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นิพนธ์ต้นฉบับ Original Article

Hepatic Dysfunction in Children with Dengue Shock Syndrome

ความผิดปกติของตับในผู้ป่วยเด็กที่เป็นไข้เลือดออกชนิดช็อก

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ABSTRACT

A prospective observation study was conducted in children with dengue shock syndrome for associated hepatic dystunction and its consequence. Among 34 children with DSS, 11 (32.4%) had hepatic dysfunction with mean of alanine aminotransferase level of 1,412 U/liter compared to 86 in those without hepative dysfunction. It occurred in 25% of children with dengue hemorrhagic fever grade 3, and 67% with grade 4. There was spontaneous bleeding in 82% of children with hepatic dysfunction and in 70% of those without ($p = 0.682$). Spontaneous bleeding also correlated with disease severity, 68% of children in grade 3 and 100% in grade 4, with high level of alanine aminotransferase (647 vs. 149 U/liter) as an early indicator. Thrombocytopenia was present in all cases as well as minor prolongations of prothrombin and partial thromboplastin times. Three children died from fulminant hepatic failure. All of them had acidosis and abnormal coagulograms. Hepatic dysfunction is common in children with DSS; spontaneous bleeding should be alerted especially when aminotransferase levels are high.

บทคัดย่อ

ศึกษาอุบัติการณ์ของความผิดปกติของการทำงานของตับในผู้ป่วยเด็ก 34 คนที่เป็นไข้เลือดออกชนิดช็อก ในหอผู้ป่วยวิกฤต พบว่าเด็ก 11 คน ร้อยละ 32.4 มีความผิดปกติของตับ โดยมีระดับค่าเฉลี่ยของ alanine aminotransferase เท่ากับ 1,412 หน่วย/ลิตร เมื่อเทียบกับ 86 หน่วย/ลิตร ในเด็กกลุ่มที่ไม่มีความผิดปกติของตับ อุบัติการณ์จะแปรผันกับความรุนแรงของโรคโดยเด็กที่เป็นไข้เลือดออกที่มีความรุนแรงระดับ 3 จะพบมีความผิดปกติของตับร้อยละ 25 ในขณะที่เด็กที่มีความรุนแรงระดับ 4 พบร้อยละ 67 ปัญหาที่ตามมาก็คือภาวะเลือดออกซึ่งในเด็กที่มีความผิดปกติของ

ตับพบว่ามีเลือดออกร้อยละ 82 ส่วนในเด็กที่ไม่มีความผิดปกติของตับมีเลือดออกร้อยละ 70 (p = 0.682) ภาวะเลือดออกขึ้นกับระดับความรุนแรงของโรค ในเด็กที่มีความรุนแรงระดับร้อยละ 3 จะพบเลือดออก 68 ขณะที่เด็กที่มีความรุนแรงระดับ 4 จะพบร้อยละ 100 โดยเด็กที่มีเลือดออกจะมีระดับของ alanine aminotransferase สูงกว่า (647 vs. 149 U/liter) ร่วมกับมีเกล็ดเลือดต่ำและมีค่าการแข็งตัวของเลือดผิดปกติ มีเด็กเสียชีวิตจากภาวะตับวาย 3 คน ทุกคนมีภาวะเลือดเป็นกรดและมีค่าการแข็งตัวของเลือดผิดปกติ ดังนั้นความผิดปกติของตับพบได้บ่อยในเด็กที่เป็นไข้เลือดออกชนิดช็อก ต้องระวังเลือดออกโดยเฉพาะในรายที่มีระดับ aminotransferase ขึ้นสูง

INTRODUCTION

Dengue infection has been a major problem of mosquito-borne viral disease in children in tropical countries[1]. Its severe forms include dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[2]. Recently, it has become an important re-emerging disease with appreciable numbers of mortality since there have been increasing reports of unusual manifestations associated with dengue infection, mainly with hepatic and cerebral involvement[3-9]. Liver is a target organ of dengue infection ; the involvement has been reported to be mildly elevated aminotransferase enzymes to the most severe form of fulminant hepatic failure causing death[3-5].

We examined the incidence of hepatic dysfunction in children with DSS, its consequence and looked for any clinical or biochemical predictors.

METHODS

A prospective observation study was conducted in the pediatric intensive care unit at Prachomklao Hospital, a provincial referral center in the central part of Thailand where dengue is endemic. Children under the age of 15 were admitted during January 2002-December 2003 with a diagnosis of DSS (DHF grade 3 and 4) and confirmed by hemagglutination inhibition tests according to WHO criteria[10] Hepatic dysfunction was defined as alanine aminotransferases level mose than 200 U/L. Vigilant care was instituted including frequent recording of vital signs, determination of serial hematocrits, early volume replacement and the early correction of acidosis according to the National DHF Guideline.[11]

A full history of drugs and other potential hepatotoxins was inquired. Hematocrit, white-blood cells, lymphocytes, atypical lymphocytes, platelets, aspatate and alanine aminotransferases (AST, ALT), albumin, coagulograms, and electrolytes were performed at the diagnosis of DSS. Physical examination was done every day by house staff. Children with hepatitis, thalassemia and G6PD deficiency were excluded. The study protocol was approved by the Hospital Review Board.

Data were analysed and numbers are expressed as means. Difference between means was performed by t-test and chi-square with 0.05 as a level of significance.

RESULTS

There were 34 children with a diagnosis of DSS, 16 were female (47%) and 18 were male

Table 1 Clinical features of children with DSS

Patient	GR	COMPLI	HCT1	WBC	L	AL	PLT	AST	ALT	ALB	HCT2	PT	PTT	CO2	INFX	D
1 (f/7)	3	gib	43	4400	47	12	34	84	38	-	52	22	70	20	2	-
2 (m/7)	3	-	48	7500	34	-	32	164	57	2.0	54	36	90	16	2	-
3 (f/6)	3	-	46	5500	40	2	18	237	144	-	46	23	90	-	2	-
4 (m/12)	3	gib	46	6000	44	3	27	177	131	-	53	20	180	-	2	-
5 (m/6)	3	gib	47	7800	30	1	32	797	478	3.7	54	-	-	-	2	-
6 (m/13)	3	epis	44	6500	47	6	31	656	413	3.1	50	-	-	24	2	-
7 (m/10)	3	-	41	2500	44	18	15	205	76	3.4	47	-	-	-	2	-
8 (f/4)	3	gib	35	2000	27	-	88	112	23	2.7	47	-	-	21	2	-
9 (f/13)	3	gib	37	5500	40	-	81	568	348	2.8	43	15	53	21	2	-
10 (f/7)	3	-	38	3900	55	13	50	247	107	3.2	47	-	-	17	2	-
11 (m/13)	3	gib	42	3700	11	12	93	101	30	-	53	-	-	20	2	-
12 (m/5)	3	gib	52	12000	24	8	40	444	194	-	52	-	-	19	2	-
13 (m/11)	3	-	43	4800	30	6	46	563	325	-	54	-	-	21	2	-
14 (f/9)	3	gib	36	2200	53	4	55	154	54	3.1	48	-	-	22	2	-
15 (m/7m)	4	gib,encep	29	7200	40	3	32	10252	3960	2.9	30	27	78	14	1	-
16 (f/12)	4	gib	48	3500	35	5	12	85	11	2.9	53	19	60	12	2	-
17 (m/13)	3	gib	48	4500	37	5	14	75	40	4.5	55	12	23	34	2	-
18 (f/10)	3	hemat	42	3800	23	1	87	268	126	3.6	48	20	98	20	2	-
19 (f/5)	3	gib	36	6000	60	13	30	1181	403	-	43	13	46	21	2	-
20 (f/3)	4	gib, encep	36	3700	23	4	74	3562	1136	-	50	28	166	11	2	D
21 (m/12)	3	gib	39	2700	21	5	73	43	104	-	52	-	-	20	2	-
22 (f/12)	4	gib	48	11500	27	-	5	12800	6420	2.9	51	20	124	8	2	D
23 (m/7)	3	-	43	2200	45	-	85	141	125	4.4	48	-	-	-	2	-

Table 1 Clinical features of children with DSS

Patient	GR	COMPLI	HCT1	WBC	L	AL	PLT	AST	ALT	ALB	HCT2	PT	PTT	CO2	INFX	D
24 (m/12)	3	gib	42	4600	24	3	73	58	42	2.9	48	-	-	-	2	-
25 (f/13)	3	epis	34	7300	36	5	51	178	104	3.4	36	16	42	-	2	-
26 (m/6)	3	gib	34	8100	40	2	32	297	140	2.1	37	16	51	-	2	-
27 (m/12)	4	gib	27	3100	19	4	22	644	1361	2.8	34	20	154	8	2	D
28 (f/13)	3	-	52	4100	51	4	25	278	155	3.0	52	-	-	21	2	-
29 (f/12)	3	gib	48	3800	40	13	21	173	79	3.1	54	-	-	19	2	-
30 (m/5)	3	fl over	36	5700	39	5	26	57	9	3.5	42	-	-	22	2	-
31 (m/5)	3	fl over	42	7100	53	14	40	619	345	2.8	44	17	55	19	2	-
32 (f/11)	3	gib	52	4000	47	3	38	123	59	2.0	57	24	62	18	2	-
33 (f/11)	4	gib	44	2600	23	4	84	186	139	-	54	16	45	-	2	-
34 (m/7)	3	gib	47	3000	41	-	42	560	350	-	53	21	85	-	2	-
$\bar{X}$	-	-	42	5082	37	6	44	1064	515	3.0	48	20	83	19	-	-

GR = dengue hemorrhagic fever grade; COMPLI = complications (gib-gastrointestinal bleeding epis-epistaxis en-encephalitis hemat-hematuria fl overfluid overload); HCT1 = hematocrit at diagnosis of DSS (%); WBC = white-blood cells (per mm^3); L = lymphocytes (%); AL = atypical lymphocytes (%); PLT = platelets ($10^3/mm^3$); AST = aspartate aminotransferase (U/liter); ALT = alanine aminotranferase (U/liter); ALB = albumin (g/dl); HCT2 = maximum hematocrit (%); PT = prothrombin time (sec); PTT = partial thromboplastin time (sec); CO2 = bicarbonate (mmol/liter); INFX = type of infection (1-primary, 2-secondary); D = dead.

(53%). Twenty-eight of them were in DHF grade 3 (82.4%), and 6 in grade 4 (17.6%), all had secondary dengue infection. Mean age was 9.0 years (ranged 7 months-13 years). Hepatomegaly was found in all children. No jaundice was found. Hepatitis B vaccine was given at birth. Two children had taken ibuprofen, others had acetaminophen as an antipyretics before the appearance of shock. Abnormal laboratory values such as atypical lymphocytes, platelets, aminotransferases and coagulograms were noted in children with DSS (Table 1). Levels of AST were higher than those of ALT in every case.

Hepatic dysfunction was noted in 11 children (32.4%) who had ALT more than 5 times upper normal values (ALT > 200 U/L). Seven of 28 children (25%) with DHF grade 3, and 4 of 6 children (67%) with grade 4 had hepatic dysfunction, indicating that not all children with DSS had hepatic dysfunction. The mean level of ALT in children with hepatic dysfunction was 1,412 compared to 86 U/L in those without. Hematocrits increased from a mean value of 42% (range 27-52%) at the diagnosis of DSS to 48% (range 30-57%) at the maximal value of treatment.

There was a 7-month old boy with severe hepatic dysfunction and encephalopathy who was the only one who had primary dengue infection

Table 2 Parameters of children with and without hepatic dysfunction.

Parameter	Hepatic Dysfunction (N =11)	No Dysfunction (N = 23)	p
AGE (yr)	8	9	0.440
HCT (%)	39	43	0.075
WBC (per mm^3)	6320	4567	0.065
L (%)	37	37	0.966
AL (%)	6	6	0.990
PLT ($10^3/mm^3$)	39	46	0.467
AST (U/liter)	3164	185	0.068
ALT (U/liter)	1412	86	0.050
ALB (g/dl)	3	3	0.701
HCT2 (%)	45	50	0.085
PT (sec)	19	20	0.602
PTT (sec)	68	75	0.745
CO2 (mmol/liter)	16	20	0.105
STAY (day)	4	5	0.549
Grade 3	7	21	-
Grade 4	4	2	-

(patient number 15). He had no shock. His aminotransferases and coagulograms were abnormal.

There was no significant difference in age, hematocrit, white cell count, platelets, atypical lymphocytes, albumin, prothrombin and partial thromboplastin times (PT, PTT) between children with and without hepatic dysfunction (Table 2). These levels gradually returned to normal over the next 1-2 weeks.

Hemorrhagic tendencies, evidenced by epistaxis, gastrointestinal bleed and hematuria, were prevalent in most of the children (Table 1). The incidence of any bleeding in children with hepatic dysfunction (82%) did not differ significantly from the other group without (70%, p = 0.682) (Table 3).

There was no significant difference between children with and without bleeding in hematocrits, platelets, AST, ALT, PT, PTT and carbon dioxide. Children who bled had higher level of AST and ALT. All children in grade 4 had bleeding as well

Table 3 Bleeding in children with and without hepatic dysfunction.

Bleed	Hepatic Dysfunction (N = 11)	No Dysfunction (N = 23)
Epistaxis	1	1
Gastrointestinal bleed	8	14
Hematuria	0	1
Total	9	16

Table 4 Parameters of children with and without bleeding.

Parameter	Bleed (N = 25)	No Bleed (N = 9)	p
HCT (%)	41	43	0.480
PLT (103/mm^3)	47	37	0.354
AST (U/liter)	1343	288	0.330
ALT (U/liter)	647	149	0.316
PT (sec)	19	25	0.096
PTT (sec)	84	78	0.857
CO2 (mmol/liter)	18	19	0.738
Grade 3	19	9	-
Grade 4	6	0	-

Table 5 Parameters of children who died.

Parameter	Dead (N = 3)	Alive (N = 31)	p
AGE (yr)	9	9	0.440
HCT (%)	37	42	0.165
WBC (per mm^3)	6100	4984	0.721
L (%)	23	38	0.032
AL (%)	4	7	0.011
PLT ($10^3/mm^3$)	34	45	0.458
AST (U/liter)	5669	618	0.302
ALT (U/liter)	2972	277	0.258
ALB (g/dl)	3	3	0.601
HCT2 (%)	45	49	0.368
PT (sec)	23	20	0.445
PTT (sec)	148	71	0.002
CO2 (mmol/liter)	9	20	0.000
STAY (day)	2	5	0.078

as 68% of children in grade 3 (Table 4).

There were 3 children who died of fulminant hepatitis, with additional encephalopathy in 1 child. All had massive elevation in aminotransferase enzymes and prolonged PTT. There was statistical difference in acidosis, PTT, lymphocytes and atypical lymphocytes between the 2 groups of children. They had a hospital stay of 2 days compared to 5 in those who survived (Table 5).

DISCUSSIONS

Liver is a target site for dengue virus. Lin YL et al had elucidated the action of dengue virus on hepatoma cells and found that dengue virus replicated actively and caused severe cytopathic effects in differentiated hepatoma cells[12]. The pathology ranged from severe, diffuse hepatitis to focal necrosis of hepatic cells, swelling, appearance of Councilman bodies and hyaline necrosis of Kupffer cells as the target cells supported virus replication[10,12,13].

Hepatic dysfunction is common in dengue infection; it is characterized by an increase in ALT[14]. Its frequency depends upon disease severity[15]; 12% in dengue fever (DF), 16% in DHF grade 1 and 2, and in the present study 25% in grade 3 and 67% in grade 4. As there was a correlation between biochemical changes and severity

of dengue infection in pediatric patients[16], there was a possibility of developing hepatic dysfunction when aminotransferases reached high level. The mean ALT level in our children with hepatic dysfunction was 1,412 U/liter, much higher than that of 86 U/liter in those without dysfunction. It is noted that levels of AST were higher than those of ALT, a condition which was distinct from other viral hepatitis[17].

Most of our cases had secondary infection; only a 7-month old boy with severe hepatic dysfunction and encephalopathy had primary infection which was common in infants[18,-21]. He had a massive bleeding from mucous membrane and gastrointestinal tract. There was much increase in aminotransferases. He had no shock and improved afterwards.

Dengue infection induces transient aberrant immune responses affecting monocytes, endothelial cells, hepatocytes and platelets. The proposed pathogenesis of hemorrhage involves the unbalance between coagulation and fibrinolysis leading to consumption coagulopathy and vascular alteration, increasing the likelihood of severe hemorrhage in DHF[21-23].

Bleeding also correlated with disease severity. It occurred in 68% in children with grade 3 and 100% with grade 4. The high level of aminotransferases might be an early indicator to predict the possibility of bleeding; children who bled had higher value than those who did not (ALT = 647 vs.149 U/liter). There were only minor prolongations of PT and PTT and thrombocytopenia but there was no significant difference in these values. Bleeding occurred in children with and without hepatic dysfunction, although the aminotransferase level was high in the bleeding group[25,26]. The ALT and AST levels were higher in DHF patients with spontaneous bleeding than those without.

Children who died developed fulminant hepatitis with a markedly increase in aminotransferase levels (mean ALT = 2,972, AST = 5,669 U/liter), thrombocytopenia and abnormal coagulograms leading to severe hemorrhage, metabolic derangement, acidosis and death within 2 days of admission. The management of children with hepatic failure posed a difficult problem. The early detection of highly elevated levels of serum ALT in children who exhibited an unusual change in consciousness or abnormal neurological signs will have an impact on prognosis and survival. Metabolic acidosis usually occurs in severe cases. If uncorrected in time, it may lead to disseminated intravascular coagulation and to a more complicated course. In general, frequent recording of vital signs, determination of serial hematocrits early volume replacement and the early correction of acidosis with sodium bicarbonate result in favorable outcome[10].

CONCLUSIONS

Hepatic dysfunction is common in DSS. Close monitoring and vigorous therapy of shock should be instituted promptly to avoid DSS. Aminotransferase level is useful in predicting the occurrence of hepatic dysfunction and spontaneous bleeding. Fulminant hepatic failure and acidosis are bad prognostic indicators.

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