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Clinical Spectrum of Dengue Fever and Dengue like Infection in Children, Central Karnataka, India

N.K. Kalappanvar[1], C.S.VinodKumar[2], K.G. Basavarajappa[2], Chadrasekar Gouli[1], D. Sanjay [1] and R. Chandana[1]

[1]Department of Pediatrics, [2]Department of Microbiology,
S. S. Institute of Medical Sciences and Research Centre, NH-4, By pass, Davangere - 577 005, India.

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Dengue infection is endemic in many parts of India, including the state of Karnataka. This study describes the clinical picture of dengue fever and dengue like viral infections observed by us in children admitted to a teaching hospital at Davangere. All patients admitted with a suspected diagnosis of dengue were studied in detail regarding the clinical features, laboratory profile and demographic features. Their ages ranged from 2 to 15 years with a mean of 9.5 + 3.2. our of 570 clinically suspected dengue patients, 21.6% were serologically positive and 78.4% were negative for dengue serology. Commonest presentation in dengue fever was fever (100%), retro orbital pain (61%), rash (74.8%), acute respiratory distress syndrome (27.6%), spleenomegaly (22.8%), ascitis (22.8%) and encephalopathy in 5.7%. The commonest clinical presentation in dengue like illness were fever (98.6%), retro orbital pain (49.2%), encephalopathy (4.5%) and Malena (3.5%). Thrombocytopeina as lower than 20,000/mm^3. was seen in 21.1% in dengue fever group and 14.1% in dengue like illness. Liver enzymes sGOT and sGPT were increased in both the groups. 8.1% in dengue fever group and 3.6% in dengue like illness died and the most common clinical features were ARDS and encephalopathy. The results indicated a significant proportion of children presented with little described features of splenomegaly, and acute respiratory distress syndrome. These features were not noted during the past epidemics in previous years and also there were no statistically significant difference in clinical features between dengue and dengue like illness. Hence molecular diagnosis could be the adjunt to differentiate dengue fever and dengue like illness

Key words: Dengue fever, Dengue like illness, Clinical presentation.

Dengue infections are a significant cause of morbidity and mortality and lead to adverse economic effects in many developing tropical countries [1]. The incidence of dengue fever is on the rise worldwide, and in some areas of Asia, complications of the disease are a leading cause of serious illness and death in children [2-3]. Over the past two decades in India there has been dramatic global increase in *Dengue fever*, (DF) Dengue haemorrhagic fever (DHF), and Dengue shock syndrome (DSS) and their epidemics [4-9].

The identification of dengue cases is by distinct clinical features, but they can present with varied manifestations. Dengue remains a puzzling disease in many aspects, such as the virus-vector and host-virus relationship, and clinical expression variability [3]. The dengue epidemics in India are cyclical and are more frequent, expanding geographically into the rural areas and all forms of serotypes are circulating in the community [7-9]. The purpose of the present study is to correlate the difference in clinical features, laboratory diagnosis and outcome between dengue and dengue like illness.

* To whom all correspondence should be addressed.
Mob.: +91-9964402525
E-mail: vinodmicro@yahoo.com

MATERIALS AND METHODS

Ethical clearance

Protocol was approved by Institutional Ethical Review Board. Consent was obtained from all the cases

Type of the study

One year prospective study between June 2009 and May 2010

S. S. Institute of Medical Sciences and Research Centre is a 750-bed tertiary care hospital located in central Karnataka, Davangere. The patients were referred from various hospitals in a radius of 200 kilometres.

Inclusion criteria

According to specific inclusion criteria, 570 clinically suspected patients with fever (presenting within 5-7 days of onset with body temperature above 100°F at the time of blood sample collection) and fulfilling the case definition criteria of dengue fever (DF) and dengue haemorrhagic fever (DHF) of WHO were included in the study [7].

Clinical and demographic data were collected through interviewing the patients or their attendants and meticulous physical examination of the patients conducted by their treating physician. Reports of haematological investigations, dengue serology, and data obtained from daily follow-up were analyzed.

Hospitalized patients were categorized into Dengue Fever, Dengue Hemorrhagic Fever and Dengue Shock Syndrome according to the World Health Organization (WHO) severity grading scale[11]. The blood indices were initially measured on a continuous scale and then categorized on the basis of clinically meaningful cut offs. Thrombocytopenia was defined as a platelet count <100,000 cells/mm^3 blood. A haemotocrit >20% rise was considered raised. Similarly, leucopenia was defined as a white cell count <4000 cells/mm^3.

Dengue IgM antibodies were detected using the Calbiotech Inc. ELISA test system (Catalog No. DE051M). This is a commercial Enzyme-Linked ImmunoSorbent Assay for detecting IgM antibodies against dengue virus in human serum or plasma. Optical density (OD) was read at dual wavelength with reference filter of 600–650nm. Antibody Index was calculated using the OD value and the cut-off value (Calibrator OD 6 Calibrator Factor). Antibody index of .1.1 was considered positive for acute dengue infection and those between 0.9 and 1.1 were included in borderline positive category. Hence, samples with indexes below 0.9 were concluded as negative for dengue infection[10-13].

All these patients were treated according to the standard protocol and outcome was evaluated

Statistical analysis

Data were analysed using Epi-info software. The categorical data was shown in terms of numbers and percentages and analysed using Z test for proportions and chi square test.

RESULTS

Of 570 patients including 348 males (61.1%) and females 222 (38.9%) were hospitalized at S. S. Institute of Medical Sciences and Research Centre. The age distribution is shown in Table 1. Their age ranged from 2 years to 15 years with the mean age of 9.5±3.2 years. Two hundred fifty seven were from rural area and 172 (39.1%) were from urban region (Table 1). Out of 570 clinically suspected dengue patients, 123 were found to have positive serology (IgM or IgM and IgG) to dengue virus by ELISA (Dengue fever) and 447 were negative dengue IgM antibodies (Dengue like illness). Among the of 123 serologically positive dengue cases, 56 (45.5%), 37 (30.1%) and 30 (24.4%) were classified as DF, DHF and DSS, similarly among dengue like illness, 252 (56.4%, 127 (28.4%) and 68 (15.2%) were classified as DF, DHF and DSS, respectively according to WHO classification Table 1). The involvement of all age groups, especially an age group of 6-10 yrs was predominance in both the categories.

Clinical features in dengue fever

Various clinical features are summarized in Table 2. Fever was the most common clinical presentation occurring in all patients. There was no specific pattern of fever and height of fever ranged from 38°C to 40°C. Other common clinical features were retro orbital pain (61%), flushing in 65% and rashes were seen in 74.8%. ARDS was seen in 27.6%, spleenomegaly in 22.8%, ascitis in 22.8% and encephalopathy in 5.7%.

Clinical features in dengue like fever

Various clinical features in dengue like fever in summarized in Table 2. Among this cohort,

the most common presenting features were fever (86.6%), flushing (73.3%), rashes (46.6%), retro orbital pain (33.3%) followed by hepatomegaly (93.3%), spleenomegaly (60.0%), encephalopathy (46.6%) and Malena was seen in 6.6% cases

Laboratory profile in dengue fever

The most common haematological abnormalities were thrombocytopenia and

Table 1. Demographic features of the study subjects

Features	Dengue	Dengue like illness	P- value
Rural	72(58.5)	275(61.5)	0.55 NS
Urban	51(41.5)	172(38.5)	0.56 NS
Sex			
Male	66(53.7)	282(63.1)	0.06 NS
Female	57(46.3)	165(26.9)	0.06 NS
Age			
< 5 Yrs	40 (32.5)	172 (38.5)	0.21 NS
6-10 Yrs	62 (50.4)	178 (39.8)	0.04 S
11-15 Yrs	16 (13.0)	66 (14.7)	0.61 NS
>15 Yrs	05 (4.0)	31(6.9)	0.18 NS

* Z test for proportions

Table 2. Clinical Manifestations of patients with dengue fever and dengue like illness

Clinical Features	Dengue fever(n=123)	Dengue like illness(n=447)	P** Value, sig
Fever	120 (97.5)*	441 (98.6)	0.46 NS
Retro orbital pain	75 (60.9)	220 (49.2)	0.02 NS
Flushing	80 (65.0)	322 (72.0)	0.14 NS
Rash	92 (74.7)	282 (63.0)	0.01 S
ARDS	34 (27.6)	40 (8.9)	<0.001 HS
Encephalopathy	07 (5.7)	20 (4.5)	0.59 NS
Hepatitis	14 (11.8)	25 (5.2)	0.06 NS
Malena	10 (8.1)	16 (3.5)	0.08 NS
Epitaxis	01 (0.8)	09 (2.0)	0.69 NS
Haemetemesis	01 (0.8)	02 (0.4)	0.52 NS
Hepatomegaly	77 (62.6)	136 (30.4)	<0.001 HS
Spleenomegaly	28 (22.8)	49 (11.0)	0.004 S
Ascitis	28 (22.8)	26 (5.8)	<0.001 HS
Pleural effusion	15 (12.1)	18 (4.0)	0.008 NS
Cyanosis	01 (0.8)	00	0.22 NS
Convulsion	05 (4.0)	12 (2.6)	0.47 NS
Olguria	02 (1.6)	01 (0.2)	0.12 NS
Hypoglycemia	02 (1.6)	00	0.046 S
Abscess	01 (0.8)	02 (0.4)	0.52 NS
Pneumoniae	01 (0.8)	03 (0.6)	1.0 NS
Hematuria	00	04 (0.8)	0.58 NS
Gum bleeding	00	02 (0.4)	1.0 NS
Sub conjunctival haemorrhage	00	06 (1.3)	0.35 NS
Dengue fever	56(45.5)	252(56.4)	0.03 S
Dengue hemorrhagic fever	37(30.1)	127(28.4)	0.72 NS
Dengue shock syndrome	30(24.4)	68(15.2)	0.03 S

* Percentage, ** Z test for proportions

leukopenia. Platelet count below 20,000 / mm^3 was seen in 26 (21.1%) patients (Table 3). Ninety six (70%) had total white cell count below 4000 / mm^3. Hematocrit value of > 20% for age and sex was noticed in 47 (38.2%) cases.

Liver enzymes sGOT and sGPT were raised above the normal limit in 14 (11.3%) cases and 25 (20.3%) cases respectively.

Laboratory profile in dengue like illness

The haematological profiles are given in

Table 3. Platelet and Leukocyte count during the admission among the patients with dengue fever and dengue like illness

Platelet and leucocytic count	Dengue	Dengue like illness	P values
Platelet range			
< 10,000	04 (3.2)	08 (1.8)	P<0.001 HS, X^2 for trend
10,000-19999	22 (17.8)	55 (12.3)	
20,000-39,999	56 (45.5)	123 (27.5)	
40,000-59,999	18 (14.6)	91 (20.3)	
60,000-79,999	07 (5.6)	53 (11.8)	
80,000-99,999	06 (4.8)	30 (6.7)	
> 1,00,000	10 (8.1)	87 (19.4)	
Leucocytic count			
d”4,000	96 (78.0)	287 (61.9)	P=0.13 NS
>4000	27 (22.0)	170 (38.1)	

* Percentage

Table 4. Clinical Manifestations of patients who died with dengue fever and dengue like illness

Clinical Features	Dengue fever(n=10)	Dengue like illness(n=15)	P** Value, sig
Fever	07 (70.0)	13 (86.6)	0.36 NS
Retro orbital pain	03 (30.0)	05 (33.3)	1.0 NS
Flushing	05 (50.0)	11 (73.3)	0.39 NS
Rash	06 (60.0)	07 (46.6)	0.69 NS
ARDS	08 (80.0)	10 (66.6)	0.66 NS
Encephalopathy	04 (40.0)	07 (46.6)	1.0 NS
Hepatitis	04 (40.0)	04 (26.6)	0.67 NS
Malena	03 (30.0)	01 (6.6)	0.27 NS
Epitaxis	01 (10.0)	00	0.40 NS
Haemetemesis	00	02 (13.3)	0.50 NS
Hepatomegaly	09 (90.0)	14 (93.3)	1.0 NS
Spleenomegaly	04 (40.0)	09 (60.0)	0.43 NS
Ascitis	05 (50.0)	07 (46.6)	1.0 NS
Pleural effusion	02 (20.0)	01(6.6)	0.54 NS
Convulsion	03 (30.0)	07 (46.6)	0.68 NS
Olguria	01 (10.0)	00	0.40 NS
Hypoglycemia	01 (10.0)	01(6.6)	1.0 NS
Hematuria	02 (20.0)	02 (13.3)	1.0 NS
Dengue fever	01 (10.0)	05 (33.3)	0.34 NS
Dengue hemorrhagic fever	02 (20.0)	05 (33.3)	0.66 NS
Dengue shock syndrome	07 (70.0)	05 (33.3)	0.11 NS

* Percentage ** Z test for proportions

Table 3. Platelet count was below 100,000 / mm^3 in 360 (80.5%) cases. In 63(14.1%) patients, platelet count below 20,000/cumm was observed. Total white cell count below 4000 / mm^3 was seen in 277(62%) patients. Hematocrit value of > 20% for age and sex was noticed in 151 (33.8%) cases in dengue like illness during admission. Liver enzymes sGOT and sGPT were raised above the normal limit in 27 (6.0%) cases and 32(7.2%) cases respectively.

Mortality

Ten out of 123 cases of dengue fever and 3.36% cases of dengue like fever died. The most common clinical features observed in dengue fever cases were acute respiratory distress syndrome (80%), and 40% had encephalopathy (Table 5). While in dengue like fever, 66.7% showed acute respiratory distress syndrome and 46.7% had encephalopathy (Table 4).

Dengue shock syndrome was seen in 70% in dengue positive cases and 33.3% in dengue like illness (Table 4)

DISCUSSION

Dengue virus causes a broad spectrum of illness ranging from mild undifferentiated fever to classical dengue fever, as well as dengue hemorrhagic fever and dengue shock syndrome [14]. Dengue is a major public health problem in central Karnataka. Over the last 8 years we have been observing varied clinical manifestations of dengue, which are rather different from the past reports from this region as well as from other parts of the country.

Majority of patients (61.1%) in our series were males and from rural area (60.9%). Commonest age group involved were young children varying from 7 to 10 years of age. In the present study, 570 patients were admitted with suspected diagnosis of dengue fever. Among these, 123 patients (21.6%) were confirmed to have the disease by the presence of IgM alone or IgM and IgG antibodies against dengue fever.

Most developing countries have epidemics of febrile illnesses which can be confused with dengue fever [15]. A recent review of published studies were unable to make any conclusions on the signs and symptoms that can clinically distinguish dengue from other febrile illness [7-9-15]

Even in the present study there was not much significant difference in the clinical features of dengue fever and dengue like illness. Dengue fever is generally described as a short febrile illness. The WHO criteria mention an illness of 2–7 days' duration [5]. In the present study we have observed a longer duration of fever than in previous years. The mean duration of fever in survivors in this study was almost 8 days and the longest duration of fever was more than 4 weeks in 6 patients. The predominant clinical features were fever, retro orbital pain, flushing, myalgia and vomiting was the most frequent symptoms, has also been observed in other studies. The major difference from the previous report is frequent occurrence of acute respiratory distress syndrome, splenomegaly, prolonged fever and encephalopathy. 27.6% of dengue fever cases showed ARDS, while 8.9% of dengue like cases showed ARDS.

Although hepatomegaly is among the WHO clinical criteria for DF, splenomegaly is not generally held to be a feature of dengue infection. Earlier studies in India do not describe a high frequency of splenomegaly [4,5-7, 9,]. But in our study we observed 22.8% of the cases had spleenomegaly among dengue fever. Peripheral smears for malaria and serology for typhoid were negative in all cases. Our study corroborates with a recent study from Delhi which has reported a higher percentage (32.4%) of splenomegaly in the children with dengue [7].

Even though high incidence of encephalopathy has been reported in several studies, it was observed in 5.7% of cases in dengue fever and 4.5% in dengue like fever in our study.

On an analysis of the laboratory findings, it was observed that platelets were below 100 000/ mm in a 91.9% among dengue fever cases and 80.5% in dengue like illness. 21.1% of cases of dengue fever group and 14.1% of cases in dengue like illness had the platelet count less than 20,000 / cumm. Thrombocytopenia is thought to be due to depression of bone marrow observed in acute stage of dengue virus infection. Other explanations are direct infection of the megakaryocytes by virus leading to increased destruction of the platelets or the presence of antibodies directed against the platelets [17]. Leukocyte less than 4000 /cumm was seen in 70% of dengue cases and 62% in dengue like fever. Coagulopathy is also frequent in most patients with DSS. In our study, prolongation of

PTT was quite common in DSS cases of both groups. The other important abnormality was raised liver enzymes. sGOT and sGPT were raised above the normal limit in 14 cases and 25 cases respectively among dengue fever group and in 26 and 32 cases respectively in dengue like fever and mortality rate among dengue fever was 8.1% and 3.4% among cases of dengue like fever. The most common clinical features among these patients were ARDS (80%) and encephalopathy (40%) in dengue fever cases and 66.7% and 46.7% in dengue like illness. Encephalopathy in dengue was believed to be due to cerebral edema, hyponatremia, hypoperfusion or intracranial bleed, but, more recently the actual dengue viral invasion of the brain recognized.

The current study revealed not much of statically significance in spectrum of clinical presentation, haematological and biochemical profile between dengue fever and dengue like illness. So in any given epidemic its amounts to suggest that though the seroconversion not present with standard clinical features of dengue fever, one should clinically suspects, evaluate and anticipate the presentation of dengue fever even in serological negative cases. The outcome as is shown in this study as not made much difference when treated by the standard protocol in both dengue fever and dengue like illness.

REFERENCES

1. Atul Garg, Jaya Garg, Y. K. Rao, G. C. Upadhyay and Suman Sakhuja. Prevalence of dengue among clinically suspected febrile episodes at a teaching hospital in North India *J. Infect. Dis. Immun*. 2011; **3**(5): 85-89.
2. Martina BE, Koraka P, Osterhaus A. Dengue virus pathogenesis, an integrated view. *Clin. Microbiol. Rev.* 2009; **22**: 564–581
3. Ayub M, Khazindar AM, Lubad EH & Barlas S. Characteristics of dengue fever in large public hospital, Jeddah, Saudi Africa. *Journal Ayub Med College Abbotabad.* 2006; **18**(2): 60-72.
4. Ratageri VH, Shepur TA, Wari PK, Chavan SC, Mujahid IB, Yergolkar PN. Clinical profile and outcome of Dengue fever cases. *Indian J Pediatr.* 2005; **72**(8): 705-6.
5. Kumar R, Tripathi S, Tambe JJ, Arora V,Srivastava A, Nag VL. Dengue encephalopathy in children in northern India: Clinical features and comparision with nondengue. *J. Neurol. Sci*. 2008; **269**: 41-8.
6. Kumar R, Tripathi P, Tripathi S, Kanodia A, Venkatesh V. Prevalence of dengue infection in north Indian children with acute hepatic failure. *Ann Hepatol*. 2008; **7**: 58-61.
7. Ashwini Kumar, Rao CR, Pandit V, Shetty S, Bammigatti C, Samarasinghe CM. Clinical manifestations and trend of dengue cases admitted in a tertiary care hospital, Udupi district, Karnataka. *Indian J Community Med*. 2010; **35**: 386-90
8. Kabra SK, Jain Y, Singhal T, Ratageri VH. Dengue hemorrhagic fever: clinical manifestations and management. *Indian J Pediatr*. 1999; **66**(1): 93-101.
9. P. Gunasekaran, K. Kaveri, S. Mohana, Kavita Arunagiri, B.V. Suresh Babu, P. Padma Priya, R. Kiruba, V. Senthil Kumar & A. Khaleefathullah Sheriff. Dengue disease status in Chennai (2006-2008): A retrospective analysis. *Indian J Med Res* , 2011; **133**: 322-325
10. Chaterji, S., Allen, J. C., Jr., Chow, A., Leo, Y. S. and Ooi, E. E. Evaluation of the NS1 Rapid Test and the WHO Dengue Classification Schemes for Use as Bedside Diagnosis of Acute Dengue Fever in Adults. *Am J Trop Med Hyg,* 2011; **84**(2): 224-8.
11. Wilder-Smith A, Earnest A, Paton NI. Use of simple laboratory features to distinguish the early stage of severe acute respiratory syndrome from dengue fever. *Clin Infect Dis*. 2004; **39**(12): 1818-23.
12. Kalayanarooj S, Vaughn DW, Nimmannitya S, et al. Early clinical and laboratory indicators of acute dengue infection. *J Infect Dis*. 1997; **176**(2): 313-21
13. Murgue B, Deparis X, Chungue E. Dengue: an evaluation of dengue severity in French Polynesia based on an analysis of 403 laboratory-confirm cases. *Trop Med Int Health.*, 1999; **4**(11): 765-73
14. Gibbons GV, Vaughn DW. Dengue: an escalating problem. *BMJ*. 2002; **29**: 1563-6.
15. Akram DS. Igarashi A. Takasu T. Dengue virus infection among children with undifferentiated fever in Karachi. *Indian Journal of Pediatrics*. 1998; **65**(5): 735-40.
16. Krishnamurti C, Kalayanarooj S, Cutting MA. Mechanisms of haemorrhage in dengue without circulatory collapse. *Am J Trop Med Hyg*. 2001; **65**(6): 840-7.
17. Bielefeldt-Ohmann H. Pathogenesis of dengue virus diseases: missing pieces in the jigsaw. *Trends Microbiol*. 1997; **5**(10): 409-13.