khan AH et al,[33] only 5% patients had bleeding while 40% had thrombocytopenia.

Low leukocyte count in DF, may be due to virus induced inhibition/destruction of myeloid progenitor cells. In our study 42% cases had leucopenia. But in study of Itoda et al,[21] leucopenia was detected in 71% cases, while Ageep AK et al,[34] reported leucopenia in 90%.

Dengue fever can cause hepatic injury and transaminase elevation similar to viral hepatitis. We found that in 64% patients, ALT and AST were raised. In the study by Khan AH et al,[33] serum ALT was >40 U/L in 40% cases. In study by Kularatne SA et al,[35] 88% patients showed elevated ALT and AST, with 122 of them having a two-fold increase.

Ascites and pleural effusion from capillary leak syndrome are one of those features, more and more reported in recent years of outbreaks, by the help of technological advances like ultrasonography. We have detected 3rd space collection in the form of ascites and pleural effusion in 30% and 34% of cases and also in 26% of cases there was hemoconcentration from increase vascular permeability. In the study by Singh NP et al.24, ascites was in 1.08% and pleural effusion was also in 1.08% cases while haemoconcentration (Hct>20% of expected for age and sex) was found in much higher frequency of 52% of the cases.

The observed association between duration of stay among different age groups was statistically significant (**2א**-value=14.88, p-value=0.001). Our study showed that across all age groups among children, 84% were treated and discharged from hospital within 9 days of admission and classifying them as per the new WHO criteria.

The observed association between the level of hypotension among different age groups was statistically significant (**2א**-value=20.66, p-value=0.0001). 84% of these cases were classified under severe dengue and required Pediatric Intensive Care.

Severity of dengue among different age groups varied significantly (**2א**-value=18.25, p-value=0.005). Severity was more among less than 10 years old in our study.

Co morbidities were seen in 22% of the total cases. Out of that 55% presented with urinary tract infection. Co morbidities were seen more so in cases which were classified under dengue with warning signs and severe dengue. The observed association between them was statistically significant (**2א**-value=10.44, p-value=0.005).

In the present study, out of the 50 cases sampled, 18% required blood products while 6% required ventilator.

CONCLUSION

Majority of the patients with dengue infection have hepatitis. Severe hepatitis in dengue infection has got worse outcome in terms of length of stay, mortality and complications as compared to mild to moderate hepatitis. Therefore severe hepatitis can be considered as a bad prognostic indicator of outcome in dengue infection. Urinary tract infections and enteric fever were the co morbidities associated with dengue fever in a few cases in our study. In our

study, 2007 WHO revised classification for dengue was used to classify the cases. This classification helped us a lot in classifying patients according to their clinical presentation and laboratory parameters. Management was initiated accordingly and those classified as severe dengue were admitted in Pediatric Intensive Care. The outcome was 100% as all the patients in the study survived and are on regular follow up with no disability. We conclude that the revised WHO classification is more effective than the traditional classification for identifying severe cases of dengue. The revised classification exhibits greater practical applicability in developing countries such as India because it is less dependent on complementary exams.

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