Original Article

Clinical manifestations and hematological and serological findings in children with dengue infection

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Abstract

Background Dengue hemorrhagic fever (DHF) is endemic to Indonesia and remains a public health problem, with its highest incidence in children. There have been few reports on the clinical, hematological and serological data in children with dengue.

Objective To assess the clinical and laboratory profiles of children with dengue infection in Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Methods Clinical, hematological and serological information from children diagnosed with dengue infection in Cipto Mangunkusumo Hospital were collected from 2007 to 2009.

Results Of 611 children admitted with dengue, 143 (23.4%) had dengue fever (DF), 252 (41.2%) had DHF grades I and II; and 216 (35.4%) had DHF grades III and IV. Of the 81 cases where dengue serotypes were identified, 12.3% were DENV-1, 35.8% were DENV-2, 48.2% were DENV-3 and 3.7% were DENV-4. Mean age of subjects was 8.9 years (SD 4.4), and 48.4% of cases were boys. The mean length of fever before hospital admission was 4.2 days (SD 1.1) and mean length of stay in the hospital was 4 days (SD 2.7). Common symptoms observed were petechiae, hepatomegaly and epistaxis. Complications found mostly in those with dengue shock syndrome (DSS) were hematemesis (30 cases, 4.9% of all patients), encephalopathy (19 cases, 3.1%) and melena (17 cases, 2.8%).

Conclusion Signs and symptoms of fever, bleeding manifestations and thrombocytopenia were present in children with DF and DHF, while signs of increased vascular permeability were found only in those with DHF. Encephalopathy and gastrointestinal bleeding were found mostly in DSS cases. At admission, leukopenia was found in more DF patients than in DHF patients. Absence of leukopenia may be a sign of more severe dengue infection. **[Paediatr Indones. 2011;51:157-62].**

Keywords: *dengue hemorrhagic fever, children*

Dengue infection is considered to be one of the most important mosquito-borne viral diseases in the world. The World Health Organization (WHO) reported that around 2.5 billion people living in subtropical countries have been infected with one or more dengue viruses.[1] About 50-100 million individuals are infected every year, and about 500,000 are admitted to a hospital annually. Many factors are thought to be responsible for the increasing incidence of both DF and DHF, such as changes in demographics, climate, virulence of the dengue virus, and population growth.[1-4]

Children have a 40 times higher risk of severe dengue than adults, due to increased vascular permeability during secondary infections.[6] DHF is still a leading cause of death in children. In past years, DHF has occurred primarily in children aged less than 15 years, with its highest attack rate in the 5-9 year olds.[7-12]

Since clinical and laboratory data in children in Indonesia have been scarce, this study will report the clinical presentations, hematological and serological findings of all children admitted with suspected dengue infection to Cipto Mangunkusumo Hospital in Jakarta from 2007 to 2009.

Methods

A retrospective cohort study was carried out in all children suspected of having dengue and admitted to the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta from 2007 to 2009.

The diagnosis of DF/DHF/DSS was made according to the WHO criteria (WHO 1997).[4] Dengue fever is an acute, febrile illness with the following typical symptoms: headache, retro-orbital pain, myalgia, arthralgia, rash, and hemorrhagic manifestations (e.g. epistaxis, petechiae or gingival bleeding), with thrombocytopenia.

Dengue hemorrhagic fever was diagnosed by the presence of fever and hemorrhagic manifestations including at least a positive tourniquet test and minor or major bleeding phenomena, hepatomegaly, with thrombocytopenia ($\leq$ 100000 platelets/mL^3) and hemoconcentration (increased $\geq$ 20%) or objective evidence of capillary permeability in the form of pleural effusion.

Dengue shock syndrome was diagnosed by the presence of criteria listed for DHF in combination with hypotension or narrow pulse pressure (<20 mmHg). Severity of DHF cases were further graded as I to IV, according to WHO guidelines 1997.[4] Those with grades III and IV were diagnosed as DSS.

For all patients, baseline hemograms, hematocrite by microcentrifuge technique, and absolute platelet counts by cell counters were measured. Other investigations such as serum electrolytes, serum transaminases, prothrombin time and right lateral decubitus chest X-ray, were done when indicated. Serum was collected for virus isolation and tested with Dengue Duo IgM and IgG rapid serological tests to confirm the diagnoses.

Data were collected from the medical records of the Department of Child Health in Cipto Mangunkusumo Hospital. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia.

Descriptive statistics were used to analyze the distribution of patient characteristics, signs and symptoms, and the immunological and serological parameters. Clinical and laboratory findings in DF, DHF and DSS cases were compared by Chi-square tests and ANOVAs. All analyses were performed with SPSS version 17.

Results

A total of 611 children suspected of having dengue were admitted to Cipto Mangunkusumo Hospital from January 2007 to December 2009. After clinical and serological confirmation, 415 (68%) children were diagnosed to have dengue virus infection. The peak of dengue cases was found in the month of April, following the rainy season. The mean age of subjects was 8.9 years (SD 4.4). Dengue fever (DF), DHF without shock (DHF grades I and II), and DHF

Table 1. Basic characteristics of inpatients with DF, DHF and DSS

Clinical features	Dengue fever	DHF without shock	DSS
Number of cases, n (%)	143 (23.4)	252 (41.2)	216 (35.4)
Mean age, years (SD)	8.6 (4.2)	10.4 (4.3)	7.4 (3.9)
Gender (female/male)	74/69	128/124	113/103
Mean duration of fever, days (SD)	4.06 (1.2)	4.10 (1.2)	4.36 (1.0)
Mean duration of hospitalization, days (SD)	3.8 (1.7)	3.9 (2.7)	4.4 (3.2)

Table 2. Clinical manifestations of inpatients with dengue

Clinical features	Dengue fever	DHF without shock	DSS
Number of cases, n	143	252	216
Petechiae, n (%)	37 (25.9)	121 (48.0)	114 (52.8)
Epistaxis, n (%)	11 (7.7)	29 (11.5)	11 (5.1)
Gum bleeding, n (%)	4 (2.8)	4 (1.6)	13 (6.0)
Hematemesis, n (%)	0	3 (1.2)	27 (12.5)
Melena, n (%)	0	1 (0.4)	16 (7.4)
Positive tourniquet, n (%)	62 (43.4)	138 (54.8)	84 (38.9)
Hepatomegaly, n (%)	18 (12.6)	45 (17.9)	87 (40.3)
Pleural effusion, n (%)	0	3 (1.2)	5 (2.3)
Encephalopathy, n (%)	0	2 (0.8)	17 (7.9)

with shock (DHF grades III and IV, or DSS) was diagnosed in 143 (23.4%), 252 (41.2 %), and 216 (35.4%) children, respectively. The mean duration of fever before hospital admission was 4.2 days (SD 1.1). The mean length of stay in the hospital was 4 days (SD 2.7). **Table 1** shows the basic characteristics of dengue patients classified into dengue fever, DHF without shock and DHF with shock.

Clinical manifestations of the dengue patients are shown in **Table 2.** Fever, bleeding tendencies and thrombocytopenia were present in children with DF and DHF, whereas pleural effusion, hepatomegaly and gastrointestinal bleeding were only reported in those with DHF. Of children experiencing epistaxis, positive tourniquet test and petechiae, most were in the category of DHF without shock (comprising 56.9%, 48.6% and 44.5%, respectively). However, in children experiencing melena, hematemesis and encephalopathy, most were in the DSS category (comprising 94.1%, 90.0% and 89.5%, respectively). Of patients with gum bleeding, there were significantly more DSS patients compared to DHF without shock

(61.9% vs 19%, P=0.030). Similarly, in patients with hematemesis`(90% vs 10%, P<0.0010), melena (94.1% vs 5.9%, P<0.001), hepatomegaly (58% vs 30%, P<0.001), and encephalopathy (89.5% vs 10.5 %, P<0.001), DSS patients were significantly greater.

Figure 1 A-D shows the levels of hemoglobin, hematocrite, leukocytes, and platelets in our subjects. At the time of admission (4th day of fever), the mean hematocrite of DSS was 41.4%, DHF without shock 40.7% and DF 36.8%. Thus, at admission (4th day of fever), the mean hematocrite was significantly higher in the DSS group compared to other groups (P=0.003). The mean leukocyte counts at admission in DSS, DHF without shock and DF, were 5925, 4214, and 4497/mm^3, respectively.

Furthermore, at admission, the mean platelet counts in children with DSS, DHF without shock, and DF were 76,216, 94,273, and 111,429/mm^3, respectively.

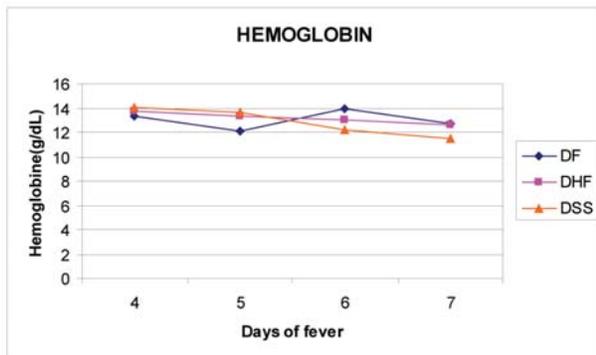The majority of children requiring blood or blood products were diagnosed with DSS. Out of 611
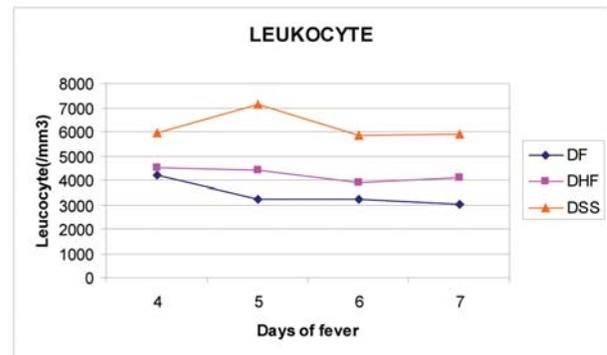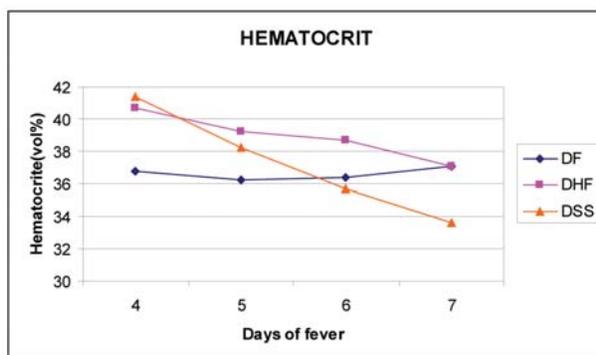

Figure 1A. Hemoglobin levels

Figure 1B. Hematocrite levels

Figure 1C. Leukocyte counts
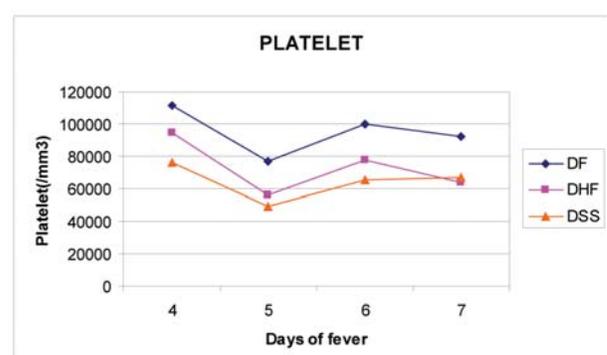
Figure 1D. Platelet counts

Table 3. Serologic test

Serologic test	DF	DHF without shock	DHF with shock
Primary infection	26 (38.8%)	21 (31.3%)	20 (29.9%)
Secondary infection	63 (18.1%)	146 (42.0%)	139 (39.9%)

Table 4. Virus isolations in 2007-2009

Serotype	Total n=81
DENV-1	10 (12.3%)
DENV-2	29 (35.8%)
DENV-3	39 (48.2%)
DENV-4	3 (3.7%)

children admitted due to suspected dengue, 7 (1.15%) died. Of the deaths, all were admitted to the hospital late in the course of disease, and all suffered from severe gastrointestinal bleeding.

The results of the positive serologic tests (n=415) are presented in **Table 3**. The test showed that most patients with dengue fever had a primary infection, whereas patients with both DHF and DSS more often had a secondary infection.

Table 4 shows the results of positive virus isolation in the 81 cases out of the 209 isolates in 2007-2009. Dengue serotype 3 (DENV-3) was found in 39 (48.2%) of the positive isolates, followed by DENV-2 in 29 (35.8%) of the positive isolates, DENV-1 in 10 (12.3%) of the positive isolates, and DENV-4 in 3 (3.7%) of the positive isolates.

Discussion

In the last 3 years, of 611 patients admitted for dengue in Cipto Mangunkusumo Hospital, there were 143 (23.4%) dengue fever (DF) cases, 252 (41.2 %) DHF without shock (DHF grades I and II) cases, and 216 (35.4%) DSS (DHF grades III and IV) cases. In our pediatric population, the mean age of dengue patients was 8.9 years (SD 4.4). The patients came to the hospital with a mean length of fever of 4.2 days (SD 1.1). Mean length of hospital stay was 4 days (SD 2.7). Similar results were also found in two Thai studies.[5,13] The mean age in our study was similar to that in previous studies in Nicaragua and Thailand.[14,15]

In Taiwan and Saudi Arabia most dengue patients were adults.[16,17] Reports of rising age in DHF cases may be explained by demographic transition, decreased birth rates and mortality.[15]

The tourniquet test was positive in 62 (43.4%) DF cases, 138 (54.8%) DHF without shock cases and 84 (38.9%) DSS cases. In the DSS group, there were fewer positive tourniquet tests, possibly due to hypotension. However, tourniquet tests may become positive after restoration of depleted intravascular volume.[4] Low sensitivity of the tourniquet test even in DHF was also reported due to difficulties in performing the test on sick and irritable young children. Also, pediatric blood pressure cuffs may not be available. An investigation into the usefulness of slow capillary filling as a surrogate marker for low blood pressure as measured by sphygmomanometer may be warranted.[4]

Severe gastrointestinal bleeding usually occurred after patients developed shock. This finding contrasts with other studies[10,18,19] that showed upper gastrointestinal bleeding occurred before onset of shock and without hemoconcentration. It has also been suggested that this latter type of hemorrhagic condition probably has a different pathogenesis from classic DHF/DSS.[20]

Some findings in our study were similar to reports from Asia[13] while others were comparable to those of the Americas.[1,14] These differences highlight the need to study region-specific clinical features of dengue infection. We found gum bleeding, hematemesis, melena, hepatomegaly, and encephalopathy were more commonly associated with serious illness. Dengue encephalopathy in DHF/DSS may be due to intracranial hemorrhage, electrolyte imbalance or hypoxic ischemic encephalopathy due to profound circulatory failure. In an endemic area, dengue virus should be considered as a possible etiologic agent in children presenting with encephalopathy.[12] However, we did not attempt viral isolation or IgM antibody measurements in cerebrospinal fluid.

At the time of admission, the mean hematocrit was higher in the DSS group. The mean platelet count was lower in the DSS group, while the mean leukocyte count was lower in the DF group. In children, the higher the degree of thrombocytopenia or hemoconcentration, the greater the severity of dengue is observed.[5] Early severity prediction using clinical features is difficult, but peripheral blood counts help predict severity, which may be useful in

smaller, rural hospitals, where resources are limited. A study in Thailand showed that absence of leukopenia and a low percentage of typical lymphocytes are factors that may predict severe dengue illness. Simple hematological parameters may be used to reduce unnecessary admission of patients with suspected dengue infection in the absence of more sophisticated predictors. [21]

In our study, a greater percentage of DF was caused by primary infection compared to DHF or DSS. In all three groups, secondary infection was more common than primary. Indonesia is endemic for dengue virus and many children have experienced dengue infections earlier in life. This observation is in agreement with other studies that noted increased severity to be correlated with secondary infection.[13] Secondary immune status was a risk factor for severe dengue disease.[6,16] There are numerous theories describing potential contributing factors to dengue disease severity, one of which is the antibody-dependent enhancement of infection theory. This theory suggests that secondary infection with a dengue virus of a different serotype increases the risk of developing DHF. In Nicaragua, the great majority of dengue cases were due to secondary infection; 59% of 1 year old children had secondary infection, and by age 3, more than 90% of confirmed DEN-positive cases were due to secondary infections.[14]

Virus isolation was positive in 81 out of 209 samples, predominantly with dengue serotype 3 (DENV-3). A negative RT-PCR test result does not exclude a dengue infection diagnosis, since blood samples taken after the viremic state (after 5 days of fever) may give a negative result. This finding was similar to a Thai study where the majority of dengue cases were DENV-3.[5] In contrast, studies in Nicaragua, Delhi and Taiwan showed that DENV-2 was predominant and associated with secondary infection.[12,14,16]

We have provided information comparing dengue infections in children and highlighted differences in clinical manifestations, hematological and serological findings which can be applied in rural settings where resources to do further testing may be limited. However, as a retrospective study, some limitations need to be addressed. First, the study was conducted at a single hospital and the patient population may have been biased by referral patterns. Second,

laboratory testing and imaging studies may biased by clinician selection based on personal recognition of clinical dengue severity, leading to unavailability of follow-up information.

In conclusion, the signs and symptoms of fever, bleeding manifestations and thrombocytopenia were present in children with DF and DHF, while signs of increased vascular permeability (such as hemoconcentration, pleural effusion, and hepatomegaly) were only found in DHF. Encephalopathy and gastrointestinal bleeding were mostly found in those with DSS. At admission, signs of leukopenia were more often found in DF compared to DHF patients. Absence of leukopenia may, therefore, be a sign of more severe dengue infection.

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