Dengue haemorrhagic fever in children in Delhi*

S.K. Kabra,[1] I.C. Verma,[2] N.K. Arora,[3] Y. Jain,[4] & V. Kalra[5]

An epidemic of dengue haemorrhagic fever occurred in Delhi during 1988. A total of 21 paediatric patients with dengue haemorrhagic fever/dengue shock syndrome were evaluated from September to November 1988. All the patients had fever, restlessness, ecchymotic spots and ascites. Pleural effusion occurred in 19 patients (90%), and 18 (86%) exhibited each of the following: vomiting, thrombocytopenia, and haemoconcentration. Hepatomegaly was observed in 15 patients (71%) and splenomegaly in three (14%). Titres of haemagglutination inhibition (HI) antibodies against dengue virus type 2 were raised in all the 15 cases from whom sera were collected during the acute stage. Convalescent sera from five patients had increased titres of HI antibodies to dengue virus type 2. The remaining 10 cases exhibited raised IgM antibody levels against dengue virus type 2. The fatality rate for serologically proven cases was 13% (2 of 15 patients), while for all patients (including those diagnosed clinically (6) and serologically (15)) it was 33.3% (7 of 21). Patients who survived had no sequelae, except one who had transient hypertension that lasted for two weeks.

Dengue has a worldwide distribution (*1, 2*). In India, dengue virus was first isolated in 1945 and many epidemics have since been reported (*3–10*). The more severe and fatal forms of the disease, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), although common in south-east Asia, have rarely been reported in India except during some dengue epidemics. DHF was reported in Calcutta, West Bengal, in 1963 (*11*) and 1964 (*12*), in Visakapatnam, Andhra Pradesh, in 1964 (*13*), in Kanpur, Uttar Pradesh in 1968 (*14*), in Ajmer, Rajasthan, in 1969 (*8*), and in Jalore, Rajasthan, in 1985 (*15*). Epidemics of DHF/DSS were reported in Thailand (*16*), Cuba (*17*), and the Philippines (*18*) during 1981–84, as well as in the Caribbean during 1989–90 (*19*). The following clinical signs were observed in all these epidemics: myalgia, malaise, anorexia, and haemorrhagic manifestations. During the winter of 1988 there was an epidemic of dengue in Delhi. Cases of DSS/DHF were admitted to the All India Institute of Medical Sciences (AIIMS) Hospital. The clinicopathological features of the adult patients have been briefly reported (*20*), and a clinical study of 24 paediatric cases in another hospital in Delhi has been published (*21*). In the present article we describe the clinical features, laboratory investigations, and outcome of the paediatric patients in the AIIMS Hospital after management according to the WHO protocol (*16*).

Materials and methods

Patients

From September to November 1988, 21 cases diagnosed as DSS/DHF were admitted to the paediatric ward of the AIIMS Hospital, New Delhi. The first four cases were studied from the case records, since the diagnosis was tentative at the time; however, the remaining 17 cases were studied prospectively.

Clinical evaluation and diagnosis

Diagnosis of DHF/DSS was made according to WHO criteria (*16*). The case definition of DHF consisted of the presence of fever, haemorrhagic manifestations, including at least a positive tourniquet test and sometimes minor or major bleeding phenomena, thrombocytopenia (≤100 000 platelets per μl), haemoconcentration (increase in erythrocyte volume fraction by ≥20%), or objective evidence of increased capillary permeability.

DSS was diagnosed by the presence of the criteria listed for DHF in addition to hypotension or narrow pulse pressure (≤20 mmHg). All the patients in the study exhibited fever, ecchymotic spots and ascites, with sterile blood cultures for bacterial growth; and thus satisfied the case definition. DSS was present in 20/21 (92.5%) of the patients.

Each patient received a detailed physical examination, and vital signs such as heart rate, respiratory rate, blood pressure, and temperature were monitored at 2-hour intervals. The severity of DHF was classi-

* From the Department of Pediatrics, All India Institute of Medical Sciences, Old Operation Theatre Building, Ansari Nagar, New Delhi - 110 029, India.

[1] Pool Officer.

[2] Professor. Requests for reprints should be sent to this author.

[3] Senior Resident.

[4] Junior Resident.

[5] Professor.

Reprint No. **5253**

fied as follows: grade I — fever accompanied by nonspecific constitutional symptoms (the only haemorrhagic manifestation was a positive tourniquet test); grade II — spontaneous bleeding in addition to the manifestations of grade I patients, usually in the form of skin and/or other haemorrhages; grade III — circulatory failure manifested by rapid and weak pulse, pulse pressure ≤20 mmHg or hypotension with the presence of cold clammy skin and restlessness; and grade IV — profound shock with undetectable blood pressure and pulse. Grade III and IV together were termed DSS.

For all the patients a haemogram was recorded, the packed cell volume (PCV), platelet count, blood urea level, and level of electrolytes were determined, and a chest X-ray film was taken. Pleural and ascitic fluids were aspirated, their biochemistry investigated and analysed for the presence of cells and microorganisms. Studies of disseminated intravascular coagulation were carried out on two patients. Samples of blood were collected from 15 patients during the acute stage of their illness. A second sample was collected from five patients 14–21 days after the first sample had been taken. The sera were tested for haemagglutination inhibition (HI) antibodies (*22*) against all four dengue virus types, chikungunya virus, and Japanese encephalitis (JE) virus at the National Institute of Communicable Diseases, New Delhi. IgM antibodies to dengue virus type 2, and JE and West Nile viruses were assayed by IgM-capture enzyme-linked immunosorbent assay (*23*) at the National Institute of Virology, Pune. Dengue fever was diagnosed if there was at least a fourfold increase in the level of HI antibodies to dengue virus type 2 in paired sera, and a conversion or increase in the antibody titre to other viruses was either absent, or if present, was at least four times lower than that to dengue virus. There were five cases in this category. Dengue was also diagnosed if there was a high titre of HI antibody (≥1:160), the titre being at least four times greater than that to other viruses, together with a titre of IgM antibody against dengue virus type 2 that was greater than that to other viruses. There were 10 cases in this category.

Treatment

All the patients were treated according to guidelines published by WHO (*16*). Those patients with low blood pressure were infused rapidly with 20 ml per kg body weight of half-strength saline solution through a central venous pressure (CVP) line. If their blood pressure remained low, Haemacol[a] or plasma was infused rapidly till the CVP was 10 ± 3 cm of water. Once the blood pressure was normal, half-strength saline solution was infused at a rate of 5–10 ml per kg per hour and the CVP, PCV, and blood pressure were monitored. When the patient was stable for 24 hours, normal maintenance fluids were administered and oral fluids allowed. The CVP line was removed after the clinical state of the patient remained stable for 48 hours.

[a] Hoechst AG, Frankfurt am Main, Germany.

Results

Of the 21 cases that fulfilled the WHO case definition for DHF/DSS, 14 were girls and 7 were boys. A total of 17 patients were from Delhi, while the others originated from the neighbouring areas of Haryana state (3 patients) and Uttar Pradesh (one patient). All the patients were older than 6 years of age: three were 6–8 years, eight were 8–10 years, and 10 were 10–12 years old.

The clinical features consisted predominantly of fever of 3–9 days' duration and haemorrhagic manifestations (Table 1). Fourteen cases were classified as grade III and seven as grade IV. Evidence of disseminated intravascular coagulation was present in one of the two cases who were investigated for this condition; pleural and ascitic fluids were blood-tinged and exhibited characteristics of a transudate. The level of blood urea was >40 mg/dl in seven cases, but returned to normal in all those who survived. The fluid requirement during the first 24 hours varied from 1.3 to 10.7 litres.

Seven (33.3%) patients died; of these, four were included in the study retrospectively. Exclusion of these four patients gives a case fatality rate of 17% (3 out of 17 cases). If only serologically proven cases are considered (n = 15), the case fatality rate is 13% (2 out of 15 cases). Fourteen patients survived without experiencing any major problem, except one who developed hypertension for 2 weeks during convalescence; the hypertension required therapy with hydralazine.

All the patients whose antibodies were assayed exhibited an HI antibody titre of ≥1:160 against dengue virus type 2. An increased titre of HI antibodies against dengue virus type 2 was demonstrated in five cases, while the remaining 10 cases had an increased level of IgM antibodies against dengue virus type 2.

Discussion

DHF is an acute illness characterized clinically by haemorrhagic diathesis and a tendency to develop a shock syndrome (DSS) that may be fatal. Thrombocytopenia with concurrent haemoconcentration are

Table 1: **Clinical features and laboratory findings for the study patients**

	All cases[a] (n = 21)	Serologically proven cases (n = 15)
Clinical features		
Fever	21 (100)[b]	15 (100)
Restlessness	21 (100)	15 (100)
Ecchymotic or petechial spots	21 (100)	15 (100)
Ascites	21 (100)	15 (100)
Shock at some stage of illness	20 (95.2)	14 (93)
Pleural effusion	19 (90.5)	13 (87)
Vomiting	18 (85.7)	14 (93)
Hepatomegaly (> 2 cm)	15 (71.4)	13 (87)
Abdominal pain	11 (52.3)	8 (53)
Splenomegaly	5 (23.8)	4 (27)
Melaena	3 (14.2)	–
Convulsions	3 (14.2)	3 (20)
Laboratory findings		
Thrombocytopenia	18 (85.7)	14 (93)
Haemoconcentration (PCV>55)	18 (85.7)	14 (93)
TLC[c] (per µl):		
5000	2 (9.5)	2 (13)
5000–11 000	11 (52.3)	9 (60)
>11 000	2 (95)	4 (27)
Lymphocytes (> 40%)	2 (9.5)	1 (7)
Polymorphs (> 60%)	17 (80.9)	12 (80)
Pleural effusion		
Right side	15 (71.4)	13 (87)
Bilateral	2 (9.5)	0
Mortality	7 (33.0)	2 (13)

[a] This includes 15 serologically proven cases and six cases with clinical features that were consistent with the diagnosis of dengue haemorrhagic fever (four retrospective, two prospective).

[b] Figures in parentheses are percentages.

[c] TLC = total leukocyte count.

always present. DHF was first recognized in 1953 in the Philippines, and between 1953 and 1964 it was described in India, Malaysia, Philippines, Singapore, Thailand, and Viet Nam. Evidence from recent epidemics of DHF in Cuba and Thailand demonstrates clearly that DHF/DSS occurs during a second and not an initial dengue infection (*1*). It has been suggested that if a person infected with one dengue virus type is reinfected with another type he or she may develop severe DSS. The postulated pathogenesis for this phenomenon is antibody-dependent enhancement of viral infection (*17*).

In the present study an increased level of HI antibodies against dengue virus type 2, even in the first blood sample taken, suggests secondary infection. A widespread epidemic of dengue due to virus types 1 and 2 was observed in Delhi in 1982 (*9,14*); however, at that time no cases of DHF/DSS were documented. All of our patients were more than 6 years of age. In a recent report of DHF among 24 paediatric cases in Delhi, the majority were also aged 6–10 years (*21*). It is plausible that these patients might have suffered from dengue due to dengue virus type 1 or 2 in the 1982 epidemic, and that reinfection with dengue virus type 2 in 1988 manifested itself as DHH/DSS. This would explain the complete absence of cases of DSS/DHF among under-6-year-olds in the present study. Only our study and that by Srivastava et al. (*21*) have reported data on the 1988 epidemic; the government surveillance laboratories have not yet published information on the epidemic.

Two main pathophysiological changes occur in DHF/DSS: one is an increased permeability that gives rise to a loss of plasma from the vascular compartment. This results in haemoconcentration, low pulse pressure, and other signs of shock if plasma loss becomes critical. The second change is a haemostatic disorder that involves vascular defects, thrombocytopenia, and coagulopathy.

A major epidemic of DHF involving children was reported from Thailand in 1986 (*16*). Comparison of the clinical features of the 1988 epidemic in Delhi with that in Thailand showed that in Delhi a significantly larger proportion of patients exhibited restlessness, vomiting, and splenomegaly ($P<0.05$). In both our study and that by Srivastava et al. (*21*) the proportions of patients with fever, restlessness, vomiting, hepatomegaly and convulsions were similar (*21*); however, subcutaneous haemorrhages, ascites and pleural effusion occurred in a larger proportion of patients in our study (90–100%) than in that by Srivastava et al. (12–38%).

The case fatality rate for serologically proven cases of DHF was 13%, which is similar to the rate (12.5%, 3 of 24 serologically proven cases) reported by Srivastava et al. (*21*). If we include all cases clinically diagnosed as DHF, the mortality rate in our study is 33%, which is attributed to delays in reporting cases to hospital and initial misdiagnosis. The first four cases were suspected to be due to meningococcaemia, because epidemics of this condition have occurred in New Delhi during the past few winters. After more cases were reported to hospital with petechiae, fever and shock, combined with the failure to detect meningococci, the correct diagnosis of viral haemorrhagic fever was made. Subsequently, the cases were managed according to guidelines described by WHO. Thereafter mortality decreased significantly (3 out of 17 patients). The first four cases who were admitted died.

Since dengue infection is endemic in India, and introduction of dengue virus type 2 is evident from our study, as well as from previous studies of adults (*16*) and children (*21*), it is likely that further epidemics of DHF/DSS will occur in the country. Appropriate measures should therefore be taken to reduce the transmission of DHF as a matter of priority.

Acknowledgements

We thank Dr Mohan Bharadwaj, Division of Virology, National Institute of Communicable Diseases, New Delhi, and the Director, National Institute of Virology, Pune, for carrying out the assays of haemagglutination inhibition antibodies against dengue and other viruses, and IgM antibodies against dengue and other viruses, respectively; and Professor M.B. Singh and Professor R.N. Srivastava for permitting us to study the cases admitted to their units.

Résumé

Dengue hémorragique chez des enfants à Delhi

Une épidémie de dengue hémorragique s'est déclarée à Delhi au cours de l'année 1988. Au total, 21 enfants atteints de dengue hémorragique/syndrome de choc de la dengue ont été suivis de septembre à novembre 1988. Tous présentaient de la fièvre, un purpura ecchymotique, une ascite et étaient agités. Dix-neuf (90%) ont présenté un épanchement pleural et 18 (86%) des vomissements, une thrombopénie et une hémoconcentration. On a observé une hépatomégalie chez 15 malades (71%) et une splénomégalie chez trois (14%). Chez les 15 malades chez lesquels on a prélevé du sérum en phase aiguë, les titres d'anticorps dirigés contre le virus de la dengue de type 2 mis en évidence par la réaction d'inhibition de l'hémagglutination étaient tous augmentés. Le sérum prélevé en période de convalescence chez 5 malades avait des titres élevés d'anticorps dirigés contre le même type 2, dosés par la même réaction. Les dix malades restants ont montré une élévation des IgM contre le même type. Le taux de létalité a été de 13% (2 malades sur 15) pour les cas dont la sérologie était positive, alors que pour l'ensemble des malades (diagnostic clinique (6) et sérologique (15)) il a été de 33,3% (7 sur 21). Les malades qui ont survécu n'ont présenté aucune séquelle, à l'exception de l'un d'entre eux qui a montré une hypertension transitoire pendant 2 semaines.

References

1. **Halstead, S.B.** Pathogenesis of dengue; challenge to molecular biology. *Science*, **239**: 476–481 (1988).
2. **Sabin, A.B.** Research on dengue during World War II. *American journal of tropical medicine and hygiene*, **1**: 30–50 (1952).
3. **Balaya, S. et al.** Investigation of an outbreak of dengue in Delhi in 1967. *Indian journal of medical research*, **57**: 767–774 (1969).
4. **Rodrigues, F.M. et al.** Etiology of the 1965 epidemic of febrile illness in Nagpur City, Maharashtra State, India. *Bulletin of World Health Organization*, **46**: 173–179 (1972).
5. **Padbidri, V.S. et al.** An investigation of the etiology of the 1971 outbreak of febrile illness in Jaipur City, India. *Indian journal of medical research*, **61**: 1737–1743 (1973).
6. **Diesh, P. et al.** An outbreak of dengue fever in Delh—1970. *Journal of communicable diseases*, **4**: 13–20 (1972).
7. **Karamchandani, P.V.** Study of 110 cases of dengue fever in Madras penitentiary. *Indian medical gazette*, **72**: 532–534 (1973).
8. **Ghosh, S.N. et al.** Investigation on the outbreak of dengue fever in Ajmer City, Rajasthan state in 1969. Part 1. Epidemiological, clinical and virological study of the epidemic. *Indian journal of medical research*, **62**: 511–522 (1974).
9. **Mohan, R.C.V.R. et al.** The 1982 epidemic of dengue fever in Delhi. *Indian journal of medical research*, **152**: 660–675 (1964).
10. **Rao, C.V.R.M.** Dengue fever in India. *Indian journal of pediatrics*, **54**: 11–14 (1987).
11. **Sarkar, J.K. et al.** Sporadic cases of haemorrhagic and/or shock during dengue epidemics. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **66**: 875–877 (1972).
12. **Aikat, B.K. et al.** Haemorrhagic fever in the Calcutta area. *Indian journal of medical research*, **152**: 660–675 (1964).
13. **Krishnamurthy, K. et al.** Clinical and pathological studies of an outbreak of dengue-like illness in Visakapatnam. *Indian journal of medical research*, **53**: 800–812 (1965).
14. **Rodrigues, F.M.** Epidemiology of arboviral diseases of man in India; known facts and unsolved questions. *National Institute of Virologybulletin*, **6**: 3–15 (1988).
15. **Chouhan, G.S. et al.** Clinical and virological study of dengue fever outbreak in Jalore City, Rajasthan, 1985. *Indian journal of medical research (A)*, **91**: 414–418 (1990).
16. *Dengue haemorhagic fever: diagnosis, treatment and control.* Geneva, World Health Organization, 1986.
17. **Khorshed, P.** Why dengue haemorrhagic fever in Cuba? *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **82**: 511 (1982).
18. **Hayes, C.G. et al.** Dengue infections in the Philippines: clinical and virological findings in 517 hospitalized patients. *American journal of tropical medicine and hygiene*, **39**: 110–116 (1988).
19. An update on dengue fever in the Caribbean. *West Indian medical journal*, **39**: 131 (1990).
20. **Acharya, S.K. et al.** Outbreak of dengue fever in Delhi. *Lancet*, **2**: 1485–1486 (1988).
21. **Srivastava, V.K. et al.** An epidemic of dengue hemorrhagic fever and dengue shock syndrome in Delhi: a clinical study. *Annals of tropical pediatrics*, **10**: 329–324 (1990).
22. **Clarke, D.H. & Casal, J.** Technique for hemagglutination and hemaggulination inhibition with arthropod-borne viruses. *American journal of tropical medicine and hygiene*, **7**: 561–567 (1958).
23. **Gadkari, D.A. & Shaikh, B.H.** IgM antibody-capture ELISA in the diagnosis of Japanese encephalitis, West Nile and dengue virus infections. *Indian journal of medical research*, **80**: 613–619 (1984).