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An epidemic of dengue haemorrhagic fever & dengue shock syndrome in & around Vellore

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This report describes an epidemic of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) in the North Arcot Ambedkar district and the adjoining districts in Tamil Nadu and Andhra Pradesh. Nineteen children who fulfilled the clinical criteria for the diagnosis of DHF/DSS were admitted to the Christian Medical College Hospital, Vellore, during June through November, 1990. The clinical presentation was similar to that described in South-east Asian children and the case fatality rate was 26.3 per cent. Serology was confirmatory or suggestive of recent dengue virus infection in 16 children, uninterpretable in 2 and not consistent with recent dengue virus infection in 1 child. All children over 1 yr of age had very high antibody titres suggesting a secondary response whereas infants had lower titres consistent with primary response. The occurrence of recurrent epidemics in this region in the last few years with associated high case fatality emphasizes the urgent need for public health measures to curtail further epidemics.

Key words Dengue haemorrhagic fever - dengue shock syndrome-epidemic - serology

Epidemic dengue haemorrhagic fever and dengue shock syndrome (DHF/DSS) were first reported[1] in The Philippines in 1956. Since then, epidemics have occurred periodically in other South-east Asian countries. However, for reasons not well understood, such epidemics were mainly confined to this region for many years though dengue fever of the classical type was endemic in other regions, including India[2,3]. An epidemic of haemorrhagic fever was reported in Calcutta in 1963. This epidemic had a biphasic pattern and was thought to be caused by two viruses, dengue virus and chikungunya virus[4,5]. The next documented epidemic of DHF/DSS outside South-east Asia was reported from Cuba[6] in 1981. Since then epidemics have been reported from Hainan Island in China[7] in 1985 and from India in Delhi[8,9] in 1988, and in Madras (Mohan, S. and Mohandas, P., personal communication). This report describes an epidemic of DHF/DSS in Vellore town, the North Arcot Ambedkar district in Tamil Nadu and adjoining districts in Tamil Nadu and Andhra Pradesh during June through November in 1990.

Material & Methods

An epidemic of DHF/DSS was suspected when two children with clinical features of this syndrome were seen in the Department of Child Health of our hospital in June and July of 1990. Subsequently, all children with a febrile illness attending our hospital were examined for clinical evidence of DHF/DSS and those fulfilling the WHO diagnostic criteria were prospectively investigated[1]. Clinical and laboratory data from these patients were collected using a standardized proforma. Blood samples were collected at

admission and again approximately two weeks later from those who survived the acute phase of the illness. The sera were separated and stored at - 20°C till they were tested for the presence and titre of haemagglutination inhibiting (HI) antibody against each of the four dengue virus serotypes using the method described by Clarke and Casals[10]. The sera were also tested for the presence of 2-mercaptoethanol (2-ME) sensitive IgM antibody to dengue virus using previously described methods[11].

Results

Nineteen children fulfilling the clinical criteria for the diagnosis of DHF/DSS were seen in our hospital during June through November, 1990 (Fig.). The patients included 13 girls and 6 boys. Two were infants, one girl and one boy. The ages of the remaining 17 ranged from 1 to 12 yr with most patients being under six years of age (Table I).

Eleven children hailed from three districts in Tamil Nadu state (North Arcot Ambedkar - 8, Tiruvannamalai - 2, Salem - 1) and eight were residents of two neighbouring districts in Andhra Pradesh (Chittoor - 7 and Cuddappah - 1).

Among the 19 children with DHF/DSS, 17 had spontaneous haemorrhage from various sites. Of the two children with no overt bleeding, one had a positive tourniquet test and the other had thrombocytopenia and shock but no bleeding (the tourniquet test was negative presumably because of shock). Haemorrhage into the skin (petechiae, purpura or ecchymoses) was the commonest manifestation of bleeding (13 children) followed by gastrointestinal bleeding (haematemesis and/or melena; 12 children). In four children, these haemorrhages were noted along with other manifestations of bleeding *viz.*, haemorrhagic pleural and pericardial effusions, epistaxis and bleeding from the gums in 1 child each, respectively. Isolated haematuria was encountered in one child.

The other clinical findings and the grading of DHF/DSS in these 19 children are shown in Table II. Pleural effusion, diagnosed by chest roentgenogram, or ascites, diagnosed clinically by the presence of shifting dullness or fluid thrill over the abdomen, was present in 8 children including four who had both. In two children the pleural effusion was haemorrhagic; one of them also had haemorrhagic ascites and pericardial effusion.

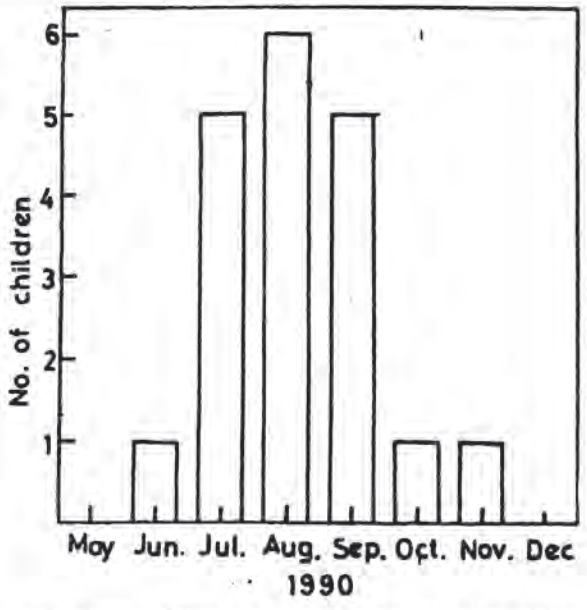

Fig. The month of onset of disease in children with DHF/DSS seen in the hospital during 1990.

Table I. Age and sex distribution of children with DHF/DSS

Age (yr)	No. of children		
	Male	Female	Total
0 - 3	3	3	6*
4 - 6	2	6	8
7 - 9	1	3	4
> 9	0	1	1
All ages	6 (32%)	13 (68%)	19 (100%)

* 2 (1 male and 1 female) were infants
DHF/DSS, dengue haemorrhagic fever/dengue shock syndrome

Thrombocytopenia (platelet count < 100,000/cu.mm) was documented in 18 children including 16 in whom the counts were < 60,000/cu.mm. The remaining child had a normal count at admission to our hospital on the seventh day of illness but platelet counts done earlier at the referring hospital were reported to be low. In 13 children who survived and in whom serial platelet counts were done, the count returned to normal (over 100,000/cu.mm) 7 to 18 days after the onset of illness (mean 10.3 days).

Table II. Clinical findings in children with DHF/DSS

Clinical sign	No. (%) of children
Coma	7 (36.8)
Palmar erythema	2 (10.5)
Maculopapular rash	1 (5.3)
Hepatomegaly (liver > 2 cm)	15 (78.9)
Splenomegaly	1 (5.3)
Ascites	6 (31.6)
Pleural effusion	6 (31.6)
Shock	10 (52.6)
Grade of DHF/DSS*	
grade 1	1 (5.3)
grade 2	8 (42.1)
grade 3	7 (36.8)
grade 4	3 (15.8)

* WHO grading of DHF (Ref. 1)
DHF/DSS, dengue haemorrhagic fever/dengue shock syndrome

Haematocrit was measured at admission and again after recovery in 11 of the 19 children. In 6 of them there was a 20 per cent fall in the haematocrit at recovery signifying haemoconcentration at the time of admission; two children had been transfused with packed cells and hence it was difficult to interpret haematocrit values, one child had massive haematemesis and a low haematocrit at admission and two children did not have a significant fall in the haematocrit. The prothrombin time was prolonged in 5 of the 18 patients in whom it was tested.

The serum glutamic pyruvic transaminase (SGPT) levels were elevated in 17 of the 18 patients in whom it was estimated; in four of them the values were above 1000 U/l. The serum glutamic oxaloacetic transaminase (SGOT) level was elevated in 14 of the 15 patients in whom it was estimated; 5 patients had levels above 3000 U/l. Serum electrolytes were determined in 15 patients; 12 patients had hyponatraemia, seven had hyperkalaemia and two had hypokalaemia. Seven children had blood urea levels greater than 40 mg/dl but less than 100 mg/dl; one child had blood urea level of 153 mg/dl but this returned to normal six days later with just conservative management.

The results of the dengue virus serology are shown in Table III. In 10 children there was serological evidence of recent dengue virus infection; in six of these patients there was a four-fold increase in HI antibody titre in paired sera, including one with the presence of 2-ME sensitive IgM antibody, and in four others 2-ME sensitive IgM antibody was detected but there was no four-fold rise in titre. In three additional patients the HI antibody titres were > 1:2560 (patient 11 - dengue serotype 2; patient 12 - serotypes 1 and 3; patient 14 - serotype 2) but no demonstrable four-fold rise in titre or IgM antibody was seen and thus they would be classified as probable recent dengue virus infection by the WHO criteria[1]. In three other children the antibody titres were 1:1280 (patients 1 and 19 - serotypes 1, 2 and 3; patient 13 - serotype 3) with no four-fold rise in titre or IgM antibody and we believe that these also probably represented recent dengue virus infection. In two children only acute serum samples were available and the serology results were uninterpretable and in one patient the antibody titre was 1:320 but there was no rise in titre in paired sera (patient 6). By definition this result was not consistent with recent dengue virus infection. The three infants with DHF/DSS seen during this epidemic had four-fold rise in antibody titres or presence of 2-ME sensitive IgM antibody but the titres were all below 1:160 suggesting primary infection. The older children had very high antibody titres suggesting secondary infection (Table III).

Supportive treatment was used in all children. This included volume replacement to correct shock, if present, as recommended in the WHO protocol[1]. In addition, fresh frozen plasma, platelet and red blood cell transfusion were given as required to patients with bleeding. Pleural effusions were drained if they were thought to be causing respiratory compromise. One patient who later succumbed to her illness required mechanical ventilation. All patients were given broad spectrum antibiotics empirically at admission. These were discontinued if blood cultures were negative or, in very sick children who had been receiving antibiotics prior to presentation to our hospital, continued for an empiric course of 10 to 14 days. Four children, two with grade 4 and two with grade 3 disease, respectively, died in hospital and one child with grade 3 disease left the hospital against medical advice and died at home.

Table III. Results of dengue virus serology in children with DHF/DSS

Patient no.	Age (yr)	Day of illness	HI antibody titre against Den-1	Den-2	Den-3	Den-4
2	4	5	320	1280	1280*	ND
4	7	6	640	640	1280	160
		17	2560	2560	1280	320
5	3	4	1280	640*	640	80
		19	640	1280*	1280	160
8	1	5	<10	40*	10	<10
		22	80	80	40	10
9	12	5	640	1280	1280*	80
		15	640	1280	640*	160
10	4	4	2560	1280	2560	40
		47	10240	1280	1280	40
15	7	4	2560	2560	640	160
		17	10240	5120	10240	320
16	9/12	6	<20	<20	40	<10
		17	160	40	320	<10
17	9/12	11	80*	80	80	<10
18	3	4	80	80	40	<20
		37	2560	320	320	80

* 2-ME sensitive IgM antibody present. ND, not done; HI, haemagglutination inhibition
DHF/DSS, dengue haemorrhagic fever/dengue shock syndrome

Discussion

Though all four serotypes of dengue virus have been prevalent in southern India for many years[2,3], there have only been isolated cases of DHF/DSS in this region[12]. In 1987 and 1989 epidemics of DHF/DSS occurred in Madras city (Mohan, S. and Mohandas, P., personal communication). However, during this period cases were not reported from elsewhere in southern India, including Vellore. From June to November in 1990 we observed 19 children with clinical features of DHF/DSS, most of whom had serological evidence for recent dengue virus infection. The age group of children affected, the clinical manifestations and outcome of the disease as seen in our patients was almost identical to those described in South-east Asian children. As in the series reported from Delhi, there was an increased frequency of disease in girls and except for the fact that splenomegaly and restlessness were less frequent in our patients, the clinical manifestations were similar to those in Delhi[8,9].

Serology confirmed recent dengue virus infection in the majority of the children. Published data on the prevalence and titres of dengue virus antibody in the population in this region are not available. However, unpublished data from our virology laboratory, which routinely tests sera from children and adults with encephalitis for antibody to dengue 2 virus, suggests that antibody titres ≥ 1:80 are very unusual. Among the three children in this series in whom serology was not diagnostic, two had titres of 1:320 and 1:640, respectively and therefore probably had DHF/DSS. The remaining patient had undetectable antibody in the acute sample and died before a second sample could be collected. This patient met the clinical criteria for the diagnosis and multiple blood cultures for bacteria were negative. Because of cross-reacting epitopes, the identity of the serotype(s) of virus responsible for this epidemic could not be established by serological tests.

The last documented case of DHF/DSS in our hospital was a single case in 1986 and these 19 cases

clearly represented an epidemic which, to our knowledge, is the first in southern India outside of Madras. Since this study was hospital-based, the extent of the epidemic is difficult to estimate but since we had patients from several adjoining districts, it appears that it was fairly widespread. The reasons for recent appearance of recurrent and widespread epidemics of DHF/DSS in India after many years of endemic dengue virus activity is not very clear. There are several theories to explain the pathogenesis of DHF/DSS[13]. Of these, the theory proposed by Halstead[14] that postulates that sequential infection and immunoenhancement of infection by heterotypic antibody is responsible for DHF/DSS has the most supportive epidemiological as well as laboratory evidence. The low antibody titres among infants and very high titres in the older children in this series suggesting that primary infection in infants with passively acquired antibody or secondary infection in the older children are associated with severe disease support this theory. This still does not explain why there were no such epidemics in the past though all four serotypes of dengue virus have been prevalent in this region for many years[2,3]. There are several possible explanations for this. Firstly, the sequence of infection with different serotypes of dengue virus is important in the pathogenesis of DHF/DSS. Those who have type 1 infection followed by type 2 infection are at highest risk whereas individuals who have primary infection with type 2 virus are at low risk[15] Also, there is a heterogeneity in the distribution of enhancing and neutralizing epitopes among different strains of dengue virus[16]. Thus, it is possible that the sequence and periodicity with which the circulation of different serotypes of dengue virus occurred in India in earlier years was not conducive to the occurrence of epidemic DHF/DSS. Recent changes in the pattern of dengue virus infection may have resulted in children in this region becoming more susceptible to this condition. This is supported by data from Delhi which suggest that the epidemic there was caused by secondary infection with type 2 dengue virus[8]. The increased virulence of certain strains of virus has also been postulated to be the cause for epidemic DHF/DSS[17]. Indeed, dengue virus strains isolated from patients with DHF/DSS have been shown to be more virulent in the laboratory compared to strains from patients with milder disease[13,14]. Thus, the introduction of a new, more virulent strain of dengue virus in combination with the above epidemiological changes may have been responsible for the recent appearance of epidemic DHF/DSS.

In South-east Asia epidemics of DHF/DSS occur periodically. The occurrence of three epidemics in four years in southern India suggest that this disease may follow a similar pattern here. One can therefore expect to see further epidemics unless steps are taken to prevent them. Several candidate dengue virus vaccines have been tested in volunteers and found to be immunogenic and safe[18]. However, dengue virus vaccination is complicated by the fact that DHF/DSS occurs in persons previously infected with heterologous virus. Moreover, it is not known whether attenuated vaccine virus would remain avirulent when given to a person with pre-existing heterologous antibody. To overcome these problems work has begun on second generation vaccines using recombinant DNA technology. However, it may be several years before effective vaccines will become available for routine use. Till such time, vector control seems to be the only viable preventive method available[19]. Several South-east Asian countries have significantly reduced the incidence of DHF/DSS by the use of vector control methods. In a country with the size and population of India, effective vector control seems a formidable task. However, intensive campaigns in areas of high risk should be attempted to prevent further epidemics.

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