ORIGINAL ARTICLE

Profile of Dengue Fever Complication in Infant at Tertiary Referral Hospital in East Java, Indonesia

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ABSTRACT

Introduction: Dengue virus infection is caused by the dengue virus and transmitted through the bites of infected Aedes aegypti or Aedes albopictus mosquitoes. The spectrum of clinical manifestations is varied from asymptomatic, undifferentiated fever, dengue fever, dengue hemorrhagic fever, dengue shock syndrome, to expanded dengue syndrome. Data from 2016 in Indonesia revealed that dengue virus infection is common in the population, with a total of 333.821 cases of dengue hemorrhagic fever.
Methods: This was a descriptive study with a cross-sectional design. The subjects in this study were children under 1-year-old, diagnosed with dengue virus infection, and had a complication. The number of subjects used is 60 infants.
Results: Infection of dengue virus in infants is often found in the 7-9 month age group (36,6%). Clinical manifestations found were fever (100%), vomiting (62%), diarrhea (43%), petechiae (22%), bleeding (12%), and irritable (5%). Thrombocytopenia and leukopenia were found in 93,3% and 26,6% of infants respectively. Complications were found in the form of pleural effusion (66%), hypoalbuminemia (62%), hyponatremia (51%), liver involvement (49%), hypocalcemia (43%), hypokalemia (23%), bleeding (21%), brain involvement (21%), kidney involvement (13%), and ascites (11%).
Conclusion: The most common clinical manifestations are fever, diarrhea, and vomiting, while the most common complications are pleural effusion, hypoalbuminemia, hyponatremia, liver involvement, and hypocalcemia.

Introduction

Dengue Virus Infection (DVI) is an infection caused by the dengue virus. This virus has four serotypes, namely DENV-1, DENV-2, DENV-3, and DENV-4. The dengue virus is transmitted through the bites of infected Aedes aegypti and Aedes albopictus mosquitoes. Generally, DVI occurs in countries with tropical climates.[1] The spectrum of clinical manifestations varies, ranging from asymptomatic fever, undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), to Expanded Dengue Syndrome.[2]

Dengue virus infections still occur in infants around the world. The research by Halstead in four countries in Southeast Asia found that 1,439 infants were admitted to hospitals with DHF/DSS. This number represents 1-5% of all DVI cases of all ages in the endemic area each year.[3] Hammond in 1999-2001 revealed that 64%, 55%, and 36% of infants, children, and adults respectively, experienced severe clinical manifestations (internal organ bleeding, platelet count ≤50.000/mm^3, plasma leakage, and shock).[4] However, the complications that can be found in DVI include massive bleeding, severe organ disorders, ascites, edema, hypoalbuminemia, and electrolyte disorders.[5,6] From 2015 to 2016 in Indonesia, there were 333.821 cases of dengue hemorrhagic fever (DHF).[7]

Compared to adults, DVI in infants is unique, because of its relatively higher mortality rate and risk of becoming a DHF/DSS.[5,8] Knowing dengue virus infection in infants can be useful in making strategies or managing treatment with various spectrums of clinical manifestations and complications. There is not much data regarding complications of DVI in infants in Indonesia. This study aims to describe the clinical profile of dengue virus infection and its complications in infants at a single-center tertiary referral hospital.

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Methods

Ethical clearance was taken from the Health Research Ethics Committee RSUD Dr. Soetomo General Academic Hospital, Surabaya (No.04/Pan.KKE/1/2018). This study was a descriptive study with a cross-sectional design. The subject used in this study was a patient with dengue virus infection who was admitted to the inpatient ward of Dr. Soetomo General Academic Hospital, Surabaya, East Java in 2015-2016 with the following criteria: infant (≤1 year old), diagnosed with dengue virus infection and did not have multiple infections. The total sampling method was used in this study, and the number of subjects was 60 infants. The secondary data was used and taken from the medical records of patients suffering from DVI at the Pediatric Inpatient Installation Dr. Soetomo General Hospital from the 2015-2016 period. The collected data was presented in tables, images, and narratives. The statistical analysis in this study used descriptive calculations.

Results

Of all 60 infants with dengue virus infection, 46 (76.67%) were diagnosed with dengue hemorrhagic fever (DHF) and 14 (23.33%) with dengue fever (DF). Complications occurred in 44 DHF and 3 DF patients. Of all the DVI infants, the highest number of cases was found in the 7-9th (n=22, 36.67%) and 10-12th (n=21.35%) months group. In Table 1, the average age, sex, temperature, and day of complications can be seen. Of the 47 infants infected with the dengue virus, complications occurred most frequently on the 5th (n=16) and 6th (n=11) day of illness. Between the fourth and eighth day of illness, DHF/DSS infants with complications are admitted to the hospital. The most common symptoms in DVI infants were fever, vomiting, and diarrhea. As for laboratory results, thrombocytopenia was found in 56 (93%) infants and leukopenia in 23 (38%) infants. With a mean level of 2.6 mg/dL, hypoalbuminemia is an intriguing laboratory finding. Clinical manifestations and laboratory results are listed in Tables 1, 2, and 3.

The most common complication, as shown in Table 4, were pleural effusion (n=31, 65.95%), hypoalbuminemia (n=29, 61.70%), hyponatremia (n=24, 51.06%), liver involvement (n=23, 48.93%), and hypocalcemia (n=20, 42.55%). While the other complications were hypoalbuminemia (n=11, 23.40%), brain involvement (n=10, 21.27%), bleeding (n=9, 19.14%), kidney involvement (n=6, 12,76%), and hypoalbuminemia (n=5, 10.63%). Cardiac involvement was not found in this study.

The limitation of this study is the lack of DVI cases. Fifty-eight subjects were excluded because they were more than 1 year old (overlapping data), had multiple infections, or were missing medical record data.

Table 2. Clinical Manifestation of DVI in Infants with Complications and Non-Complications

Clinical Manifestation	With Complication (n=47)	Without Complication (n=13)	Total (n=60)
Fever	47 (100%)	13 (100%)	60 (100%)
Diarrhea	21 (45%)	5 (38%)	26 (43%)
Bleeding	7 (15%)	0 (0%)	7 (12%)
Petechiae	13 (28%)	0 (0%)	13 (22%)
Irritable	3 (6%)	0 (0%)	3 (5%)
Vomiting	28 (60%)	9 (69%)	37 (62%)

Table 1. Characteristics of Subjects

Variable	With Complication (n=47)	Without Complication (n=13)	Total (n=60)
Age (Mean±SD)	8±3	7.85±2.30	8±2.64
Sex			
Male	28 (60%)	8 (62%)	36 (60%)
Female	19 (40%)	5 (38%)	24 (40%)
Highest Temperature (Mean±SD)	37.90±0.87	38.40±0.77	38±0.86
Day of Complication (Mean±SD)	6±1.48	-	-
Leucocyte (cell/mm3)			
<5.000	19 (40%)	4 (31%)	23 (38%)
>5.000	28 (60%)	9 (69%)	37 (62%)
Platelet (cell/mm3)			
<150.000	45 (96%)	11 (85%)	56 (93%)
>150.000	2 (4%)	2 (15%)	4 (7%)

Table 3. Laboratory Result of Infant with DVI

Laboratory Result	With Complication	Without Complication	Total
	Mean±SD/Median	Mean±SD/Median	Mean±SD/Median
Hemoglobin(g/dL)	10.90±1.65	12.10±1.02	11.30±1.59
Hematocrit(%)	32.70±5.09	36.20±2.98	33.80±4.94
Leukocyte*(cell/mm3)	7050	5810	5775
Platelet*(cell/mm3)	35000	60000	35000

Neutrophil(%)	31.20±17.59	31.40±12.31	31.50±16.01
Lymphocyte(%)	51.80±19.19	52.50±12.38	52.30±17.21
AST*(U/L)	222	91	220
ALT*(U/L)	78	36	66
PPT**(second)	24.40±37.36	11.50	23.10±35.05
aPTT**(second)	104.90±79.68	51	104.90±80.21
Albumin(mg/dL)	2.60±0.65	4.10	2.60±0.69
Potassium(mmol/L)	4.40±0.81	4.2±0.30	4.50±0.85
Sodium(mmol/L)	134.20±6.60	139.7±1.92	134±6.69
Calcium(mg/dL)	7.50±0.88	8.90±0.69	7.70±0.84
BUN(mg/dL)	15.30±10.21	14.5±0.71	15.80±9.27
Creatinine(mg/dL)	0.40±0.16	0.5±0.01	0.40±0.14

Table 4. The complication in DVI infants

Complication	DF (n=3)	DHF Grade I & II (n=23)	DSS (n=21)	Total (n=47)
Pleural Effusion	0	18 (78%)	13 (62%)	31 (66%)
Ascites	0	1 (4%)	4 (19%)	5 (11%)
Bleeding	1	2 (9%)	7 (33%)	10 (21%)
Organ Involvement				
Liver	2	7 (30%)	14 (67%)	23 (49%)
Renal	1	0 (0%)	5 (24%)	6 (13%)
Brain	1	1 (4%)	8 (38%)	10 (21%)
Cardiac	0	0 (0%)	0 (0%)	0 (0%)

Discussion

Infants are one of the age groups that are vulnerable to dengue virus infection. In India (2009-2019), among 395 children with dengue, 99 (25%) are infants.[6] Infants are also at high risk for DHF/DSS.[8] From the results of this study, the authors found that infants had more DHF than DF (46/60). Of all the DHF cases, 44 had complications, while the DF cases had only three. Complications were often found in DHF patients due to the response to infection, such as involvement of blood vessels, coagulation, dengue virus serotypes, and numerous cytokines from T cells (Th1, Th2, Th17, Treg) in large quantities. TNF-α and IL-10 are the two important cytokines in dengue pathogenesis.[9,10]

The Characteristics of dengue virus infection in this study were 8 months old infants on average, males were more than females (36/24), and the highest temperature was 38°C. In infants with complications, the results are not much different. The infant with severe dengue is typically between 4-11 months old.2 A previous study in Surabaya also had an average age of 7-8 months.[11] For the sexes of infants who suffered from DVI, the results were males in dominance. The research in Malaysia from 2010 to 2016 showed more slightly male subjects were affected by DVI than females (60% vs 40%).[12] The average temperature was 38°C, which means that infants have passed a fever phase where the temperatures can reach 40°C.[13] Most of the subjects have entered the critical phase during hospital admission, so the temperature is not too high. In the critical phase, the temperature drops below 38°C.[2,3]

In this study, the most common symptoms in DVI infants were fever, vomiting, and diarrhea. From the complications group, these three symptoms also appear most frequently. Fever and complications in cases of DVI are due to the immune response to fight infection, which in dengue infection is large quantities of cytokine/soluble factors (TNF-α, IL-1, IL-6, IL-10), also called a cytokine storm.[9,14] They activated the preoptic area in the hypothalamus and also increased the permeability of blood vessels. Plasma leakage, which happens due to increased blood vessels permeability, causes the albumin to release from the bloodstream resulting in hypoalbuminemia. Not only plasma leakage, but liver damage also contributes to hypoalbuminemia. A study found that hypoalbuminemia occurs in 7.8% of DVI patients. Hypoalbuminemia was found to have a significant association with the severe manifestation of DVI.[15]

Non-specific gastrointestinal symptoms are common and can be useful for diagnosing dengue infection.[2] Vomiting, diarrhea, and abdominal pain are also reported in some DVI studies, ranging from 28 to 46%. 6.15,[16] A previous study in Surabaya (2010) found diarrhea in 37.73% of DVI infants.[11] Liver involvement occurs because hepatocytes and Kupffer cells are the targets of dengue virus infection. The process of hepatocyte damage starts with the attachment of the virus to the cell with E protein, enters the dengue virus into hepatocytes by Heparin Sulfate, fusion or endocytosis, and then replicates. However, infection of these hepatocytes will also cause apoptosis through viral cytopathic effects, mitochondrial dysfunction, and immune responses. So if there are massive hepatocytes damaged, signs of liver involvement will get heavier.[17]

In dengue virus infection, pancytopenia can occur due to bone marrow suppression.[18,19] This condition occurs because of the direct and indirect impact of the dengue virus on the bone marrow.[20,21] Due to direct effects in the hematopoietic process, leukopenia can be found at the beginning of DF disease and most viruses.[22] The results of the study showed that 16 infants had leucopenia when they were hospitalized. Thrombocytopenia is often found in dengue virus infections. This occurs because of bone marrow suppression and an increase in peripheral platelet destruction in the fever phase and the beginning of the recovery phase. Hematocrit during the critical phase and recovery phase is used for the diagnosis of both DF and DHF. If there is an increase of 5-10% in the critical phase, then the possibility of DF increases, while in DHF is more than 20%.[2]

Based on the normal value of neutrophils at 40-80%, the average value in this research is below normal (31.2%). Neutropenia, along with thrombocytopenia and leukopenia are associated with DVI compared to patients with other febrile illnesses, and also can guide the early diagnostic approach to DVI.23 The mean lymphocyte percentage in this study was 52.3%, which means that this result exceeds the normal value (23-49%). Lymphocytes generally increase in viral infections.[24]

The mean serum sodium level decreased to 134 mmol/L. Hyponatremia was also found in the study of Bhagyamma with a mean level of 130.6 mmol/L.[25] The average serum potassium level in this study was normal (4.4-4.5 mmol/L). While calcium levels had a slight decrease from the average of 7.5 mmol/L in DVI infants with complications. Hypocalcemia should be added to the laboratory examination in cases of complications or severe cases because it is often asymptomatic.[2]

In this study, six infants with complications had elevated BUN levels, while the others did not. Differently, the level of creatinine serum does not increase. Another study showed that the BUN and creatinine level in patients with DVI was higher than normal.[26] The large proportion of complications in this study is found because Dr. Soetomo Hospital is a tertiary referral hospital. The most common DVI complications in infants were pleural effusion, hypoalbuminemia, hyponatremia, liver disorders, and hypocalcemia. Pleural effusion is a buildup of fluid into the pleural cavity with a disruption of hydrostatic-oncotic pressure balance or lymphatic flow. In the critical phase of DVI, there is an increase in capillary permeability, and especially in DHF, the presence of plasma leakage results in the accumulation of extravascular fluid. In addition, there is selective plasma leakage from the endothelial cells of the lungs and abdomen cavity in the cases of DHF/DSS.[27]

Hyponatremia can occur due to salt depletion, excessive water from increased metabolism, decreased renal excretion, or the influx of sodium into cells due to sodium-potassium pump dysfunction. Hyponatremia is the most common electrolyte disorder in DF and its level has a contribution to DF prognosis and other DVI complications (bleeding and brain disorders).[25,28] Hypocalcemia itself is included in the list of laboratory examinations (ABCS: Acidosis, Bleeding, Calcium, Blood Sugar) that must be performed during dengue with shock or complications, as well as in cases where there is no clinical improvement after adequate volume replacement is given. Hypocalcemia is found in almost all cases of DHF, but it is often asymptomatic.[2]

Conclusion

Infants are at high risk for DHF/DSS manifestation. High fever, pleural effusion, hypoalbuminemia, and other manifestations may be the result of plasma leakage in DVI pathogenesis. Classical blood abnormalities such as thrombocytopenia and leukopenia were found as a result of depression in the bone marrow.

Further research is needed with a larger scale of subjects to see the significance of the symptoms and complications in infants with dengue virus infection. Other studies regarding primary and secondary infections and their relationships to complications in infants are also needed, especially in Indonesia.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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