Trop. Med., 36 (3), 93−101, September, 1994

Clinical Manifestations and Treatment of Dengue Hemorrhagic Fever (DHF) by 13 Years Experience, More Than 10,000 Cases

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Abstract: Clinical manifestations and treatment on dengue hemorrhagic fever (DHF) were summarized based on 13 years experience of the first author at the Pediatric Department, Nakorn Phanom Provincial Hospital, Thailand. DHF is an acute febrile disease, characterized by hemoconcentration, thrombocytopenia, and coagulopathy. The underlying mechanism of increased vascular permeability, leads to hemoconcentration, hypovolemic shock, metabolic abnormalities, then disseminated intravascular coagulation (DIC), if not properly treated. Direct cause of death in DHF is either circulatory failure or massive hemorrhage. Therefore, DHF case management should be directed to correct determination of the stage and grade of the disease, and prescribe proper recipes, such as intravenous infusion and blood transfusion.

Key words: Dengue hemorrhagic fever, symptoms, treatment

INTRODUCTION

Dengue virus infection has been prevailing over the world tropics. In the southeast Asia including Thailand, the appearance of severe clinical manifestation of dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) has posed serious problems for medical personnels (Hammon *et al.*, 1960; Halstead, 1966; World Health Organization, 1966). Besides, increasing number of patients and enlarging epidemic areas in recent years have made dengue virus infection as a major health problem in the tropical areas (Halstead, 1992).

Dengue viruses with 4 different serotypes (D1, D2, D3, & D4) belong to the genus flavivirus, family *Flaviviridae* (Westaway *et al.*, 1985; Wengler, 1991), and are transmitted by bite of mosquitoes. The principal vector species is *Aedes aegypti* which breeds in man−made containers in and around human dwellings. The epidemic season corresponds rainy season when sufficient precipitation creates abundant mosquito breeding sites and high humidity pro-

Received for Publication, July 26, 1994
Contribution No. 3025 from the Institute of Tropical Medicine, Nagasaki University

vides favorable condition for the activity of vector mosquitoes. In Thailand, the first outbreak of DHF occurred in Bangkok Metropolitan Area, which was followed by spread into rural areas. Presently, all Provinces in Thailand are endemoepidemic, especially in Northeast and Central Part of Thailand. The epidemiological characteristics of dengue in Nakorn Phanom Province were described in an accompanying paper (Nimnakorn *et al.*, 1994).

In spite of a number of descriptions on the epidemiology and virology of dengue, reports on clinical manifestations and treatment of DHF are relatively limited (Halstead *et al.*, 1964; Nimmannitya *et al.*, 1969; 1987; World Health Organization, 1986; Nimmannitya, 1987, 1993a; b). In this communication, the authors intend to summarize the clinical manifestations and treatment of DHF based on the 13 years experience of the first author at the Pediatric Department, Nakorn Phanom Provincial Hospital, Thailand.

Materials and Methods

Materials and data: These were summarized from clinical records at the Pediatric Department, Nakorn Phanom Provincial Hospital.

Results and Discussions

Clinical manifestation of typical DHF

Age distribution of the hospitalized DHF cases in Nakorn Phanom Provincial Hospital during 1987 to 1992 is shown in Table 1. Similar to other dengue epidemic areas in Thailand, most of the cases were children under 14 years old.

Clinical characteristics of DHF are: (1) acute high fever, (2) hemorrhagic diathesis, (3) hepatomegaly with tenderness, and (4) circulatory disturbances and shock.

The course of the disease can be classified into 3 stages (Fig. 1). Stage 1 (Febrile stage) lasts for 2−7 days, with average of 4 days, and seldom persists more than 14 days. Among more than 10,000 cases observed at the Pediatric Department, Nakorn Phanom Provincial Hospital, only a single case was recorded for each of the febrile period of 2 days, 7 days and 10 days.

Table 1. Age distribution of hospitalized DHF Cases in Nakorn Phanom Provincial Hospital, Thailand, 1987−1992

Age group (years old)	Years					
	1987	1988	1989	1990	1991	1992
0 − 4	486	121	245	167	350	58
5 − 9	750	178	370	198	497	97
10−14	367	113	147	95	262	68
15−	131	16	32	22	28	10
Total	1734	428	794	482	1137	233

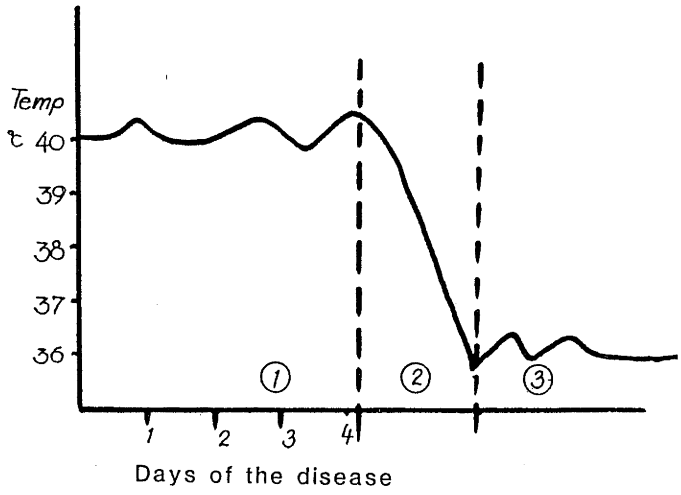


Fig. 1. Stages in DHF
(1) Fever stage, (2) shock stage, (3) recovery stage. Ordinate: body temperature in ℃, abscissa: days of the disease

Stage 2 (shock stage) does not usually last more than 48 hours, but rare cases show more than 72 hr shock period.

Stage 3 (recovery stage) is also the stage of complications

Pathophysiology and pathogenesis of DHF

As described by several literatures (Halstead *et al.*, 1964; Nimmannitya *et al.*, 1969; 1987; World Health Organization, 1986; Nimmannitya, 1987, 1993a), clinical manifestations of DHF are caused by (1) increased vascular permeability, (2) abnormal hemostasis, and (3) bleeding tendency, which could be accompanied by thrombocytopenia, coagulopathy, and disseminated intravascular coagulation (DIC). Increased vascular permeability lead to extravasation of plasma, which can be manifested in pleural effusion (Fig. 2) or ascitic fluid (Fig. 3), and resulting in hypovolemic shock. Clinical classification of DHF into 4 grades has been well-documented (World Health Organization, 1986), therefore will not be reiterated here.

Major manifestations in DHF

Fever is a major manifestation in DHF and persists 2-4 days in 70% of the cases, while the remaining 30% shows 5-7 days of fever. Exceptional cases with shorter or longer febrile period have been described above.

Next major manifestation of DHF is hemorrhagic tendency. Its mildest form can be demonstrated by positive Tourniquet test, and its positive rate along the day of the disease is shown in Table 2. More pronounced hemorrhagic tendency will be seen as spontaneous bleeding such as, petechiae, epistaxis, gum bleeding, ecchymosis, melena, and hematemesis, the frequency of which is shown in Table 3. The petechiae can be observed in anterior chest wall, axillary, and neck. In patients less than 1 year old, the petechiae occurs in the extre-

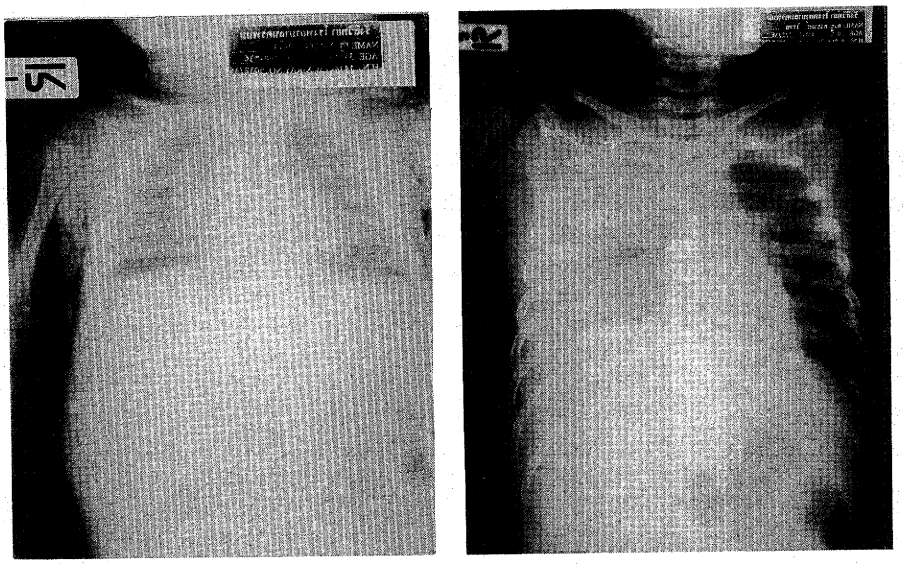
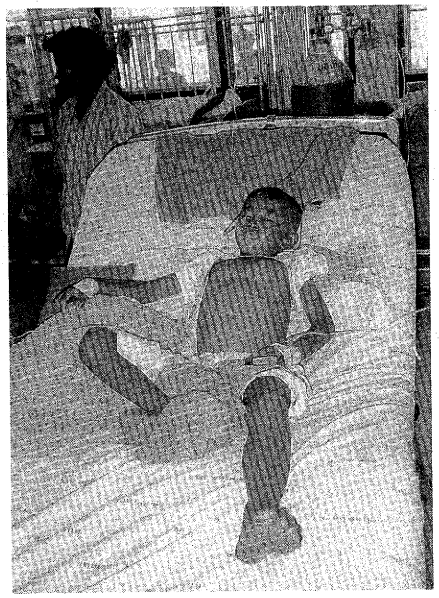


Fig. 2. Chest X ray film of DHF cases with pleural effusion, Nakorn Phanom Provincial Hospitral, Thailand
Panel A: bilateral plueral effusion with cardiomegaly; Panel B: right unilateral pleural effusion,



Fi.g 3. A DHF patient with distended abdomen by ascitic fluid, Nakorn Phanom Provincial Hospital, Thailand

Table 2. Frequency of positive Tourniquet test found in DHF patients on days of the disease

Day of the disease	Percent positive Tourniquet test
1	10%
2	30%
3	90%
4	95%

Remarks: in shock stage, the test turns into negative, then returns to positive in recovery stage

Table 3. Spontaneous bleeding manifestations and their frequency in DHF

Bleeding manifestations	Frequency
Epistaxis	5%
Gum bleeding	3%
Ecchymosis	1%
Melana, hematemesis	10%

mities. Hepatomegaly is another major clinical manifestation in DHF. Although negative on the 1st day of the disease except in the patients less than 1 year old, hepatomegaly can be observed with increasing rate along the days of the disease (20% on the 2nd day, 90% on the 3rd day, and 100% on the 4th day, respectively). Adult patients often shows hepatomegaly on the 4th day of the disease.

Nonspecific symptoms in DHF

Table 4 shows nonspecific symptoms seen in DHF cases and their frequencies. It should be pointed out that significant proportion of DHF cases show injected pharynx or complain abdominal pain and headache, which could lead to mis−diagnosis of respiratory or gastroenteric infections.

Diagnosis on DHF

Diagnosis on DHF depends on above−mentioned clinical manifestations as well as laboratory findings. Demonstration of thrombocytopenia (< 100,000/cm^3) and hemoconcentration (more than 20% increase in the hematocrit) are diagnostic. These clinical and laboratory findings should be supported by the virological confirmation, the principle of which consists of serological test and virus isolation. The former was routinely carried out by the hemagglutination−inhibition (HI) test, but was improved by the introduction of IgM−ELISA. Virus isolation requires several days long and expertise, however, recent introduction of PCR detection of viral genome made the procedure much shorter and simpler.

Table 4. Nonspecific symptoms observed in DHF patients

Symptoms	Frequency	Remarks
Injected pharynx	95%	No sore throat
Vomiting: 1st, 2nd day	20%	
3rd, 4th day	60%	
Abdominal pain	90%	Usually on the 3rd to the 4th day
Headache	50%	
Generalized lymphadenopathy	5%	
Conjunctival injection	3%	
Cough, rhinorrhea	10%	
Maculopapular rash	15%	Recovery phase
Myalgia, arthralgia	12%	In young patients
Diarrhea	10%	Under 1 years old
Splenomegaly	10%	In young patients
Encephalitis	2 cases	Less than 6 months

Case management of DHF

Principle of the case management for DHF depends on the identification of the stage and the grade of the disease.

The outpatients in the 1st stage of fever should be given (1) oral rehydration (ORS) to correct dehydration, (2) anticonvulsive drugs in the case of convulsions, (3) antipyretic (preferably acetaminophen), and (4) 5% dextrose: physiological saline (1:1 mixture) if necessary.

The DHF grade I and II patients in hemorrhagic and shock stage in the outpatients should be given symptomatic recipes such as ORS and should be followed up every day. In the case of inpatients, intravenous infusion should be given, with following recipes; isotonic solutions (5% dextrose−physiological saline 1:1 mixture, or 5% Ringer−lactose), 7−10 ml/kg body weight/hr. Vital signs should be examined every hour and hematocrit should be examined every 4 hr to monitor hemoconcentration and impeding shock.

The grade III and IV inpatients with shock should be given intravenous infusion depending on the clinical manifestations. The shock management should be aimed to correct major pathophysiological changes. It should be reminded that DSS is hypovolemic shock due to massive leakage of plasma which continues for 24−48 hours in most of the cases. Also, it is important to remember that hyponatremia and metabolic acidosis are common, particularly in severe cases. There is a high potentiality to develop DIC which can lead to fatal massive hemorrhage, because stagnant acidemic blood can precipitate DIC.

Along the above−mentioned principles, the first choice in the DHF treatment is the rapid replacement of existing plasma loss. This can be achieved by intravenous infusion with 5% dextrose−physiological saline, dextrose−Ringer−lactate, 10−20ml/kg body weight/hr. In the case of profound shock, colloidal solution (dextran 40, or plasma) should be given at doses of 20ml/kg body weight. The continuation of the replacement therapy depends on the

hematocrit values; reducing the speed from 20 to 15, 10, and 5ml/kg/hr when hematocrit is decreasing; or other way around when hematocrit shows increasing trend. It is important to provide minimum essential intravenous infusion to maintain adequate tissue perfusion. The case which shows worsened vital signs in spite of decreasing hematocrit should be suspected of massive (internal) hemorrhage and transfusion with fresh whole blood should be indicated.

Correction of electrolytes and acid−base imbalance is also important. Particular attention should be paid to correct hyponatremia, water intoxication which can lead to convulsion, metabolic acidosis, which predispose DIC.

Blood transfusion (fresh whole blood 10−20ml/kg) should be prescribed for the cases with significant bleeding, particularly internal bleeding. Such cases show decreased hematocrit, reduced blood pressure and weak pulse. For very severe cases, fresh frozen plasma, concentrated platelet, or cryoprecipitate (Factor Ⅷ) should be given.

Other supportive cares, oxygen therapy and calm down therapy with chloral hydrate (15−50㎎/kg/dose; maximum 1gm) should be prescribed when necessary.

Monitoring patients' conditions

This should be carried out by frequent recording vital signs (blood pressure and pulse every 30 min during shock, and every hr after the shock). Hematocrit should be measured every 1−3 hr for the 1st 6 hrs, then every 4−6 hrs. Fluid balance sheet with type and rate of intravenous infusion intake and urine output should be prepared.

In the case of prolonged shock, central venous pressure (CVP) should be measured. When CVP is greater than 15㎜ H_2O, Furosamide 1㎎/kg should be given intravenously. The patients showing pulmonary edema should be treated with blood letting.

Treatment in the recovery stage

Following complications can occur in this stage: (1) overloaded intravenous infusion can cause pulmonary edema, which should be treated by Furosamide or blood letting; (2) pneumonia particularly in the case of massive pleural effusion, (3) septicemia due to prolonged shock, urinary catheter, or central venous line, (4) intracerebral hemorrhage as a result of DIC, (5) hyponatremia, and (6) hypocalcemia.

Unusual manifestation of DHF

Followings unusual manifestations can be seen in DHF:

(1) In the infants less than 1 year old

The case showed high fever, convulsion, diarrhea, hepatomegaly on the 1st day, but plasma leakage was not remarkable, petechiae at forearms and legs, bleeding is rare but once occurred could be massive and fatal.

(2) Children between 1.5−3 years old

Approximately 10% of the cases show pneumonia until the 3rd or 4th day of the fever before DHF symptoms can be detectable.

(3) Rare case with viral encephalitic syndrome

High fever is accompanied by severe headache, vomiting, and stiff neck. Cerebrospinal fluid shows characteristics of viral encephalitis. Such symptoms lasts until the 3rd to 4th day of the fever before DHF symptoms were observed. In relation to this unusual manifestation,

dengue encephalopathy was documented with elevated serum transaminases and symptoms similar to Reye's syndrome and hepatic encephalopathy. The best recipes is early exchange transfusion.

(4) In adult

Tourniquet test remains negative during the early days, then turns into positive on the 3rd or 4th day. Hepatomegaly is always positive on the 4th day of the fever. Plasma leakage is not remarkable. Bleeding is rare, but once occurs may be massive and fatal.

ACKNOWLEDGMENTS

This work was supported by the Grant-in-Aid for International Research, Project No. 04041082, from the Ministry of Education, Science and Culture of Japan, in the fiscal years of 1992 and 1993.

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