

Dengue and other Febrile Illnesses among Children in the Philippines

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Abstract

In view of the increasing trend of DHF in the Philippines, a prospective study was undertaken to define the clinical and haematological differences between DF/DHF and other febrile illnesses (OFI) between 1999 and 2001. A total of 503 paediatric patients, who had acute febrile illness without an apparent focus of infection and who were admitted to St. Luke's Medical Center in Metro Manila, Philippines, were enrolled in this study. Of these, 359 cases (71.4%) were diagnosed with a dengue virus infection and 144 cases (28.6%) were OFI, respectively. Most of the cases with dengue virus infection were associated with DENV-1 and DENV-2. One third of the patients with dengue virus infections were DHF, and most of these were without shock. A low incidence of dengue shock syndrome and a low fatality rate among paediatric patients with dengue virus infection was found. The white blood cell counts were significantly lower in DF or DHF than in OFI. The platelet count was also significantly lower in DHF than in DF or OFI. On the other hand, the haematocrit was significantly higher in DHF than in OFI. Coagulation abnormalities associated with a majority of DHF patients were thrombocytopenia and an increased fibrinolysis, but not disseminated intravascular coagulation. We present here clinical and laboratory data on paediatric patients with acute febrile illness lacking an apparent focus of infection that can be used for an early diagnosis and appropriate clinical management of patients with dengue virus infections in Metro Manila, Philippines.

Keywords: Dengue fever, dengue haemorrhagic fever, serotype, other febrile illness, Philippines.

Introduction

Dengue has emerged as the most important mosquito-borne human viral disease in the Philippines. Ever since the first outbreak of dengue haemorrhagic fever (DHF) in 1956,

similar epidemics have occurred in the country at approximately five-year intervals with increasing numbers of cases until 2001.^{1,21} Previous reports have also characterized the view that dengue has become highly endemic and is a leading cause of childhood

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hospitalizations during the 1980s in the Philippines.^[3,4]

Dengue fever (DF) is a self-limiting febrile illness, while DHF is characterized by prominent haemorrhagic manifestations with thrombocytopaenia and increased vascular permeability. Thrombocytopaenia may be caused by a virus-induced suppression in bone marrow and an immune mechanism such as platelet-associated immunoglobulins.^[5,6] The early clinical diagnosis of dengue illness is difficult, because the clinical and laboratory criteria for DF involve non-specific symptoms and signs. In addition, a variety of acute, undifferentiated febrile illnesses can typically occur in urban and rural areas of Asian countries.^[7,8]

This prospective study was, therefore, undertaken to determine the differences in the clinical features between DF/DHF and other febrile illness (OFI) and the differences in haematological abnormalities between DF and DHF among hospitalized paediatric patients in Metro Manila, Philippines, between 1999 and 2001.

Materials and methods

Patients and study design

Patients admitted to St. Luke's Medical Center (SLMC), Quezon City, the Philippines, between January 1999 and December 2001 satisfying the following criteria were enrolled: (i) age between 2 to 17 years; (ii) fever for ≤ 5 days; (iii) temperature of at least 37.8 °C; and (iv) no apparent focus of infection.^[9] The history of the illness was obtained and a physical examination was performed by paediatricians on the day of enrolment, and daily until discharge. The clinical symptoms and signs, including nutritional status, were recorded in case record forms. Blood was drawn on the

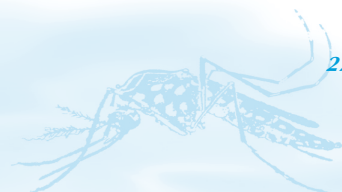
first, third, fourth and seventh days of their hospital stay. Complete serial blood counts were done until the day of discharge. The diagnostic tests for dengue were RT-PCR for flaviviruses and ELISA for IgM, an antibody to dengue viruses.^[9] All cases of dengue virus infections that were confirmed by any of the diagnostic tests were categorized as either DF or DHF according to the criteria of the World Health Organization (WHO).^[10] The diagnostic criteria included: a platelet count nadir of less than 100 000/ μ l, haemorrhagic manifestations, and an increase in haematocrit 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 (PA view) was routinely done to detect pleural effusion on the third day of hospitalization. Other febrile illnesses were defined as cases with no evidence of dengue infection by IgM ELISA or RT-PCR and no obvious bacterial, rickettsial or protozoan etiology.

Disseminated intravascular coagulation (DIC)

To assess the presence of DIC in these patients, the DIC scores of all patients enrolled between September 2000 and December 2001 were examined.^[11] The DIC score included an evaluation of the following parameters: the underlying disease and clinical symptoms (haemorrhagic manifestations or visceral signs), 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 in the DIC scoring system.

Statistical analysis

Statistical analyses were performed using SPSS 14.0 for Windows. All data are expressed as



the mean \pm SD or as frequencies and proportions. Differences in the demographic and clinical data, and DIC scores among patients with DF, DHF or OFI were tested by the chi-square test for nominal variables, and one-way analysis of variance (ANOVA) followed by the Bonferroni method for continuous variables. A *P*-value of less than 0.05 was considered to be significant.

Results

Subject characteristics

Of the 503 subjects screened for acute febrile illness without apparent focus of infection, 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, while 102

Table 1: Demographic and clinical profile of the subjects

Parameter	DF n=239	DHF n=120	OFI n=144	Total N=503	<i>P</i> -value
Mean age (years) (SD)	9.9 (4.2)	9.8 (3.7)	8.6 (4.2)	9.5 (4.1)	^a 0.008
Male-female ratio	1.49	1.50	1.07	1.36	0.250
Mean no. of days with fever before admission (SD)	3.4 (1.3)	3.5 (1.4)	3.3 (1.5)	3.4 (1.4)	0.335
Mean duration of hospital stay (SD)	4.4 (1.7)	5.6 (1.7)	4.2 (1.8)	4.7 (1.8)	^b <0.001
Symptoms before admission	No./Total no. (%)	No./Total no. (%)	No./Total no. (%)	No./Total no. (%)	
Abdominal pain	76/238 (31.9)	55/119 (46.2)	59/142 (41.5)	190/499 (38.1)	^c 0.019
Epistaxis	46/233 (19.7)	23/119 (19.3)	22/142 (15.5)	91/494 (18.4)	0.564
Symptoms at the time of admission	No. /Total No. (%)	No. /Total No. (%)	No. /Total No. (%)	No. /Total No. (%)	
Restlessness	0/238 (0.0)	4/119 (3.4)	3/144 (2.1)	7/501 (1.4)	^d 0.027
Epistaxis	26/236 (11.0)	23/117 (19.7)	12/140 (8.6)	61/493 (12.4)	^e 0.018
Abdominal pain	69/237 (29.1)	51/119 (42.9)	51/140 (36.4)	171/496 (34.5)	^f 0.031
Petechiae	195/239 (81.6)	102/120 (85.0)	104/144 (72.2)	401/503 (79.7)	^g 0.022
Gum bleeding	11/232 (4.7)	6/113 (5.3)	2/136 (1.5)	19/481 (4.0)	0.208
Haematoemesis	1/222 (0.5)	2/108 (1.9)	0/133 (0.0)	3/463 (0.6)	0.180
Breathlessness	0/238 (0.0)	2/119 (1.7)	0/144 (0.0)	2/501 (0.4)	0.040

DF: dengue fever, DHF: dengue haemorrhagic fever, OFI: other febrile illness, SD: standard deviation, ^a*P*=0.010 (DF vs OFI), ^b*P*<0.001 (DF vs DHF), *P*<0.001 (DHF vs OFI), ^c*P*=0.008 (DF vs DHF), ^d*P*=0.012 (DF vs DHF), ^e*P*=0.010 (DHF vs OFI), ^f*P*=0.010 (DF vs DHF), ^g*P*=0.013 (DHF vs OFI).

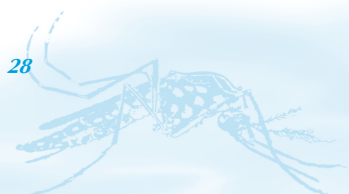


Table 2: Clinical diagnosis for 144 cases of other febrile illness

Specific illnesses	Frequency	Percentage
AURI	4	2.8
ALRI	20	13.9
AGE	2	1.4
Meningitis	1	0.7
Measles	1	0.7
Typhoid fever	1	0.7
UTI	1	0.7
Unknown	114	79.2
Total	144	100.0

AURI=acute upper respiratory infection,
ALRI=acute lower respiratory infection,
AGE=acute gastroenteritis, UTI=urinary tract infection

Table 3: Age distribution of subjects

Age distribution	DF	DHF	OFI	Total
2–5	48 (20.1)	16 (13.3)	43 (29.9)	107 (21.3)
6–10	77 (32.2)	53 (44.2)	50 (34.7)	180 (35.8)
11–15	91 (38.1)	43 (35.8)	41 (28.5)	175 (34.8)
>15	23 (9.6)	8 (6.7)	10 (6.9)	41 (8.2)
Total	239	120	144	503

DF=dengue fever, DHF=dengue haemorrhagic fever,
OFI=other febrile illness

$P=0.014$ (DHF vs OFI), $P=0.016$ (DF vs OFI)

(28.4%) were positive for both tests. The other 144 cases (28.6%) of the total enrolled cases were diagnosed as OFI (Table 1). Of the 359 laboratory-confirmed cases, 239 (66.6%) and 120 (33.4%) were diagnosed as DF and DHF,

respectively. The mean age of all dengue cases was 9.8 years. Patients with OFI were significantly younger than those with DF or DHF (Table 1). Although most of the cases with OFI (79.2%) were undiagnosed, 20 (13.9%) were diagnosed as acute lower respiratory infections (ALRI) (Table 2). Of these, 7 were diagnosed as radiological pneumonia. Other illnesses, such as acute gastroenteritis, meningitis, measles, typhoid fever and urinary tract infection were also involved. The age distribution of the 503 subjects is shown in Table 3. Most of the patients diagnosed with DF/ DHF were in the range of 6–15 years of age. On the other hand, the frequency of OFI was higher than that of DF or DHF in the 2–5-year range of age. A significant difference in age distribution was found between OFI and DF or DHF ($P<0.05$). Seventy-nine patients (DF 23, DHF 19, OFI 37) were enrolled in 1999, 95 patients (DF 37, DHF 38, OFI 20) in 2000 and 329 patients (DF 179, DHF 63, OFI 87) in 2001 (Figure). The proportion of DHF or OFI of the total cases differed in each year (24.1% in 1999, 40.0% in 2000 and 19.1% in 2001 for DHF; 46.8% in 1999, 21.1% in 2000, 26.4% in 2001 for OFI). The distribution of serotypes (DENV-1, DENV-2, DENV-3, DENV-4) determined by RT-PCR was (6, 1, 1, 1) in 1999, (7, 5, 0, 1) in 2000, and (24, 84, 4, 0) in 2001, respectively. An outbreak of dengue illness occurred between June and October in 2001. These cases were primarily associated with DENV-2 and DENV-1. With respect to the severity of the disease, 120 patients diagnosed as 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 noted, most of the DHF patients were not in a state of shock.

The duration of hospital stay was significantly longer in cases of DHF compared to DF or OFI ($P<0.001$, Table 1). A significant increase in the frequency of abdominal pain

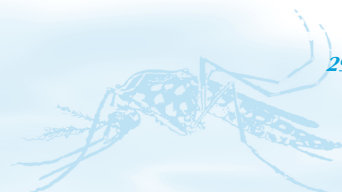
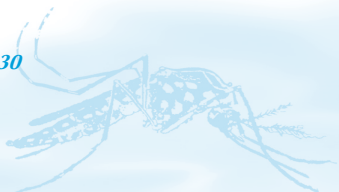
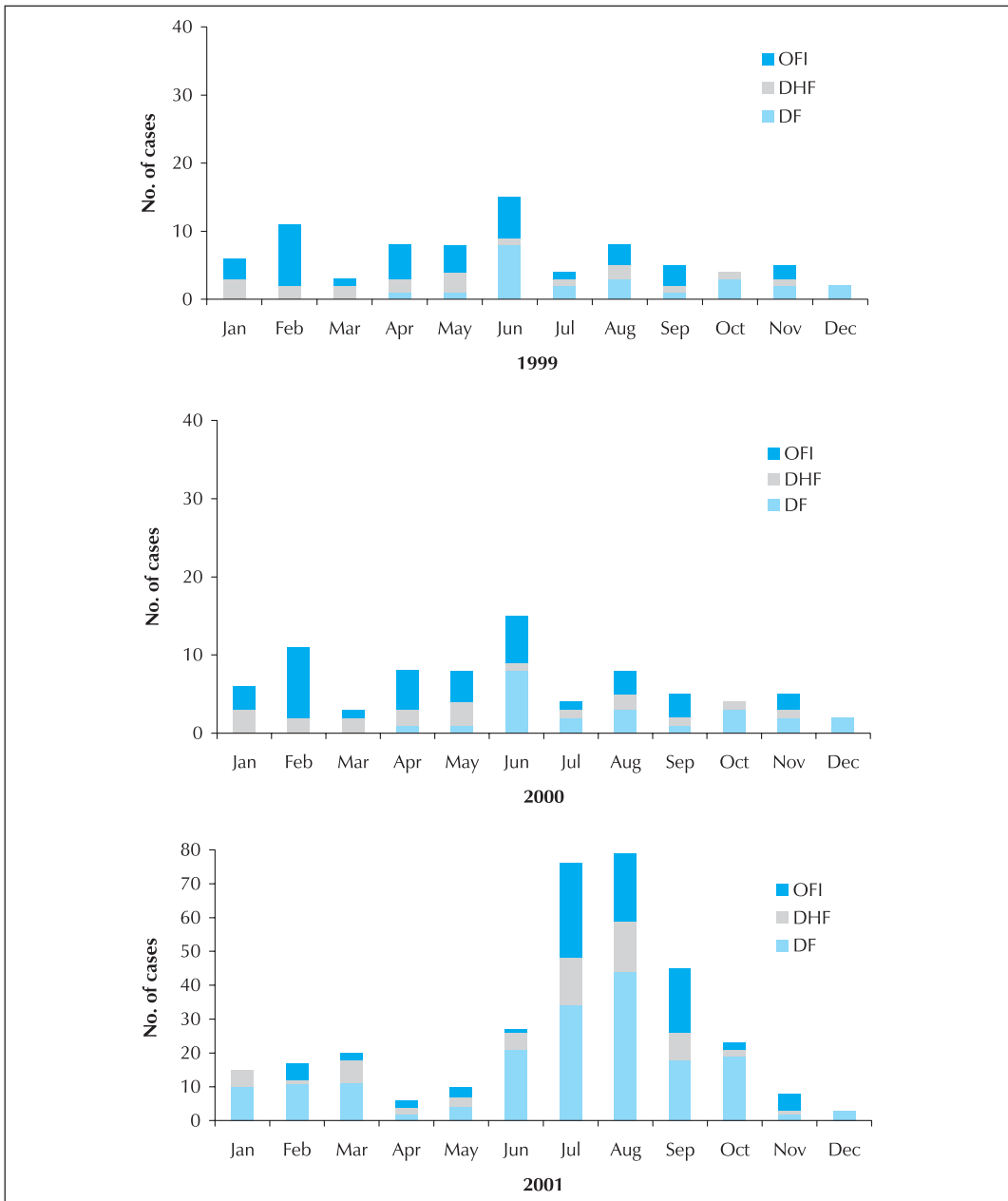


Figure: *Distribution of cases of dengue virus infection and other febrile illness by year of enrollment.*

The number of laboratory-confirmed dengue cases and cases with other febrile illness are plotted at monthly intervals from January 1999 to December 2001.

(DF=dengue fever; DHF=dengue hemorrhagic fever; OFI=other febrile illness)



was found in DHF before admission and at the time of admission, compared with the DF but not with the OFI group. The frequency of epistaxis and petechiae at the time of admission was also significantly higher in the DHF group than that in the OFI group ($P=0.010$ for epistaxis, $P=0.013$ for petechiae; Table 1).

Laboratory data

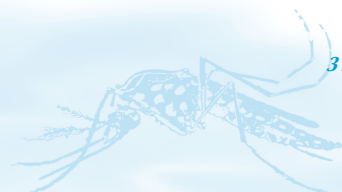
The laboratory data on admission were compared among the three groups of DF, DHF and OFI (Table 4). The WBC count was significantly lower in DF ($P<0.001$) or DHF ($P<0.01$) than in OFI, and the neutrophil count was also significantly lower in DF than in OFI ($P<0.01$). In addition, the platelet count was significantly lower in DHF than in DF ($P<0.001$) and lower in DF than in OFI ($P<0.001$). On the other hand, the haematocrit was significantly higher in DHF than in OFI ($P<0.001$). Among the parameters evaluated for the DIC scores, the frequency

distribution of platelet score in the DHF group ($n=94$) was significantly different from that in the DF group ($n=163$) with higher scores observed for the DHF group (Score 1; 23.9%, Score 2; 18.4%, Score 3; 12.9% for DF and Score 1; 16.0%, Score 2; 19.1%, Score 3; 60.6% for DHF; $P<0.001$). The frequency of fibrinogen score in the DHF was also significantly different from that in the DF group (Score 1; 26.4%, Score 2; 5.5% for DF and Score 1; 28.7%, Score 2; 14.9% for DHF; $P=0.027$). Bleeding manifestations, such as petechiae, were frequently observed in both the DF and DHF patients, and no difference in clinical score was found between the two groups (Score 1; 85.9% for DF, Score 1; 87.2% for DHF). A few cases of DF and DHF had increased FDP and PT ratios with no significant differences in these scores between the two groups (data not shown). Consequently, the frequency of cases with a DIC score of ≥ 7 was significantly higher in the DHF group than in the DF group (2.5% for DF and 13.8% for DHF; $P<0.001$).

Table 4: Laboratory profile of subjects upon admission

Parameter	DF n=239	DHF n=120	OFI n=144	Total n=503	P-value
Mean WBC (SD)	4.1 (3.6)	4.4 (2.4)	5.7 (3.9)	4.6 (3.5)	^a <0.001
Mean neutrophils (SD)	50.2 (18.0)	52.4 (18.9)	56.3 (17.5)	52.5 (18.2)	^b 0.007
Mean monocytes (SD)	6.1 (2.9)	5.0 (3.0)	6.6 (2.8)	6.0 (2.9)	^c <0.001
Mean platelet count (SD)	153.1 (55.3)	113.3 (68.4)	185.5 (85.4)	152.8 (72.8)	^d <0.001
Mean haematocrit (SD)	39.9 (5.9)	41.5 (6.6)	38.3 (7.3)	39.8 (6.6)	^e <0.001

DF=dengue fever, DHF=dengue haemorrhagic fever, OFI=other febrile illness, WBC=white blood cell, ^a $P<0.001$ (DF vs OFI), $P=0.007$ (DHF vs OFI), ^b $P=0.005$ (DF vs OFI), ^c $P=0.001$ (DF vs DHF), $P<0.001$ (DHF vs OFI), ^d $P<0.001$ (DF vs DHF), $P<0.001$ (DF vs OFI), $P<0.001$ (DHF vs OFI), ^e $P<0.001$ (DHF vs OFI).



Discussion

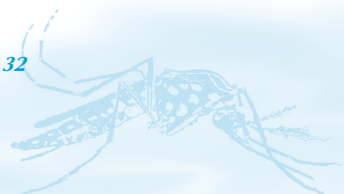
Acute undifferentiated febrile illness among children may involve rubella, measles, influenza and chikungunya in Asian countries.^[7,12] While the proportion of non-dengue self-limited febrile illness was reported to be 55.7~59.3% among enrolled patients with undifferentiated fever in Thailand,^[7,13] 28.6% of the enrolled subjects were classified into OFI in our study. The difference in the proportion of OFI may be explained by the incidence of circulating febrile illnesses, presumably due to the virus, between the two countries, although 79.2% of etiological diagnoses of cases with OFI were not available for this study. While DHF required a longer hospital stay, DF or OFI also required a hospital stay exceeding four days. This finding indicates that DF and OFI, as well as DHF, impose a considerable burden on the health care system in Metro Manila, Philippines. Since the characteristic features of thrombocytopenia, mild leukocytopenia and a relative increase in the haematocrit were found among patients with DF/DHF, the laboratory data for the platelet count, the haematocrit and the WBC of OFI were found to be distinct from those of DF/DHF (Table 4). The differences in clinical manifestations, including the frequency of epistaxis and petechiae, between DHF and OFI can, in part, be explained by a significant difference in platelet count between these two groups.

Although the present study lacked information on primary or secondary infections, our recent publication in Metro Manila confirmed that approximately 80% of patients with dengue virus infection were associated with a secondary infection.^[6] Under these circumstances, one third of the cases with dengue virus infection were diagnosed as DHF. While the case-fatality rate of paediatric patients with dengue infection

in this study was low (0.3%), it typically varies from 0.5% to 3.5% in Asian countries.^[14] Interestingly, the proportion of dengue shock syndrome in DHF cases in this study (2.5 %) was much lower than that reported in the previous studies (16–32%) in Viet Nam and Thailand,^[13,15,16] although the clinical management is similar for patients with DF/DHF in these countries.

Regarding the DIC score, a few cases of DF and DHF had an increased PT ratio, while thrombocytopenia was more prominent in the DHF group than in the DF group. Furthermore, only a mild increase in FDP was found in both the DF and DHF groups. These data are not in agreement with a previous report,^[17] 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, consistent with previous findings concerning DHF.^[17,18] Although an increased frequency of cases with a DIC score of ≥ 7 was found in the DHF group compared to the DF group, most of these cases were free of consumptive coagulopathy. These data suggest that coagulation abnormalities involve a combination of thrombocytopenia and increased fibrinolysis, but not classical DIC in most patients.

In summary, the incidence and clinical and laboratory data for paediatric patients with acute febrile illness without an apparent focus of infection among children at St. Luke's Medical Center in Quezon City, Metro Manila, Philippines, are reported for the period between 1999 and 2001. Of these, 71.4% and 28.6% were diagnosed as dengue virus infection and OFI, respectively. One third of the patients with a dengue virus infection were DHF. The low incidence of dengue shock syndrome and the low case-fatality rate in dengue illness among children were both low.



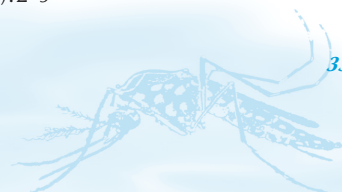
The clinical features of dengue virus infections can be used for the early diagnosis and subsequent treatment for the dengue virus. Since a prolonged increase in the number of admitted dengue cases has been reported in the recent years in this country, vector control in the Metro Manila area is strongly recommended. The support of the community should be encouraged in controlling *Aedes aegypti* in this area.^[19]

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