Clinical Presentations of Dengue Hemorrhagic Fever in Infants Compared to Children

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Abstract

Background : Dengue infections are endemic in Thailand. Infants are at risk of developing dengue fever (DF) and dengue hemorrhagic fever (DHF). Many infants have severe DHF with unusual manifestations and may suffer from complications and even death because of difficulties in early diagnosis and improper management.

Objective : To study the incidence of infants DHF and to compare clinical and laboratory findings of DHF between infants and children in order to improve diagnosis and management of infants with DHF.

Material and Method : A retrospective review of hospital charts of DHF patients who were admitted to the Children's Hospital between 1995-1999 was carried out. Only confirmed DHF cases, either by serologic or virologic studies were included. Clinical and laboratory findings were compared using the standard software package SPSS.

Results : There were 4,595 confirmed dengue patients admitted to the Children's Hospital during this 5-year period and among these 245 infants were under one year old (5.3%). Unusual presentations of DHF including upper respiratory tract infection (URI) symptoms, diarrhea, convulsions and encephalopathy were found more in the infants (4.5%, 13.1%, 12.7% and 4.1%) than in the children (1.7%, 2.0%, 2.0% and 0.6%) but shock was found less in the infants (25%) than in the children (30.9%). The percentages of Tourniquet test positive and low WBC ($\leq$ 5,000 cells/mm^3) which help in the early diagnosis of dengue were less in the infants (50.2% and 26.8%) than in the children (92.2% and 71.9%). Liver involvement and/or dysfunction were found more in the infants as shown by mean aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevation and prolonged prothrombin time. Duration of IV fluid was shorter in the infants than in the children (21.9 *vs* 38.2 hours). Complications of fluid overload were found more often in the infants than in the children (9% *vs* 3.6%). The case fatality rate was 1.2 in the infants and 0.3 in the children.

Conclusion : Management of infants with DHF is critical because early diagnosis is rather difficult and they sometimes present with unusual manifestations (convulsions, encephalopathy and

associated infections). Complications such as hepatic dysfunction and fluid overload are more commonly found in infants than in children and adults and also the case fatality rate is higher. Judicious IV fluid resuscitation and replacement is critical to the outcome of infants with DHF. It seems that the degree of plasma leakage is less in infants and the duration of plasma leakage is shorter in infants than in children.

Key word : DHF, Infants, Early Diagnosis, Unusual Manifestations, Complications

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Dengue infections are endemic in Thailand. Since the first outbreak in 1958, the annual case report has ranged from 15,000-180,000 cases with the latest case fatality rate (CFR) of 0.16 per cent[1]. Infants are at risk of dengue infections and most of them have mild dengue illness. Only 5 per cent of infants were admitted to the Children's Hospital in 1987 and the CFR was 6 per cent which is much higher than 1.2 per cent CFR in older children in the same year[2]. Other reports of infant DHF ranged from 1.3 per cent to 6.5 per cent while the reported CFR range was from 0 to 11.1 per cent[3-8]. Many DHF infants present with unusual manifestations or suffer from complications and even death because of difficulties in early diagnosis and improper management.

Objective

To study the incidence of DF/DHF in infants and to compare clinical and laboratory findings of DHF between infants and children in order to improve diagnosis and management of infants with DHF.

MATERIAL AND METHOD

A retrospectively review of hospital charts of DHF patients who were admitted to the Children's Hospital (now known as Queen Sirikit National Institute of Child Health) between 1995-1999 was carried out.

DF and DHF were classified according to WHO criteria.

Confirmed laboratory tests for dengue infections were done at the Armed Forces Research Institute of Medical Sciences (AFRIMS). Serology was done by Enzyme linked immunosorben assay (ELISA) or hemagglutination inhibition technique (HI). Dengue virus was identified either by polymerase chain reaction (PCR) or viral isolation (mosquito inoculation technique).

Management of all DF and DHF patients was done by staff physicians, nurses and pediatric residents of the DHF Unit, Children's Hospital using the standard DHF management guidelines of the hospital which was the same as the WHO guidelines for DHF management.

Clinical and laboratory findings were compared using the standard software package SPSS.

RESULTS

Incidence and demographic data

There were 4,595 confirmed DF and DHF cases admitted to the Children's Hospital during 1995-1999. There were 245 infants under 1 year of age (5.3%). Most of the admitted cases were DHF (56.3%) while 24.7 per cent were shock cases (Table 1). The percentage of shock in the infants (25%) was lower than in the children (30.9%) ($p = 0.036$). The male to female ratio in the infants was 1 : 1.01 and in the children it was 1 : 1.08. The mean age of the infants with DF and DHF was 7.12 and 7.23 months ($p = 0.874$) (median age = 7.22 and 7.67 months) while the

mean age of all DF and DHF patients was 7.88 and 8.03 years, respectively (p = 0.338).

Age distribution of infants DHF

The youngest infant in the present study was 1 month old. The peak incidence was at 8 months. The majority of cases were between 5-11 months (Fig. 1).

Dengue serotype

Dengue serotypes that cause DF and DHF in infants and children are not different (p = 0.609 and 0.885). During this period Den 3 was the most common serotype accounting for 25.8 per cent of the total cases. Den 1, Den 2 and Den 4 accounted for 25.8, 20.9 and 2.7 per cent respectively.

Serology

Ninety per cent of the infants with DHF had primary dengue infections while 84.5 per cent of DHF children had secondary dengue infections. Ninety-two per cent of infants with DF had primary dengue infections while 36.2 per cent of DF children had primary dengue infections.

Clinical presentations (Table 2)

Mean duration of fever in the infants and children was not different (4.9 days *vs* 5 days). Petechiae (72.2% *vs* 46.2%) and maculo-papular rash (17.1% *vs* 6.7%) were found more frequently in the infants than in the children while epistaxis (8.2% *vs* 20.5%), gum bleeding (0.8% *vs* 2.4%) and hematemesis (10.6% *vs* 14.6%) were found more frequently in children than in the infants. Positive tourniquet test was observed less in the infants than in the children (50.2% *vs* 92.2%).

Physical examinations which were more positive in the infants than in the children were hepatomegaly (92.2% *vs* 89.4%), splenomegaly (5.7% *vs* 0.8%) and convalescence rash (24.1% *vs* 18.9%).

Other unusual presentations of DHF were found more often in the infants than in the children e.g. convulsion (12.7% *vs* 2%), URI symptoms (4.5% *vs* 1.7%), diarrhea (13.1% *vs* 1.9%) and encephalopathy (4.1% *vs* 0.6%).

Associated infections were found more often in the infants than in the children (10.7% *vs* 2.9%).

Laboratory findings

CBC

Mean maximum hematocrit (Hct) in infants was 39 per cent while in the children it was 44 per cent (p = 0.000). The average per cent of rising Hct was more in the infants (24.9%) than in the children (18.3%) (p = 0.000). The mean WBC was higher in the infants (7,924 cells/mm^3) than in the children (4,573 cells/mm^3) (0.000). WBC ≤ 5,000 cell/mm^3 was found in 26.8 per cent of the infants and 71.9 per cent of the children (p = 0.000). Platelets below 100,000 and 50,000 cells/mm^3 were found in 95.1 per cent and 58.4 per cent of the infants and 84.4 per cent and 31 per cent of the children.

Liver function test (LFT) (Table 3)

The mean AST and ALT in infants was 689 and 286 U while in the children it was 209 and 88 U, respectively (p = 0.000). All except one infant (99.6%) had elevation of AST > 40U while 94.7 per cent of the children had elevation of AST (0.000). Elevation of ALT was found in 87.4 per cent and 53.5 per cent of the infants and children (p = 0.000).

Mean albumin in infants and children are 4.25 and 4.48 g% (p = 0.008) while the mean albumin during leakage period in infants and children are 3.75 and 3.97 g% (p = 0.168).

Table 1 Age distribution of DF and DHF patients.

Age range (year)	DHF	%	DSS	%	DF	%	Total	%
< 1	174		58		13		245	5.3
1-4	470		184		191		845	18.4
5-9	1,086		522		410		2,018	43.9
10-14	795		354		247		1,396	30.4
> 15	60		19		12		91	2.0
Total	2,585	56.3	1,137	24.7	873	19.0	4,595	100.0

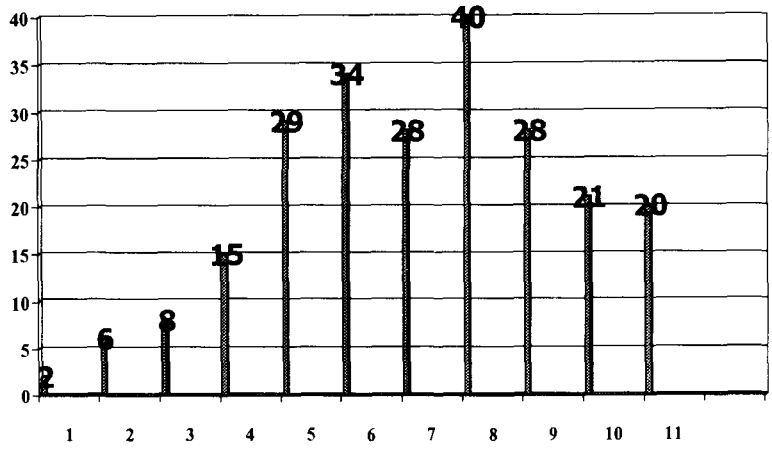

Fig. 1. Age distribution of DHF infants.

Table 2. Signs and symptoms of dengue infections in infants and children.

	Infants		Children		P-value
	N = 245	%	N = 4,350	%	
Vomiting	15	6.1	386	8.9	0.611
URI symptoms	11	4.5	75	1.7	0.001
Diarrhea	32	13.1	87	2.0	0.000
Abdominal pain	7	2.9	1,738	39.9	0.000
Convulsion	31	12.7	85	2.0	0.000
Encephalopathy	10	4.1	25	0.6	0.000
Petechiae	177	72.2	2,008	46.2	0.000
MP rash	42	17.1	288	6.6	0.000
Epistaxis	20	8.2	891	20.5	0.000
Gum bleeding	2	0.8	102	2.4	0.062
Hematemesis	26	10.6	635	14.6	0.048
Melena	26	10.6	283	6.5	0.011
Hepatomegaly	225	92.2	3,887	89.4	0.000
Tourniquet test		50.2		92.2	0.000
Splenomegaly	14	5.7	34	0.8	0.000
Convalescence rash	59	24.1	823	18.9	0.025
Associated infections		10.7		2.9	0.000
Associated conditions		2.5		2.6	0.983

Mean cholesterol in the infants and children was 112 and 150 mg% (p = 0.000) while the mean cholesterol during the leakage period in the infants and children was 96 and 124 mg% (p = 0.000).

Mean total bilirubin, direct and indirect bilirubin were normal in almost all the uncomplicated cases of DHF patients.

Prothrombin time was prolonged (International normalization ratio > 1.3) in 16.8 per cent of the infants and 5.5 per cent of the children (p = 0.000).

Electrolyte

Hyponatremia was found in 55.2 per cent of the infants and 37.9 per cent of the children (p = 0.001) while hypocalcemia was found in 85.1 per cent of the infants and 90.7 per cent of the children (p = 0.079).

Management (Table 4)

The mean duration of IV fluid given to the infants was shorter (21.4 hours) than in the children

Table 3. Laboratory findings in infants and children with dengue infections.

	Infants		Children		P-value
	N = 245	%	N = 4,350	%	
WBC ≤ 5,000 (cells/mm^3)	64/239	26.8	3072/4285	71.9	0.000
Mean platelet (cells/mm^3)	49,885		71,201		0.000
Platelet ≤ 100,000 cells/mm^3	231/243	95.1	3539/4194	84.4	0.000
Platelet ≤ 50,000 cells/mm^3	142/243	58.4	1302/4194	31.0	0.000
Mean AST (U)	689		209		0.000
Mean ALT (U)	286		88		0.000
AST > 40 U	237/238	99.6	4020/4246	94.7	0.000
ALT > 40 U	208/238	87.4	2272/4245	53.5	0.000
Mean albumin (g%)	4.25		4.48		0.008
Mean albumin at leakage phase (g%)	3.75		3.97		0.168
Mean Cholesterol (mg%)	112		150		0.000
Mean Cholesterol at leakage period (mg%)	96		124		0.000
Prolonged INR	16.8		5.5		0.000
Hyponatremia	53/96	55.2	258/681	37.9	0.001
Hypocalcemia	74/87	85.1	547/603	90.7	0.079

Table 4. Management of DHF in infants and children.

Management	Infants	Children	P-value
IV duration (hours)	21.4	30.8	0.000
IV per kg (ml)	65	59	0.115
Received dextran (%)	8.2	8.8	0.433
Received blood transfusion (%)	5.8	3.8	0.035

Table 5. Outcomes and complications of infants and children with DHF.

Management	Infants	Children	P-value
Length of stay (days)	4.5	3.8	0.000
Hypoglycemia (%)	2.0	0.1	0.264
Fluid overload (%)	9.0	3.6	0.004
CFR (%)	1.2	0.3	0.000

(30.8 hours) (p = 0.000) and the total IV fluid given was 65 ml/kg in the infants and 59 ml/kg in the children) (p = 0.115). Dextran-40 was administered in 8.2 per cent and 8.8 per cent of the infants and children (p = 0.433). Blood was transfused in 5.8 per cent and 3.8 per cent of the infants and children, respectively (p = 0.035).

Outcomes (Table 5)

The average length of stay of the infants was longer, 4.5 days compared to3.8 days for the children (p = 0.000).

Hypoglycemia was found in 2 per cent of the infants and 0.1 per cent of the children (p = 0.264).

Complications of fluid overload were more common in the infants 9 per cent compared to 3.6 per cent in the children (p = 0.004).

The CFR in the infants was higher 1.2 per cent compared to 0.3 per cent in the children (p = 0.000).

DISCUSSION

The infants with more severe dengue infections who needed hospitalization at the Queen Sirikit

National Institute of Child Health (QSNICH) between 1995-1999 accounted for 5.3 per cent of the total number of admitted cases. The percentage was in the range of a previous report from QSNICH[2] and others[3-8]. Most of the admitted infant cases were DHF (94.7%). DSS accounted for 25 per cent of all the infant DHF cases. Only 5.3 per cent of infants with DF were admitted. Whether the clinical presentation of dengue infections in the infants were mostly DHF or DF infants were very mild cases and did not need to come to the hospital or did not need admission has to be further studied[8].

The peak incidence of the infants with DHF was at 8 months of age. The majority of infants with DHF were aged between 5-11 months and most of them had primary dengue infections. Immune enhancement was explained previously by Kliks SC et al. These infants acquired maternal dengue antibody since birth and by 5 to 11 month of age, these passively acquired antibodies are very low to a certain level that they enhance primary dengue infection in these infants and result in DHF[9].

Early clinical diagnosis of infants with dengue infections is rather difficult because the signs and symptoms are mostly non-specific except for petechiae which were more frequently found in the infants than in the children (72.2% *vs* 46.2%). In addition, some of them presented with URI symptoms, diarrhea, encephalopathy and convulsions which suggested other diseases rather than dengue. A useful screening test for dengue infection is the tourniquet test[9] which was positive in only half of the infant cases so it is less helpful in the early diagnosis of dengue. Leukopenia (WBC $\leq$ 5,000 cells/mm^3) that is usually helpful in early diagnosis of early dengue and also helps in identifying critical period of DHF[10,11] was found in only 26.8 per cent of the infants with dengue. Other helpful parameters for the diagnosis of dengue in infants include hepatomegaly which was found in 92.2 per cent. Splenomegaly may be found in infants (5.7%). In order to make the diagnosis of DHF in infants, every infant with a high fever, even with URI symptoms, diarrhea, encephalopathy or convulsions, should have close follow-up of CBC and if thrombocytopenia (platelet $\leq$ 100,000 cells/mm^3) and rising hematocrit (Hct) are present, DHF is the likely diagnosis[12].

Sometimes, rising Hct in infants is missed because the mean maximum Hct in the infants was only 39 per cent in the present study. Almost all the infants had mild anemia and the mean lowest Hct was 32 per cent.

Liver involvement was found more often in infants. All except one infant had elevation of AST and the average value of AST was higher in the infants (689 U) and was about 17 times that of normal values. The average value of AST in the children was 209 U which is about 5 times that of normal values. The average value of ALT in the infants was about 7 times that of normal value compared to twice the normal value in children. Shock/liver ischemia alone, cannot explain the degree of liver involvement in infants because the percentage of shock in infants is significantly less than in children. Infants' liver function may not be as good compared to older children. Multiple drugs or even paracetamol that have to be metabolized *via* the infants' liver may cause liver impairment in young infants as shown in a higher percentage of prolonged prothrombin time in the infants (16.8%) compared to the children (5.5%).

The mean albumin in the infants and children was not different (4.25 *vs* 4.48 g%) but the mean cholesterol in the infants was less than in the children (112 *vs* 150 mg%). The mean albumin and cholesterol, both in the infants and the children was lower at the time of leakage. The average reduction of albumin of 0.5 g% and cholesterol of 16-26 mg% from the previous value suggested plasma leakage.

The percentage of shock was less in the infants (25%) compared to the children (30.9%) in the present study. Even the diagnosis in infants is more difficult than in children the percentage of shock is lower in infants. This may indicate that the degree of plasma leakage is less in infants. The duration of plasma leakage in infants is also shorter as shown by the duration of IV fluid administration which was shorter in the infants (27.9 hours) compared to the children (38.2 hours). Careful monitoring of clinical, vital signs, Hct and urine output are critical in infants because complications of the fluid overload was more common in the infants (9%) compared to the children (3.6%). Infants have less lung compliance and less ability to compensate for compromised respiratory function. Hypoxia and respiratory failure occur rapidly if they have fluid overload.

Convulsions in infants with DHF are more common in infants than children. More than half of these convulsions are likely to be febrile convulsions

and they occur early during the febrile phase of DHF illness and the prognosis is not different from other uncomplicated cases. Electrolyte imbalance (hyponatremia and hypocalcemia) and hypoglycemia may be responsible for some cases of convulsion. Other causes include hepatic encephalopathy, intracranial bleeding or cerebral ischemia. If convulsions occur during the critical phase, the prognosis is guarded. If the causes are identified to be electrolyte imbalance or hypoglycemia, the prognoses are better if the abnormalities can be corrected promptly(13).

The present study has shown that infants with DHF are a high risk population that require more intensive monitoring because they usually present with unusual manifestations and additional laboratory investigations e.g. LFT, Coagulogram, serum electrolytes (Na, Ca), blood sugar are necessary in the management of infants with DHF.

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โรคไข้เลือดออกเด็งกี่ในเด็กทารกเปรียบเทียบกับเด็กโต

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บทนำ : ประเทศไทยมีการระบาดของโรคไข้เลือดออกเด็งกี่ ดังนั้นทารกมีความเสี่ยงในการที่จะติดเชื้อไวรัสเด็งกี่ ทารกหลายรายเป็นไข้เลือดออกอย่างรุนแรง บางครั้งมีอาการผิดไปจากปกติหรือมีโรคแทรกซ้อน บางรายเสียชีวิต เนื่องจากการวินิจฉัยจะยากมากในระยะแรก

วัตถุประสงค์ : เพื่อศึกษาอุบัติการณ์โรคไข้เลือดออกเด็งกี่ในทารกและเปรียบเทียบอาการ รวมถึงผลการตรวจทางห้องปฏิบัติการกับผู้ป่วยเด็กโต เพื่อปรับปรุงการวินิจฉัยและรักษาโรคไข้เลือดออกในทารกให้ได้ผลดียิ่งขึ้น

วัสดุและวิธีการ : ศึกษาย้อนหลังจากเวชระเบียนผู้ป่วยไข้เลือดออกเด็งกี่ที่รับไว้รักษาที่โรงพยาบาลเด็กระหว่างปี 2538-2542 โดยเลือกเฉพาะรายที่มีการตรวจยืนยันการติดเชื้อไวรัสเด็งกี่เท่านั้น การวิเคราะห์ข้อมูลการเปรียบเทียบอาการและผลการตรวจทางห้องปฏิบัติการใช้โปรแกรมสำเร็จรูปมาตรฐาน SPSS

ผล : มีผู้ป่วยไข้เลือดออกที่ได้รับการตรวจยืนยันการติดเชื้อเด็งกี่และรับไว้รักษาในโรงพยาบาลเด็ก 4,595 ราย ระหว่าง พ.ศ. 2538 ถึง 2542 ในจำนวนนี้มีทารกอายุน้อยกว่า 1 ปี 245 ราย (5.3%) อาการนำที่ผิดปกติที่พบในทารกมากกว่าเด็กโตได้แก่ อาการติดเชื้อทางเดินหายใจ ท้องเสีย ชักและอาการทางสมอง (4.5%, 13.1%, 12.7%, 4.1% ในทารก และ 1.7%, 2.0%, 2.0% และ 0.6% ในเด็กโต) อาการช็อกพบในทารก (24%) น้อยกว่าเด็กโต (30.9%) การตรวจที่ช่วยในการวินิจฉัยระยะแรกได้แก่การตรวจทูนิเกต์ให้ผลบวก และเม็ดเลือดขาวต่ำ $\leq$ 5,000 เซล/มม^3 พบในทารก (50.2% และ 26.8%) น้อยกว่าเด็กโต (92.2% และ 71.9%) อาการตับอักเสบพบในทารกมากกว่าเด็กโตโดยดูจากค่าเฉลี่ยของเอนซัยม์ AST/ALT และการที่มี Prothrombin time ยาวผิดปกติ ระยะเวลาเฉลี่ยในการให้น้ำเกลือทางหลอดเลือดดำในทารก (21.9 ชั่วโมง) จะสั้นกว่าในเด็กโต (38 ชั่วโมง) แต่จะพบภาวะแทรกซ้อนน้ำเกินมากกว่าในทารก (9%) เมื่อเทียบกับเด็กโต (3.6%) อัตราป่วยตายในทารก = 1.2% ส่วนในเด็กโต = 0.3%

สรุป : การดูแลรักษาทารกโรคไข้เลือดออกเด็งกี่ยากเนื่องจากการวินิจฉัยในระยะแรกลำบาก เนื่องจากทารกอาจแสดงอาการที่ผิดออกไปจากปกติเช่น ชัก อาการทางสมอง หรือการที่มีการติดเชื้ออื่น ๆ ร่วมด้วย นอกจากนี้ยังพบโรคแทรก เช่น การทำงานของตับผิดปกติ การมีภาวะน้ำเกิน ที่รุนแรงมากอาจทำให้เสียชีวิตได้ อัตราป่วยตายในทารก (1.2%)จะสูงกว่าในเด็กโต (0.3%) การให้สารน้ำอย่างระมัดระวังสำคัญมากในผู้ป่วยทารก จากการศึกษานี้พบว่าความรุนแรงของการรั่วของพลาสมาจะน้อยกว่าในเด็กโตและเป็นเวลาสั้นกว่าในเด็กโต

คำสำคัญ : ไข้เลือดออกเด็งกี่, ทารก, การวินิจฉัยในระยะแรก, อาการแสดงที่ผิดไปจากปกติ, ภาวะแทรกซ้อน

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* ศูนย์ความร่วมมือในการรักษาโรคไข้เลือดออกระหว่างองค์การอนามัยโลก และสถาบันสุขภาพเด็กแห่งชาติมหาราชินี, กรุงเทพ ฯ 10400