Dengue Haemorrhagic Fever with Encephalopathy/Fatality at Petchabun Hospital: A three-year Prospective Study (1999-2002)

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Abstract

During the three-year period from 1 May 1999 to 30 April 2002, there were 1,465 cases of dengue haemorrhagic fever (DHF) admitted to the Department of Paediatrics, Petchabun Hospital. The male to female ratio was 722:743 (1:1.03). Their ages ranged from 80 days to 15 years with a median of 9 years. Thirty-two patients (2.2%) were under one year of age with a median of 8 months, and all except two had primary dengue infection.

There were 34 DHF patients with encephalopathy (2.3% of all DHF cases). The male to female ratio was 17:17 (1:1). The median age was 8 years and 11 months (range 10 months to 13 years). Thirty patients (88.2%) were older than 5 years. Thirty and four patients respectively developed encephalopathy in shock and convalescent stages. All 17 fatal cases (1.16% of the total DHF cases, male:female = 8:9) had both prolonged shock and massive gastrointestinal haemorrhage since admission. About 64.7%, 76.4% and 58.8% of the seventeen non-fatal cases (male:female = 9:8) had gastrointestinal haemorrhage, shock state and massive fluid overload since admission respectively. The risk factors for encephalopathy included prolonged shock, severe gastrointestinal haemorrhage, severe hepatic dysfunction and prior fluid overload.

Keywords: Dengue haemorrhagic fever, encephalopathy, fatality, gastrointestinal haemorrhage, shock, fluid overload, hepatic dysfunction.

Introduction

The major pathophysiological hallmarks in dengue haemorrhagic fever (DHF) are leakage and abnormal haemostasis that leads to hypovolemic shock and/or haemorrhage. Generally, vital organs are not primarily involved in DHF but unusual manifestations, mainly the involvement of the central nervous system (CNS) and severe hepatic dysfunction, are increasingly being detected[1-6]. The incidence of CNS involvement in dengue infection was about 0.88-5.4%[7-11] first reported in 1976[12]. Although dengue encephalitis existed as evident from the direct dengue viral invasion[13-17], the more common conditions were encephalopathy secondary to fluid extravasation, cerebral oedema, hypoperfusion, haemorrhage, hyponatremia, liver failure and renal failure[2,18-19]. The treatment of DHF with CNS involvement is supportive and symptomatic. Early detection and proper fluid management of DHF should be done to prevent any risk factors.

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Materials and methods

There were 1,465 cases of DHF admitted to the Department of Paediatrics, Petchabun Hospital, Petchabun province, Thailand, from 1 May 1999 to 30 April 2002. The diagnosis methods used followed the WHO criteria[20] and about 82% of cases were serologically confirmed using either enzyme-linked immunosorbent assay or haemagglutination inhibition tests. The treatment consisted of general measures (closely observed vital signs, general appearance and serially recorded haematocrit in 24-48 hours after fever, no medication except antacid for moderate to severe abdominal pain) and fluid therapy (minimal amount to normalize vital signs and haematocrit: 5% dextrose saline for infants, 5% dextrose Ringer acetate for older patients, Dextran-40 in normal saline for impending or fluid overload and fresh whole blood or packed red cells for significant bleeding, platelet concentrate and plasma not used).

Patients with encephalopathy (drowsy, stuporous, comatose and convulsion) were closely observed for blood sugar or dextrostix every six hours. Serum transaminase was done once a day until recovery. Vitamin K_1 and 10% calcium gluconate were administered for three days. Lumbar puncture was performed cautiously if there was no other risk.

The statistical analysis included the percentage, mean, standard deviation and range for demographic data and Student's *t* and chi-square tests for comparing non-categorized and categorized variables, respectively.

Results

Of the 1,465 cases of DHF admitted to the Department of Paediatrics, Petchabun Hospital, from 1 May 1999 to 30 April 2002. The male to female ratio was 722:743 (1:1.03). The patients' age ranged from 80 days to 15 years with the median of 9 years. The highest incidence was in the 5-10-year age group (57%) and the second highest was in the 10-15-year age group (26.2%). Thirty-two patients (2.2%) were under one year of age with the median of 8 months, and all of them except two had primary dengue infection. Eighty-seven per cent of all cases were found in the rainy season during May-October. The patients were from all 11 districts in the Petchabun province, 84% from the central district alone. There were DHF patients from all villages (178) of all the subdistricts (17) of the central district.

There were 34 DHF patients with encephalopathy (2.3%). The male to female ratio was 17:17 (1:1). The median age was 8 years 11 months (range 10 months to 13 years). Thirty patients (88.2%) were older than 5 years. Thirty and four patients developed encephalopathy in the shock and convalescent stages respectively. There were 7, 18 and 9 patients with encephalopathy stage II (drowsy), stage III (stuporous) and stage IV (comatose) respectively. Twenty-eight patients (82.3%) were referred from district hospitals and 17 patients (50%) had a massive fluid overload. Lumbar puncture was performed in 2 non-fatal cases with normal findings. Their serology indicated secondary dengue response.

About 17 fatal cases (1.6% of total DHF cases, male:female = 8:9 , median age 8 years and 4 months, range 10 months to 12

years) had the median duration of 13 hours for deaths (range 1-26 hours, mean±SD = 13.4±8.4 hours). Sixteen of the 17 cases (94.1%) were dead within 24 hours. Profound shock and massive gastrointestinal haemorrhage since admission were detected in all patients. Hepatic failure, comatose stage and massive fluid overload were detected since admission in 12 (70.6%), 9 (52.9%) and 7 (41.1%) cases respectively. There was no history of taking acetaminophen more than 60 mg per kg/day. Aspirin and non-steroidal anti-inflammatory drug (NSAID), Ibuprofen, were taken by each patient for many days during the febrile stage. Convulsion was detected in 4 cases (Tables 1 and 2).

Table 1. *Clinical manifestations of 17 fatal cases*

Patients	Age (years)	Sex	Weight (kg)	TDF/DI	L/S (cm)	DHF grade	Haemorrhage manifestations	Encephalopathy signs/onset	Fluid overload	Associated diseases	Referral*
1NW	1.3	F	8[1]	3/3	3/-	4	GIH	Comatose/s	+	Diarrhea convulsion	+
2SS	11.7	F	42	6/7	2/-	4	GIH	Comatose/s	–	-	–
3TR	13	M	37	4/3	2/-	4	GIH	Stuporous/s	+	ASA	+
4KB	6	F	13[2]	3/3	10/4	4	GIH	Comatose/s	–	Thalasemia convulsion	+
5SM	7	M	20	5/6	3/-	4	GIH	Stuporous/s	–	Pneumonia G6PDdef	+
6KC	7	F	19[1]	4/4	2/-	4	GIH	Comatose/s	+		+
7UA	2.11	F	21	7/7	3/-	4	GIH	Comatose/s	+	NSAID convulsion	+
8WT	10	M	50	5/5	2/-	4	GIH	Stuporous/s	+		+
9KF	6-36.3	M	40	5/6	3/-	4	GIH	Stuporous/s	–		–
10RM	0.10	F	7[1]	4/4	4/-	4	GIH	Stuporous/s	–		+
11JP	10	F	31	4/5	3/-	4	GIH	Stuporous/s	+	ARDS, DIC	+
12DP	9.0	M	17	5/6	3/-	4	GIH	Comatose/s	+		+
13BP	9.5	F	23[1]	4/4	5/-	4	GIH	Comatose/s	–		+
14NO	8.4	F	24	6/7	3/-	4	GIH	Comatose/s	–		–
15TW	8.10	M	20[1]	5/6	3/-	4	GIH	Drowsy/s	–	Hypoglycemia convulsion	+
16WK	10	M	35	4/4	3/-	4	GIH	Comatose/s	–		+
17PL	12	M	45	5/6	2/-	4	GIH	Stuporous/s	–		–

TDF = total duration of fever; DI = duration of illness
GIH = gastrointestinal haemorrhage; S = shock stage; kg = kilograms
[1,2] = first, second degree protein energy malnutrition
* or prior medications especially excessive fluid replacement
ARDS = Adult respiratory distress syndrome
DIC = Disseminated intravascular coagulation
NSAID = Non-steroidal anti inflammatory drug
L/S = liver/spleen

Table 2. *Laboratory investigations of 17 fatal cases*

Patients	Platelets/ Hct (max-min)	AST/ALT (IU/L)	PT/PTT* (sec)	Sodium (mEq/L)	DHF serology	Duration in hospital
1NW	23,00 (37-)	481/161	20.2/96.6	129	SDI	6 h
2SS	27,000 (50-34)	10,081/2,410	20.9/97.9	135	SDI	24 h
3TR	98,000 (39-21)	1,880/636	29.0/>180	130	SDI	26 h
4KB	35,000 (20-12)	1,346/420	137.0/58.0	130	SDI	7.5 h
5SM	15,000 (28-8)	50/20	26.2/42.0	138	SDI	2 h
6KC	33,000 (47-27)	9,729/4,821	24.0/170	134.9	SDI	21 h
7UA	24,000 (48-37)	10,043/3,734	19.7/171	129.6	SDI	13 h
8WT	17,000 (49-34)	3,537/1,599	20.1/>180	134	SDI	8.5 h
9KF	18,000 (57-47)	600/1,524	13.8/77.7	136	SDI	17.5 h
10RM	22,000 (29-27)	2,582/671	23.1/119.6	128	SDI	6 h
11JP	46,000 (42-6)	3,298/1,274	43.9/472	136.7	SDI	16 h
12DP	12,000 (48-31)	1,452/797	17.1/84.8	137	SDI	24 h
13BP	25,000 (42-34)	10,215/5,015	43.1/172	135	SDI	21 h
14NO	10,675 (35-26)	1,486/631	35.6/>180	138	SDI	1 h 10 m
15TW	2,000 (48-28)	3,940/1,592	35.3/>180	134.0	SDI	12 h
16WK	2,000 (56-32)	234/99	12.6/41.1	136	SDI	20 h
17PL	89,000 (41-)	17,950/10,446	45.2/160.8	135	SDI	2 h15 m

* normal (10-14)/(23-35) sec
h = hours, m = minutes
SDI = secondary dengue infection

There were 17 non-fatal cases (male:female = 9:8, median age = 9 years, range = 3-12 years). Massive gastrointestinal haemorrhage, shock and massive fluid overload were detected since admission in 11 (64.7%), 13 (grade 3-9, grade 4-4, 76.4%) and 10 (58.8%) cases respectively. There were 5 cases with acute renal failure and one with liver failure since admission. Fifteen of the 17 cases were referred from district hospitals. Haemodialysis and plasmapheresis were done in 3 renal failure cases and 2 cases with only supportive treatment. All 17 cases recovered completely without neurological sequelae. The average (mean ± SD) hospitalization duration and recovery period from encephalopathy were 8.3 ± 5.31 days and 5.1 ± 3.7 days respectively (Tables 3, 4).

Table 3. *Clinical manifestations of 17 non-fatal encephalopathy cases*

Patients	Age (y.m)	Sex	Weight (kg)	TDI/DI	L/S (cm)	DHF grade	Hemato manifes	Enceph signs/onset	Fluid over-load	Associated diseases	Referral
1YB	9	M	25	4/4	3/-	4	GIH	Stuporous/s	+	ARF	+
2PS	4.4	F	12[1]	5/3	3/-	4	Petichiae	Stuporous/s	–	Pneumonia	–
3ST	10.3	F	29	6/6	3/-	3	GIH	Stuporous/s	+	-	+
4SU	6	F	15[1]	7/7	3/-	3	GIH	Stuporous/s	+	Pneumonia, Tracheitis	+
5CP	5.9	M	17	7/7	1/-	2	GIH	Stuporous/s	–	-	+
6WD	9.9	F	43	5/5	JP	3	GIH	Stuporous/s	+	ARF	+
7WB	6.6	M	18[1]	3/3	3/-	3	Petichiae	Stuporous/s	+	-	+
8SSr	9	F	41.5	5/5	2/-	3	GIH	Stuporous/s	–	Hypoglycemia, ARF	+
9SN	11	F	30[1]	4/7	4/-	2	GIH	Stuporous/s	–	ARF	+
10PP	11	M	34	5/5	2/-	4	GIH	Stuporous/s	+	-	+
11Sma	9.11	M	28	5/5	5/-	3	GIH	Drowsiness/s	+	-	+
12WL	6.11	F	19	5/5	8/6	3	GIH	Stuporous/s	+	Thalasemia, ARDS, pneumonia	+
13ThP	7.9	M	22	5/5	4/-	2	GIH	Stuporous/s	–	-	+
14SL	5.9	M	25[1]	5/6	5/-	3	Petichiae	Stuporous/s	+	ARF	+
15KN	11.11	M	23[2]	5/5	1/-	4	Petichiae	Drowsiness/s	–	-	+
16MK	10.4	M	49	6/6	2/-	3	Petichiae	Drowsiness/s	–	-	–
17WTh	3	F	13.5	5/7	2/-	2	Petichiae	Drowsiness/s	+	Rhinitis	+

[1,2] = first, second degree protein energy malnutrition
ARF = acute renal failure; ARDS = Adult respiratory distress syndrome
GIH = gastrointestinal haemorrhage; JP = just palpable

Table 4. *Laboratory investigations of 17 non-fatal encephalopathy cases*

Patients	Platelets/ Hct (max-min)	AST/ALT (IU/L)	PT/PTT* (sec)	Sodium (mEq/L)	DHF serology	Duration**
1YB	62,000(51-30)	9,420/2,239	23.4/>120	128	SDI	13/7
2PS	17,000(50-26)	2,023/458	14.4/59.9	135	SDI	9/5
3ST	16,000(50-38)	1,098/452	14.7/121.6	130	SDI	4/2
4SU	44,000(46-34)	255/148	16.8/48.5	135	SDI	17/10
5CP	90,000(52-30)	168/110	18.4/64.5	140.3	SDI	13/10
6WD	36,000(41-30)	13,895/5,200	24.6/77.6	127	SDI	11/7
7WB	4,000(58-34)	2,128/918	15.1/67.8	128	SDI	6/3
8SSr	20,000(48-32)	14,580/5,852	16.4/56.0	134	SDI	10/7
9SN	68,000(49-27)	6,987/3,789	32.5/57.2	138	SDI	7/3
10PP	21,000(42-27)	3,810/1,935	15.3/52.5	129	SDI	4/2
11Sma	34,000(48-33)	2,250/448	14.9/78.9	128	SDI	6/3
12WL	20,000(42-27)	3,436/1,841	15.0/89.3	143	SDI	21/15
13ThP	56,000(42-30)	1,315/549	12.4/61.5	134	SDI	2/2
14SL	45,000(56-33)	4,746/1,470	15.9/1,133	131.6	SDI	2/2
15KN	40,000(49-32)	8,150/4,450	16/72.2	137	SDI	7/4
16MK	3,000(51-35)	2,996/1,482	13.8/64.0	132.8	SDI	5/3
17WTh	60,000(32-30)	275/599	15.4/66.7	128	SDI	4/3

* normal: (10-14)/(23-35) sec
** duration in hospital/consciousness change (days)

A comparison between the clinical manifestations and laboratory investigations of the fatal and non-fatal cases, usual manifestations and encephalopathy cases are shown in Tables 5, 6 and 7 respectively.

Table 5. *Comparison between clinical manifestations and laboratory investigations of fatal and non-fatal cases*

Clinical manifestations or laboratory investigations*	Fatal cases (n=17)	Non-fatal cases	*P*-value
Shock (grade IV)	17	4	<0.001
Internal bleeding	17	11	0.007
Onset of encephalopathy in shock stage	17	13	0.035
Coma since admission	9	0	<0.001
Platelets (/cubic millimeters)**	29,33.8 (26,662.1)	37,411.7 (24,153.3)	0.362
AST (IU/L)	4,641.4 (5082.7)	4,560.7 (4,545.8)	0.961
ALT (IU/L)	2,108.8 (2,655.1)	1,878.8 (1,838.6)	0.771
PT in sec	25.5 (11.1)	17.3 (5.0)	0.011
PTT in sec	146.1 (98.8)	75.9 (25.5)	0.011
Serum sodium (mEq/L)	133.9 (3.3)	132.8 (4.8)	0.471

* mean (standard deviation, SD)
** minimum value
PT = Prothrombin time
PTT = Partial thromboplastin time

Table 6. *Comparison between clinical manifestations of usual manifestations and encephalopathy cases*

Clinical data	Usual manifestations (n=1431)	Encephalopathy (n=34)	*P*-value
Age <1 yr	31 (2.1%)	1 (2.9%)	0.775
1 – 4 yr	210 (14.6%)	4 (11.7%)	0.661
5 – 10 yr	812 (56.7%)	23 (67.6%)	0.219
10 – 15 yr	378 (26.4%)	6 (17.6%)	0.252
Female	726 (50.7)	17 (50.0%)	>0.993
Shock	332 (23.2) (grade 3=330, 4=2)	30 (88.2%) (grade 3=9, 4=21)	<0.001
Referal or prior medications	266 (18.6%)	28 (82.3%)	<0.001
Internal bleeding	130 (9.1%)	28 (82.3%)	<0.001
Malnutrition[21]	716 (50.0%) (1°=511, 2°=192, 3°=13)	12 (35.3%) (1°=10, 2°=2)	0.091
Death	–	17 (50%)	<0.001
Duration in hospital (days):mean (standard deviation)	3.4 (1.38)	83 (5.31)*	0.002

* only non fatal cases

Table 7. *Comparison between laboratory investigations of usual and encephalopathy cases*

Laboratory data*	Usual manifestations (n=1431)	Encephalopathy (n=34)	*P*-value
AST (IU/L)	257.3 (250.6)	4601.0 (4748.3)	<0.001
ALT (IU/L)	119.5 (138.1)	1993.8 (2251.8)	<0.001
Platelets (minimum)	70697.9 (2975.7)	33372.8 (2538315)	<0.001
PT (10-14 sec)	11.2 (1.1)	21.4 (9.4)	<0.001
PTT (23-35 sec)	51.9 (13.4)	111.0 (79.5)	<0.001

* mean (standard deviation, SD)

Discussion

DHF patients from all the 11 districts in the Petchabun province were included in this study. The minors were referred from 10 other districts. The adults were from the 178 villages in all 17 subdistricts of the central district. This epidemic was similar to the previous dengue epidemic in 1997[22]. This data implied that the dengue virus had spread nationwide. The percentage of DHF patients with CNS involvement in this study was 2.3%, the same as in the previous study[22] as well as in other studies[7-11]. Female patients were reported to be more severely affected and accounted for more fatalities than male patients but without any significant difference[18,23-25]. In this study, the number of both sexes was equal and both had usual manifestations and encephalopathy cases. Young patients, especially those less than 1 year of age, had the tendency to be more severely and fatally affected[18,23-25]. Age itself was not a risk factor of disease severity in this study. Although there was one fatal case aged 10 months (10 RM), 85% of those who died were older than 5 years. Most of the DHF/DSS patients were well-nourished but patients with CNS involvement were more undernourished without significant difference[24,26]. In this study, patients with usual manifestations and encephalopathy were underweight[21] by about 50% and 35.3% respectively. Patients with encephalopathy were mainly in stage III[7,8,18,27] (88.2%) initially developed in shock stage (52.9%), more than in febrile or convalescent stage[7,9,28]. Seizure in DHF with encephalopathy had been reported in about 18.8-100%[7-9,13,18,24,27,29,30]. In this study seizure was detected in 4 out of 34 patients (11.7%). Two patients (1NW, 7UA), under 5 years, developed seizure in afebrile stage, indicating that the seizure might have had a specific primary cause[10]. However, some children had possible confounding factors such as hyponatremia (3 patients, 1NW, 4KB, 7UA), hypoglycemia (15TW), and liver failure (3 patients, 1NW, 7UA, 15TW). Other factors could be a history of previous febrile seizure, co-infection[10] and drug ingestion.

The causes or factors contributing to CNS manifestations included the following: direct CNS infection – a rare entity, CNS

bleeding[6,18] and severe hepatic dysfunction. Lumbar puncture was done in only two patients (5CP, 15KN) in the convalescent stage with normal findings. Direct CNS infection could not be evaluated in this study. There was massive gastrointestinal haemorrhage in 28 out of 34 cases (82.3%). Acute liver failure could be the direct or indirect cause of encephalopathy[31,32] and an important cause of death in DHF[33]. Twelve of the 17 fatal cases (70.5%) had this severe condition. Severe hepatic dysfunction could be due to profound shock, massive gastrointestinal haemorrhage or immune complex mechanism[34]. The liver pathology in profound shock stage might be centrilobular hepatocellular necrosis[35] or extensive necrosis of hepatocytes usually in a massive or submassive distribution[33]. Massive gastrointestinal haemorrhage might cause hepatic dysfunction and vice versa. Immune complexes, detected in 80% of DHF patients[36], might be deposited in hepatocytes and then destroyed as in hepatitis B virus infection[34]. Excessive use of hepatotoxic drugs such as acetaminophen, an antiemetic drug, might interfere with liver function. There was no history of excessive use of such drugs in this study. Two fatal cases with liver failure and massive gastrointestinal haemorrhage had taken aspirin (3TR) and non-steroidal anti-inflammatory drug, Ibuprofen (7UA), for many days during the febrile stage. Both drugs aggravated the gastrointestinal haemorrhage and aspirin could have induced Reye syndrome[37].

Thalassemia, of which two cases with a large liver and spleen were included in this study (4KB, 12WL), was a risk factor for hepatic failure[18]. Acute renal failure (ARF) was a rare complication of DHF but could occur in severe cases with prolonged shock, DIC and also hepatorenal syndrome[37]. There were five patients with ARF in this study. All of them recovered completely, three (6WD, 8SSr, 14SL) with haemodialysis and plasmapheresis and two (1YB, 9SN) with only supportive and symptomatic therapy. Hyponatremia was a factor in CNS involvement. Serum sodium of encephalopathy patients in this study was slightly low. It was due to excessive hypotonic solution replacement. The risk factors of encephalopathy in this study were profound shock, massive gastrointestinal haemorrhage, excessive fluid overload and severe hepatic dysfunction. Among the fatal and non-fatal encephalopathy cases, laboratory investigations except for coagulogram, were not significantly different. But fatal cases had more severe shock conditions, gastrointestinal haemorrhage and onset and depth of encephalopathy (Table 5).

Conclusion

In conclusion, encephalopathy in DHF was a severe complication with high mortality, although neurological sequelae in recovered patients were rare. Prevention should be attempted by early diagnosis and proper management of fluid therapy.

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References

[1] Nogueira RMR, Filippis AMB, Coelho JMO, Segueira PC, Schatmayr HG, Paiva FG, Ramos AMO and Miagostovich MP. Dengue virus infection of the central nervous system (CNS): a case report from Brazil. Southeast Asian J Trop Med Public Health, 2002, 33: 68-71.

[2] Jimerez DR, Santana JL and Ramirez-Ronda CH. Neurological disorders associated with dengue infection. Bol Assoc Med PR, 1988, 80: 208-211.

[3] Ramos C, Sanchez G, Pando RH, Baquera J, Hernandez D, Mota J, Ramos J, Flores A and Llausas E. Dengue virus in the brain of a fatal case of haemorrhagic dengue fever. J Neurovirol, 1998, 4: 465-468.

[4] Hendarto SK and Hadinegoro SR. Dengue encephalopathy. Acta Paediatr Jpn, 1992, 34: 350-357.

[5] Chauhan GS, Khangaro DK, Shah PK and Rodrigues FM. "Encephalitis" as a manifestation or co-incidence in case of classical dengue fever. J Assoc Physicians India, 1987, 35: 658-659.

[6] Patey O, Ollivaud L, Breuil J and Lafaix C. Unusual neurological manifestations occurring during dengue fever infection. Am J Trop Med Hyg, 1993, 48: 793-802.

[7] Pongrithsukda V. Dengue haemorrhagic fever and hepatic encephalopathy. Ramathibodi Med J, 1986, 9: 11-18.

[8] Sirisanthana V. Dengue haemorrhagic fever at the Department of Pediatrics Chiangmai University Hospital in 1987. Thai J Pediatr, 1988, 27: 36-43.

[9] Vasanawathana S. Encephalopathy in DHF in Khon Kaen Hospital. Khon Kaen Med J, 1992, 16: 91-103.

[10] Pancharoen C and Thisyakorn U. Neurological manifestations in dengue patients. Southeast Asian J Trop Med Public Health, 2001, 32: 341-345.

[11] Attavinijtrakarn P. Hepatic dysfunction in dengue haemorrhagic fever in Paholpolpayuhasaena Hospital. Thai J Pediatr, 2000, 39: 265-276.

[12] Sanguansermsri T, Poneprasert B and Pornphutkul B. Acute encephalopathy associated with dengue infection. Conference on dengue haemorrhagic fever, current knowledge. SEAMEO TROPMED, 1976, 10-11.

[13] Lum LCS, Lam SK, Choy YS, George R and Harun F. Dengue encephalitis: a true entity? Am Trop Med Hyg, 1996, 54: 256-259.

[14] Thisyakorn U, Limpitikul W and Nisalak A. Dengue infection with central nervous system manifestations. Proceedings of the 4th international symposium on dengue fever, Tahiti, 1997: 47.

[15] Miagostovich MP, Ramos RG, Nicol AF, Nogueira RMR, Cuzzi-Maya T, Oliveira AV, Marchevsky RS, Mesquita RP and Schatzmayr HG. Retrospective on dengue fatal cases. Clin Neuropathol, 1997, 16: 204-208.

[16] Kankirawatana P, Chokepaibulkit K, Puthavathana P, Yoksan S, Apintanapong S and Pongthapisit V. Dengue infection presenting with central nervous system manifestation. J Child Neurol, 2000, 15: 544-547.

[17] Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LTT, Rangsakulrach B, Loan HT, Day NPJ, Farrar J, Myint KSA, Warrell MJ, James WS, Nisalak A and White NJ. Neurological manifestations of dengue infection. Lancet, 2000, 355: 1053-1059.

[18] Nimmannitya S, Thisyakorn U and Hemsrichart V. Dengue haemorrhagic fever with unusual manifestations. Southeast Asian J Trop Med Public Health, 1987, 18: 398-406.

[19] Lum L, Lam SK, George R and Devi S. Fulminant hepatitis in dengue infection. Southeast Asian J Trop Med Public Health, 1993, 24: 467-471.

[20] World Health Organization. Dengue haemorrhagic fever: diagnosis, treatment and control, 2nd ed. Geneva, WHO, 1997.

[21] Thailand, Ministry of Public Health, Department of Health. Reference scales of weight, height and indicators of nutritional status of Thai population - 1 day to 19 years old. Bangkok, 1999.

[22] Witayathawornwong P. Dengue haemorrhagic fever patients with encephalopathy at Petchabun hospital: A prospective study for two years during May 1997 to April 1999.Thai Pediatr J, 2001, 8: 65-73.

[23] Nimmannitya S. Dengue haemorrhagic fever in Thailand. Southeast Asian J Trop Med Public Health, 1987, 18: 281-284.

[24] Thisyakorn U and Thisyakorn C. Dengue infection with unusual manifestations. J Med Assoc Thai, 1994, 77: 410-413.

[25] Kalayanarooj S, Nimmannitya S and Eaksangsri P. Fatal cases of dengue haemorrhagic fever at children's hospital 1987. Bull Dept Med Serv, 1989, 14: 771-778.

[26] Thisyakorn U and Nimmannitya S. Nutritional status of children with dengue haemorrhagic fever. Clin Infect Dis, 1993, 16: 295-297.

[27] Kho LK, Sumarmo, Wulur H, Jahja E and Gubler DJ. Dengue haemorrhagic fever accompanied by encephalopathy in Jakarta. Southeast Asian J Trop Med Public Health, 1981, 12: 83-86.

[28] Suvattee V, Vajaradule C and Laohapand T. Liver failure and hepatic encephalopathy in dengue haemorrhagic fever/dengue shock syndrome: a co-relation study with acetaminophen usage. Southeast Asian J Trop Med Public Health, 1990, 21: 694-695.

[29] Sumarmo, Wulur H, Jahja E, Gubler DJ, Sutomenggolo TS and Saroso JS. Encephalopathy associated with dengue infection. Lancet, 1978, 1: 449-450.

[30] Tin U, Aye M, Swe TN, Khin MM and Rosen L. Dengue haemorrhagic fever with encephalitic symptoms. SEAMEO TROPMED conference, Bangkok, 1976: 29-30.

[31] [31] Hoyumpa AM Jr, Desmond PV and Avan GR. Hepatic encephalopathy. Gastroenterology, 1979, 76: 184.

[32] Rueff B and Benhamou JP. Acute hepatic necrosis and fulminant hepatic failure. Gut, 1973, 14: 805-815.

[33] Innis BL, Myint KSA, Nisalak A, Ishak KG, Nimmannitya S, Laohapand T, Tanprasertsuk S, Pongritsukda V and Thisyakorn U. Acute liver failure is one important cause of fatal dengue infection. Southeast Asian J Trop Med Public Health, 1990, 21: 695-696.

[34] Woolf I, El Sheilk N and Cullens H. Enhanced HBsAb production in pathogenesis of fulminant hepatitis type B. Br Med J, 1976, 2: 669-671.

[35] Nunes G, Blasdell FW and Margaretten W. Mechanism of hepatic dysfunction following shock and trauma. Arch Surg, 1970, 100: 546-566.

[36] Ruangjirachuporn W, Boonpucknavig S and Nimmannitya S. Circulating immune complexes in serum from patients with dengue haemorrhagic fever. Clin Exp Immunol, 1979, 36: 46-53.

[37] Committee on infectious diseases: Aspirin and Reye syndrome. Pediatrics, 1982, 3: 321.