Clinical Features of and Risk Factors for Rhabdomyolysis Among Adult Patients with Dengue Virus Infection

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Abstract. Among 1,076 dengue patients, 9 patients with rhabdomyolysis and 1,067 patients without rhabdomyolysis (controls) were retrospectively analyzed. Of nine patients with rhabdomyolysis, the most commonly reported symptom other than fever was myalgia; dengue hemorrhagic fever (DHF) was found in seven cases, and acute kidney injury was found in six cases. Furthermore, one (11.1%) patient died. The median duration from hospital admission to rhabdomyolysis diagnosis was 3 days. Patients with rhabdomyolysis had higher age, proportion of men, prevalence of hypertension, frequency of myalgia, and incidences of DHF, pleural effusion, and acute kidney injury than controls. Multivariate analysis showed that hypertension (odds ratio [OR] = 14.270), myalgia (OR = 20.377), and acute kidney injury (OR = 65.547) were independent risk factors for rhabdomyolysis. Comparison of cytokine/chemokine concentrations in 101 DHF patients, including those with ($N = 4$) and without ($N = 97$) rhabdomyolysis, showed that interleukin-6 and tumor necrosis factor- α levels were significantly increased in the former.

INTRODUCTION

Dengue is one of the most important mosquito-borne diseases in humans.¹ There are four dengue virus (DENV) serotypes—DENV-1, -2, -3, and -4—that cause a spectrum of illness, ranging from clinically unapparent infection, mild febrile illness, and classic dengue fever (DF) to the severe and fatal dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS).² Approximately 2.5 billion people are estimated to be living in dengue-endemic regions, and 50–100 million persons are annually infected by DENV.^{1,3} In addition, dengue is currently a more common cause of febrile illness than malaria among travelers returning from southeast Asia, where this disease is endemic.⁴ The number of cases of dengue among travelers returning to the United States has been increasing steadily in the past decades.^{5,6} As the number of dengue cases is increasing globally,¹ the incidence of rhabdomyolysis associated with DENV infection is also increasing.^{7–18} Rhabdomyolysis is a potentially life-threatening syndrome characterized by the breakdown of skeletal muscle.¹⁹ Inappropriate treatment of this condition can lead to electrolyte disturbances, metabolic acidosis, coagulation defects, and acute kidney injury.¹⁹ Rhabdomyolysis caused by viral infections, such as influenza viruses, parainfluenza viruses, echoviruses, and coxsackievirus has been well-described.^{19–24} However, only a few studies on rhabdomyolysis associated with DENV infection are available, and all of them are case reports or literature reviews.^{7–18} The uncommon and atypical manifestation of dengue-related rhabdomyolysis has limited clinician awareness. Delayed or missed diagnosis and inappropriate treatment of dengue-related rhabdomyolysis could result in serious complications, such as acute kidney injury and even death.^{7–18} To elucidate the clinical features of and risk factors for dengue-related rhabdomyolysis, we conducted a retrospective analysis of patients with dengue that was diagnosed over an 11-year period in a large medical center. We aimed to better understand the demographic, clinical, and laboratory characteristics of

rhabdomyolysis in adult dengue patients and identify the risk factor(s) for developing rhabdomyolysis as well as cytokine/chemokine responses in dengue patients with rhabdomyolysis.

MATERIALS AND METHODS

Ethics statement. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH; document no. 103-2908B). All data were analyzed anonymously, and patient consent was waived for the study.

Patients and setting. In this retrospective study, 1,076 adult patients (age ≥ 18 years old) with laboratory-confirmed DENV infection admitted to Kaohsiung (KS) CGMH during 2002–2013 were included. KSCGMH is a 2,700-bed medical facility serving as a primary and tertiary referral center in southern Taiwan. We excluded dengue-affected patients with nosocomially acquired infection by positive bacterial culture of blood sampled > 72 hours after admission. The included patients were divided into two groups: those who developed rhabdomyolysis (study group; $N = 9$) and those who did not develop rhabdomyolysis (control group; $N = 1,067$). The medical records were reviewed using a standardized form. Data on demographic characteristics, medical history before onset of dengue illness, initial symptoms/signs, and initial and entire laboratory test results as well as imaging before occurrence of rhabdomyolysis were collected for analyses. Initial symptoms/signs and laboratory features referred to data detected from the dengue-affected patients on their arrival at KSCGMH.

All dengue cases included in this study were confirmed by at least one of the following criteria: (1) positive DENV-specific real-time reverse transcription polymerase chain reaction (RT-PCR; QuantiTect SYBR Green RT-PCR Kit; QIAGEN GmbH, Hilden, Germany), (2) a fourfold increase in DENV-specific immunoglobulin G (IgG) antibody in convalescent serum compared with the acute phase, and (3) acute-phase serum positive for DENV-specific non-structural glycoprotein-1 antigen (Bio-Rad Laboratories, Marnes-la-Coquette, France).²⁵ These diagnostic tests were performed by the Center for Disease Control in Taiwan.

Definitions. Patients with a discharge diagnosis of rhabdomyolysis were reviewed in detail. Rhabdomyolysis was defined as a fivefold increase in serum concentration of creatine

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phosphokinase (CPK) above the upper limit of the normal range (reference value = 13–130 U/L), with a CPK-muscle fraction of > 95% after hospitalization for dengue illness.^{26–28} The 1997 World Health Organization (WHO) classification and case definitions were used to classify the dengue cases into DF, DHF, or DSS.² Hypertension was confirmed if the patient was taking antihypertensive medication for previously diagnosed hypertension. Acute kidney injury was defined as a rapid increase in serum creatinine level of > 0.5 mg/dL above baseline within 48 hours of hospital admission.²⁹ Severe thrombocytopenia was defined as a peripheral platelet count < 20×10^9 cells/L. Severe hepatitis was defined as an increase in serum alanine aminotransferase (ALT) level to > 1,000 U/L (reference value = 40 U/L).¹ Leukopenia was defined as a peripheral white cell count < 3,000/mL, and leukocytosis was defined as a peripheral white cell count > 12,000/mL. Hypoalbuminemia was defined as a serum albumin level < 3.0 mg/dL. Hemoconcentration referred to a > 20% increase in hematocrit value, which was calculated as (maximum hematocrit value – minimum hematocrit value) $\times$ 100/minimum hematocrit value.^{2,25}

Cytokine/chemokine detection. Blood samples were drawn from 101 DHF patients between 2009 and 2013. The median interval from the onset of dengue illness to blood sampling was 3 days (range = 1–7). The whole blood was immediately separated into plasma and blood cells by centrifugation at 2,500 rpm ($150 \times g$) for 20 minutes. Plasma was dispensed into several aliquots and kept frozen at -80°C until use.³⁰ Estimation of cytokine/chemokine levels in the plasma samples was done using the MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel (Millipore Corporation, Billerica, MA) according to the manufacturer's instructions.³¹ The following cytokines and chemokine were evaluated in this study: granulocyte macrophage colony-stimulating factor (GM-CSF), interferon- γ (IFN- γ), interleukin (IL)-10, IL-2, IL-6, tumor necrosis factor- α (TNF- α), and monocyte chemoattractant protein-1 (MCP-1). The measurements were performed at the same time by an experienced technologist in a research laboratory of KSCGMH.

Statistical analysis. The demographic and initial clinical and laboratory features as well as imaging before occurrence of rhabdomyolysis were compared between the study and control groups using univariate analysis; the Mann–Whitney *U* test was used to compare continuous variables, whereas the Fisher's exact test was used to compare dichotomous variables. To determine the independent risk factor(s) for development of rhabdomyolysis in dengue patients, the significant variables from univariate analyses were entered into a multivariate logistic regression model for additional analysis. Cytokine/chemokine data were expressed as median and range (pictograms per milliliter). Regression analysis and a standard curve were used to estimate the cytokine/chemokine concentration, and the Mann–Whitney *U* test was used to assess the differences in cytokine/chemokine concentrations between dengue patients with rhabdomyolysis (study group) and those without rhabdomyolysis (control group). A two-tailed *P* value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics. Of 1,076 adults with dengue illness (median age = 53 years; range = 18–88 years), 498 (46.3%)

patients were men, 255 (23.7%) patients had hypertension, 165 (15.3%) patients had diabetes mellitus, and 46 (4.3%) patients were receiving statin therapy before the onset of dengue illness. Furthermore, DHF was found in 355 (33%) patients, acute kidney injury in 15 (1.4%), rhabdomyolysis in 9 (0.8%), and severe hepatitis in 7 (23.3%) of 745 patients with ALT data available. The three leading symptoms at the time of hospital presentation among the included patients were fever (94.5%), bone pain (50.7%), and headache (43.1%). Of a total of 886 DENV serotypes identified, DENV-2 was the most common (91%) followed by DENV-3 (7.3%), DENV-1 (1.6%), and DENV-4 (0.1%). Among 1,076 patients, 12 patients died, accounting for a mortality rate of 1.1%. Chikungunya was not tested for, because based on the clinicians' experiences, chikungunya was not a major cause of febrile illness in Taiwan.^{32,33} The demographic, clinical, and laboratory features as well as imaging data of the included patients are summarized in Tables 1 and 2.

Characteristics of patients with rhabdomyolysis. Nine men (median age = 65 years; range = 30–71 years) with DENV infection developed rhabdomyolysis (median CPK = 1,826 U/L; range = 906–119,046 U/L). Myoglobinemia was detected in six patients with data available (median myoglobin = 588.8 ng/mL; range = 574–14,196 ng/mL; reference value = 17.4–105.7 ng/mL). Data on lactate dehydrogenase, aldolase, and urine myoglobin were not available in this series. Pharyngeal or nasopharyngeal swabs were collected from three patients for rapid influenza diagnostic test, and the results were negative. None of the patients were reported to have alcohol and illicit drug abuse, received intramuscular injection, and a history of trauma. Details on nine patients with rhabdomyolysis are summarized in Table 3. Among nine patients, eight (88.9%) patients (patients 1–6, 8, and 9) had hypertension, and four (44.4%) patients (patients 1, 4, 6, and 8) received statin therapy before the onset of dengue illness. Furthermore, the time lapses from onset of illness to hospital admission ranged from 1 to 7 days (median = 3 days) and from hospital admission to diagnosis of rhabdomyolysis ranged from 1 to 6 days (median = 3 days). DENV-2 and -3 were identified in four (each 44.4%) patients each, and DENV-1 was identified in one (11.1%) patient.

A variety of symptoms/signs at the time of hospital presentation was found among nine patients (Table 1). Following fever (88.9%), the most frequently noted presentations were myalgia (77.8%), bone pain (66.7%), and headache (55.6%). Of nine patients with rhabdomyolysis, two (22.2%) patients (patients 3 and 9) had DF, and seven (77.8%) patients (patients 1, 2, and 4–8) had grade 2 DHF. Clinical manifestations of plasma leak in seven DHF patients included hemoconcentration (patients 4 and 5–8), presence of pleural effusion (patients 2, 4, 5, 7, and 8), and hypoalbuminemia (patients 1, 5, and 7). Five DHF (55.6%) patients (patients 1, 5, 6, 7, and 8) experienced severe muscle weakness in either the arm(s) or leg(s) (Figure 1). Six DHF (66.7%) patients (patients 1, 2, 4, 5, 6, and 7) developed acute kidney injury before the diagnosis of rhabdomyolysis was established. Among these six patients, the median interval from hospital admission to the diagnosis of acute kidney injury was 1 day (range = 1–2 days), the median interval from hospital admission to the diagnosis of rhabdomyolysis was 3 days (range = 1–6 days), and the median interval from acute kidney injury to diagnosis of rhabdomyolysis was 2 days (range = 1–5 days); furthermore, four

TABLE 1
Demographic, clinical features and outcomes of the included patients

Variable	Total cases (N = 1,076)	Study group (N = 9)	Control group (N = 1,067)	P*
Median age, years (range)	53 (18–88)	65 (30–71)	53 (18–88)	0.019
Male, number (%)	498 (46.3)	9 (100)	489 (45.8)	0.001
Comorbid condition,† number (%)				
Type 2 diabetes mellitus	165 (15.3)	1 (11.1)	164 (15.4)	> 0.99
Essential hypertension	255 (23.7)	8 (88.9)	247 (23.1)	< 0.001
Chronic kidney disease	22 (2)	2 (22.2)	20 (1.9)	> 0.99
Ischemic heart disease	20 (1.9)	0	20 (1.9)	> 0.99
Solid cancer	43 (4)	0	43 (4)	> 0.99
History of stroke	27 (2.5)	3 (33.3)	24 (2.2)	> 0.99
Patients receiving statin therapy, number (%)	46 (4.3)	4 (44.4)	42 (4)	> 0.99
Patients with hypertension receiving statin therapy/patients with hypertension (%)	36/255 (14.1)	4/8 (50)	32/247 (13)	> 0.99
DENV serotype, number/total (%)				
DENV-1	14/886 (1.6)	1/9 (11.1)	13/877 (1.5)	0.927
DENV-2	806/886 (91)	4/9 (44.4)	802/877 (91.4)	0.962
DENV-3	65/886 (7.3)	4/9 (44.4)	61/877 (6.9)	0.928
DENV-4	1/886 (0.1)	0/9 (0)	1/877 (0.1)	1 (reference)
DHF, number (%)	355 (33)	7 (77.8)	348 (32.6)	0.008
Grade 1	83 (23.4)	1 (14.3)	82 (23.6)	–
Grade 2	242 (68.2)	6 (85.7)	236 (67.8)	–
Grades 3 and 4	30 (8.4)	0	30 (8.6)	–
Image findings, number/total (%)				
Pleural effusion	172/706 (24.4)	5/9‡ (55.6)	167/697 (23.9)	0.043
Ascites	120/524 (22.9)	0/9‡ (0)	120/515 (23.3)	0.221
Hepatomegaly	4/524 (0.8)	0/9‡ (0)	4/515 (0.8)	> 0.99
Splenomegaly	38/524 (7.3)	0/9‡ (0)	38/515 (7.4)	> 0.99
Gallbladder swelling	220/524 (42)	2/9‡ (22.2)	218/515 (42.3)	0.315
Complications, number (%)				
Acute kidney injury	15 (1.4)	6§ (66.7)	9 (0.8)	< 0.001
Fatal	12 (1.1)	1 (11.1)	11 (1)	> 0.99
Symptoms/signs at the time of hospital presentation,¶ number (%)				
Fever	1,017 (94.5)	8 (88.9)	1,009 (94.6)	> 0.99
Abdominal pain	316 (29.4)	2 (22.2)	314 (29.4)	> 0.99
Orbital pain	124 (11.5)	2 (22.2)	122 (11.4)	> 0.99
Bone pain	546 (50.7)	6 (66.7)	540 (50.6)	0.506
Myalgia	332 (30.8)	7 (77.8)	325 (30.5)	0.005
Headache	464 (43.1)	5 (55.6)	459 (43)	0.511
Rashes	409 (38)	4 (44.4)	405 (38)	> 0.99
Vomiting/nausea	345 (32)	1 (11.1)	344 (32.2)	0.286
Diarrhea	172 (15.9)	0	172 (16.1)	0.369
Petechial	405 (37.6)	4 (44.4)	401 (37.6)	> 0.99
Gastrointestinal bleeding	168 (15.6)	4 (44.4)	164 (15.4)	> 0.99
Gum bleeding	173 (16)	0	173 (16.2)	0.369
Cough	317 (29.5)	3 (33.3)	314 (29.4)	> 0.99
Dizzy	68 (6.3)	1 (11.1)	67 (6.3)	> 0.99
Hemoptysis	38 (3.5)	0 (0)	38 (3.6)	> 0.99

*For univariate analyses of variables in study and control groups.

†An individual patient might have more than one underlying disease/condition.

‡The median interval from the imaging study to the diagnosis of rhabdomyolysis was 1 day (range = 1–5 days).

§The median interval from acute kidney injury to the diagnosis of rhabdomyolysis was 2 days (range = 1–5 days).

¶An individual patient might have more than one symptom and/or sign.

(66.7%) patients (patients 1, 4, 5, and 7) experienced gastrointestinal bleeding.

Table 2 shows the laboratory test results during the entire clinical course as well as at the time of hospital presentation. With regard to the data on signs and symptoms at the time of presentation for nine patients with rhabdomyolysis, severe thrombocytopenia was seen in three (33.3%) patients; the median hematocrit concentration and platelet count were 41.6% and 82×10^9 cells/L, respectively. An increased aspartate aminotransferase level of $> 1,000$ U/L was found in one (12.5%) of eight patients with available data at the time of presentation. In terms of image findings of nine patients with rhabdomyolysis, pleural effusion was detected in five (55.6%)

patients, and gallbladder swelling was seen in two (22.2%) patients. Median duration from imaging study to the diagnosis of rhabdomyolysis was 1 day (range = 1–5 days). All patients received conservative management of rhabdomyolysis with intravenous fluid hydration. One patient (patient 5) experienced rapid clinical deterioration with acute renal, hepatic, and respiratory failure. Hemodialysis was required because of the presence of oliguria but was deferred because of his unstable hemodynamics; the patient eventually died of multiorgan dysfunction. None of patients underwent muscle biopsy and electromyography. Of note, the mortality rate was higher in patients with rhabdomyolysis than in those without rhabdomyolysis (11.1% versus 1%) (Table 1).

TABLE 2
Laboratory findings of 1,076 included patients

Variable	Study group (N = 9)		Control group (N = 1,067)		P*
	Data during the entire clinical course	Data at the time of hospital presentation	Data during the entire clinical course	Data at the time of hospital presentation	
Leukopenia (WBC < 3.0 × 10 ⁹ cells/L), no./total no. (%)	3/9 (33.3)	0/9	391/1,039 (37.6)	307/1,029 (29.8)	0.065
Leukocytosis (WBC > 12.0 × 10 ⁹ cells/L), no./total no. (%)	2/9 (22.2)	0/9	46/1,039 (4.4)	21/1,029 (2)	> 0.99
Median hematocrit, % (range; no.)	43.3 (33.4–49.4; N = 9)	41.6 (30.8–49.4; N = 9)	40.3 (23.7–66.7; N = 1,051)	39.1 (22.3–66; N = 1,021)	0.079
Median platelet count, × 10 ⁹ cells/L (range; no.)	18 (0.7–79; N = 9)	82 (0.2–139; N = 9)	35 (1–306; N = 1,052)	88 (1.0–441; N = 1,045)	0.289
Platelet count < 20 × 10 ⁹ cells/L, no./total no. (%)	6/9 (66.7)	3/9 (33.3)	346/1,052 (32.4)	175/1,045 (16.7)	> 0.99
ALT > 1,000 U/L (normal value < 40 U/L), no./total no. (%)	0/8	0/8	7/745 (23.3)	5/526 (0.9)	> 0.99
AST > 1,000 U/L (normal value < 40 U/L), no./total no. (%)	1/8 (12.5)	1/8 (12.5)	14/817 (1.7)	9/642 (0.9)	> 0.99

ALT = alanine aminotransferase; AST = aspartate aminotransferase; no./total no. = number of cases/number of overall cases with data available for evaluation; WBC = white blood cell.

*Comparison of the data at the time of hospital presentation between study and control groups.

Comparison of demographic, initial clinical, and laboratory features as well as image findings before occurrence of rhabdomyolysis between the study and control groups. Compared with the controls, patients with rhabdomyolysis had a significantly higher age (65 years versus 53 years; $P = 0.019$), proportion of men (100% versus 45.8%; $P = 0.001$), prevalence of hypertension (88.9% versus 23.1%; $P < 0.001$), frequency of myalgia (77.8% versus 30.5%; $P = 0.005$), and incidences of DHF (77.8% versus 32.6%; $P = 0.008$), pleural effusion (55.6% versus 23.9%; $P = 0.043$), and acute kidney injury (66.7% versus 0.8%; $P < 0.001$) (Table 1). Multivariate analysis showed that hypertension (odds ratio [OR] = 14.270, 95%

confidence interval [CI] = 1.057–192.571; $P = 0.045$), myalgia (OR = 20.377, 95% CI = 1.994–208.266; $P = 0.011$), and acute kidney injury (OR = 67.547, 95% CI = 8.884–513.553; $P < 0.001$) were independent risk factors for rhabdomyolysis in patients with DENV infection.

Comparison of cytokine/chemokine levels between the study and control groups. The cytokine/chemokine concentrations in 101 DHF patients with rhabdomyolysis ($N = 4$; median age = 64 years; range = 30–71 years) and those without rhabdomyolysis ($N = 97$; median age = 53 years; range = 18–82 years) are summarized in Table 4. IL-6 and TNF- α were significantly increased in patients with rhabdomyolysis

TABLE 3
Characteristics of nine dengue patients with rhabdomyolysis

Patient no.	Age (years)/sex	Underlying condition/statin	Severity of dengue/DENV serotype	Location of muscle weakness	Days from illness onset to hospital admission	Days from hospital admission to rhabdomyolysis diagnosis	Plasma leak signs	Complications	Outcome
1	61/M	HTN/rosvastatin	DHF grade 2/3	Both upper and lower limbs	3	2	Hypoalbuminemia	GI bleeding, acute kidney injury	Survived
2	67/M	HTN/–	DHF grade 2/3	–	2	3	Pleural effusion	Acute kidney injury	Survived
3	65/M	HTN/–	DF/3	–	7	1	–	–	Survived
4	65/M	HTN, CKD, history of stroke/rosvastatin	DHF grade 2/2	–	3	1	Hemoconcentration (Hct > 20%); pleural effusion	GI bleeding, acute kidney injury	Survived
5	68/M	HTN, DM, CKD, history of stroke/–	DHF grade 2/2	Both upper and lower limbs	2	3	Hemoconcentration (Hct > 20%); pleural effusion; hypoalbuminemia	GI bleeding, acute kidney and hepatic failure	Died
6	71/M	HTN, history of stroke/rosvastatin	DHF grade 1/2	Both lower limbs	1	6	Hemoconcentration (Hct > 20%)	Acute kidney injury	Survived
7	30/M	–	DHF grade 2/3	Right arm	6	6	Hemoconcentration (Hct > 20%); pleural effusion; hypoalbuminemia	GI bleeding, acute kidney injury	Survived
8	63/M	HTN/atorvastatin	DHF grade 2/1	Both lower limbs	6	2	Hemoconcentration (Hct > 20%); pleural effusion	–	Survived
9	57/M	HTN/–	DF/2	–	5	5	–	–	Survived

CKD = chronic kidney disease; DHF = dengue hemorrhagic fever; DF = dengue fever; DM = diabetes mellitus; GI = gastrointestinal; Hct = hematocrit; HTN = hypertension; M = male.

FIGURE 1. Computed tomographic scan of the right upper limb shows muscle swelling with an ill-defined low-density lesion (arrow) within the biceps muscle.

compared with those without rhabdomyolysis. The levels of IFN- γ , IL-10, and MCP-1 in patients with rhabdomyolysis were higher than in those without rhabdomyolysis, but the difference was not statistically significant.

DISCUSSION

Remarkably, unlike dengue, chikungunya is not endemic to Taiwan, and only sporadic imported cases in returned travelers were reported.^{32,33} Thus, none of the patients in this series were tested for chikungunya. Because our patients did not have any history suggestive of other well-known causes of rhabdomyolysis, such as alcohol or illicit drug abuse, trauma, and intramuscular injection,^{19,34} the occurrence of rhabdomyolysis after DENV infection makes the diagnosis of dengue-related rhabdomyolysis more apparent.

With regard to the risk factors, we found that, in contrast to previous findings showing that rhabdomyolysis occurred in 0.04–0.2% of patients who were on statin treatment,³⁴ our study revealed that 0.8% of patients with dengue had rhabdomyolysis and that rhabdomyolysis was not associated with statin therapy (Table 1). In addition, we found that individuals with hypertension who were receiving statin therapy did

not have an increased risk of developing rhabdomyolysis (Table 1). However, patients who had hypertension regardless of statin therapy were at a higher risk for developing rhabdomyolysis during DENV infection. Comorbidities, such as asthma, chronic kidney disease, diabetes mellitus, and hypertension, were associated with severe manifestation of dengue.^{30,35–37} To the best of our knowledge, the association between hypertension and rhabdomyolysis in dengue patients has not yet been examined. Hypertension is characterized by increased arterial stiffness, and it is a major risk factor for stroke, myocardial infarction, and chronic kidney disease.³⁸ In this study, chronic kidney disease and a history of stroke were found in 22.2% and 33.3% of dengue patients with rhabdomyolysis, respectively. Although it is not clear how hypertension contributes to the pathophysiology of rhabdomyolysis in dengue patients, vascular complications of hypertension may play a role in development of rhabdomyolysis. Additional studies are required to address the pathophysiological links between hypertension and rhabdomyolysis in dengue.

The common clinical features of dengue include abrupt-onset fever, headache, retro-orbital pain, myalgia, arthralgia, and rash.^{1,2} Our study showed that approximately 70% of patients with rhabdomyolysis experienced myalgia and that more than one-half of the patients developed severe muscle weakness involving the upper and/or lower limbs. As such, myalgia was a predictive risk factor for the development of rhabdomyolysis in our study. Remarkably, the median interval from hospital admission to diagnosis of rhabdomyolysis was 3 days. Early diagnosis is crucial in patients with rhabdomyolysis.^{27,28} Total CPK elevation is a sensitive marker for rhabdomyolysis.³⁴ For early diagnosis, we believe that measurement of serum CPK levels is the most reliable screening test, because CPK is not removed from the plasma by the kidneys, and it persists in the blood for a longer duration than myoglobin.³⁴ In addition, the degree of CPK elevation correlates with the amount of muscle injury and is predictive of the development of renal failure.³⁹

The incidence of acute kidney injury in rhabdomyolysis from any cause usually ranges from 13% to 50%.¹⁹ However, in our study, the incidence of acute kidney injury was comparatively higher (66.7%) among dengue patients with rhabdomyolysis. Among rhabdomyolysis cases, acute kidney injury predominantly occurred in patients with DHF, and most of them experienced gastrointestinal bleeding. DHF is characterized by increased vascular permeability resulting in plasma leakage.² This finding suggests that rhabdomyolysis is not the only cause of acute kidney injury and that intravascular volume deficit resulting from plasma leakage and gastrointestinal bleeding plays an additional important role in damaging renal function. In our study, the median diagnostic times of acute kidney injury and rhabdomyolysis were 1 and 3 days, respectively, suggesting a delay in diagnosing rhabdomyolysis after the onset of kidney injury. We believe that this delay is caused by clinicians' lack of alertness to this disease. Thus, there is an urgent need for improving clinicians' awareness of dengue-related rhabdomyolysis and the importance of timely appropriate treatment.

This study showed that DHF is not a risk factor for rhabdomyolysis. Severe complications, such as encephalopathy, hepatic failure, cardiomyopathy, and rhabdomyolysis, have been previously described in patients with DF.⁴⁰ Manifestations of severe dengue, particularly organ dysfunction, were

TABLE 4

The circulating cytokine/chemokine levels in 101 patients with DHF with rhabdomyolysis (study group) and without rhabdomyolysis (control group)

Cytokine/chemokine	Median (range), pg/mL		P
	Study group (N = 4)	Control group (N = 97)	
GM-CSF	0.95 (0.7–14.01)	2.45 (0.14–177.27)	0.330
IFN- γ	35.1 (2.17–1,607)	16.07 (0.7–2,394)	0.756
IL-10	638.16 (91.18–1,664)	176.98 (22.12–2,189)	0.348
IL-2	0.69 (0.52–1.24)	1.45 (0.1–666)	0.273
IL-6	115.45 (16.28–1,241)	16.57 (2.5–395.94)	0.034
TNF- α	55.28 (18.89–267.59)	17.63 (2.52–121.31)	0.016
MCP-1	2,606.03 (271.7–5,378)	813.3 (87.45–7,128)	0.433

GM-CSF = granulocyte macrophage colony-stimulating factor; IFN- γ = interferon- γ ; IL = interleukin; TNF- α = tumor necrosis factor- α ; MCP-1 = monocyte chemoattractant protein-1.

not included in the DHF/DSS definitions.² Notably, recent studies show that approximately 20% of patients with severe dengue did not fulfill the criteria for DHF/DSS.⁴¹ Thus, our study highlights the importance of clinicians' alertness toward potentially fatal rhabdomyolysis during treatment of a DF patient.

The pathogenesis of rhabdomyolysis in dengue is unclear. Direct invasion by DENV or production of myotoxic cytokines, particularly TNFs, has been postulated.^{8,17} In this study, IL-6 and TNF- α levels were significantly elevated in patients with rhabdomyolysis compared with those without rhabdomyolysis. TNF- α is a proinflammatory cytokine involved in systemic inflammation, and it is associated with increased disease severity.⁴² Additionally, IL-6 has both pro- and anti-inflammatory effects and contributes to the regulation of TNF- α levels.⁴³ Also, IL-6 is released by the skeletal muscle fibers in response to muscle contraction or muscle injury.⁴⁴ Our study provides preliminary evidence suggesting that both IL-6 and TNF- α play an important role in the development of rhabdomyolysis in dengue patients.

There are some limitations to this study, including the small number of rhabdomyolysis cases studied and the retrospective nature of the study, which resulted in missing data for some included patients. Furthermore, our study included only adult patients, and therefore, it is uncertain whether similar risk factors are found in pediatric patients. Moreover, we found that 0.8% of patients with dengue had rhabdomyolysis. However, because this value was derived from cases at a single medical center, it may not definitively reflect the incidence of rhabdomyolysis in dengue patients, because patient population at a medical center might be biased by referral patterns. Despite these limitations, this study has several strengths. First, it represents the largest cohort of dengue-related rhabdomyolysis reported to date. Second, it documents the clinical findings of rhabdomyolysis associated with DENV infection, which have been poorly defined previously. Third, it identifies the predictive risk factors for the development of rhabdomyolysis and cytokine/chemokine responses in dengue patients with rhabdomyolysis.

In summary, dengue-related rhabdomyolysis may be overlooked in countries where dengue is endemic. Our study emphasizes the urgent need for improving clinicians' awareness of this potentially fatal complication when treating dengue patients, especially those with muscle pain, acute kidney injury, and past hypertension. Given the high fatality rate of dengue-related rhabdomyolysis, these risk factors can be used to guide triaging of dengue patients who need closer monitoring and implement timely appropriate management to avoid otherwise preventable mortality and morbidity.

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