A CLINICAL STUDY OF THE PATIENTS WITH DENGUE HEMORRHAGIC FEVER DURING THE EPIDEMIC OF 1996 AT LUCKNOW, INDIA

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Abstract. This paper describes the clinical findings in 206 patients with dengue fever (DF) or with dengue hemorrhagic fever (DHF) during the epidemic of 1996 at Lucknow. The age group affected most was 11 to 30 years and 21% of the patients were less than 10 years old. The male:female ratio was 1.9:1. The onset was abrupt in all the patients, severe frontal headache was observed in 97%, myalgia in 90%, skin rash in 40%, vomiting in 29% and arthralgia in knee and hip joints in 9%. Anuria was seen in two patients. Lymphadenopathy was noted in 14%, hepatomegaly in 4%, being associated with mild jaundice in one patient, and splenomegaly in 2% of the patients. Involvement of the heart and lungs was seen in one patient each and no case with encephalitis was recorded. Hemorrhages from various sites were observed in 54% patients and 17 patients had profound shock. The commonest bleeding site was gums. Profound shock was preceded by various warning signs, the commonest being sudden hypotention. Among the patients with profound shock the mortality was 47% while the overall fatality rate was 3.8%. A number of the risk factors existed for a long time in this part of the world, but what precipitated the present epidemic at this time, is not known.

INTRODUCTION

Dengue virus infection causes a spectrum of illness ranging from an inapparent or mild febrile illness to severe dengue hemorrhagic fever. Dengue is endemic in India and has caused a large number of epidemics at different places.The years 1963-64 were marked by extensive epidemics of dengue (and Chikungunya) along the eastern coast of India (reviewed by Chaturvedi *et al*, 1970a). This was followed by epidemics at Delhi in 1967 (Balaya *et al*, 1969), and in various parts of the State of Uttar Pradesh during 1968 to 1970. Very few patients with hemorrhagic manifestation were seen in these epidemics (Chaturvedi *et al*, 1970a; b; 1972; 1974a). The intervening period witnessed small outbreaks at different places. Patients with dengue hemorrhagic fever (DHF) were noticed for the first time in this country at Delhi in the year 1988 followed by those in Madras in 1989, Calcutta in 1990 and another outbreak in Delhi in 1991 (reviewed by Banerjee, 1996). During 1993, a small outbreak of DHF was noted near Lucknow (Chaturvedi, unpublished). This simmering dengue activity culminated into an explosive epidemic of DHF involving a large part of the Northern India in 1996. The cases were reported first, from Delhi (Sharma, 1997) and soon other adjoining States (Kaur *et al*, 1997), including Uttar Pradesh were affected. The present study reports the clinical presentation of the patients during this epidemic at a Lucknow, the capital of Uttar Pradesh.

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PATIENTS AND METHODS

Patients

The present study was carried out on patients suffering from typical dengue-like illness or dengue hemorrhagic fever reporting to the Gandhi Memorial and Associated Hospitals, Lucknow during the epidemic. Depending upon their clinical condition, they were admitted to the hospital or were treated in the Out Patients Department. Every patient was examined thoroughly by a physician and the laboratory investigations were done. At the time of reporting to the hospital, the clinical presentation of every patient was recorded, tourniquet test was done and his/her hematocrit value and platelet counts were measured; the last two tests were repeated daily during the course of the stay in the hospital. Depending upon the severity of the illness (clinical presentation) and the laboratory findings, they were classi-

fied as dengue fever (DF) or dengue hemorrhagic fever (DHF) grades I, II, III or IV according to the criteria of the World Health Organization (Nimmannitya, 1993). A patient was labeled as of DF when he had fever with typical dengue-like illness, as of DHF grade I when in addition, his hematocrit values were increased more than 20%; grade II when he had, in addition, spontaneous bleeding in skin or other sites; grade III had hypotension and/or narrowing of pulse pressure to 20 mm Hg or less, with cold clammy skin and restlessness; and grade IV had undetectable blood pressure or pulse (profound shock). The grade of the illness at the time of admission, was recorded and the subsequent progression of illness has been taken into consideration.

Diagnosis of dengue virus infection

Blood samples were collected from these patients in the plain vials. The first sample was collected at the time of first reporting to the hospital and the second sample after one to two weeks of collection of the first sample. The samples were transported to the laboratory on ice-bath and the serua were separated, divided into aliquots (to avoid repeated freezing and thawing) and quickly frozen and were stored at -60°C till further testing. Efforts were made to inoculate freshly collected serum for virus isolation. From a number of patients paired sera could also be collected to study the rising antibody titers. The diagnosis of dengue virus infection was established either by virus isolation in infant mice followed by neutralization test (Chaturvedi *et al*, 1970b) or by detection of virus-specific IgM in the sera using standard protocol (Gentry *et al*, 1982); in a number of cases dengue IgM capture ELISA was also done using commercial kits (Pan Bio, Brisbane, Australia).

RESULTS

Laboratory findings

In all the 206 patients included in the present study a diagnosis of dengue virus infection was established by detection of specific IgM antibodies and/or rising HI antibody titers in paired sera (more than four fold rise in 24 out of 28 patients) and in two of the patients by isolation of dengue type 2 virus in infant mice followed by neutralization test (data to be published). All the patients were negative for malarial and filarial parasites on the examination of blood films stained by Giemsa stain. Thrombocytopenia was a common finding (62%). A large number of the patients had neutropenia with relative lymphocytosis (52%). Only one case had raised fibrin degradation products. A few patients showed raised eosinophil counts (3%). SGOT and/or SGPT were highly raised in 10 patients. Evidence of dual infection (coinfection) was presented by three patients. In two patients the Widal test was positive indicating coinfection with *Salmonella typhi*, one of them was a 30 years old female, with DHF grade II, having bleeding per vaginum and the other patient was a 24 years old male with DHF grade III having hemetemesis and platelet count of 46,000/mm^3. Another patient had coinfection in the throat with *Klebsiella* species . These three patients had prolonged illness lasting for more than 15 days. All the three patients recovered with appropriate therapy.

Clinical findings

The epidemic of dengue hemorrhagic fever occurred in Lucknow during the last week of October to the first week of December, 1996, with peak in the early weeks of November. Records were available from a total of 206 patients, therefore they have been included in this study. Age- and sex-wise distribution of the patients is summarized in Table 1. The age group affected was 5 months to 58 years and the maximum incidence was seen in the age group 11 to 30 years. Male : female ratio was 1.9 : 1. The clinical features presented in Table 2 show that the onset of illness was acute in all the patients and all of them presented with fever and symptoms like, severe frontal headache (97%), backache, mainly in the lumbosacral region, myalgia (90%) mainly involving calf and thigh muscles, skin rash (40%) , vomiting (29%), conjunctival congestion, constipation, pain in abdomen, arthralgia involving knee and hip joints and retro-orbital pain *etc* in varying number of cases. Five patients also had symptoms of diarrhea and two patient had anuria. Hemorrhages were seen in 112 patients (54%) and 17 patients

Table 1
Age- and sex-wise distribution of the patients.

Age groups (Years)	Males (No)	Females (No)	Total (No)	Percent of total
< 5	11	8	19	9
6 - 10	16	8	24	12
11 - 20	28	20	48	23
21 - 30	43	18	61	30
31 - 40	23	13	36	17
41 - 50	7	3	10	5
> 50	5	3	8	4

Table 2
Clinical features.

Findings	Total No.	% of total
Acute onset	206	100
Fever	206	100
Headache	200	97
Myalgia	186	90
Arthralgia	19	9
Skin rash	83	40
Conjunctival congestion	11	5
Pain in abdomen	10	5
Vomiting	59	29
Diarrhea	5	2
Anuria	2	1
Hemorrhages	112	54
Shock	17	8

Table 3
Duration of illness.

Duration (Days)	No. of patients	% of total
1 - 4	96	47
5 - 7	66	32
> 8	44	21

(8%) had profound shock. A sparse maculopapular rash associated with intense itching developed on the chest, dorsal aspect of both the arms, on the back and abdomen in 40% of the patients. Rash developed between 3-5 days of illness and was maximum in patients with DHF grade II . The rash subsided within 2-3 days but itching persisted upto 3-4 weeks.

In most of the patients the duration of the illness was less than 7 days and in 44 patients (21%) it lasted more than 8 days (Table 3). In three patients the illness lasted for more than 15 days. Relative bradycardia was a common finding and one patient with DHF grade IV illness also showed electrocardiographic abnormalities in the form of premature ventricular contraction and irregular rhythm. One patient with DHF grade IV had pleural effusion. Lymphadenopathy was noted in 29 patients (14%), hepatomegaly in 8 (4%), being associated with mild jaundice in one of them(serum bilirubin, 2.7 mg/ml) and splenomegaly in 5 patients; majority of these presentations were seen among the patients with DHF grade II (Table 4). Hemorrhagic manifestations of varying degree and from different sites were observed in 112 out of 206 (54%) patients as summarized in Table 5. Epistaxis was the commonest bleeding manifestation followed by bleeding from

Table 4
Enlargement of organs.

Sites	DF	DHF I	DHF II	DHF III	DHF IV	Total No.	% of total
Lymphadenopathy	5	3	18	1	2	29	14
Hepatomegaly	1	0	5	1	1	8	4
Splenomegaly	1	0	3	0	1	5	2

Table 5
Sites of bleeding according to the grades of illness.

Sites of bleeding	DHF II No.	% of total	DHF III No.	% of total	DHF IV % of Total	% of total	Total No.	% of total
Epistaxis	44	39	1	1	3	3	48	43
Hematemesis	19	17	2	2	5	4	26	23
Malena	26	23	0	0	2	2	28	25
Gum	33	29	2	2	1	1	36	32
Hematuria	8	7	1	1	0	0	9	8
Hemoptysis	4	3	0	0	1	0	5	4
Vagina	4	3	0	0	0	0	4	3
Rectum	4	3	0	0	0	0	4	3
Skin	4	3	0	0	2	2	6	5

Total number of patients with hemorrhagic manifestations was 112.

gums. Fresh bleeding per rectum or per vaginum was the lowest in incidence. Hemorrhages with profound shock was observed in 17 patients and it usually developed around 3-7 days of illness. This was preceded by various warning signs as summarized in Table 6.

Prognosis

All the patients with DF or with DHF grades I, II or III recovered but the convalescence was prolonged and patients felt weak, tired and lethargic upto 4-6 weeks after the illness. Out of the 17 patients with profound shock 8 patients died of peripheral vascular failure inspite of best possible care. The progression of the illness in these fatal cases has been summarized in Table 7.

Table 6
Warning signs presented by patients with DHF grade IV.

Signs	No. of patients	Percentage*
Sudden fall of blood pressure	8	47
Hypothermia with sweating	7	42
Unconciousness	6	35
Severe pain in abdomen	3	18
Vomiting	4	23
Restlessness	3	18
Paralytic ileus	1	6
Convulsions	1	6

*Out of the 17 cases

DISCUSSION

This study describes the clinical presentation of the patients infected with dengue virus during the epidemic of DHF at Lucknow in 1996. In Southeast Asian countries DHF is primarily a disease of childhood while in the tropical Americas all the age groups are involved (reviewed by Rigau-Perez *et al*, 1998). In the present study 21% of patients were less than 10 years old while 53% were aged between 11 to 30 years. The spectrum of the clinical findings was similar in all the age groups. During the epidemic of dengue fever at Kanpur in 1968 the age group affected most was 11 to 30 years (71%) while 9% of the patients were below 10 years of age (Chaturvedi *et al*, 1970a). This epidemic also affected the State of Punjab where the age group affected most was 21 to 40 years and the male: female ratio of the patients was 2.5 : 1 (Kaur *et al*, 1997) while at Lucknow it was 1.9 : 1.

The commonest bleeding site in this study was nose followed by gums.The finding of gross hematuria is reported rarely (Nimmannitya, 1993) while it contributed to 8% of total bleeding manifestation in our study. Lymphadenopathy was noted in 14% of the patients, hepatomegaly in 4%, being associated with mild jaundice in one of them and splenomegaly in 2%; the majority of these presentations were seen among the patients with DHF grade II. Hepatic damage in dengue is recognized as unusual manifestation that is associated with high risk of death (Nimmannitya *et al*, 1987). Splenomegaly is not common in dengue infections but in some studies it has been observed in 5 to 24% of the cases (reviewed by George and Lum, 1997).

Table 7
Progression of the illness in the fatal cases.

ID No.	Age (Years)	Sex	Progression of illness	Main site of bleeding	Cause of death
967661	10	M	DF to DHFIII to DHF IV	Epistaxis, GIT	PVF*
967688	26	M	DF to DHF I to DHF IV	Hematuria	PVF
967790	5	M	DF to DHF IV	Hematemesis	PVF
967880	5	M	DHF I to DHF IV	Epistaxis, hematuria	PVF
967970	8	M	DHF I to DHF IV	Hemoptysis	PVF
968049	11	F	DF to DHF II to DHF IV	Epistaxis, vagina	PVF
968256	3	F	DF to DHF II to DHF IV	Epistaxis, rectum	PVF
968258	5	M	DF to DHF II to DHF IV	Hematemesis	PVF

*PVF: Peripheral vascular failure; M : Male; F : Female.

Dengue virus infection is known to damage heart tissues (Chaturvedi *et al*, 1974b). Cardiac involvement has been reported in the patients with DHF at Delhi during the present epidemic (Wali *et al*, 1998),but only one patient with DHF grade IV at Lucknow had minor electrocardiographic changes. In some of the studies myalgia and osteoarthralgia has been reported in 60 to 100% of the cases (reviewed by George and Lum, 1997) while in the present study myalgia was observed in 90% of the patients and arthralgia of knee and hip joints in 9% patients. Another rare finding at Lucknow was pleural effusion in one patient while in some studies the incidence of pleural effusion has been as high as 84% (Lum *et al*, 1995; reviewed by Rigau-Perez *et al*, 1998). Similarly, encephalitis due to dengue virus infection has been recorded in a number of studies (Lam, 1995; Lum *et al*, 1996) but no such case was recorded at Lucknow. An interesting finding was the evidence of coinfection with bacteria in three of the patients; being *Salmonella typhi* in two and by the *Klebsiella* species in one of them. In a recent report significance of coinfection in patients with dengue has been described (Pancharoen and Thisyakorn, 1998).

The prognosis of DHF depends on prevention and early treatment of shock. Once shock has set in the mortality may be as high 12 to 44% (reviewed by Rigau-Perez *et al*, 1998). In the present study 17 patients developed shock out of whom 8 died (47%) inspite of treatment. On close scrutiny of the records it was realized the most of the fatal patients were admitted to the hospital in a state of shock. The patients who were already in the hospital could be managed well. Early recognition of the warning signs (see Table 6) was helpful in successful management of the patients. The over all mortality in this study was 8 out of 206 patients (3.8%) which is similar to the cumulative case fatality rate of 0.5 to 3.5% observed in 12 Asian countries (Halstead, 1999).

All the four sero-types of dengue viruses are endemic in India and have been causing outbreaks off and on (reviewed by Banerjee, 1996). This epidemic provided an opportunity to answer some of the questions with regards to the pathogenesis of DHF (Agarwal *et al*, 1998; 1999; Raghupathy *et al*, 1998; Chaturvedi *et al*, 1999). But the question that remains unresolved is why DHF did not occur in India for such a long time when it was present in the close neighborhood; and when it did emerge in such a big way as in 1996, we do not know why it emerged. The factors that have been implicated in the global emergence of DHF are new strains and serotype of the virus, the immune status, age and genetic background of the human host, population growth, unplanned and uncontrolled urbanization, increased air travel and lack of effective mosquito control (reviewed by Monath, 1994; Lam, 1995; Gubler, 1998; Rigau-Perez *et al*, 1998). Most of these risk factors existed in India, therefore, which of them precipitated the emergence of DHF in this country is not known.

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