DENGUE HEMORRHAGIC FEVER IN INFANTS

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Abstract. A report of 19 cases of serologically-proven dengue hemorrhagic fever (DHF) in infants aged 3-12 months who were admitted to the Department of Pediatrics, Chon Buri Regional Hospital, Thailand, during 1995 to 1998. Subjects were 8 males and 11 females, with the peak age of 8 months. Four cases (21%) had DHF and other common co-infections *ie* pneumonia (2 cases), *Staphylococcus aureus* sepsis (1 case) and *Haemophilus influenzae* meningitis (1 case). The clinical manifestations of the 15 DHF cases were high fever (100%), coryza (93.3%), hepatomegaly (80%), drowsiness (53.3 %), and vomiting (46.7%); rash was observed in only 27%; one-fifth developed febrile convulsions. Sites of bleeding were the skin (petechiae) 58%, gastrointestinal system (melena) 16%, and mucous membrane (epistaxis) 5%; thrombocytopenia and increased hematocrit (≥20%) were noted in 95% and 84% respectively. The majority of the patients (18 cases, 95%) had primary infection; only one (5%) had secondary infection. The clinical severity of the DHF was Grade I, II, and III (dengue shock syndrome) in 21%, 47% and 32% of cases respectively. After appropriate and effective management, all the infants recovered fully.

INTRODUCTION

Dengue is caused by dengue virus serotypes 1-4 and the principal vector is the mosquito, *Aedes aegypti*. In the past 20 years, dengue fever and the severe forms of the disease, dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS), have emerged as the most important arthropod-borne viral disease of humans. It is estimated that up to 100 million cases of dengue fever and 250,000 cases of DHF occur annually worldwide (Pinheiro and Corber, 1997). In Thailand DHF is most common in children of less than 15 years of age and causes a significant number of deaths (Nimmannitya, 1987; Burke *et al*, 1988): from 1990 to 1994, 8,603 infants were diagnosed with dengue infection, this was approximately 3% of all reported cases of dengue infection and 6% of deaths (Division of Epidemiology, 1990-1994). DHF is less common during infancy but when it does occur the mortality is higher than in older children (Shekhar and Huat, 1992). Infants are also prone to concurrent life-threatening infectious diseases, *ie* pneumonia and bacterial sepsis/meningitis, as well as febrile convulsions. Early and effective replacement of plasma loss with plasma, plasma expanders and/or fluid and electrolyte solutions, results in a favorable outcome in most cases (Anonymous, 1986; Nimmannitya, 1987). Early diagnosis of DHF and other co-infection in infants is essential. Whereas the clinical manifestations and laboratory findings of DHF in older children are well established (Anonymous, 1986; Nimmannitya, 1987; Burke *et al*, 1988), only a few studies on DHF in infants have been reported (Trong-Lan *et al*, 1997; Pancharoen and Thisyakorn, 1998a; Witayathawornwong, 1999). The purpose of this study was to evaluate the clinical features and laboratory findings of serologically-confirmed DHF in infants.

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MATERIALS AND METHODS

Chon Buri Regional Hospital, situated some 80 km from Bangkok, has 823 beds, 100 of which are for pediatric patients. The medical

records of all children of 15 years of age or younger with clinical and serological confirmation of dengue who were admitted to the Department of Pediatrics, Chon Buri Hospital, between January 1995 and December 1998, were examined; the records of infants (≤12 months old) diagnosed with DHF were reviewed. Criteria for the clinical diagnosis and severity of DHF used in this study were those described previously (Anonymous, 1986). The severity of DHF is classified as follows: Grade I, fever accompanied by non-specific constitutional symptoms and the only hemorrhagic manifestation is a positive tourniquet test; Grade II, spontaneous bleeding is observed, in addition to the manifestations of Grade I, usually in the form of skin and or other hemorrhages; Grade III, includes circulatory failure (shock) manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness; Grade IV, includes profound shock with undetectable blood pressure and pulse. The presence of thrombocytopenia with concurrent hemoconcentration differentiates Grades I and II DHF from dengue fever.

Serological diagnosis, based on an enzyme-linked immunosorbent assay (ELISA) or a hemagglutination-inhibition test (HI), was performed at the Armed Forces Research Institute of Medical Sciences, Bangkok, or the Department of Medical Sciences, Ministry of Public Health, Bangkok. IgM and IgG to dengue and Japanese encephalitis virus (JEV) were measured in the sera of 9 patients by antibody capture ELISA (Innis *et al*, 1989; Vaughn *et al*, 1999). For single specimens, 40 U of IgM to dengue (with dengue IgM greater than JEV IgM) was considered evidence of a dengue infection (30 U if from paired sera with <15 U of antibody in the acute specimen). A dengue IgM-to-IgG ratio ≥1.8:1 defined a primary dengue infection; a ratio <1.8:1 defined a secondary dengue infection. With serial specimens, a 2-fold increase in IgG to dengue with an absolute value of ≥100 U indicated a secondary infection in the absence of IgM to dengue of ≥40 U. Hemagglutination-inhibition antibody against dengue virus types 1-4 and JEV were measured in the sera of all the patients (Charke and Casals, 1958). A 4-fold increase was considered positive for acute dengue infection. The infection was diagnosed as primary if titers a week or more after onset of illness were less than 1:2560 (Anonymous, 1986). A serological diagnosis was assigned to each patient on the basis of ELISA/HI results. Data were analyzed using descriptive statistics.

RESULTS

There were 20 infants among 983 children aged ≤15 years with clinically diagnosed and serologically confirmed dengue infections (2% of all cases); nineteen infants (95%) had DHF and one (5%) had dengue fever.

The group of 19 infants with DHF was composed of 9 males and 11 females whose ages ranged from 3 to 12 months, with a mean and a median age of 7.2 and 8 months respectively. Most (70%) were in the 5 to 9 month age-range. Four (21%) of them had DHF with other co-infections. All except one were admitted firstly to the Chon Buri Hospital; a DHF patient with meningitis co-infection was referred from a community hospital on day 9 of his illness.

Fifteen infants who had DHF without other infection had a history of fever for 2 to 9 days (mean 4.5 days) before admission; Table 1 shows the presenting symptoms and signs of these 15 infants; enlargement of the liver was observed in 80%; hemorrhagic manifestations/bleedings were noted in 80%; petechiae (11 cases, 58%) were the major manifestation of bleeding, followed by melena (3 cases, 16%), including one case, with *Staphylococcus aureus* sepsis co-infection, of severe melena. Epistaxis was noted in only one patient (5%). Tourniquet test positivity was noted in 75% (6 of 8 cases); the test was not performed in the other seven cases due to the detection of thrombocytopenia and a diagnosis of DHF made in the outpatients' department prior to admission. Non-specific constitutional symptoms included: a majority (93.3%) with runny nose (coryza) and

Table 1
Presenting symptoms and signs of dengue hemorrhagic fever (DHF) in 15 infants.

	Case (s)	Percentage
Specific symptoms and signs		
1. High fever[a]	15	100
2. Hepatomegaly	12	80.0
3. Hemorrhagic manifestations	12	80.0
Tourniquet test positive	6 of 8	75.0
Skin (petechiae)	11	58.0
Gastrointestinal system (melena)	3	16.0
Mucous membrane (epistaxis)	1	5.0
Non-specific constitutional symptoms		
1. Coryza	14	93.3
2. Drowsiness	8	53.3
3. Vomiting	7	46.7
4. Rash	4	26.7
5. Febrile convulsions	3	20.0
6. Diarrhea	1	6.7
7. Abdominal pain	1	6.7

[a]Average days of pyrexia before admission 4.5 days.

cough; approximately half of the patients had drowsiness and vomiting, one quarter had rash and one-fifth had febrile convulsions (on day 1 of their illness). Diarrhea and abdominal pain were rare: each was a feature in one case only.

Co-infections in the four cases were pneumonia (2 cases), *Staphylococcus aureus* septicemia (one case) and *Haemophilus influenzae* meningitis (one case). All four satisfied the clinical criteria for DHF (fever, hepatomegaly, and hemorrhagic manifestations) and their hematocrit was increased by 20% or more. Three of them had thrombocytopenia (platelets ≤100,000/mm^3), while the platelet count of another was 102,000/mm^3 (determined on day 2 of fever). One case had a right-sided pleural effusion; another case had both a right-sided pleural effusion and ascites. All had a clinical severity of grade II and had serological confirmation of the diagnosis of DHF. The criteria for the diagnosis of DHF and the details of the four cases are shown in Tables 2 and 3 respectively. For the patient with meningitis, clinical diagnosis of DHF was made after 5 days of fever at a community hospital; he continued to have fever and a few episodes of vomiting and developed convulsions on day 9 when he was referred to Chon Buri Hospital. On admission he was found to have central nervous system involvement (positive Kernig's and Brudzinski's signs), lumbar puncture was performed with special precautions although there was no bleeding from the puncture site. Results of cerebrospinal fluid (CSF) examinations were compatible with bacterial meningitis. *Haemophilus influenzae* was recovered from the cultures of both CSF and blood.

Specific laboratory findings of the 19 cases are shown in Table 4. Thrombocytopenia (platelets <100,000/mm^3) and hemoconcentration (hematocrit increased by 20% or more) were observed in 95% and 84% respectively. Eighteen cases (95%) were serologically proven as having primary dengue infection, only one (5%) had a secondary dengue response. Clinical severity of DHF in these 19 infants was 21%, 47%, and 32% for Grades I, II and III respectively. All received appropriate treatment and completely recovered.

DISCUSSION

In Thailand DHF is common in children of 15 years and younger. We report on 19 dengue infections in infants among nearly 1,000 cases of dengue infections that required the hospitalization of children aged ≤15 years. The prevalence of 2% in infants is close to the national figure of 3% (Division of Epidemiology, 1900-1994). The ratio 19:1 for DHF to dengue fever in infants is probably due to the fact that the more severe symptoms of DHF tend to result in hospitalization.

In addition to the clinical manifestations and laboratory findings usually observed in older children, *ie* high fever, hemorrhagic manifestations, enlargement of liver, thrombocytopenia, and hemoconcentration (Anonymous, 1986; Nimmannity, 1987; Burke *et al*, 1988), the majority of the infants who had DHF without co-infection also had coryza (93%) and approximately one-half had drowsiness. The rate of positive tourniquet tests (75%) was similar to that cited in other reports (Eram *et al*, 1976; Nimmannitya *et al*, 1969). A twenty percent occurrence of febrile convulsions in our series suggests that close observation for febrile convulsions in infants and the provision of appropriate management are vital.

Pneumonia and bacterial sepsis/meningitis are common life-threatening illnesses in infancy; all were found as co-infections in the group of infants. Duration of fever in DHF was 2 - 7 days (Anonymous, 1986; Nimmannitya, 1987). The infant who had *Haemophilus influenzae* meningitis developed convulsions nine days after the onset of fever; co-existing CNS infection should therefore be excluded, especially in infants who develop late convulsions. Dyspnea and cough were recorded only in patients with pneumonia. We would like to emphasize that co-infection in infants who suffer DHF is not uncommon. Before concluding that a clinical presentation of DHF in an infant differs from that of other age groups, co-infections should be ruled out (Hongsiriwon, 1996; Panchareon and Thisyakarn, 1998b). Full recovery of all infants is mostly due to the

Table 2
Clinical data for diagnosis of dengue hemorrhagic fever of four infants with coinfections.

Patients	JT	SB	KJ	PV[a]
Chief complaints	Fever and cough (5 days), convulsion (on day 1)	Fever, and cough (4 days)	High fever, drowsiness and poor feeding (2 days)	High fever for 5 days.
Hemorrhagic manifestations	Petechiae	Petechiae	Tourniquet test positive	Easy to bruise, concealed bleeding
Hepatomegaly (cm)[a]	5	2	4	5
Hct % Max-Min	40-33	31-25	38-27	27-16
Platelets/mm^3	9,900	46,000	102,000	44,000
Chest film positive for pleural effusion	No	Yes, right-sided plus ascites	Yes, right-sided	No
Serology	HI 1:320 to DEN-2 and 1:160 to DEN-4 IgM/IgG =169/25	Increased HI titer from 1:80 to 1:320 to DEN-2 and 1:40 to 160 to DEN-4 IgM/IgG =107/22	Increased HI titer from <1:20 to 1:160 to DEN-2 and <1:20 to 1:320 to DEN-4	Increased HI titer from <1:20 to 1:160 to DEN-2 and 1:40 to 1:160 to DEN-4
DHF grade	II	II	II	II

[a]Diagnosis of DHF was made after 5 days of fever at a community hospital. However, he continued to have fever and a few episodes of vomiting and developed convulsions on day 9 and was then referred to Chon Buri Hospital where lumbar puncture was performed with special precautions althought there was no bleeding from the lumbar puncture.

Table 3
Details of co-infections in the four infants with dengue hemorrhagic fever.

Case	Sex	Age (months)	Severity	Co-infections				Distinct clinical clues
				Organism	Organ	Diagnosis	Diagnosis by	
JT[a]	F	7	DHF Grade II	None	Chest	Pneumonia	Clinical and CXR	Acute onset of fever, hepatomegaly and dyspnea
SB[b]	M	9	DHF Grade II	Coagulase-negative staphylococcus	Chest	Pneumonia	Culture (Nasopharyngeal)	Acute onset of fever, hepatomegaly and cough (4 days)
KJ	F	8	DHF Grade II	*Staphylococcus aureus*	Systemic	*S. aureus* sepsis	Culture (Blood)	Acute onset of fever, hepatomegaly and sepsis
PV	F	8	DHF Grade II	*Haemophilus influenzae*	Systemic	*H. influenzae* menigitis, sepsis	Culture (CSF and blood)	Prolonged fever (10 days), hepatomegaly, convulsions and positive Kernig's and Brudzinski's signs (on day 9)

DHF=Dengue hemorrhagic fever; CXR=Chest film; CSF=Cerebrospinal fluid
[a]Ceftriaxone intravenously prior to admission, no growth on blood and nasopharyngeal culture, chest radiograph showed patchy infiltration both upper lobes.
[b]Ampicillin intravenously 24 h prior to admission

Table 4
Specific clinical laboratory findings and serological response of 19 infants with dengue hemorrhagic fever, admitted to Department of Pediatrics, Chon Buri Hospital, Thailand, between January 1995 and December 1998.

	Cases (19)	Percentage
Laboratory findings		
Thrombocytopenia (platelets ≤ 100,000/mm^3)	18	95
Hematocrit increased ≥ 20%	16	84
Serological response		
Primary infection	18	95
Secondary infection	1	5

early and effective management of both DHF and co-infections.

Convincing data suggest that young children are protected from dengue by passive antibody from their mothers. Watanaveeradej *et al* (1999) conducted a birth cohort study in Bangkok and showed that maternally-acquired antibodies rapidly disappear during infancy: at birth, 97% of the mothers and all their infants were seropositive for dengue antibodies (from any serotype); three percent of the infants had lost their dengue antibodies by 2 months; 19% by 4 months; 72% by 6 months; 99% by 9 months and 100% by 12 months of age. Based on the this study, the majority of the infants aged 5 - 9 months with the DHF commonly observed in this study would already have lost their maternal antibodies.

Eighteen cases reported here had primary dengue infection while only one had secondary infection. From epidemiological, clinical, and virological studies in humans, these could be due to viral virulence (Barnes and Rosen, 1974; Gubler *et al*, 1978; Gluber and Clark, 1995) as well as passive heterotypic maternal dengue IgG antibody in infants with primary infection that cause DHF/DSS (Halstead, 1988; Kliks *et al*, 1988; 1989).

In conclusion, dengue hemorrhagic fever in infancy is not uncommon. Specific clinical manifestations and laboratory findings are similar to those in older age groups. However, non-specific constitutional symptoms, namely coryza and drowsiness, are differences. Febrile convulsions were noted in three cases; pneumonia and bacterial sepsis/meningitis were co-manifestations of another four cases. All infants except one had primary dengue infection and no cases were fatal.

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