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Original Article

Clinical risk factors for dengue shock syndrome in children

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Abstract

Background Dengue shock syndrome (DSS) is a serious complication of dengue hemorrhagic fever (DHF) which may cause death in more than 50% cases if not treated properly and promptly. Clinical, viral, and epidemiological risk factors determine the occurrence of DSS. Identifying risk factors for the development of shock in patients with DHF can increase the awareness of clinicians to perform a close monitoring.

Objective To determine the clinical risk factors for DSS.

Methods This case control study was conducted on DHF and DSS patients admitted to the Department of Child Health, Medical School, University of Padjadjaran, Dr. Hasan Sadikin Hospital Bandung from January 2004 to December 2005. The subjects were patients aged less than 14 years who fulfilled WHO criteria (1997). The exclusion criteria were history of asthma, diabetes mellitus, sickle cell anemia, typhoid, sepsis, and measles. The risk factors for DSS were analyzed using chi-square test, calculation of odds ratio, and logistic regression analysis.

Results Of 1,404 patients with suspected DHF, 600 met the study criteria; 200 patients of DSS and 400 patients of DHF as control group were identified. Univariate analysis showed that there was association between DSS and age 5-9 years (OR=1.67, 95%CI 1.08;2.58), overweight (OR=1.88, 95%CI 1.22;2.90), vomiting (OR=1.44, 95%CI 1.02;2.04), abdominal pain (OR=2.07, 95%CI 1.46;2.92), and severe bleeding (OR=13.6, 95%CI 5.96;31.03). By logistic regression analysis, it was found that age 5-9 years (OR=1.62, 95%CI=1.03–2.53), overweight (OR=1.97, 95%CI=1.29–3.08), and persistent abdominal pain (OR=2.08, 95%CI =1.44–2.99) were independent risk factors for DSS.

Conclusion Age 5-9 years, overweight, and persistent abdominal pain are the risk factors for DSS. **[Paediatr Indones 2007;47:7-11]**.

Keywords: *dengue hemorrhagic fever, dengue shock syndrome, risk factors*

Dengue shock syndrome (DSS) is a serious complication of dengue hemorrhagic fever (DHF) which may cause death in more than 50% cases if not treated properly and promptly;[1,2] Twenty to thirty percents of DHF patients develop DSS;[3,4] with early recognition and appropriate treatment, most patients can recover without sequels.[5] Knowledge about risk factors for DSS is important because it can increase the awareness of clinicians to perform a close monitoring on such patients so that the necessary intervention can be administered promptly in order to prevent fatal outcome.

An integral hypothesis for development of DHF epidemics was published in 1987 taking into account the International and Cuban experiences on DHF/DSS. Individual, viral, and epidemiological risk factors determine the occurrence of DSS.[6-9] Sex, age, nutritional status, chronic diseases, genetic, and race may determine the severity of the disease.[8-10] Other features should be taken into account including signs of impending shock (intense and sustained abdominal pain), persistent vomiting, abrupt change from fever to hypothermia,

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restlessness, and severe bleeding.[11,12] Epidemiological and laboratory evidence suggest that viral strain, virulence, and secondary infection with a different virus type may also be important as risk factors for DSS.

Previous studies about risk factors for DSS were focused on viral strain and host immune response,[13] which were hard to apply in rural hospital or standard laboratory. DSS was influenced by multifactorial interaction of agent, host, and environment. The aim of this study was to determine clinical risk factors for DSS.

Methods

This was a hospital-based case control design conducted on DHF and DSS patients who were admitted to Department of Child Health, Medical School, Padjadjaran University/Hasan Sadikin General Hospital Bandung from January 2004 to December 2005. Subjects were patients aged less than 14 years who fulfilled the WHO criteria (1997). Patients with history of bronchial asthma, diabetes mellitus, sickle cell anemia, typhoid fever, sepsis, and measles were excluded. Subjects were divided into two groups, the case group (DSS) and the control group (DHF).

The database included individual factors e.g., sex, age, and nutritional status based on weight/height (W/H) WHO-NCHS. The nutritional status was defined according to W/H as follows: obese (>120%), overweight (110-119%), well nourished (90-<110%), undernourished (70-<90%), and severe malnutrition (<70%). Clinical factors such as persistent abdominal pain, prolonged vomiting, and severe bleeding were established by history of illnesses and physical examination. Laboratory data included hemoglobin, hematocrit, and platelet count were recorded. The IgG and IgM dengue blot tests were performed during acute illness only.

Table 1. Subject's characteristics

Characteristics		Group			
		DSS		DHF	
		(n=200)	%	(n=400)	%
Sex	Male	93	46.5	203	50.8
	Female	107	53.5	197	49.3
Age (years)	Mean	7.1		7.3	
	Median	7		7	
	SD	3.2		3.5	
Nutritional status	Obesity	18	9.0	33	8.2
	Overweight	47	23.5	55	13.8
	Well nourished	79	39.5	201	50.2
	Undernourished	56	28.0	111	27.8
	Poor malnutrition	-	-	-	-
Admission	Referred	154	77	193	48.4
	By him/herself	46	23	207	51.6
Duration of fever	Mean	4.6		4.1	
	Median	5		4	
	SD	1.1		1.2	
Hepatomegaly	Yes	83	42.1	45	11.3
	No	114	57.9	354	88.7
Lowest platelet (/mm^3)	Mean	22,597		50,867	
	Median	19,000		41,000	
	SD	15,187		53,891	
	Range	3,000-100,000		3,000-112,000	
Highest hematocrit level (%)	Mean	43.3		41.3	
	SD	5.6		3.8	
	Range	43-57		36-54	
Dengue blot	IgM(+)	5	2.5	35	8.7
	IgG(+)	97	48.5	178	44.5
	IgM(+)	83	41.5	135	33.7
	IgG(+)	6	3	19	4.75
	IgM(-) IgG(-)	9	4.5	33	8.3

Table 2. Univariate analysis on individual and clinical risk factors

Risk Factors	Group				OR	CI 95%	P
	Case		Control				
	n=200	%	n=400	%			
Individual Factors							
Age							
5-9 year old	104	52.0	170	42.5	1.67	1.08-2.58	0.015*
Sex							
Female	107	53.5	197	49.3	1.19	0.84-1.66	0.325
Nutritional status							
Overweight	65	32.5	88	22.0	1.88	1.22-2.90	0.011*
Clinical Factors							
Vomiting	88	44.0	141	35.3	1.44	1.02-2.04	0.038*
Abdominal pain	119	59.5	166	41.5	2.07	1.46-2.92	<0.001*
Massive bleeding	39	19.0	7.0	1.8	13.6	5.96-1.03	<0.001*

*Odds ratio (OR) >1, P<0.25

The risk factors for DSS were analyzed with univariable chi-square test and odds ratio with 95% confidence interval; a logistic regression analysis was performed to evaluate the magnitude of risk factors. Data were analyzed using SPSS version 10.00 for windows.

The study was approved by the Health Study Ethical Committee at Medical School Padjadjaran University /Hasan Sadikin General Hospital Bandung.

Results

Between January 2004 and Desember 2005, there were 1,404 children with suspected DHF admitted to Hasan Sadikin Hospital Bandung and enrolled in this study. Of 1,404 subjects, only 600 subjects fulfilled the study criteria. Subjects were classified into two groups, 200 DSS and 400 DHF groups.

In the case group (DSS), female were predominant (53.5%) but in the control group (DHF), male (50.8%) and female (49.3%) had similar distribution. The mean age distribution were similar in all groups, DSS (7.1 years) and DHF (7.3 years). In this study, shock occurred on the fifth day of fever (**Table 1**).

Table 3. Logistic regression analysis of factors in association with DSS

	β	SE	Exp(B)	CI 95%	P
Age of 5-9 years	0.438	0.229	1.619	1.03-2.53	0.036*
Overweight	0.681	0.216	1.975	1.29-3.08	0.002*
Vomiting	0.229	0.187	1.258	0.87-1.81	0.219
Abdominal pain	0.731	0.198	2.078	1.44-2.99	<0.001*
Massive bleeding	-2.550	0.430	0.078	0.03-1.80	0.305

β: Coeffisien regression; constant: -1.158, * P<0.05

Using univariate analysis, factors associated with risk factors for DSS were aged 5-9 years, overweight, prolonged vomiting, persistent abdo-minal pain, and massive bleeding. All of the independent variables were analyzed using logistic regression for P<0.25 except for sex (**Table 2**).

In multivariate analysis, it was concluded that aged 5-9 years, overweight, and persistent abdominal pain were significant risk factors for DSS (P=0.036, P=0.002, and P=0.000, respectively) (**Table 3**).

Discussion

Using univariate analysis and multivariate logistic regression tests, aged 5-9 years had 1.6 times higher risk of developing DSS. This might be due to higher microvascular and permeability compared to age of less than 5 years or more than 9 years. Increased vascular permeability might be caused by several factors, such as greater vascular bed and greater plasma leakage.[10] Huang *et al*[14] in their study suggested that vascular endothelial cells can be a target for dengue virus infection. Endothelial cells are known to play an important role in regulating vessel permeability, maintaining hemostasis and also playing role in cytokines production. Dengue virus can induce interleukin (IL) -6 and IL-8 productions by endothelial cells and may contribute to the pathogenesis of dengue hemorrhagic fever. The more the cells infected, the more the interleukins produced, this will increase the capillary permeability and therefore increase the risk of DSS.

In our study, gender did not show a role in the development of DSS (P=0.32). This is different from the result of Phuong *et al*[15] in Vietnam. This might be due to different study design. Other possibility is that many Asian women prefer to visit to easy-to-access places, such as traditional practitioners. Recent Asian study showed that females were less exposed to medical care and usually came to hospital after the condition worsened, while more males were infected with dengue virus because of their mobility and activity that enabled more virus transmission. Determining sex differences both in infection and severity of disease require well-designed and targeted studies to capture both biological and social factors that drive disease patterns.[5]

The effect of nutrition on the development of DSS was shown in previous studies. Kalayanarooj and Nimannitya in their retrospective reviews proved that nutritional status significantly affected the risk for the development of DSS (30.2%; P=0.000).[16] Our study had similar result; overweight children had 1.98 times higher risk for DSS (CI 95%= 1.29-3.08) compared to well nourished and undernourished children. Malnourished children were more resistant to dengue infection compared to well nourished ones. Malnutrition will inhibit viral proliferation, because of decreased supply of acids for anabolic process. This is the mechanism of dengue viral infection protection in severe malnutrition. It is related with immunity system (antibody dependent enhancement). While T-cell maturation arrested and interferon production decreased in malnutrition, inversely, in over-nutrition, immune system activity is well developed, enabling increased viral proliferation and more severe disease manifestations.[17,18]

In this study abdominal pain was the highest risk factor for DSS. It was two times higher than that in patients without abdominal pain (CI 95%: 1.44-2.99, P<0.001). This is similar to other study which found that abdominal pain can be a good predictor for DSS.[19] Abdominal pain in DHF might be caused by occult gastrointestinal bleeding or the strain of enlarged liver.[15] Other literature suggested that in preshock or shock condition, the body responded by decreasing blood flow to organs except the vital ones such as the heart and brain, causing tissue hypoxia and subsequent abdominal pain.[20]

Vomiting and severe bleeding did not increase the risk of DSS in this study. Different results were yielded from Espinosa *et al*[21] in adult patients. Severe bleeding might be affected by the presence of disseminated intravascular coagulation, the number of platelets, and immediate or appropriate treatment of bleeding. In our study most subjects with DSS were referred from other hospitals (77%), thus it was difficult to distinguish whether bleeding occurred before, during, after shock, or due to prolonged shock. No data about the time limit of this symptom and we only used the information obtained during hospitalization. The relation between massive bleeding and DSS was not increasing risk, but merely causative.

Our study has some limitations, mainly because the data obtained were secondary data documented in medical records. Furthermore IgG and IgM dengue blot examinations were not quantitative results, and not all patients were tested. The time of tests varied as well, while the test results might be affected by the timing of blood sampling. Undefined time of massive bleeding was another limitation of this study. More complete data would be helpful for explaining factors affecting the analysis results. Further prospective study is needed to find other risk factors for DSS.

We conclude that aged 5-9 years, overweight, and persistent abdominal pain are independent risk factors for dengue shock syndrome in patients with dengue hemorrhagic fever.

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