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Research Report

PLASMA LEAKAGE PROFILES OF DENGUE HEMORRHAGIC FEVER PATIENTS IN RSUD Dr. SOETOMO, SURABAYA, EAST JAVA, INDONESIA JANUARY – JUNE 2014

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ABSTRACT

Plasma leakage is one crucial point of dengue hemorrhagic fever (DHF) that differentiates it from dengue fever (DF). DHF has to meet 4 criteria which are 2 – 7 days of acute fever, hemorrhagic manifestation, thrombocytopenia (≤100.000 cells/mm^3) and evidence of plasma leakage. Plasma leakage consists of increasing hematocrit ≥20%, hypoalbuminemia or evidence of pleural effusion or ascites. Often doctors only base their DHF diagnosis on the presence of thrombocytopenia. This study analyzed the presence of plasma leakage between adult and pediatric patients with a DHF diagnosis in RSUD Dr. Soetomo in order to make the diagnosis and healthcare services better in the future. This was a retrospective study which used medical records of DHF patients admitted from January to June 2014. 78 cases were included, 24 adult patients (31%) and 54 pediatric patients (69%). 29/78 (37%) patients had no evidence of plasma leakage. No adult patients had ascites whereas 11/54 (20%) pediatric patients presented with ascites. No adult patients had pleural effusion whereas 25/54 (53%) pediatric patients did. Most adult patients that had serum albumin checked had normal albumin levels (12/14 [86%]) while only 14/28 (52%) pediatric patients had normal albumin level. 5/22 (23%) adult patients versus 32/53 (60%) pediatric patients showed hematocrit increments ≥20%. Patients admitted with dengue virus infection may currently be often misclassified as DHF because there are no plasma leakage manifestation in some patients.. There are significant differences in plasma leakage manifestations between adult and pediatric patients which poses a theory that pediatric patients are more susceptible to have plasma leakage manifestations than adult patients.

Keywords: *plasma leakage, dengue hemorrhagic fever, dengue fever, pediatric patients, adult patients*

ABSTRAK

Kebocoran plasma adalah salah satu gejala penting demam berdarah dengue (DBD) yang membedakan dengan demam dengue (DD). Ada 4 kriteria dalam penegakan diagnosis DBD yaitu demam tinggi mendadak 2 – 7 hari, manifestasi perdarahan, trombositopenia (≤100.000 sel/mm^3) dan bukti dari kebocoran plasma. Kebocoran plasma terdiri dari peningkatan hematokrit ≥20%, hipoalbuminemia, bukti dari efusi pleura atau asites. Masih banyak dokter yang hanya berpatokan pada kriteria trombositopenia saja pada penegakan diagnosis DBD. Penelitian ini bertujuan untuk menganalisis profil dari kebocoran plasma dari pasien DBD dewasa dan anak di RSUD Dr. Soetomo pada periode Januari – Juni 2014 sehingga bisa didapatkan diagnosis dan pelayanan kesehatan yang lebih baik ke depannya. Penelitian ini adalah penelitian studi retrospektif dengan menggunakan rekam medik pasien DBD. 78 rekam medik pasien DBD ditemukan, terdiri dari 24 pasien dewasa (31%) dan 54 pasien pediatri (69%). 29/78 (37%) pasien ditemukan tanpa adanya manifestasi kebocoran plasma. Sama sekali tidak ditemukan pasien dewasa dengan asites tetapi ditemukan 11/54 (20%) pasien pediatric dengan asites. Tidak ada pasien dewasa dengan manifestasi efusi pleura sama sekali sedangkan pada pasien pediatri ditemukan 25/54 (53%) pasien dengan efusi pleura. Mayoritas pasien dewasa yang telah dicek serum albumin memiliki kadar albumin normal (12/14 [86%]), di sisi lain hanya 14/28 pasien pediatri yang telah dicek serum albumin memiliki kadar albumin normal. 5/22 (23%) pasien dewasa berbanding 32/53 (60%) pasien anak menunjukkan kenaikan hematokrit ≥20%. Dalam penelitian ini dapat disimpulkan bahwa masih cukup banyak terjadi misdiagnosis dari DBD karena dapat ditemukan beberapa pasien yang tidak memiliki manifestasi kebocoran

plasma. Pasien anak dan pasien dewasa memiliki perbedaan yang signifikan sehingga dapat memunculkan teori bahwa pasien anak lebih rentan untuk memiliki manifestasi kebocoran plasma.

Kata kunci: *kebocoran plasma, demam berdarah dengue, demam dengue, pasien pediatri, pasien dewasa*

INTRODUCTION

WHO classifies symptomatic dengue virus infection into four groups which are undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), and expanded dengue syndrome. Dengue Hemorrhagic Fever (DHF) remains one of the tropical diseases with an enormous worldwide caseload. Around 50 million dengue virus infections happen annually of which 500,000 people are diagnosed with DHF and need hospitalization. Approximately 90% of DHF patients are children aged less than five years and 2.5% die.[1] Indonesia in 2014 had 100,347 cases of DHF of which 907 (0.9%) were lethal.[2]

DF and DHF mostly have similar symptoms. The requirement for DHF diagnosis is acute onset of fever lasting 2 – 7 days, hemorrhagic manifestation, a platelet count ≤100,000 platelets/mm^3 and evidence of plasma leakage.

Plasma leakage is the main hallmarks of DHF and it differentiates DHF from DF. DHF and DF nearly have a similar sign & symptom (like thrombocytopenia, hemorrhagic manifestation, fever etc.). Plasma leakage manifestation is essential for the diagnosis making of DHF because any signs and symptoms of dengue viral infections without plasma leakage manifestations is considered to be DF.

Plasma leakage is considered to have occurred in case of a suddenly rising hematocrit to ≥20% from baseline or decrease in convalescence, the presence of ascites, a new pleural effusion on lateral decubitus chest x-ray (CXR), or low serum albumin or protein for age and sex.[1]

Many doctors base their diagnosis of DHF only on the presence of thrombocytopenia.[3] WHO changed the classification of dengue in 2011 which refers back to the classification from 1997 with some changes. Many doctors were confused about the 2009 WHO dengue classification since the WHO 2009 classification created about twice the workload for health care personnel and required a dengue confirmatory test.[4] The changes made in 2009 created confusion among healthcare personnel and may have had unwanted consequences for healthcare services.

By the latest 2011 dengue classification, most patients did not fulfill the DHF case definition: evidence of plasma leakage in the presence of thrombocytopenia.[4] In the early phase of mild cases of DHF one might not find evidence of plasma leakage by physical examination.[1] This phenomenon makes it easier misclassify patients with dengue virus infection.

This goal of study was to analyze the presence of plasma leakage between adult and pediatric patients with a DHF diagnosis in RSUD Dr. Soetomo Surabaya in the period of January – June 2014.

MATERIAL AND METHOD

This study was a retrospective study using medical record of patients that had had a DHF diagnosis in RSUD Dr. Soetomo, Surabaya between January – June 2014. DHF patients which had unusual manifestations or complications that were not correlated with dengue virus infection were excluded. These exclusions were based on the 'Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Hemorrhagic Fever' published by WHO in 2011. These exclusions would minimalize plasma leakage manifestations that caused by non - dengue virus infection.

Variables recorded in this study consisted data regarding plasma leakage, i.e. increasing hematocrit ≥20%, hypoalbuminemia, and evidence of pleural effusion and ascites. There were no data available regarding the baseline levels of hematocrit in Indonesia, instead we therefore subtract the lowest hematocrit level from the highest hematocrit level, then dividing that value by the lowest hematocrit level and multiplying by 100.[5] As normal albumin levels in this study we used 3.4 – 5 g/dl. Pleural effusion were checked by Chest X-Ray (CXR) and the presence of ascites was ascertained by physical examination only.

Table 1. Grading of disease severity among patients admitted to RSUD Dr. Soetomo academic hospital with a diagnosis of Dengue Hemorrhagic Fever.

Diagnosis	Adult Patients		Pediatric Patients	
	Frequency	Percentage (%)	Frequency	Percentage (%)
DHF Grade I	13	54.2	16	29.6
DHF Grade II	11	45.8	19	35.2
DHF Grade III	0	0	16	29.6
DHF Grade IV	0	0	3	5.6
Total	**24**	**100**	**54**	**100**

p value calculated by Mann – Whitney test = 0.002

Adult data are the data of patients treated in Internal Medicine department and pediatric data are from cases treated in Pediatric Medicine department.

RESULT AND DISCUSSION

48 patients were excluded based on exclusion criteria. There were 78 DHF patients who fulfilled this study's criteria in RSUD Dr. Soetomo between January – June 2014 that consisted of 24 adult patients (31%) and 54 pediatric patients (69%). 76% patients enter the hospital in critical phase while 6% and 18% enter the hospital in febrile and recovery phase.

No dengue shock syndrome (DSS) happened in adult patients while in pediatric patients there were 19 DSS patients. The clinical presentation of adult and pediatric with DHF differed significantly (Table 1).

Overall, 29/78 patients (37%) did not have any evidence of plasma leakage. These 29 patients consisted of 17 adult patients and 12 pediatric patients (Table 2).

None of the adult patients had ascites on physical examination while 11 pediatric patients did have ascites. Among the 11 pediatric patients with ascites, 9 patients had developed ascites before entering the hospital and 2 patients developed ascites during their hospital stay.

None of the adult patients had radiological evidence of pleural effusion while pleural effusions were detected in 25/34 (74%) pediatric patients that had CXR taken. 11 adult patients and 20 pediatric patients did not have a CXR taken during their hospital stay.

From the albumin level data presented in Table 3 it is become evident that there were more patients which had normal albumin level than patients that had hypoalbuminemia. 12/14 (86%) adult patients had normal albumin levels while only 14/27 (52%) pediatric patients

Table 2. Distribution of clinical and laboratory manifestations of plasma leakage in patients admitted with a Dengue Hemorrhagic Fever diagnosis.

Manifestation	Frequency	Percentage (%)	Percentage with No Manifestations (%)
No evidence of plasma leakage	29	37.2	-
Ascites only	1	1.3	2.0
Pleural effusion only	4	5.1	8.2
Hypoalbuminemia only	2	2.6	4.1
Hematocrit increase š20% only	19	24.4	38.8
Pleural effusion + Hypoalbuminemia	1	1.3	2.0
Pleural effusion + Hematocrit increase š20%	7	9.0	14.3
Hypoalbuminemia + Hematocrit increase š20%	1	1.3	2.0
Ascites + Hematocrit increase š20%	1	1.3	2.0
Ascites + Pleural effusion + Hematocrit increase š20%	3	3.8	6.1
Pleural effusion + Hypoalbuminemia + Hematocrit increase š20%	4	5.1	8.2
Ascites + Pleural effusion + Hypoalbuminemia	3	3.8	6.1
Ascites + Pleural effusion + Hypoalbuminemia + Hematocrit increase š20%	3	3.8	6.1
Total	**78**	**100**	**100**

Table 3. Albumin level distribution of DHF patients

Albumin	Adult			Pediatric		
	Frequency	Total	Percentage (%)	Frequency	Total	Percentage (%)
Normal	12	14	85.7	14	27	51.9
Hypoalbuminemia	2		14.3	13		48.1
No Data	10			27		
Total	**24**		**100**	**54**		**100**

p value calculated by Chi – square test = 0.03

Table 4. Changes in hematocrit in adult and pediatric patients with a Dengue Hemorrhagic Fever diagnosis.

Hematocrit	Adult			Pediatric		
	Frequency	Total	Percentage (%)	Frequency	Total	Percentage (%)
Increased š20 %	5	22	22.7	32	53	60.4
Negative	17		77.3	21		39.6
Only tested once	2			1		
Total	**24**		**100**	**54**		**100**

p value calculated by Chi – square test = 0.003

had normal albumin level (Table 3, p = 0.03). However, in a large proportion of patients suspected of DHF, their serum albumin level was not determined.

37/75 (49%) patients had hematocrit increments ≥20 %. More so among pediatric patients (32/53 [60%]) than among adult patients (only 5 out of 22 patients [22.7%]), a highly significant difference (Table 4, p = 0.003. In three patients their increments could not be determined because they had their hematocrit level determined only once during their hospital stay.

DISCUSSION

Plasma leakage is a crucial point that differentiates DHF from DF. The possibility to misdiagnose DF into DHF is high because plasma leakage manifestations are difficult to observe and ascertain. Evidence of plasma leakage may not be detectable by physical examination alone, especially in the early phase of plasma leakage or in mild cases of DHF.

29 out of 78 patients (37.2%) had no evidence of plasma leakage. However, many of those did not receive a full clinical and laboratory work-up. This poses the question how did doctors make the DHF diagnosis in these cases if there was no plasma leakage evidence? These 29 patients included 17 adult patients and 12 pediatric patients.

For the first manifestation of plasma leakage, ascites, there were no cases among the adult patients while there were 11 cases among the pediatric patients, nine had already developed ascites before entering the hospital. Patients with ascites in RSUD Dr. Soetomo, Surabaya received a full physical examination. Other studies showed varied results. Srikiatkhachorn et al.[6] (2011) in his research in pediatric patients with DHF found that 34% had ascites, while Navarrete-Espinosa et al.[7] (2005) shows that there were only 4 ascites cases among a cohort of 898 DHF patients. Another study by Balasubramanian et al.[8] (2005) showed that by using ultrasonography, 91% of their DHF patients had ascites. This big gap between physical examination and USG results showed that in many, possibly in the majority of them, ascites cannot be detected by physical examination alone.

Ascites developed during the patient's stay in the hospital may not be the direct consequence of the virus infection but rather should be considered as an early symptom of fluid therapy overload.[1] Routine usage of ultrasonography is thus recommended as the method of choice in detecting cases with ascites which couldn't be detected by physical examination alone. Presence of fluid leakage by ultrasound might differentiate cases with borderline hematocrit levels (10 – 20%).[9]

Classification of patient's data based on the course of dengue illness in febrile phase, critical phase and recovery phase based on WHO 2009 guidelines.[10] Mostly, patients enter the hospital in the critical phase. The most important things to do in the critical phase is give fluid therapy as fast as possible. It is better to use ultrasound but it is overrated because we could use other sign and examination which cheaper and easier in critical phase like temperature, potential clinical issues, and laboratory changes to make a dengue viral infection suspect. Because of fluid therapy importance, probably there were patients with possible over fluid therapy.

The other plasma leakage manifestation, pleural effusions did not occur in adult patients with DHF. In contrast, a large majority, approximately 74% of pediatric patients had radiological evidence of pleural effusions. In the study by Navarrete-Espinosa et al.[7] (2005), 3/898 DHF patients had pleural effusions whereas Srikiatkhachorn et al.[6] (2011) reported that 78% of their cases had pleural effusions. The study by Balasubramanian et al.[8] (2005) in 89% of DHF patients checked by ultrasonography had pleural effusions. There were no significant difference in the presence of pleural effusions when examination by CXR and ultrasonography were compared. However, 31 patients in our retrospective were not checked by CXR.

Transudates pleural effusion could be caused by hypoalbuminemia.[11] Minimum volume of pleural effusion that become visible in CXR is 50 ml.[12] Mild pleural effusion/less than 50 ml couldn't be analyzed by CXR. This number is probably relative based on thoracic volume. 74% of pediatric patients had radiological evidence of pleural effusion while none of adult patients had radiological evidence of pleural effusion. Smaller thoracic volume in pediatric patients make the ratio between fluid volume and thoracic volume bigger than the same fluid volume in adult thoracic volume.

Hypoalbuminemia was found in only a minority of the cases enrolled in this study, especially among adult patients whereas in pediatric patients, hypoalbuminemia was detected in close to half of the patients tested. However, not all of the patients got their albumin level tested (37/78 patients had not been tested). This study is somewhat contradictive with a study by Villar-Centeno et al.[13] (2008) reported that 57% of their DHF patients presented with hypoalbuminemia.

Albumin levels less than 4 g/dL may be an early indicator of vascular permeability alteration.[13] Lower albumin levels could be caused by liver involvement in DENV infections which makes severe liver damage that leading to decreased production of albumin.[14] Mostly DHF patients in this study have normal albumin level.

The final plasma leakage manifestation was the hematocrit. Nearly half number patients had increases of their hematocrit ≥20%. Only few adult patients have developed increasing hematocrit ≥20% while 60% of pediatric patients have increasing hematocrits of ≥20%. This finding corresponds with Srikiatkhachorn et al.[6] (2011) and Guilarde et al.[15] (2008) who showed that among pediatric patients, increasing hematocrit ≥20% is the rule, whereas other studies found that among adult patients with hematocrits increasing ≥20% constituted a minority, albeit a sizable minority of 49%.

Increasing hematocrit levels is a consequence of plasma leakage. Extravasations of plasma without RBC makes the ratio between RBCs and total volume of blood is higher. A rising hematocrit, e.g. 10% to 15% above baseline, is the earliest evidence of plasma leakage[1] but DHF would be misdiagnosed if only based on hematocrit as a diagnostic criterion.[9] Highly significant difference of hematocrit level and albumin level between adult and pediatric patients poses a theory which pediatric patients are more susceptible to have a plasma leakage than adult patients.

CONCLUSION

Plasma leakage is the most important signs / symptoms for the diagnosis making of DHF. Signs and symptoms of dengue viral infection without any of plasma leakage manifestations is not classified as DHF but is classified as DF. This study found that patients admitted with dengue virus infection may currently be often misclassified as DHF because there are no evidences of plasma leakage manifestations. There are significant differences in plasma leakage manifestations between adult and pediatric patients which poses a theory that pediatric patients are more susceptible to have plasma leakage manifestations than adult patients.

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