HEMORRHAGIC MANIFESTATIONS AND ENCEPHALOPATHY IN CASES OF DENGUE IN INDIA

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Abstract. Thirty-seven serum samples and five serum-CSF pairs collected from 42 acutely ill patients admitted to hospitals in Maharashtra (Bombay, Pune and Nasik); Orissa (Raurkela) and South Goa were referred to the National Institute of Virology (NIV), Pune (Maharashtra, India) for serodiagnosis. These patients had clinical manifestations of fever, hemorrhagic manifestations, hepatomegaly, shock syndrome and encephalopathy. Sixty-six percent of patients were children below ten years of age. Serological investigations revealed infection to dengue virus in all the patients as indicated in detection of IgM antibodies predominantly to dengue viral antigens. An important outcome of the study is that 10 patients referred to NIV with a provisional diagnosis of viral encephalitis proved to be dengue.

INTRODUCTION

Outbreaks of dengue fever have been known to occur in India for more than a century. Despite frequent outbreaks of dengue, reports of severe hemorrhagic manifestations with or without shock have been rare. Dengue hemorrhagic fever (DHF) was reported in Calcutta in 1963, when a number of cases with hemorrhagic manifestations were occurred during a dengue epidemic (Sarkar, 1967). Since then a few cases of DHF were recorded (Sarkar *et al*, 1972; Krishnamurthy *et al*, 1965; Ghosh *et al*, 1974). Encephalopathy as a rare complication has also been recorded in patients with dengue (Sarkar *et al*, 1969; Myers *et al*, 1969; Nimmannitya *et al*, 1988). In this communication we report 42 cases of DHF/DSS with a number of cases showing encephalopathy.

MATERIAL AND METHODS

NIV, Pune receives specimens for viral diagnosis from different parts of the country. During the period 1990-1995 we received serum samples from 42 patients, clinically diagnosed as pyrexia of unknown origin (PUO). The serological tests showed that the patients were infected with dengue virus (DEN).

There were 16 patients from Bombay, 9 from Pune, 1 from Nasik (Maharashtra State); 14 from Raurkela (Orissa State) and one each from New Delhi and South Goa. The samples from Raurkela and Nasik were collected during dengue epidemics, while the sample from South Goa was collected during an epidemic of Japanese encephalitis (JE). The youngest was a 6 month old child while the oldest case was of 60 years of age. There were 35 males and 7 females. Thirty-seven serum samples and 5 serum-CSF pairs were collected during hospitalization (acute phase of illness). The clinical features of patients were obtained from attending physicians. The number of cases as per their clinical manifestations are as follows:

Category 1 (n = 15):- Dengue hemorrhagic fever (DHF)

Category 2 (n = 7):- Degue hemorrhagic fever with shock syndrome (DHF/DSS)

Category 3 (n = 5):- DHF with encephalopathy

Category 4 (n = 5):- DHF and DSS with encephalopathy

Category 5 (n = 10):- Provisional diagnosis of encephalitis.

As per WHO criteria (Nimmannitya, 1993) patients with hemorrhagic manifestations were graded as grade II (20 patients) while 12 patients were in grade III.

The samples were tested by IgM antibody capture (MAC) ELISA (Gadkari and Shaikh, 1984), by hemagglutination inhibition (HI) (Clarke and Casals, 1958) and complement fixation (CF) (Sever, 1962) tests against JE (strain P20778), West Nile (WN) (Strain G22886) and DEN (strain 23085)

viral antigens. Samples having HI titer < 10 and CF titer < 8 were recorded as negative.

RESULTS

Fever with other symptoms such as chills, vomiting, cough, joint pain, body ache and headache were recorded in all patients. Hemorrhagic manifestations recorded in 32 patients (category 1 to category 4) were in the form of or in the combinations of hematemesis, epistaxis, gastrointestinal (GI) tract bleeding, melena, coffee ground aspirate, pleural effusion, ecchymoses and purpuric or maculopapular rash. Disseminated intravascular coagulopathy (DIC) was recorded in 4 patients (2 from category 2 and 1 each from category 3 and 4).

Clotting abnormalities, *viz* poor clot retraction time, prolonged prothrombin time were recorded in 6 patients. (two each from categories 2 and 4, and 1 each from categories 1 and 3). Thrombocytopenia (platelets ranging from 26,000 to 100,000) was recorded in 11 patients (2 each from category 1 and 2; 3 patients from categories 3 and 4 from categories 4).

Hepatomegaly was present in 13 patients (5 from category 1, 4 from categories 2, 3 from categories 4 and 1 from categories 3) six of them were recorded to have elevated levels of SGOT (70 to 2,500 IU/liter) and SGPT enzymes (34 to 2,250 IU/titer). Pleural effusion was noted in 10 patients (five from categories 2; two each from categories 1 and 4 while one from categories 3). Ascites was recorded in 2 patients from categories 1 and one from categories 2. The symptoms of shock, *viz* pallor, breathlessness, low blood pressure, cold extrimities and absence of peripheral pulse were present in 12 patients (7 from categories 2 and 5 from categories 4).

Symptoms suggestive of encephalopathy, *viz* altered sensorium, convulsion and decerebration were present in patients categorised as 3 and 4. They also exhibited hemorrhagic manifestations with or without symptoms of shock. CT scan of one of the patients from category 3 showed right thalamic infarct.

Striking clinical features of patients from category 5 were as follows: neck rigidity, positive kernig's sign, increased tone, unconsciousness, disorientation, pin point pupil; up rolling of eye balls and mild right sided hemiparesis. CT scan of one of the patients showed involvement of thalamus, basal ganglia, brain stem and cerebellum.

Clinical details of patients from categories 1 to 4 are given in Table 1 while details of patients from category 5 are given in Table 2.

Serological investigations on patients

IgM type of antibodies predominantly to dengue viral antigens were detected in serum samples of 27 patients from categories 1 to 4. Categories 5 was marked by detection of IgM type of antibodies to dengue viral antigens not only in serum but also in CSF samples of 2 patients.

HI titers were ≥ 1,280 in serum samples of 13 patients. It ranged from 64 to 128 for 7 patients, while for 11 patients it ranged from < 10 to 80. HI antibody data was not available for two patients.

CF titers were ≥ 256 in serum samples of 19 patients It ranged from 64 to 128 for 7 patients, while it ranged from < 8-32 for 7 patients. For remaining 9 patients either CF antibody data was not available due to insufficiency of samples or samples were found to be anticomplementary. Table 3 summarizes the results of serological investigations.

Data on outcome of patients was available for 7 patients. Two patients each from categories 4 and 5, and one patient from category 2 recovered. One patient each from categories 2 and 5 expired.

DISCUSSION

During a period of 1990 to 1995, while investigating serum samples received from all over India for arbovirus infections, evidence of infection of dengue virus was recorded in a number of patients with fever. In the present study only the cases of dengue viral infection with hemorrhagic manifestations, shock symptoms and encephalopathy were included.

The classical symptomatology, namely hemorrhagic manifestations, was observed in patients from categories 1 and 3 while hemorrhage and symptoms of shock were observed in patients from categories 2 and 4. There was definite evidence of serological evidence of recent infection of dengue

Table 1
Clinical details of patients from categories 1 to 4.

Parameters	Category 1 DHF n = 15	Category 2 DHF/DSS n = 7	Category 3 DHF/EN* n = 5	Category 4 DHF/DSS EN* n = 5
Clinical details:				
1. Hemorrhage				
n = 32	15	7	5	5
DIC				
n = 4	-	2	1	1
Clotting abnormalities				
n = 6	1	2	1	2
Thrombocytopenia				
n = 11	2	2	3	4
2. Hepatomegaly				
n = 13	5	4	1	3
3. Effusions				
pleural				
n = 10	2	5	1	2
Ascites				
n = 3	2	1	-	-
4. Shock syndrome				
n = 12	-	7	-	5
5. Encephalopathy				
n = 10	-	-	5	5

* EN: Encephalopathy

virus infection in these patients. Both these observations are favorable to DHF/DSS diagnosis. Thirty-one percent of patients from categories 1 to 4 had HI antibody titers > 1,280 in their acute phase serum samples. Fifty percent of patients from same categories had CF antibody titers > 256. These results suggest these patients have probably experienced flavivirus infection before.

Interestingly there were some patients from the same categories (1 to 4) who had hemorrhagic manifestations and symptoms of shock, with evidence of recent dengue virus infection but had low HI and CF antibody titers. It is hypothesized that immune enhancement by secondary infection by different DEN subtype can lead to complications of DEN namely DHF/DSS (Halstead, 1993). On the other hand Songco *et al* (1988) observed hemorrhagic manifestations and symptoms of shock in patients even with primary DEN virus infection. Virulence of dengue virus strain, chronic illness and nutritional status may be the reasons for DHF/DSS (Monath, 1994; Rigau-Perez *et al*, 1994). In the present series however it is not possible for us to specify any of the above parameters.

Encephalopathy in cases of DHF/DSS have been reported earlier (Nimmannitya *et al*, 1988; Annual Report, 1994; Wei-Junechen *et al*, 1992). The suggested various reasons for encephalopathy in dengue virus infection are intracranial hemorrhage, hyponatremia or gastrointestinal hemorrhage and hypovolemia, commonly found in DHF/DSS which could precipitate portosystemic encephalopathy (Nimmannitya, 1988).

An important feature of this series is a group of 10 cases (category 5) referred to NIV with provisional diagnosis of viral encephalitis by the physicians. These patients presented with clinical manifestations of febrile convulsions, various degrees of unconsciousness and focal neurological deficits.

Table 2
Clinical details of patient from category 5 (n = 10).

Patient	Age/ sex	Clinical details
*1	4/F	Neck stiffness, +ve kernig's sign, Drowsy, convulsion, increased tone.
2	28/M	Unconsciousness involvement of thalamus, brain stem, basal ganglia, cerebellum in CT scan.
*3	21/M	Disorientation followed by convulsion, pin point pupil.
4	2/M	Drowsy, inability to see, mild right sided hemiparesis.
5	60/M	Seizure, unconsciousness
6	18/M	Altered sensorium
7	2/M	Altered sensorium, Semicomatose, meningoencephalitis
8	4/M	Convulsion, drowsy uprolling of eye balls, planter; neck stiffness
9	20/M	Altered sensorium
10	40/M	Convulsion

* Virus specific IgM antibodies were detected in CSF samples of patients No. 1 and 3.

The patients did not demonstrate any of the hemorrhagic manifestations or symptoms of shock. There was serologic evidence that these were DEN cases as virus specific IgM antibodies were detected in serum samples, and also in CSF of 2 cases. Earlier, dengue virus isolations have been reported from cases of encephalitis (Sarkar *et al*, 1969; Myers *et al*, 1969). Presence of dengue specific RNA in some cases have been confirmed by PCR technique (Annual Report, 1994).

It seems therefore that the at least a few cases of dengue during an epidemic may present as cases of encephalopathy.

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REFERENCES

Annual Report, WHO Collaborating Centre, University of Malaya, 1994.

Table 3
Results of serological investigations.

Serological tests	No. of samples from				
	Category 1 (n = 15)	Category 2 (n = 7)	Category 3 (n = 5)	Category 4 (n = 5)	Category 5 (n = 10)
1. MAC ELISA positive	15	7	5	5	10
2. HI titers					
> 1,280	4	4	1	1	3
160-640	8	3	2	2	1
< 10-80	2	-	2	2	5
QNS	1	-	-	-	1
3. CF titers					
> 256	8	6	1	2	2
64-128	4	-	-	2	1
< 8-32	1	-	2	-	4
QNS/AC	2	1	2	1	3

QNS: Quantity not sufficient, AC: Anticomplementary.

Clarke DH, Casals J. Technique for hemagglutination and hemagglutination inhibition with arthropod-borne viruses. *Am J Trop Med Hyg* 1958; 7 : 561-67.

Gadkari DA, Shaikh BH. IgM antibody capture ELISA in the diagnosis of Japanese encephalitis, West Nile and Dengue virus infections. *Ind J Med Res* 1984; 80 : 613-9.

Ghosh SN, Pavri KM, Singh KRP, *et al.* Investigations on the outbreak of dengue fever in Ajmer city, Rajasthan State in 1969. Part I. *Ind J Med Res* 1974; 62 : 511-22.

Halstead S. Pathophysiology and pathogenesis of Dengue haemorrhagic fever, Chapter 6, pages 80-103, In : Monograph on Dengue/Dengue Haemorrhagic Fever, WHO, 1993.

Krishnamurthy K, Kasturi TE, Chittipantulu G. Clinical and pathological studies of an outbreak of dengue-like illness in Visakapatannam. *Ind J Med Res* 1965; 53 : 800-12.

Monath TP. Dengue : The risk to developed and developing countries. *Proc Natl Acad Sci USA* 1994; 91 : 2395-400.

Myers RM, Thiruvangadam KV, Krishnaswamy S, Kalyanasundaram V, Jesudass ES. Isolation of dengue type 2 from a child with encephalitis : cause or coincidence. *Ind J Med Res* 1969; 57 : 2030-35.

Nimmannitya, S. Clinical manifestations of Dengue/ Dengue haemorrhagic fever. Chapter 2, page 48-54 in Mongraph on Dengue/Dengue Haemorrhagic Fever. WHO, 1993.

Nimmannitya S, Thisyakorn U, Hemsrichart V. Dengue Haemorrhagic fever with unusual manifestations. *Southeast Asian J Trop Med Public Health* 1988; 18 : 398-406.

Rigau-Perez JG, Ayuso-Lamadrid A, Wolfe D, Reiter P, Kuno G. The Puerto Rico Association of Epidemiologists. *Am J Trop Med Hyg* 1994; 51 : 408-15.

Sakar JK. Calcutta experience and findings in haemorrhagic fever and Chikungunya fever epidemic. *Jpn J Med Sci Biol* 1967; 20 (suppl) : 88-90.

Sarkar JK,Chakravarty SK, Sarkar RK. Sporadic cases of haemorrhage and/or shock during Dengue epidemics. *Trans R Soc Trop Med Hyg* 1972; 66 : 875-7.

Sarkar JK, Modnal A, Chakravarty SK, Chatterjee SN, Pal SR. Isolation of Dengue virus from the blood of a clinical case of encephalitis. *Ind J Med Res* 1969; 57 : 1616-20.

Sever JL. Application of microtechnique to viral serological investigations. *J Immunol* 1962; 88 : 320-29.

Songco RS, Hayes CG, Leus CD, Manaloto COR. Dengue fever/dengue haemorrhagic fever in Filipino-children : Clinical experience during the 1983-1984 epidemic. *Southeast Asian J Trop Med Public Health* 1988; 18 : 284-90.

Wei-Junechen, Kag-pin Hwang, Ay-Huey Fang. Detection of IgM antibodies from cerebrospinal fluid and sera of dengue fever patients. *Southeast Asian J Trop Med Public Health* 1992; 22 : 659-63.