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A study of Hematological & Radiological profile of patients of Dengue fever in Paediatric Age group

Nishantkumar Pravinbhai Rathod DNB Resident at HBTMC & DR R N Cooper Hospital. MUMBAI

Nusrat Jahan Rafique Ansari Assistant Professor(Paediatrics) at HBTMC & DR R N Cooper Hospital. MUMBAI

Dr. Dinesh Kumar Singh Honorary Consultant (Paediatrics) at HBTMC & DR R N Cooper Hospital. MUMBAI

ABSTRACT Dengue fever becomes a major public health issue constituting a major burden of monsoon related illnesses. WHO Guidelines for management of Dengue fever changes from time to time. There is a need to study the factors which can predict the severity of dengue fever for timely interventions and management to decrease the mortality and morbidity.

Objective Of study was to study correlation between severity and laboratory parameters (haematological & radiological) in patients with dengue fever.

This study was an observational prospective study conducted in the Paediatric Ward and Paediatric Intensive Care Unit in one of the Medical Colleges in Mumbai over a period of 2 years, with case proforma and consent which was previously reviewed and accepted by the hospital's Ethics Committee.

Appropriate history was taken and detailed clinical examination was carried out. Investigations based on progress of the disease in dengue fever like CBC, RFT, LFT, ABG, Serum electrolytes and Chest X-ray, Ultrasonography of abdomen or thorax were done and recorded in case record form .Patients were classified based on clinical presentation and laboratory investigations for their severity based on WHO revised criteria 2009. All the data accumulated was compiled systematically and conclusions drawn from the same.

Qualitative data were represented as frequency and percentage. Association between qualitative variables were assessed by Chi-Square test. Quantitative data was represented using mean±sd and Median & IQR (Interquartile range).

Analysis of Quantitative data between a qualitative variable with two subgroups was done using unpaired t-test.

Results: This study spanning 2 years period enrolled 100 hospitalised patients. Mean age of presentation was 5.82 years. Male: Female ratio being 1.43: 1.

Of the laboratory parameters studied maximum children had abnormal total counts, followed by thrombocytopenia, deranged liver function tests, hemoconcentration, deranged renal function test, electrolyte disturbances and metabolic acidosis. Among the radiological findings in the Study group 48% children had pleural effusion and 33% had ascitis.

Conclusion: A significant association of hemoconcentration, platelet count, deranged renal function test, electrolyte disturbances, deranged liver function test, metabolic acidosis, pleural effusion and ascitis with severity of Dengue Fever was found. There was no significant association found between severity of Dengue Fever with age, gender & abnormal total count.

KEYWORDS : Dengue hemorrhagic fever/diagnosis; Dengue virus; Dengue/blood; Hematologic tests

INTRODUCTION

Dengue Fever is one of the arthropod borne diseases that are on the rise in India [1]. Dengue Fever and Dengue Haemorrhagic Fever have emerged as a global public health problem, infact hyperendemic in many urban, periurban and rural areas with frequent epidemics [2]. The south-east Asia region is one of the regions at highest risk of DF/DHF accounting for 52% of global risk [3]. Dengue outbreaks now occur in India, as in other high burden countries in the region, such as Indonesia, Myanmar and Thailand, with over 16,000 cases reported in India every year, presenting only the tip of the iceberg.

Dengue fever is an acute febrile disease characterized by sudden onset of fever of 3-5 days, intense headache, myalgia, retro-orbital pain, anorexia, gastrointestinal disturbances and rash.

Dengue viruses are flavivirus, which include four serotypes 1, 2, 3 and 4. These same viruses are responsible for Dengue Hemorrhagic Fever (DHF). The viruses are transmitted to man by the bite of infective mosquitoes, mainly Aedes aegypti.

Typically, people infected with Dengue virus are asymptomatic/ have mild symptoms (80%), others have more severe illness (5%), and in a small proportion it is life threatening. The incubation period ranges from 3-14 days, but most often 4-7 days [4].

Severe disease is more common in infants and young children and in contrast to many other infections it is more common in well nourished children [5].

According to WHO criteria 2009 the patients are classified as [6]

- Dengue Fever (either probable or laboratory-confirmed)
- Dengue Fever with warning signs
- Severe Dengue (under which may have manifestations of severe plasma leakage, severe haemorrhage, severe organ impairment)

Dengue Fever may be diagnosed by microbiological laboratory testing [7]. Tests include virus isolation in cell cultures, nucleic acid detection by PCR, viral antigen detection or specific antibodies (serology). Early detection based on clinical suspicion and corroboratory laboratory evidence can help to limit number of cases that progress to developing complications with timely intervention. The whole idea is to capture early the group of patients that may potentially deteriorate due to Plasma leakage, Haemorrhage or Organ impairment. Dengue fever (DF) with its severe manifestations such as DHF and DSS has emerged as a major public health problem of international concern.

Today, Dengue is most important mosquito- borne viral disease in the World, resulting annually 100 million cases of dengue fever and half a million cases of DHF worldwide. Early recognition and prompt initiation of treatment are vital if disease related morbidity and mortality are to be limited.

With there being an increasing number of cases detected, a study of the basic clinical, haematological & radiological aspect of the disease is important. Given the morbidity and mortality associated with dengue fever, classification of the disease is imperative. Thus

this study was undertaken classify the patients with dengue fever (as per WHO guidelines 2009) and study their haematological & radiological profile at a tertiary care centre in Mumbai.

METHODOLOGY

This study was an observational prospective study conducted in the Paediatric Ward and Paediatric Intensive Care Unit in one of the Medical Colleges in Mumbai over a period of 2 years, with case study proforma and consent which was previously reviewed and accepted by the hospital's Ethics Committee.

1. STUDY DURATION : 2 yrs.(Dec 2013 to Dec 2015)

2. SAMPLE SIZE: All the patients over a period of 2 yrs were included in study.

3. STUDY POPULATION: All children in the age group of 1 month-12years, hospitalized fulfilling the inclusion criteria.

4.INCLUSION CRITERIA:

I. Any patient, male/female, between age 1 month to 12 years diagnosed as having Dengue Fever which was laboratory confirmed (on the basis of blood test)
a. Presence of antibodies (IgM/ IgG) against Dengue virus
b. Testing positive for Dengue Ns1antigen
c. Testing positive for Dengue PCR
II. Fulfilling the WHO criteria (2009) for Dengue Fever
III. Patient meeting inclusion criteria, whose parents /guardians were willing to give written informed consent.

5.EXCLUSION CRITERIA:

I. Patients having other co-infections like malaria, typhoid or infective hepatitis, interfering with interpretation of the laboratory data
II. Immunocompromised patients

6. STUDY METHODOLOGY:

Hospitalised patients with clinical features suggestive of Dengue Fever were included & evaluated further using case study proforma. Clinical data was collected using a structured proforma which included case history, clinical findings, laboratory investigations (haematological & radiological) and management.

Certain criteria present in history and clinical examination have been defined from standard references for uniformity in data collection and to decrease the fallacies in research work.

1. Patients were selected based on the inclusion and exclusion criteria.
2. Appropriate history was taken & detailed clinical examination carried out.
3. Detailed demographic profile of patients, IPD no., duration of stay, PICU admission, duration of PICU stay, nutritional status according to WHO classification & Outcome were noted.
4. Laboratory investigations like complete hemogram, RFT, LFT, ABG, Serum electrolytes were done.
5. Patients were classified as probable dengue, dengue with warning signs or severe dengue based on history, clinical examination & laboratory investigations according to the new WHO classification 2009.
6. Treatment was given according to severity based on WHO 2009 protocols.
7. These data were compiled and analysed.

7. STATISTICAL ANALYSIS:

Qualitative data were represented as frequency and percentage. Association between qualitative variables were assessed by Chi-Square test with Continuity Correction for all 2 X 2 tables & with or without Continuity Correction in rest and Fisher's Exact test for all 2 X 2 tables where p-value of Chi-Square test was not valid due to small counts. Quantitative data was represented using mean±sd and Median & IQR (Interquartile range).

Analysis of Quantitative data between a qualitative variable with two subgroups was done using unpaired t-test if data passes 'Normality test' and by Mann-Whitney Test if data fails 'Normality test'. Analysis of Quantitative data between a qualitative variable with more two subgroups were done using One-way ANOVA if data passes 'Normality test' and by Kruskal-Wallis test if data fails 'Normality test', with application of appropriate Post Hoc test if P-value of ANOVA comes statistically significant. Relationship between Quantitative data was assessed using Pearson's Correlation if data passes 'Normality test' and by Sperman's correlation if data fails 'Normality test'. SPSS Version 17 was used for most analysis.

Results

Total 100 patients were enrolled in our study over a period of 2 years fulfilling the inclusion criteria. The results were as follows.

S N0	Parameter	No.	Percentage
1	**Disease Classification**		
	Severe Dengue	11	11.0%
	Dengue with warning signs	44	44.0%
	Probable Dengue	45	**45.0%**
	Total	100	100.0%
2	**Age wise distribution (years)**		
	1month to 1 year	11	11.0%
	1 to 5	36	36.0%
	6 to 12	53	**53.0%**
	Total	100	100.0%
3	**Sexwise distribution**		
	Female	41	41.0%
	Male	59	**59.0%**
	Total	100	100.0%
4	**Nutritional status**		
	Severe undernutrition	8	8.0%
	Moderate undernutrition	28	28.0%
	Normal nutrition	64	**64.0%**
	Total	100	100.0%

Table 1:Demographic details & disease classification of Study group

Parameter					Statical Analysis				
1. Age (years)	**Classification**								
	Severe Dengue	**Dengue with warning signs**	**Probable Dengue**	**Total**	**Chi-Square Tests**	**Value**	**Df**	**p-value**	**Association is-**
< 1	0(0.0%)	3(27.3%)	8(72.7%)	11(100%)	**Pearson Chi-Square ***	5.038	4	0.283	**Not significant**
1 to 5	4(11.1%)	15(41.7%)	17(47.2%)	36	**Pearson Chi-Square †**	2.477	2	0.29	**Not significant**
6 to 12	7(13.2%)	26(49.1%)	20(37.7%)	53(100.0%)	*** 4 cells (44.4%) have expected count less than 5. †Row data pooled & Chi-Square Test reapplied.**				
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					
2. Sex									
Female	6(14.6%)	19(46.3%)	16(39.0%)	41(100%)					
Male	5(8.5%)	25(42.4%)	29(49.2%)	59(100.0%)	**Pearson Chi-Square**	1.472	2	0.479	**Not significant**
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					

3. Nutritional status									
Severe undernutrition ^	0(0.0%)	4(50.0%)	4(50.0%)	8(100.0%)					
Moderate undernutrition ^	2(7.1%)	11(39.3%)	15(53.6%)	28(100.0%)	**Pearson Chi-Square ***	2.810	4	0.590	**Not significant**
Normal nutrition	9(14.1%)	29(45.3%)	26(40.6%)	64(100.0%)	*** 4 cells (44.4%) have expected count less than 5. †Row data pooled & Chi-Square Test reapplied**				
Total	11(11%)	44(44%)	45(45%)	100(100%)					

Table 2:Association between Demographic Parameters & Severity of Dengue

S No	Haematological findings	No.	Percentage (n=100)	S no	Radiological findings	No	Percentage (n=100)
1	**Hemoconcentration**	41	41.0%	**1**	**Pleural effusion on chest X-ray/ USG thorax**	48	48.0%
2	**Total counts altered**	72	72.0%	**2**	**Ascitis on USG abdomen**	33	33.0%
3	**Thrombocytopenia**	58	58.0%				
4	**Renal parameters deranged**	22	22.0%				
5	**Serum electrolytes deranged**	13	13.0%				
6	**Liver function deranged**	45	45.0%				
7	**Metabolic acidosis**	6	6.0%				

Table 3: Distribution of Haematological & Radiological findings among the study group

Parameter					Statical Analysis				
1. Hemoconcentration Classification	**Classification**								
	Severe Dengue	**Dengue with warning signs**	**Probable Dengue**	**Total**	**Chi-Square Tests**	**Value**	**Df**	**p-value**	**Association is-**
Present	11(26.8%)	29(70.7%)	1(2.4%)	41(100.0%)					
Absent	0(0.0%)	15(25.4%)	44(74.6%)	59(100.0%)	**Pearson Chi-Square**	55.088	2	0.0109	**Significant**
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					
2. Platelet count									
Thrombocytopenia	11(19.0%)	30(51.7%)	17(29.3%)	58(100.0%)					
Normal	0(0.0%)	14(33.3%)	28(66.7%)	42(100.0%)	**Pearson Chi-Square**	17.392	2	0.000167	**Significant**
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					
3.Total count									
Leucocytosis ^	1(6.3%)	8(50.0%)	7(43.8%)	16(100.0%)	**Pearson Chi-Square $**	0.905	4	0.924	Not significant
Leucopenia ^	6(10.7%)	25(44.6%)	25(44.6%)	56(100.0%)	**Pearson Chi-Square ^**	0.596	2	0.742	Not significant
Normal	4(14.3%)	11(39.3%)	13(46.4%)	28(100.0%)	**$ 2 cells (22.2%) have expected count less than 5. ^ Row data pooled & Chi-Square Test reapplied.**				
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					
4.Renal parameters									
Deranged	9(40.9%)	12(54.5%)	1(4.5%)	22(100.0%)					
Normal	2(2.6%)	32(41.0%)	44(56.4%)	78(100.0%)	**Pearson Chi-Square**	33.908	2	0.0434	**Significant**
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					
5.Liver function test									
Deranged	11(24.4%)	20(44.4%)	14(31.1%)	45(100.0%)					
Normal	0(0.0%)	24(43.6%)	31(56.4%)	55(100.0%)	**Pearson Chi-Square**	16.955	2	0.000208	**Significant**
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					
6.Serum electrolytes									
Abnormal	4(30.8%)	6(46.2%)	3(23.1%)	13(100.0%)					
Normal	7(8.0%)	38(43.7%)	42(48.3%)	87(100.0%)	**Pearson Chi-Square**	6.921	2	0.031	**Significant**
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					
7.Metabolic acidosis									
Present	6(100.0%)	0(0.0%)	0(0.0%)	6(100.0%)	**Pearson Chi-Square $**	51.644	2	0.0460	
Absent	5(5.3%)	44(46.8%)	45(47.9%)	94(100.0%)	**Pearson Chi-Square #**	42.426	1	0.0007	
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)	**Fisher' Exact Test #**			0.0026	
					$ 3 cells (50.0%) have expected count less than 5. ^ Column data pooled & Chi-Square Test reapplied with Continuity Correction.				
					# 1 cell (25.0%) has expected count less than 5. P-value of Fisher's test will be used.				

Table 4. Association between Hematological parameters and severity of Dengue

Parameter					Statical Analysis				
8.Chest x-ray/ USG thorax	Classification								
	Severe Dengue	Dengue with warning signs	Probable Dengue	Total	Chi-Square Tests	Value	Df	p-value	Association is-
Pleural effusion	9(18.8%)	24(50.0%)	15(31.3%)	48(100.0%)					
Normal	2(3.8%)	20(38.5%)	30(57.7%)	52(100.0%)	Pearson Chi-Square	9.674	2	0.00793	Significant
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					
9.USG abdomen									
Ascitis	11(33.3%)	16(48.5%)	6(18.2%)	33(100.0%)					
Normal	0(0.0%)	28(41.8%)	39(58.2%)	67(100.0%)	Pearson Chi-Square	30.430	2	0.0247	Significant
Total	11(11.0%)	44(44.0%)	45(45.0%)	100(100.0%)					

Table 5: Association between Radiological parameters and severity of Dengue

A. Hematological findings	Our study	Sahana KS et al [09]	C. V. Prathyusha [08]	Singh NP et al [10]	Jamb R et al [11]
Hemoconcentration	41.0%	72.8%		52%	5.26%
Total count altered	72.0%	34.5%	72%	68%	38%
Thrombocytopenia	58.0%	82.7%	85%	61.39%	100%
Renal parameters deranged	22.0%				13.1%
Serum electrolytes deranged	13.0%				
Liver function deranged	45.0%	33.3%	17.5%		
Metabolic acidosis	6.0%				
B. Radiological findings					
	Our Study	AnjuDayal et al [33]	Sahana KS et al [09]		
Pleural effusion on chest x-ray/ USG thorax	48.0%	53%	39.5%		
Ascitis on USG abdomen	33.0%	70%	48.1%		

Table6: Comparison of Our Study group Laboratory Parameters (haematological & Radiological) with other studies

Discussion

In our study a significant association ($p<0.05$) between the presence of hemoconcentration, decreased platelet count, deranged renal function tests, electrolyte disturbances, deranged liver function tests and metabolic acidosis with severity of Dengue Fever was found.

There was no significant association ($p>0.05$) found between severity of Dengue Fever with abnormal total count.

On reviewing literature:

Presence of Hemoconcentration is a prognostic factor for dengue infection severity particularly DSS, a finding corroborated by many studies [12, 13, 14]. Vasculopathy in dengue infection causes increased vascular permeability, leading to hemoconcentration and shock. Hemoconcentration (hematocrit ≥ 20% of initial value) is one of the WHO criteria to diagnose DHF. No such association was however found by Gupta V et al [15].

K. Jayashree et al and Mourao et al showed that a falling trend in the platelet count during the course of hospitalization was associated with poor outcome [16, 17].

C. V. Prathyusha et al crease in the incidence of bleeding with increasing severity of thrombocytopenia. [08].

Some studies concluded that white cell count > 5,000/µL is a prognostic factor for dengue severity [18, 19] while others found leucopenia to be a significant prognostic factor [15, 13]. Normoleukocytosis or mild leukocytosis may be found in early dengue infection. When body temperature declines, most patients experience leucopenia because of bone marrow suppression [20].

Our study however did not show any significant association with leucopenia or leukocytosis.

Similar to many studies, platelet counts ≤ 100,000/µL increased the risk of severity; a finding similar to our study [21, 12, 22, 14]. Platelets decrease rapidly before patients enter the state of shock. WHO also used platelets to categorize dengue infection into DHF grade I-IV [23]. Low platelet was explained by bone marrow suppression and immune-response induced platelet destruction by liver and spleen [20, 24,and 25].

Acute renal failure complicates severe dengue infection in 2-5% of the cases and carries a high mortality rate. Proteinuria has been detected in as high as 74% of patients with severe dengue infection. Hematuria has been reported in up to 12.5% of patients. Various types of glomerulonephritis have been reported during or shortly after dengue infection in humans and mouse models of dengue infection. Mesangial proliferation and immune complex deposition are the dominant histologic features of dengue-associated glomerulonephritis. On a rare occasion, dengue infection is associated with systemic autoimmune disorders involving the kidneys [26]. AKI is associated with an increased mortality in DF in a study by Mehra N et al [27].

Elevated liver enzymes (SGOT and SGPT) are known to be prognostic factors for DSS [19,28] and have a significant association with severity [29]. When liver cells are infected, SGOT levels are higher than SGPT particularly in severe cases [25]. The averaged SGOT and SGPT levels are higher in DHF than in DF [30]. Prolonged PTT and prolonged PT are prognostic factors for DHF and DSS [22, 31]. However, two studies by Pongapan S et al and Tantracheewathorn T et al did not find such an association [21,32]. Elevated liver enzymes, prolonged PT and prolonged PTT normally occur after shock [32], which are too late to be used as prognostic indicators. Furthermore, SGOT, SGPT, PT, PTT may not be done in some hospitals, limiting their use as prognostic indicators.

A retrospective study by Nimmanittya S. et al on 18 cases of DHF who presented with jaundice and neurological signs which were considered unusual manifestation of DHF reveals that the causes or contributing factors are multifactorial. Most commonly found associated conditions were prolonged shock with metabolic acidosis[29].

In our study a significant association ($p<0.05$) between the presence of pleural effusion and ascitis with severity of Dengue Fever was found.

Similar findings linking the presence of pleural effusion and ascitis with severity of Dengue was found in studies by Sahana KS et al and AnjuDayal et al was found. [33,09]

Conclusion

We conducted this study based on the new WHO classification 2009 of dengue fever to know which factors can predict severity so as to facilitate timely intervention. Following conclusion can be drawn from our study:

1. Of the total 100 patients enrolled in the study, 45% of the children were probable dengue followed by 44% dengue with warning signs and 11% were severe dengue.
2. Maximum children were in the age group of 6-12 years and age was found to have no significant association with the severity of dengue fever.
3. A 1.4:1 male preponderance was observed in our patients with dengue fever but gender had no significant association with severity of dengue fever.
4. Amongst the laboratory investigations, maximum patients had an abnormal total count, followed by thrombocytopenia, deranged liver function tests, hemoconcentration, deranged renal function test, electrolyte disturbances and metabolic acidosis all of which except abnormal total count were predictors of severity of dengue fever.
5. Amongst the radiological findings in the study group 48% children had pleural effusion and 33% had ascitis both of which were significantly associated with severity of dengue fever.

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