IS DENGUE SEVERITY RELATED TO NUTRITIONAL STATUS?

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Abstract. A retrospective review of dengue patients admitted to Queen Sirikit National Institute of Child Health (previously known as Children's Hospital) from 1995 to 1999 revealed 4,532 confirmed cases of dengue infection; 80.9% were dengue hemorrhagic fever (DHF) and 19.1% were dengue fever cases (DF). Among the DHF patients; 30.6% had shock. The majority of them, 66.6%, had a normal nutritional status, while 9.3% were malnourished and 24.2% had obesity as classified by weight for age. Compared with control patients with other diagnoses (excluding HIV/AIDS patients), malnourished children had a lower risk of contracting dengue infection (odds ratio=0.48, 95%CI=0.39-0.60, p=0.000) while obese children had a greater risk of infection with dengue viruses (odds ratio=1.96, 95% CI=1.55-2.5, p=0.000). The clinical signs, symptoms and laboratory findings of dengue were almost the same among the 3 groups of malnourished, normal, and obese patients. The minor differences observed were that in obese children liver enlargement was found less often; maculopapular/convalescence rash and elevations of alanine aminotransferase were found more often. Malnourished patients had a higher risk of developing shock (37.8%) than normal (29.9%) and obese patients (30.2%) (p= 0.000). Obese patients had more unusual presentations: encephalopathy (1.3%) and associated infections (4.8%), than normal (0.5% and 2.7%) and malnourished patients (1.2% and 3.1%). Complications of fluid overload were found more in obese patients (6.5%) compared to normal (3.2%) and malnourished patients (2.1%) (p=0.000). The case-fatality rates (CFR) in malnourished patients and obese patients were 0.5% and 0.4%, respectively, while in normal patients the CFR was 0.07%. Under and over nutrition DHF patients had either a greater risk of shock or unusual presentations and complications, which can lead to severe disease or complications and probably a higher CFR.

INTRODUCTION

Dengue infection is currently one of the most important mosquito-borne viral diseases in the tropical parts of the world (WHO, 1999). The disease is characterized by high fever and hemorrhagic manifestations. Dengue fever (DF) and dengue hemorrhagic fever (DHF) are two well recognized clinical presentations of dengue infections. DHF (Nimmannitya, 1997, 2002) is more severe than DF because it has the distinct pathophysiologic hallmark of selective plasma leakage into the pleural and abdominal cavities, which can result in shock if the plasma leakage is extensive (Halstead, 1997). Delay or untreated shock can lead to complications of hepatic, renal or multiple organ failure and death. Massive bleeding due to disseminated intravascular coagulation (DIC) and hepatic failure after prolonged shock is another characteristic of severe and complicated DHF patients before death ((Nimmannitya, 1997, 2002).

The annual reported cases of DF/DHF in Thailand from 1999 to 2003 were quite high, ranging from 30,000-120,000 cases, with case fatality rates (CFR) of 0.12-0.21% (Bureau of Epidemiology, 1999-2003). Obese children are considered to be higher risk because obese patients are more likely to have complications or death (Nimmannitya *et al* 1999; Kalayanarooj *et al*, 2003a). There are no reported studies regarding the nutritional status of DHF patients and the severity of the illness. Many studies confirm that most DHF patients have good nutritional status and malnourished children are less commonly observed to have DHF (Thisyakorn and Nimmannitya, 1992; Nimman-

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nitya, 2002). This study was planned to discover whether nutritional status has any effect on the severity of the dengue illness.

MATERIALS AND METHODS

Retrospective review of hospital charts of all admitted dengue patients at Queen Sirikit National Institute of Child Health (QSNICH, previously known as Children's Hospital) was done for the period of 1995-1999. Only dengue confirmed cases with recorded body weights (BW) on admission were included for analysis. Laboratory confirmation was done by the Armed Forces Research Institute of Medical Sciences (AFRIMS) using the antibody test, enzyme linked immunosorbent assay (ELISA) and/or hemagglutination inhibition test (HI). The serotype was identified by polymerase chain reaction (PCR) and or virus isolation (mosquito inoculation technique).

Dengue was classified as dengue fever (DF), dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) according to WHO criteria (WHO, 1997).

Dengue patients were divided into 3 groups according to their nutritional status. Nutritional status was classified by percent ideal body weight (IBW), using the weight for age standard growth curve for Thai children from the Department of Health (2000). Group 1 (normal)-normal/mild protein energy malnutrition (PEM) was a BW=75-110% of IBW. Group 2 (malnourished)-moderate to severe PEM was a BW= <75% of IBW. Group 3 (obesity)-overweight to obesity was a BW>110% of IBW.

Seven hundred thirty-four records of patients admitted to the QSNICH dengue ward during the same period with other diagnoses (excluding HIV/AIDS patients) were used to compare nutritional status with the dengue patients.

Demographic data, history, physical examination, and laboratory investigations which were relevant were recorded.

Statistical analysis of the data was done using SPSS for Window version 10.0.

RESULTS

There were 4,532 confirmed dengue patients admitted to QSNICH from 1995 to 1999. Of the dengue patients; 3,667 had DHF (80.9%) and 865 had DF (19.1%). The majority of DF/DHF patients (65-67%) had a normal nutritional status, while 9-11% had moderate to severe PEM and 23-24% were overweight/obese. There was no statistical difference between the nutritional status of the DF and DHF patients (Table 1). Malnourished patients had DSS more than patients with a normal nutritional status. Patients with normal nutritional status and obesity had no difference in the number of cases of DSS (Table 2). Control patients with other diagnoses had significantly more malnourished patients (19.6%) and fewer obese patients (12.5%) (Table 3).

The male to female ratios of malnourished, normal, and obese dengue patients were 1.09:1, 1.1:1, and 1.1:1, respectively (p = 0.881).

The mean ages of the dengue and the control patients were 7.9±3.8 and 5.8± 3.5 years, respectively (p=0.000). The mean ages of the

Table 1
Nutritional status of DF/DHF patients.

	DHF		DF		Odd ratio (95% CI)	χ^2	p-value
	N	%	N	%			
Malnourished	323	8.8	96	11.1	0.78 (0.6-1.0)	4.09	0.43
Normal	2,452	66.9	566	65.4			
Obese	892	24.3	203	23.5	1.01 (0.85-1.22)	0.02	0.876
Total	3,667	100.0	865	100.0			

Table 2
Nutritional status of DHF/DSS patients.

	DSS		DHF		Odd ratio (95% CI)	χ^2	p-value
	N	%	N	%			
Malnourished	122	10.9	201	7.9	1.43 (1.11-1.83)	8.4	0.004
Normal	732	65.2	1,720	67.6			
Obese	269	24.0	623	24.5	1.01 (0.86-1.2)	0.03	0.865
Total	1,123	100.0	2,544	100.0			

Table 3
Nutritional status of DF/DHF and control patients.

	DF/DHF		Control		Odd ratio (95% CI)	χ^2	p-value
	N	%	N	%			
Malnourished	419	9.2	144	19.6	0.48 (0.39-0.60)	47.67	0.000
Normal	3,018	66.6	498	67.9			
Obese	1,095	24.2	92	12.5	1.96 (1.55-2.5)	33.27	0.000
Total	4,532	100.0	734	100.00			

Table 4
AST range.

AST (U)	Malnourished		Normal		Obese		Total (%)
	N	%	N	%	N	%	
0-40	21	5.1	150	5.1	56	5.2	227 (5.1)
>40-200	278	67.6	2,058	69.9	719	67.3	3,055 (69.1)
>200-1,000	112	27.3	736	25.0	293	27.4	1,141 (25.8)
Total	411	100.0	2,944	100.0	1,068	100.0	4,423

p = 0.205

dengue patients who were malnourished, normal, and obese patients were 9.7±3.1, 7.8±3.7, and 7.6±4.0 years, respectively (p=0.000).

The dengue serotypes were not different between the patients with different nutritional status (p=0.394). Dengue 3 was the most common serotype found (50.6%), and dengue 1, 2, and 4 were found in 25.8%, 21%, and 2.6%, respectively.

The percentage of primary and secondary dengue infections were not different between the patients with different nutritional status (p=0.066). There were 22.9% primary and 77.1% secondary dengue infections.

Most of the presenting signs and symptoms of DF/DHF (fever, tourniquet test, bleeding manifestations, nausea/vomiting, abdominal pain) were not different between the pa-

Table 5
ALT range.

ALT (U)	Malnourished		Normal		Obese		Total
	N	%	N	%	N	%	(%)
0-40	210	51.1	1,386	47.1	387	36.3	1,983 (44.8)
>40-200	165	40.1	1,303	44.2	550	51.5	2,018 (45.6)
>200-1,000	36	8.8	256	8.7	130	12.2	420 (9.5)
Total	411	100.0	2,945	100.0	1,067	100.0	4,423

p = 0.000

tients with different nutritional status, except for liver enlargement, which was found less often in obese patients (86.8%) compared to 92% and 90.1% in normal and malnourished patients, respectively (p=0.000). Maculopapular rash was found more often in obese patients (10.2%) compared to 6.5% and 5% in normal and malnourished patients, respectively (p=0.000). Convalescence rash was found more often in obese patients (25%) compared to 17.5% and 17.7% in normal and malnourished patients, respectively (p=0.000).

The laboratory findings: WBC, platelet counts, percent rising hematocrit (Hct), total protein, albumin and aspartate aminotransferase (AST) levels were not different between the patients with different nutritional status. The percentage of patients with abnormal AST elevation >200 U were not different (p=0.205) (Table 4), but abnormal ALT elevation >200 U was found more in obese patients (12.2%) compared to 8.7% and 8.8% in normal and malnourished patients, respectivley (Table 5). The mean alanine aminotransferase (ALT) level was higher in obese patients (131 U) compared to normal (101 U) and malnourished (114 U) patients (p=0.024).

Obese patients (85.2%) received less intravenous (IV) fluid than normal (88%) and malnourished patients (89.8%) (p=0.040). The duration of IV fluid was not different between each group of patients and the mean durations were 37.2, 37.5, and 38.4 hours for obese, normal, and malnourished patients, respectively (p=0.757). Obese patients received more IV fluid (86.6 ml/kg of IBW) than normal (70.8 ml/kg) and malnourished (63.5 ml/kg of IBW) patients (p=0.000). If the calculation was based on actual BW, obese patients received less IV fluid (64 ml/kg) compared to normal (76.6 ml/kg) and malnourished (85.9 ml/kg) patients (p=0.000). Blood was transfused in 4%, 3.7%, and 5.6% of obese, normal, and malnourished patients, respectively (p=0.269).

Obese patients had more unusual presentations and complications compared to normal and malnourished patients, such as encephalopathy (1.3% *vs* 0.5% and 1.2%), associated infections (4.8% *vs* 2.7% and 3.1%), and fluid overload (6.5% *vs* 3.2% and 2.1%) (Table 6).

Most DHF patients recovered completely except for 8 patients: 2 malnourished, 5 normal and 1 obese patient, who had some degree of liver impairment; all of them recovered well within 1 month. There was one obese patient who had hepatic encephalopathy, intracerebral bleeding and stayed for 3 months in the hospital. He recovered with permanent neurological sequalae, left hemiparesis and a decrease in intellectual quotient (IQ). Case fatality rates for DHF/DSS were the highest in malnourished patients (0.5%), followed by obese patients (0.4%), and normal patients (0.07%) (Table 6).

DISCUSSION

In our study, most of the DF/DHF cases

Table 6
Complications and results.

	Malnourished (M)		Normal (N)		Obese (O)		Odd ratio (95%CI) Upper-M:N Lower- O:N	χ^2	p-value
	N	%	N	%	N	%			
Encephalo-pathy	5	1.2	14	0.5	14	1.3	2.74 (0.86-8.19)	4.01	0.045
							2.78 (1.25-6.19)	7.85	0.005
Fluid overload	9	2.1	98	3.2	71	6.5	0.69 (0.32-1.42)	1.13	0.288
							2.08 (1.50-2.88)	21.41	0.000
Associated infections[a]	13	3.1	81	2.7	53	4.8	1.23 (0.64-2.30)	0.45	0.500
							1.85 (1.28-2.68)	11.84	0.000
Associated conditions[b]	19	4.5	76	2.5	23	2.1	1.95 (1.13-3.36)	6.69	0.009
							0.83 (0.50-1.36)	0.62	0.431
Hepatic[c] dysfunction (DHF)	2	1.6	5	0.7	1	0.1	2.42 (0.23-14.99)	1.18	0.278
							0.54 (0.01-4.88)	0.32	0.571
Death[c] (CFR for DHF)	2	0.5	2	0.07	4	0.4	7.63 (0.55-105.49)	5.73	0.016
							5.52 (0.79-61.06)	4.92	0.026

[a]*eg* pneumonia, diarrhea, phlebitis, UTI, etc.
[b]*eg* thalassemia, G-6-PD deficiency, congenital heart disease, etc.
[c]Fisher exact test

had a better nutritional status than the control patients with other diagnoses, as previously reported (Thisyakorn *et al* 1992; Nimmannitya, 2002). In addition, our study suggests that obese children are at higher risk (odds ratio=1.96, 95%CI=1.55-2.5, p=0.000), while malnourished children are at lower risk of contracting dengue viruses (odds ratio=0.48, 95%CI=0.39-0.60, p=0.000). The development of DF/DHF depends on the host immune response. Malnourished children are spared from severe DHF/DSS because they have a suppressed cellular immune response (Halstead, 1997). In contrast to malnourished children, obese children are expected to have a stronger immune response than normal children, so they are at higher risk of developing DF/DHF. This hypothesis was supported by our data.

The mean age of the controls (5.8±3.5 years) was lower than in the dengue patients (7.9 ± 3.8 years). The control patients were mostly patients with other common infectious diseases, such as diarrhea, pneumonia, and other viral infections. Their mean age was lower than the dengue because admission to dengue ward was restricted to patients ≥ 2 years old. The mean age of the dengue patients in our study was the same as in previously reports (Halstead, 1997; Nimmannitya, 1997, 2002).

The ratio of admitted cases of DF:DHF was

not different among different nutritional status groups, but malnourished patients were observed to have a greater risk of DSS compared to normal children (odds ratio=1.43, 95%CI=1.11-1.83, p=0.004). This is explained by the smaller volume of extra-cellular fluid and plasma volume in the malnourished patients (Greenbaum, 2003) so that they developed shock more rapidly when a lesser degree of plasma leakage occurred. Other factors may play a role in this and need further study.

The classical clinical pictures of dengue; fever, positive tourniquet test, bleeding manifestations, leukopenia, thrombocytopenia, rising Hct, pleural effusion and ascites (WHO, 1997) were almost the same for different groups of patients, except for liver enlargement, which was less often palpated in obese patients, possibly due to the thick abdominal wall. Rashes, including petechii, maculopapular and convalescence rashes, were more commonly observed in obese patients. This suggests that obese patients have a stronger immune response, since rashes are usually the result of interactions between host cells and infected viruses (Boonpucknavig *et al*, 1979). Some petechii may be the result of increased mechanical trauma to skin in obese patients, who have a larger body surface area.

Obese patients had higher mean ALT (131 U) levels and larger numbers of patients with ALT>40 U (63.7%), which is higher than has previously been reported at QSNICH (53.5%) (Kalayanarooj *et al*, 2003). It needs to be studied further whether this is related to the metabolic, endocrine, or other factors, and whether this resulted in the larger number of encephalopathy cases observed in obese patients. Most of the encephalopathy cases in DHF had a hepatic cause (Nimmannitya *et al*, 1987). Associated infections, pneumonia, diarrhea, UTI, and phlebitis were more commonly observed in obese patients. This may be due to more complications of fluid overload seen among them and the need for more invasive interventions, making them bed-ridden and more prone to nosocomial infections.

During admission, 85.2% of obese DHF patients received IV fluid, which was less than in the normal (88%) and malnourished (89.8%) patients. This is likely due to their natural habit of eating and drinking more. The total amount of IV fluid needed for these obese individuals (86.6 ml/kg IBW) was more than in the normal (70.8 ml/kg IBW) and in the malnourished (63.5 ml/kg IBW) patients. Fluid estimation in obese patients is more difficult and IV fluid based on BW may be too much for obese patients and may relate to the higher complication rate for fluid overload seen in obese patients. The thick thoracic wall may add to the observed signs and symptoms of fluid overload in these obese individuals.

The overall CFR was 0.2%; CFR seemed to be higher in malnourished (0.5%) and obese (0.4%) patients while it was very low, 0.07% in normal nutritional status patients.

In conclusion, malnourished children have a lower risk of dengue infection, but if they contract dengue they are at higher risk of developing DSS. Obese children have a higher risk of contracting dengue with more unusual presentations; encephalopathy, associated infections and complications of fluid overload. Further study of the immune, metabolic, endocrine and other factors in malnourished and obese patients should be done in order to have improved management in these high risk children.

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