Original Article

Frequency and Clinical Presentation of Dengue Fever at Tertiary Care Hospital of Hyderabad/Jamshoro

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ABSTRACT

OBJECTIVES: The aim of this study is to observe the clinical presentation and frequency of dengue as a cause of fever in our setup.

METHODS: This retrospective study comprising of clinically suspected dengue infection, admitted to Liaquat University Hospital Hyderabad, during an epidemic from August 2006 to August 2007. Only adults with acute febrile illness were evaluated for clinical features of dengue fever, dengue hemorrhagic fever and dengue shock syndrome.

RESULTS: Patients with acute febrile illness were evaluated during this study. Fifty (5%) patients presented with typical features of dengue fever. Age of the patients ranged between 13 and 70 years. All patients were males with mean age of 35 years. Only 20/50 (40%) were dengue proven while 30/50 (60%) were dengue suspected. Out of dengue proven, 18 patients had dengue fever and 2 had dengue hemorrhagic fever. Typical clinical features included chills and rigors in 16 (80%), myalgia in 14 (70%), vomiting in 12 (60%), headache in 10 (50%), rash in 5 (25%). Unusual clinical features were pharygitis in 7 (35%) and bleeding manifestations in 5% of patients. Laboratory investigations showed leucopenia (<4.0x10^9/L) in 80%, thrombocytopenia (<150x10^9/L) in 90%, and serum ALT was elevated (>40 U/L) in 40% cases.

CONCLUSIONS: Fever associated with chills and rigors, bodyaches, bone pain, headache, myalgia, rash, low platelet count, decreased total leukocyte count, raised serum ALT, and hemorrhagic manifestations are satisfactory and important parameters to screen the cases of suspected dengue virus infection; however the diagnosis cannot be confirmed unless supported by molecular studies or dengue specific IgM.

KEYWORDS: Dengue fever, Dengue hemorrhagic fever, dengue shock syndrome, Adults, Clinical presentation.

INTRODUCTION

Dengue is a major cause of morbidity and mortality in tropical and subtropical regions comprising more than 100 countries. Two-fifths of the world's population or 2500 million peoples are now at risk for dengue, and every year approximately 50 million new cases occur world wide [(1)]. The global prevalence of dengue infection has increased dramatically in recent decades, particularly in the Americans, western Pacific and south-east Asia[(2)].

Based on data from 112 national vital registration systems, 12,000 deaths in South East Asia, 4000 deaths in the Western Pacific and 2000 deaths in America for the year 2002 have been estimated to be due to dengue.[(3)]

Dengue fever is caused by dengue viruses (DENVS) - members of the Flaviviridae family. There are four (DEN 1 to DEN 4) serologically distinct, but closely related viruses that cause dengue. Dengue infection is transmitted to humans via bite of Aedes aegypti mosquito. [(4)]

Recovery from one infection provides life long immunity against that serotype but confers only transient and partial protection against heterologous serotype infections and sequential infections may increase the risk of more serious disease with complications and high mortality [(5)]. Secondary infection with a different serotype following primary infection is associated with an increased risk of DHF.

Clinically, dengue virus infection presents in three forms classical dengue fever, dengue hemorrhagic fever and dengue shock syndrome. Classical dengue fever is characterized by sudden onset of high grade fever, often accompanied by severe retro-orbital headache, myalgias, artharlgias, nausea, vomiting and macular or maculo-papular rash. Other features are flushed facies, sore throat and cutaneous hyperaesthesia.

Dengue Hemorrhagic Fever (DHF) is characterized by hemorrhagic features like petechiae, ecchymoses or purpura, bleeding from injection sites or bleeding from mucosa, gastro-intestinal bleeding in addition to classical dengue fever features. Dengue Shock Syndrome (DSS) is characterized by rapid weak pulse, narrow pulse pressure (<20-mmHg), persistently low blood pressure, cold/clammy extremities, altered mental

status and delayed capillary filling [6,7].

First outbreak of DF was noticed in Pakistan during 1994. Another outbreak occurred in Punjab mostly in upper parts of province during 2003, in addition to it sporadic cases occurred at Rawalpindi – Islamabad, Peshawar, Jhelum, Abbottabad, Mangla and Haripur.[8]

In Sindh the climate is mostly hot and humid and due to improper sanitation, mosquitoes continue to breed throughout the year and hence epidemics of mosquito -born-diseases rise sharply. Aodes aegypti, being a fresh water specy, breeds throughout the year.

During August and September 2006, we received patients with high grade fever, altered blood counts and negative blood test for malarial parasites.

Dengue fever was suspected and dengue specific serology was performed that revealed positive serology for dengue specific IgM. The suspected outbreak was confirmed and we aimed to report the frequency of dengue as a cause of fever in our setup and to describe the clinical presentation of dengue fever patients.

MATERIALS AND METHODS

This study took place at Liaquat University Hospital Hyderabad/Jamshoro, a tertiary care hospital, attached with Liaquat University of Medical and Health Sciences, Jamshoro.

The data were retrieved from medical charts and out patient card of the patients who were admitted with dengue like infection between August 2006 to August 2007. The evaluation was conducted in adults above thirteen years of age. Subjects were labled as dengue suspected and dengue proven. Dengue fever was suspected as per WHO criteria **(Table I)**.[9,10] Patients with clinical features suggestive of dengue fever (DF), and proved by positive serology of dengue specific IgM, were labeled as dengue confirmed cases. Patients with suggestive clinical features and by cytopaenia on peripheral blood smear, negative for dengue serology, negative MP (malarial parasites) and normal widal test were labeled as dengue suspected.

Patients lacking typical clinical features of dengue fever and negative anti-dengue serology were excluded from the study.-

For laboratory investigations 2mls of blood in anticoagulant, 2.8-mls blood in 0.21-ml citrate anticoagulant and 3-mls blood in plain bottle was collected for complete blood picture, malarial parasite, anti-dengue IgM, prothrombin time (PT), widal test and typhi-dot IgM anti body and serum alanine amino transferase (ALT).

Blood count including red cell count (RBC), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelets count, total leucocyte count (TLC), differential leucocyte count (DLC) were performed on automated hematology analyzer Expert hematologist examined blood film for malarial parasites. Bleeding time (BT) and clotting time (CT) were performed by noticing blood clot formation visually. Serum ALT was performed by standardized method as described by manufacturer using micro lab 200 (Merck Marker). Dengue specific –IgM performed by standard enzyme linked immunosorbent assay (ELISA), at Diagnostic Research Laboratory of Liaquat University of Medical and Health Sciences, a more than four fold rise in titres was considered positive for acute dengue infection.

Hemorrhagic tendencies included a positive tourniquet test, skin bleeding (petechiae, ecchymosis or purpura), bleeding from mucosa (epistaxis, gum bleeding), hematemesis or melena.

Data were recorded and analyzed using statistical software (SPSS version 11.0; SPSS. Descriptive statistics were used to describe the symptoms and signs of dengue infection and laboratory investigations. Clinical features and results of laboratory investigations were compared between dengue suspected cases and dengue proven cases by using Chi-square test; P-values up to 0.05 were considered significant.

RESULT

From August 2006 to August 2007, 50 patients presented with typical features of dengue fever, and they were included in this study. Age of the patients ranged between 13 and 70 years and the mean was 35 years. All patients were males. Twenty (40%) patients were dengue proven while 30 (60%) were dengue suspected. Out of dengue proven 18 were of dengue fever and 2 were of dengue hemorrhagic fever, one presented with fits and altered mentation.

Out of 30 dengue suspected cases, one patient developed bleeding manifestations in the form of ecchymosis and conjunctival hemorrhages. Fever 1-10 day duration was present in all cases. Day 1 temperature ranged 99-105ºF and the mean was 101ºF. Day 7 temperature ranged between 97-100ºF and the mean was 99ºF. Clinical feature of both dengue proven and dengue suspected are summarised in **Table II**.

Leucopenia (count<$4x10^9$/L) was noted in 80%, neutrophil count (<$2x10^9$/L) in 50%, lymphocyte count (<$2x10^9$/L) in 95%, platelet count (<$150x10^9$/L) in 90% and serum ALT (>40U/L) in 55% cases. Serum creatinine was marginally raised in 1 (5%) case of dengue suspected. Coagulation profile was disturbed in 2 cases of dengue proven and 1 case of dengue suspected. Laboratory findings of dengue proven and

suspected cases are summarized in **Table III**.
Mean total leukocyte count (TLC) initially was $5x10^9$/L, which began to decrease later and was lowest ($2x10^9$/L) on day 5, after that it rose to $4x10^9$/L on day-7. Mean platelet count kept on falling from $150x10^9$/L (day 1) and was lowest on day 4, after which it began to rise and was $150x10^9$/L on day 7.

TABLE I: WHO CRITERIA FOR DENGUE FEVER

Probable dengue

- Live in/travel to dengue endemic area.
- Fever and 2 of the following criteria:
  - Nausea, vomiting
  - Rash
  - Aches and pains
  - Tourniquet test positive
  - Leukoplakia
  - Any of the following "warning sign"
    - ◊ Abdominal pain and tenderness
    - ◊ Clinical fluid accumulation
    - ◊ Mucosal bleed
    - ◊ Lethargy, restlessness
    - ◊ Liver enlargement >2-cm
    - ◊ Labority: increase in HCT concurrent with rapid decrease in platelet count.

TABLE II: CLINICAL FEATURE OF DENGUE FEVER CASES (n=50)

Symptoms/ Signs	DEN Proven (20)	DEN Suspected (30)	P-value
Chills/rigors	16 (80%)	21 (70%)	<0.05
Diarrhoea	4 (20%)	3 (10%)	<0.05
Vomiting	12 (60%)	15 (50%)	<0.05
Sweating	8 (40%)	12 (40%)	>0.05
Headache	10(50%)	18(60%)	>0.05
Myalgia	14(70%)	21(70%)	>0.05
Pharyngitis	7(35%)	6(20%)	<0.05
Rash	5(25%)	6(20%)	>0.05
Purpura	2(10%)	1(3%)	<0.0f
Bleeding	1(5%)	1(3%)	>0.05
Lymph nodes palpable	0	1(3%)	<0.05
Liver palpable	0	1(3%)	<0.05
Spleen palpable	2(10%)	3(10%)	>0.05

TABLE III: LABORATORY FINDINGS OF DENGUE FEVER CASES (n=50)

Parameter	DEN Proven (20)	DEN Suspected (30)	p-value
Leucopenia	16(80%)	21(70%)	>0.05
Neutrophils $<2x10^9$ /L	10(50%)	15(50%)	>0.05
Lymphocytes $<2x10^9$ /L	19(95%)	28(93%)	<0.05
Platelet<$150x10^9$ /L	18(90%)	21(70%)	<0.05
ALT >40U/L	8(40%)	18(60%)	<0.05

DISCUSSION

Dengue virus infection presentation is usually variable. It may be asymptomatic or may cause undifferentiated high grade fever. The clinical presentation depends on age, immune status of the host, and the virus strain.[11,14] After an average incubation period of 4-6 days (range 3-14 days), various non-specific undifferentiated clinical features like headache, backache and general malaise may develop. The differential diagnoses associated with DF include a wide variety of viral infections that produce a similar presentation. It is very difficult to diagnose mild dengue infection clinically. A definitive diagnosis is made by virus isolation and serology.[15,16] Wilder Smith et al have concluded after multivariate analysis that 3 laboratory features, when present, are highly predictive for diagnosis of DF. These include platelet count of $<140x10^9$/L, white blood cell count of $<5x10^9$ cells/L and aspartate aminotransferases level of >34 IU/L. A combination of these 3 laboratory tests has sensitivity of 75% and specificity of 100%.[17,18] In our study there were a large number of cases during this epidemic that were clinically suspected of dengue fever, having all these 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 initial phase of infection. It is possible that these may be the cases of dengue fever as there was no statistically significant difference of clinical and laboratory data of two groups (Table II-III) However the possibility of an other viral epidemic like Chikungunya cannot be excluded since the vector is same but not proven in our set up.[19,20]
Typically, the onset of dengue fever in adults is sudden, with a sharp rise in temperature occasionally accompanied by chills, and is invariably associated with severe bone pain, body ache, headache and flushed face. The body temperature is usually between 39°C

and 40°C, and the fever may be continuous or biphasic, lasting 5-7 days. Clinically 5% of all our patients with fever were of dengue fever while only 2% proved on serology. In study by Wilder-Smith A et al performed in Vietnam, out of all fever cases DF were 33.6%, however it depends upon severity of epidemic.[17] In a study by Singh NP in Delhi, India in 2005, fever was present in all the case with an average duration of fever being 4.5±1 days with headache (60%), backache (58%), vomiting (51%) and abdominal pain (21%) being the other presenting complaints. Hemorrhagic manifestations in the form of the positive tourniquet test (21%), gum bleeding and epistaxis (40%), hematemesis (22%), skin rashes (20%) and melena (14%) were also observed.[21] In our study fever was present in all cases; chills/rigors were noted in 80%, diarrhea in 12%, vomiting in 55%, sweating in 40%, headache in 50%, myalgia in 70%, pharygitis in 35% and rash in 25%. A drop in platelet count to below (<100,000/cumm) is usually found in first week between the second and sixth days of illness. We found platelet count less than $150x10^9$/L in 85%. In study of Ageep AK, thrombocytopenia was found in 88% cases; in study by Singh NT thrombocytopenia (with a platelet count of <100,000/cmm) was found in 61.39% of cases[22]. In study by Zhang FC, thrombocytopenia found in 60.8%; in study by Rahim MA Bangladesh, thrombocytopenia developed in 97.7% cases; in study by Itoda thrombocytopenia was detected in 57%[23,25]. It can be concluded that thrombocytopenia is a persistent finding in dengue fever and it can be regarded as strongest indicator of dengue fever, however, absence of thrombocytopenia should not rule out the possibility of dengue infection. The leucopenia is also a common initial finding, with neutrophilia. Towards the end of the febrile phase there is a fall in the total number of white cells as well as in the number of polymorph nuclear cells. A relative lymphocytosis with more than 10% atypical lymphocytes is commonly observed towards the end of the febrile phase (critical stage) and at the early stage of shock. In our study we found leucopenia in 80%; neutrophils ($<2x10^9$/L) in 50%, lymphocytes ($<2x10^9$/L) in 95%. In study of Singh NP they found leucopenia (WBC <3,000/cmm) in 68% that agrees to our study. In study of Ageep AK leucopenia was detected in 90% cases, Itoda reported that leucopenia was detected in 71%.[22,25] In our study we also found that TLC starts rising towords normal near convalescence **(Figure-1)**. A rise in hematocrit occurs in all DHF cases, particularly in shock cases. Haemo-concentration with hematocrit increase by 25% or more is considered objective evidence of increased vascular permeability and may be affected by early volume replacement and by bleeding. In study by Singh NP haemoconcentration (Hct>20% of expected for age and sex) was found in 52% of the cases. In our study, we did not found haemoconcentration or rise in hematocrit in any case, however a fall in hematocrit was noticed during hospital stay once patient was afebrile and rehydrated adequately. In our study we found serum ALT >40 U/L in 40% cases. In study by Kularatne SA, 88% patients showed elevated liver enzymes ALT and AST, with 122 of them having a two-fold increase. In study by Mendez A, hepatitis was detected in 27% cases; it may be noticed that AST or ALT can be taken as a strong predictor of dengue infection; however absence of elevated liver enzymes should not be taken as evidence to exclude possibility of DF.[26-28]

Diffuse flushing and wide spread pinpoint eruptions were observed on the face, neck and chest during the first half of the febrile period. A conspicuous rash that may be maculopapular or morbiliform appears on mostly third or fourth day. Towards the end of febrile period or immediately after defervescence, the generalized rash fades and localized clusters of petechiae may appear over the dorsum of the feet, on the legs, and on the hands and arms. This confluent petechial rash is characterized by scattered pale and round areas of normal skin. Occasionally the rash is accompanied by itching. In our study we found rash in 25% cases, not associated with significant itching, mostly morbiliform. In study by Itoda et al, rash was more frequent in 82% cases possibly due to serious secondary infection in 60% cases, however strong evidence to prove it is absent.[25] Moreover, short lived mild generalized erythematous rash without significant itching may go unrecognized in usually dark skinned Pakistani population. The liver is usually palpable early in the febrile phase, varying from just palpable to 2-4 cm below the right costal margin. In few epidemics, hepatomegaly is not a consistent finding correlated with disease severity. In our study we found liver palpable only in one case that too was a suspected dengue, not proved by serology. Hepatomegaly and splenomegaly were observed in 10% and 5% of cases respectively in a study by Singh NP in Delhi, India. In a study performed by Ali N et al Attock-Pakistan, splenomegaly was not a part of pathogenic processes involved in DF, and it may be due to malaria; concrete evidence to support it is lacking.[8] DHF occurs most commonly in individuals who have experienced secondary dengue infection, but it has also been docu-

mented rarely in primary infections. We received 2 cases with bleeding manifestations. One case with hematuria, epistaxis, ecchymosis, and gum bleeding while other case presented with central nervous system symptoms like headache, fits, confussional state and drowsiness in which CT scan of brain reveals multiple intracerebral haemorrhages. The patient improved with supportive management and discharge from hospital after one week when he was asymptomatic.

In a study by Kamath SR performed in India, neurological manifestations were noticed in 20% of the patients. In study of Mendez A, 25% patients had neurological manifestations.[29,32] An outbreak of DF and DHF was experienced in Karachi in 1994.[33] 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 dengue hemorrhagic fever or dengue shock syndrome. In study by Shahid Ahmed at Karachi almost similar results are seen.[34] In study of Arboleda M, almost half (49%) patients were with DHF while in our study only 2% presented with DHF. It can be suggested that previous outbreak in Hyderabad and adjoining area has little effect on frequency of DHF and DSS cases; however the situation may not be that same in future outbreaks if preventive measures are not instituted.[35]

Limitations: During this study epidemic, we lacked the facility of specific diagnostic test for dengue virus isolation by cell culture, and polymerase chain reaction (RT-PCR) in Hyderabad, the case detection were based on IgM antibody only, which was performed at the end of 1st week. No paired sera samples were taken, although IgM titres raised enough to be detectable on 7th day. However the possibility of missing few cases cannot be excluded.

RECOMMENDATION

Comprehensive studies needed to identify the dengue endemic areas in Pakistan, IgG seroprevalence and sub-typing of the virus to formulate the effective preventive strategies and early detection. Effective measures and efforts to prevent the future outbreaks and to minimize further serious complications are recommended. Public perception of dengue needs to be clarified, by awareness of general population as well as medical community through media, effectively. An effective disease prevention program should include vector control by chemical, biological and/or environmental measures. The aim of such program is to reduce the vector density, so that disease activity should not reach an epidemic level.

CONCLUSION

Fever associated with chills and rigors, bodyaches, bone pain, headache, myalgia, rash, low platelet count, decreased total leukocyte count, raised serum ALT, and hemorrhagic manifestations are satisfactory and important parameters to screen the cases of suspected dengue virus infection; however the diagnosis cannot be confirmed unless supported by molecular studies or dengue specific IgM.

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