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ORIGINAL ARTICLE

Dengue Fever Outbreak: A Clinical Management Experience

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ABSTRACT

Objective: To determine the frequency of dengue as a cause of fever and compare the clinical and haematological characteristics of Dengue-probable and Dengue-proven cases.

Study Design: An observational study.

Place and Duration of Study: The Combined Military Hospital, Malir Cantt., Karachi, from August 2005 to December 2006.

Patients and Methods: All patients with age above 14 years, who were either hospitalized or treated in medical outdoor clinic due to acute febrile illness, were evaluated for clinical features of Dengue Fever (DF), Dengue haemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS). Patients showing typical clinical features and haematological findings suggestive of Dengue fever (As per WHO criteria) were evaluated in detail for comparison of probable and confirmed cases of Dengue fever. All other cases of acute febrile illness, not showing clinical features or haematological abnormalities of Dengue fever, were excluded. The clinical and laboratory features were recorded on SPSS 11.0 programme and graded where required, for descriptive and statistical analysis.

Results: Out of 5200 patients with febrile illness, 107(2%) presented with typical features of DF, 40/107(37%) were Dengue-proven while 67/107(63%) were Dengue-probable. Out of Dengue-proven cases, 38 were of DF and 2 were of DHF. Day 1 temperature ranged from 99-105^{0}C (mean 101^{0}C). Chills and rigors were noticed in 86 (80%), myalgia in 67%, headache in 54%, pharyngitis in 35%, rash in 28%, and bleeding manifestations in 2% cases. Hepatomegaly in 1(0.5%), lymphadenopathy in 1(0.5%) and splenomegaly in 12 (11.2%) cases. Leucopoenia (count < 4x10^9 /L) was noted in 73%, platelet count <150 x10^9 /L in 84% and ALT > 40 U/L in 57% cases.

Conclusion: Frequency of clinically suspected dengue virus infection was 107 (2%), while confirmed dengue fever cases were 40 (0.8%) out of 5200 fever cases. Fever with chills and rigors, body aches, headache, myalgia, rash, haemorrhagic manifestations, platelet count, total leukocyte count, and ALT, are parameters to screen the cases of suspected dengue virus infection; the diagnosis cannot be confirmed unless supported by molecular studies or dengue specific IgM .

Key words: *Dengue fever (DF). Dengue haemorrhagic fever (DHF). Dengue shock syndrome (DSS). Management.*

INTRODUCTION

The global prevalence of dengue fever spectrum has grown dramatically in recent decades. Every year about 50-100 million cases of dengue infection, 500,000 cases of DHF and at least 12,000 deaths occur worldwide.[1] In 1970 only 9 countries had known epidemics of dengue hemorrhagic fever. This number increased by more than four-fold in 1995 and about 2500 million of people are now exposed to the risk of Dengue fever.[2] Dengue viruses (DENVs), members of the Flaviviridae family contain four closely related serotypes: DENV-1, DENV-2, DENV-3 and DENV-4.[3] All are transmitted between humans by mosquitoes of genus Aedes, principally *Ades aegypti*. Significant increases in the mosquito larval populations are seen during the rainy season. This may be a reason why the epidemics of dengue tend to coincide with the rainy season.[4] A person infected by one of the serotypes will never be infected by the same serotype, but loses immunity to the three other serotypes in 12 weeks time. Residual antibodies produced during the first infection are unable to neutralize a second infection with another serotype, and the second infection, under the influence of enhancing antibodies, results in severe infection and disease. This phenomenon is referred to as antibody-dependent enhancement.[5]

Clinically dengue virus infection manifests in one of the three forms: classical Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). The DF is characterized by high-grade fever, musculoskeletal pains, retrobulbar headaches and morbilliform rash. Appearance of haemorrhagic rash or haemorrhagic manifestations in addition to classical DF characterizes the Dengue

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Hemorrhagic Fever (DHF). Dengue shock syndrome is characterised by hypotension, altered mental status and delayed capillary filling.[6]

An outbreak of DF was encountered in Karachi in 1994 and another at upper parts of Punjab in 2003, in addition to sporadic cases in Rawalpindi, Mangla, Peshawar, Abbottabad and Haripur.[7,8] Above mentioned studies elaborated clinical and haematological features of Dengue fever cases, with particular emphasis on haemorrhagic manifestations. The present study was conducted with an aim to determine the frequency of Dengue fever in patients of acute febrile illness, in the studied period. In addition, the characteristics of disease were noted to find out any difference of clinical and haematological presentation of disease in Dengue-probable and Dengue-proven cases.

PATIENTS AND METHODS

This observational study was carried out from August 2005 to December 2006 at Combined Military Hospital, Malir Cantt., Karachi. All patients with age above 14 years, who were either hospitalized or treated in medical outdoor clinic due to acute febrile illness, were evaluated for clinical features of DF, DHF and DSS. All patients with typical clinical features of Dengue fever as per WHO criteria[9] and associated thrombocytopenia or haemoconcentration, were included in the study. All other cases of acute febrile illness, whether with confirmed diagnoses or of some non-specific origin, but not showing typical features or haematological abnormalities of Dengue fever, were excluded from the study. Patient with clinical presentation suggestive of DF, and supported by positive serology of dengue specific IgM were labelled as Dengue confirmed cases.[10] Patients with suggestive clinical features and bicytopenia, negative for dengue serology, malarial parasites, normal blood widal test were labelled as Dengue probable. Probable and confirmed patients of DF, DHF and DSS were admitted; and clinical features were recorded. Treating consultant determined graded response of features.

Two millilitres of blood in EDTA anticoagulant, 2.8 ml blood in 0.2 ml citrate anticoagulant and 3 ml blood in plain bottle was collected for blood counts, malarial parasite, dengue specific IgM, Prothrombin Time (PT), Partial Thromboplastin Time with Kaolin (PTTK), Widal test, and aminotransferase (ALT). Blood counts including Red Cell Count (RCC), Haemoglobin (Hb), Hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), platelet count, Total White Cell Count (TWBC), Differential Leukocyte Counts (DLC) were performed on Sysmax automated haematology analyzer. Qualified haematologist examined the blood film for malarial parasites. PT and PTTK were performed by noticing clot formation visually. Serum ALT was performed by standardized method as described by manufacturer using microlab 200 (Merck Marker). Dengue specific IgM were performed by standard enzyme linked immunosorbent assay (ELISA).[11,12] Blood counts were serially monitored till the platelet counts started showing a rising trend and were in the safe limits.

Symptomatic treatment was advised for Dengue fever patients. In case, where malarial parasites were positive, anti-malarial treatment was also advised. In case of haemorrhages, platelet concentrate was advised. In case if PT or PTTK was also disturbed, fresh frozen plasma (FFP) in addition to platelet support was advised. In case of haemoglobin below 7 g/dl, red cell concentrate or whole blood transfusion was advised.[13] Patients were discharged once asymptomatic. Clinical features and laboratory findings were recorded. SPSS 11.0 programme was used for statistical analysis. Chi-square test was applied to find out the statistical significance.

RESULTS

A total of 5200 patients with febrile illness were received during the study period. One hundred and seven (2%) presented with typical features of DF, and were included in the study. Age of patients ranged between 14 to 67 years (mean 31 years). All were male. Forty (37%) were Dengue-proven, while 67/107 (63%) were Dengue-probable. Out of Dengue-proven, 38 were of DF and 2 were of DHF. One presented with a fit and confusional state fit due to multiple small intracerebral haemorrhages and the second developed epistaxis, ecchymosis and gum bleeds at platelet count less than 10×10^9/ l.

Out of 67 dengue probable cases, one patient developed bleeding manifestation in the form of conjunctival haemorrhages. Fever of 1-10 days duration was present in 107/107 (100%) cases. Day 1 temp ranged between 99-105^{o}C (mean 101^{o}C), day 3 temp ranged 99-103^{o}C (mean 99.5^{o}C), day 5 temp ranged 98-102^{o}C (mean 98.1^{o}C) and day 7 temp ranged 98-100^{o}C (mean 98^{o}C). Clinical features of both Dengue-proven and Dengue-probable are summarized in Table I. Leukopenia (count < $4x10^9$/L) was noted in 73%, neutrophil count < $2x10^9$/L in 53%, lymphocyte count < $2x10^9$/L in 97%, platelet count <150 $x10^9$ /L in 84% and ALT > 40 U/L in 57% cases. Serum creatinine was marginally raised in one case of dengue probable. Coagulation profile was disturbed in 2 cases of Dengue proven and one case of Dengue probable. Laboratory findings of Dengue proven and probable cases are summarised in Table II. Mean total leukocyte count was lowest on day 3 of admission and started rising on day 7. Mean hematocrit was highest at admission that declined after starting the oral and intravenous fluids.

Table I: Clinical features of dengue fever cases (n=107).

Symptom	DEN Proven (40)	DEN Probable (67)	p-value
Chills/rigors	30 (75%)	56 (84%)	0.5
Diarrhoea	4 (10%)	13 (19%)	0.5
Vomiting	19 (47%)	41 (61%)	0.5
Sweating	15 (37%)	29 (43%)	0.5
Headache	25 (63%)	33 (50%)	0.01
Myalgia	29 (73%)	34 (64%)	0.05
Pharyngitis	13 (32%)	24 (36%)	0.5
Rash	12 (30%)	16 (24%)	0.1
Purpura	4 (2.68%)	4 (10%)	0.5
Bleedings	1 (0.67)	2 (5%)	0.5
Lymphadenopathy	1 (1.5%)	0	-
Hepatomegaly	1 (1.5%)	0	-
Splenomegaly	8 (12%)	4 (10%)	0.05

Table II: Laboratory findings of dengue fever cases (n=107).

Parameter	DEN Proven (40)	DEN Probable (67)	p-value
Leukopenia	31(77%)	46(69%)	0.1
Neutrophils < $2x10^9$/L	21(52%)	36(53%)	0.5
Lymphocytes < $2x10^9$/L	39(97%)	65(97%)	0.02
Platelet < $150x10^9$/L	34(85%(	58(87%)	0.5
ALT > 40 U/L	19(47%)	42(63%)	0.1

Platelet count kept on falling and was lowest between day 3 and day 5 of admission and started improving at day 7 (Figure 1).

All cases improved and were discharged from hospital on 10th day of admission except 3, who were discharged after 2 weeks.

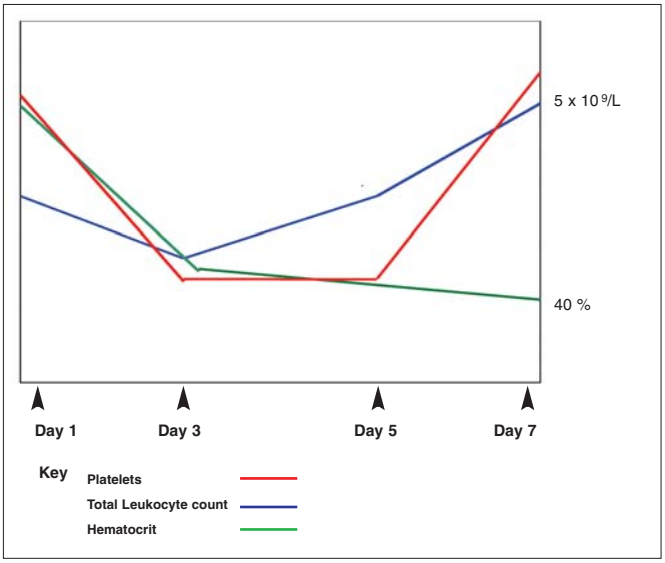

Figure 1: Changes in platelet count, total leukocyte count , and hematocrit in dengue fever.

DISCUSSION

The differential diagnoses associated with DF include a wide variety of viral including Çhikungunya, bacterial, rickettsial and parasitic infections that produce a similar syndrome. It is impossible to diagnose mild Dengue infection clinically. A definitive diagnosis is confirmed by virus isolation and/or serology.[12,14] Multivariate analysis in a study by Wilder-Smith *et al.* identified 3 laboratory features that together were highly predictive of a diagnosis of dengue: platelet count of <140 x 10^9/L, white blood cell count of < $5x10^9$ cells/L, and aspartate aminotransferases level of > 34 IU/L. A combination of these parameters had a sensitivity of 75% and a specificity of 100%.[15] There was a large number of cases during this epidemic that were clinically suggestive of DF, fulfilling the above three criteria, negative for malarial parasites and typhoid serology. The limitation was that molecular studies were not available while IgM may not be detectable during the early phase of infection. It is possible that these may be the cases of DF as there was no statistically significant difference of clinical and laboratory data of two groups (Tables I-II) However, the possibility of an other viral epidemic with likelihood of Chikungunya virus infection can not be excluded since the vector is the same.[16]

Typically, the onset of DF in adults is sudden, with a sharp rise in temperature occasionally accompanied by chills, and is invariably associated with severe headache and flushed face. The body temperature is usually between 39°C and 40°C. The fever may be biphasic, lasting 5-7 days. Clinically 2% patients with fever were of DF while only 0.8% proved on serology. In the study by Wilder-Smith *et al.* 2006 performed in Vietnam, DF out of all fever cases were 33.6% among all febrile cases, however, it depends upon severity of epidemic.[15] In a study by Singh, in India, fever was present in all the cases with an average duration of fever being 4.5 +/- 1.2 days with headache (61.6%), backache, (57.8%), vomiting (50.8%) and abdominal pain (21%) being the other presenting complaints. Hemorrhagic manifestations in the form of a positive tourniquet test (21%), gum bleeding and epistaxis (40%), haematemesis (22%), skin rashes (20%) and malaena (14%) were also observed.[17] In the present study, fever was also present in all cases; chills/rigors were noted in 84% diarrhoea in 19% vomiting in 61% sweating in 43%, headache in 50% myalgia in 64%, pharyngitis in 36% and rash in 24%.

A drop in platelet count to below 100,000/mm^3 is usually found between the third and eighth days of illness. The platelet count was less than $150x10^9$/L in 85%. In the study by Ageep *et al.*, thrombocytopenia was found in 88% cases while Singh *et al.* found thrombocytopenia (with a platelet count of < 100,000/microl) in 61.39% of cases.[17,18] In the study by Zang thrombocytopenia was found in 60.8%.[19] Rahim from Bangladesh found thrombocytopenia in 97.7% cases, While Itoda *et al.* detected thrombocytopenia in 57%.[20,21] It can be inferred that thrombocytopenia is a consistent finding in

Dengue fever, can be regarded as strong predictor, however, absence of thrombocytopenia should not be taken to exclude the possibility of Dengue infection.

The leukopenia is common with initially neutrophils predominating. Towards the end of the febrile phase, there is a drop in the total number of white cells as well as in the number of polymorphonuclear cells. A relative lymphocytosis with more than 15% atypical lymphocytes is commonly observed towards the end of the febrile phase (critical stage) and at the early stage of shock. In this study leukopenia was found in 77%, neutrophils < $2x10^9$/l in 52%, Lymphocytes < $2x10^9$ /L in 97%. Singh found leukopenia (WBC <3,000/mm^2) in 68%. Ageep detected leukopenia in 90% cases, In study by Rahim, 4.1% patients developed leucopenia while Itoda found leukopenia in 71%.[20,21]

A rise in hematocrit occurs in all DHF cases, particularly in cases with shock syndrome. Haemoconcentration with hematocrit increased by 20% or more is considered objective evidence of increased vascular permeability and leakage of plasma. In the study by Singh haemoconcentration (Hct >20% of expected for age and gender) were found in 52% of the cases. In this study, haemoconcentration or rise in hematocrit was not found in any of the cases, however, a fall in hematocrit was noticed during hospital stay once patients were afebrile and rehydrated adequately.

In this study, ALT > 40 U/L is found in 47% of cases. In a study by Mendez, hepatitis was detected in 27% cases. The liver may be involved in a considerable number of patients, however, absence of raised enzymes should not be taken as evidence to exclude possibility of DF.[22]

In this study, skin rash was noted in 24% cases, not associated with significant itching, mostly scarlatiniform. In the study by Itoda *et al.* rash was noticed in 82% cases. This difference can be explained on the basis that 60% cases in Itoda study were of secondary infection which is expected to be more serious, however, concrete evidence to support the hypothesis is lacking. Moreover, short-lived mild generalized erythematous rash without significant itching, may go unrecognized in dark skinned population such as the local one.

Liver size is not correlated with disease severity, but hepatomegaly is more frequent in cases of shock. In this study liver was palpable only in 1 case, that too was a probable Dengue, not proved by serology. Hepatomegaly and splenomegaly were observed in 10% and 5% of cases, respectively in the study by Singh. In the present study, splenomegaly was found in 10%. In the study performed by Ali *et al.*, splenomegaly was found in 50% cases. Splenomegaly is not a part of pathogenic processes involved in DF but may possibly be due to past episode or concomitant malaria, however, it is only a suggestion not proven.[7]

DHF occurs most commonly in individuals who have experienced secondary dengue infection; it has also been documented in primary infections. In this study, 2 cases with bleeding manifestations, one of mucosal bleeding and the other having neurological symptoms due to intracerebral hemorrhages. In the study by Kamath, 20% of the patients had neurological manifestations.[23] While In the study by Mendez, 25% patients presented with neurological manifestations.[22]

The type-specific immunity is life-long while heterotype immunity lasts 2-12 months. In areas, where dengue virus is endemic, cases with second infection are common, with higher incidence of DHF or DSS.[24] In the study by Arboleda, 49% patients were with DHF while in this study, only 5% presented with DHF.[25] It can be inferred that previous outbreak in Karachi has little effect on frequency of DHF and DSS cases; however, the situation may not be the same in future outbreaks if effective measures are not instituted. Epidemiological studies regarding the sub-typing and IgG seroprevalence of the virus are lacking. Comprehensive studies are recommended to identify the dengue endemic areas in Pakistan, IgG seroprevalence and sub-typing of the virus to formulate effective preventive strategies.

During this epidemic, the facility of Dengue virus isolation by cell culture, and type by reverse transcriptase polymerase chain reaction (RT-PCR) was lacking. The case definitions were based on IgM detection only. IgM was performed on day 7 samples only. No paired sera samples were taken. Although IgM titres rose enough to be detectable on 7th day, however, the possibility of missing the late responders cannot be excluded.

CONCLUSION

In this study, 2% patients of acute febrile illness (107/5200) were strongly suspected to have Dengue fever and 0.8% were confirmed on serologic testing. Clinical features and laboratory findings in confirmed and probable Dengue fever cases were closely related. The frequency of Dengue fever cases was much higher in hot and humid months from August to October in Karachi, with more than usual rains in both years.

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