Clinical Characteristics, Risk Factors, and Outcomes in Adults Experiencing Dengue Hemorrhagic Fever Complicated with Acute Renal Failure

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Abstract. In a retrospective study, acute renal failure (ARF) was found in 10 (3.3%) among 304 hospitalized adults with dengue hemorrhagic fever (DHF), and 6 (60%) of the 10 patients with ARF died, whereas all 294 patients without ARF (controls) survived (P < 0.001). Compared with the controls, DHF patients with ARF were found to be significantly older (P = 0.002) and male predominant (P < 0.001) and to have higher frequency of previous stroke (P = 0.005), chronic renal insufficiency (P = 0.046), dengue shock syndrome (DSS; P < 0.001), gastrointestinal bleeding (P < 0.001), and concurrent bacteremia (P = 0.009), lower hemoglobin (P = 0.003) and serum albumin levels (P = 0.003), and higher incidences of prolonged prothrombin time (P < 0.001), elevated aspartate aminotransferase (P < 0.001), and alanine aminotransferase levels (P < 0.001). Multivariate analysis showed DSS (odd ratio = 220.0; P < 0.001) was an independent risk factor for development of ARF in DHF patients. The high fatality rate in DHF patients complicated with ARF in our series underscore the importance of clinicians’ alertness to this potentially fatal complication so that initiation of timely appropriate treatment is possible.

INTRODUCTION

Dengue virus infection is one of the major emerging infectious diseases in the world.1 Dengue illness covers a broad spectrum of clinical manifestations with diverse severity and prognosis, which include dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).1,2 DSS is the most severe form of dengue infections.1,2 In Taiwan, a number of dengue epidemics have occurred since the 1980s,3,4 and among the recent dengue epidemics on this island, one dengue outbreak caused by dengue virus serotype 1 (DEN-1) occurred in 1987–1988 in southern Taiwan, followed by a large dengue epidemic caused by DEN-2 involving > 5,000 symptomatic cases in 2002.3,4 Most of the patients with DHF in the dengue epidemic in 2002 were of secondary dengue infection.4 In this epidemic, 10 DHF patients complicated with acute renal failure (ARF) were found at Chang Gung Memorial Hospital-Kaohsiung (CGMH-KS), Taiwan. ARF is a rare complication in dengue infections.5 Development of ARF was reported to be an ominous sign indicating poor prognosis in patients with bacterial sepsis.6 However, little is known about the implications of ARF in dengue illness, although limited number of reports suggested that timely recognition of ARF in patients with DHF might not only reduce morbidity but also significantly decrease mortality.7–9 The objectives of this study are to better understand the clinical characteristics and outcomes of DHF patients with ARF and to identify risk factor(s) for development of ARF in patients experiencing DHF.

MATERIALS AND METHODS

Patients > 18 years of age with the diagnosis of DHF admitted to CGMH-KS between June and December 2002 were included in this retrospective study. CGMH-KS is a 2,500-bed primary care and tertiary referral medical center in southern Taiwan. The medical charts of the included patients were reviewed for collection of demographic, clinical, laboratory, and imaging information for analyses.

The diagnosis of dengue infection was made based on at least one of the following criteria: 1) a positive reverse transcriptase-polymerase chain reaction result, 2) a positive enzyme-linked immunosorbent assay result for specific dengue immunoglobulin M antibody to dengue virus in acute phase serum, and 3) at least 4-fold increase of dengue-specific hemagglutination inhibition titers in convalescent serum when compared with acute phase serum.13 In the serologically confirmed dengue-infected patients, the diagnosis of DHF and the stratification of severity of DHF (Grades I–IV) were in accordance to the World Health Organization criteria.14 Plasma leakage was defined by the presence of hemococoncentration (> 20% increase in hematocrit compared with the corresponding value at discharge), pleural effusion, ascites, and/or hypoalbuminemia (< 3.5 g/dL), which developed upon the patient’s arrival or during his or her hospital stay. DHF Grades III and IV were grouped as DSS.14 ARF was defined as a rapid elevation of serum creatinine (Cr) level that was ≥ 2.0 mg/dL (normal Cr value, 0.4–1.4 mg/dL) in a hospitalized patient for DHF within a few days or doubling of the pre-existing serum Cr level in the DHF patient with chronic renal disease.15 Chronic renal disease referred to the baseline serum Cr level ≥ 2.0 mg/dL in a patient with bilateral small-size kidneys shown by renal sonography.15 Concurrent bacteremia was defined as a positive bacterial growth from blood, which was sampled for culture within 72 hours after the patient was hospitalized for DHF. Acute elevated liver enzyme was defined in a patient if he or she had an elevated serum alanine aminotransferase (ALT), which was at least 10-fold higher than the normal serum ALT level (normal value, < 40 U/L).16 Prolongation of the activated partial thromboplastin time (APTT) was defined as an increased APTT value > 20% of the control value and prolongation of the prothrombin time (PT) as an elevated PT value > 3 seconds compared with the control value. Fatality was defined as death within 2 weeks after the patient was hospitalized for DHF.

The included DHF patients were divided into two groups: patients who developed ARF (study group) and those who did not (control group). The demographic, clinical, laboratory, and imaging data of the study group were compared with those
of the control group using univariate analysis. In univariate analysis, the Student t test or Mann-Whitney U test was used in comparison between continuous variables, whereas the χ² test or Fisher exact test was used to assess differences between dichotomous variables. To determine the independent risk factor(s) for development of ARF in patients with DHF, the significant variables in univariate analyses were entered into a multivariate logistic regression model for further analysis. A two-tailed P < 0.05 was considered statistically significant.

RESULTS

During the dengue epidemic in 2002 in southern Taiwan, among 714 adults with dengue illness found in CGMH-KS, 304 experienced DHF and were included in this study. Ten (3.3%) men (median age, 69.5 years; age range, 33–78 years) with DHF developed ARF, and the other 294 without DHF were grouped as controls.

The clinical manifestations of patients with ARF were summarized in Table 1. DSS was found in 8 (80%) of the 10 DHF patients complicated with ARF. Of these eight patients, four presented with DSS at admission, whereas the other four (Patients 1, 3, 5, and 8 in Table 1) presented with either DHF Grade I or II (all with pleural effusion and hypoalbuminemia) on their admission to the hospital, which evolved into DSS during their hospitalization (median time lapse, 2.5 days; range, 2–4 days). Among the 10 DHF patients with ARF, acute gastrointestinal bleeding was found in 8 (80%); acute elevated liver enzyme was found in 6 (66.7%) of 9 patients in whom serum ALT was assayed. Eight patients with ARF had their blood urea nitrogen (BUN) assayed, and among them, three (37.5%) had a high BUN/Cr ratio > 20 (normal BUN/Cr ratio, 8–10), suggesting renal hyperperfusion. On admission, all 10 DHF patients with ARF received empiric antibiotic treatment before their DHF was serologically confirmed. Of note, concurrent bacteremia developed in three (30%; Patients 2, 7, and 10) patients. Among the three patients with concurrent bacteremia, bacterial meningitis was found in one patient (Patient 7) and primary bacteremia in two patients (Patients 2 and 10). Although all of the six patients with data available had a prolonged APTT, prolonged PT was found in only three (42.9%) of seven patients in whom serum PT was assayed. Of note, three (50%) of the six patients in whom both serum APTT and PT data were assayed had concurrent prolongation of APTT and PT.

Six (Patients 1, 5, 6, 7, 8, and 10) of the 10 DHF patients with ARF died, giving a fatality rate of 60%. Among the six deceased patients, hemodialysis was indicated in three (Patients 1, 5, and 8) caused by severe metabolic acidosis, hyperkalemia, and oliguric renal failure (pulmonary edema was additionally found in Patient 8); however, because it was hemodynamically unstable as a result of DSS, hemodialysis was deferred. Another two deceased patients (Patients 6 and 10) experienced severe gastrointestinal bleeding and profound shock (Patient 10 had concurrent primary bacteremia). One patient (Patient 7) died of concomitantly developed bacterial meningitis.

Comparisons between the study and control groups are summarized in Tables 2–4. Significantly different variables found between DHF patients with ARF and those without ARF included age (median, 69.5 versus 55 years; P = 0.002), male sex (100% versus 43.2%; P < 0.001), previous stroke (40% versus 7.1%; P = 0.005), chronic renal disease (20% versus 5.7%; P = 0.046), DSS (80% versus 3.4%; P < 0.001), gastrointestinal bleeding (80% versus 15.3%; P < 0.001), concurrent bacteremia (42.8% versus 4.5%; P = 0.009), hemoglobin (median, 8.6 versus 13.6 g/dL; P = 0.003), serum albumin levels (median, 3.2 versus 3.2 g/dL; P = 0.003), prolonged PT (42.9% versus 1.2%; P < 0.001), aspartate aminotransferase levels (median, 1.136 versus 117 U/L; P < 0.001), ALT levels (median, 637 versus 73.5 U/L; P < 0.001), and fatality rate (60% versus 0%; P < 0.001). Multivariate analysis showed DSS (odd ratio = 220.0, with 95% confidence interval = 19.804–2,443.890; P < 0.001) was an independent risk factor for development of ARF in patients with DHF.

DISCUSSION

The incidence of complicated renal dysfunction was found to be ~0.3% in one reported series that included 6,154 DHF patients whose ages were not mentioned.9 Our series showed 3.3% of ARF in 304 adults with DHF. As a tertiary referral medical center, the higher incidence of complicated ARF in patients with DHF in our series might be biased by patient selection and referral pattern. Because large dengue epidemics usually involved a huge number of affected patients in rural areas where medical resources are deficient,9,17 symptom-oriented supportive treatment rather than laboratory data–guided therapy for dengue disease is a norm; therefore, it is reasonable to speculate that complicated ARF in DHF patients has been under-reported.

Multifactorial cause may lead to ARF in patients with dengue infection.11,12,18–21 It was reported that dengue viral particles and its ribonucleic acid were detectable in the renal tissue of patients who died of DHF,20 and that, however, dengue-related immune complex did not play a significant role in the development of ARF in patients with dengue illness if their kidney function was otherwise normal because the immune complex is much smaller than the diameter of the glomeruli and will not be locally trapped.21 The finding that ARF predominantly developed in patients with DHF in this series and others11,12,18–20 as opposed to those with non-hemorrhagic dengue illness, suggests that direct dengue viral invasion of the kidney is not the only cause of ARF in patients with dengue infections if it does play a role in damaging renal function.

The coagulation–fibrinolysis system may be abnormal during dengue infection, and development of disseminated intravascular coagulation (DIC) in patients with dengue illness was previously reported.22,23 In our series, concomitant APTT and PT prolongation was found in 50% of ARF patients with data available, suggesting the potential of DIC development. In addition to thrombocytopenia, APTT, and PT prolongation, the definitive diagnosis of DIC requires the presence of decreased fibrinogen and increased fibrin degradation products,24 which were unfortunately not assayed in our patients. Nevertheless, the possibility of DIC development in our ARF patients with simultaneous APTT and PT prolongation was high, especially in those with concurrent bacteremia.

A retrospective study of 287 patients (57.5% were elderly) with ARF irrespective of the primary cause found at an emergency service of a medical center in northern Taiwan between 1983 and 1994 showed a particular high mortality rate of 74.4% in patients with pre-renal ARF, whereas the overall mortality rate was 63%,25 which was similar to the 60% in affected adults with ARF in the dengue epidemic in 2002 in southern
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years), sex</th>
<th>Underlying disease(s)</th>
<th>Severity of DHF at arrival</th>
<th>Day evolved into DSS</th>
<th>Serum creatinine (mg/dL) [day]*</th>
<th>BUN: Cr ratio</th>
<th>Major bleeding event</th>
<th>Bacterium isolated from blood culture</th>
<th>Bacterial infection source</th>
<th>Antibiotic treatment</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>33, Male</td>
<td>—</td>
<td>Grade II</td>
<td>D4</td>
<td>1.0 [D1]; 1.7 [D4]; 5.4 [D5]; 7.8 [D6]; 10.3 [D7]</td>
<td>6.9</td>
<td>GI bleeding</td>
<td>—</td>
<td>—</td>
<td>CFZ plus GEN, switched to CRO</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>55, Male</td>
<td>—</td>
<td>Grade III</td>
<td>—</td>
<td>4.6 [D1]; 2.5 [D3]; 1.2 [D8]</td>
<td>NA</td>
<td>GI bleeding</td>
<td>Klebsiella pneumoniae</td>
<td>Primary bacteremia</td>
<td>CFZ plus GEN</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>67, Male</td>
<td>Hypertension, old stroke</td>
<td>Grade II</td>
<td>D2</td>
<td>3.2 [D1]; 4.1 [D3]; 1.5 [D6]</td>
<td>31.5</td>
<td>GI bleeding</td>
<td>—</td>
<td>—</td>
<td>CXM plus GEN, switched to FEP plus TEC</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>65, Male</td>
<td>Hypertension, old stroke, chronic renal disease†</td>
<td>Grade II</td>
<td>—</td>
<td>2.1 [D1]; 3.9 [D5]; 4.6 [D6]; 5.9 [D9]</td>
<td>9.1</td>
<td>GI bleeding</td>
<td>—</td>
<td>—</td>
<td>CRO</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>69, Male</td>
<td>Diabetes mellitus, old stroke, chronic renal disease‡</td>
<td>Grade II</td>
<td>D2</td>
<td>7.6 [D1]; 5.4 [D7]; 6.0 [D10]; 11.5 [D12]</td>
<td>21.6</td>
<td>GI bleeding</td>
<td>—</td>
<td>—</td>
<td>ATM plus OXA, switched to MEM</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>78, Male</td>
<td>Hypertension</td>
<td>Grade III</td>
<td>—</td>
<td>1.7 [D1]; 3.4 [D2]</td>
<td>12.4</td>
<td>GI bleeding</td>
<td>Ecchymosis</td>
<td>Klebsiella pneumoniae</td>
<td>CRO</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>70, Male</td>
<td>Hypertension</td>
<td>Grade II</td>
<td>—</td>
<td>2.1 [D1]; 2.9 [D2]</td>
<td>20</td>
<td>GI bleeding</td>
<td>Ecchymosis</td>
<td>Klebsiella pneumoniae</td>
<td>PIP plus AMK, switched to CRO</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>72, Male</td>
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<td>Grade II</td>
<td>D3</td>
<td>1.6 [D1]; 3.8 [D2]; 6.2 [D3]</td>
<td>14.7</td>
<td>GI bleeding</td>
<td>—</td>
<td>Meningitis</td>
<td>CFZ plus GEN, switched to MEM</td>
<td>Died</td>
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<tr>
<td>9</td>
<td>74, Male</td>
<td>—</td>
<td>Grade III</td>
<td>—</td>
<td>2.1 [D1]§</td>
<td>NA</td>
<td>Ecchymosis</td>
<td>Enterococcus faecalis</td>
<td>Primary bacteremia</td>
<td>PEN plus CRO</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>70, Male</td>
<td>Hypertension, old stroke</td>
<td>Grade III</td>
<td>—</td>
<td>1.8 [D1]; 2.3 [D2]; 2.7 [D4]</td>
<td>25.7</td>
<td>GI bleeding</td>
<td>—</td>
<td>—</td>
<td>PEN plus CRO</td>
<td>Died</td>
</tr>
</tbody>
</table>

* The day of serum creatinine assayed is presented in the brackets.
† The baseline serum creatinine level of this patient was of 2.0 mg/dL.
‡ The follow-up serum creatinine level after the patient was released from hospital was of 1.0 mg/dL.
§ The follow-up serum creatinine level after the patient was released from hospital was of 2.0 mg/dL.
CFZ = cefazolin; GEN = gentamicin; CRO = ceftriaxone; CXM = cefoxime; FEP = cefepime; TEC = teicoplanin; ATM = aztreonam; OXA = oxacillin; MEM = meropenem; PIP = piperacillin; AMK = amikacin; PEN = penicillin; M = male; Cr = creatinine; BUN = blood urea nitrogen; GI = gastrointestinal; DHF = dengue hemorrhagic fever; NA = no data available.
Taiwan. Given the already high background mortality rate, our data suggested that dengue virus infection did not substantially increase risk of fatality caused by ARF in DHF adults with this complication. Information about ARF in dengue-infected patients is limited. The high mortality rate in DHF adults complicated with ARF in our series underscores the importance of clinicians’ alertness to this potentially fatal complication, so that initiation of appropriate management in a timely fashion is possible. Our data showed that DSS was an independent risk factor for development of ARF in adults with DHF. DHF is characterized by increased vascular permeability resulting in plasma leakage, which leads to development of DSS if plasma leakage is severe enough. Pre-renal azotemia reflected by the high BUN/Cr ratio developed in 37.5% of eight ARF patients with data available in this series, which was consistent with kidney hypoperfusion caused by intravascular volume deficit resulting from overwhelming plasma leakage. ARF was found in 14 (1.5%) of 913 children with dengue virus infection in a single medical center in Colombia, and whether DSS is an independent risk factor for ARF in pediatric patients remains uncertain.

There has been no specific treatment for dengue-associated ARF thus far, but, intensively monitored fluid status in the affected host and correct dengue-associated coagulopathy, and maintain electrolyte balance, if any. How to ensure safe hemodialysis when it is indicated (e.g., severe metabolic acidosis, hyperkalemia, and pulmonary edema) is a large challenge if the DHF patient complicated with ARF is hemodynamically unstable. Under such critical circumstances, continuous venovenous hemodialysis is a proposed alternative to the normally used veno-arterial hemodialysis.

Some limitations in this study must be addressed. First, the small number of study cases with ARF made the statistical power quite small. Second, histopathology of the kidney in the fatal patients was not available to provide information regarding pathogenesis of ARF. Third, being a retrospective study, clinical outcomes of the ARF patients may be biased by the lack of a standardized protocol for management of patients with DHF/DSS; for example, the choice of fluid (i.e., crystal or colloid solution) and volume optimizing, which are very important in treatment of DF/DSS, are not standardized.

Some of the patients involved in this study were included in our recently published research, in which a 12.1% ARF rate and a 7.6% fatality rate were found among 66 elderly DHF patients ≥65 years of age, and DSS was found to be the only independent risk factor for development of ARF, emphasizing that once ARF developed in these patients, the mortality rate was as high as 60% as shown in the Results section.

In summary, our data showed that DSS is an independent risk factor for development of ARF in patients with DHF and that the fatality rate is high once ARF developed. Clinicians should be alert to the potential complicated ARF in DHF patients and start timely treatment. Cases of complicated ARF in DHF in this study highlight the need for further research to optimize hemodialysis in DHF patients who are critically ill when it is indicated.
### REFERENCES