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Original Research Article

Clinical and diagnostic features of dengue haemorrhagic fever in children

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ABSTRACT

Background: Diagnosis of dengue hemorrhagic fever (DHF) in children is based on clinical suspicion and prompting laboratory criteria.
Methods: This prospective study in children (6 months-14 years) presenting with features of DHF aimed to identify symptoms and signs, laboratory parameters for in early detection and assessed the association between clinical, laboratory, immunological parameters and outcome.
Results: Of 50 children, 26 were females, mean±SD age was 8.3±3.02 years; age group 8-12 years were affected the most (38.0%) and infants the least (4.0%). Fever (100%), followed by skin rash (56.0%), myalgia (52.0%) and head ache (48.0%) were the symptoms. Fever of 4-5 days (52.0%), high grade fever (84.0%) and of sudden onset (76.0%) were common. Ascitis was seen in nine. Peteche and malena (48.0%) were predominant manifestation of bleeding tendency (100%). Positive tourniquet test (48.0%) did not correlate with bleeding tendency. Lower levels of Hemoglobin (<12gms%, 100%), hematocrit (<40%, 98.0%), platelet count (<100000/mm3, 100%), serum albumin (76.0%), and abnormal liver enzymes (64.0%) along with prolonged prothrombin time (44.0%) and aPTT (18.05%) were noted. Ultrasound abdomen confirmed Pleural effusion (36.0%), ascitis (22.0%), hepatomegaly (68.0%). Mean detection time was 4 days. Positive dengue IgM and IgG (60.0%), IgM (16%), and IgG (24%) were observed with increase of IgM in early phase.
Conclusions: lower platelet count, raising haematocrit, increased liver enzymes with low serum albumin levels are early indicators. Prolonged PT and APTT are associated with severe bleeding manifestations. Apart from clinical expertise, chest X-ray, abdominal ultrasonogram are useful diagnostic tools.

Keywords: Bleeding tendency, Dengue haemorrhagic fever, Immunological parameters, Low platelet count, Raised liver enzymes

INTRODUCTION

Dengue fever (DF), a mosquito borne viral fever and its severe manifestations Dengue Haemorrhagic Fever (DHF) and Dengue Shock syndrome (DSS), is an increasing health problem with increasing global burden.[1] Exact prevalence is not known due to underreporting and misdiagnosis. Data indicate that globally, 390 million are affected annually and clinical manifestations are seen in 96 million.[2] Nearly half of global population is at risk of contracting dengue makes it an important notifiable disease, yet many countries do not do so. It is estimated that annual incidence in India to be 7.5 -32.5 million.[3]

Geographical distribution has greatly expanded over the last 30 years, because of increased potential for breeding of Aedes aegypti. This, aided by demographic explosion, rapid growth of urban centers with strain on public services, such as potable water and augmented by rainwater harvesting in diverse types of containers resulting in multiple storage practices.[4]

Clinical presentation of dengue is varied from being asymptomatic, with mild fever and to severe form of haemorrhage, shock and plasma leakage. This variation poses a challenge to the pediatrician in diagnosing, particularly differentiating from the pool of etiology of fever in children.

Time lost in the early disease course, may prove expensive later, with the onset of complications and mismanagement. Confirmation of dengue taking >5 days in many cases, diagnosis is based on clinical suspicion and management on other laboratory investigations; monitoring haematological parameters, administering symptomatic treatment, and preventing complications are the essentials in the disease management.

Early identification of warning symptoms of disease progression, maintaining fluid and electrolyte balance and blood transfusion when required, will reduce the associated morbidity and mortality.

Early recognition and prompt initiation of treatment are vital if disease related morbidity and mortality are to be limited. Early diagnosis is still big challenge even with the availability of battery of modern investigations. An alarmingly increasing epidemic of dengue was noticed in our region, with more number of admissions in the paediatric age group.

Hence, authors conducted this study for early detection of dengue haemorrhagic fever by clinical, haematological, biochemical and immunological parameters. Authors attempted to record, identify clinical and laboratory signals for early diagnosis and prompt intervention to prevent disease progression to life threatening complications.

METHODS

This prospective study was conducted by the department of Pediatrics of a medical college hospital and a tertiary care centre for a period of 32 months from December 2010 to August 2012 after obtaining approval from Institutional Ethics Committee.

Children aged 6 months - 14 yrs presenting with symptoms and signs suggestive of DHF as per WHO criteria were screened after obtaining a written informed consent and eligible patients meeting the selection criteria were included in the study.[5,6]

The primary objective was to identify laboratory parameters which are deranged early in the course of the disease, for rapid diagnosis of Dengue haemorrhagic fever. Secondary objectives included identification of symptoms and signs that can help the health care providers at community level in early detection of DHF and study of the association between clinical, laboratory, and immunological parameters and outcome.

A detailed medical history was taken and all included children were examined thoroughly by the same pediatrician. The tourniquet test was done as per the World Health Organization (WHO) guidelines using blood pressure (BP) cuff method.

The WHO guidelines stipulate that BP cuff should be inflated on the upper arm of the patient to a point mid-way between systolic and diastolic pressure for 5min, and the number of resulting petechiae in 2.5cm^2 on the volar aspect of the forearm just distal to the antecubital fossa should be counted. A test is considered positive when 20 or more petechiae are observed in the 2.5cm^2.

Investigations (Complete blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), blood grouping, liver function tests, chest X-ray, ultrasound abdomen) were performed as per the proforma. Dengue serology was done for all. All were treated as per the WHO algorithm on DHF and outcome was recorded.[5-7]

Statistical methods

Descriptive statistics was used to describe the results. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (n) and percentage (%). Significance is assessed at 5% level of significance. Authors used the Stata 10.1, MedCalc 9.0.1 and R environment ver.2.11.1 for the data analysis and Microsoft Word Excel worksheet to generate graphs. Student t test was used for analysis.

Assumptions

- Dependent variables should be normally distributed
- Samples drawn from the population should be random, and Cases of the samples should be independent.

RESULTS

Authors included 50 eligible children meeting the selection criteria. There were 26 (52.0%) females and 24 (48.0%) males. Mean±SD age of children was 8.3±3.02 years, with a median of 08 years (range 06 months- 14 years). Children between 8-12 years were affected the most (38.0%) while infants the least (4.0%) (Table 1).

Fever (100%), followed by skin rash (n=28, 56.0%), myalgia (n=26, 52.0%) and headache (48.0%) were the main presenting complaints (Table 2).

Table 1: Age wise distribution of study population.

Age (year)	n	%
0.5-1 year	2	4
1 -5	11	22
5.1- 8	14	28
8.1-12	19	38
12.1-14	4	8
Total	50	100

Table 2: Clinical presentation of dengue.

Symptoms	n (%)	p value
Fever	50 (100.0)	
Rash	28 (56.0)	0.374
Myalgia	26 (52.0)	0.206
Headache	24 (48.0)	0.449
Malena	22 (44.0)	0.849
Retro-orbital pain	18 (36.0)	0.254
vomiting	14 (28.0)	0.802
Abdominal pain	12 (24.0)	0.425
Edema	03 (06.0)	0.849
Hematemesis	02 (04.0)	0.640

Fever of 4-5 days duration was the most common presentation (n=26, 52.0%) followed by 1-3 days duration (n=12, 24.0%); duration of 6-7 days (n=09, 18.0%) and >7 days (n=03, 06.0%) was less frequent. High grade fever (n=42, 84.0%) was common while fever of sudden onset was noted in 38 (76.0%). High grade fever with rigor was seen in 16 (32.0%).

Table 3: Distribution of hemoglobin, hematocrit and total leukocyte count among study population.

Parameter	Mean	SD	Range
Haemoglobin	11.2gms%	2.5	6-14gms%
Haematocrit	34.7%	6.7	20%-42%
Total leukocyte count	10392 cells/mm^3	6080	4500-16000 cells/mm^3

Table 4: Platelet counts at admission.

Platelet in thousands	n	%
<20.000	7	14
20,001 - 30,000	6	12
30,001 - 50,000	12	24
50,001-75000	12	24
75001-1,00,000	13	26
Total	50	100

All our patients had bleeding tendency. Peteche and malena (n=22, 48.0%) were most common. Epistaxis (n=04), and hemetemesis (n=02) were less frequent. Tourniquet test was positive in 24 (48.0%) children but did not correlate with platelet count.

Table 5: Association between various parameters and platelet count.

Parameters	Platelet count				p value
	<49000		>49000		
	n	%	n	%	
Age (mean)					
<8.3	7	53.8	19	51.4	0.877
>8.3	6	46.2	18	48.6	
Gender					
Male	8	61.5	17	45.9	0.475
Female	5	38.5	20	54.1	
Fever					
High	13	100	30	81.1	0.091
Moderate	0	0	7	18.9	
Headache					
Yes	5	38.5	21	56.8	0.256
No	8	61.5	16	43.2	
Vomiting					
Yes	9	69.2	27	73	0.796
No	4	30.8	10	27	
Rash					
Yes	5	38.5	17	45.9	0.640
No	8	61.5	20	54.1	
Retroorbital pain					
Yes	10	76.9	22	59.5	0.259
No	3	23.1	15	40.5	
Myalgia					
Yes	5	38.5	20	54.1	0.333
No	8	61.5	17	45.9	
Bleeding					
Yes	11	84.6	33	89.2	0.662
No	2	15.4	4	10.8	
Malena					
Yes	4	30.8	18	48.6	0.264
No	9	69.2	19	51.4	
Haemoglobin					
<10.5	8	61.5	14	37.8	0.139
>10.5	5	38.5	23	62.2	
Haematocrit					
<36.8	4	30.8	22	59.5	0.075
>36.8	9	69.2	15	40.5	
Serum albumin					
<3.81	8	61.5	18	48.6	0.424
>3.81	5	38.5	19	51.4	
Liver enzymes					
Not raised	4	30.8	14	37.8	0.648
Raised	9	69.2	23	62.2	
Pleural effusion					
B/L	7	30.8	3	8.1	0.051
Normal	32	38.4	27	73.0	
Right	11	30.8	7	18.9	
Immunology					
IgG	3	23.1	9	24.3	0.865
IgM	2	15.4	8	21.6	
IgM and IgG	8	61.5	20	54.1	

All had hemoglobin <12gms%. Low hematocrit (<40.0%) was reported in 49 (98.0%) patients while only one had hematocrit >40% and this was statistically significant (p=0.001) (Table 3).

The range of platelet count at admission was 7000 - 98000/mm3, with a mean of 58000 (P>0.05) (Table 4). The WHO criteria of low platelet count of <100000/mm3 was seen in all (100.0%).

Association of pleural effusion and Platelet count was found to be statistically significant (p=0.05) (Table 5).

Serum albumin of <3g/dL was seen in 12 (24.0%) and >3g/dL in 38 (76.0%) of children and this was statistically significant (p=0.001). Serum levels of Aspartite aminotransferase (AST) and alanine aminotransferase (ALT) ranged between 18-356 Units/L and 24-258 Units/L. Abnormalities in liver enzymes (n=32, 64.0%) was statistically significant for both AST & ALT (p=0.004) (table 6). Prothrombin time (11-16 sec) was prolonged in 22 (44.0%) and aPTT in nine (18.05%). Ascitis was seen in nine patients, all these had pleural effusion, serum albumin levels 3-3.2g/dL, hepatomegly, and raised liver enzymes. all had IgM and IgG antibodies except one.

Chest X-ray was done for all; Pleural effusion (n=18, 36%, Right side -22.0% and Bilateral -14.0%) was the common finding. Ultrasound abdomen revealed pleural effusion (36.0%), ascitis (22.0%) and Hepatomegaly in 34 (68.0%) children. Mean detection time was four days.

Table 6: Profile of liver enzymes among study population.

Parameter	Mean±SD	Normal n (%)	Increased n (%)
AST	134.5±99.6	18 (36.0)	32 (64.0)
ALT	111.5±72.27	18 (36.0)	32 (64.0)

Dengue serology was performed in all. Positive dengue IgM and IgG (n=30, 60.0%) IgM (n=08, 16%), and IgG (n=12, 24%) were noted. All were treated as per WHO algorithm for dengue hemorrhagic fever.

Outcome

All patients recovered completely with the supportive management. There was no other complications and death in this study.

DISCUSSION

Severe dengue is the cause for hospitalization and mortality, particularly in pediatric population from Asia and Latin Americia; it was reported first during 1950s in Philipines and Thailand during the epidemics and currently, more frequent in Asian and Latin American countries.[8] Current estimates report that, at lest 112 countries are endemic for Dengue and about 40% of the world populations (2.5-3 billion people) are at risk in tropics and sub-tropics. Annually, 100 million cases of dengue fever and half a million cases of DHF occurs worldwide. 90% of patients with DHF are <15 years of age. Flamand C et al report that children aged <7 years comprised >20% of their study population, and prevalence was less in infants (4.0%) while Dias JJ Júnior reported that 66.0% of the study population wih severe dengue were children <15 years.[9,10] These reports indicate that case of fever in pediatric patients needs careful evaluation. Report from Malaysis is indicating a declining trend among pediatric patients.[11]

Age is reported to be an important risk factor for severe dengue >10 years is at higher risk. Mean age in this study was 8.3 years, with 5-11 years (66.0%) being most affected and in accordance with previous reports.[10,12-14] Dhooria GS et al noted that 59.0% of their study population belonged to 10-15 years and 92.0% had DHF.[15] Studies have shown male preponderance, but this study showed equal distribution. Infants were less affected, and our observation supports this.

Fever was the presenting complaint in all our patients as reported by previous studies by Narayanan et al (98.3%), Dhoria et al (91.0%).[14-17] Onset of fever has been varying with both grdual and sudden onset.[18,19] Authors report sudden onset in 76.0% patients.

Namvongsa V et al compared the clinical presentation of dengue and DHF between children (38.5%) and adults; median age of children was 11 years in their study, with a male preponderance (60.0%).[20] Anorexia (81.0%), nausea/vomiting (79.0%), headache (51.4%) and bleeding tendency were common features. In comparison to adults, apart from these symptoms, positive tourniquet test, abdominal tenderness, convalescent rash, pleural effusion and ascitis due to plasma leakage as a result of low serum albumin and sodium were also reported. This study showed a higher association of bleeding in children, but requirement of transfusion was more in adults compared to children.

Saraswathy MP et al too reported male preponderance (74.0%) and a higher prevalence of DHF (61.0%) in their study.[21] Thrombocytopenia and haemorrhagic manifestations were seen in all DHF cases; elevated liver enzymes (96.0%), abdominal pain (96.0%), Hepatomegaly (92.0%), ascitis (88.0%) were more frequent compared to vomiting (60.0%), spleenomegaly (48.0%) and cholecystitis (36.0%). Similar reports are available globally.[23]

Apart from fever (100%), common presentation in our study was myalgia (52%), headache (48%), malena (44%) followed by retro Orbital Pain (36%), vomiting (28%), abdominal pain (24%). These observations are similar to previous studies.[15,17,18]

Haemorrhage is considered to be a fatal complication of severe dengue, affecting skin and subcutaneous tissues, mucosa of the GI tract; Internal bleeding in heart and liver are often seen clinically, while intracranial and subarachnoid bleed are less common. GI bleeding may be

severe necessitating prompt attention. High proteinaceous serous effusion in the body cavities may be seen. [23] Laoprasopwattana K et al from Thailand report that 18.5% of their patietns with severe dengue had hemorrhages and associated with a greater mortality rate (63.6%).[24] They showed a high correlation between international normalized ratio and transaminase enzymes.[24] Petechae was common form of bleeding (56.0%) in the present study, followed by malena (44.0%); hemetemesis (4.0%) was less frequent. Prevalence of Malena in previous studies ranged from 46-66.0%, hemetemesis (31.20%) and epistaxis (52.60%) were the most common bleeding manifestation reported in other studies.[14,16,25,26] There was no complication due to hemorrhage/bleeding tendency was seen in the present study.

Tourniquet test not always correlate with platelet count, and bleeding tendency and negative test may not be a sufficient evidence to exclude a diagnosis of DHF in a febrile patient; test positivity ranged between 20%-83.90%.[14,27-29] Present study supports these observations as test was positive only in 48.0%. However, Cao Xuan Phuong T et al suggest that the simple, less expensive elastic tourniquet may be useful in diagnosing dengue infection in busy rural health stations in dengue endemic areas of the tropics.[30] A positive test should prompt close observation or early hospital referral, but a negative test does not exclude dengue infection.

Routine haematological investigations though revealed increased haematocrit values, its diagnostic utility in dengue is limited as it does not correlate with clinical staging. Platelets counts carry one of the most important key for diagnosis. Authors report a low platelet count <100000/mm^3 in all patients. The platelet count at the admission was neither an indicator of prognosis nor of bleeding tendencies or disease progression. However, studies include only DHF cases correlation between low platelet count and bleeding manifestations.[13,14,31] But platelet count provides a very useful means of diagnosis at the screening level. Hence, the platelet count is a sensitive indicator for diagnosis, but it did not correlate with the outcome. Bleeding manifestations are more frequent with low platelet count.

Hepatomegaly is a frequent finding in dengue (52.50%-90.0%) and 68.0% of the patients had hepatomegaly.[14,29,32] Acute hepatic failure is reported to be in 18.5% of children with dengue with hepatomegaly and elevated liver enzymes common associated featurs.[4,14,26,32-34] Latter is not of any prognostic value, but serve as useful marker for early diagnosis. Prothrombin time is a sensitive indicator of synthetic function of liver. Prolonged aPTT in the acute phase may be due to hepatic injury. In our study, prolonged PT and aPTT were seen in 44%, and 18%, respectively. However, no correlation was possible between prolonged PT, APTT and prognosis. Hypoalbuminemia was seen in 38.0% and comparable to previous sudy by Srivastava et al; higher percentage (76.0%) of hypoalbuminemia was reported by Aggarwal A et al. [31,35]

Mishra S et al report the prevalence of DHF to be 13.4% (n=13) in their paediatric patients, with greater affliction in >11 years (n=09).[36] There were more number of males (n=09) with severe dengue. Severe dengue resulted in prolonged hospitalization; majority were hospitalised after 3-6 days of fever. Fever was the main complaint in all followed by myalgia (76.8%), and abdominal pain (54.3%). Hepatomegaly was reported in 43.8%. petechiae (22.1%). GI bleeding was seen in those with severe dengue. Increased liver enzymes, abnormal prothrombin time and activated partial thromboplastin time, thrombocytopenia was seen in severe dengue. Raised haematocrit was seen in 34.02% patients, though statistically not significant. Pleural effusion, hepatomegaly, ascitis and gall bladder oedema were confirmed radiologically. There was no correlation between bleeding tendency and thrombocytopenia, hepatomegaly and abnormal liver enzymes. Unlike this study, tourniquet test was negative in majority of patients. Dengue serology revealed that those with severe dengue had both IgM and IgG positive (06, 46.15%) followed by IgM (15.38%), IgM (15.38%). None of these patients with severe dengue were positive for IgG.

IgM and IgG have been extensively used for diagnosis of DHF. IgM antibodies, first to appear are detectable in 50% of patients by days 3-5 after onset of illness, increasing to 80% by day 5 and 99% by day 10. IgM levels peak about two weeks after the onset of symptoms and then decline generally to undetectable levels over 2-3 months. Anti-dengue serum IgG is generally detectable at low titers at the end of the first week of illness, increasing slowly thereafter, with serum IgG still detectable after several months, and probably even for life. During a secondary dengue infection (a dengue infection in a host that has previously been infected by a dengue virus, or sometimes after non-dengue flavivirus vaccination or infection), antibody titres rise rapidly and react broadly against many flavi viruses. The dominant immunoglobulin is IgG which is detectable at high levels, even in the acute phase, and persists for periods lasting from 10 months to life. In, early convalescent stage IgM levels are significantly lower in secondary infections and may be undetectable in few, depending on the test used. In our study, dengue IgM was tested positive in 16%, IgG in 24%, IgM and IgG both in 60%, tested by ELISA rapid method.

In summary, children between 5-15 years are at a greater risk of contracting dengue; pain abdomen and vomiting being the most common presenting symptom, children need to be evaluated thoroughly if present with these symptoms; however atypical presentations cannot be ruled out. Presence of Ascites, pleural effusion, hepatomegaly, warrant elaborate investigations and raise the suspicion of severe dengue cases. Gall bladder wall thickening and abnormally high LFT in such cases

indicate severe dengue. Haematological and biochemical parameters along with serology are required to confirm the diagnosis.[37]

Chest X-ray may be a complementary tool to evaluate the clinical course of DHF and should be taken during the first week after the onset of dengue. WHO mentions pleural effusion, a supporting evidence of plasma leakage, as a consistent finding of dengue and the distinguishing feature of DHF. The extent of pleural effusion correlates with the severity of the disease and bilateral pleural effusion is common in shock and similar such correlation was found in this study. In this study, pleural effusion was seen in 36.0% of whom, 22.0% had right sided effusion, which is considered as a consitant feature of dengue; seven had bilateral effusion. Dietz VJ, Gubler DJ et al recorded pleural effusions in 84% (22/26) of DHF cases.[38]

Ultrasonography is a useful non-invasive technique to confirm the clinical and radiological findings and Mia MW et al [39]suggest that it can be considered as primary test to confirm clinical suspecion, early prediction of severity of the disease. It should also be noted that serological confirmation of dengue fever needs about 5 days after its onset. Most of the manifestations of this disease can be visualized by ultrasonography before this period of time.

In the absence of specific treatment, symptomatic and supportive management is adopted. Blood products for transfusion in severe cases may be required. We managed all patients with supportive treatment; all recovered and there was no complication or death reported in our study. This indicates, diagnostic accuracy, early detection and administering treatment can give good outcome in DHF.

Majumdar I et al assessed the association of various clinical and laboratory parameters and report a significant association of these factors with outcome.[40] As dengue prevalence is high among clinically unsuspected cases of fever, investigations that lead to diagnosis should be considered in children with fever.

CONCLUSION

Sudden onset high grade fever, frequently associated with shivering along with severe myalgia, retroorbital pain, vomiting, abdominal pain particularly in the absence of other systemic involvement will go a long way in early detection of DHF by clinical examination.

Chest X-ray and ultrasound abdomen are useful diagnostic tools for early detection of pleural effusion, ascites and other ultrasonographic features of DHF. Falling platelet levels <1,00,000/mm^3, raising haematocrit >20%, increased transaminase levels and falling serum albumin levels are early laboratory indicators of DHF. Prolonged PT and aPTT were consistently associated with severe bleeding manifestations in the form of malena and hematemesis. IgM was increased early in the course of illness.

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