Original Article *นิพนธ์ต้นฉบับ*

Risk Factors of Dengue Shock Syndrome in Kalasin Hospital

Tiwawan Piyakulmala
Department of Pediatrics, Kalasin Hospital, Kalasin

Abstract Dengue infection, the most common mosquito-borne viral diseases, is one of the important health problems in Thailand. It has been identified as clinical entity since 1789. In patients with dengue shock syndrome, delay in detection and management usually lead to high morbidity and mortality from prolonged shock or massive bleeding. The severity of the disease can be modified by early diagnosis and adequate replacement of plasma loss. Hence it would be of value to identify risk factors that can predict shock in dengue illness. A retrospective analytical study was done by reviewing the charts of all dengue patients admitted to Kalasin hospital during 2004-2006. Clinical and laboratory data of dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) were collected and compared. One Way ANOVA was used to compare between the 3 groups and chi-square or Fisher's exact test was used to compare between the 2 groups and the results were also reported as Odd ratio and 95%Confidence Interval. There were 247 cases admitted: 117 DF (47.4%), 107 DHF (43.3%) and 23 DSS (9.3%). Age, sex, fever, retro orbital pain, abdominal pain, petechiae were not significantly different in comparisons between the DHF and DSS patients. Risk factors of DSS were rash, gum bleeding, melena hematemesis, platelet count less than 50,000 cell/mm^3 and hemoconcentration more than 22 percent from baseline. DHF patients with risks should be closely observed for early signs of shock. Adequate fluid replacement can prevent the progression of shock which results in less complications and lower case fatality rate in DHF patients.

Key words: **risk factors, dengue fever, dengue hemorrhagic fever, dengue shock syndrome**

Introduction

Dengue infection is one of the most common mosquito-borne viral diseases in Thailand. It has been identified as clinical entity since 1789.[1] Clinical descriptions of the Australian outbreak in 1897 reported that 30 children died.[2] The first and second epidemics of dengue infection occurred in Manila in 1954 and 1956, followed by the third in Bangkok in 1958. Since then, dengue infection has spread throughout tropical Asian countries and has expanded globally.[3]

Dengue infection caused by four serotypes of dengue viruses (DEN 1-4). Most primary infections result in dengue fever (DF), a mild disease characterized by biphasic fever, intense headache, myalgia, skin

rash, lymphadenopathy and leucopenia.[4] The severe forms of the disease, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), are usually associated with secondary infections.[5] DHF is characterized by high fever, associated hemorrhagic phenomenon with the reduction of temperature, the patients have sudden clinical deterioration and signs of circulatory failure appear.[6] In patients with DSS, if detection and management of shock are delayed, the complications and mortality from prolonged shock and massive bleeding will be very high. The severity of the disease can be modified by early diagnosis and adequate replacement of plasma loss.[3]

Hence it would be of value to identify factors that predict shock in dengue illness. The aim of the study was to identify the predictive factors for shock in dengue illness in children admitted to Kalasin Hospital.

Methodology

Medical records of patients with DF, DHF and DSS admitted to Kalasin Hospital between January 2004 and December 2006 were reviewed after selected by simple random sampling. There were 247 cases admitted: 117 cases of DF (47.4%), 107 cases of DHF (43.3%) and 23 cases of DSS (9.3%). Inclusion criteria were children, 15 year-old or under, who were compatible with definitions of DF, DHF or DSS. Data collection included age, sex, clinical signs, and symptoms and laboratory data (before defervescence). Complete blood count was repeated during admission.

In a retrospective analytical study, children who were suspected to run early course of dengue viral infection were included in order to identify early clinical and laboratory predictors of the risk of DHF before the critical stage of disease , that was before defervescence and the onset of bleeding and plasma leakage. Statistical analysis was performed by computer. One Way ANOVA was used to compare between the 3 groups and chi-square or Fisher's exact test was used to compare between the 2 groups. Odd ratio and 95 percent Confidence Interval were also reported.

Results

The peak transmission periods for dengue infections in this study (January 2004 - December 2006) were during July and August (Fig. 1).

In the present study, there were 247 cases admitted: 117 cases of DF (47.4%), 107 cases of DHF (43.3%) and 23 cases of DSS (9.3%). The age group of the affected children was between 8 months to 15 years with a mean age of 8.82 years. Sex and mean age distribution were similar in all groups (Table 1). Most of the patients presented with fever ranging

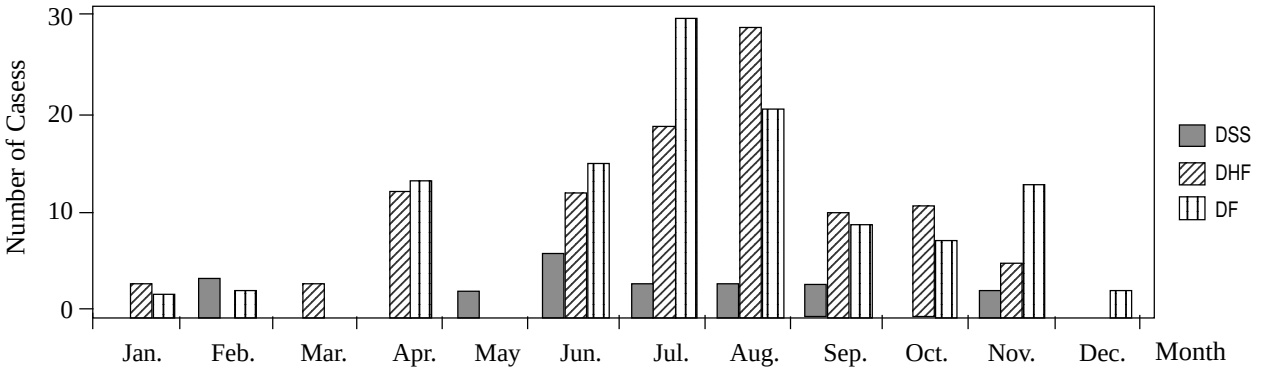

Figure 1 Hospitalized cases of DF/DHF/DSS. (January 2004-December 2006)

Table 1 Demographic data of DF/DHF/DSS patients

	Number of patients (%)					p-value
	DF n = 47	DHF n = 107	DSS n = 23	DHF+DSS n = 130	Total	
Sex - Male	55 (47.0)	41 (38.3)	11 (47.8)	52 (40.0)	107 (43.3)	0.381*
- Female	62 (53.0)	66 (61.1)	12 (52.2)	78 (60.0)	140 (56.7)	
Age (years)						
0-4	20 (17.1)	25 (23.4)	3 (13.0)	28 (21.5)	48 (19.4)	0.542*
5-9	55 (47.0)	46 (43.0)	14 (60.9)	60 (46.2)	115 (46.6)	
10-14	42 (35.9)	36 (33.6)	6 (26.1)	42 (32.3)	84 (34.0)	
Mean, SD	8.33, 3.56	9.20, 3.27	8.64, 3.39	8.57, 3.34	8.82, 3.23	0.489**

***chi-square, **ANOVA**

Table 2 Clinical signs/ symptoms and bleeding manifestations compared between DF and DHF/DSS

Clinical signs/symptoms	Number of patients (%)			OR (95% CI)	p- value
	DF n = 117	DHF/DSS n =130	Total n = 247		
Nausea	90 (76.9)	102 (78.5)	192 (77.7)	1.09 (0.57 - 2.08)	0.772
Vomiting	87 (74.4)	91 (70.0)	178 (72.1)	0.80 (0.44 - 1.46)	0.446
Retro orbital pain	65 (55.6)	74 (56.9)	139 (56.3)	1.06 (0.62 - 1.81)	0.829
Myalgia	58 (49.6)	87 (66.9)	145 (58.7)	2.06 (1.69 - 3.56)	0.006
Bone pain	78 (66.7)	64 (49.2)	142 (57.5)	0.48 (0.28 - 0.84)	0.006
Abdominal pain	93 (79.5)	109 (83.8)	202 (82.1)	1.34 (0.67 - 2.69)	0.376
Rash	25 (21.4)	45 (34.6)	70 (28.3)	1.95 (1.06 - 3.59)	0.021
Petechiae	52 (44.4)	68 (52.3)	120 (48.6)	1.37 (0.81 - 2.34)	0.217
Gum bleeding	43 (36.8)	58 (44.6)	101 (40.9)	1.39 (0.81 - 2.39)	0.209
Epistaxis	49 (41.9)	52 (40.0)	101 (40.9)	0.93 (0.54 - 1.59)	0.764
Melena	22 (18.8)	42 (32.3)	64 (25.9)	2.06 (1.10 - 3.89)	0.016
Hematemesis	5 (4.3)	34 (21.6)	39 (15.8)	7.93 (2.91 - 26.82)	0.000
Hepatomigaly	14 (13.1)	15 (11.5)	29 (11.7)	0.0 (0.40 - 2.26)	0.917

chi-square test

between 102-104˚ F and duration of fever was 3-7 days.

General symptoms were fever, headache, nausea, vomiting, abdominal pain, retro orbital pain, and presented in similar proportion in each group without any statistical difference (Table 2). Bone pain was more frequent in DF group. On the other hand, myalgic, rash and hemorrhagic manifestations such as hematemesis , melena were found in the DHF/DSS groups. (Table 2, 3)

Table 3 Clinical signs/ symptoms and bleeding manifestations compared between DHF and DSS

Clinical signs/symptoms	Number of patients (%)			OR (95% CI)	p- value
	DHF n = 107	DSS n =23	Total n = 130		
Nausea	81 (75.7)	21 (91.3)	192 (77.7)	3.37 (0.73 -31.37)	0.099
Vomiting	72 (67.3)	19 (82.6)	178 (72.1)	2.31 (0.09 - 9.98)	0.146
Retro orbital pain	63 (58.9)	11 (47.8)	139 (56.3)	0.64 (0.24 - 1.73)	0.331
Myalgia	69 (64.5)	18 (78.3)	145 (58.7)	1.98 (0.64 - 7.34)	0.203
Bone pain	53 (49.5)	11 (47.8)	142 (57.5)	0.93 (0.35 - 2.51)	0.882
Abdominal pain	87 (81.3)	22 (95.7)	109 (83.8)	0.93 (0.35 - 2.51)	0.899
Rash	30 (28.0)	15 (65.2)	45 (34.6)	4.81 (1.69 -14.0)	0.017
Petechiae	52 (48.6)	16 (69.6)	68 (52.3)	2.42 (0.85 - 7.11)	0.068
Gum bleeding	43 (40.2)	15 (65.2)	58 (44.6)	2.79 (1.0 - 7.95)	0.028
Epistaxis	40 (37.4)	12 (52.2)	52 (40.0)	1.83 (0.68 - 4.97)	0.189
Melena	29 (27.1)	13 (56.5)	42 (32.3)	3.5 (1.26 - 9.79)	0.016
Hematemesis	21 (19.6)	13 (56.5)	34 (26.1)	5.32 (1.87 -15.41)	0.000

chi-square test, significant difference at p , 0.05

Table 4 Laboratory parameters in DF and DHF/DSS

Clinical signs/symptoms	Number of patients (%)			OR (95% CI)	p- value
	DF n = 117	DHF/DSS n =130	Total n = 247		
Hemoconcentration ≥ 20%	0	130 (100)	130 (52.63)	-	0.000*
Hemoconcentration ≥ 22%	0	77 (59.23)	77 (31.17)	-	0.000*
WBC < 3,000 cell/mm^3	78 (66.7)	97 (74.6)	19 (70.85)	1.47 (0.82-2.65)	0.170**
Platelet count < 50,000 cell/mm^3	29 (24.8)	60 (46.2)	89 (36.03)	2.6 (1.46-4.65)	0.000**

***fishers's test, **chi-square test**

The laboratory data showed that percentage of WBC< 3,000 cells/mm^3. were not different when comparing between DF and DHF/DSS patients while it was significantly found in DSS than DHF patients. The percentage of platelet count< 50,000 cells/mm^3 is 24.8, 36.4 and 91.3 percent in DF ,DHF and DSS patients, respectively (p=0,000). (Table 4)

Discussion

The wide spectrum of signs and symptoms are associated with dengue infection and identification of those are required to distinguish and classify DSS cases

Table 5 Laboratory parameters in DHF and DSS

Parameter	Number of patients (%)			OR (95% CI)	p- value
	DHF n = 107	DSS n =23	Total n = 130		
Hemoconcentration ≥ 20%	107 (100)	23 (100)	130 (100)		
Hemoconcentration ≥ 22%	50 (46.73)	22 (95.65)	77 (59.23)	25.08 (3.71-1052.76)	0.000
WBC < 3,000 cell/mm^3	74 (69.2)	23 (100.0)	97 (74.62)	-	-
Platelet count < 50,000 cell/mm^3	39 (36.4)	21 (91.3)	60 (46.15)	18.31 (4.04-165.98)	0.000

chi-square test

from DHF/DF cases. In patients with DSS, if detection and management of shock are delayed, the morbidity and mortality from prolonged shock and massive bleeding are usually high. Among the total 247 cases in this study, 117 cases were classified as DF, 107 cases as DHF and 23 cases as DSS. The age range of the affected children was between 8 months to 15 years with a mean age of 8.82 year. The peak incidence of dengue in this study was in patients 5-9 years old which is difference from the report from Bureau of Epidemiology that the peak incidence is between in patients 5-14 years old and 15-24 years old.

The peak transmission periods for Dengue infection in this study were during July and August as in the previous studies of Thailand and East Timor.[7] Mean age, sex distribution were similar in all groups as reported in the study in Mexico.[8] Most of the patients presented with fever ranging between 102-104 ˚F and duration of fever was 3-7 days. General symptoms as fever, headache, nausea, vomiting, abdominal pain, retro orbital pain, were presented in similar proportions for each group. The frequency of symptoms, except fever were lower in the present study as compared to the study in Dhaka children Hospital, Bangladesh.[9] The study in Mexico[8] showed that a higher proportion of digestive symptom such as vomiting and abdominal pain were found in DHF/DSS.

Rash, bleeding such as hematemesis, melena were mostly found in DHF/DSS groups. (table 2)

But epistaxis was similar in all groups and commonly associated with DHF different from study in the Philippines[10] that found it more in DHF. The frequency of hepatomegaly (11.3%) in this study was lower than that reported in Thai population (45-90%)[11,12] and in India. (71%)[13] For laboratory data, leucopenia was well described as a feature of dengue infection and seemed to relate to bone marrow suppression by dengue virus.[14,15] Leucopenia, platelet count less than 50,000 cell/mm^3 and hemoconcentration more than 22 percent were also found more commonly in DSS group in our study.

To demonstrate the differences of clinical features and hematologic abnormalities between DF and DHF/DSS, mean age and sex distribution were similar in all groups. General symptoms such as fever, headache, nausea, vomiting ,abdominal pain, retro orbital pain, were present in similar proportions in each group. The proportions of fever and headache were found similar to the report in Mexico.[8]

Abdominal pain was more commonly associated with DHF patients in The Philippines.[10] Retro orbital pain was found commonly associated with DHF.[8]

Gum bleeding and petechiae were similar in each group yet different from those reported in Mexico[8] and in Nepal[9]

Bleeding manifestations such as hematemesis and melena were significantly higher in DHF/DSS groups and similar to those reported in Mexico[8] and in Nepal.[9]

Rash was found in DF less than DHF/DSS groups which is different from the previous report that more rash is observed in DF especially in adults.

The platelet count was significantly lower in the DHF group than in the DF group and similar to that in another report in the Philippines.[16] The maximum increase of hematocrit in the DHF group was higher than 20 percent, and significantly higher than those in DF group, which supports WHO definition of the disease. The hematocrit was significantly increased in the DHF group than The DF group.[10]

A documented risk factor of DSS was primary infection with dengue virus serotype 1, 3, or 4 followed by a secondary infection with dengue virus serotype 2.[3,17] However, the recognition of dengue titer or secondary infection is not helpful for prediction and management of shock as its results usually become known after defervescence or shock. Risk factors of DSS in the present study were hematemesis, hemoconcentration more than 22 percent and platelets count less than 50,000 cell/mm^3. Sex was similar in all groups , mean ages of the DHF and the DSS in this study were not statistically significant as in the study of Narayanan M et al.[18]

Hemorrhagic manifestations in DHF were usually mild. Petichiae was the most common hemorrhagic manifestations in DF, DHF and DSS groups. In the present study bleeding, melena was found to be risk factors of DSS same as the previous study in Vajira hospital.[19]

Hemoconcentration ≥ 20 percent from baseline is one of the diagnostic criteria of DHF.[3,20] Furthermore, the present study also found that hemoconcentration ≥ 22 percent is one of the risk factor of DSS and similar to that in the previous study in Vajira hospital.[19] The leakage subsequently causes an elevation of hematocrit and lead to hypovolemic shock. Therefore, frequent hematocrit determinations are essential because they reflect the extent of plasma leakage and the adequacy of volume replacement. There was a strong association between lower platelet count and the severity of dengue.[21] In the present study, platelet count less of than 50,000 cell/mm^3 was one of the risk factors of DSS group.

Conclusion

Risk factors of DSS were rash, gum bleeding melanic hematemesis, platelet count less than 50,000 cell/mm^3 and hemoconcentration more than 22 percent from baseline. Patients with DHF who have risk factors should be closely observed for early signs of shock. Adequate fluid replacement can prevent the progression of shock which results in lower complications and case fatality rate in DHF patients.

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References

1. Rush B. An account of the bilous remitting fever, as it appeared in Philadelphia in the summer and autumn of the year 1780. In: Rush B (ed.). Medical Inquires and Observations. Philadelphia: PA: Prichard and Hall; 1989, p. 104.
2. Hare FE. The 1897 epidemic of dengue in North Queensland. Australia Med Gaz 1898; 17:98.
3. World Health Organization. Dengue haemorrhgic fever: diagnosis, treatment, prevention and control. 2 nd ed. Geneva: WHO; 1997.
4. Lei HY, Yeh TM, Liu HS, Lin YS, Chen SH, Liu CC. Immunopathogenesis of dengue virus infection. J Biomed Sci 2001; 8:377-88.
5. Hayes A, Gubler D. Dengue and dengue hemorrhagic fever.

Pediatric Inf Dis J 1992; 11:311-7.
6. Thein S, Aung M, Shwe T, Aye M, Zaw A, Aye K, et al. Risk factors in dengue shock syndrome. Am J Trop med hyg 1997; 56: 566-72.
7. World Health Organization, Dili Office, East Timor health sector situation report:January-June 2000. [cited 2008 Feb 2]; Available from: URL: http://www.who.int/eha /emergenc /etimor /14082000.htm
8. Kalayanarooj S, Vaughn DW, Nimmanitya S, Suntayakorn S, Nisalak A, Green S, et al. Early clinical and laboratory indicators of acute dengue illness. JID 1997; 176:313-21.
9. Shah GS, Islam S, Das BK.Clinical and laboratory profile of dengue infection in children. Kathmandu University Medical Journal 2006;4 (1): 40-3.
10. Carlos AM.Comparison of clinical features and hematologic abnormalities between dengue fever and dengue hemorrhagic fever among children in the Philippines. AJTMH 2005; 73(2):435-40.
11. Halstead SB. Dengue and hemorrhagic fevers of Southeast Asia. YJBM 1965; 37(6):434-54.
12. Nelson E, Chulajata R.Danger signs in Thai hemorrhagic fever (dengue).Trop Pedia 1965; 67(3):463-70.
13. Kabra SK, Verma IC, Arora NK, Jain Y, Kaira V. Dengue hemorrhagic fever in children in Delhi. Bull WHO 1992; 70(1):105-8.
14. Bhamarapravati N, Tuchinda P, Boonyapaknavik V. Pathology of Thailand haemorrhagic fever: a study of 100 autopsy cases. Ann Trop Med Parasitol 1967; 61:500-10.
15. Larussa VF, Innis BL. Mechanisms of dengue virus-induced bone marrow suppression. Baillieres Clin Haematol 1995; 8:249-70.
16. Dizon JJ, The occurrence of dengue haemorrhagic fever in the Philippines. Asian J Infect Dis 1978;2:15-7.
17. Sangkawibha N, Rojanasuphot S, Ahandrik S, Virityapongse S, Salitul V, Jatanasen S, et al. Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. The 1980 outbreak. Am J Epidemiol 1984; 120:653-69.
18. Narayanan M, Aravind MA, Thilothammal N, Prema R, Sargunam CS, Ramamurty N. Dengue fever epidemic in Chennai - a study of clinical profile and outcome. Indian Pediatric 2002; 39:1027-33.
19. Tantracheewathorn T,Tantracheewathorn S.Risk factors of dengue shock syndrome in children. J Med Assoc Thai 2007; 90(2): 272-7.
20. Nimmannitya S, Kalayanarooj S,Vitayasuporn A .Guideline for diagnosis and treatment of dengue hemorrhagic fever. Nonthaburi: Ministry of Public Health; 1999.
21. Diaz-Quijano FA, Villar-Centeno LA, Martinez-Vega RA.Complications associated to severe thrombocytopenia in patients with dengue. Rev Med chile 2006; 134:167-73.

บทคัดย่อ **ปัจจัยเสี่ยงในโรคไข้เลือดออกที่ช็อกในโรงพยาบาลกาฬสินธุ์**

ทิวาวรรณ ปียกุลมาลา

กลุ่มงานกุมารเวชกรรม โรงพยาบาลกาฬสินธุ์ กาฬสินธุ์

วารสารวิชาการสาธารณสุข **2551; 17:SIII605-12.**

ไข้เลือดออกเป็นโรคจากไวรัสโดยมียุงเป็นพาหะนำโรค เป็นหนึ่งในปัญหาสำคัญทางสาธารณสุขไทยซึ่งมีการระบาดตั้งแต่ พ.ศ. 2501 มีอัตราการป่วยและเสียชีวิตสูงโดยเฉพาะผู้ป่วยที่มีภาวะช็อกเป็นเวลานานหรือมีเลือดออกอย่างรุนแรง การทราบถึงปัจจัยเสี่ยงของการเกิดภาวะช็อก ช่วยให้มีการเฝ้าระวังและวินิจฉัยได้ตั้งแต่ระยะแรกจึงมีความสำคัญในการลดการเกิดภาวะแทรกซ้อนและการเสียชีวิต การศึกษาย้อนหลังเชิงวิเคราะห์ เพื่อหาปัจจัยเสี่ยงของการเกิดภาวะช็อกในผู้ป่วยไข้เลือดออกานี้ ทบทวนย้อนหลังเวชระเบียนผู้ป่วยในเด็กของโรงพยาบาลกาฬสินธุ์ระหว่างปี 2547 - 2549 จำนวน 247 ราย เป็นผู้ป่วยไข้เดงกี (DF) 117 ราย ไข้เลือดออก (DHF) 107 รายและไข้เลือดออกที่ช็อก (DSS) 23 ราย เปรียบเทียบข้อมูลทางคลินิก ได้แก่ อายุ เพศ อาการ อาการแสดงและผลการตรวจเลือด(CBC) วิเคราะห์ปัจจัยเสี่ยงโดยโปรแกรมคอมพิวเตอร์วิธีวิเคราะห์โดย One Way ANOVA, chi-square test or Fisher's exact test หา Odd ratio และ 95% Confidence Interval

ไม่พบความแตกต่างในด้าน อายุ เพศ อาการไข้ ปวดตา ปวดท้อง เลือดออกตามผิวหนัง ระหว่างผู้ป่วยไข้เลือดออกที่ไม่ช็อกและช็อกอย่างมีนัยสำคัญทางสถิติแต่พบปัจจัยเสี่ยงของผู้ป่วยไข้เลือดออกที่มีโอกาสช็อก ได้แก่ ผื่น เลือดออกตามไรฟัน ถ่ายดำ อาการอาเจียนเป็นเลือด เกล็ดเลือดน้อยกว่า 50,000 เซลล์/ลูกบาศก์มิลลิเมตรและความเข้มข้นของเลือดเพิ่มขึ้นมากกว่าร้อยละ 22 ดังนั้นผู้ป่วยที่มีปัจจัยเสี่ยงดังกล่าวควรได้รับการสังเกตอาการอย่างใกล้ชิดเพื่อป้องกันการเกิดภาวะเลือดออก ภาวะช็อกนานเพื่อลดการเกิดภาวะแทรกซ้อนและการเสียชีวิต

คำสำคัญ: **ปัจจัยเสี่ยง, ไข้เดงกี, ไข้เลือดออก, ไข้เลือดออกที่ช็อก**