

Interleukin-8 (IL-8) Role in Children with Dengue Hemorrhagic Fever

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ABSTRACT

Background: Dengue hemorrhagic fever (DHF) is an infectious disease caused by dengue virus and still become a health problem in Indonesia. Interleukin-8 (IL-8) has been widely accepted as a factor correlated with severity of DHF. However, its role in Dengue Haemorrhagic Shock Syndrome (DHSS) was still poorly understood. This study was conducted to elucidate correlation of IL-8 and DHSS in children.

Objective: To determine the correlation between IL-8 and DHF in children.

Methods: We conducted across sectional study in pediatric ward general hospital of Prof.Dr.R.D.Kandou Manado in March until August 2011. Fourty children aged 1-13 years old was conducted consecutively and divided in to shock and without shock DHF. IL-8 was examined in each group and the correlation with DHF was analyzed with Spearman rho test using SPSS software with $P < 0.05$.

Result: The mean of IL-8 level in DHF children without shock was 45.63 (95% CI 31.88 to 59.37) ng/ml and in DHF with shock was 411.13 (95% CI 311.46 to 510.80) ng/ml. The correlation between IL-8 and DHF was statistically significant ($r_s = 0,774$, $p < 0.001$).

Conclusions: The IL-8 level in DHF in these two groups were increase, and higher in severe DHF (with shock). Higher level of IL-8 correlated with increasing severity of DHF.

Keywords: IL-8; DHF; children, interleukin, hemorrhagic fever

Introduction

Dengue hemorrhagic fever (DHF) is an infectious disease caused by dengue virus and still become a health problem in Indonesia including North Sulawesi. All of Indonesian region has a risk infected by DHF from mild until severe Dengue Hemorrhagic Shock Syndrome (DHSS) which tends to bring about shock and death.⁽¹⁻³⁾ According to clinical manifestation and laboratorial examination, DHF classified into four grade from unsymptomatic into the most sever DHSS. However its pathogenesis of DHSS was still clearly unknown. Many

theories had tried to explain DHF pathogenesis but the main determinant not clearly known.⁽⁴⁻⁶⁾

The dengue virus is a single-stranded RNA virus with the primary target being monocyte or macrophage cells. Dengue virus envelope proteins are capable of binding endothelial cells, thus endothelium is also a target for dengue virus.⁽⁷⁻⁹⁾

Recent research has reported that disharmony of immune system seems has role in the pathogenesis of DHF. Many immunological mechanism has been considered involved in tis pathomechanism. Interleukin 8 (IL-8) as poten immunologic cytokine has been proposed have a role in pathogenesis of DHF and severity of DHF as previous studies in adult.^(3, 10-12) Then, many symptom base therapy has been tried to applied in DHSS treatmet, however DHSS is still a dangerous situtation problem in children and it maight be IL-8 suspected as a main

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factor that contribute in DHSS severity. This study was conducted to explain the correlation of IL-8 and DHF in children.

Method

This study was an observational analytic with cross-sectional approach. The sample of 40 children aged 1-13 years with the diagnosis of DHF without shock on the degree I and II and DHF with shock in degrees III and IV treated in the nursery / Irina E at BLU. RSUP Prof. Dr.R.D. Kandou Manado. The diagnosis of DHF was confirmed by WHO criteria 1997 and confirmed by Dengue NS1 examination for hot ≤ 3 days or rapid test anti-dengue IgG and IgM in heat >3 days.

The inclusion criteria was included age of 1-13 years, diagnosed as dengue hemorrhagic fever based on WHO 1997 criteria and confirmed with serological examination, parents approved and filled out the study form. Exclusion criteria suffered from viral infections rather than dengue or acute bacterial infections, received treatment with corticosteroids, and received blood transfusions, suffered from pneumonia, sepsis, bronchiolitis, and typhoid fever. The study was conducted

by examining blood samples including hemoglobin, hematocrit, leucocytes, platelets, Dengue NS1 or IgM IgM anti-dengue and IL-8 levels.

This study had obtained the approval of ethical clearance from the ethical committee of RSUP Prof. Dr.R.D. Kandou Manado. Data analysis used hypothesis test correlation coefficient analysis Spearman rho. Statistical analysis was found to be significant if p <0.05. The data collected had processed by using SPSS program version 17. (SPSS.Inc. Chicago, IL)

Result

Characteristics of Respondents: Sex distribution of the respondents was 14 (35%) boys and 26 (65%) girls suffering from DHF. Where in dengue without shock was 10 (71,43%) boys and 19 (73,08%) girls, whereas in dengue fever with 4 (28,57%) boys and 7 (26, (Table 1) The age range of 29 children with unobtrusive DHF ranges from 2.0 years to 13.0 years with mean age of children of 7.6 years and standard deviation (SD) of 3.1 years. The age range of 11 dengue fever children ranged from 3.0 years to 12.0 years with mean age of children 6.8 years and SD 3.3 years. (Table 2)

Table 1: Distribution of the sex of a child with dengue hemorrhagic fever

Sexuality n (%)	DHF without Shock n (%)	DHF with Shock n (%)	Total n (%)
Boy	10 (71,43%)	4 (28,57%)	14 (100,00%)
Girl	19 (73,08%)	7 (26,92%)	26 (100,00%)
Total	29 (72,50%)	11 (27,50%)	40 (100,00%)

Table 2: Descriptive distribution of children’s age with dengue hemorrhagic fever

DHF	n	Mean (tahun)	SD (tahun)	Mean for 95% KI		Minimum (Year)	Maximum (Year)
				LB (Year)	UB(Year)		
Without Shock	29	7,6	3,1	6,4	8,8	2,0	13,0
With Shock	11	6,8	3,3	4,6	9,0	3,0	12,0
Total	40	7,4	3,1	6,4	8,4	2,0	13,0

The physical examination was indicated RL (Rumple Leede)/positive tooth-proof test was found at 28 (70.0%), petechial at 8 (20%), epistaxis at 6 (15.4%), hematemesis at 4 (10%) and melena at 7 (17.5%). In non-shock dengue fever a positive RL test was found in 26 (89.7%), petechial 6 (20.7%), epistaxis 5 (17.9%), hematemesis 2 (6.9%), and melena at 3 (10.3%). Whereas in dengue fever patients, there were 2 (18.2%) positive RL test, 2 petechial (18.2%), epistaxis 1 (9.1%), 2 hematemesis (18.2%), and Melena counted 4 (36.4%). (Table 3)

Table 3: Manifestation of child bleeding with dengue hemorrhagic fever

Manifestation of Bleeding	DHF		Total
	Without Shock	With Shock	
RL/torniket test	26 (89,7%)	2 (18,2%)	28 (70,0%)
Petechial	6 (20,7%)	2 (18,2%)	8 (20,0%)
Epistaxis	5 (17,9%)	1 (9,1%)	6 (15,4%)
Hematemesis	2 (6,9%)	2 (18,2%)	4 (10,0%)
Melena	3 (10,3%)	4 (36,4%)	7 (17,5%)

DHF patients who have hepatic enlargement had a range of 1-1 centimeters (cm) below the arcus costae (bac) to 4-4 cm in the bac. In dengue fever patients there were 11 (37.9%) felt liver 1-1 cm in bac, there were 16 (55.2%) 2-2 cm in bac and 2 (6.9%) with 3-3 cm in bac. In dengue hemorrhoids there was 1 (9.1%) felt liver 1-1 cm in bac, 5 (45.5%) at 2-2 cm in bac, 4 (36,4%) at 3-3 cm in bac and 1 (9.1%) at 4-4 cm in bac.

A description of routine blood laboratory results beside the WHO 1997 criteria of hematocrit and platelets. The hematocrit in children with DHF without shock had the lowest value of 30.50% and the highest value of 45.30% with mean of 39.13%, whereas DBD with shock the lowest hematocrit value of 34.30% and the highest value is 55,60% with average 45,20%. Thrombocyte picture of children with dengue fever dengue DBD 22.000/mm³ and highest 218.000/mm³ with platelet

average 90.482,76/mm³, while for dengue fever with the lowest value 16.000/mm³ and highest value 167.000/mm with platelet average 52.000/mm³.

Interleukin-8 levels in children with dengue hemorrhagic fever: The results of the examination on 40 children with DHF such as the lowest IL-8 levels were 7.00 ng/ml and the highest IL-8 level of 674.50 ng/ml, with mean IL-8 concentration of 146.14 ng/ml. Examination of 29 children with unobtrusive DHF where the lowest IL-8 score range was 7.00 ng/ml and highest 168.20 ng/ml with mean of 45,63 ng/ml, while 11 children with dengue fever were found in IL-8 lowest 211.80 ng/ml and highest of 674,50 ng/ml and average 411,13 ng/ml. (Table 4) The relationship between IL-8 with dengue hemorrhagic fever in children was analyzed by Spearman rho correlation analysis. Based on this test, the correlation coefficient is obtained by $r_s = 0.774$ with $p < 0.001$.

Table 4: Interleukin-8 levels in children with dengue hemorrhagic fever

DHF	n	Everage (ng/ml)	SD (ng/ml)	Everage for 95% KI		Minimum (ng/ml)	Maximum (ng/ml)
				LB (ng/ml)	UB (ng/ml)		
Without Shock	29	45,63	36,13	31,88	59,37	7,00	168,20
With Shock	11	411,13	148,36	311,46	510,80	211,80	674,50
Total	40	146,14	184,12	87,26	205,02	7,00	674,50

Discussion

Dengue hemorrhagic fever was still become a health problem in Indonesia including North Sulawesi. All of Indonesian region has a risk infected by DHF from mild until severe grading which tends to bring about shock as well as death.⁽¹⁻³⁾ Severe DHF can cause dengue shock syndrome (DSS), a potentially fatal plasma leakage syndrome. Capillary leakage has been linked to mediators that are secreted by cells in the circulation.⁽¹¹⁾

The pathogenesis of DHF and its severity was still under debate. Many varies of theories which was tried

to explain about determinant factor not clearly known.^(5, 13, 14) Dysregulation of immune system seemed to constitute the pathogenesis of DHF. Varies mechanism considered involved, i.e. virus virulence, antigen-antibody, complement and its products, all mediator soluble including IL-8 as cytokine which was suggested a role in pathogenesis of DHF.⁽¹⁵⁻¹⁷⁾

The distribution of dengue fever shown that girls were more than boys, 26 (65%) girls and 14 (35%) boys.^(17, 18) But overall there was no difference between the sexes in DHF patients, although deaths were more common in girls than boys.^(3, 18)

In established the diagnosis of DHF based on the WHO (1997) criteria of sudden and persistent high fever for 2 to 7 days. Dengue hemorrhagic fever was preceded by sudden fever accompanied by non-specific clinical symptoms, this fever was the main symptom in all cases. A sudden high fever was an early clinical symptom of DHF and this was found in all the cases studied. In this study, the heat in diagnosing dengue fever treated in the hospital had a range in dengue fever without shock minimal day second and maximum fifth day with the average value of day to 3.76. In DHF with shock ranged from a minimum of fourth day and maximum of fifth day with the average value of day to 4.64. In general, this study was hot in the diagnosis of DHF ranging from 2-5 days with the average day to 4.20.^(17, 19, 20)

Hepatomegaly as one of the benchmarks for clinical diagnosis of DHF in WHO criteria was reported to vary. In this study all subjects had hepatomegaly with a range of 1-1 centimeters (cm) below the arcus costae (bac) to 4-4 cm in bac. In dengue sufferers without shock hepatomegaly at least 1-1 cm in bac and maximum 3-3 cm in bac. In DHF with hepatomegaly shock was palpable at least 1-1 cm in bac and max 4-4 cm in bac.^(4, 19, 21)

Hematocrit and thrombocyte examination were a very helpful examination in the diagnosis of DHF. The value of hematocrit usually was begin to increase on the third day of illness and reaches the highest value during the shock or shock phase. In this study, hematocrit in patients with DHF without shock had the highest value of 45.30% with mean of 39.13%, while dengue hematocrit with shock was 55,60% with mean of 45,20%. This was in accordance with other studies that have been conducted in several countries.⁽²¹⁻²³⁾

The number of DHF thrombocyte was the lowest dengue fever with 22,000/mm³ and the highest 218.000/mm³ with the mean of platelet 90482,76/mm³, while for the DBD with shock had the lowest value 16.000 /mm³ and the highest value 167.000/mm³ with platelet average of 52,000/mm³. The decrease in platelet counted in dengue hemorrhagic fever might be below 100000/mm³ usually found on the third and eighth day, often before or simultaneously with a change in hematocrit.⁽⁴⁾ The lowest platelet value to watch out for was 20,000-50.000/mm³. The lowest platelet was value less than that range tended to be more shocked than in other

cases. Platelets were secretory cells that have granules containing various mediators. Endothelial dysfunction would result in aggregation of activated platelets and thrombocytes that release histamine like substance and 5-hydroxytryptamine which may lead to increased capillary permeability.⁽¹⁶⁾ Research conducted in Manado states there was a significant relationship between low platelet values and DHF remediation.^(24, 25)

This study showed that there was an significant correlation between IL-8 and DHF in children analyzed with Spearman rho test used SPSS 17 ($r_s=0.774$, $p<0.001$) Thus, it conceivable that high levels of IL-8 in DHF children may correlate with risk of DHF severity. Similar result from previous study of Wihandani in 2009 concluded IL-8 level was correlated with severity of dengue virus infections. This study concluded too that there was a significant difference of IL-8 level in health patient as control with mild and severe DHF.⁽²⁶⁾

Interleukin-8 is a cytokine with potential proinflammatory effect and a chemotactic molecule with chemoattractant activity, is able to activate eosinophil, neutrophil and naive T cells to the surface of the endothelium.^(11, 27) Similar with previous study held by Juffrie in 2000 found IL-8 are increased in most patients with dengue virus infection and correlate with degranulation of neutrophyl as well as with some clinical and hemodynamic variables.⁽²⁷⁾ Talavera in 2004 stated IL-8 modulates endothelial cells permeability and play an important role in immunopathogenesis and severity of DHF by *tight junction and actin cytoskeleton functional* and neutrophil degranulation.⁽²⁸⁾

Conclusion

There was an increase in IL-8 levels in children with DHF. Patients with dengue fever without shock had a lower value range of IL-8 levels than dengue without shock. There was a statistically significant relationship between IL-8 levels and dengue hemorrhagic fever in this study which means that the higher the IL-8 the more severe the dengue.

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