

Dengue fever in patients admitted in tertiary care hospitals in Pakistan

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Abstract

Objectives: To assess the gaps in the diagnosis and management of dengue fever cases.

Methods: The retrospective descriptive analytical study was done with a case record analysis of patients with dengue fever admitted from January to December 2010 at five tertiary care hospitals in different Pakistani cities. Using a questionnaire, information was gathered on demography, haematological profile, management, use of blood and platelet transfusions and the outcome. For comparison, data of serologically-confirmed dengue patients from a private laboratory in Islamabad was collected to see the age, gender and month-wise distribution of cases tested over the same period. SPSS 16 was used for statistical analysis.

Results: Out of the 841 confirmed dengue cases, 514 (79%) were males and 139 (21%) females. The overall mean age was 31.3±14.0 years. Dengue fever was seen in 653 (78%) and dengue haemorrhagic fever (DHF) in 188 (22%) patients. Most cases were between 20 and 49 years of age. A gradual increase in dengue fever and dengue haemorrhagic fever was seen from August, with a peak in October/November.

Tourniquet test was done only in 20 (2.3%) cases, out of which 11 (55%) were positive and 9 (45%) were negative. Serial haematocrit was not done in any case. Total deaths were 5 (0.6%).

Conclusions: Most cases were seen in October/November with the majority being in the 20-39 age group. Tourniquet test and serial haematocrit were infrequently used. No standard national guidelines were employed.

Keywords: Dengue fever, Dengue haemorrhagic fever, Dengue shock syndrome, Retrospective study, Platelets. (JPMA 64: 553; 2014)

Introduction

Dengue is a mosquito-borne viral disease affecting humans. Dengue fever (DF) and its more severe form i.e. dengue haemorrhagic fever (DHF), are caused by any one of the four serotypes of dengue virus (DEN-1, DEN-2, DEN-3, DEN-4) belonging to the genus *Flavivirus* transmitted by *Aedes aegypti*. Infection by one serotype generates life-long immunity against the same serotype, but gives transient/partial protection against the other serotypes.^{1,2} Sequential infection with another serotype can result in the more severe DHF.³

Dengue infection represents a considerable disease burden in many tropical and sub-tropical countries, particularly in children and young adults, living in urban and semi-urban areas.⁴ Globally about 50 million infections occur which is projected to increase.⁵ In endemic areas, dengue infection is a leading cause of hospitalisation and deaths among children.⁶ The average case fatality rate is up to 5% mainly affecting children and

young adults.⁷ In Pakistan, the first outbreak of DHF was reported in 1994.⁸ In 1998 DEN1 and DEN2 was confirmed on enzyme-linked immunosorbent assay (ELISA).⁹ A DEN3 epidemic was reported in 2005.¹⁰ The 2006 outbreak was dominated by DEN2 and DEN3¹¹ which was related to DEN3 (subtype III) that caused an outbreak in New Delhi in 2004¹² and since then increasing frequency and severity of dengue infection has been reported from all over Pakistan. High levels of anti-dengue immunoglobulin M (IgM) antibodies have been reported in children living in Pakistani slums.¹³

The incubation period of DF ranges from 3 to 15 (usually 5-8) days. Clinical manifestations vary from asymptomatic infection to DF, DHF and dengue shock syndrome (DSS). Most dengue infections are asymptomatic or cause mild symptoms of high-grade fever with or without rash and resolve without specific treatment. Typical dengue fever is characterised by high fever, severe headache, myalgia, arthralgia, retro-orbital pain and maculopapular rash. About 5-10% patients progress to DHF which is characterised by high-grade fever, haemorrhagic phenomenon (presence of at least one i.e. positive tourniquet test; petechiae, ecchymoses, or purpura; epistaxis or bleeding from mucosa, gastrointestinal tract, injection sites or others), thrombocytopenia (moderate to

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marked drop in platelets), and haemoconcentration (raised Packed Cell Volume). Plasma leakage may result in pleural effusion and ascites. Some may progress to DSS which is characterised by the presence of all four clinical manifestations of DHF along with circulatory failure i.e. rapid and weak pulse, narrow pulse pressure, hypotension, cold/clammy skin and altered consciousness. Severe dengue can also produce hepatic damage, cardiomyopathy, encephalopathy and encephalitis — although these manifestations are rare, but the risk of death in such cases is high.^{14,15} Both DHF/DSS can cause high mortality if not managed urgently and appropriately.

There are no specific antiviral treatments for dengue infection and patients usually recover with timely fluid and electrolyte replacement.¹⁶ Timely and appropriate case management can reduce the mortality to below 1%.

In the absence of national dengue case management guidelines and treatment protocols the clinicians are treating patients on the basis of their clinical acumen which at times results in over or under management. This study was conducted to retrospectively analyse clinical records of all patients admitted with DF and its complications in 5 tertiary care hospitals of Pakistan, and to assess the gaps in the diagnosis and management of these cases.

Patients and Methods

The retrospective descriptive analytical study was done with a retrieval of case records of all clinically suspected and laboratory-confirmed cases of DF who were admitted to five hospitals from January to December 2010, using a questionnaire. The hospitals were Jinnah Postgraduate Medical Centre, Karachi (335 cases), Civil Hospital, Hyderabad (160 cases), Jinnah Hospital, Lahore (222 cases), Ayub Medical Complex Abbottabad (99 cases), and Pakistan Institute of Medical Sciences, Islamabad (25 cases).

Only dengue IgM/IgG positive cases who had complete demographic and laboratory details were included. The information included patient's demography, signs/symptoms and blood complete picture (CP) including haematocrit, treatment given including platelets transfused and the ultimate outcome i.e. death or discharge. Patients were classified into DF if they had fever, while bleeding from any mucosal site along with fever was taken as DHF, and those in shock were classified as DSS.

Data of serologically-confirmed dengue patients from a private laboratory (Citi Lab, Islamabad) were also analysed to compare the age, gender and the monthly cases tested over the same time period. The sensitivity and specificity

of kits dengue IgM (Nova Tec Immudiagnostica GmbH) and non-structural protein 1 antigen (NS1Ag) (Inverness medical) used were 97.6%:90% and 71.1%:96% respectively.^{17,18}

SPSS 16 was used for statistical analysis. Demographic, clinical, laboratory features and results were presented as mean \pm standard deviation for quantitative variables (age, stay in hospital, platelet count and unit of platelet transfused) and number and percentage for qualitative variables (gender, age grouping, clinical presentation, haemorrhage etc.). Statistical comparison was performed by using Chi-square/Fisher exact test (less than 5) for qualitative variables and student t-test was used for comparison of platelet between DF and DHF, one-way analysis of variance (ANOVA) was used for the number of transfusions. All p values were two-sided, and considered significant if <0.05 .

Results

Out of the 841 dengue cases, 665 (79%) were males and 176 (21%) females, with an overall mean age of 31.3 ± 14.0 years. Of the total, 653 (78%) cases were suffering from DF and 188 (22%) had associated DHF of whom 5 (2.65%) had DSS.

The overall age distribution of DF and DHF was worked out (Figure-1). Maximum cases of DF 439 (67%) and DHF 141 (75%) were seen between 20 to 49 years with highest

Table-1: Characteristics of patients with dengue fever (DF) and dengue haemorrhagic fever (DHF).

Characteristics	DF (n=653) No. (%)	DHF (n=188) No. (%)	P-value
Demographics			
Age in years (Mean \pm S.D)	31.5 \pm 14.4	30.6 \pm 12.1	0.453
Gender			
Male	514 (79)	151 (80)	0.633
Female	139 (21)	37 (20)	
Clinical Presentation			
Fever	69 (82.1) out of 84	64 (73.6) out of 87	0.177
Headache	36 (19.5) out of 185	21 (14.6) out of 144	0.246
Nausea and /or vomiting	86 (13.4)	39 (20.7)	0.014*
Rash	20 (11.0) out of 182	23 (15.5) out of 148	0.221
Haemorrhage			
Patechiae	-	12 (6.4)	
Epistaxis	-	73 (38.8)	
Malena	-	13 (6.9)	
Other sites of bleeding**	-	101 (53.7)	
Shock	-	5 (2.6)	
Mean number of days patient's stay at the hospital	3.7 days (Range: 3-15 days) Median = 3.0 days		

*Statistically significant $p < 0.05$.

**Bleeding gum and mouth, haemoptysis, haematuria, etc.

Table-2: Haemoglobin, white blood cell count, haematocrit and platelet count in Dengue fever and Dengue haemorrhagic fever patients.

Characteristic	DF (n=653)	DHF (n=188)	P-value
Low Haemoglobin <10 mg/dL	9 (10.2%) Out of 88	14 (15.2%) Out of 92	0.316
Leucopaenia (TLC < 4000)	178 (58.4%) Out of 305	60 (54.5%) Out of 110	0.487
Leukocytosis (TLC > 10,000)	2 (0.7%) Out of 305	1 (0.9%) Out of 110	0.487
Haematocrit (10-20% above normal)	28 (46.7%) Out of 60	19 (31.7%) Out of 60	0.092
Platelet Count (Mean ± S.D)	355, 50,000±37000	138, 40,000±37000	0.003

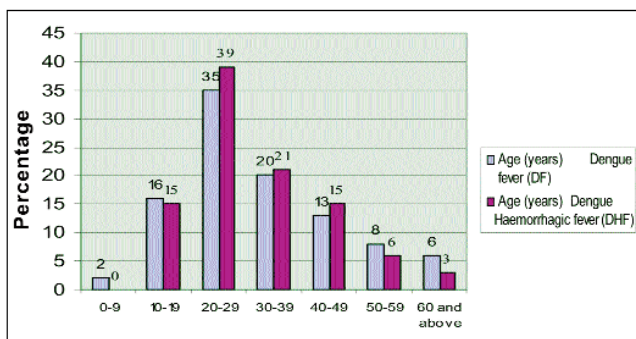


Figure-1: Age (years) distribution of confirmed dengue cases (Hospital Data).

peak between 20 to 29 years. Slightly more 68 (36%) DHF cases were seen between 20 and 49 years. However, no case of DHF was found in the age group of 0-9 years.

Month-wise distribution showed a gradual increase in the cases from September DF 39 (6%), DHF 12 (6%) with maximum seen in October 278 (43%) DF, 75 (40%) DHF and November 317 (48%) DF, 85 (45%) DHF and a decline thereafter (Figure-2).

The common presenting symptoms in patients with DF and DHF are shown in Table-1. Nausea/vomiting was

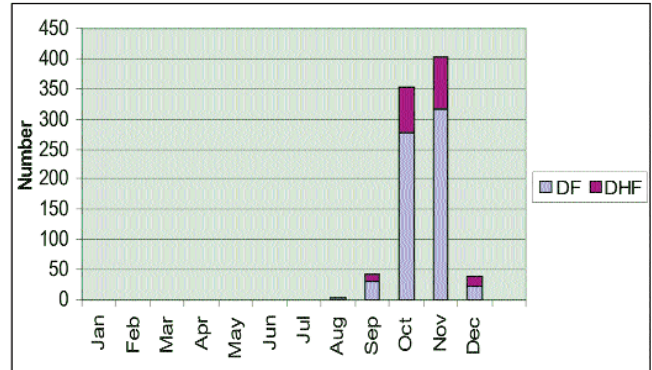


Figure-2: Number of Dengue Fever and Dengue Haemorrhagic Fever cases by month (Hospital Data).

significantly more in DHF 39 (20.7%) compared to DF 86 (13.2%) ($p < 0.010$), while other symptoms did not show any significant difference. Tourniquet test was done in 20 (2.3%) cases and was positive in 11 (55%). Range of hospital stay was 3-15 days (mean 3.7 ± 2.44 ; median 3 days).

Except for platelets count, which was significantly lower in DHF, no significant difference was found in other laboratory parameters when compared between DF and DHF patients (Table-2).

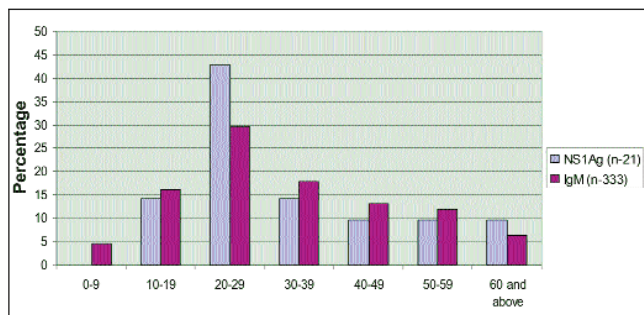
Platelets were transfused in 35 (83.3%) of the 42 cases with severe thrombocytopenia i.e. (platelet count $\leq 10,000$), while in among the 449 patient having platelets range from 11,000 - $>150,000$ transfusion was given to 98 (21.8%) (Table-3).

Overall, 720 (86%) recovered and were discharged, 24 (3%) left against medical advise (LAMA), whereas 5 (0.6%) patients died. No information was available for 92 (11.2%) cases regarding their outcome. Death details were available in 1 (16.6%) of the 6 patients only. He was a 42-year male from Karachi who was admitted to a tertiary care hospital with fever (102°F), and massive bleeding. His

Table-3: Platelet transfusions to the admitted dengue patients (n=506).

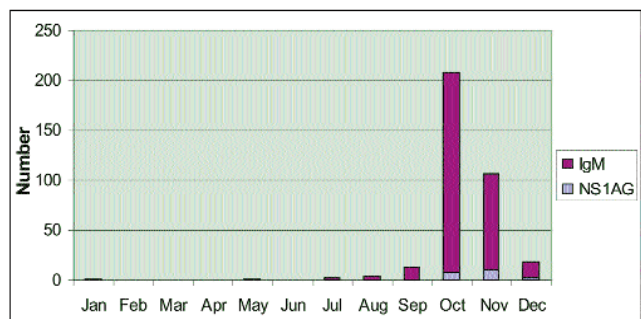
Platelet count	No. (%) of Subject	Gender		Platelets transfused			No. Units transfused Mean ± S.D.
		M	F	Yes	No	DK	
$\leq 10,000$	42 (8.3)	37	5	35 (83.3%)	-	4	1.17 ± 0.62
11,000-20,000	69 (13.6)	54	15	20 (29.0%)	29	20	1.55 ± 1.31
21,000-50,000	214 (42.3)	175	39	54 (25.2%)	115	45	1.46 ± 0.92
51,000-100,000	142 (28.1)	110	32	19 (13.5%)	81	42	1.32 ± 0.95
101,000-150,000	24 (4.7%)	18	6	3 (12.5%)	16	5	1.33 ± 0.58
$>150,000$	15 (3.0%)	11	4	2 (13.3%)	7	6	1.00 ± 0.00
P-value				0.001			0.886

DK = don't know.



NS1Ag: Non-structural protein 1 antigen. IgM: Immunoglobulin M.

Figure-3: Age (years) distribution of NS1Ag and IgM positive dengue patients (Lab Data).



NS1Ag: Non-structural protein 1 antigen. IgM: Immunoglobulin M.

Figure-4: Number of NS1Ag and IgM positive dengue cases by month (Lab Data).

haematocrit was 50%, haemoglobin 4.8 gm/dl, and platelet count 15000/cumm.³ He was transfused 2 units of whole blood, 08 bags of fresh frozen plasma, and 02 mega units of platelets. The patient went into shock and hepatic coma and was transferred to another private hospital where he expired. The total span from admission to death was 4 days.

For comparison, data of 354 dengue IgM (ELISA) and NS1Ag (Early Rapid kits) confirmed cases from a private laboratory were analysed to see the age distribution, gender and the number of cases tested over the study period. Age, gender and seasonal distribution of hospitalised patients was similar to the laboratory data (Figures 3 and 4).

Discussion

The present study showed dengue peak in October/November with most cases having fever and few having haemorrhagic tendency and shock. Male predominance was seen in all ages and has been reported

earlier too^{19,20} which might be due to gender bias in seeking healthcare.²¹ Proper covering of body and maximum indoor stay in females could be another reason for the low female preponderance.^{20,21} However, there are studies that have not reported any gender difference.^{22,23}

DF is regulated by seasonal variations in the South Asian region where ideal condition for vectors' survival and propagation exist, especially during monsoon period when there is abundant rainfall and high humidity, with daily temperature reaching 30°C. These climatic conditions provide excellent ground for mosquito breeding.²⁴⁻²⁷ In the present study a gradual increase in cases was seen from September with a peak in October/November and a decline thereafter, indicating a post-monsoon infection which has also been observed by others.²⁸⁻³¹ A study from Lahore also showed an increase in dengue cases in September-December with a peak in November.¹⁹ It appears that in Pakistan, this season is highly favourable for vector breeding i.e. *Aedes aegypti*.

DF and its complications maximally affect young adults and the same was seen in the present study and those reported by others from Pakistan.²¹ This finding is consistent with other countries in South Asia.^{29,31} One of the limitations of the study was that as the present study retrieved records from adult medical wards and not paediatric wards, therefore it is difficult to say what proportion of children got infected with the disease. It may also be kept in mind that dengue is an emerging disease in Pakistan, and the population at large is not yet completely immune, therefore, all age groups can be infected, particularly the young adults, with this virus. One potential source of bias might be the catchment areas and accessibility, in terms of physical distances and costs involved of the hospitals from where data was collected.

Fever is the commonest symptom in dengue patients^{19,32} and the same was found to be true in the present study which was also in accordance with two earlier studies reported from Pakistan.^{19,29} However, according to the World Health Organisation (WHO), the clinical features of DF vary according to the age. Adults may have either a mild febrile syndrome or the classical incapacitating disease with abrupt onset of high-grade fever, severe headache, pain behind the eyes, muscle and joint pains, and rash. DHF is a deadly disease characterised by high fever, haemorrhagic tendency and circulatory failure.³⁰ Other symptoms in the present study were headache nausea/vomiting and rash, and these are comparable with those documented by others though their frequencies varied.^{11,19,33,34}

In the current study, key haemorrhagic manifestations

were seen in lesser number of patients (6.4-53.7%) as compared to 67% reported from Malaysia.³⁵

Thrombocytopenia constitutes one of the most common clinical findings in dengue disease³⁶⁻³⁸ and low platelet count is currently used as a criterion for the diagnosis of DHF.³⁹ The cause of thrombocytopenia in dengue is unknown but decreased production of platelets has been described.^{40,41} In the present study thrombocytopenia was seen in 92% cases which is much higher than 8.6% reported from Indonesia,⁴² 48% in Sri Lanka,⁴³ 54% in Bangladesh,⁴⁴ 70% in India⁴⁵ and 78% in Cuba.⁴⁶ Thrombocytopenia has also been reported in other studies from Pakistan.¹⁹ Thrombocytopenia is a risk factor for haemorrhage and the threshold for prophylactic platelet transfusion is 10,000/mm³ in non-dengue patients.⁴⁵ The WHO recommends platelet transfusion in adults only with underlying hypertension and very severe thrombocytopenia (less than 10,000 cell/mm³).⁴⁷ No association has been found between the degree of thrombocytopenia and active bleeding in other studies.⁴⁸⁻⁵¹ It has been suggested that since there is no specific treatment for DHF/DSS, therefore patients with bleeding tendency and those having a platelet count of less than 20,000/mm³ may be empirically transfused platelets.⁵² The crux of treatment of dengue patients is maintenance of good hydration, monitoring for any overt bleeding and not to "panic" if the platelet count is less than 50,000/mm³ (normal platelet count is 150,000-450,000/mm³).⁵² Most patients as well as healthcare providers often get panicky and tend to chase platelet counts; this was evident in the present study and also in an outbreak in north India⁵³ where it was labelled as "Dengue Panic Syndrome". The role of platelet transfusion in the management of dengue patients in a tertiary care hospital was studied and it was recommended that patients with <20,000/cumm are at high risk of bleeding and require urgent platelet transfusion, whereas patients with a count between 21000-40,000/cumm are at moderate risk and require platelet transfusion only if they have haemorrhagic manifestations.⁴⁸ The role of platelet transfusion for the management of dengue needs special attention.

In the present study, raised haematocrit (above 10-20%) was observed in 47% DF and 32% DHF patients. However, according to WHO,³⁰ a rise in the haematocrit level, indicating plasma leakage, is present even in non-shock cases but is more pronounced in shock cases. Haemoconcentration with increase in haematocrit of 20% or more is considered to be a definitive evidence of increased vascular permeability and plasma leakage. A rising haematocrit and falling platelet count is typical of

DHF. In the present study, the review of hospital record showed that haematocrit is not being monitored as per WHO guidelines and most cases had only one or two laboratory readings available in the followup.

The current study showed leucopenia in over 55% cases. Leucopenia, or low white blood cell (WBC) count, has been reported among dengue patients in many studies, as well as by the WHO, except a retrospective study which did not show any association between low WBC and dengue.^{30,54,55}

Tourniquet test (TT) is recommended as a screening tool for dengue infection. A positive TT indicates haemorrhage³⁰ and, according to WHO guidelines, a positive test with leucopenia (≤ 5000 cells/mm³) at an early stage is suggestive of dengue illness.⁴⁷ In the current study, TT was done in 2.3% cases only. The validity and sensitivity of this test has been debated in some studies.^{32,56-58}

The variation in the diagnosis and management of dengue patients in Pakistan showed lack of standard operating procedures according to international guidelines. National guidelines need to be developed urgently so that healthcare providers can be trained timely. Till then revised WHO guidelines 2011 can be adapted and endorsement by the national and provincial authorities is mandatory. Furthermore, data management and record keeping in hospitals need to be strengthened as per WHO requirements which may help in future planning to optimally manage the dengue cases and for epidemic preparedness and response. Community awareness campaign for prevention against dengue needs to be more vigorously pursued.

Conclusion

Keeping in view the rising trend in the dengue cases in Pakistan, it is recommended that dengue prevention and control should be made part of the provincial malaria control programmes for regular surveillance, monitoring and control.

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