Clinical profile of dengue fever and dengue haemorrhagic fever in Indonesian children: A six year retrospective study

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Abstract

Background: Dengue infection is still a significant public health problem in Indonesia. An appropriate clinical profile is helpful in early identification of patients with a high risk for severe dengue infection.

Objectives: To report the prevalence, characteristics, and clinical outcomes of patients with dengue fever (DF) and dengue haemorrhagic fever (DHF).

Method: This was a retrospective study of childhood hospitalisation in Siloam Hospitals Lippo Village, Indonesia from January 2015 to December 2020. Demographic data, clinical signs, and laboratory findings were collected and processed using SPSS version 26.

Results: Of 528 patients, 85.6% were DF, 10.4% were DHF grades I and II, and 4% were DHF grades III and IV. Median ages of patients with DF, DHF grades I and II, and DHF grades III and IV were 10.9, 12.4 and 8.5 years respectively. Common clinical symptoms of DF patients were headache (67.5%), loss of appetite (41.8%), and vomiting (40.9%). While 52.7% patients with DHF grades I and II had respiratory symptoms, 42.9% patients with DHF grades III and IV had hepatomegaly.

Conclusions: Common clinical symptoms of DF and DHF patients were headache, loss of appetite and vomiting. Whilst 52.7% patients with DHF grades I and II had respiratory symptoms, 42.9% patients with DHF grades III and IV had hepatomegaly.

(Key words: Dengue fever, Dengue haemorrhagic fever, Clinical spectrum, Children)

Background

As there are four dengue serotypes a person can be infected four times[1]. The number of dengue fever (DF) cases reported by the World Health Organization (WHO) increased from 505,430 in 2000 to 5.2 million in 2019[2]. Based on data from the 2019 Indonesian Health Profile, dengue cases increased from 65,502 in 2018 to 138,127 in 2019. Deaths from dengue increased from 467 in 2018 to 919 in 2019. In 2019 ten Indonesian provinces had case fatality rates >1%[3]. There are about 500,000 dengue haemorrhagic fever (DHF) patients annually most of whom are children[4]. DF generally manifests as a biphasic fever, severe headache, myalgia, arthralgia, skin rash, leucopenia, and thrombocytopenia[5]. DHF cases have similar symptoms to DF but at the end of the febrile phase tend to develop hypovolaemic shock or dengue shock syndrome due to plasma leakage[1,5].

DHF frequently causes epidemics in Bangladesh, India, Indonesia, Maldives, Myanmar, Sri Lanka, and Thailand[1]. DF and DHF remain challenging due to the high population density in Indonesia[6]. Vector factors, host factors and environmental factors are associated with increased dengue transmission[5,7,8]. An appropriate clinical profile aids in early identification of patients at risk for severe dengue[4].

Objectives

To report the prevalence, characteristics, and clinical outcomes of patients with DF and DHF at Siloam Lippo Village Hospital, Indonesia.

Method

A cross-sectional study was conducted from January 2015 to December 2020 using purposive sampling. We used medical records to include patients aged 0-18 years with a diagnosis of DF and DHF based on 2011 WHO criteria[1]. DF was diagnosed if there were clinical manifestations like headache, retro-orbital pain, myalgia, arthralgia and bleeding manifestations and laboratory tests showed leucopenia (white blood cell count <5,000 /cu mm), thrombocytopenia (platelet count <150,000 cells/cu mm), and an increase in haematocrit (5%-10%). DHF grade I was diagnosed if the diagnostic criteria for DF was accompanied by plasma leakage, characterized by an increase in haematocrit (≥ 20%). DHF grade II diagnosis included criteria for grade I DHF plus spontaneous bleeding. DHF grade III was diagnosed if it met the criteria for grades I and II with a decrease in pulse pressure, hypotension, weak pulse, and restlessness. Grade IV was diagnosed if it met the criteria for grade III with signs of shock like weak pulse and undectable blood pressure[1]. Patients were excluded if they had a history of long-term steroid use, had congenital or acquired immunodeficiency or had co-infection with other pathogens before laboratory testing.

Demographic data included gender, age, history of previous dengue infection, duration of fever, clinical manifestations and nutritional status. Bleeding manifestations included petechiae, purpura, epistaxis, bleeding gums, hypermenorrhea, melaena and haematemesis. Respiratory symptoms included shortness of breath, cough, rhinitis, and sore throat. Laboratory data included haemoglobin, haematocrit, white blood cell

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count, platelet count, erythrocyte sedimentation rate, C-reactive protein and neutrophil-lymphocyte ratio. Immunoglobulin M, immunoglobulin G and immunoglobulin A were also taken for analysis. We also looked at therapies like fluid boluses, dopamine, dobutamine, adrenaline, and blood transfusions.

Ethical issues: Study approval was obtained from the Ethics Committee of Pelita Harapan University, Tangerang, Indonesia (No. 174/K-LKJ/ ETIK/ XII/ 2020. Being a retrospective study informed consent was not possible.

Statistical analysis: Data normality was checked using Kolmogorov test as sample exceeded 50. Data with normal distribution were tabulated using mean and standard deviation, while median and range were used for data with non-normal distribution. Data were processed using SPSS version 24.

Results

There were 528 children comprising 452 DF, 55 DHF grades I and II, and 21 DHF grades III and IV (Table 1). In DF patients 67.5% had headache, 41.8% had loss of appetite and 40.9% had vomiting. In DHF grades I and II, 52.7% had respiratory symptoms, 47.3% had loss of appetite and 43.6% had vomiting. In DHF grades III and IV 57.1% had loss of appetite, 52.4% had headache, 52.4% had abdominal pain and 42.9% had hepatomegaly. Table 2 shows the laboratory findings of patients with DF and DHF.

Table 1: ***Demographic findings of patients with dengue fever (DF) and dengue haemorrhagic fever (DHF) (n=528)***

Variable	Category	Dengue fever *(n=452)*	DHF grades I & II *(n=55)*	DHF grades III &IV *(n=21)*
Sex: n (%)	Male	263 (58.2)	37 (67.3)	10 (47.6)
	Female	189 (41.8)	18 (32.7)	11 (52.4)
Age (years): Median (range)		10.9 (0-18)	12.4 (0.5-17.8)	8.5 (3.4-15.3)
Age (years): n (%)	0 to <3	41 (09.1)	02 (03.6)	0 (0)
	3 to <6	65 (14.4)	04 (07.3)	06 (28.6)
	6 to 10	84 (18.6)	12 (21.8)	07 (33.3)
	>10	262 (58.0)	37 (67.3)	08 (38.1)
Nutritional status: n (%)		*n=427*	*n=51*	*n=21*
	Severe undernutrition	03 (0.7)	0 (0)	0 (0)
	Underweight	45 (10.5)	08 (14.5)	05 (23.8)
	Normal	272 (63.7)	30 (54.5)	10 (47.6)
	Overweight	52 (12.2)	07 (12.7)	04 (19.0)
	Obese	55 (12.9)	06 (10.9)	02 (09.5)
Previous dengue infection: n (%)	Positive	21 (04.6)	08 (14.5)	01 (04.8)
	Negative	431 (95.3)	47 (85.5)	20 (95.2)
Fever duration before hospital admission: days (range)		3 (1-10)	3 (1-5)	3 (1-6)
Fever duration before hospital admission: n (%)	0-3	270 (59.7)	34 (61.8)	02 (09.5)
	4-6	171 (37.8)	21 (38.2)	15 (71.4)
	7-9	09 (02.0)	0 (0)	03 (14.3)
	10 or more	02 (0.4)	0 (0)	01 (04.8)
Fever duration upon hospitalization: days (range)		5 (1-15)	5 (2-9)	3 (1-6)
Fever duration upon hospitalization: n (%)	0-3	41 (09.1)	02 (03.6)	02 (09.5)
	4-6	271 (60.0)	40 (72.7)	15 (71.4)
	7-9	127 (28.1)	13 (23.6)	03 (14.3)
	10 or more	13 (02.9)	0 (0)	01 (04.8)
Clinical manifestations: n (%)	Headache	305 (67.5)	11 (20.0)	11 (52.4)
	Retrorbital pain	35 (07.7)	07 (12.7)	03 (14.3)
	Muscle and joint pain	74 (16.4)	09 (16.3)	07 (33.3)
	Back pain	11 (02.4)	02 (03.6)	04 (19.0)
	Abdominal pain	69 (15.2)	17 (30.9)	11 (52.4)
	Decreased appetite	189 (41.8)	26 (47.3)	12 (57.1)
	Vomiting	185 (40.9)	24 (43.6)	07 (33.3)
	Diarrhoea	53 (11.7)	08 (14.5)	05 (23.8)
	Bleeding manifestations	61 (13.5)	17 (30.1)	04 (19.0)
	Pleural effusion	01 (0.2)	01 (01.8)	06 (28.6)
	Hepatomegaly	07 (01.5)	05 (09.1)	09 (42.9)
	Ascites	0 (0)	01 (01.8)	02 (09.5)
	Oedema	0 (0)	0 (0)	01 (04.8)
	Respiratory symptoms	156 (34.5)	19 (52.7)	05 (28.6)
Pulse pressure (mmHg) Median (range)		*n=421* 40 (10-80)	*n=53* 40 (20-60)	*n=21* 27.5 (15-40)

Table 2: ***Laboratory findings of patients with dengue fever (DF) and dengue haemorrhagic fever (DHF) (n=528)***

Variable	Normal value	Dengue fever *(n=452)*	DHF grades I and II *(n=55)*	DHF grades III and IV *(n=21)*
Haemoglobin (g/dL): Median (range)	10.0-15.5	13.2 (8.2-17.8)	13.7 (9.8-17.9)	13.2 (9.5-18.0)
Haematocrit (%):Median (range)	32-44	39.5 (6.71-53.4)	41 (13.6-51.2)	38.5 (28.4-52.4)
Total leucocyte count (10^3/cu mm): Median (range)	5-10	3.9 (1.1-38.5)	3.5 (1.5-16.1)	5.6 (2.6 -15.1)
Differential leucoyte count (%)		*(n=339)*	*(n=43)*	*(n=20)*
Basophil:Median (range)	0.5-1.0	0 (0-1)	0 (0-1)	0 (0-9)
Eosinophil: Median (range)	1-4	0 (0-10)	0 (0-5)	0 (0-9)
Immature neutrophil: Median (range)	0-15	3 (0-8)	3 (0-4)	3 (0-3)
Segmented neutrophil: Median (range)	40-60	55 (4-89)	57 (20-86)	47 (23-84)
Lymphocyte: Median (range)	20-40	34 (4-84)	32 (4-65)	40.5 (9-69)
Monocyte: Median (range)	2-8	8 (0-20)	8 (0-11)	7.5 (4-9)
Platelet count (10^3 cell/cu mm): Median (range)	150-400	157 (15.8-440.2)	126 (12-281)	130 (46-333.6)
Erythrocyte sedimentation rate (mm):		*(n=320)*	*(n=41)*	*(n=19)*
Median (range)	0-15	10 (1-78)	10 (3-35)	11 (2-31)
C-reactive protein (mg/L):		*(n=179)*	*(n=14)*	*(n=5)*
Median (range)	<10	9 (1-185)	10.5 (0.5-108)	12 (4,8-25)
Neutrophil to lymphocyte ratio:	Not	*(n=339)*	*(n=43)*	*(n=20)*
Median (range)	available	1.68 (0.08-22.75)	1.88 (0.34-22)	1.18 (0.39-9.33)
Non-structural protein 1(NS1)		*(n=320)*	*(n=38)*	*(n=11)*
Positive: n (%)	Negative	283 (88.4)	34 (89.5)	09 (81.8)
Negative: n (%)		37 (11.6)	04 (10.5)	02 (18.2)
Immunoglobulin M:		*(n=127)*	*(n=18)*	*(n=6)*
Positive: n (%)	Negative	56 (44.1)	06 (33.3)	03 (50.0)
Negative: n (%)		71 (55.9)	12 (66.7)	03 (50.0)
Immunoglobulin G:		*(n=127)*	*(n=13)*	*(n=5)*
Positive: n (%)	Negative	45 (38.4)	06 (46.2)	03 (50.0)
Negative: n (%)		72 (61.6)	07 (53.8)	03 (50.0)
Immunoglobulin A:		*(n= 14)*	*(n=0)*	*(n=1)*
Positive: n (%)	Negative	10 (71.4)		0 (0)
Negative: n (%)		04 (28.6)		01 (100.0)

Table 3 gives the medications given and mortality of patients with DF and DHF. There were no deaths in children with DF and DHF grades I and II but there was one death in a child with grade III and IV DHF.

Table 3: ***Medication and mortality of patients with dengue fever (DF) and dengue haemorrhagic fever (DHF)***

Variable	Dengue fever *(n=452)*	DHF grades I and II *(n=55)*	DHF grades III and IV *(n=21)*
Admission to the intensive care unit			
Positive: n (%)	0 (0)	0 (0)	01 (04.8)
Negative: n (%)	452 (100.0)	55 (100.0)	20 (95.2)
Fluid bolus			
Positive: n (%)	01 (0.2)	0 (0)	05 (23.8)
Negative: n (%)	451 (99.8)	55 (100.0)	16 (76.2)
Dopamine			
Positive: n (%)	0 (0)	0 (0)	01 (04.8)
Negative: n (%)	452 (100.0)	55 (100.0)	20 (95.2)
Dobutamine			
Positive: n (%)	0 (0)	0 (0)	02 (09.5)
Negative: n (%)	452 (100.0)	55 (100.0)	19 (90.5)
Adrenaline			
Positive: n (%)	01 (0.2)	0 (0)	01 (04.8)
Negative: n (%)	451 (99.8)	55 (100.0)	11 (95.2)
Blood transfusion			
Positive: n (%)	07 (01.5)	08 (14.5)	11 (52.4)
Negative: n (%)	445 (98.5)	47 (85.5)	10 (47.6)
Outcome			
Alive: n (%)	452 (100.0)	55 (0)	20 (95.2)
Dead: n (%)	0 (0)	0 (0)	01 (04.8)

Discussion

In our study 85.6% had DF, 10.4% had DHF grades I and II and 4% had DHF grades III and IV. Mishra S, *et al*[9] found 86.6% DF cases and 13.4% DHF cases. Hartoyo E, *et al*[10] found 48% DHF grade I and II, 35% DHF grade III and IV and 17% DF. Selvan T, *et al*[11] found that the highest proportion of DF and DHF cases was in the 10-18 year category. However, in another study[9] average age of DF and DHF patients was 8.7 years, close to the age of patients with DHF grades III and IV in our study. The younger age in patients with grade III and IV DHF may be related to lack of ability of younger children to compensate for plasma leakage, making them more susceptible to more severe DHF[12]. In addition, the difference in age distribution in DF and DHF may be caused by the tendency of *Aedes aegypti* mosquito to be active during the day, which matches the peak activity of children and adolescents outside home[13].

Raihan R, *et al*[14] obtained results similar to our study that most DHF patients had good nutritional status. This is related to patients with good nutritional status having a good immune response with the potential to trigger severe DHF[15,16]. Patients with moderate or severe malnutrition tend to experience immune suppression through decreased production of $CD4^+$ and a lower $CD4^+/CD8^+$ ratio. There is also a decrease in the production of secretory IgA antibodies and complement components C3, C4, and factor B so that malnutrition is said to protect children from severe dengue[15]. Picchaniarong N, *et al*[17] found that DHF and DSS were commoner in obese patients. This is due to occurrence of low-grade chronic inflammations in obese patients due to excessive production of interleukin-1ß, interleukin-6 and tumour necrosis factor-α which can worsen infection[18].

In our study patients with DF and DHF grades I and II were predominantly male. Hartoyo E, *et al*[10] and Chairulfatah A, *et al*[19] had similar results. Another study that analysed the occurrence of DF in six Asian countries also reported that DF cases were more common in males[20]. This difference may be due to wearing clothes that tend to be more closed in women, reducing the possibility of being bitten by Aedes mosquitoes[9]. In our study incidence of DHF grades III and IV in males and females was close to each other. This may be due to the smaller sample of patients with DHF grades III and IV.

In our study most patients came to hospital for treatment from the first to third day of fever. This is similar to previous research conducted at the Central General Hospital which found that children treated for DF and DHF had fever for average 4.1 days before being admitted to hospital[14]. Santosa B, *et al*[21] also found that the average duration of fever in children with DHF was 4.1 days.

In our study common symptoms of DF were headache, loss of appetite and vomiting. Other studies have reported that fever, vomiting, headache, and abdominal pain are prominent symptoms in patients with DF[10,22,23]. In addition to decreased appetite and vomiting, most DHF grade I and II patients in our study also experienced respiratory symptoms. Respiratory symptoms were found in several other studies, although not as a predominant symptom[10,11]. Our study found hepatomegaly as a prominent feature in patients with grade III and IV DHF. Jagadishkumar K, *et al*[24] found that 88.5% of DHF patients and 96% of DSS patients had hepatomegaly. Increasing incidence of hepatomegaly with increasing severity of dengue infection is associated with incidence of shock, reduced liver perfusion due to plasma leakage and apoptosis of hepatocyte cells due to direct invasion of the virus[25]. Hepatomegaly was also a prognostic factor for shock in DHF patients[14].

In our study leucopenia in patients with DHF grades I and II was more severe than in DF patients. Leucopenia may result from direct viral suppression of bone marrow or through production of proinflammatory cytokines[26]. Leucopenia may also be due to destruction or inhibition of myeloid progenitor cells, as evidenced by bone marrow examination showing mild hypocellularity in first seven days of fever[27]. Thrombocytopenia in DHF patients occurs due to platelet destruction, bone marrow suppression or shortened platelet life span[28]. Incidence of thrombocytopenia in most DHF patients was seen in several other studies[10,16,29,30]. In our study, thrombocytopenia was more severe in DHF grades I and II compared to grades III and IV DHF. This explains the geater frequency of bleeding manifestations in DHF grades I and II compared to DHF grades III and IV.

There is a difference in sensitivity of NS1 with ELISA for detecting primary dengue (89.2%) compared to secondary dengue (20%)[31]. IgG levels are produced approximately two weeks after primary dengue, lasting up to one or two years or even for life[31]. Therefore, the high number of positive NS1 and negative IgG in our study may be due to the high number of patients with primary dengue. IgM antibody levels show acute and primary events and are often not detected in secondary dengue. IgM antibodies appear on the fifth day of infection and persist for three to eight months[12]. In our study, most patients with DF and DHF had negative IgM. This may be because most patients came for treatment at the beginning to three days after symptoms appeared. Nawa M, *et al*[33] reported that IgA antibodies appeared on day six but persisted for a shorter time than IgM. They also found that IgA response was higher in secondary dengue compared with primary infection[33]. This is in contrast to our study where the high positive rate of IgA in grade III and IV DHF was not accompanied by a high rate of secondary dengue.

Rapid fluid bolus administration helps increase cardiac output and restore adequate circulating volume to save the brain from hypo-ischaemia[1]. Dopamine helps treat hypotension in children with poor peripheral perfusion despite having adequate intravascular volume. Dobutamine resolves hypoperfusion resulting from increased systemic vascular resistance. Adrenaline is used to treat hypotension that is non-responsive after cardiopulmonary and fluid resuscitation[34,35]. Blood transfusions are given when there is massive bleeding or very low platelets, although the exact number of platelets at which the transfusion should be given is debated[35]. In our study, fluid boluses, dobutamine, dopamine, adrenaline, and blood transfusions were given primarily in patients with DHF grade III and IV. This finding is related to the signs of shock found more in patients with DHF grade III and IV due to massive plasma leakage[1].

In our study one child with grade III and IV DHF was treated in the intensive care unit. In this child, pleural effusion was found on AP and decubitus chest x-ray

examination although the rise of the patient's haematocrit was still less than 20%. The occurrence of a pleural effusion indicates a plasma leakage that has reached more than 20% of the pleural tissue. Right-sided pleural effusion is also associated with the severity of DHF. However, pleural effusion can occur bilaterally in DHF shock[36]. The child also suffered from secondary dengue infection and had a low pulse pressure of 10 mmHg accompanied by hypotension (90/80 mmHg). A study in Paraguay comparing the characteristics of primary and secondary infection found that elevated liver enzymes, hypoalbuminaemia and thrombocytopenia were significantly associated with secondary infection. In addition, patients with secondary dengue were more likely to go into shock and thus require more frequent fluid therapy and treatment in the intensive care unit[37]. A low pulse pressure (≤20 mmHg) accompanied by increased diastolic pressure or hypotension is a sign of shock[1]. The child also has elevated liver enzymes, thrombocytopenia of 51,840 cells/cu mm, associated with shock and therefore required intensive care[14,25].

In our study, there were no deaths in children with DF and DHF grades I and II. However, one child with grade III and IV DHF died. Several aggravating factors were found in this patient, such as decreased consciousness (Glasgow coma scale score 13), headache, a high difference in haematocrit increase (41.4%), leucopenia (2,570 cells/cu mm), thrombocytopenia (7,000 cells/cu mm) and elevated liver enzymes (aspartate transaminase 264 IU/L, alanine transaminase 216 IU/L) accompanied by hepatomegaly. Changes in consciousness accompanied by elevated liver enzymes and hepatomegaly in this patient may indicate hepatic encephalopathy as the cause of death. According to Dhevianty A, *et al*[38] dengue encephalopathy mainly occurs in patients with DHF grade III and IV, with most children experiencing gastrointestinal bleeding, shock, sepsis, acute hepatitis, and acute renal failure.

Our study has several limitations, one of which is using secondary data from medical records so that the variables cannot be controlled as desired by the researcher. In addition, only hospitalized patients are included in this study. This means that the study only involved DF and DHF patients who need further monitoring. However, our study has a large sample size to describe the pattern of clinical signs and symptoms, laboratory findings, and management of DF and DHF patients.

Conclusions

Common clinical symptoms of DF and DHF patients were headache, loss of appetite and vomiting. Whilst 52.7% patients with DHF grades I and II had respiratory symptoms, 42.9% patients with DHF grades III and IV had hepatomegaly.

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