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COMPARISON OF CLINICAL FEATURES AND HEMATOLOGIC ABNORMALITIES BETWEEN DENGUE FEVER AND DENGUE HEMORRHAGIC FEVER AMONG CHILDREN IN THE PHILIPPINES

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Abstract. To demonstrate the differences of clinical features and hematologic abnormalities between dengue fever (DF) and dengue hemorrhagic fever (DHF), 359 pediatric patients admitted St. Luke's Medical Center in Quezon City, between 1999 and 2001 in Metro Manila, and adjoining provinces the Philippines, with a laboratory-confirmed dengue virus infection were evaluated. One third of the patients had DHF, and most of these patients were without shock. Restlessness, epistaxis, and abdominal pain were more associated with DHF. The platelet count was significantly lower in the DHF group than in the DF group before and after defervescence. In the DHF patients, the hematocrit was significantly increased before defervescence, and decreased the day after due to administration of intravenous fluid. Coagulation abnormalities associated with most DHF patients were thrombocytopenia and an increased fibrinolysis, but not disseminated intravascular coagulation. We present recent data on readily obtained clinical and laboratory data that can be used for early diagnosis and consequently earlier appropriate treatment of dengue virus infections.

INTRODUCTION

Dengue virus, a mosquito-borne human viral pathogen, has recently become a major public health concern particularly in tropical and subtropical countries, predominantly in urban and periurban areas. The geographic distribution of dengue viruses has greatly expanded and the number of cases has dramatically increased during the past three decades.[1] Two and a half billion people in more than one hundred countries are at risk of infection, with an estimated 50 million infections per year.[2] Since the first report of an outbreak of dengue hemorrhagic fever (DHF) in the Philippines in 1956,[3] dengue epidemics have occurred in the country at approximately five-year-intervals.[4,5] Previous reports have also characterized the view that dengue has been hyperendemic and a leading cause of childhood hospitalization during the 1980s in the Philippines.[6,7] Although dengue fever (DF) is a self-limited febrile illness, DHF is characterized by prominent hemorrhagic manifestations with thrombocytopenia, an increased vascular permeability, and is associated with a high mortality rate.[8]

An early clinical diagnosis of DHF is difficult because the World Health Organization (WHO) clinical and laboratory criteria for DHF may be manifested only in the late phase of acute illness.[9] Although previous reports have characterized the clinical features of DF and DHF,[9,10] differences in these features, including hematologic abnormalities between the two conditions, are poorly defined in hospitalized pediatric patients under appropriate treatment according to WHO guidelines. Therefore, this prospective study was undertaken to determine the differences in the clinical features and hematologic abnormalities between DF and DHF among hospitalized pediatric patients in Metro Manila, the Philippines from 1999 to 2001.

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PATIENTS AND METHODS

Patients and study design. All patients admitted at the St. Luke's Medical Center in Quezon City, the Philippines between January 1999 and December 2001 who satisfied the following criteria were enrolled in the study: 1) age between 2 and 17 years, 2) fever for $\leq$ 5 days, 3) temperature of at least 37.8°C, and 4) no apparent focus of infection. Informed consent was obtained from the patient's legal guardian.

Medical histories were obtained and physical examinations were conducted by one of the pediatrician investigators (CCC and MTDDC.) on recruitment and on a daily basis until discharge. The clinical symptoms and signs, including nutritional status, were recorded on case record forms. The day of defervescence was defined as day 0.[11] The days before and after defervescence were reported consecutively as follows: –2, –1, 0, +1, +2, etc.

Blood was drawn on the first, third, fourth, and seventh days of the hospital stay. Serial complete blood counts were obtained until the day of discharge. Diagnostic tests for dengue included reverse transcriptase–polymerase chain reaction (RT-PCR) for flaviviruses and determination of IgM antibody to dengue viruses by an enzyme-linked immunosorbent assay (ELISA).[12,13] Because the diagnostic sensitivity was 90–93% for the IgM ELISA and 80–100% for the RT-PCR, the combined diagnostic sensitivity of the RT-PCR and the IgM ELISA will be greater than 90%.[14–16]

All cases with dengue virus infections confirmed by any of the diagnostic tests were categorized as either DF or DHF according to the criteria of the WHO.[17] The diagnostic criteria included a platelet count nadir of less than 100,000/μL, hemorrhagic manifestations, and an increase in hematocrit greater than 20% above the average or the presence of pleural effusion or ascites. Cases of DHF were further graded as I–IV. A chest radiograph (posterioanterior view) was routinely done to detect pleural effusion on the third day of hospitalization. Treatment, including intravenous fluids (IVF) and fresh frozen plasma (FFP) was given to each patient based on the WHO guidelines,[17] and the total

TABLE 1
Disseminated intravascular coagulation (DIC) score*

Items	Test results	Score
Underlying disease	Yes	1
Clinical symptoms		
Hemorrhagic manifestations	Yes	1
Visceral symptoms†	Yes	1
Test results		
Serum FDP level (μg/mL)	≥ 40	3
	≥ 20 to < 40	2
	≥ 10 to < 20	1
Platelet count ($\times 10^4/\mu L$)	≤ 5	3
	> 5 to ≤ 8	2
	> 8 to ≤ 12	1
Plasma fibrinogen level (mg/dL)	≤ 100	2
	> 100 to ≤ 150	1
Prothrombin time ratio	≥ 1.67	2
(divided by the normal value)	≥ 1.25 to < 1.67	1

* FDP = fibrin degradation product.
† Signs of circulatory insufficiency due to microthrombus caused by DIC.

volume of IVF or FFP administered to each patient was recorded.

Disseminated intravascular coagulation (DIC) score. To assess the presence of DIC in the patients, all patients enrolled between September 2000 and December 2001 were examined for DIC scores.[18] The DIC scoring system used is shown in Table 1. The DIC score included an evaluation of the following parameters: the underlying disease and clinical symptom (hemorrhagic manifestations or visceral signs), and an assessment of platelet count, fibrinogen, prothrombin time (PT) ratio (divided by the normal value), and fibrin degradation product (FDP). Dengue virus infection was the underlying disease referred to the DIC scoring system for purposes of this study. The concentration of fibrinogen was measured with Dadethrombin reagent (Dade Behring, Inc., Newark, DE), and PT was determined with Thromborel S reagent (Dade Behring, Inc.). Citrated blood was used for the determination of the PT ratio and fibrinogen levels. The concentration of FDP was determined by means of a commercially available kit (Eiken Chemical Co., Ltd., Tokyo, Japan). The study protocol was reviewed and approved by the Institutional Ethics Review Board of the St. Luke's Medical Center.

Statistical analysis. All data are expressed as the mean ± SD or as frequencies and proportions. Differences in laboratory data between patients with DF and DHF were analyzed using the Student's *t*-test for continuous variables. Differences in the demographic and clinical data and DIC scores between patients with DF and DHF were tested by the chi-square test or Fisher's exact test for nominal variables, whichever was appropriate. A *P* value less than 0.05 was considered significant. The statistical software SPSS version 12.0 (SPSS, Inc., Cary, NC) was used for data analysis.

RESULTS

Subject characteristics. Of the 503 subjects screened, 359 (71.4%) were confirmed as having a dengue virus infection: 322 (89.7%) by IgM-capture ELISA and 139 (38.7%) by RT-PCR. A total of 102 (28.4%) had positive results for both tests. Of the 359 laboratory-confirmed cases, 239 (66.6%) and 120 (33.4%) were diagnosed as DF and DHF, respectively (Table 2). Forty-two patients (23 with DF and 19 with DHF) were enrolled in 1999, 75 (37 with DF and 38 with DHF) in 2000, and 242 (179 with DF and 63 with DHF) in 2001. The proportion of DHF differed in each year (45.2% in 1999, 50.6% in 2000, and 26.0% in 2001). The distribution of dengue virus serotypes (DEN1, DEN2, DEN3, DEN4) determined by RT-PCR was (6, 1, 1, and 1) in 1999, (7, 5, 0, and 1) in 2000, and (24, 84, 4, and 0) in 2001, respectively. Double-positive reactions in the RT-PCR occurred in 10 cases for serotype DEN 1 + 2, one case each for serotype DEN 1 + 3 and DEN 1 + 4, and three cases for serotype DEN 2 + 3. An outbreak of dengue illness occurred between June and October 2001 (Figure 1). These cases were primarily associated with DEN 2 and DEN 1. The mean age of all subjects was 9.8 years. With respect to severity of disease, 120 patients diagnosed as having DHF were further classified as follows: DHF I (n = 7), DHF II (n = 110), DHF III (n = 2), and DHF IV (n = 1). Although a fatal case with DHF grade IV was observed, most DHF patients were without shock. Of these, 57 (47.5%) were associated with pleural effusion.

The duration of the hospital stay was significantly longer in those with DHF than in those with DF ($P < 0.001$; Table 2). A significant increase in the frequency of abdominal pain was

TABLE 2
Demographic and clinical profile of subjects*

Parameter	DF (n = 239)	DHF (n = 120)	Total (n = 359)	*P*
Mean age (years) (SD)	9.9 (4.2)	9.8 (3.8)	9.8 (4.0)	0.877
Male:female ratio	1.49	1.50	1.49	0.976
Days with fever before admission (SD)	3.4 (1.3)	3.5 (1.4)	3.5 (1.3)	0.670
Duration of hospital stay, days (SD)	4.4 (1.7)	5.6 (1.7)	4.8 (1.8)	< 0.001
Symptoms before admission, no./total no. (%)				
Abdominal pain	76/238 (31.9)	55/119 (46.2)	131/357 (36.7)	0.008
Epistaxis	46/233 (19.7)	23/119 (19.3)	69/352 (19.6)	0.926
Symptoms at time of admission, no./total no. (%)				
Restlessness	0/238 (0.0)	4/119 (3.4)	4/357 (1.1)	0.012†
Epistaxis	26/236 (11.0)	23/117 (19.7)	49/353 (13.9)	0.027
Abdominal pain	69/237 (29.1)	51/119 (42.9)	120/356 (33.7)	0.010
Petechiae	195/239 (81.6)	102/120 (85.0)	297/359 (82.7)	0.420
Gum bleeding	11/232 (4.7)	6/113 (5.3)	17/345 (4.9)	0.819
Hematemesis	1/222 (0.5)	2/108 (1.9)	3/330 (0.9)	0.251†
Breathlessness	0/238 (0.0)	2/119 (1.7)	2/357 (0.6)	0.110†

* DF = dengue fever; DHF = dengue hemorrhagic fever.
† Fisher's exact test.

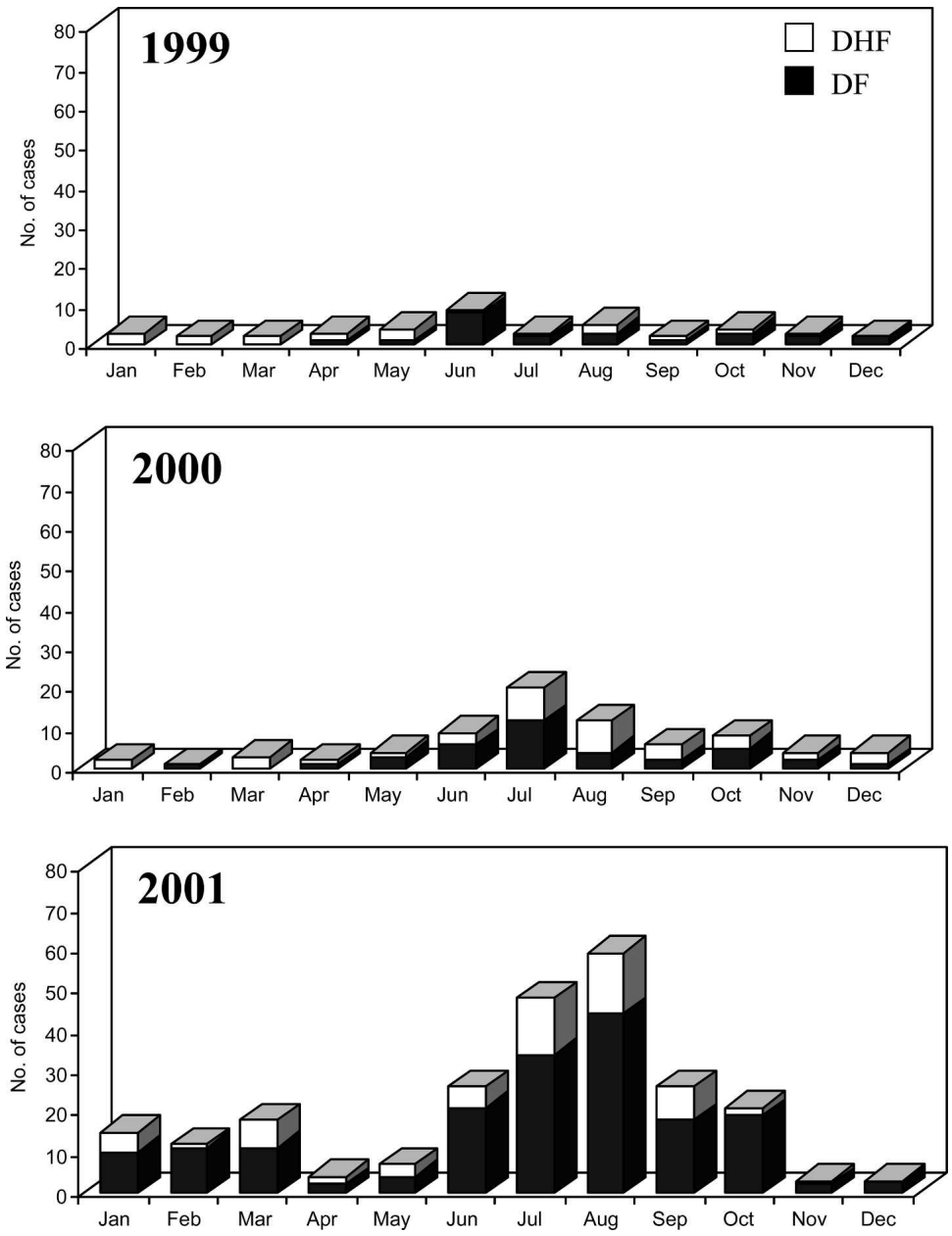

FIGURE 1. Distribution of dengue cases by month and year of enrollment. The number of laboratory confirmed dengue cases is plotted at monthly intervals from January 1999 to December 2001. DF = dengue; DHF = dengue hemorrhagic fever.

found in the DHF group before admission ($P = 0.008$) and at the time of admission ($P = 0.010$), compared with the DF group. The frequency of restlessness ($P = 0.012$) and epistaxis ($P = 0.027$) at the time of admission in the DHF group were also significantly higher than that in the DF group. No significant difference in nutritional status was found between the DF and DHF groups according to the Centers for Disease Control and Prevention classification.[19] The positive and negative predictive values of abdominal pain before admission for the development of DHF were 42.0% and 71.7%. These predictive values of symptoms upon admission were 42.5% and 71.2% for abdominal pain, 100% and 69.0% for restlessness, and 46.9% and 69.1% for epistaxis, respectively.

Laboratory data. Although the peripheral white blood cell (WBC) count of all subjects was generally below normal values prior to defervescence, the peripheral WBC count was significantly higher in the DHF group than in the DF group on days -1, 0, +1, +2, and +3 of defervescence (Figure 2A). The lymphocyte fraction in the peripheral WBC count was also significantly higher in the DHF group than in the DF group from days -1 to +2 (Figure 2B). No difference was found in the absolute monocyte, eosinophil, and basophil counts between the two groups. The laboratory data also confirmed that the platelet count was significantly lower in the DHF group than in the DF group from days –3 to +5 (Figure 2C). The lowest peripheral platelet count was noted at day +1 for both groups. The nadir of platelet count ($\times 10^3/\mu L$) was 113.8 ± 58.3 in the DF group and 58.5 ± 84.1 in the DHF group, respectively. The hematocrit was significantly higher in the DHF group from days -2 to +0 (Figure 2D). The maxi-

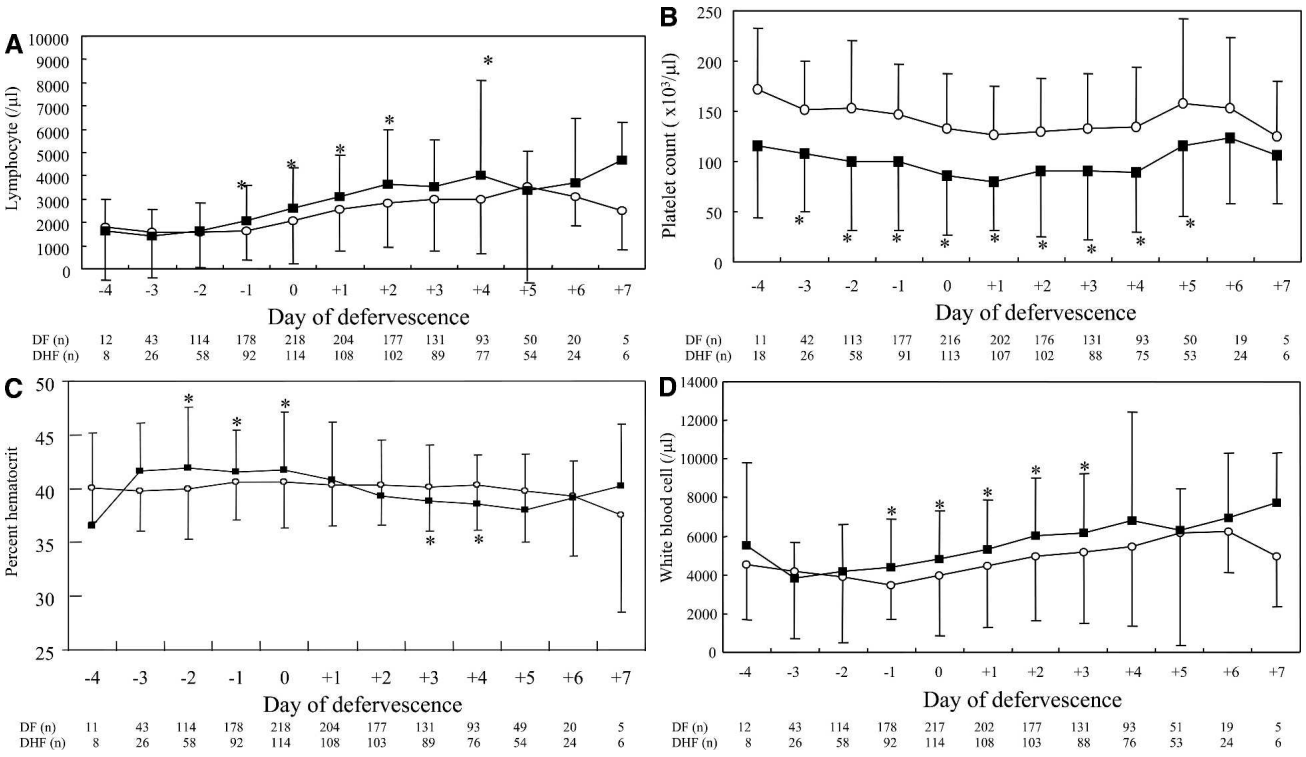

FIGURE 2. Comparison of the total white blood cell count (**A**), lymphocyte count (**B**), platelet count (**C**), and the hematocrit (**D**) in peripheral blood between pediatric patients with dengue fever (DF) and dengue hemorrhagic fever (DHF). The number of cases with DF and DHF are shown below each figure. Open circles show cases with DF and filled squares show cases with DHF. Data represent the mean ± SD *$P < 0.05$ versus patients with DF.

mum increase in the hematocrit was significantly higher in the DHF group (24.3 ± 13.8%) than that in the DF group (11.4 ± 7.7%) ($P < 0.001$). Interestingly, a significant decrease in the hematocrit was also found in the DHF group, compared with the DF group at day +4. This finding may be influenced by an intravenous fluid correction that was previously administered in addition to a shift of fluid to the intravascular space with recovery from the illness in patients with DHF. Therefore, we compared the total volume of IVF or FFP administered to each patient during admission between the DF and the DHF group. The total volume of IVF administered to each patient was significantly higher in the DHF group (n = 117, 3,265 ± 1,560 mL) than that in the DF group (n = 230, 2,687 ± 1,216 mL) during their hospital stay in this study ($P < 0.001$). No significant difference was found in the total volume of FFP used in between the DF group (n = 11, 307 ± 133 mL) and the DHF group (n = 38, 401 ± 471 mL).

DIC score. Among the parameters evaluated for the DIC scores, the frequency distribution of platelet and fibrinogen scores in the DHF group were significantly different than those in the DF group ($P < 0.05$), with higher scores observed for the DHF group (Table 3). Bleeding manifestations were frequently observed in both DF and the DHF patients, and no difference in clinical score was found between the two groups. A few cases of DF and DHF had an increased FDP and PT ratios with no significant differences in these scores between the two groups. Consequently, the frequency of cases with a DIC score ≥ 7 was significantly higher in the DHF group than in the DF group ($P < 0.001$). Of 17 cases with a DIC score of ≥ 7, 13 were DHF and 4 were DF. Of 13 DHF cases, 11 were DHF II and 1 case each of DHF I and IV, respectively. Only one death, a case of DHF grade IV, was associated with a marked increase in the PT ratio. Two cases of DHF were associated with a mild increase in the PT ratio. Only 7 of 17 cases were associated with a mild increase in FDP.

DISCUSSION

The findings herein serve to demonstrate the differences in clinical and laboratory features between DF and DHF during

TABLE 3
Comparison of DIC scores between those with DF and those with DHF*

		DF (n = 163)		DHF (n = 94)		Total (n = 257)		
Parameter	Score	No.	%	No.	%	No.	%	*P*
Platelet score	0	73	44.8	4	4.3	77	30.0	< 0.001
	1	39	23.9	15	16.0	54	21.0	
	2	30	18.4	18	19.1	48	18.7	
	3	21	12.9	57	60.6	78	30.4	
Clinical score	0	23	14.1	12	12.8	35	13.6	0.762
	1	140	85.9	82	87.2	222	86.4	
PT score	0	160	98.2	90	95.7	250	97.3	0.327
	1	3	1.8	3	3.2	6	2.3	
	2	0	0.0	1	1.1	1	0.4	
Fibrinogen score	0	111	68.1	53	56.4	164	63.8	0.027
	1	43	26.4	27	28.7	70	27.2	
	2	9	5.5	14	14.9	23	8.9	
FDP score	0	132	81.0	72	76.6	204	79.4	0.403
	1	31	19.0	22	23.4	53	20.6	
Total score	< 7	159	97.5	81	86.2	240	93.4	< 0.001
	≥ 7	4	2.5	13	13.8	17	6.6	

* DIC = disseminated intravascular coagulation; DF = dengue fever; DHF = dengue hemorrhagic fever; PT = prothrombin time; FDP = fibrin degradation product.

admission under appropriate treatment according to WHO guidelines. Abdominal pain and epistaxis were more commonly associated with DHF patients during the acute phase of the illness in this study, although previous studies reported conflicting data on the frequency of abdominal pain and bleeding manifestations.[5,6] Since abdominal pain and epistaxis were also found in DF, a diagnostic value of these symptoms for the severity of disease is limited. Although DHF required a longer hospital stay, DF also required a hospital stay longer than four days. This finding indicates that DF and DHF impose a considerable burden in the health care system in the Metro Manila, the Philippines. Although the etiology of abdominal pain in dengue illness remains obscure, Setiawan and others reported that most pediatric patients with DHF and epigastric pain also had increased serum levels of amylase or lipases and an enlarged pancreas.[20] Another study reported hemorrhagic gastritis as a most common finding of gastroendoscopy among patients with dengue fever in Taiwan.[21] Since we could not specify any definite reasons for abdominal pain in this study, further studies will be necessary. Although abdominal pain or epistaxis yielded a low positive predictive value for the development of DHF, restlessness was associated with a high positive predictive value. Therefore, this rare symptom could be used as a predictor of DHF.

Our laboratory data confirmed the increasing mean total WBC and lymphocyte counts that approached normal levels around the day of defervescence (Figure 2A and B). These findings are consistent with previous reports, although an examination for atypical lymphocytes was not done.[22–24] The maximum increase in the hematocrit in the DHF group was higher than 20%, and significantly higher than those in the DF group in this study, which supports the WHO definition of the disease.[17] Increased vascular permeability would allow plasma to flow out of the intravascular compartments, leading to hypovolemic shock. The present study also demonstrated that the volume of IVF administered to prevent hypovolemic shock in the DHF group was significantly higher than in the DF group. The increased administration of IVF for preventing dengue shock syndrome subsequently could lead to a significant decrease in the hematocrit in the DHF group, compared with the DF group, after defervescence.

In this study, we attempted to apply the diagnostic criteria of DIC to 257 patients with dengue virus infections.[18] Although thrombocytopenia was more prominent in the DHF group than in the DF group, a few cases of DF and DHF had an increased PT ratio. In addition, only a mild increase in FDP was found in both the DF and DHF group. These data are not in agreement with previous reports,[25,26] and may be explained by the limited number of patients with dengue shock syndrome in this study. The high frequency of low fibrinogen levels in the DHF group is indicative of increased fibrinolysis, which is consistent with previous findings concerning DHF.[25,27,28] Krishnamurti and others also reported an increased activated partial thromboplastin time and decreased fibrinogen levels in patients with DF and DHF.[29] These investigators suggested that platelet activation, rather than consumptive coagulopathy, was likely to cause hemorrhage in dengue without shock.

Although an increased frequency of cases with a DIC score of ≥ 7 was found in the DHF group compared with the DF group, most of these cases were free of consumptive coagulopathy. Serious bleeding manifestations such as melena caused by DIC were found in only one fatal case of DHF grade IV. Collectively, our data suggest that coagulation abnormalities involve a combination of thrombocytopenia and increased fibrinolysis, but not classic DIC in most patients in this study.

In summary, our present data demonstrated a low incidence of dengue shock syndrome among pediatric patients undergoing appropriate treatment in Metro Manila, the Philippines. Our data also show the differences in the frequency of clinical symptoms, such as restlessness, epistaxis, and abdominal pain, between patients with DF and DHF. Administration of increased volumes of IVF during the period of increased vascular permeability, a typical pathophysiologic feature of DHF 2–3 days after defervescence, can prevent dengue shock syndrome. Significantly low platelet counts and increased fibrinolysis in the peripheral blood were found in the DHF group, compared with the DF group. Coagulation abnormalities in most patients involve a combination of thrombocytopenia and increased fibrinolysis, but not classic DIC.

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