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Serum transaminase levels and dengue shock syndrome in children

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Abstract

Background Clinical and biochemical impacts on liver dysfunction, as manifested by an increase in serum transaminase levels, are common in dengue infection. However, an association of elevated serum transaminase and dengue shock syndrome (DSS) has not been well-established.

Objective To assess for an association between serum transaminase levels and the presence of DSS in children.

Methods A nested, case control study was conducted on children aged 1 month to 12 years admitted to Sanglah Hospital who were diagnosed with dengue infection. Baseline characteristics and serum transaminase levels were recorded. Patients who were included in the study were observed for the presence of DSS. Those who had DSS were selected as cases, and those who did not develop DSS were selected as controls. Data was analyzed using bivariate and multivariate methods with 95% confidence intervals and P value <0.05 was considered as statistically significant.

Results Ninety-four children were involeved, 47 children in the case group and the other 47 were in the control group. Baseline characteristics of the subjects were similar between the case and control groups. Serum aspartate transaminase (AST) level of ≥128 U/L and alanine transaminase (ALT) of ≥40 U/L were associated with DSS (OR 10; 95%CI 2.3 to 44.4; P=0.002) and (OR 7.3; 95%CI 1.6 to 32.9; P=0.009), respectively.

Conclusion Elevated AST and ALT levels were associated with an increased risk of DSS in children with dengue infection. **[Paediatr Indones. 2014;54:181-5.]**

Keywords: *dengue shock syndrome, aspartate transaminase, alanine transaminase*

Dengue is a mosquito-borne viral disease with the most rapid spread in the world.[1] It is a major cause of morbidity and mortality in Southeast Asia.[2] Disease severity ranges from undifferentiated acute febrile illness to dengue fever (DF) to dengue hemorrhagic fever (DHF) to dengue shock syndrome (DSS), which is associated with a degree of plasma leakage.[3] Dengue may occasionally affect other body systems. The liver is a target organ of the Dengue virus.[4] Hepatic dysfunction is common in dengue infection, and is attributed to a direct viral effect on liver cells or as a consequence of dysregulated host immune responses against the virus.[5] Hepatic dysfunction may be reflected by elevated transaminase levels, which may range from mild to severe.[4]

Studies on transaminase levels have been reported and show varying results. Elevation of aspartate transaminase (AST) and alanine transaminase (ALT) levels were significantly different in DF, DHF, and DSS patients in some studies,[5-9] while other studies showed no significant difference

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in transaminase levels.[10-13] Therefore, we evaluated for a possible association between serum transaminase levels and DSS in children.

Methods

A nested, case-control study was conducted in children with dengue infection aged 1 month to 12 years admitted to the Department of Child Health, Udayana University Medical School/Sanglah Hospital, Denpasar, from June 2011 to March 2012.

We included all children with a diagnosis of suspected dengue infection according to the WHO 1997 criteria.[2] Patients diagnosed with malignancies, immune disorders, hemato-oncology disorders, or had a history of hepatitis were excluded. We also excluded patients whom we were unable to observe, such as those who died or were referred to another hospital. Patients were observed for presumed DSS during treatment according to standard medical care for dengue infection. Patients who had DSS were selected as cases and those who did not develop DSS (DF, DHF I, and DHF II) were selected as controls. At the admission, in addition to routine blood examinations, all patients' blood serum were taken, coded and stored. Serum transaminase level then evaluated if patient met the criteria as case or control. We obtained subjects' histories, including duration of fever, presence of abdominal pain, vomiting, and bleeding.

Serum transaminase levels were examinded on the first day of admission. Hematocrit, leukocyte count, hemoglobin, and platelet measurements were obtained from blood counts with the highest hematocrit was taken as a baseline value on the first day of admission. This study was approved by the Research Ethics Committee of Udayana University Medical School/Sanglah Hospital, Denpasar.

A minimum required sample size was calculated for an unpaired, case control study, according to assumed odds ratios (OR) of each variable (AST and ALT). The sample size calculated using the highest OR of AST, with a type I error of 5% and power of 80% was 47 subjects in each group. Data was analyzed separately for each factor by bivariate analysis (Chi-square test and unpaired T-test). Multivariate analysis was performed using backward logistic regression (LR). Results are presented in OR, with 95% confidence intervals, and a statistical significance value of $P < 0.05$.

Results

During the study period, 109 children with suspected dengue infection were admitted in Sanglah Hospital. Two patients in this study were excluded because they had history of hepatitis. During observation, 47 patients with DSS were assigned as cases. Sixty children did not experience shock, and out of these, 47 were consecutively selected as the control based on the duration of fever at the time of admission. Subjects' ages ranged from 9 months to 12 years. Baseline characteristics of the subjects and variables associated with DSS in children are shown in **Table 1**.

Based on multivariate analysis, variables associated with DSS were liver enlargement (hepatomegaly), abdominal pain, hematocrit level ≥46%, AST level ≥128.5 U/L, and ALT level ≥40 U/L (**Table 2**).

Based on the multivariate analysis, we determined the risk of DSS based on AST level [OR 10 (95% CI 2.3 to 44.4), P=0.002] as shown in **Table 3**, and ALT level [OR 7.3 (95% CI 1.6 to 32.9), P=0.009] as shown in **Table 4.**

Based on **Table 3,** every patient with dengue infection who were found with abdominal pain, hepatomegaly, hematocrit ≥46% and AST ≥128.5 U/L had a probability of DSS of as high as 99.49%. In patients with abdominal pain, hepatomegaly, hematocrit <46% and AST ≥128.5 U/L, the probability of DSS was as high as 89.4%. Patients with dengue infection and abdominal pain, hepatomegaly, hematocrit <46% and AST <128.5 U/L, had a probability of DSS of 45.7%. In patients with abdominal pain and AST ≥128.5 U/L, the DSS probability was 57.3%, while if abdominal pain alone was found, the probability for DSS was only 11.84%

Based on **Table 4**, in patients with dengue infection who were found to have abdominal pain, hepatomegaly, hematocrit ≥46% and ALT ≥40 U/L, their probability of having DSS was 99.55%. In patients with abdominal pain, hepatomegaly, hematocrit <46% and ALT ≥40 U/L, the probability of having DSS was 88.6%. Furthermore, if patients had abdominal pain, hepatomegaly, hematocrit <46%

Table 1. Characteristics of study subjects and bivariate analyses of variables associated with dengue shock syndrome

Characteristics	DSS group (n = 47)	Non-DSS group (n= 47)	P value	OR	95%CI
Mean age (SD), months	75.5 (36.9)	88 (35.3)	0.79*		
Gender, n (%)				1.29	
Male	26 (55)	23 (49)	0.536		0.57 to 2.9
Female	21 (45)	24 (51)			
Nutritional status, n (%)					
Underweight	12 (26)	9 (19)	0.268		
Normal weight	24 (51)	32 (68)			
Overweight	11 (23)	6 (13)			
Mean duration of fever at admission (SD), days	4.3 (0.73)	4.5 (0.8)	0.569*		
Clinical findings, n (%)					
Petechiae	10 (21)	11 (23)			
Epistaxis	6 (13)	4 (9)	0.503	1.57	0.4 to 5.98
Hepatomegaly	35 (75)	14 (30)	0.000	6.8	2.78 to 17
Abdominal pain	37 (79)	12 (26)	0.000	10.8	4.1 to 28
Nausea and vomiting	25 (53)	22 (47)	0.536	1.29	0.57 to 2.9
Leucocytes count, n (%)					
≤4000/µL	12 (26)	23 (49)	0.019	0.36	0.2 to 0.85
>4000/µL	35 (75)	24 (51)			
Hemoglobin, n (%)					
≥14 g/dL	45 (96)	23 (49)	0.000	23.4	5.1 to 188
<14 g/dL	2 (4)	24 (51)			
Hematocrit, n (%)					
≥46 %	34 (72)	3 (6)	0.000	38.4	10 to 145.4
<46 %	13 (28)	44 (94)			
Platelets count, n (%)					
≤50,000/µL	30 (64)	34 (72)	0.376	0.68	0.3 to 1.6
>50,000/µL	17 (36)	13 (28)			
Serology, n (%)					
IgG and IgM positive	37 (79)	34 (72)	0.472	1.4	0.5 to 42.8
IgG or IgM positive	10 (21)	13 (28)			
Transaminase levels (IU/L)					
AST, n (%)					
≥128.5 IU/L	37 (79)	9 (19)	0.000	15.6	5.7 to 42.8
<128.5 IU/L	10 (21)	38 (81)			
ALT, n (%)					
≥40 IU/L	20 (43)	2 (4)	0.000	8.46	3 to 23.7
<40 IU/L	27 (58)	45 (96)			
Mean length of hospital stay (SD), days	4.7 (1)	3.15 (1)			

*Unpaired T-test

Table 2. Multivariate analysis of variables associated with DSS

Step	Variables	B	OR	P value	95% CI
Step 1	Hepatomegaly	2.154	8.620	0.023	1.35 to 55.10
	Abdominal pain	1.742	5.709	0.04	1.08 to 30.19
	Leucocyte ≤4.000/µL	-1.168	0.311	0.262	0.04 to 2.40
	Hematocrit ≥46%	2.289	13.313	0.011	1.8 to 98.66
	Hemoglobin ≥14 g/dL	2.219	9.198	0.007	0.84 to 100.98
	AST ≥128.5 IU/L	2.374	10.739	0.008	1.85 to 62.38
	ALT ≥40 IU/L	1.859	6.42	0.047	1.03 to 40.10
	Constant	-5.956			
Step 2	Hepatomegaly	1.959	7.094	0.027	1.25 to 40.23
	Abdominal pain	1.911	6.763	0.023	1.3 to 35.33
	Hematocrit ≥46 %	2.651	14.166	0.012	1.80 to 111.43
	Hemoglobin ≥14 g/dL	2.086	8.05	0.056	0.95 to 68.15
	AST ≥128.5 IU/L	2.206	9.082	0.01	1.70 to 48.41
	ALT ≥40 IU/L	1.859	7.402	0.03	1.22 to 45.02
	Constant	-6.146			

Table 3. Multivariate analysis of AST level associated with DSS

Step	Variables	B	OR	P value	95%CI
Step 1	Abdominal pain	2.083	8.1	0.005	1.9 to 34.7
	Hepatomegaly	1.834	6.3	0.015	1.4 to 27.6
	Hematocrit ≥46%	3.153	23.4	0.000	4 to 135.7
	AST ≥128.5 IU/L	2.303	10	0.002	2.3 to 44.4
	Constant	-4.091			

Table 4. Multivariate analysis of ALT level associated with DSS

Step	Variables	B	OR	P value	95%CI
Step 1	Abdominal pain	2.087	8.1	0.005	1.9 to 34.1
	Hepatomegaly	1.879	6.6	0.011	1.5 to 28.1
	Hematocrit ≥46%	3.376	29.3	0.000	5.5 to 156.3
	ALT ≥40 IU/L	1.991	7.3	0.009	1.6 to 32.9
	Constant	-3.910			

and ALT <40 U/L, the probability of DSS was 51.4%. When patients were found with abdominal pain and ALT ≥40 U/L, DSS probability was 54.2%.

Discussion

Liver damage with elevated serum transaminase levels is a common complication of dengue virus infection. Therefore, measurement of serum AST and ALT levels are required to determine liver involvement.[6] Our results were consistent with that of previous studies.[5-9] Sutriani *et al*. reported an association between AST level and DSS, with an OR of 199 (95% CI 9.74 to 4093.1), while ALT level was not statistically significant associated to DSS.[5] Differences in results were likely due to different cut-off points used for transaminase levels (AST >103 U/L and ALT>50 U/L), different times at which serum samples were taken for transaminase examination, and exclusion of patients with fever ≥5 days. Serum transaminase levels begin to rise on the third day of fever, reaching the highest level on the ninth day of illness, then decreasing gradually in 2-3 weeks.[14,15]

Several studies had contrasting results with no association between increased transaminase level and the clinical spectrum of dengue infection.[10-12] This difference is likely due to different cut-off points for the AST and ALT levels used in each study. A Vietnamese study reported that elevations in AST and ALT levels were significantly different in DHF II and DHF IV, and elevations of serum transaminase levels in DHF ranged from mild to moderate (less than five times from the normal value). The study showed increased ALT levels of more than five times in patients with severe dengue infection.[16] The liver damage that occurs is not a primary process of dengue virus infection, but may be due to shock, which leads to ischemia in the liver cells.[12] Elevation of serum transaminase levels in dengue infection is temporary and will gradually decrease to normal after two to three weeks.[7]

The mechanism of liver involvement in dengue infection is not entirely clear. Liver cell damage may be due to one or more of the following mechanisms: (1) direct cytopathic effects of the virus, (2) death of infected liver cells induced by cells of the immune system, and (3) non-specific effects of shock and hypotension.[12] Dengue infection may lead to the following liver histology changes: microvesicular steatosis, hepatocellular necrosis, destruction and hyperplasia of Kupffer cells, and cellular infiltrates in the portal tract.[17] Necrosis of liver cells is generally found in the mid- and centro-lobular zones, possibly due to higher sensitivity of liver cells to anoxia or cytokines in these regions.[13]

In this study, based on multivariate analysis, we created prognostic models to determine the probability of the occurrence of DSS if these variables were found simultaneously in patients with dengue infection. Prognostic models in **Table 3** consisted of abdominal pain, hepatomegaly, hematocrit ≥46% and AST ≥128.5 U/L. The prognostic models in

Table 4 consisted of abdominal pain, hepatomegaly, hematocrit ≥46% and ALT ≥40 U/L .

The degree of hepatic injury (increased transaminase levels) has been strongly associated with the presence of severe complications of dengue infection. Therefore, at a minimum, transaminase examinations should be performed regularly during follow-up of dengue patients.[17] Understanding of variables related to DSS should make physicians more alert to early signs of DSS. Although plasma leakage and bleeding cannot be prevented, deterioration into DSS may be prevented with close monitoring for early signs of shock and adequate fluid therapy.[18]

Limitations to our study included the exclusion of patients with a history of hepatitis only by history-taking and transaminase examinations performed only once at the time of admission. Future studies should be conducted using the cohort method with serial transaminase examinations to determine a causal relationship between serum transaminase levels and severity of dengue infection.

In conclusion, elevated serum transaminase is associated with increased risk of DSS in children with dengue infection. In addition, abdominal pain, hepatomegaly, and hematocrit level of ≥ 46% may also be associated with increased risk for DSS.

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