

Dengue: A Clinicopathological Correlation

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Abstract: Dengue fever is an acute febrile disease in the tropical and subtropical areas and today is being acknowledged as one of the world's major emerging infectious disease. In the last 50 years, incidence has increased 30 folds. An estimated 2.5 billion live in over 100 endemic countries and areas where dengue can be transmitted. Up to 50 million infections occur annually with 500,000 cases of dengue hemorrhagic fever and 22,000 deaths in children with wide spectrum of clinical features⁽¹⁾. Hence the study was undertaken to study the clinical features in dengue patients. **Aims and Objectives:** The study is undertaken to study the clinical spectrum of dengue fever and to correlate various haematological and biochemical parameters with severity of dengue. **Materials and methods:** A prospective observational hospital based study carried out in Mahatma Gandhi Memorial Hospital, Kamothe, Mumbai over a period of two years in 100 IPD and OPD patients with fever who were investigated and found to be either NS1 antigen Positive or IgM antibody positive or both positive, for dengue. Patients diagnosed with malaria, typhoid and leptospirosis or any other illness after admission or aged less than 12 years were excluded from study. The relationship of occurrences of various clinical manifestations and complications as well as their relationship to gender and age group were analyzed in the study. **Result:** The most common symptom seen in patients with dengue was fever followed by headache. Hemorrhagic manifestations were significantly more common in patients with Dengue Hemorrhagic Fever (DHF) than Dengue fever. Thrombocytopenia is common in both Dengue fever (DF) and DHF which correlated well with clinical incidence of plasma leakage like hypoalbuminemia & haemoconcentration. Most of the patients with DF were managed with intravenous crystalloids. Patients with DHF, who needed platelet transfusions were given platelet transfusions, for the correction of thrombocytopenia, haemoconcentration or bleeding tendency than DF patients. **Conclusion:** The two fundamental pathological attributes in DHF were plasma leakage and intrinsic coagulopathy, and they were more severe in DHF as compared to DF. Appropriate interventions with judicious fluid therapy and platelets could offset adverse outcomes and ensure a favourable outcome.

Keywords: Dengue fever, Dengue Hemorrhagic Fever, NS1 antigen, IgM antibody

1. Introduction

Dengue fever is an acute febrile disease in the tropical and subtropical areas and today is being acknowledged as one of the world's major emerging infectious disease. A major dengue outbreak in 2013 in India with more than 55,000 reported cases triggered largely by heavy torrential rains, led to a study to be conducted by India's national vector borne diseases control programme which reported an annual average of 20,474 dengue cases and 132 dengue related deaths since 2007.^[2] The etiological agent comprises of four serotypes belonging to genus flavivirus, the principal vector is mosquito, Aedes Aegypti. The clinical manifestations of dengue fever vary with age and in addition in apparent infection can be classified into five presentations

- 1) Non specific febrile illness
- 2) Classic dengue fever
- 3) Dengue hemorrhagic fever
- 4) Dengue shock syndrome
- 5) Other unusual syndromes such as encephalopathy and liver failure.^[3]

2. Aim

To study the clinical spectrum of dengue fever included following

- 1) Age and gender wise incidence of dengue.

- 2) The incidence of severity of dengue.
- 3) Distribution of various symptoms
- 4) The correlation between various laboratory investigations and clinical features and severity.
- 5) The incidence of various complications.

3. Methodology

Total 100 IPD and OPD patients were enrolled on the basis of inclusion and exclusion criteria. It was a prospective observational hospital based study carried out in Mahatma Gandhi Memorial Hospital, Kamothe, Mumbai, a tertiary care teaching hospital for over a period of 2 years. Patients with fever either with NS1 antigen positive or IgM antibody positive or both positive, for dengue were included in the study.

Patients less than 12 years and patient diagnosed with malaria, typhoid and leptospirosis or any other illness after admission were excluded from the study.

Informed written consent was obtained from all patients enrolled in the study. Institutional ethical clearance was obtained. History and clinical features of all the patients were recorded in detail. Laboratory diagnosis included investigations like CBC, PCV, LFT, Dengue NS1 & IgM (Dengue check WB by Zephyr Biomedicals), Chest X Ray & USG abdomen.

Patients with symptoms of fever with two or more of following signs: headache, retro orbital pain, myalgia, arthralgia with laboratory evidence of leucopenia, thrombocytopenia and no evidence of plasma loss were classified as dengue fever.

Patients with above symptoms and laboratory evidence of thrombocytopenia and raised hematocrit by 20% or more is classified as DHF type 1. Patients with above symptoms plus evidence of spontaneous bleeding were classified as DHF type 2. DHF type 3 included patients with above symptoms plus circulatory failure. DHF type 4 consisted of patients with above symptoms plus undetectable BP and pulse.

4. Statistical Analysis

The relationship between the frequencies of various clinical manifestations and complications were analyzed using Chi Square tests and odds ratio. Statistical analysis of the data was conducted by trained biostatistician using SPSS software.

5. Results

A total of 100 patients of dengue fever were included in the study. The maximum incidence was observed in the age group of 20-30 yrs (53%). The male:female ratio in the present study was 62% were males and 38% females. Out of patients studied 79% patients were diagnosed with DF and 21% patients had DHF, while there was no patient with DSS. Out of 21% cases of DHF, 5% had DHF I, 15% had DHF II and 1% had DHF III (Table 1)

Table 1: Distribution of Patients with DHF in Study Population

Diagnosis	Frequency	Percent
DHF type 1	5	5.0%
DHF type 2	15	15.0%
DHF 3	1	1.0%
Dengue Fever	79	79.0%
Total	100	100.0%

Fever was the most common clinical manifestation present in 100% of the individuals followed by headache. Arthralgia/ Bodyache was seen in 40-50% of patients. More than 1/3rd of patients had rash, abdominal pain and vomiting. (Figure 1).

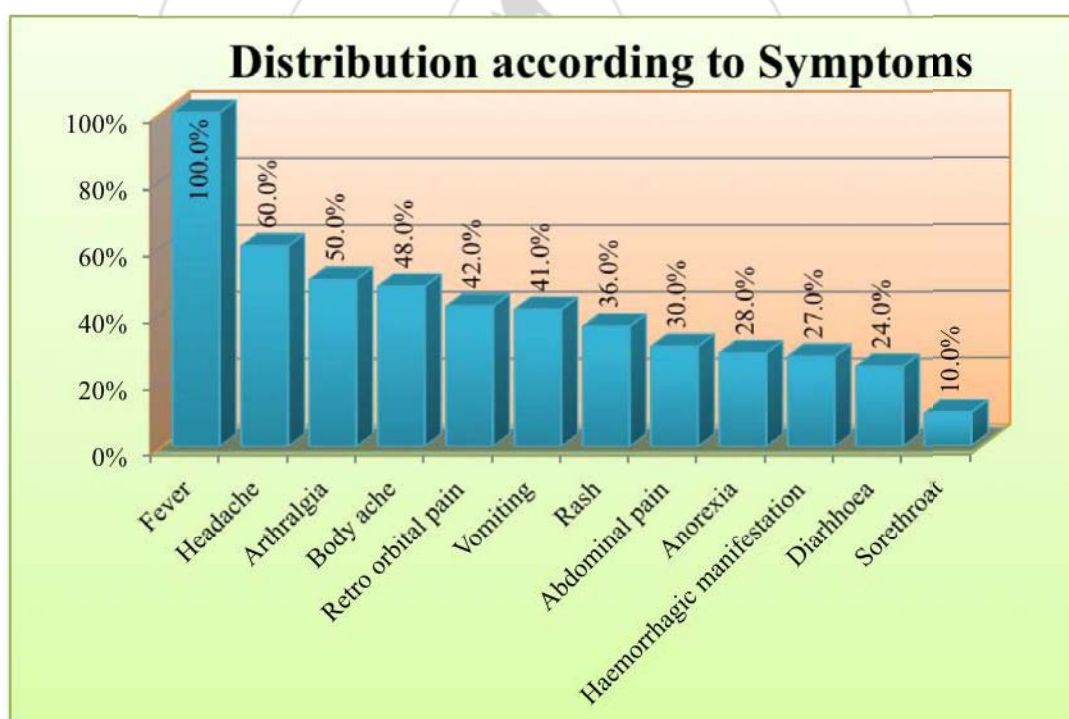


Figure 1: Distribution of Degree of Symptom Involvement.

27% of total patients had hemorrhagic manifestations. Most common hemorrhagic manifestation was petechiae followed by hematemesis and malaena (33%). A significant number of patients (70.4%) with DHF had hemorrhagic manifestations as compared to only 34% in dengue fever.

All 100 patients had platelet count below 100000/mm³. Out of these 36 patients (36%), patients had platelet count

between 50000-100000/mm³ and only 1 patient (1%) reported platelet count below 10000/mm³. Patient with DHF had low platelet count as compared to DF (P=0.007). Bleeding manifestations were statistically more common in patients with platelet count below 20000/mm³ (p=0.005) (Table 2)

Table 2: Showing Platelet Count in DF and DHF

Platelets					Total
	Dengue Fever		DHF		
	no	%	no	%	
100000-50000	32	40.0%	4	19%	36%
50000-20000	32	40.5%	7	33.33%	39%
20000-10000	15	19.5%	9	42.87%	24%
<10000	0	0%	1	4.7%	1%

It was observed that a low white cell count was present in a significant number of patients with DF and DHF respectively.

Biochemical analysis of these patients with various grades of DHF presented elevation in the activity of alanine transaminase and aspartate transaminase. Hypoalbuminemia was also one of the notable features. Refer to Table 3.

Table 3: Showing Transaminases in DF and DHF

	Alanine transaminase/Aspartate transaminase				Total
	Elevated		Normal		
	no	%	no	%	
DHF type 1	1	3.0%	4	6.0%	5
DHF type 2	14	42.4%	1	1.5%	15
DHF type 3	1	3.0%	0	0.0%	1
Dengue Fever	17	51.5%	62	92.5%	79
	33	100.0%	67	100.0%	100

Renal function test revealed derangement of renal parameters like serum creatinine and urea. Refer to Table 4.

Table 4: Showing RFT in DF and DHF

	RFT				Total
	Elevated		Normal		
	n	%	n	%	
DHF type 1	5	38.4%	0	0.0%	5
DHF type 2	8	61.6%	7	8.04%	15
DHF type 3	0	0.0%	1	1.11%	1
Dengue Fever	0	0.0%	79	90.8%	79
	13	100.0%	87	100.0%	100

Radiological findings showed no evidence of pleural effusion or ascites in any of the patients with DF. Pleural effusion was found in 13 patients of DHF and ascites was found in 12 patients of DHF. Hepatomegaly was observed in 9 patients with DF and 15 patients with DHF. No patient of DF and DHF had splenomegaly. Refer to Table 5.

Table 5: USG Findings in DHF and DF

USG	Diagnosis				Total
	DHF type 1	DHF type 2	DHF type 3	Dengue Fever	
Normal	5	15	1	79	
Hepatomegaly	3	11	1	9	24
Pleural Effusion	0	12	1	0	13
Ascites	2	9	1	0	12

Management of patients included only intravenous fluids in the form of crystalloid while 16 patients (20.25%) required platelet transfusions and none required blood transfusions. In patients with DHF apart from the intravenous fluids, 17

patients (80.95%) received platelet transfusions. None of the patients received blood transfusions and fresh frozen plasma transfusions.

6. Discussion

Present study showed that maximum patients presented with DHF II which is comparable to the study reported by Rajashekhar et al^[2], O'Brien et al^[3](100%), Jelinek et al^[4](86%), Abul Kalam Azad et al^[5](100%). Fever was the most common symptom (100%) followed by headache (60%). Significant number of patients reported retroorbital pain, arthralgias myalgias, bodyache, nausea and vomiting.

Another common significant observation was lower levels of platelets. Lowest values of platelets were observed in patients with DHF and DF. This is mainly because all patients with DHF have plasma leakage, the magnitude and progression of which will impact outcome.

The pathogenesis of bleeding in DHF is unclear even though well-recognised coagulation disturbances do exist. The clinical haemorrhagic manifestations range from a mere positive tourniquet test, skin petechiae and ecchymoses to epistaxis, and gum bleeding to severe gastrointestinal haemorrhages. In the present study, hemorrhagic manifestations was not seen. The relatively higher incidence of petechiae (58%) noted in our study correlates well with the findings of studies conducted by Wittesjo.B.et al^[6] (17.39%) and G.N Malavige^[7](15.7%). In the present study while the mean platelet count was between 20000 – 10000 for 42.8% of the patients with DHF and in patients with DF mean platelet count is between 50000 - 200000. At the time of discharge, the mean platelet count was 137000/mm³, in patients with DF and 124000 /mm³ in patients with DHF.

Thrombocytopenia is another consistent finding, while prolonged partial thromboplastin time and reduced fibrinogen concentration are the other abnormal haemostatic indices evident from early in the disease course. These haematological abnormalities seem to correlate better with the timing and severity of plasma leakage rather than the clinical haemorrhagic manifestations⁽⁸⁾. These recent findings raise the possibility for common pathogenic mechanisms responsible for both plasma leakage and abnormalities in the haemostatic indices. The true nature of the intrinsic coagulopathy evident early in the disease course and in mild forms of dengue can be confounded by the advent of hypovolemic shock and hypoxia in DHF with severe plasma leakage with less than optimal correction. Thrombocytopenia is initially due to bone marrow suppression during the febrile viraemic phase of the illness. Progressive thrombocytopenia with defervescence result from immune mediated platelet destruction. Virus-antibody complexes have been detected on the platelet surface of DHF patients suggesting a role for immune-mediated destruction of platelets⁽¹⁰⁾.

Thrombocytopenia is best used as a marker of severe disease particularly when it is < 100,000 cells/c.mm or when there is a rapid drop. Its usefulness is as an indicator of prognosis during the disease course rather than a parameter for therapeutic interventions. Recognising the poor

correlation of thrombocytopenia with bleeding should caution the clinician against the futility albeit danger of prophylactic platelet transfusions. Similarly thrombocytopenia in patients with DF has been reported by many other authors also including Gubler GJ^[11] and Watt G et al^[12]. In the present study all 100 patients were admitted with platelet count below (100000/mm³) out of which 64% patients had platelet count <50000/mm³. Patients with DHF had lower platelet count on admission than patients with DF. In the present study, there is significant correlation of age with thrombocytopenia ($p=0.005$). Lower platelet counts were noted in patients in the age group of 41-50 yrs. In the present study 45% of the patients with DHF had increased haematocrit. A similar rise in haematocrit has been reported in 41.1% cases with DHF by Joel Navarrete Espinosa et al (2005)^[13]. In the present study platelet count correlates well with haemoconcentration ($p=.042$) and hypoalbuminaemia ($p=.032$) and which were found significant statistically. Similarly Mourao MP et al^[14] showed a positive correlation between platelet count and plasma albumin levels.

According to WHO criteria for distinguishing DF and DHF, one of the most important features of DHF is the evidence of plasma leakage that is seen as ascites, pleural effusion, haemoconcentration and hypoproteinemia. Ultrasonographic evidence of pleural effusion was seen in 13% of patients and ascites was seen in 12 % of patients which is comparable to the findings of Chatterjee et al (2014)^[15] which showed 13% incidence of pleural effusion and 17.7 % of ascites in dengue fever patients. Another ultrasonographic finding was hepatomegaly which was seen in 11% with DF and 71% patients with DHF. Similar findings have been reported by Chatterjee et al(2014)^[15]

In the present study liver enzymes were elevated in 81% of the patients with DHF as compared to only 21% patients with DF. This was statistically significant with a P value of .001. Deranged renal function test was seen in 61.6% of patients with DHF and none in dengue fever. This is in contrast to the studies done in Taiwan, in which the incidence of ARF in patients of DHF was found to be 3.3% in a sample size of 304 cases.

7. Conclusion

On the basis of this study we can say that, the most common presenting symptom seen in patients with dengue was Fever followed by headache. In a large percentage of patients bodyache, arthralgia and retro orbital pain was seen. Hemorrhagic manifestations are significantly more common in patients with Dengue Hemorrhagic Fever (DHF). Thrombocytopenia is an important hematological finding in both DF & DHF. However lower platelet counts were seen in patients with DHF. The most common hemorrhagic manifestation was petechiae followed by gastrointestinal bleed. Lower platelet counts seen in dengue fever correlated well with clinical incidence of plasma leakage like hypoalbuminemia & haemoconcentration. Leukopenia was seen in majority of patients with DF and DHF. Most of the patients with DF could be managed with intravenous crystalloids, intravenous fluids. Patients with DHF needed platelet transfusions more commonly, for the correction of thrombocytopenia, haemoconcentration or bleeding

tendency than DF patients. The mean duration of stay in hospital of patients with DHF was longer as compared to DF patients.

Thus Dengue Fever must be diagnosed early and in all such patients clinicians need to be alert and vigilant to identify DHF patients early before shock sets in.

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