

An Epidemic of Dengue Fever in Karachi - Associated Clinical Manifestations

Pages with reference to book, From 178 To 181

Jazibeh A. Qureshi, Nasreen J. Notta, Naseem Salahuddin, Javaid A. Khan (Departments of Medicine, Aga Khan University, Stadium Road, Karachi.)

Viqar Zaman (Departments of Microbiology, Aga Khan University, Stadium Road, Karachi.)

Abstract

Dengue is a mosquito borne disease with worldwide distribution. Depending on virulence factors and host immune status, infection can manifest as a severe but non fatal viral syndrome or a rapidly progressive and a frequently fatal haemorrhagic fever. During the course of an outbreak of viral fever in Karachi, Pakistan from June, 1994 to September, 1995, we studied 145 cases admitted at the Aga Khan University Hospital. 43% of the cases were between the age group of 20-30 years, majority of these being male (75%). Amongst the clinical signs and symptoms, the most frequent findings were fever, vomiting and abdominal pain. Spontaneous hemorrhagic manifestations occurred in 66 patients and of these petechiae and mucosal bleed were the commonest, that is, 42% and 38% respectively. At presentation thrombocytopenia (platelet count $\leq 50,000$ per cubic millimeter) was present in 78%, leucopenia (white cell count $< 4,000$ per cubic millimeter) in 34%. Apart from one patient who died from hemorrhagic shock on the 5th day of admission, the remaining patients recovered and their platelet counts normalized on an average in 9 days. This is the first reported epidemic in Karachi of dengue infection (JPMA 47:178, 1997).

Introduction

Dengue is the most important arbovirus disease of humans, in terms of both morbidity and mortality¹. Since the end of World War II, the incidence of dengue disease has greatly increased. Coincident with that increase has been the emergence and spread of a severe and fatal form of the disease. Dengue Hemorrhagic fever/Dengue Shock Syndrome (DHF/DSS), as a major public health problem in many areas of the tropics. Today DHF is a leading cause of hospitalization and death among children in many countries of South East Asia and in recent years, it has become increasingly important in the Pacific Islands and the Americas. Dengue fever is a human arbovirus infection caused by a ribonucleic acid (RNA) virus of the Flavivirus genus. There are 4 distinct serotype of dengue viruses, capable of including life long specific immunity and 3 clinical patterns of the disease: a mild atypical form, the classic dengue and dengue hemorrhagic fever². In 1986, the World Health Organization (WHO) defined DHF as an acute febrile disease caused by one of the four serotypes of dengue viruses and characterised by a bleeding diathesis which may evolve to shock (DSS). Dengue hemorrhagic fever is generally a secondary infection. Hemoconcentration and thrombocytopenia are frequent findings³. An extensive epidemic of dengue virus was recognised in Karachi, Pakistan from June, 1994 to September, 1995. Since serologic testing on all patients was not cost effective and laboratory facilities for serotyping were not available, therefore, 16 samples were sent to Singapore and of these, 15 were positive for IgM against dengue virus. In this communication, we have described various clinical features present in our cases and also highlighted more effective methods for prevention and control of dengue infection.

Patients and Methods

From March, 1994 to September, 1995, we studied 145 cases with clinically suspected dengue fever admitted at the Aga Khan University Hospital in Karachi, a seaport of Pakistan. 15 of these cases were serologically proven positive for dengue virus. A retrospective case series was done and frequencies of various clinical features was studied. Alongwith these we also analysed laboratory data which included initial complete blood count (taken at admission), daily platelet counts, coagulation profile, liver function tests and cultures.

Results

A total of 145 cases of dengue fever were studied, 109 (75%) were males and 36 (25%) were females, with a mean age of 33 years. Sera of 15 patients belonging to this same series of patients were positive for IgM Ab against dengue virus. The method used was Enzyme Linked Immunosorbant Assay (ELISA). Serotyping for subtypes of dengue virus was not done. The clinical features observed in ourcases are shown in Table I.

Table I. Clinical features of patients with dengue fever.

| Sign or symptom | % of cases |
|-----------------------------------|-------------------|
| Fever | 98.6 |
| Vomiting | 68.3 |
| Abdominal pain | 31.0 |
| Diarrhoea | 25.5 |
| Rash | 16.6 |
| Nausea | 23.4 |
| Headache | 15.2 |
| Mucosal bleed | 17.2 |
| Muscle ache | 12.4 |
| Hematemesis | 8.3 |
| Epistaxis | 7.6 |
| Melena | 6.9 |
| Sore throat | 6.2 |
| Cough | 4.8 |
| Backache | 4.1 |
| Confusion | 3.4 |
| Hemoptysis | 2.1 |
| Perrectal bleed | 2.1 |
| Rhinorrhea | 2.1 |
| Oliguria | 1.4 |
| Hematuria | 1.4 |
| Conjunctival bleed | 1.4 |
| Joint pain | 0.7 |
| Upper respiratory tract infection | 0.7 |

Spontaneous hemorrhagic manifestations occurred in 66 patients and of these petechiae and mucosal bleed were the commonest, that is 42% and 38% respectively, followed by gastrointestinal bleed in 21.2%. Of the 28 patients who had rash, 71.5% had petechiae and 28.5% had ecchymoses and from those who had mucosal bleed, the most predominant site was gumbleed found in 13 of 25 patients.

None of four patients gave definite history of exposure to mosquitoes, though 5 cases had a history of receiving injections prior to admission. From drugs used, 28 of 145 cases, that is 19.3% had taken Fansidar (an antimalarial) after the onset of the febrile illness. At presentation, 8 cases had bradycardia (pulse rate <60 beats per minute) with fever. Rash was found predominantly on the legs in 11 of 28 cases (39.3%), followed by generalised rash (that is, involving whole body) in 25% of patients. Liver was palpable in 20 cases (13.7%) and of these 12 cases had deranged liver function tests. When considering laboratory data, Hematocrit $\geq 45\%$ was seen in 47.5% of patients, as shown in Table II.

Table II. Distribution of hematocrit.

| Hematocrit (%) | Cases No. | % of cases |
|----------------|-----------|------------|
| <36 | 8/141 | 5.5 |
| 36.1-44.7 | 65/141 | 46 |
| ≥ 45 | 67/141 | 47.5 |

Of the patients who had hemoconcentration (Hematocrit ≥ 45), 8 had blood pressure <90/60 and 6 of the 8 cases had tachycardia (pulse rate > 100 beats per minute). Two patients had clinical manifestations of dengue shock syndrome, of whom 1 died. One of our cases was a primigravida in her third trimester who went on to have a preterm twin vaginal delivery at 33 weeks. Twins were 1.5 kg and 1.9 kg respectively and did well. Leucopenia (white cell count <4,000 per cubic millimeter) was found in 34% of patients. At presentation, thrombocytopenia (platelet count <50,000 per cubic millimeter) was present in 78%. Since thrombocytopenia is a feature of dengue infection, platelet count was evaluated. Maximal thrombocytopenia occurred on day 6 to 7 after onset of fever with a mean platelet count of 21,000 per cubic millimeter. No statistical significance was found between low platelet count and gastrointestinal bleed ($P > 0.05$). The prothrombin time was normal, that is, 12-14/12 in all the cases while activated partial thromboplastin time was abnormal > 39 with a control of 32 in 77% of cases. Blood cultures were done in 88 patients and were all negative. Bone marrow cultures were done in 8 patients only, all of whom reported no growth. Proteinuria was found in 31 of 53 cases in which a urine detailed report was done and microscopic hematuria (that is, RBC 4 per high power field) was found in 16 patients (30.2%). Hypoalbuminemia (albumin < 3.2 mg/dl) was found in 25.7% and hyperbilirubinemia was seen in 12.8% of cases (bilirubin > 1.25 mg/decilitre).

Discussion

Attempts to describe the spectrum of dengue disease and identify risk factors are often difficult because of the insensitivity of clinical diagnosis, the frequent co-circulation of other viral illnesses and the lack of adequate laboratory facilities in countries with endemic dengue. Estimates of the number of dengue cases during both endemic and epidemic periods have generally relied on notification systems based on clinically diagnosed cases, usually without laboratory verification⁴. In our study except for 15 cases, all the rest were identified to have dengue fever on basis of their clinical symptomatology. Initial investigation of acute phase sera from 16 patients seen at the Aga Khan University Hospital showed that 15 of them had Dengue Immunoglobulin, M (IgM) antibodies assay using dengue type 2 antigen and

monoclonal antibody⁵. According to a study in Thailand, IgM Ab shown onELISA had a 97% sensitivity⁶. Majority of our cases fell in the age group of 20-40 years which was very different from that reported in literature where children are said to be most commonly affected by this disease⁸. Dengue hemorrhagic fever in Asia is a disease of childhood with one peak observed in children under 1 year and a second in children aged 3 to 5 years⁷. In the first epidemic of dengue hemorrhagic fever in Indonesia, most of the cases were in children under 15 years of age. In our study, males were 75% while reports from Cuba and Brazil⁸ have shown a predominance of dengue hemorrhagic fever in women, that is, 65% and 61% respectively. As regards the clinical manifestations of dengue hemorrhagic fever, experience from numerous outbreaks with laboratory confirmed cases, however, has shown that the illness associated with dengue infection can differ from country to country⁴. Clinically, the epidemic was similar to others reported in South East Asia⁹⁻¹⁴ with a high percentage of patients suffering from non-specific symptoms such as vomiting and abdominal pain. Although headache has more frequently been reported as a non-specific symptom in the studies mentioned, was found in only 15.2% of our cases.

In a 1976 dengue epidemic in Indonesia¹⁵, backache and joint pain were each reported by only 2.1% of serologically confirmed dengue cases. Similarly in our study, these symptoms were rarely reported in 4.1% and 0.7% of cases respectively. Bleeding is one of the major problems encountered in dengue fever and contributes to a worsening morbidity¹⁶. In the Island of Tahiti, French Polynesia, severe hemorrhagic disease was observed in an unusual number of patients shortly after the onset of a febrile illness. Gastrointestinal bleeding was the most common type of severe hemorrhage observed and gross hematuria was next most common¹⁷. In our study, there was one fatality secondary to hemorrhage (upper gastrointestinal bleed) and gastrointestinal bleed was found in 17.3% of cases. Gross hematuria was reported in only 2 cases. The spectrum of hemorrhagic manifestations observed in Karachi was comparable to that in other epidemics reported in South East Asia in which petechiae, epistaxis and hematemesis occurred most frequently⁹⁻¹⁴. It is important to emphasize the lack of association in our study between gastrointestinal bleed and low platelet levels, contrary to a significant association between these two parameters¹⁶. Hematopoiesis is affected in dengue hemorrhagic fever, neutropenia and thrombocytopenia occur early in the disease, coincident with the febrile stage. In our study leucopenia (white cell count <4,000 per cubic millimeter) was found in 34% of patients and thrombocytopenia (platelets <50,000 per cubic millimeter) was present in 78% with the lowest platelet count approaching 2000 per cubic millimeter which is in contrast quite low compared to other studies. Hepatomegaly was found in 13.7% of cases, that is 20 Patients. This figure is similar to that reported in literature¹⁵. On the contrary, higher rates have been reported in Bangkok, Thailand where 80-90% of confirmed cases had hepatomegaly¹⁵. Rates in other countries, however, vary considerably from as low as 1% in the 1966 Philippine outbreak¹¹, 24% in Burma¹⁴, 54-63% in Singapore¹³ and 66% in Vietnam¹². It is clear from these reports that hepatomegaly is not a consistent clinical sign associated with dengue hemorrhagic fever and a closer study of this parameter should be made during epidemics in different regions and in association with different viruses. Possibly, the extent of liver involvement may be associated with the strain or serotype of virus¹⁵.

Of the 145 cases of dengue hemorrhagic fever, 2 had features consistent with dengue shock syndrome (DSS), 1 of whom succumbed to the illness. The fatality occurred because of not receiving immediate treatment, although the patient came to the hospital within hours of onset of shock, demonstrating urgency of medical assistance in this condition. In conclusion, therapy for dengue fever is supportive. Immediate and adequate medical assistance permitted a favourable outcome in most cases. Close monitoring of the vital signs and hematocrit (not done in our fatality) in order to evaluate plasma loss or hemorrhage is mandatory to reduce morbidity. If shock develops, aggressive fluid therapy should be

initiated in an intensive care setting. Patients with severe hemorrhage will require transfusions and careful observation for surgical intervention. Although none of our patients had a history of exposure to mosquitoes (not that mosquitoes are a variety) but recent dengue epidemics in Brazil¹⁸ demonstrate the need to maintain programmes to reduce population of vector mosquito (*Aedes aegyptii*, the only known way of keeping this arbovirus under control).

Prevention and control

Aedes aegyptii is an anthropophilic domestic mosquito which lives intimately with its human hosts. These mosquitoes breed primarily in man-made containers such as water storage containers and flower vases in and around human dwellings. Elimination of these breeding sites is an effective and definitive method of controlling the vector and therefore of preventing transmission of dengue. Non-residual insecticides such as malathion, which kills mosquitoes on contact, have been used in attempts to control dengue epidemics. New efforts should focus on community education and behaviour modification in an attempt to encourage neighbourhoods to control the vector through breeding site reduction. There is no dengue vaccine currently available for widespread public health use. Research continues on developing an effective and safe tetravalent vaccine that would circumvent the potential hazards predicted by the immune enhancement theory. Currently the only effective way to avoid dengue infection in areas where the disease is endemic or epidemic is to avoid being bitten by injected mosquitoes through the use of insect repellent and other insect barriers¹⁹.

Acknowledgements

We are grateful to Mr. Qureshi and Ms. Laila for their secretarial assistance.

References

1. Rosen, L. The global importance and epidemiology of Dengue infection and disease. in: T. Pang and Pathmansthen, R eds. Proceedings of International Conference on Dengue Hemorrhagic fever, Kuala Lumpur, Malaysia 1984, pp. 1-6.
2. Gubler, D.J. The arboviruses: Epidemiology and ecology. In: Monath, T.P. ed Boca Raton, Florida, CRC Press, 1988, pp. 223- 260.
3. Halstead, SB. Pathogenesis of Dengue: Challenges to molecular biology. *Science*, 1988;234:476-480.
4. Dietz, V.J., Gubler, D.J., Rigan-Perez, J.G. et al. Epidemic dengue I in Brazil, 1986; Evaluation of a clinically based Dengue Surveillance system. *Am. J. Epidemiol.*, 1986; 131:693-701.
5. Chan, V.C., Salahuddin, N.I., Khan, J. et al. Dengue hemorrhagic fever outbreak in Karachi. Pakistan, 1994. *Trans. R. Soc. Trop. Med. Hyg.*, 1995;89:619-620.
6. Innis, B.L., Nisalak, A., Nimmanitya, S. et al. An enzyme linked immunosorbent assay to characterize Dengue infections where Dengue and Japanese encephalitis Co-circulate. *Am. J. Trop. Med. Hyg.*, 1989;40:418-427.
7. Sanford, J.P. Arbovirus infections. In: Sanford, J.P. et al. Harrison's principles of Internal Medicine, 12th ed. New York. McGraw Hill, Inc. 1991, pp. 730-731.
8. Guzman, M.G., Kouri, G., Bravo, J. et al. Dengue hemorrhagic fever in Cuba. II Clinical investigations. *Trans. R. Soc. Trop. Med. Hyg.*, 1984;78:239-241.
9. Winter, P.E., Yuill, T.M., Vdomsakdi, S. et al. An insular outbreak of dengue Hemorrhagic fever. I. Epidemiologic observations. *Am. J. Trop. Med. Hyg.*, 1968;17:590-599.
10. Nimmanitya, S., Halstead, SB., Cohen, SN. et al. Dengue and Chikungunya virus infection in man in Thailand, 1962-1964. I. Observations on hospitalized patients with hemorrhagic fever. *Ant. J. Trop. Med. Hyg.*, 1969;18:954-971.

11. Venzon, EL., Rudnick, A., Marchette, N.J. et al. The greater Manila Dengue Hemorrhagic fever epidemic of 1966. *Philip. J. Sci.* 1972;48:297-313.
12. Halstead, SB., Voulgaropoulos, E., Thien, N.H. et al. Dengue hemorrhagic fever in South Vietnam: Report of the 1963 outbreak. *Am. J. Trop. Med. Hyg.*, 1965;14:819-830.
13. Chan, Y.C., Lint, K.A. and Ho, B.C. Recent epidemics of Hemorrhagic fever in Singapore. *Jpn. J. Med. Sci. Biol.*, 1969;20:81-88.
14. Thaung, U., Ming, C.K. and Them, M. Dengue hemorrhagic fever in Burma. *South East Asian J. Trop. Med. Public Health*, 1975;6:580-591.
15. Eram, S., Setyabudi, Y., Sadono, T.L et al. Epidemic Dengue hemorrhagic fever in rural Indonesia. II. Clinical studies. *Am. J. Trop. Med. Hyg.*, 1979;28:711-716.
16. Tsai, C.J., Kuo, C.H., Chen, P.C. et al. Upper gastrointestinal bleeding in Dengue fever. *Am. J. Gastroenterol.*, 1991 ;86:33-35,
17. Gubler, D.J., Suharyono, W., Lubis, I. et al. Epidemic Dengue hemorrhagic fever in Rural Indonesia. I. Virological and Epidemiological studies. *Am. J. Trop. Med. Hyg.*, 1979;28:701-710.
18. Zagne, S.M.O., Alves, V.G.F., Nogueira, R.M.R. et al. Dengue hemorrhagic fever in the state of Rio de Janeiro, Brazil: A study of 56 confirmed cases. *Trans. R. Soc. Trop. Med. Hyg.*, 1994,801:677-679.
19. Hayes, E.B. and Gubler, D.J. Dengue and Dengue hemorrhagic fever. *Pediatr. Infect. Dis. J.*, 1992;11 :311-317.