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Original Research

Organ Dysfunction in Severe Dengue among Children in a Vietnamese Hospital

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ABSTRACT

Background: Dengue fever (DF) is an infectious disease with a high incidence in most developing countries, and organ dysfunction is a serious complication of the disease that can lead to death in children. The aims of study to identify the clinical and subclinical characteristics of organ dysfunction in severe dengue fever at Children Hospital N2, Ho Chi Minh City.

Methods: A retrospective descriptive study of 403 cases of severe DF in children admitted to the Department of Infectious Disease at Children Hospital N2 from January 2013 to December 2015.

Results: Characteristics of organ dysfunction: Circulatory: 87.3% had shock, comprising 22.7% severe shock, 9.7% prolonged shock, 11.9% re-shocked, and 3.4% re-shocked multiple times. Respiratory: 26.3% respiratory failure, comprising 17.9% ARDS with 89% at medium-severe levels. 23.8% severe liver injury. 4% acute kidney injury. 18.9% had upper gastrointestinal bleeding with 8.6% severe level. 73.2% coagulopathy and 17.1% met the disseminated intravascular coagulation (DIC) standards. Neurological: 6.2% had cognitive disorders, and 5.2% had convulsions during treatment. Metabolism: 9.2% severe metabolic acidosis; 5.5% hypoglycaemia, 74.6% hyponatremia; 10.1% hypocalcaemia. The death rate in the study was 4.2%.

Conclusions: Organ dysfunction mainly comprised circulatory failure, respiratory failure, coagulopathy, severe liver injury, and gastrointestinal bleeding. Patients with acute kidney injury, DIC, elevated liver enzymes (>1,000 UI/L), and cognitive disorders are high risk factors for death.

Keywords: Dengue fever, DF, hospital, organ dysfunction, Vietnam.

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INTRODUCTION

Dengue fever (DF), a mosquito-borne tropical disease, has long been one of the most discussed health problems globally. This disease is caused by the dengue virus (DEN), a small single-stranded RNA virus with distinct serotypes (DEN -1 to -4).[1] Worldwide, there are an estimated 2.5 billion people living in dengue epidemic zones. Among them, some 1.8 billion (more than 70%) of this population are living in member states of the South-East Asia Region and Western Pacific Region, as defined by the World Health Organization (WHO).[1] In Vietnam, various studies have researched the cost of DF, including medical, non-medical, and indirect costs.[2, 3] Generally, these studies emphasized DF's high treatment cost, which poses a huge economic burden in the developing world. Despite the costs, Trung Vo Quang et al.[4] reported a high number of participants who were willing to pay for the dengue vaccination. Preventing DF is still a priority for many Vietnamese people. However, Vietnam still lacks public knowledge and services related to treating and preventing the disease.[5-7]

Because of these factors, many difficulties arise in the treatment of DF, especially in complicated cases. One of the serious complications of the disease is organ dysfunction, which can lead to death in children. Therefore, it is important to study organ dysfunction caused by this disease to reduce its mortality rate. This study investigated severe cases of DF in pediatric patients, focusing on organ dysfunction.

METHODS

Study sites and populations

This retrospective study was conducted between January 2013 and December 2015 at Children Hospital N2, Ho Chi Minh City, Vietnam. The hospital is one of the three largest health facilities in southern Vietnam and specializes in pediatrics.

Data collection

All pediatric patients under 16 years of age hospitalized in the Department of Infectious Disease from January 2013 to December 2015 were enrolled. According to WHO 2009, the diagnosis of severe DF was based on a subclinical laboratory test, including positive NS1Ag or Elisa Dengue IgM.[1] The exclusion criteria were as follows: (i) dysfunction of organs before contracting DF or (ii) cyanotic or non-cyanotic congenital heart defects with heart failure or pulmonary hypertension.

We retrospectively studied medical records of all children diagnosed with severe DF. Selected infants had to meet study criteria based on anamnesis, current diagnosis, and echocardiogram results for the abovementioned period. All information related to the study of selected children will be recorded in a unified data collection form.

Data analysis

Data was entered into Microsoft Excel for systematic management. SPSS 21.0 software was used for data analysis. Nominal variables were presented as frequencies and percentages. Continuous variables were presented as averages and standard deviations.

A chi-squared test with an odd ratio was used to compare percentages between groups of living and dead participants. Statistical significance was considered the when p-value was less than 0.05.

Ethical approval

Ethics approval was granted by the Council of Medical Ethics at Children Hospital N2. Participating patients were informed about the research purpose, and all interviews were voluntary.

RESULTS

Table 1. Epidemiological characteristics

Characteristics		Frequency	%
Gender	Male	200	50.0
	Female	203	50.0
Age (years)	≤1	35	8.7
	2–5	90	22.3
	6–10	205	50.9
	>10	73	18.1
Nutritional status	Obesity	152	37.7
	Normal weight	216	53.6
	Underweight	35	8.7
Living area	Ho Chi Minh City	149	37.0
	Other provinces	254	63.0

Table 2. Clinical characteristics

	Characteristics	Frequency	%
Shock (n=352)	Severe shock	80	22.7
	Prolonged shock	34	9.7
	Re-shocked	42	11.9
	Re-shocked many times	12	3.4
	First symptom of shock (days after the beginning of shock, mean±SD)		4.9±0.8
Respiratory failure (n=106)	Breathlessness	103	97.2
	Rapid breathing	98	92.5
	The decrease of SpO_2	29	27.4
	Cyanosis	11	10.4
	Apnea	3	2.8
	ARDS	19	17.9
	Medium level	9	8.5
	Severe level	8	7.5
Severe liver injury* (n=96)	Hepatomegaly	83	86.5
	Jaundice	6	6.3
Bleeding (n=403)	Blood spots	307	76.2
	Gastrointestinal bleeding	76	18.9
	Mucosal bleeding	60	14.9
	Bleeding plaques, hematoma	58	14.4
	Abnormal vaginal bleeding	12	3.0
Neurological (n=403)	Cognitive disorder	25	6.2
	Convulsion	21	5.2
	Brain bleeding	1	0.2

*AST or ALT ≥ 1000 UI/L

Note: Values are n (%) unless stated otherwise.

Abbreviation: ARDS: acute respiratory distress syndrome

During the study period, there were 403 cases of severe DF admitted to the Department of Infectious Disease, Children Hospital N2, which met the study criteria.

Table 1 shows the frequencies of DF according to epidemiological characteristics, including sex, age, nutritional status, and accommodation of participants in this study. Participants were divided equally between males and females. Half of the patients were between the ages of 6 and 10 (50.9%) and at a normal weight (53.6%). Two-thirds of them were not living in Ho Chi Minh City.

Table 2 shows the frequencies of DF according to each type of organ dysfunction, including shock, respiratory failure, serve liver injury, bleeding, and neurological dysfunction. The average time from the onset of the disease to the first symptoms of shock was 4.9±0.8 days. Among respiratory symptoms, breathlessness was highest (97.2%). Only 0.2% to 6.2% of patients suffered from neurological symptoms.

Table 3 indicates the frequencies of the subclinical tests used for evaluating organ dysfunction, including chest X-ray, abdominal supersonic, SaO_2, liver enzymes, renal function, hematology, coagulopathy, and metabolic disorder.

Table 4 presents the relationship between organ dysfunction and death by recording the percentages of living and dead participants. There were significant differences between the percentages of patients with shock symptoms between the two groups (all $P<0.001$).

DISCUSSION

In our study, the distribution of disease incidence across sexes was similar: both men and women accounted for 50% (200/203) of the participants; previous studies on DF at Children Hospital No. 1 and Children Hospital No. 2 and in foreign countries also had the same proportion of men and women.[8-11]

About 63% of patients came from provinces that neighbor Ho Chi Minh City (mainly in the eastern region, such as Binh Duong, Dong Nai, Binh Phuoc and Ba Ria-Vung Tau) and 37% came from Ho Chi Minh City (mainly the eastern border of the city, including Thu Duc, District 9, Go Vap and Binh Thanh). Pham Thai Son's research on DF conducted at Children Hospital No. 2 in 2010 also had a greater distribution of patients from provinces outside Ho Chi Minh City (57.5% compared to 42.5%).[11]

There were 352 cases (87.3%) of severe DF with shock: 22.7% experienced severe shock, 9.7% prolonged shock, 11.9% were re-shocked, and 3.4% were re-shocked multiple times. Previous studies demonstrated shock rates from 80.6% to 95.8%: severe shock occurred from 11% to 35%, prolonged shock from 1.8% to 26.6%, and re-shock from 25.1% to 33.3%.[10-16] In our study, the average number of days until shock was 4.9 days since the onset of the disease.

There were 106 cases (26.3%) of respiratory failure, with 19 cases (17.9%) meeting ARDS criteria and 89% of them were medium to severe level. In Nguyen Minh Tien's research, the ARDS rate was 22%: similar to ours,[10] but higher than in foreign researches.[13-17] The 89% of moderate-severe cases of ARDS required equipment for treating respiratory failure at special treatment facilities. Clinically significant symptoms in the respiratory failure group were as follows: 97.2% breathlessness, 92.5% rapid breathing, 27.4% decreased oxygen via SpO_2 < 90%, 10.4% clinical cyanosis, and 2.8% apnea after seizures. Respiratory failure is one of the most severe manifestations of DF: it prolongs hospital stays, requires expensive treatment, and has a high mortality rate.

Table 3. Subclinical characteristics

Characteristics		Frequency (%)	AM±SD
Chest X-ray (n=100)	PE (R) large volume	55 (55.0)	
	PE (L) large volume	10 (10.0)	
	PE both sides with large volume	10 (10.0)	
	Respiratory injury	22 (22.0)	
Abdominal supersonic (n=70)	Peritoneal effusion with large volume	29 (41.4)	
	Multilayer effusion	22 (31.4)	
SaO_2 (n=87)	$PaO_2/FiO_2 < 100$	13 (14.9)	
	PaO_2/FiO_2 100–200	20 (23.0)	
	PaO_2/FiO_2 200–300	23 (26.4)	
Liver enzyme >1,000 UI/L (n=96)	AST	96 (100.0)	5,011±5,095
	ALT	96 (100.0)	1,592±1,325
Renal function (n=403)	Creatinine > 2 times upper limit of normal for age	16 (4.0)	
Hematology (n=403)	Average number of WBC		5,842±4,576
	WBC < 5,000/mm^3	220 (54.6)	
	Initial Hct of simple shock group	225 (55.8)	48.1±4.6
	Initial Hct of severe shock group	80 (19.9)	48.9±5.8
	Initial Hct of prolonged shock group	34 (8.4)	46.8±7.2
	Initial Hct of re-shocked group	42 (10.4)	47.9±4.9
	Average number of platelets		37,000±22,575
	PLT < 20,000/mm^3	101 (25.1)	
Coagulopathy (n=295)	PT (s)		20.1±14.6
	PT > 20s	69 (23.3)	
	aPTT (s)		63.3±34.1
	aPTT > 60s	130 (44.1)	
	Fibrinogen (g/L)		1.4±0.7
	Fibrinogen < 1g/L	132 (44.7)	
	DIC	69 (23.4)	
Metabolic disorder	Severe metabolic acidosis (n=87)	8 (9.2)	
	pH		7.06±0.08
	HCO_3^- (mmol/L)		5.6±1.7
	Hypoglycemia (< 40 mg/dL)	22 (5.5)	
	Hyponatremia	258 (74.6)	124±3.9
	Severe hyponatremia (< 120meq/L)	43 (10.6)	117.6±2.9
	Hypocalcemia (< 2 meq/L)	41 (10.1)	1.84±0.15

Abbreviations: ALT: alanine aminotransferase; AM: arithmetic mean; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; DIC: disseminated intravascular coagulation; PE (L): pleural effusion (left); PE (R): pleural effusion (right); PLT: platelet; PT: prothrombine time; SD: standard deviation; WBC: white blood cell

Table 4. The relationship of organ dysfunction to death

Organ injury	Alive n (%)	Dead n (%)	P-value	OR	Confidence interval (CI)
Shock	335 (95.2)	17 (4.8)	< 0.001	1.05	1.0–1.1
Respiratory failure	89 (84.0)	17 (16.0)	< 0.001	1.2	1.1–1.3
Gastrointestinal bleeding	62 (81.6)	14 (18.4)	< 0.001	24.4	6.8–87.4
DIC	53 (76.8)	16 (23.2)	< 0.001	100.5	13.1–773.9
Liver enzymes >1,000 UI/L	80 (83.3)	16 (16.7)	< 0.001	61.2	7.9–468.4
Acute kidney injury	3 (18.8)	13 (81.2)	< 0.001	414.9	84.1–2.046.3
Cognitive disorder	14 (56.0)	11 (44.0)	< 0.001	48.7	15.8–150.6
HAI	7 (70.0)	3 (30.0)	< 0.001	11.6	2.7–49.7

Note: The chi-squared test was used for the statistical hypothesis.

Abbreviations: DIC: disseminated intravascular coagulation; HAI: hospital-acquired infection; OR: Odds ratio

According to Ly To Khanh,[18] the rate of respiratory failure in patients with DF shock was 44.4%; according to Nguyen Thanh Hung,[19] in DF infants, the rate of respiratory failure was 96.7%.

In the respiratory failure group, 100 cases involved chest X-rays, which recorded that 55% of cases had PE (R) with large volume; 10% had PE (L) with large volume, and 10% had PE both sides with large volume. Pulmonary injuries accounted for 22% of the cases, including 2 cases of acute pulmonary edema due to overloading infusion and 19 cases of alveolus injury. There were 70 cases of abdominal supersonic, of which 41.4% had peritoneal effusion and 31.4% had multi-membrane effusion. Nguyen Minh Tien also recorded that 87.4% had PE (R), 74.2% had PE (L) with average–large volume, and 97.8% had peritoneal effusion with average–large volume.[10] In the severe DF group, Roy recorded that 59.6% had PE and 27.4% had peritoneal effusion.[20] Siddhart also showed that 44% of cases had plasma loss in the form of multilayer effusion compared to 31.4% in our study.[16]

In this study, there were 96 cases (23.8%) of severe liver injury with AST and/or ALT >1,000 UI/L. In the severe liver injury group, there were 86.5% cases of hepatomegaly and 6.3% of clinical jaundice. Previous studies showed that the ratio of hepatomegaly to jaundice were 93.4%:5.5%, 79%:4.5%, and 80.8%:6%, respectively.[10,20,21] There was no association between elevated liver enzymes and hepatomegaly levels. The average AST in this study was 5,011 UI/L, and the average ALT was 1,592 UI/L. There were 16 cases (4%) of acute kidney injury in this study. Nguyen Minh Tien noted that 14.2% of children had renal dysfunction as a result of shock, with reduced perfusion to the kidneys; 5.3% of cases progressed to severe renal failure and death from multi-organ dysfunction.[22] Manjunath also reported 1.3% of renal failure in the severe DF group.[17] Clinical bleeding manifestations were very diverse: 76.2% had skin hemorrhagic spots; 18.9% had upper gastrointestinal bleeding; 14.9% had mucosal bleeding; 14.4% had hemorrhagic plaque (hematoma); and 3% had abnormal vaginal bleeding. Previous studies showed similar rates of bleeding manifestations. [10,19,21,23]

In our study, the average number of white blood cells was 5,842/mm^3, and the proportion of children with WBC reduction <5,000/mm^3 was 54.6%, similar to previous studies.[10,23,24] There was no difference in initial erythrocyte capacity at shock among groups of simple shock, severe shock, prolonged shock, and re-shocked (P=0.78). The number of platelets was 37,000/mm^3, with 25.1% reduced severity (<20,000/mm^3). In our study, there were 295 cases (73.2%) of coagulopathy, with an average PT of 20.1s and 23.3% of prolonged PT >20s; the average aPTT was 63.3s, and there were 44.1% aTTP > 60s; the average fibrinogen was 1.4g/L, and there were 44.7% with fibrinogen <1g/L. There were 69 cases (23.4%) in the coagulopathy group that met the DIC criteria. Research of Liem Huynh Nguyen Duy on DF children with coagulopathy also showed 18.4% of prolonged PT >20s and 24.8% aPTT >60s.[23] In our study, there were 25 cases (6.2%) of cognitive disorders with the Glasgow average score being 7.9 points; 21 cases (5.2%) had convulsions during the illness; and there was 1 case of cerebral bleeding. In Tien Nguyen Minh's research,[22] there were 1.2% of children in a deep coma with a Glasgow score <5 points (we also had 1.7% of Glasgow cases <5 points); 5.3% of children had manifestations of cognitive disorders. Manjunath[17] also noted that there were 6% of nervous injury in the severe DF group; Wichmann[25] found that convulsive fever accounted for 8.6% of the DF group having neurological injury.

In our study, severe metabolic acidosis accounted for 9.2% of cases, with an average pH of 7.06 and an average HCO_3 of 5.6 mmol/L; hypoglycemia (<40 mg/dL) accounted for 5.5%; 74.6% had hyponatremia, with an average value of 124 meq/L; 10.6% had severe hyponatremia; and 10.1% had hypocalcemia with an average value of 1.84 meq/L. Tien Nguyen Minh also noted 8.9% of children with severe metabolic acidosis, 7.1% with hypoglycemia, 81.7% with hyponatremia, 21.3% with hypokalemia, and 14.8% with hypocalcaemia.[22] These disorders need to be noted, if not corrected, especially metabolic acidosis, which will make conditions worse, prolong shock, worsen DIC, etc. Nimmannityas noted that hyponatremia was usually found in patients with DF shock; 16.6% of the DF group had severe hyponatremia.[11,26]

By the end of this study, there were 17 cases (4.2%) of death. Considering the relationship between risk factors and death, we noted that patients had acute kidney injury (OR=414.9); DIC (OR=100.5); liver enzymes >1,000 UI/L (OR=61.2); cognitive disorders (OR=48.7); gastrointestinal bleeding (OR=24.4); and HAI (OR=11.6) - all high risks of death. Kamath recorded a mortality rate of 8.2% in the severe DF group.[13] Severe shock, DIC, ARDS, severe liver injury, and single or combined cognitive disorders are common causes of death. Kamolwish recorded a death rate of 12.6% in the severe DF group.[14] Compared to the living group (P <0.001), 96.7% of the dead group experienced severe shock; 93.3% were re-shocked; 100% had respiratory failure; 96.6% had severe liver injury; 79.3% had acute kidney injury; and 93.3% of bleeding.

CONCLUSION

Through retrospectively studying 403 cases of severe DF, we found that organ dysfunction mainly comprised circulatory failure (87.3%), coagulopathy (73.2%), respiratory failure (26.3%), severe liver injury (23.8%), and gastrointestinal bleeding (18.9%). If the patient had one of the following factors—acute kidney injury, DIC, liver enzymes >1,000 UI/L, cognitive disorders, gastrointestinal bleeding, or HAI—there would be a high risk of death.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare in this work.

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