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Original Research Article

The incidence and clinical profile of dengue hemorrhagic fever among patients diagnosed with dengue fever in a tertiary care centre in south India

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ABSTRACT

Background: An understanding of factors predictive of severe forms of dengue fever would be helpful in risk stratification. The objective of the study was to determine incidence of and the factors associated with the development of dengue hemorrhagic fever (DHF) among patients admitted with dengue fever.
Methods: Consenting patients were consecutively enrolled in the study and were followed forward in time to establish if they had DHF rather than milder dengue. Several factors were studied to ascertain their relation to conversion to DHF.
Results: Cases included were 160 (103 males), with a mean age of 39.4 years (age range: 13-78). Fifty one (32%) developed DHF. On multivariate analysis; hepatomegaly, high alanine transaminase, low serum albumin and systolic blood pressure ≤100 mm Hg were independent predictors for the development of DHF.
Conclusions: Nearly a third of patients with dengue fever develop DHF. The predictors identified, should alert the physician to this impending complication.

Keywords: Dengue fever, Dengue haemorrhagic fever, Hospital incidence, Risk factors

INTRODUCTION

Dengue has a vast spectrum of severity, ranging from asymptomatic infection to hemorrhagic fever or shock. The incidence of severe forms of dengue fever has been found to be heavily dependent on the study setting, with tertiary care centres reporting up to 40%.

Given the high burden of dengue cases in endemic areas which are often resource-poor settings, it becomes imperative to stratify cases. Early identification of potentially severe cases may facilitate early referral to higher centres for intensive monitoring and treatment. On the other hand, if there are no danger signs, the patient may be managed in the primary or secondary care setting with periodic reassessment and restratification. Accordingly, the World Health Organization (WHO) has given a set of warning signs in dengue fever.[1] These include severe abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement >2 cm and increasing hematocrit with rapid fall in platelet count. These signs are specifically designed to be used in resource-poor settings and only clinical signs and simple blood counts are included. Studies on dengue fever in developing countries are few in number and data on outcome show significant

heterogeneity as reported in a 2018 review from the National institute of epidemiology in Chennai.[2]

We aimed to find out the incidence of dengue hemorrhagic fever among patients with dengue fever in our institution. We had a secondary objective to find the determinants predicting dengue hemorrhagic fever in our patients.

METHODS

We did a cross sectional study among patients admitted with dengue fever to our hospital during the study period, January 2018 to December 2018 with follow up of the cohort until discharge.

Study setting

The study was conducted in a tertiary referral centre, catering to patients above 12 years of age in South India.

Participants

All admitted patients with an acute febrile illness were evaluated for clinical and haematological features of dengue fever. We included patients aged above 12 years, diagnosed as dengue fever based on WHO classification and case definitions (acute or abrupt onset of fever, accompanied by white blood cell count ≤5,000/ml and positive serology (NS1 antigen or IgM dengue antibody)). Exclusion criteria included- patients not consenting to the study, patients who had pre-existing chronic liver disease, bleeding disorders, coagulation abnormalities, or who were on anticoagulants, patients with dengue hemorrhagic fever (DHF) at admission.

Variables, data source and measurements

Semi structured questionnaires were used for data collection. Details of the clinical, haematological and biochemical profile of the patients were ascertained by clinical examination, daily follow up until discharge and by daily perusal of the patient record. The major outcome variable was Dengue Hemorrhagic Fever as defined by the world health organization.

The co variates included clinical features (rash, systolic blood pressure, diastolic blood pressure, pulse pressure, headache, vomiting, myalgia, pedal edema, altered sensorium, seizures, abdominal pain, breathlessness, hepatomegaly (>2cm from the right costal margin), cardiac failure, pleural effusion and ascites) at admission, haematological profile at admission (haemoglobin, hematocrit, white blood cell count and platelet count), biochemical profile (serum cholesterol, serum creatinine, serum albumin, liver enzymes and urine albumin) and status of dengue serology. The blood pressure was recorded at least once a day using a mercury sphygmomanometer. The clinical, biochemical and haematological findings were recorded serially until discharge. All other causes of fever were excluded by appropriate tests following the institutional protocol. Complete blood count and coagulation profile was done at least once a day. Two or more episodes of vomiting per day was taken as significant.

Operational definitions[1]

Dengue infection

(DF) Acute or abrupt onset of fever, accompanied by white blood count ≤5,000/μL and positive serology (NS1 antigen or IgM dengue antibody).

Dengue hemorrhagic fever

All of the following items-

Acute or abrupt fever for 2–7 days,

At least one of the following bleeding episodes: positive tourniquet test, petechiae, ecchymoses, or purpura,

bleeding from mucosa, gastrointestinal tract, injection sites, or other location, hematemesis or melena,

Platelet≤ 100,000/μL

At least one of the following plasma leakage evidence items: hemoconcentration assessed by an increase in hematocrit ≥20% from previous hematocrit, signs of plasma leakage, such as pleural effusion or ascites, or evidence of hypoalbuminemia

Sample size calculation

Sample size was calculated as per the formula $(1.962\times p\times q)/d2$ based on the incidence of dengue hemorrhagic fever found in the study "Development of Dengue Infection Severity Score" by Pongpan et al.[3] The sample size obtained was 157 which was rounded up to 160 using a precision of 20%.Sample size was also calculated separately for each variable to be used in analysis using the formula $(1.962\times p\times q)/d2$ for qualitative variables and $(1.962\times\sigma2)/d2$ for quantitative variables where σ is standard deviation and d is 20% of mean. All such sample sizes calculated were less than 160 and hence 160 was adopted as the sample size for the study.

Sampling technique

Consecutive cases eligible for the study were taken.

Statistical analysis

Continuous and categorical variables were presented as mean (standard deviation) and n (%) respectively. Student's t-test for quantitative variables and chi-square test for qualitative variables were used for bivariate analysis. Odds ratio was calculated for risk factors.

Logistic regression was performed to ascertain the independent risk factors. Parameters found to be significant by bivariate analysis was used for logistic regression. The multiple logistic regression models were fit to the data by using a stepwise selection method. P value less than 0.05 was taken as significant. IBM® SPSS® Statistics 25.0 was used for data analysis.

Ethical considerations

The study was approved by the institutional review board and ethical committee of Government Medical College Trivandrum. Participation in the study was voluntary after a written informed consent.

RESULTS

One hundred and sixty patients fulfilling the diagnostic criteria were admitted with dengue fever during the study period. All patients admitted with dengue fever during the duration of the study were included as all of them consented to inclusion in the study and none had DHF at admission. They were then followed forward in time to establish if they had DHF rather than milder Dengue The mean age was 39.4 (age range 13 to 78; maximum number of cases in the 21 to 30 year age group) and 103 were male. Fifty one patients (31.8%) developed hemorrhagic fever. Table 1 shows the clinical profile of the cohort.

Headache was the commonest symptom. Neither the sex, mean age nor the age range (taken as the different decades of life) could significantly predict the occurrence of dengue hemorrhagic fever (DHF), though there was a slight female preponderance in our series.

Dengue hemorrhagic fever was significantly more in patients with abdominal pain, vomiting, myalgia, rash, hepatomegaly, breathlessness, altered sensorium, systolic blood pressure ≤100 mm Hg, skin and mucosal bleeds, prior history of dengue fever, albuminuria, dengue IgM positivity and serum alanine transaminase (ALT) above 200 U/L on bivariable analysis. (Table 2)

The mean systolic blood pressure and pulse pressure at admission (Table 3), mean haemoglobin, platelet count, ALT level, serum albumin and serum creatinine levels and the lowest platelet count attained were significantly associated with DHF (Table 4). A high serum cholesterol was found to be protective and augured a more benign course (p=0.000).

Table 1: The clinical profile of the whole cohort.

Characteristic	Number of patients (%) (Total=160)
Headache	124 (77.5)
Vomiting	80 (50.6)
Myalgia	72 (45)
Abdominal pain	64 (40)
Rash	28 (17.5)
Pedal edema	16 (10)
Hepatomegaly	13 (8.1)
Past history of Dengue fever	11 (7)
Pleural effusion	10 (6.3)
Breathlessness	7 (4.4)
Altered sensorium	
Ascites	7 (4.4)
Seizure	2 (1.3)
Systolic BP </= 100 mm Hg	55 (34.4)
SGPT >200 IU/ml	28 (17.5)

However on multivariate analysis, only hepatomegaly (aOR:5.44, 95% CI 1.033-28.67, p=0.046), systolic blood pressure ≤100 mm Hg (aOR:5.27, 95% CI 2.118-13.109, p<0.01), a raised ALT on admission (aOR:8.482, 95% CI 2.633-27.321, p<0.01), and presence of albuminuria (aOR:10.472, 95% CI 3.640-30.124, p<0.01), were associated with occurrence of DHF (Nagelkerke R square; 0.504).

Table 2: Result of bivariable analysis of factors that predict dengue haemorrhagic fever.

Variable	Category	DHF (n%)	Classical DF(n%)	Odds ratio[2)]	95% confidence interval	p value
Clinical features						
Sex	Male	31 (60.8)	72 (66.1)	1.255	0.631-2.498	0.517
Headache	Present	43 (84.3)	81 (74.3)	1.858	0.78-4.428	0.158
Abdominal pain	Present	30 (58.8)	34 (31.2)	3.151	1.582-6.279	0.001
Pedal edema	Present	8 (15.7)	8 (7.3)	2.349	0.828-6.665	0.101
Vomiting	Present	36 (70.6)	45 (41.3)	3.413	1.673-6.963	0.001
Myalgia	Present	31 (60.8)	41 (37.6)	2.571	1.299-5.088	0.006
Rash	Present	21 (41.2)	7 (6.4)	10.20	3.96-26.304	0.000
Hepatomegaly	Present	10 (19.6)	3 (2.8)	8.618	2.26-32.899	0.001[1]
Breathlessness	Present	6 (11.8)	1 (0.9)	14.40	1.69-123.05	0.004[1]
Altered sensorium	Present	5 (9.8)	2 (1.8)	5.815	1.09-31.072	0.034[1]

Continued

Variable	Category	DHF (n%)	Classical DF(n%)	Odds ratio[2)]	95% confidence interval	p value
Systolic BP ≤ 100 mm Hg	Present	32 (62.7)	23 (21.1)	6.297	3.03-13.077	0.000
Seizures	Present	1 (2)	1 (0.9)	2.160	0.13-35.238	0.537*
Skin and mucosal bleed	Present	13 (25.4)	5 (4.5)	7.116	2.38-21.298	0.000
Prior history of Dengue	Present	10 (19.6)	1 (1)	26.341	3.27-212.30	0.000[1]
Investigations						
Urine albumin	Present	23 (45.1)	10 (9.2)	8.132	3.47-19.079	0.000
Dengue IgM	Present	21 (41.2)	31 (28.4)	1.761	0.88-3.532	0.109
Dengue IgG	Present	10 (19.6)	8 (7.3)	3.079	1.14-8.354	0.022
Dengue NS1	Present	31 (60.8)	76 (69.7)	0.673	0.34-1.348	0.263
SGPT >200 U/L	Present	21 (19.3)	7 (13.7)	10.200	3.96-26.30	0.000
Serum cholesterol ≥160 mg/dl	Present	23 (45.1)	93 (85.32)	0.141	0.066-0.304	0.000

DHF Dengue haemorrhagic fever DF dengue fever SGPT alanine amino transferase. [1]Fischer's exact test done [2]adjusted odds ratio.

Table 3: Blood pressure at admission.

Variable	Dengue hemorrhagic fever mean (SD)	Classical dengue fever mean (SD)	P value
Systolic BP	104.5 (14.1)	116.2 (15.8)	0.000
Diastolic BP	75.1 (8.3)	74.6 (9.3)	0.738
Pulse pressure	29.6 (10.5)	41.1 (11.2)	0.000

Table 4: Blood parameters.

Test	DHF mean (SD)	Classical dengue fever mean (SD)	P value
On admission			
Hemoglobin	15.1 (2.0)	14.5 (1.7)	0.043
Total WBC count	5304.9 (4274,7)	5235.8 (2588.7)	0.899
Platelet count	34076.5 (23392.8)	49210.1 (47036.6)	0.031
ALT	220.3 (204 .9)	89.1 (73.1)	0.000
AST	310.1 (362.7)	167.2 (619.9)	0.129
Creatinine	1.03 (0.33)	0.95 (0.17)	0.049
Serum albumin	3.37 (0.62)	3.71 (0.54)	0.001
Cholesterol	147.8 (29.1)	185.6 (39.2)	0.000
In hospital			
Lowest platelet count	20607.8(8534.8)	32697.2 (20302.6)	0.000

DHF Dengue haemorrhagic fever; ALT alanine transaminase AST aspartate amino transaminase

DISCUSSION

Dengue is a disease of the tropical countries and India has a huge burden of dengue and its complications. All patients who present with dengue cannot be admitted to the ward for monitoring as beds are limited and huge numbers are affected especially in the rainy season. Even if admitted there is a need to screen patients and discharge early to vacate beds for patients who are likely to proceed to complications. Hence there is a felt need for predictors of DHF. We evaluated patients with Dengue fever to find the incidence of DHF and to find predictors of the same. More males were affected with dengue fever than females as observed in most other series.[4,5]

Though we observed headache as the most common symptom, other than fever, in patients with dengue, others have described vomiting.[3,4,6] This could possibly be under reporting by our patients, referral bias with patients complaining of headache being referred by the first contact doctor or a difference in the manifestation in our population. The age distribution of our cohort peaking at 21 to 30 years, is in agreement with the findings of Khan et al whose mean age of dengue fever patients was 24 years.[7]

Nearly one third of our cohort developed DHF. However reports in the literature vary (8.8%, 11.8% and 38.1%.[3,8,9] This could be due to genetic variation in the virus at a given time or a different strain of the virus or due to

population characteristics. The higher number of DHF cases in our series may be due to its setting in a tertiary referral hospital and due to inclusion of only inpatients. Furthermore it is well known that DHF emerges in certain geographic regions.

The challenges faced by a tropical country like ours, is the prevention of dengue transmission, prevention of DHF and decreasing the fatality of DHF. To this end, any factor that could point to some among a cohort of dengue fever, as suspect candidate to develop DHF would help in triaging patients. A thorough understanding of the serotypes of dengue and the propensity of each serotype to culminate in DHF is necessary.[10] In the absence of virological labs in developing countries, it is necessary to clinically suspect evolution to DHF, which is potentially fatal.

Despite the fact that DHF was first reported from Manila Philippines in 1953 to 1954, the disease rapidly spread in 20 years' time to the other South Asian countries including India.[11] The clinical spectrum of DHF and the factors associated with the same have been studied by various authors. Each group has studied different factors and found varied factors as associated with progression to DHF. Age above 40 years, secondary infection, diabetes, lethargy, a thick gall bladder and delayed hospitalization were reported in a Malaysian study in 2015.[8] Haematocrit and APTT ratio were the only two independent risk factors described in another Malaysian study in 2009.[12] Vasanwala has shown a high urine protein creatinine ratio as predictive of severe dengue infection.[13] A recent pediatric series from our institution found clinical fluid accumulation, persistent vomiting and hematocrit $\geq$0.40 concurrent with platelet count $<100 \times 109$/L prognosticative of severe dengue.[14]

Wahid in his series matched our observation that an elevated ALT was predictive of DHF.[15] Lee observed that, an elevated ALT was seen in severe dengue fever but could not predict DHF or severe dengue.[16] Ahamed noted a raised ALT in addition to many manifestations including abdominal pain, purpuric rash, ascites, thrombocytopenia and coagulopathy as statistically significant predictors for developing DHF.[17]

Albeit a raised ALT has been studied by many, hepatomegaly has not been addressed in other series and possibly the reason why this finding of ours does not conform to other series. A low blood pressure has also not been included in the multivariate regression model of others.

A high serum cholesterol though it lost its significance in our multivariate regression model, was seen to protect the patient from hemorrhagic fever. Biswas found that lower total serum cholesterol and LDL-C levels at presentation were associated with subsequent risk of developing dengue hemorrhagic fever using the WHO 1997 dengue severity classification.[18] Viral replication is linked to fatty acid synthesis with phosphatidylserine and phosphatidylethonolamine involved in entry of flaviviruses into cells. Viral assembly and pathogenesis also need sphingolipids and cholesterol. The interaction of flaviviruses with cellular lipid metabolism has recently been comprehensively reviewed.[19]

One of the strengths of our study is the use of the WHO criteria to define dengue fever and DHF. Studies on risk factors for development of DHF are less in India. Limitations of this study include the fact that being a tertiary referral hospital, patients may in fact not be typical of those presenting to other centers, as it is likely that only more severely ill patients were referred. The incidence of DHF we found reflects the hospital incidence in a tertiary referral center. The strength of association of many of the factors studied would have been better on a larger sample.

CONCLUSION

From the results of our study we could possibly assume that nearly a third of patients admitted with dengue fever in a tertiary care hospital are liable to have DHF. A clinician can look out for two clinical signs; hepatomegaly and a low systolic blood pressure and two laboratory values; ALT >200 U/L and albuminuria to triage patients with dengue fever for closer monitoring and precise remedy. This could possibly bring around a patient before he actually starts bleeding and in all likelihood prevent death.

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