Clinical profile and warning sign finding in children with severe dengue and non-severe dengue

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Abstract. Dengue fever is one of the most important emerging vector-borne viral diseases. Approximately 500,000 out of 100 million cases develop to severe dengue infection. Patient with severe dengue (SD) can be predicted by clinical profile, laboratory and warning sign which could be saved by early interventions.This was a retrospective descriptive-analytic study to investigate clinical manifestations, laboratory and warning signs ofchildren with dengue infection in Haji Adam Malik hospital during January 2014–May 2016. Through medical records, we had selected 140 cases which fulfilled research criteria.Cases were classified as SD (n=28) and NSD (n=112). Most common clinical manifestations for NSD were abdominal pain (39.3%), myalgia (39.3%), headache (37.1%), mucosal bleeding (36.4%) while for SD were shock (15.7%), mucosal bleeding (15.7%), clinical fluid accumulation (15%), shortness of breath (14.3%). SGPT >1000IU/L (5 cases), SGOT >1000IU/L (9 cases), PT (10 cases) and aPTT (16 cases) were abnormal in SD. Severe dengue was frequently found in the range of white cell count 1000-4000/L and platelet count 20,000-50,000mm/uL. Clinical manifestations, warning sign, and laboratoryfinding, were different between SD and NSD.

1. Introduction

Dengue viral infections are one of the most important mosquito-borne diseases in the world. Globally, 100 million cases of dengue fever and half a million cases of dengue hemorrhagic fever(DHF) occur in a year.[1] Among those infected, 500,000 patients had asevere infection and had required hospital admission with the majority of patients were children. Approximately 2.5% of them died from the infection.[2] Based on data from Republic of Indonesia Health Ministry in 2012, the number of DHF patients in Indonesia were 90245 cases with the number of deaths were 816 patients (IR=3.27 per 100.000 population and CFR = 0.90%).[3] In North Sumatera in the same year, 4367 cases are registered which means that 33 persons in 100,000 populations were infected.[4]

Dengue is an acute febrile disease caused by a flavivirus with four known serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). The four serotypes can lead to variable clinical presentations, ranging from asymptomatic to severe forms.[5] Children represent more peculiar characteristics since dengue diagnosis, and recognition of severe forms are both more difficult to find than in adults. The common signs and symptoms are fever, headache, myalgia, arthralgia, and bleeding manifestations. The exact clinical profile is necessary for the patient's management and hence, crucial for saving life.[6]

Dengue-suspected patients are often hospitalized for close monitoring. Plasma leakage occurs around the time of defervescence. Prior to this critical phase, it has proven confusing to differentiate

mild with severe dengue illness. Ideally, only severe cases of dengue fever (DF) and dengue hemorrhagic fever (DHF) should be hospitalized. However, early identification of signs to severe dengue (SD) finding may save lives by facilitating early initiation of interventions and frequent monitoring.[7] Therefore, in 2009 The World Health Organization (WHO) and the Special Program for Research and Training in Tropical Diseases (TDR), suggest seven warning signs (abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement in 2 cm, increase of hematocrit concurrent with rapid decrease in platelet count) to identify patients at risk of SD. These warning signs were found to have practical value in the next case management of the dengue infection.[8]

Although their evidence as predictors of severity in children is not consistent, Indonesia pediatric society remains to use the warning signs for clinical case management. The majority of studies showed that most frequently associated of signs and symptoms to children with SD were: spontaneous bleeding, hepatomegaly, and signs of plasma leakage, such as ascites and pleural effusion, abdominal pain, hemoconcentration and thrombocytopenia, and elevated plasma levels of the liver enzyme such serum glutamic pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT).[5,9,10] These findings on severe dengue infection should be given attention to prevent complications and deaths. Therefore, the aim of this study is to investigate clinical profile and to find the warning signs of dengue infection in children also their association with severe dengue.

2. Methods

2.1. Study design and sample

This study was a retrospective descriptive-analytic study by collecting data from the medical records of children aged <18 years old, who were diagnosed with dengue infection based on 1997 WHO criteria. The study was conducted from January 2014 to May 2016 at Haji Adam Malik Hospital. The inclusion criteria were children with dengue fever, dengue hemorrhagic fever, and shock dengue syndrome, with serological confirmation of IgG, IgM anti-dengue and or NS1, and a complete medical record. Patients with hematologic disease or malignancy, treatment history of consuming drugs that suppress bone marrow were excluded.

2.2.Data collecting procedure

Samples were collected from medical record with findings regarding age, sex, nutritional status, clinical symptoms including body temperature (the measurement of axilla), duration of fever, headache, joint pain, retroorbital pain, skin redness, petechiae, shortness of breath, abdominal pain, nausea, vomiting, persistent vomiting, edema, ascites, mucosal bleeding, severe bleeding, awareness, liver enlargement, warning signs, signs of shock, tourniquet positive test, blood pressure, hematocrit, platelets, white cell count, AST or ALT level, organs impairment such as heart, kidneys and chest x-ray and abdominal ultrasound. Samples were grouped into severe dengue and nonsevere dengue. The gold standard of dengue infection is clinical symptoms, laboratory and serological confirmation of IgG, IgM and or NS1. The diagnosis of severe dengue infection was based on 2009 and 1997 WHO classification (stage III, IV) with severe plasma leakage, severe bleeding, and severe organ disorders.

2.3.Statistical analysis

The data were analyzed by using computerized SPSS version 17.0. Descriptive statistics were used to describe the distribution of the patients' characteristics data, signs and symptoms, and laboratory values of dengue virus infection. Comparisons of clinical, warning signs and laboratory findings in SD and NSD were analyzed by Chi-square test or Fisher's exact test as appropriate.

3. Results

A total of 199 children were admitted with the diagnosis of dengue infection, 140 cases fulfilled the inclusion and exclusion criteria. We found non-severe dengue in 112 cases and 28 cases of severe dengue.

Table 1. Patient's characteristics distribution.

Parameter	Variabels	Number	%	NSD (*n*= 112)(%)	SD (*n*= 28)(%)
Age range in years	- 0-5	36	25.7	22 (19.6)	14 (50)
	- 6-10	42	30	35 (31.2)	7 (25)
	- 11-15	41	29.3	35 (31.2)	6 (21.4)
	- 16-18	21	15	20 (17.8)	1 (3.5)
Sex	- Male	74	52.9	63 (56.2)	11 (39.2)
	- Female	66	47.1	49 (43.7)	17 (60.7)
Nutritional status	- Obesity	16	11.4	12 (10.7)	4 (14.2)
	- Overweight	13	9.3	12 (10.7)	1 (3.5)
	- Normoweght	78	55.7	58 (51.7)	20 (71.4)
	- Moderate malnutrition	32	22.9	29 (25.8)	3(10.7)
	- Severe malnutrition	1	0.7	1 (0.8)	0(0)
Temperature on admission	- Hyperpyrexia	29	20.7	25 (22.3)	4 (14.2)
	- Febrile	15	10.7	11 (9.8)	4 (14.2)
	- Normal	92	65.7	76 (67.8)	16 (51.1)
	- Hypothermia	4	2.9	0 (0)	(14.2)
Duration of fever in days	- ≤ 3	26	18.6	25 (22.3)	1 (3.6)
	- 4-5	91	65	73 (65.1)	18 (64.3)
	- 6-7	23	16.4	14 (12.5)	9 (32.1
Discharged	- Transferred Outpatient	125	89.3	105 (93.7)	20 (71.4)
	- discontinued care	8	5.7	7 (6.2)	1 (3.5)
	- In hospital dead	7	5	0 (0)	7 (25)

Majority of the cases (30%) were in agroup of 6-10 years.However, severe dengue was most common in thegroup of0-5 years. Patients were found more in Male than a female with a ratio of 1.12:1, however female were frequently found with severe dengue. Nutritional status was often found normal in both SD and NSD cases. Duration of fever ranged from 4 to 5 days for both SD and NSD. In this study, 7 cases of death were found. Most common clinical manifestations for NSD were fever (112 cases; 100%), abdominal pain (55cases; 39.3%), headache (52 cases; 37.1%), petechiae (48 cases; 34.3%), myalgia (55 cases; 39.3%), mucosal bleeding (37 cases; 26.4%), vomiting (30 cases; 21.4%), melena (20 cases; 14.3%), epistaxis (23 cases; 16.4%), while fever (28 cases; 100%), shock (22 cases; 15.7%), mucosal bleeding (22 cases; 15.7%), clinical fluid accumulation (21 cases; 15%), shortness of breath (20 cases; 14.3%), vomiting (19 cases; 13.6%), petechiae (15 cases; 10.7%), organ impairment (12 cases; 6.4%) and myalgia (10 cases; 7.14%) were found in SD. In this study, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, and hepatomegaly were significantly associated with SD, while abdominal pain and an increase of hematocrit level concurrent with rapid decrease in platelet count were significantly associated with NSD. This study showed that 50 cases were found to have pleural effusion by chest X-ray and ascites was found by USG for 11 cases. Among the liver enzymes, SGOT and SGPT were elevated in 34 cases (means: 663U/L and405U/L), elevation of SGOT and SGPT were highly found in SD. SGPT was very high (>1000IU/L) in 5 cases with SD whereas SGOT was very high (>1000IU/L) in 9 cases. Parameters like prothrombin time (PT) and activated partial thromboplastin time (aPTT) were abnormal in 10 cases and 16 cases. PT and aPTT were found abnormal in SD. IgM and IgG positive were found in 110 and 39 cases respectively, meanwhile positive NS1 was found only in 5 cases. Platelet count was frequently found in a range of 20000-50000mm/uL in 72 cases of dengue infection. However, there were four cases of SD were platelet count<10000/mm^3. Severe dengue was more frequently found in a

range of white cell count 1000-4000 /L whereas NSD was more frequently found in a range of white cell count 4000-8000/L.

Table 2. Clinical profile according to the severity of dengue infection distribution.

Characteristics	Non severe dengue(*n*= 112)	Severe dengue (*n*= 28)	Total	P Value
Headache	52(37.1%)	4 (2.85%)	56 (40%)	
Atralgia	33 (23.6%)	4 (2.85%)	37(26.4%)	
Retro orbital pain	4 (2.9 %)	2 (1.4 %)	6(4.2%)	
Rash	10 (7.14%)	2 (1.4 %)	12 (8.5%)	
Petechiae	48(34.3%)	15(10.7%)	63 (45%)	
Mialgia	55(39.3%)	10 (7.14%)	65 (46.4%)	
Vomiting	30 (21.4%)	19(13.6%)	49 (35%)	
Breathless	11(7.85%)	20 (14.3%)	31 (22.1%)	
Cough	12 (8.6%)	2(1.4 %)	14 (10%)	
Shock	2 (1.4 %)	22(15.7%)	24 (17.1)	
Melena	20 (14.3%)	9(6.4%)	11 (7.8%)	
Hematemesis	6(4.3%)	7(5%)	13 (9.2%)	
Epistaxis	23 (16.4%)	4 (2.9 %)	27 (19.35)	
Other Bleeding	6(4.3%)	9 (6.4%)	15 (10.7%)	
Organ impairment	1(0.7%)	12(8.6%)	13(9.2%)	
Warning sign				
Abdominal pain	55 (39.3%)	13 (9.3%)	68 (48.6%)	0.8 [a]
Persistent vomiting	15 (10.7%)	12 (8.6%)	27 (19.3%)	<0.001[a]
Clinical fluid accumulation	20 (14.3%)	21 (15%)	41 (29.3%)	<0.001[a]
Mucosal bleeding	37 (26.4%)	22 (15.7%)	69 (49.3%)	<0.001[a]
Lethargy	4 (2.9 %)	18 (12.9%)	22 (15.7%)	<0.001[b]
Hepatomegaly	9 (6.4%)	11 (7.8%)	20 (14.3%)	<0.001[a]
Increased hematocrit with decreased platelets	30 (21.4%)	10 (7.14%)	40 (28.6%)	0.35 [a]

[a]chi square test
[b]fisher's exact test

4. Discussion

The mean age of the study participants was 9.35 (SD ± 5, ranged from 7 months to 17 years) in 140 cases of dengue infection. It was slightly higher to WHO data which reported that the modal age of 6-8 years in the low endemic area.[11] This study found that there were 28/112 (25%) cases of severe dengue infection. It was relatively similar to the previous study in Bandung which reported the incidence of severe dengue infection in 24.6% cases[12] but the result was different compared to study in Surabaya with 15.9% of cases. Days of illness was count from the first febrile symptoms appeared inpatient. A guideline from WHO showed the critical phase of dengue infection commonly started from day 4 to 6 where severe plasma leakage usually started. This study showed that children admitted to hospital at 4-5th day of illness both severe and non severe dengue which was similar to a study by Ledika MA et al.[12] The most common presentation were mucosal bleeding in 69 cases (49.3%), followed by abdominal pain in 68 cases (48.6%), myalgia in 65 cases (46.3%), petechiae in 63 cases (45%), headache 56 cases (40%), vomiting in 49 cases (35%). Mucosal bleeding, shock, clinical fluid accumulation, shortness of breath, vomiting were commonly presented in SD while mucosal bleeding, clinical accumulation was amost common warning sign in SD.

Radiological markers such as chest X-ray and abdomen ultrasonogram can predict plasma leakage significantly in children with a warning sign to children with dengue fever. This study reported that 50 cases were found to have pleural effusion by chest X-ray and ascites was found by USG for 11 cases. Chest X-ray can predict a severe dengue infection significantly (P<0.001). This finding was similar to Ravishankar K et al. study.[13] Nevertheless, ascites was not associated with severe dengue infection

(P<0.09). Parameters like SGOT, SGPT, PT,aPTT were found abnormal in SD; it was shown that elevation of SGOT and SGPT were highly found in SD. The resulting study was similar with Mishra R et all study, valued more than 1000IU/L was seen in SD. Remarkably high levels of SGOT and SGPT indicate the severity of the disease along with morbidity and mortality.[9] Prolonged prothrombin time (PT) (10 cases) and activated partial thromboplastin time (APTT) (6 cases) were reported of SD. This study supported previous studies.[9]

Table 3. Profile laboratorium distribution.

Laboratory	**NSD (*n*=112)**	**SD (*n*=28)**	**Total**	***P Value***
Thrombocyte (mm/uL)				
< 10.000	0	4	4	<0.001[b]
10.000-20.000	9	8	17	
20.000-50.000	58	14	72	
50.000-100.000	44	2	66	
> 100.000	1	0	1	
Leukocyte (/ L)				
< 1000	0	1	1	0.02[b]
1000-4000	25	7	32	
4000-8000	26	5	31	
8000-12.000	14	5	19	
12.000-15.000	2	2	4	
> 15.000	3	0	3	
IgM				
Positive	85	25	110	0.12
Negative	27	3	30	
IgG				
Positive	30	9	39	0.5
Negative	82	19	101	
NS1 positive	3	2	5	
Tourniquet				
Positive	79	13	92	0.04
Negative	1	1	2	
No done	32	14	46	
X ray pleural effusion	31	19	50	<0.001
USG ascites	7	4	11	0.09

Lower platelet value at admission had an association with more SD spectrum. This study found that Platelet count was frequently found in a range of 20000-50000mm/uL in 72 cases of dengue infection (SD=14 cases and NSD=58 cases). However, there were four cases of severe dengue where platelet count was below 10000. Similarly, Mishra S et al. reported that Platelets <50000/mm^3 at admission was associated with severe dengue virus infection (OR 26.54 95%CI 8.59–81.99). Meanwhile, Jagadish et al. reported that severity of dengue infection was higher among cases with very low platelet values (<20,000 mm/uL).[9,10,14] This study showed that severe dengue was more frequently found in range of white cell count 1000-4000/L (51.4%) and supported by the previous study by Srinivasa S et al.[15]

5. Conclusions

It is concluded that manifestation dengue infection is different among children severe dengue and non-severe dengue. Most common clinical manifestations for NSD were fever, abdominal pain, headache, petechiae, myalgia, mucosal bleeding, vomiting, melena, epistaxis, while ashock, mucosal bleeding, clinical fluid accumulation, shortness of breath, vomiting, petechiae, organ impairment and myalgia were found in SD. The results of SGOT, SGPT, platelet count and white cell count was found to differentiate between severe and nonsevere dengue.

References

[1] Rao M G, Aparna A and Jyothi R C 2016 Clinical profile and outcome of dengue infections in children *IOSR-JDMS* **15** 7-13
[2] Ministry of Health R I 2012 *Profile of disease control and environmental sanitation in 2011* (Jakarta: Directorate General of Disease Control and Environmental Health Ministry of Health R I) pp 135-8
[3] Health Office of North Sumatera Province 2012 *Health profile of North Sumatera province 2012* (Medan: Health Office of Sumatera Province) pp 38-9
[4] Pone S M, *et al*. 2016 Clinical and laboratory signs associated with serious dengue disease in hospitalized children *J. Pediatr. (Rio J)* **92** 464-71
[5] Sicuro C L, *et al*. 2016 Use of warning sign for dengue by pediatric health care staff in Brazil *PloS ONE* **11** 1-12
[6] Potts J A, *et al.* 2010 Prediction of dengue disease severity among Thai pediatric patients using early clinical laboratory indicators *PLoS Negl. Trop. Dis*. **4** 1-7
[7] Thein T L, Gan V C, Lye D C, Fu Yung C and Sin LY 2013 Utilitiesand limitation of the world health organization 2009 warning sign for adult dengue severity *PLoS Negl. Trop. Dis*. **7** 1-6
[8] Mishra S, Ramya R and Agarwalla S K 2016 Clinical profile of dengue fever in children: a study from southern Odisha: India *Scientifica* 1-5
[9] Sahana K S and Sujatha R 2014 Clinical profile of dengue among children according to revised WHO classification: analysis of a 2012 outbreak from Southern India *Indian J. Pediatr*. 104
[10] Eregowda A and Valliappan S 2015 Clinical profile of dengue infection in a tertiary care hospital *Indian J. Child Health* **2** 68-71
[11] Ledika M A, Setia B D and Dhamayanti M 2015 Association between clinical profiles and severe dengue infection in children developing country *Am. J. Epidemiol. Infect. Dis*. **3** 45-9
[12] Ravishankar K, Vinoth P N and Venkatramanan P 2015 Biochemical and radiological markers as apredictor of dengue severity in children admitted to tertiary care hospital *Int. J. Contemp. Pediatr*. **2** 1-6
[13] Jagadish K K, Jain P, Manjunath V G and Umesh L 2012 Hepatic involvement in dengue fever in children *Iran J. Pediatr*. **22** 231-6
[14] Srinivasa S, Tanveer N and Chaithanya C N 2014 Clinical profile and ultrasonographic findings in children with dengue fever *Curr. Pediatr. Res*. **18** 87-90