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Original Article

Clinical characteristics of dengue and dengue hemorrhagic fever in a medical center of southern Taiwan during the 2002 epidemic

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Background and Purpose: This study investigated the clinical manifestations and risk factors for dengue fever (DF) and dengue hemorrhagic fever (DHF) and disease severity during the 2002 outbreak in the Kaohsiung area.
Methods: We analyzed the clinical characteristics of 644 patients with virologically or serologically positive results for dengue virus at Kaohsiung Medical University Hospital from January 1 to December 31, 2002.
Results: The case rate peaked in November. The male-to-female ratio was 1:1.2 and the mean age was 47.5 ± 17.9 years (range, 7 months to 88 years). The criteria for DHF were fulfilled in 232 cases, including 12 cases of dengue shock syndrome (DSS). The most common symptoms were fever (96.1%), myalgia (68.5%), headache (55.4%), and skin rash (53.7%). Hemorrhagic manifestations were noted in 73.0% of patients. The mean age of patients with DHF/DSS was 53.6 ± 16.3 years, and the highest incidence occurred in those aged 60-69 years (27.2%). Significant risk factors for DHF/DSS were age >65 years, diabetes mellitus, hypertension, and uremia. Gallbladder wall thickening was found in 64.7% of DHF cases who underwent abdominal ultrasound examination. 164 of the 232 DHF cases (71%) were discharged without a diagnosis of DHF. The number of DHF cases identified by our study was nearly equal to that reported through the established passive surveillance system (232 cases vs 242).
Conclusions: DHF was under-reported in hospital, suggesting that continuous surveillance and education for clinicians in the recognition of DHF, especially in elderly patients and those with chronic pre-existing comorbidities, is needed.

Key words: Dengue hemorrhagic fever, dengue virus, Taiwan

Introduction

The first reported case of dengue fever (DF) in Taiwan was in 1870, followed by 3 island-wide outbreaks of dengue virus infection in 1915, 1931 and 1942 to 1943 [1]. No cases were then reported for 38 years until an outbreak of dengue-2 (DEN-2) occurred on the island of Liuqiu in 1981. A subsequent DEN-1 epidemic occurred in southern Taiwan, mostly Kaohsiung and Pingtung, between 1987 and 1989 [2]. Since then, although dengue virus infection continues to be mostly imported from neighboring countries, it has re-emerged as a major public health problem in southern Taiwan, with cases being reported yearly and larger outbreaks occurring in 1991, 1994, 1995, 1998 and 2000 [2,3]. Dengue hemorrhagic fever (DHF), the severe form of dengue virus infection, was first reported in Taiwan with 2 cases in 1988 [4], followed by 11 cases (1 death) in 1994 and 14 cases (1 death) in 1998 [3].

During 2002, an outbreak of 15,463 reported and 5630 confirmed cases of DF (5388 DF and 242 DHF) occurred in the Kaohsiung area [5], making it the largest outbreak of DF since 1943 and the most severe DHF epidemic in the island's history. This hospital-based

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study investigated the clinical manifestations and risk factors for DF and DHF and disease severity in patients treated at a single hospital in Kaoshiung during this outbreak.

Methods

In 2002, hospitals in Taiwan were requested to report all suspected cases of dengue virus infection together with a serum sample, to the Center of Disease Control in Taiwan for confirmation. A suspected case of dengue virus infection was defined as any patient having a body temperature higher than 38°C and 1 of the following characteristic symptoms and signs: headache, retro-orbital pain, myalgia, arthralgia, rash, and pruritus. A confirmed dengue case was defined [6] as one meeting any of the following criteria: 1) positive dengue virus isolation; 2) positive for dengue virus RNA by reverse transcriptase-polymerase chain reaction; 3) 4-fold increase of dengue virus-specific immunoglobulin M (IgM) or immunoglobulin G (IgG) antibody in paired serum samples, where cross-reactions to Japanese encephalitis had been excluded; 4) positive for dengue virus-specific IgM and IgG in a single serum sample where cross-reactions to Japanese encephalitis had been excluded.

All patients with confirmed DF treated at Kaohsiung Medical University Hospital (KMUH) between January 1 and December 31, 2002 were included in this retrospective study. The hospital records were reviewed and data were collected including month of onset, age, gender, past medical history, clinical presentations, laboratory data, findings of diagnostic imaging and amount of platelet transfusion. Patients with incomplete or unrecognizable records (n = 5) were excluded from all analyses. The diagnosis of DHF was made based on the following findings: thrombocytopenia (100,000/mm^3 or less), and evidence of hemorrhage and plasma leakage such as hemoconcentration, hypoalbuminemia, hypoproteinemia, ascites or pleural effusion. Dengue shock syndrome (DSS) was diagnosed when, in addition to the above criteria for DHF, the patient presented with hypotension (for age) or narrow pulse pressure (≤20 mm Hg) in the presence of clinical signs of shock [7]. Hemoconcentration was defined as an increase of hematocrit by 20% or more compared to baseline, or decrease by 20% or more after hydration [8] and was calculated as the ratio of the difference of maximum and minimal hematocrit value, divided by the minimal value. Pleural effusion or ascites was documented by X-ray, ultrasound, or computerized axial tomography. Hypoalbuminemia was defined as a serum albumin level less than 3 g/dL. Hypotension was defined in patients more than 1 year old as systolic blood pressure below 80 mm Hg (<70 mm Hg for infants). Gallbladder wall thickening was defined as a wall thickness exceeding 3 mm on sonography.

Statistical analyses

Student's *t* test was used to analyze continuous variables in demographic and clinical data. Dichotomous variables were compared using Pearson's chi-squared test or 1-tailed Fisher's exact test. Multiple logistic regression models were estimated after the univariate analysis. Parameters with significant *p* values in the univariate analysis were included in the regression models. Before performing the statistical analysis, laboratory measurements with skewed distributions were normalized with either logarithmic or exponential transformations, according to their skewness index. A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed with Statistical Analysis System software (SAS; SAS Institute Inc., Cary, NC, USA).

Results

From January 1 to December 31, 2002, a total of 1551 suspected DF cases were reported to the Center for Disease Control (CDC) Taiwan from KMUH. Dengue viral infection was laboratory confirmed in 649 (41.8%) of these cases. Hospital records of the 649 confirmed cases were reviewed by 1 of the authors. Five outpatient cases were excluded from further study due to illegible handwriting in medical records. Of the remaining 644 confirmed cases, 477 (74.0%) had illness onset between August and November. Case numbers fell abruptly after the November peak (Fig. 1). The male-to-female ratio was 1:1.2. Most of the cases were adults, with only 4.5% below 15 years of age (Table 1 and Fig. 2).

Most patients presented classical symptoms of dengue viral infection. Fever was the most common presenting symptom (96.1%), followed by myalgia (68.5%), headache (55.4%), skin rash (53.7%), anorexia (53.7%) and malaise (49.1%). Pruritus (22.7%) and retro-orbital pain (15.8%) were also noted. Gastrointestinal and respiratory tract symptoms were common, and included abdominal pain (42.1%), nausea and vomiting (39.9%), cough (37.6%), diarrhea (35.1%), and

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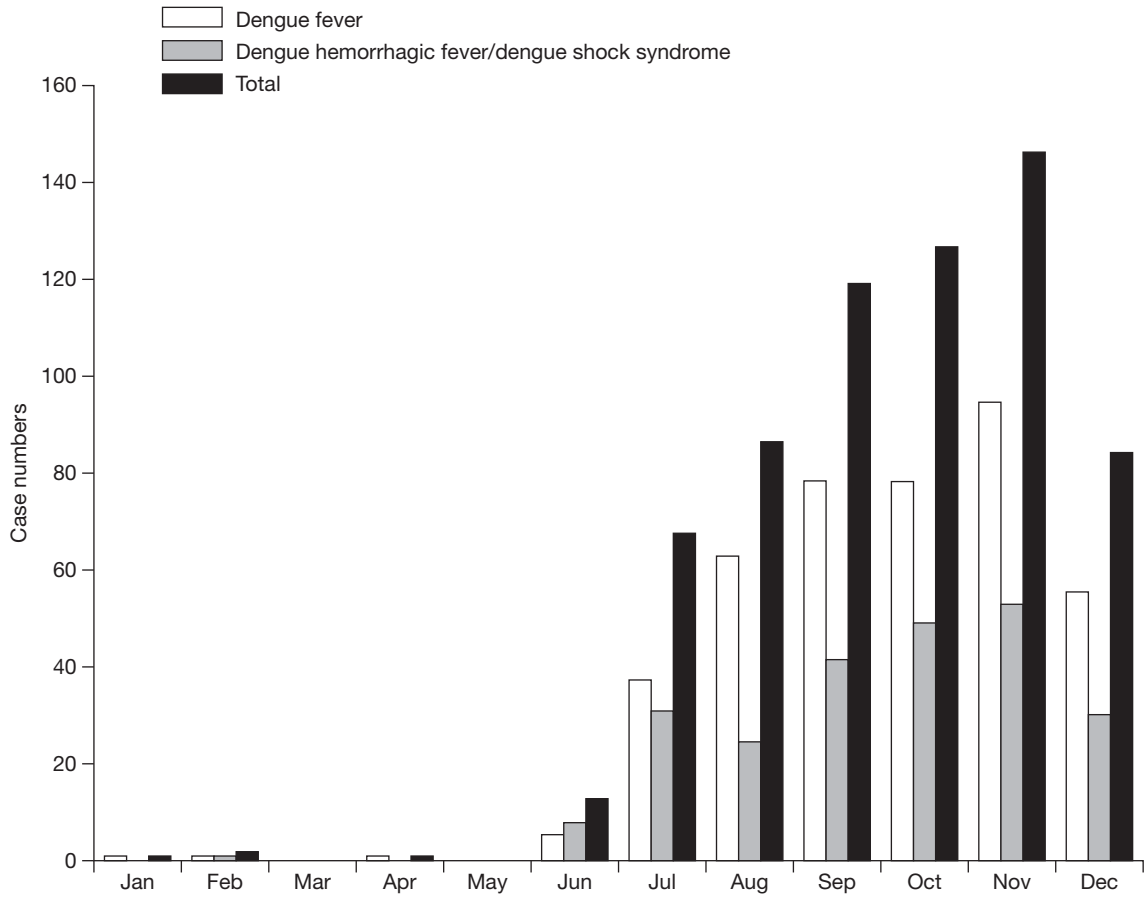

Fig. 1. Confirmed dengue cases (n = 644) at Kaohsiung Medical University Hospital by month from January through December 2002.

Table 1. Demographic and clinical data of confirmed dengue cases at Kaohsiung Medical University Hospital, 2002

	DF (n = 412)	DHF/DSS (n = 232)	Total (n = 644)
Male/female (ratio)	177/235 (0.75)	119/113 (1.05)[a]	296/348 (0.85)
Age (years) [mean ± SD; range]	44.1 ± 17.8 (0-85)	53.6 ± 16.3 (5-88)[b]	47.5 ± 17.9 (0-88)
Past history of dengue infection (no.) [%]	39 (9.5)	43 (18.5)[b]	82 (12.7)
Chronic disease (no.) [%]			
Diabetes mellitus	27/355 (7.6)	39/232 (16.8)[b]	66/587 (11.2)
Hypertension	58/355 (16.3)	67/232 (28.9)[b]	125/587 (21.3)
Chronic hepatitis (HBV/HCV)	33/173 (19.1)	29/161 (18.0)	62/334 (18.6)
Renal insufficiency	3/287 (1.0)	15/227 (6.6)[b]	18/514 (3.5)
Hospitalized (no.) [%]	249 (60.4)	230 (99.1)[b]	479 (74.4)
Length of hospital stay (days) [mean ± SD; range]	5.9 ± 2.9 (1-30)	8.3 ± 6.9 (3-72)	7.1 ± 5.4 (1-72)
Outcome (no.) [%]			
Deaths	0 (0.0)	7 (3.0)	7 (1.1)
Received platelet concentrate transfusion (no.) [%]	122 (29.6)	202 (87.1)[b]	324 (50.3)
Amount of platelet transfusion (units) [mean ± SD; range]	31.7 ± 15.8 (12-72)	44.6 ± 27.4 (11-168)	39.8 ± 24.5 (11-168)

Abbreviations: DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; SD = standard deviation; HBV = hepatitis B virus; HCV = hepatitis C virus

[a] $p<0.05$, chi-squared test, comparison of DF and DHF.

[b] $p<0.005$, chi-squared test, comparison of DF and DHF.

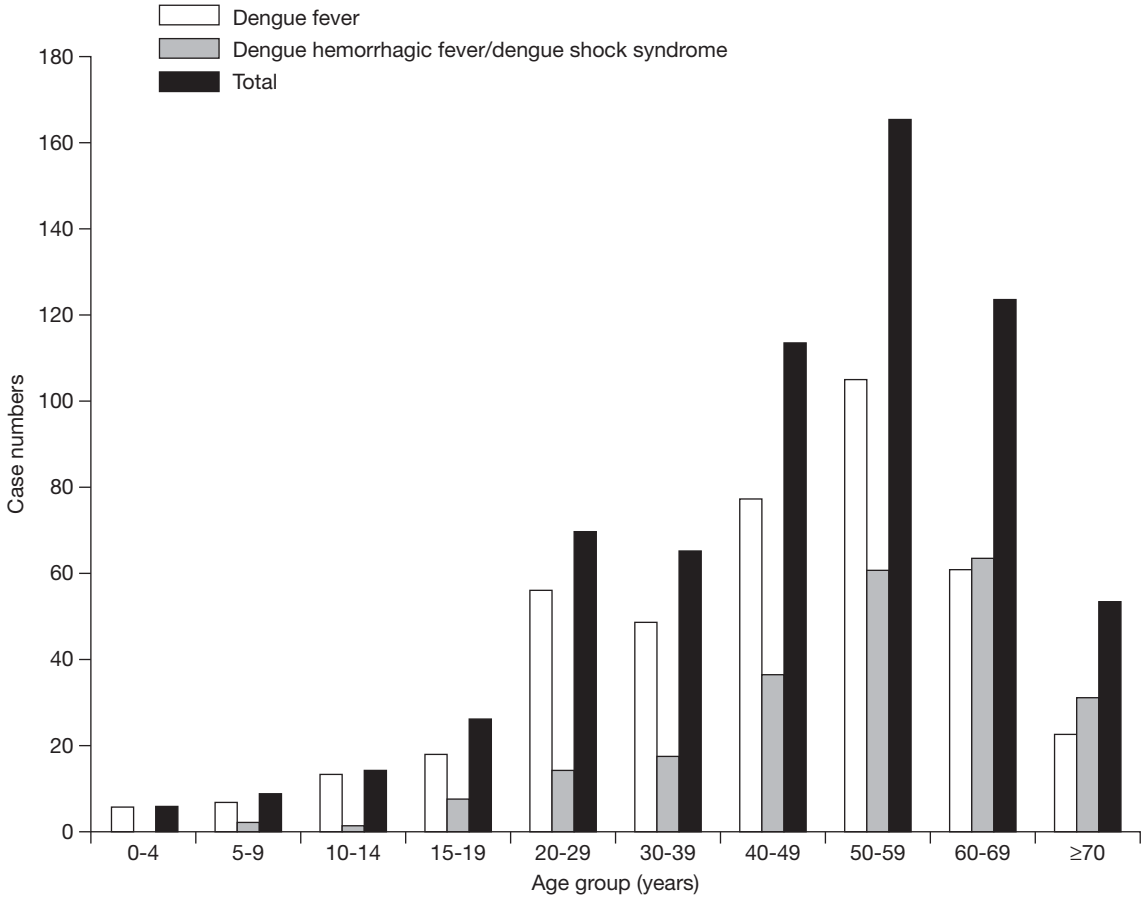

Fig. 2. Age distribution of confirmed dengue cases at Kaohsiung Medical University Hospital in 2002.

rhinitis (14.8%). Urinary symptoms such as burning sensation at micturition and dysuria were reported in 25.9% of cases. Hemorrhagic manifestations were noted in 73.0% of the patients, the most frequent being bleeding from the skin (70.6%), spontaneous petechiae, and microscopic hematuria (60.3%) [Table 2]. Both leukopenia with a white cell count less than 3000/mm^3 (55%) and thrombocytopenia (78.9%) were common.

Of the 644 confirmed cases of dengue virus infection, 479 (74.4%) were hospitalized and 8 cases (1.2%) were fatal. The average hospital stay was 7 days and 50.3% of patients received platelet concentrate transfusions during hospitalization (Table 1).

DHF/DSS cases

232 (36.0%) of the 644 confirmed cases of dengue virus infection met the criteria for DHF. Twelve of the DHF cases met the criteria for DSS. The male-to-female ratio and mean age for the DHF/DSS cases were similar to the DF group (Table 1). Among them, 154 cases (66.4%) were at least 50 years old. The age range with the highest percentage of cases was 60 to 69 years old (27.2%); only 3 cases (1.3%) involved children and adolescents below 15 years of age (Fig. 2).

Table 2. Hemorrhagic manifestations of 644 confirmed dengue patients at Kaohsiung Medical University Hospital, 2002

Findings	Number of cases (positive/tested)	Percent
Any hemorrhage	473/644	73.0
Skin bleeding[a]	334/473	70.6
Microscopic hematuria[b]	241/400	60.3
Gum bleeding	134/472	28.4
Melena	97/473	20.5
Epistaxis	47/472	10.0
Vaginal hemorrhage	22/261	8.4

[a]Skin bleeding included petechiae, ecchymosis, purpura and hematoma.

[b]Microscopic hematuria was defined as the presence of more than 5 red blood cells per high-power field or a positive result for blood in the urinalysis.

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Table 3. Clinical characteristics of 8 fatal dengue cases at Kaohsiung Medical University Hospital, 2002

Case	Gender	Age (years)	Underlying disease	Presentation of dengue	Classification	Hospital stay	Cause of death
1	Female	57	Nil	Fever, myalgia, epigastralgia, epistaxis, petechiae	DSS	2 days	Profound shock
2	Female	71	HTN	Fever, myaglgia, malaise, anorexia, abdominal pain, UGI bleeding, petechiae, hepatic encephalopathy	DSS	3 days	Profound shock
3	Female	69	Uremia	Fever, malaise, anorexia, nausea, vomiting, ecchymosis, tarry stool, liver failure	DSS	9 days	Peripheral vascular failure
4	Male	78	DM, HTN, COPD, old CVD, gout	Fever, myalgia, petechiae and UGI bleeding, hepatic encephalopathy	DHF	8 days	Nosocomial PN
5	Male	71	HTN, uremia	Fever, malaise, rhinitis, tarry stool	DHF	28 days	Nosocomial infection (*Klebsiella pneumoniae*, *Morganella morganii*)
6	Male	53	HTN, uremia	Fever, headache, myalgia, diarrhea, bloody stool	DHF	32 days	Nosocomial PN, pulmonary hemorrhage
7	Female	55	Colon cancer post OP	Fever, cough, petechiae, UGI bleeding, liver failure	DHF	5 days	Nosocomial infection
8	Male	64	HTN, uremia, gout	Fever, headache, myalgia, diarrhea petechiae, tarry stool	DHF	5 days	Nosocomial PN (*Pseudomonas aeruginosa*)

Abbreviations: HTN = hypertension; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CVD = cerebral vascular disease; OP = operation; UGI = upper gastrointestinal tract; DSS = dengue shock syndrome; DHF = dengue hemorrhagic fever; PN = pneumonia

The youngest patient was 5 years 3 months old. Forty three cases (18.5%) had a previous history of dengue infection. Diabetes mellitus was an underlying condition in 39 cases (16.8%) and hypertension in 67 cases (28.9%). Fifteen patients (6.6%) were known to be uremic and were undergoing hemodialysis. Most DHF/DSS cases were hospitalized for a little more than a week (8.3 ± 6.9 days; range 3-72 days). Only 2 of the DHF patients were treated for DF with hemorrhage on an outpatient basis (Table 1).

Mortality occurred in 8 cases, including 5 with DHF and 3 with DSS (3.4% of DHF/DSS cases). Three patients, all female, died from dengue virus infection itself (cases 1-3 in Table 3). All 3 presented typical symptoms of fever, myalgia and petechiae. Two of these 3 patients died of profound shock within 3 days of admission. Case 2 had highly elevated levels of transaminase (aspartate aminotransferase [AST] 4140 IU/L; alanine aminotransferase [ALT] 2149 IU/L) complicated with massive upper gastrointestinal bleeding and hepatic encephalopathy. Case 3 progressed from DF to DSS during hospitalization and died of peripheral vascular failure despite intensive care. The remaining 5 fatal cases had superimposed nosocomial bacterial infections which did not respond to antibiotic therapy (Table 3). Seven of the 8 fatal cases had underlying chronic diseases such as diabetes mellitus, hypertension, and uremia with regular hemodialysis. None of the 8 fatal cases had a known history of dengue virus infection.

Risk factors for DHF/DSS

The proportion of DHF/DSS cases associated with chronic diseases such as diabetes mellitus, hypertension or renal insufficiency (uremia) was significantly ($p<0.005$) higher than for DF cases (16.8% vs 7.6%, 28.9% vs 16.3%, and 6.6% vs 1.0%, respectively). Other factors associated with DHF/DSS included male, elderly, and history of dengue infection ($p<0.05$) [Table 1]. Multiple logistic regression analysis revealed a significant association between DHF/DSS and age >65 years old, history of dengue infection, diabetes mellitus, hypertension, and renal insufficiency (Table 4).

Laboratory findings in DHF/DSS

All 232 DHF patients had documented white cell, hematocrit and platelet counts. Platelet counts ranged

from 1000/mm^3 to 77,000/mm^3, with a median of 14,000/mm^3. White cell counts ranged from 880/mm^3 to 12,910/mm^3, with a median 2960/mm^3. Hematocrit ranged from 24.4% to 56.0%, with a mean of 42.9% and a median of 43.3%. Liver function test results were available for 230 (99.1%) of the DHF cases. AST (normal range, 10-33 IU/L) was as high as 508.2 IU/L (median 122.5, range 13-23,620). The highest alanine aminotransferase (ALT) [normal range, 3-34 IU/L] reading was 198.8 IU/L (median 75.5, range 7-6360).

DHF/DSS cases (33.5%) had significantly higher levels of ALT (above 100 IU/L) than DF cases (16.3%; $p<0.005$) [Table 4]. Serum albumin level (normal range, 3.85-4.95 g/dL) was assessed in 220 DHF patients, revealing a decreased mean value of 3.55 g/dL, a median of 3.57 g/dL, and a range of 1.05 to 4.51 g/dL. Activated partial thromboplastin time (aPTT) was prolonged in 64.7% of the DHF/DSS patients but in only 42.9% of the DF patients (aPTT >50% control) [$p<0.005$]. Urinalysis was performed in 211 of 232 DHF/ DSS patients and revealed that 57.3% of these patients had proteinuria compared to 32.7% of DF cases ($p<0.005$).

Some patients with DF, typically DHF patients with impending shock, experienced intense continuous abdominal pain [6], especially over the epigastrium and right upper abdominal quadrant. This clinical presentation mimics that of acute cholecystitis. Review of hospital records in this series revealed that "acute cholecystitis" had been diagnosed in 1 patient with DHF, and this patient had been prepared for surgery at the time of the finding of DF. Abdominal pain was noted in 62.1% of the DHF/DSS patients and 30.8% of those with DF ($p<0.05$). Abdominal ultrasound examination was performed in 136 DHF/DSS patients and over half (64.7%) had the finding of gallbladder wall thickening. The same ultrasound finding was made in only 22% of the DF patients ($p<0.005$).

High ALT (ALT >100 IU/L) [odds ratio (OR), 2.38; 95% confidence interval (CI), 1.04 to 5.74; $p=0.045$] and gallbladder wall thickening (OR, 6.13; 95% CI, 2.75 to 14.56; $p=0.0001$) were independently associated with the occurrence of DHF/DSS on multiple logistic regression analysis (Table 4).

Discussion

This study investigated the clinical characteristics and risk factors for DHF/DSS in patients with confirmed dengue virus infection during the epidemic of southern Taiwan in 2002. In contrast to previously reported studies from dengue hyperendemic Asian countries [9], this retrospective analysis of the 2002 epidemic in Taiwan showed a markedly higher age distribution of DHF/DSS (mean 53.6 ± 16.3 years), and elderly status was a significant risk factor for DHF/DSS. Since the island-wide outbreak of dengue infection in 1943, intervals of several years have usually passed between dengue epidemics in southern Taiwan. More adults, especially elderly, rather than children, may have been affected

Table 4. Comparison of clinical features and laboratory findings between dengue fever (DF) and dengue hemorrhagic fever (DHF) patients at Kaohsiung Medical University Hospital, 2002

Variables	DF positive/ tested (%)	DHF/DSS positive/ tested (%)	Multivariate logistic regression analysis			
			Odds ratio	95% CI	Beta	*p*
Clinical features						
Male	177/412 (42.9)	119/232 (51.3)	1.35	0.94-1.95	0.302	0.107
Age >65 years	39/412 (9.5)	51/232 (22.0)	1.84	1.11-3.08	0.611	0.019
Past history of dengue infection	39/412 (9.5)	43/232 (18.5)	2.13	1.27-3.62	0.758	0.004
Diabetes mellitus	27/355 (7.6)	39/232 (16.8)	1.86	1.04-3.37	0.618	0.039
Hypertension	58/355 (16.3)	67/232 (28.9)	1.74	1.09-2.78	0.552	0.021
Renal insufficiency	3/287 (1.0)	15/227 (6.6)	3.65	1.14-16.26	1.295	0.048
Laboratory findings						
ALT >100 IU/L	57/349 (16.3)	77/230 (33.5)[a]	2.38	1.04-5.74	0.867	0.045
Blood sugar >140 mg/dL	42/232 (18.1)	63/210 (30.0)[a]	1.32	0.57-3.17	0.279	0.522
aPTT >50% control	90/210 (42.9)	136/208 (65.4)[a]	1.30	0.58-2.86	0.263	0.515
Proteinuria	82/251 (32.7)	121/211 (57.3)[a]	1.22	0.55-2.69	0.198	0.624
Gallbladder wall thickening	18/82 (22.0)	88/136 (64.7)[a]	6.13	2.75-14.56	1.813	0.0001

Abbreviations: DSS = dengue shock syndrome; CI = confidence interval; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time

[a] $p<0.005$, chi-squared test.

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and remain susceptible to secondary infection. A previous study from Thailand found that secondary infection with DEN-2 was the most important risk factor for DHF/DSS [10].

Chronic diseases such as bronchial asthma, sickle cell anemia, and possibly diabetes have been suggested as possible risk factors for DHF, and are present in a high percentage of severe or fatal cases of DHF/DSS. Bravo et al suggested that genetic factors might play a part in the development of DHF [11]. The finding of this study that chronic diseases such as diabetes mellitus (present in approximately 4% of the Taiwanese population [12]), hypertension and uremia were significantly more prevalent in DHF/DSS patients than in DF cases supports their observations, although establishing any causal link was beyond the scope of this study. It is noteworthy that since thrombocytopenia and low hematocrit are common findings in uremic patients, clinicians need to maintain a high level of suspicion as these variations in hemoconcentration are possible early indicators of DHF.

While liver transaminases were formerly thought to be only mildly elevated even in cases of DHF/DSS, significant liver involvement has been documented in especially severe cases [13,14]. Studies of the 1987 to 1988 DEN-1 epidemics in Taiwan revealed significantly higher elevations of AST, ALT, and gamma-glutamyl transpeptidase in patients with episodes of bleeding [15]. In the present study, most DHF patients exhibited abnormal levels of AST and ALT. Moderate to severe elevation of ALT levels was almost twice as likely to be found in DHF cases compared to DF cases.

Thickening of the gallbladder wall, which normally measures no more than 3 mm in fasting subjects, is normally found postprandially but is also a nonspecific finding associated with an array of conditions, including acute or chronic cholecystitis, acute viral hepatitis, chronic liver disease, congestive heart failure, chronic renal failure, ascites, hypoalbuminemia of <3.5 g/dL, and acquired immunodeficiency syndrome [16-19]. The pathogenesis of gallbladder wall thickening in viral hepatitis is unknown, although it may be due to direct viral invasion of the gallbladder wall [20], obstruction of lymphatic drainage [17], severe hypoalbuminemia, and portal hypertension [21]. We found gallbladder wall thickening in 64.7% of DHF patients who underwent ultrasound examinations in this series. Comparison of the mean serum albumin level in DHF patients with gallbladder wall thickening with that in DHF patients with normal gallbladder did not reveal any correlation between the albumin level and the ultrasonographic findings. As can be seen from the data in Table 4, however, while a thickened gallbladder wall in patients with DHF is not pathognomic for acute cholecystitis, it is significantly associated with increased likelihood of DHF.

The prognosis of DHF depends on prevention or early treatment of shock. Once shock develops, the mortality may be as high as 44% [22]. Two of the 8 fatal cases in this series were admitted to the hospital in a state of shock. While early recognition of the above risk factors may be helpful in successful identification and management, analysis of hospital records of the fatal cases in this study revealed that most of the patients died from superimposed bacterial infection. Concomitant infections in these patients included nosocomial pneumonia caused by *Pseudomonas aeruginosa* or *Klebsiella pneumoniae*, and *Morganella morganii* bacteremia. Thus, superimposed infection may be a further risk factor. The similar overall morbidity observed in the present study and in previous series from Asia [23] suggests that close monitoring of elderly patients with DF, especially those with comorbidities or increased susceptibility to nosocomial infections, may lessen case fatality.

During 2002, physicians in all the hospitals and clinics in Kaohsiung city were required to report any suspected DHF cases who met the criteria of fever (>38°C), thrombocytopenia (platelet count, <100,000/mm^3), hemorrhagic manifestations, and evidence of increased capillary permeability such as hemoconcentration, pleural effusion, ascites, and hypoproteinemia. The observed incidence of DHF in our study was nearly equal to the incidence detected by the passive surveillance system (232 vs 242 cases). Of the 195 cases of reported suspected DHF by KMUH to the CDC during the epidemic period, confirmation was made by the CDC in 68. The remaining 164 of the 232 DHF cases (71%) identified by our study were discharged without a diagnosis of DHF. Among the 164 cases, 84 cases (51%) had evidence of pleural effusion on chest X-ray and ascites on echo in 51 (31%). Hemoconcentration was noticed after recalculation in 73 (45%) of the 164 cases. These results suggest that capillary permeability is not commonly considered a criterion for DHF diagnosis and strongly indicate that DHF was underdiagnosed in this epidemic. Since data are not available on the normal hematocrit by age and gender for the Taiwan population, the diagnostic process should emphasize the criterion of decrease in hematocrit

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by 20% or more after hydration. Further diagnostic attention is required to prevent shock and ensuing death in these DHF patients.

In Southeast Asia, DHF remains primarily a children's disease. In Latin America and the Caribbean, DHF showed similar clinical features in all age groups, although the incidence has been reported to be higher for those below the age of 15 [24,25]. In Taiwan, however, elderly patients and those with chronic pre-existing comorbidities such as diabetes mellitus, hypertension, and uremia are at higher risk of developing DHF than children. This difference in age distribution may offer other clues useful in the detection of DF in Taiwan. In addition, once dengue infection is diagnosed, liver function tests and ultrasound are useful in predicting which patients are more likely to develop DHF.

The frequency of DF outbreaks is likely to increase in Taiwan in conjunction with increasing numbers of cases of severe disease and high indices of the principal mosquito vector, *Aedes aegypti*. Epidemic DHF/DSS may therefore become an increasingly important public health problem in Taiwan. Since there remain a significant number of practical, logistic, and scientific challenges before dengue vaccines can widely and safely be applied to vulnerable populations [26], continuous surveillance and education for clinicians in the recognition of DHF and the risk factors is needed.

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