ORIGINAL ARTICLE

Clinical Observations on Hospitalized Patients With Virologically Confirmed Dengue Hemorrhagic Fever In Jakarta, Indonesia 1975 - 1983

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Abstract

From 1975 to 1983, we clinically studied 1,451 serologically confirmed cases of dengue hemorrhagic fever in Jakarta, Indonesia. Of these cases, 142 were virologically confirmed. Considering these 142 cases, dengue type 3 was the predominant virus type isolated, but all 4 dengue virus serotypes were found. Dengue type 3 was the serotype most frequently associated with severe infections. Whereas 67 (47%) of the 142 patients had a dengue type 3 infection, this serotype was associated with 27 of the 34 fatal cases (79%). Dengue type 3 was found in 42 of the 75 cases with shock (56%), 31 of the 42 cases with encephalopathy (74%), and 19 of the 30 cases with gastrointestinal bleeding (63%).

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Of the patients infected with dengue type 3, 19 (29%), and 13 of the 27 fatal case (48%) had gastrointestinal bleeding. In 6 of 27 (23%) fatal dengue type infections, this bleeding was severe enough to cause shock and death. Among nonspecific signs and symptoms associated with virologically confirmed dengue infections, there was a statistically significant correlation ($p > 0.01$) between abdominal pain and severe gastrointestinal bleeding (hematemesis, melena) in patients with DHF Grades III and IV. None of the patients with milder DHF (Grades I and II) and abdominal pain had severe bleeding. Another unusual abdominal finding was that hepatomegaly was noted in only 50% (72/142) of patients studied.

Encephalopathy was present in 42 (62.6%) of our virologically confirmed dengue infections. In 22 of the 34 fatal cases (65%), however, one or more signs of encephalopathy (primarily altered level of consciousness or convulsions) were noted. Two deaths were associated with signs and symptoms of viral encephalitis. Dengue type 3 was isolated from the serum of both patients.

These data show that in Jakarta, dengue type 3 was the predominant virus isolated, and was responsible for the highest percentage of severe and fatal infections. Abdominal pain in DHF Grades III and IV, but not in Grades I and II, was associated with severe gastrointestinal bleeding. Hepatomegaly was found less commonly then expected. Encephalitic symptoms were noted in a surprisingly large group of patients.

Introduction

Prior to WW II. Dutch investigators in Indonesia clinically recognized classical dengue fever (DF) and showed Aedes aegypti to be a vector (Snijders et al., 1931). In 1969, there was the first report of dengue with accompanying hemorrhage and shock (Kho et al., 1969; Partana et al., 1970). Not until the early 1970's was dengue virus isolated (Van Peenen et al., 1974). In Thailand, by contrast, dengue fever associated with hemorrhage and/or shock had already been extensively studied by this time.

The spectrum of disease associated with dengue infection in humans ranges from inapparent or mild febrile illness, to severe hemorrhagic disease with shock and death. It is often difficult to draw a sharp line of clinical distinction within broad spectrum of manifestations used to classify dengue disease into classical dengue fever or dengue hemorrhagic fever (DHF) (Halstead, 1978).

Strict criteria for the clinical diagnosis of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) have been outlined by the World Health Organization (WHO, 1975). These guidelines are used by most practicing physicians in Asia. In our experience in Indonesia, strict adherance to these criteria resulted in over 80% correct diagnosis of cases as serologically confirmed by HI test. We believe, however, that many other dengue infections were undiagnosed by these criteria. Most of these undiagnosed dengue patients have milder froms of the disease, but several have had severe or even fatal infection which do not conform to the classical picture described by the WHO.

The development of the mosquito inoculation technique provided a highly sensitive

method for isolation of dengue viruses (Rosen and Gubler, 1974). Using this technique in Jakarta, Indonesia, during the period from September 1975 through May 1983, we confirmed 142 dengue infections by virus isolation. This report describes the clinical aspects to these 142 virologically confirmed hospitalized dengue hemorrhagic fever patients.

Material and Methods

All patients were admitted to the Department of Child Health at the University of Indonesia hospital, Dr. Ciptomangunkusumo General Hospital, in Jakarta. Criteria for the clinical diagnosis of DHF followed the procedures outlined in the WHO's Technical Guide for Diagnosis, Treatment, and Control of DHF. Severity of illness was graded according to the following criteria. Classical dengue fever (DF) Grade accompanied by a variety of nonspecific constitutional symptoms, with or without a positive tourniquet test; dengue hemorrhagic fever (DHF) Grade II - like DF, but accompanied by skin hemorrhage or other bleeding such as epistaxis, gum bleeding, or gastrointestinal hemorrhage; DHF Grade III - circulatory failure manifest by a rapid, weak pulse, narrowing of pulse pressure (< 20 mmHg), or hypotension (systolic pressure 80 mmHg); and DHF Grade IV - moribund patients with undetectable blood pressure and pulse.

Detailed clinical records were kept on each patient. These included name, address, age, sex, date of admission, date of onset of illness, and clinical history. On admission, all patients were thoroughly examined for signs and symptoms suggestive of DHF. Examination included vital signs, search for petechiae or other skin hemorrhages, and examination for signs of circulatory failure and presence of pleural effusions. Routine hemogram, urinalysis, bleeding time, whole blood clotting time (recalcification time) and tourniquet test were performed on all patients. In some patients, fibrinogen levels, fibrin degradation products, and partial thromboplastin time were determined. In patients with suspected disseminated intravascular coagulation, a careful examination of blood smears was made for the presence of fragmented and distorted red blood cells. The clinical course of each patient was monitored continuously. Serial determinations of the hemoglobin, hematocrit and platelets were daily made, or frequently as every 4 hours in severely ill patients.

Laboratory Diagnosis

Blood samples were taken as soon as possible after admission. The blood was allowed to clot for 4-6 hours at room (ambient) temperature. Clotted blood was centrifuged, and the serum was transferred to 3 ml screw cap vials and stored in an ultra-low freezer (less than 60^0 C).

Ten-fold serial dilution of sera were tested for dengue antibodies by the microtiter hemagglutination-inhibition (HI) test using 8 units of dengue type 1 or 2 antigen (Clarke and Casals, 1958). Paired acute and convalescent sera, if available, were always tested together.

Virus isolation was attempted only for patients showing four-fold or greater HI titer increases between acute and convalescent sera, and also for all fatal cases. Viral

isolation was not attempted for patients with presumptive recent infection defined as HI antibody 1/1280 or greater in the acute specimen, without a four-fold or greater antibody rise in the convalescent specimen. All attempts at virus isolation were by the mosquito inoculation technique (Gubler et al., 1979). Intrathoracic inoculations into female Aedes aegypti or A. al bopictus mosquitoes were done with acute sera. Sera was inoculated both undiluted and at a dilution of 1 : 5 in phosphate buffered saline (PBS) with 5% heat-inactivated calf serum. Tissue biopsy specimens from fatal cases, when available were similarly inoculated. Inoculated mosquitoes were held at 30-32^{0}C for at least 14 days and then killed by freezing. The direct fluorescent antibody test was used to determine the presence or absence of viral antigen in the head and salivary glands (Kuberski and Rosen, 1977; Gubler et al., 1979).

Dengue virus isolates were serotyped by the complement fixation test using antigen in male mosquitoes (Kuberski and Rosen, 1977).

Clinical Management

Hematocrit determinations and platelet counts were performed daily, from the third day of illness until the temperature became normal, and for 1 or 2 days thereafter. These results were used to determine the need for hospitalization, fluid therapy, or both.

DHF Without Shock

Oral fluid intake was encouraged, preferably using electrolyte solutions or fruit juice. Antipyretic drugs (aspirin or acetaminophen) were used for very few patients during the febrile period. Febrile convulsions were managed with phenobarbital. Parenteral fluid therapy was given to prevent dehydration and acidosis, or when laboratory examination showed signs of hemoconcentration defined as a rising hematocrit upon serial observations or an admission hematocrit above 45%.

DHF with shock

The management of DHF with shock primarily consisted of fluid replacement with Ringer's lactate solution at a rate of 20 ml/kg/hr. This was given by intravenous push if shock was profound. When shock persisted more than one hour, plasma or a plasma expander was also given at a rate of 10 to 20 ml/hour.

After initial fluid resuscitation, the infusion was slowed to 10 ml/kg/hr. Capillary tube hematocrit determinations were used to assess hemoconcentration. Patients were clinically observed for the development of hypervolemia, pulmonary edema or congestive heart failure. Abnormal serum electrolytes and/or acid-base disturbances were promptly corrected. Whole blood was given only where there was massive uncontrolled bleeding. Fresh frozen plasma, and concentrated platelets were given in some cases.

Results

General Clinical Findings

From September 1975 to May 1983, 1,451 serologically confirmed cases of DHF were treated at our hospital. Most of these patients had DHF Grade II, as defined by the WHO. The largest group of patients (47%) were from 5 to 9 years of age. The overall male to female ratio was 1 : 1.4 or 42% and 58% respectively.

The clinical signs and symptoms associated with dengue infection in Jakarta are shown in Table 1. With only a few exceptions, the results are similar to those reported from other countries in Southeast Asia. In addition to symptoms of fever (100%) and hepatomegaly (51%), most patients had various nonspecific constitutional symptoms. Of these, abdominal pain (38%) and vomiting (29%) were the most common. Hemorrhagic manifestations are shown in Table 2. Approximately 19% of our patients suffered from either hematemesis or melena, or both. Eleven of 286 patients (4%) with hematemesis and 8 of 274 patients (3%) with melena never had shock, neither on admission nor during their hospital stay.

Table 1. *Signs and symptoms associated with 1,451 serologically confirmed cases of dengue hemorrhagic fever, Jakarta, Indonesia 1975 -1983.*

Sign or symptom	Number of Patients	%
Hepatomegaly	744	51.3
Abdominal pain	551	37.9
Vomiting	420	28.9
Constipation	162	11.2
Decreased level of consciousness	133	9.2
Convulsion	114	7.8
Headache	103	7.0
Cough	99	6.8
Conjunctivitis	89	6.1
Diarrhea	70	4.8
Joint pain	57	3.9
Backache	49	3.4
Rhinitis	42	2.9
Sorethroat	38	2.6
Myalgia	38	2.6
Lymphadenopathy	32	2.2
Splenomegaly	30	2.1
Pruritis	28	1.9
Parasthesias	26	1.8

Of the 1,451 serologically confirmed cases of DHF, 142 had virus isolated. The total number of virologically confirmed dengue patients, including fatal cases, are shown in Table 3 by serotype for the 1975-1983 study period. Dengue 3 was the predominant virus isolated in both groups. However, whereas less than one-half of all the patients (47%) had a dengue type 3 infection, over three-fourths of the fatal cases (79%) were associated with this serotype.

The age distribution of virologically confirmed dengue cases was similar to that for all confirmed dengue infections (Table 4). The majority of patients (56% of all cases and 59% of fatal cases) were in the 5-9 years age group. The male to female ratio for all dengue infections was 1:1.4 whereas the male to female ratio for fatal infections was 1.3:1.

The duration of illness before admission to the hospital ranged from 2 to 7 days, with an average of 4 days. In fatal cases, the time between admission and death ranged from 2 hours to 5 days with an average of 36 hours. These times did not differ between serotypes.

Table 2. *Hemorrhagic manifestation associated with 1,45 serologically confirmed cases of dengue hemorrhagic fever, Jakarta, Indonesia 1975 - 1983.*

Hemorrhagic manifestation	Number of Patients	Percent
Positive tourniquet test	818	56.4
Petechiae	1140	78.6
Ecchymoses	113	7.8
Epistaxis	274	18.9
Hematemesis	286	19.7
Melena	274	18.9
Gum bleeding	61	4.2
Hematuria	16	1.1

Table 3. *Serotypes of virologically confirmed dengue infection, Jakarta, Indonesia 1975 - 1983.*

	All infections		Fatal infections		Percent
Dengue serotype	No.	%	No	%	Mortality
Den -1	22	15.5	1	2.9	5
Den -2	50	35.2	6	17.7	12
Den -3	67	47.2	27	79.4	41
Den -4	3	2.1	0	0	0
TOTAL	142	100.0	34	100.0	24

Nonspecific signs and symptoms

The nonspecific constitutional signs and symptoms associated with virologically confirmed dengue infection in Jakarta, when separated by virus serotype, revealed no striking differences in the clinical picture among the four dengue serotypes (Table 5).

Table 4. *Age and sex distribution of virologically confirmed dengue infections, Jakarta, Indonesia 1975 - 1983.*

	Females		Males		Total	
Age group (yrs)	fatal infections	all infections	fatal infections	all infections	fatal infections	all infections
0 - 4	6	21	7	14	13	35
5 - 9	9	47	11	33	20	80
10 - 14	0	14	1	12	1	26
15	0	1	0	0	0	1
TOTAL	15	83	19	59	34	142

Table 5. *Frequency of nonspecific constitutional signs and symptoms associated with 142 virologically confirmed dengue infections, by serotype, Jakarta, Indonesia 1975 - 1983*

Signs/symptoms	Dengue serotype Den-1 (N = 22)*	Den-2 (N = 50)*	Den-3 (N = 67)*	Den-4 (N = 3)	Total (N = 142)*	%
Hepatomegaly	12	26	33	1	72	50.7
Abdominal pain	8	19	26	1	54	38.0
Vomiting	6	14	19	0	39	27.5
Constipation	3	6	7	1	17	11.9
Headache	2	3	5	1	11	7.7
Cough	2	4	5	0	11	77
TOTAL	22	50	67	3	142	100%

* N = number of cases in each group.

Table 6. *Frequency of encephalopathic symptoms associated with virologically confirmed dengue infection, by serotype, Jakarta, Indonesia 1975 - 1983.*

Encephalopathic Symptoms	All infections Den-1 (22)*	Den-2 (50)*	Den-3 (67)*	Den-4 (3)*	TOTAL	%
Coma/semicoma	3	6	22	1	32	22.5
Convulsions	0	4	14	0	18	12.7
Paresis	0	0	3	0	3	2.1
Stiff neck	0	0	1	0	1	0.7
Number of patients with one or more encephalopathic symptom **	3	7	31	1	42	29.6%

* Total number of patients in these isolated groups.

** Nonadditive because some patients had more than one encephalopathic symptoms.

Encephalopathic Symptoms	Fatal infections Den-1 (1)*	Den-2 (6)*	Den-3 (27)*	Den-4 (0)*	TOTAL	%
Coma/semicoma	1	2	19	0	22	64.7
Convulsions	0	1	12	0	13	38.2
Paresis	0	0	3	0	3	8.8
Stiff neck	0	0	1	0	1	2.9
Number of patients with one or more encephalopathic symptom**	1	2	19	0	22	64.7%

Table 7. *Frequency of hemorrhagic manifestations and shock associated with virologically confirmed dengue infection, by serotype, Jakarta, Indonesia 1975 - 1983.*

Hemorrhagic manifetation	All infections Den-1 (22)*	Den-2 (50)*	Den-3 (67)*	Den-4 (3)*	TOTAL	%
Petechiae	17	36	43	2	98	69.1
Positive Tourniquet test	12	28	38	2	80	56.3
Shock	10	22	42	1	75	52.8
Hematemesis/ melena	3	7	19	1	30	21.1
Epistaxis	1	8	11	0	20	14.1
Ecchymoses	1	4	5	0	10	7.1
Gum bleeding	0	1	3	0	4	2.8
Hematuria	0	1	0	0	1	0.7

* Total number of patients in these isolated groups.

Hemorrhagic manifestation	Fatal infections Den-1 (1)*	Den-2 (6)*	Den-3 (27)*	Den-4 (0)*	TOTAL	%
Petechiae	1	4	19	0	24	70.6
Positive Tourniquet test	1	3	12	0	16	47.1
Shock	1	6	19	0	26	76.5
Hematemesis/ melena	0	3	13	0	16	47.1
Epistaxis	0	0	6	0	6	17.6
Ecchymoses	0	1	3	0	4	11.8
Gum bleeding	0	1	2	0	3	8.8
Hematuria	0	0	0	0	0	0

Encephalitic symptoms

The encephalopathic symptoms associated with virologically confirmed dengue infections in Jakarta, separated by virus serotype, are shown in Table 6. A surprisingly high number of patients had symptoms of encephalopathy. Sixty-five percent of virologically confirmed fatal dengue cases had one or more of the symptoms listed. The most common encephalopathic symptoms were altered level of consciousness and convulsions. Paresis and stiff neck were noted only in three patients infected with dengue type 3. Before death, two of the patients with paresis developed spastic tetraparesis, and the other patient developed spastic hemiparesis. All cerebrospinal examinations showed normal protein, glucose, cell count and differential leucocyte count.

Hemorrhagic manifestation

The hemorrhagic manifestation associated with virologically confirmed dengue infections are shown in Table 7. Forty-eight percent of fatal cases had gastrointestinal (GI) hemorrhage, many severe enough to cause death. Signs of shock were observed in 26 of 34 fatal cases (77%), many of these patients had profound shock.

Some serotype differences were apparent when looking at hemorrhagic manifestations and shock. Considering fatal cases, of the 27 patients with dengue type 3 infection, 48% (13/27) had GI bleeding and 71% (19/27) had shock. For the fatal cases of dengue type 2,50% (3/6) had GI bleeding and all (6/6) had shock. There was 1 case of fatal dengue type 1 infection. This patient had shock without GI bleeding.

Hemorrhagic manifestation were associated with serotype differences in virologically confirmed dengue infections. Twenty-nine percent of patients infected with dengue type 3 had gastrointestinal bleeding, compared to 14% of those with dengue type 2, and 13% of those with dengue type 1 infections. This difference was significant at the ($p = 0.05$) level.

Table 8. *Features of fatal cases with proven dengue infections, by serotype, Jakarta, Indonesia 1975 - 1983.*

Salient features seen	Dengue serotype Den-1	Den-2	Den-3	Den-4	Total	%
Profound shock with hemoconcentration	1	6	19	0	26	76.5
Severe bleeding followed by shock	0	0	6	0	6	17.6
Encephalopathy	0	0	2	0	2	5.9
TOTAL	1	6	27	0	34	

Analysis of the fatal cases

Shock was present in 77% of fatal cases (Table 8). Some of our patients with gastrointestinal bleeding did not go into shock either on or after admission to the hospital. In six of the fatal cases, gastrointestinal hemorrhage was a very grave and life-threatening problem. The cause of death in these patients was considered to be shock due to blood loss from massive gastrointestinal hemorrhage. The exact cause of bleeding could not be determined in all cases. Screening laboratory tests for coagulation disorders performed on these 6 patients showed depleted fibrinogen, thrombocytopenia, prolonged bleeding time and prolonged partial thromboplastin time. Three of the patients had prolonged prothrombin time. All deaths associated with severe hemorrhage were in patients with dengue type 3 infections. Finally, two deaths occurred in patients with signs and symptoms of viral encephalitis. Dengue 3 virus was isolated from the serum of both patients.

Discussion

The basic principle in the management of DHF is correction of plasma leakage, the major pathophysiologic change, by volume replacement. Hemoconcentration reflects the degree of plasma leakage and usually precedes the characteristic changes in vital signs. A fall in the platelet count usually precedes the hematocrit rise. By performing hematocrit, hemoglobin and platelet studies periodically, and by keeping fluid balance sheets, we have steadily reduced the case-fatality rate of dengue shock syndrome, without severe gastrointestinal hemorrhage, to its nadir of 4.18% in 1982.

Presumably due to plasma leakage, children often went in and out of shock for 48 hours, even though fluid replacement was continued and the patient showed an improvement in vital signs and a declining hematocrit. Microhematocrit determination was a simple and reliable index for estimating plasma leakage. A rapid infusion of fluid was helpful if the clinical condition deteriorated.

Recovery from shock usually occurred within 24 to 48 hours. During the recovery phase, fluid from the extravascular space returned into the vascular space, causing a rise in the central venous pressure during this phase. At this time, further intravenous fluid should be administered with care to avoid hypervolemia, pulmonary oedema or heart failure. A drop in hematocrit at this stage must not be mistaken for a sign of internal hemorrhage. A strong pulse, rising blood pressure and a diuresis are good clinical signs which are often found during this reabsorption phase.

In many cases, we noted the clinical findings in our patients to vary from the currently accepted WHO diagnostic criteria of DHF. A clinical symptoms not included in the DHF diagnostic criteria is abdominal pain. This was found in 551 of our patients (37.9%) (Table 1) Although non-specific, this complaint compeled special attention since it was associated with clinically more severe disease. In the case of Grades III

and IV DHF patients, there was a statistically significant correlation between the occurrence of gastrointestinal (GI) bleeding, characterized by hematemesis or melena, and abdominal pain (Sumarmo, 1983). Fifteen percent of our DHF Grade III patients with abdominal pain had hematemesis and 21% had melena. Of DHF Grade IV with abdominal pain 22% had hematemesis and 19% had melena. On the other hand, none of our DHF Grade II patients with abdominal pain had hematemesis or melena.

According to WHO criteria, hepatomegaly is one of the four cardinal signs of DHF. In Children's Hospital in Thailand, between 80%-90% of confirmed patients had hepatomegaly (Nimmannitya and Mansuwan, 1966; Nimmannitya et al., 1969). A study done in Jakarta by one of us (Sumarmo) in 1973, showed that 81% of cofirmed patiens had hepatomegaly. The predominant serotype during that time was believed to have been dengue 2. In our present study, 51% of the patients had hepatomegaly. The predominant serotype during this time was dengue 3. In virologically cofirmed DHF cases, there were no striking differences among the four dengue serotypes in the percentage of patients with hepatomegaly (Table 5). In late 1976, during an outbreak of DHF in a rural area in Central Java, caused primarily by dengue 3 (60% of 69 isolates), only 19% of the patients had hepatomegaly (Gubler et al., 1981). A review of the literature shows that rates of hepatomegaly vary considerably from area to area (Chan et al., 1967; Venzon et al., 1972). It appears from the above mentioned data that hepatomegaly may not be a consistent clinical sign associated with dengue hemorrhagic fever. Only in Thailand is rate of hepatomegaly consistently high. Closer studies of liver involvement should be done especially during epidemics of DHF in different regions and caused by different virus types. The extent of liver involvement may possibly be associated with the strain or serotype of virus, or even with a predisposition in specific human populations. In our present study, we found that the frequency of hepatomegaly increased with the severity of the disease. Forty percent of our patients with DHF Grade II had hepatomegaly, 58% with Grade III, and 65% with Grade IV, respectively.

Bleeding manifestations varied from mild manifestations, such as epistaxis and gum bleeding, to severe and fatal gastrointestinal hemorrhage. The percentage of patients with a positive tourniquet test was low (56%) (Tables 2 and 7). This is possibly because negative or mildly positive tourniquet test, during the phases of shock or preshock on admission, were generally not repeated during hospitalization. Epistaxis and gum bleeding were usually not serious. Thirteen percent of the patients with epistaxis had a previous history of epistaxis accompanying fever.

We noted an unusual sex ratio in patients with fatal DHF. In Thailand, the male-to-female ratio for all DHF cases was 1:1.4 and in unconfirmed fatal cases it was 1:1.2 (Nimmannitya et al., 1969; Nisalak et al., 1970). These ratios are similar to our rates observed for all confirmed dengue infections (1:1.4) (Table 4). These rates are reversed for patients with virologically confirmed fatal dengue infections (1.3:1). In the Philippines, the fatality rate in unconfirmed cases was also slightly higher in males (1.1:1) (Dizon, 1978).

Forty-two of our 142 virologically confirmed dengue infections had one or more encephalitic signs (Table 6). The most common signs were coma and convulsions. Fever and convulsions were common findings in children in our hospital. In most instances, the cause of the seizure could not

be established, and these children were catagorized as having "febrile convulsions". More than 30% of all our confirmed dengue infections and fatal cases were children below 5 years of age, a group where febrile convulsions are common.

There are several reports from Southeast Asian countries associating dengue hemorrhagic fever with encephalopathy (Sanguansermsri et al., 1976; Sumarmo et al., 1978) and encephalitis. Encephalitic signs, other than convulsions, however, have not been routinely reported in clinical descriptions of DHF. A recent study from Thailand reported 18 cases of DHF with jaundice and encephalopathy (Ninunannitya et al., (1983). In these cases, associated conditions most likely contributing these findings included: prolonged shock with metabolic acidosis and severe DIC, hyponatremia, marked liver dysfunction, severe liver involvement, acute hepatic failure, fatty change of the liver, cerebral edema, and drug intoxication in small infants. These data suggest that dengue should be included in the differential diagnosis of children clinically diagnosed as viral encephalitis.

Thrombocytopenia (less than 100,000/ul) is an important laboratory finding used to differentiate dengue fever from DHF. While the majority of our patients fit the WHO criteria with regard to thrombocytopenia, there were some who did not. Platelet counts of less than 100,000/ul were found in 83.1% of the 142 virologically confirmed DHF patients studied. In DHF patients without shock, 14 out of 67 patients (21%) had platelet counts more than 100,000/ul. Of those with shock, 10 patients (13%) had platelet counts more than 100,000/ul. Of these 10 cases, the majority (8) were in mild shock and 2 patients had profound shock and platelet counts which were more than 100,000/ul. Since thrombocytopenia is used by most physicians as one of the diagnostic criteria of DHF, normal thrombocyte counts often prompt the physician to change the diagnosis. If these patients with higher thrombocyte counts are not monitored closely, preventable deaths may occur.

Profound shock was present in the majority of fatal cases. Six of our cases (17.65%) died as a result of severe gastrointestinal hemorrhage (Table 8). These patients did not have hemoconcentration before death, and shock was determined to be the result of blood loss. The exact cause of bleeding could not be determined in all cases. In two cases, however, there was evidence of disseminated intravascular coagulation (DIC) with prolongation of activated partial thromboplastin time (aPTT) and prothrombin time (PT), decreased platelet counts and fibrinogen, and fragmented and distorted red blood cells on blood smears. While DIC is considered by most investigators to be a secondary phenomenon, we feel it was a contributing factor to these patients' hemorrhage.

The most difficult situation and therapeutic challenges concern the management of patients with massive bleeding as a result of DIC. A recent study by Funahara et al. (1983) revealed that an intensive fibrinolytic process, characterized by decreace of α_2 plasmin inhibitor activity, occurred in DHF patients at time of admission. These investigators concluded that the noted decrease of the activity of antithrombin III, a heparin co- factor, would lead to a lesser response when heparin is given to DHF patients with gastrointestinal hemorrhage.

Dengue 3 infection was associated with the majority of fatal cases with confirmed dengue infection (Table 5). Moreover, all fatal cases with massive gastrointestinal hemorrhage, as well as both of the patients with symptoms of viral encephalitis, were infected with dengue type 3 virus (Table 8). Other serotypes, however, were also asso-

ciated with fatal infection. Eighteen percent of the fatalities were associated with dengue type 2 and 3% with dengue type 1. There seemed to be a strong relationship between dengue type 3 virus and the severity of disease. Overall, 19 of 30 cases (63%) with gastrointestinal bleeding, 31 of 42 virologically confirmed cases with encephalopathy (74%), and 42 of 75 cases with shock (56%) were associated with type 3 dengue virus (Table 6 and 7). Whether this represents a true difference in the virulence of dengue type 3 infections seen in Jakarta, or merely a higher transmission rate for this virus is not known. Accurate data on the epidemiology of dengue viruses in the Jakarta population is lacking. This will be a critical factor in answering this important question.

In summary, in the 142 virologically confirmed cases studied, we noted several unique aspects of dengue hemorrhagic fever in our Jakarta population. First, dengue type 3 infection accounted for 79.4% (27/34) of fatalities, 56% (42/75) of the cases of shock, and 60% (19/30) of the cases of severe GI bleeding. Second, encephalitic symptoms (seizures, altered mental status, abnormal neurologic exam) were noted in 30% (42/142) of all cases, 65% (22/34) of fatal cases, and 74% (31/42) of patients with dengue type 3. Third, hepatomegaly was noted in only 50% (72/142) of our cases. Last, abdominal pain in patients with DHF Grade III and IV correlated with severe GI bleeding during the course of the disease. There were 21% patients with DHF Grade III or IV who had abdominal pain and severe GI bleeding, whereas none of the 25 patients with DHF Grade II and abdominal pain developed severe GI bleeding. In patients with DHF Grades III and IV, we found abdominal pain to be a clinically useful sign when evaluating these patients for the potential serious complication of gastrointestinal hemorrhage.

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