Association between Nutritional Status and Severity of Dengue Infection in Children in El Salvador

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Abstract. Clinical observations and some studies suggest that dengue virus infection is more severe among children with better nutritional status. We examined the nutritional status of children in El Salvador and its relationship between this and the severity of dengue infection. Z-scores for weight-for-age, height-for-age, and body mass index (BMI)-for-age of children with dengue fever (66), dengue hemorrhagic fever (62), and healthy controls (74) were compared. There were no differences in weight-for-age or BMI-for-age Z-scores between the three groups. Children with dengue fever had a greater height-for-age than healthy controls but no significant differences in rates of stunting. There was no difference in height between children with dengue fever and dengue hemorrhagic fever. Excess nutrition does not appear to be a risk factor for severe forms of dengue infection in El Salvador, nor does malnutrition appear to be predictive of good outcomes.

INTRODUCTION

Dengue infection continues to be a major public health problem in tropical and subtropical regions of the world. In the Americas, dengue virus re-emerged during the 1980s and since then several outbreaks and epidemics have occurred in the region.^{1,2} In El Salvador, as in other countries where dengue has been an endemic disease for the last three decades, the epidemics of 2000 and 2002 affected mainly the pediatric population.^{3,4} Children, who have an increased risk of the most severe forms of dengue, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), also experience the greatest morbidity and mortality.

Informal observations have suggested that DHF and DSS are infrequent in malnourished children. Indeed, Pichainarong stated that “nearly universal anecdotal clinical observations show that DHF/DSS is rarely seen in children with protein energy malnutrition.”⁵ A robust inflammatory response appears necessary for the severe forms of DHF and DSS.^{6–8} It has been proposed that even mild degrees of malnutrition can suppress the cell-mediated immune responses associated with severe forms of dengue infection, providing biological plausibility for this hypothesis, but no systematic studies have addressed this hypothesis.^{6,7,9}

Eleven studies have examined the relationship between the severity of dengue disease and nutritional status of children, with inconclusive results.^{5,9–18} Some groups report that patients with DHF were less likely to be malnourished than children with less severe forms of disease or healthy controls,^{9,17,13} or that over-nutrition is a risk factor for progression to DHF.⁵ In contrast, Kalayanarooj reported in a review of over 4,000 cases that shock was more common in malnourished children with dengue infection.¹⁵

The majority of studies linking nutritional status with the likelihood or severity of dengue infection were conducted in Asia, and very little is known about the relationship between nutrition and severity of dengue infection in the Americas. One study of 166 Cuban children, however, found no association between nutritional status and complications of dengue.¹¹

We compared the nutritional status of pediatric patients with DHF with those with dengue fever (DF) and with healthy children in El Salvador to further our understanding of how nutrition modulates dengue infection.

MATERIAL AND METHODS

Study population and setting. Hospital Nacional de Niños Benjamín Bloom (HNNBB) in San Salvador, El Salvador, is the sole tertiary referral care center for the country's approximately 2.5 million children. From May to October 2004, children hospitalized with DHF and DF at HNNBB were prospectively identified from the Infectious Diseases Ward, the Intensive Care Unit, and the Dengue Service Area. Serotype 2 and 4 viruses circulated in El Salvador during this period. Healthy controls (HC) matched for neighborhoods of residence were recruited from schools attended by cases. A list of eligible participants, based on the age and gender of the DHF cases, was generated at each school. Consent was sought from parents or guardians of these children and participants were randomly selected from children whose guardians consented to their inclusion in the study.

Children between 5 and 12 years of age were included in the study. This age range was chosen to correspond to that of healthy classmate controls. The DHF and DF were defined according to World Health Organization (WHO) criteria and all infections were confirmed by the presence of anti-dengue immunoglobulin M (IgM) antibody in serum obtained after the fifth day of febrile illness.¹⁹ Specific IgM was measured by antibody-capture enzyme-linked immunosorbent assay (MAC ELISA) using a mixture of viral antigens. Assays were run at Unidad de Laboratorio Central “Dr. Max Bloch,” the Pan-American Health Organization national dengue reference laboratory, using a Centers for Disease Control (CDC)/WHO standardized protocol.²⁰ The MAC-ELISA has a sensitivity and specificity of approximately 90% and 98% when used 5 or more days after onset of fever.²¹ Healthy controls had no symptoms suggestive of an infectious illness during the 7 days preceding study enrollment and no history of an illness consistent with dengue in the previous 5 months. Patients with known immunodeficiency were excluded.

Anthropometric measures. The study team measured the participants' weight and height using a standardized technique. Anthropometric measurements of patients with dengue

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infection were obtained after their initial fluid resuscitation to minimize the effects of dehydration on recorded body weights. Weight in kilograms and height in centimeters were determined for all children using Detecto® (Webb City, MO) scales with a stadiometer. Scales were calibrated weekly. The same scales were used for cases and controls and re-calibrated after movement to each school. Body mass index (BMI) was calculated using the previous measures. Z-scores for three anthropometric indicators, weight-for-age (WAZ), height-for-age (HAZ), and BMI-for-age (BAZ) were derived using the WHO 2007 Global Database on Child Growth and Malnutrition for 5–19 years of age (HAZ, BAZ) and < 10 years of age (WAZ).^{22–24} Moderate-to-severe under-nutrition was defined as a WAZ index below –2.00 and/or a BAZ index below –2.00. Moderate-to-severe growth failure (stunting) was defined as a HAZ index below –2.00. Overweight was defined as a WAZ above +2.00 and/or a BAZ index above +2.00.

Socioeconomic status. The socioeconomic status (SES) of participating children was assessed using the modified Graffar scale.²⁵ Information on housing, education, occupation, and income was collected and each variable scored on a 5-grade scale. Aggregate scores were classified into five social class categories ranging from very high (4–6 points) to very low (17–20 points).

Ethics. The study was approved by the Institutional Review Board of St. Jude Children's Research Hospital and by the Biomedical Ethics Committee of HNNBB. Written informed consent was obtained from parents or guardians of all participants.

Statistical analysis. Data for weight, height, and BMI were log transformed. Two-sample *t* tests or analysis of variance (ANOVA), as appropriate, were used to analyze differences in continuous data and Fisher's exact test was used to compare categorical variables. Analysis of variance was used to compare differences between all groups. The WHO Child Growth Standards SPlus igrowup package was used to calculate Z-scores for anthropometric indicators.²⁶ Statistical analysis was performed with SAS software (version 9.1, SAS Institute, Cary, NC). A *P* value of < 0.05 was considered to be significant.

RESULTS

Seventy-seven children with DHF, 76 with DF, and 81 healthy classmate controls were enrolled in the study. A total of 15 children with DHF, 10 with DF, and 7 controls were excluded from the analysis because, in retrospect, they failed to meet inclusion criteria; therefore, 66 children with DHF,

62 with DF, and 74 healthy classmate controls were included in the final analysis.

Demographic characteristics are shown in Table 1. The mean age and gender distribution were similar between the DHF, DF, and control groups but there were significant differences in the SES between groups. The mean Graffar score of subjects with dengue infection was lower than that of healthy controls—that is, children with infection had a higher SES score (DI:12 points versus HC:15 points, *P* = < 0.0001). A larger proportion of children with DHF and DF belonged to the middle or upper class than did controls, but there was no statistical difference in the SES of cases with DHF versus DF.

Anthropometric measures and Z-scores are summarized in Table 2. The mean weight, height, and BMI of children with dengue infection were not statistically different from those of controls, although children with dengue infection were heavier than their healthy classmates. Mean WAZ and BAZ indices did not differ between groups. The mean HAZ index of children with dengue infection, however, was higher than that of healthy controls, driven by a difference between the DF and control groups. In an exploratory sub-analysis of children with DHF, those with grade I and II infection had a slightly greater HAZ than children with DSS (DHF grade III and IV), but the difference was not statistically significant. There were no significant differences in the proportions of children in each group who were underweight, overweight, or stunted (Table 3).

DISCUSSION

The baseline characteristics of children with dengue infection and controls in this study were very similar except that households of children with dengue infection had lower Graffar scores (a higher SES) and the proportion of households reporting a middle-to-high SES was also higher than that of households of healthy controls. The SES of children with DF and DHF was comparable. A similar discrepancy in socioeconomic class has been noted in previous studies.^{25–30} Authors of these reports have suggested that the higher SES of hospitalized children with dengue infection reflects their improved access to healthcare, rather than a risk factor for infection. It is possible that poorer households were less likely to have access to running water and be more likely to store rainwater in vessels for future use. Conversely, fountains, flowerpots, vases, and pools—all symbols of wealth—may serve as breeding sites for mosquito vectors.

Medical personnel who treat dengue infection in endemic countries commonly assert that severe forms of the disease occur disproportionately in children that are well nourished.⁵

TABLE 1
Demographic characteristics*

	All dengue infection	DHF <i>N</i> = 62	DF <i>N</i> = 66	HC <i>N</i> = 74
Gender (number, %)				
Male	55 (43.0)	26 (41.9)	29 (43.9)	29 (39.1)
Female	73 (57.0)	36 (58.0)	37 (56.0)	45 (60.8)
Age in months (median, IQR)	101.1 (40.0)	104.5 (43.0)	100.0 (29.0)	100.4 (25.0)
Socioeconomic score-Graffar scale† (mean, SD)	13.0 (2.8)	13.2 (2.6)	12.7 (2.9)	15.5 (2.3)
Socioeconomic status (SES)†				
Middle to high (number, %)	56 (45.2)	27 (44.3)‡	29 (46.0)§	8 (11.27)‡§
Low-very low (number, %)	68 (54.8)	34 (55.7)†	34 (54.0)§	63 (88.73)‡§

*DF = dengue fever; DHF = dengue hemorrhagic fever; HC = healthy control; IQR = interquartile range.

†For SES, DHF *n* = 61, DF *n* = 63, HC *n* = 71.

SES category: ‡ DHF vs. HC, Fisher's exact test *P* < 0.001; § DF vs. HC, Fisher's exact test *P* < .0001.

TABLE 2
Anthropometric measurements*

Findings	All dengue infection	DHF N = 62	DF N = 66	HC N = 74
Weight in kg (median, IQR)	26.7 (22.0, 34.5)	27.0 (21.0, 35.0)	26.25 (22.7, 34.4)	26.1 (22.4, 28.4)
Height in cm (median, IQR)	126.0 (118.0, 135.0)	125.0 (116.0, 135.0)	127.5 (119.0, 135.0)	124.5 (119.0, 129.0)
BMI (median, IQR)	16.7 (15.0, 19.9)	17.2 (14.8, 20.3)	16.5 (15.0, 19.6)	15.9 (14.9, 18.2)
Z-score height-for-age (HAZ) (mean $\pm$ SD)	-0.41 ($\pm$ 1.1)	-0.56 ($\pm$ 1.2)	-0.28 ($\pm$ 1.1)*	-0.75 ($\pm$ 0.9)†
Z-score weight-for-age (WAZ) (mean $\pm$ SD)	0.16 ($\pm$ 1.3)	0.16 ($\pm$ 1.4)	0.18 ($\pm$ 1.2)	-0.003 ($\pm$ 1.3)
Z-score BMI-for-age (BAZ) (mean $\pm$ SD)	0.48 ($\pm$ 1.5)	0.49 ($\pm$ 1.6)	0.46 ($\pm$ 1.3)	0.39 ($\pm$ 1.5)

* BMI = body mass index; DF = dengue fever; DHF = dengue hemorrhagic fever; HC = healthy controls; IQR = interquartile range.

† HAZ DF vs. HC $P = 0.0081$.

In this study, we found that children with DF were taller and had higher HAZ scores than healthy controls. Their HA was not significantly different, however, from that of children with DHF and there were no significant differences in rates of stunting between cases and healthy controls. There were also no differences in the median BMI between study groups, suggesting an inconsistent effect of height on the outcome of infection.

Two previous studies have correlated height with dengue disease severity, and these, in fact, also suggested that children with dengue infection were more likely to be of normal height than the general population (Table 4). In a study of 100 hospitalized Thai children, those children < 5 years of age with DHF were less likely to have a low HA than healthy controls, but HA did not vary with the severity of infection.⁹ Nguyen studied 245 Vietnamese infants with DHF and found that these cases were more likely to have a normal HA than healthy children attending immunization clinics but, again, HA was not increased among infants with shock compared to those with non-shock DHF.¹⁷ Although there is a consistent association between height and dengue severity, the small number of reports, absence of evidence supporting a dosage effect, and lack of intuitive biological plausibility suggests that the difference in stature between the DF and HC groups requires further evaluation before definitive conclusions about risk can be drawn.

With respect to body weight, our findings are consistent with most previous reports, which have not found normal or excess nutrition to be a risk factor for dengue infection or severe infection or that malnutrition is less common in children with severe dengue infection. Three studies have suggested that children with dengue infection tend to be well nourished. Thisyakorn compared 100 Thai children < 5 years of age hospitalized with DHF with 125 similarly aged

children who were hospitalized with other infectious diseases and with 184 healthy controls. The WA and upper arm circumference (UAC) of children with DHF did not differ from that of control children, but those with dengue infection were less likely to have a low WA (11% versus 71.2%) or UAC (0% versus 69.6%) than children hospitalized with other infections.⁹ Kalayanaroop compared the nutritional status of 4,532 Thai children hospitalized with dengue infection to 734 children hospitalized for other indications (mostly diarrhea and pneumonia) and found that the latter were more likely to be malnourished (19.6% versus 9.2%) and less likely to be obese (12.5% versus 24.2%).¹⁵ Nguyen found that Vietnamese infants hospitalized with DHF were less likely to have low WA (93.1% versus 88.3%), but also more likely to have low WH (14.2 versus 1.1%) than healthy children attending immunization clinics. It is debatable whether children hospitalized for other infections are an appropriate comparator for these studies as malnutrition is a frequent predisposing factor for these conditions.^{31,32} The comparability of case and healthy control groups in each of these studies is also uncertain since baseline demographic data were either not reported or limited. In any case, it is clear from these studies that malnutrition is not especially uncommon in children with DF and DHF, with rates in these studies ranging from 6.8% to 52.9%.

Seven previous studies have examined the association between nutritional status and severity of dengue infection by comparing children with DF to those with DHF, either as a primary objective or subgroup analysis.^{5,11,12,14-17} Pichainarong found that children with DHF were more likely to be obese than those with DF, but that there was no difference in rates of malnutrition.⁵ Unfortunately, data in this study were only presented as odds ratios, thus the magnitude of the difference between the two groups and its clinical significance cannot be

TABLE 3
Nutritional categories*

	All dengue infection	DHF N = 62	DF N = 66	HC N = 74
Nutritional status, (number, %) assessed by weight-for-age†				
Normal	86 (89.6)	38 (86.3)	48 (92.3)	55 (90.2)
Malnourished (WAZ < -2)	7 (7.3)	3 (6.8)	0	1 (1.6)
Overweight (WAZ > +2)	3 (3.1)	3 (6.8)	4 (7.7)	5 (8.2)
Nutritional status, (number, %) assessed by height-for-age				
Normal	121 (94.5)	56 (90.3)	65 (98.5)	70 (94.6)
Stunting (HAZ < -2)	7 (5.5)	6 (9.7)	1 (1.5)	4 (5.4)
Nutritional status (number, %) assessed by BMI-for-age				
Normal	101 (78.9)	45 (72.6)	56 (84.9)	65 (87.8)
Malnourished (BAZ < -2)	6 (4.7)	5 (8.1)	1 (1.5)	1 (1.4)
Overweight (BAZ > +2)	21 (16.4)	12 (19.4)	9 (13.6)	8 (10.8)

* BAZ = body mass index-for-age Z-score; BMI = body mass index; DF = dengue fever; DHF = dengue hemorrhagic fever; HAZ = height-for-age Z-score; HC = healthy controls; IQR = interquartile range; WAZ = weight-for-age Z-score.

† Assessed only in children under 120 months of age, DHF n = 44, DF n = 52, HC = 71.

TABLE 4
Studies assessing the relationship between nutritional status and severity of dengue infection*

Study, location	Nutritional variables/standards	Study design	Conclusion
Anto, Indonesia 1983	Harvard standards for protein-energy malnutrition	Retrospective DHF, DSS Age: 5–10 years	Malnourished: DSS 27% vs. DHF 30.2%, $P = 0.86$
Arguelles, Cuba 1987	WH index	Prospective DF, DHF, DSS Age: 2–5.9 years	Overweight: DF 76.0% vs. DHF/DSS 67.5%, $P = 0.42$
Thisyakorn, Thailand 1993	WH, WA, left arm circumference/ Gomez Nutritional Classification	Prospective DHF, other infectious diseases, HC Age: 0.25–15 years	Malnourished: DHF 13% vs. other infectious disease 71%, $P < 0.001$; DHF 13% vs. HC 33%, $P < 0.001$
Kabra, India 1993	WA/NCHS/CDC 1977 Growth Charts	Retrospective DF, DHF, DSS Age: 4 months–13 years	Malnourished: DF 55% vs. DHF/DSS 39%, $P = 0.05$
Chuansumrit, Thailand 2000	WA/Thailand National Growth References	Retrospective DHF, DSS Age: 9 months–16 years	WA > 95th percentile: DHF 13.8% vs. DSS 27.3%, $P = 0.06$
Nguyen, Vietnam 2005	WAZ, HAZ, WHZ < 2.0/ NCHS/WHO 2000 Reference	Prospective DHF, DSS, HC Age: < 12 months	Malnourished (WH): DHF 12.8% vs. HC 1.1%, $P < 0.001$, DHF 12.8% vs. DSS 19.1%, $P = 0.3$
Carlos, Philippines 2005	CDC 2000 Growth Charts	Prospective DF, DHF Age: 2–17 years	Malnourished: DF 7.0% vs. DHF 8.2%, $P = 0.06$
Kalayanarooj, Thailand 2005	WA/Thai Department of Health growth curves (2000)	Retrospective DF, DHF, other patients Age: 1–12 years	Malnourished: DF 8.8% vs. DHF 11.1%, $P = 0.43$; DF/DHF 9.2% vs. other patients 19.6%, $P < 0.001$
Malavige, Sri Lanka 2006	BMI/NCHS 2000 Growth Charts	Prospective DF, DHF Age: 1 month–12 years	Malnourished: DF 53.8% vs. DHF 51.9%, $P > 0.05$
Pichainarong, Thailand 2006	WA, WH < 1.5 SD/Thai Department of Health growth curves (2000)	Prospective DHF, DSS Age: 0–14 years	WH > 1.5 SD: DSS OR = 2.77, 95% CI 1.19–6.45
Tantracheewathorn, Thailand 2007	WA percentile/National growth references for Thai children	Retrospective DHF, DSS Age: 5 months–15 years	Malnourished: DHF 33.6% vs. DSS 27.3%, $P = 0.48$
Current study, El Salvador	WAZ, HAZ, BAZ/WHO 2007 Global Database on Child Growth and Malnutrition	Prospective DHF, DF, HC Age: 5–12 years	Malnourished: DHF 8.1% vs. DF 1.5%, $P = 0.1$; DHF 8.1% vs. HC 1.4%, $P = 0.09$

* BMI = body mass index; BAZ = BMI-for-age Z-score; CDC = Center for Disease Control and Prevention; DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; HA = height-for-age; HAZ = height-for-age Z-score; HC = healthy controls; NCHS = National Center for Health Statistics; WA = weight-for-age; WAZ = weight-for-age Z-score; WH = weight-for-height; WHO: World Health Organization; WHZ = weight-for-height Z-score.

appreciated. The remaining six studies failed to show a correlation between the severity of disease and nutritional status.

Ten previous studies have examined the association between nutritional status and severity of dengue infection by comparing children with milder forms of DHF to severe disease, most commonly by contrasting DHF without shock to DSS.^{9–18} Only one of these studies suggested that children with severe DHF were better nourished than those with non-shock forms. Chuansumrit and colleagues¹³ found that children with grade III/IV DHF were more likely to have a WA greater than the 50th percentile than those with grade I/II disease (65.9% versus 42.7%). This difference, however, was due to an increased risk only in the group with a WA between the 51st and 75th percentiles (27.9% versus 12/8%, $P = 0.024$) and not in those with body weights greater than the 75th percentile. The proportion of children with WA greater than the 95th percentile was not significantly different between the two groups (13.8% versus 27.3%, $P = 0.06$) (Chuansumrit A, personal communication). In contrast, Kalayanarooj reported that children with DSS were more likely to be malnourished than those with DHF without shock (10.9% versus 7.9%).¹⁵

Despite the accumulation of considerable data refuting the hypothesis that good nutrition is a risk factor for dengue infection and severe disease, it remains difficult to definitively con-

clude that nutritional status does not influence the course of dengue infection. Methodological differences between studies and shortcomings in their design confound analysis and may have influenced study outcomes. In general, the comparability of study participants has been difficult to assess because few or no baseline characteristics are described or recruitment strategies reported. Some studies, as previously noted, have used control groups that may not be ideal. Most investigators studied children between 0 and 15 years of age, but some restricted study inclusion or analysis to younger or older age groups.

The use of various anthropological measurements and growth standards makes comparison of different studies more difficult. Almost half of the previous studies used only WA to classify nutritional status, even though this is generally regarded as insensitive in older children because it does not account for relative height and body mass. Only one study calculated BMI-for-age, currently recognized as the best single gauge of nutritional status for school-aged children.^{16,24} About half of the previous studies assessed both over-nutrition and malnutrition. Definitions of both malnutrition and over-nutrition that were used, however, are inconsistent.

Growth standards used in previous studies include those developed by individual countries, such as the Harvard and Thailand Department of Health standards and the National

Center for Health Statistics/Centers for Disease Control and Prevention (NCHS/CDC) Growth standards. While the use of a regional growth standard renders a study more applicable to a reference population, results cannot necessarily be extrapolated to other countries or regions. Several international nutritional committees and associations endorsed the WHO Child Growth Standards in 2006, replacing the NCHS/WHO international reference for nutritional status for children aged 60 months and younger.^{33–35} The following year, growth standards for older children were reconstructed to create the WHO Reference 2007 growth curves for children and adolescents 5–19 years of age.²⁴ It may be advantageous for future studies to compare anthropomorphic characteristics to both local standards and to these international references.

Interpreting and extrapolating the results of studies associating nutrition with the incidence or severity of dengue infection may be complicated by failure to account for confounding factors. Infections caused by certain serotypes may be more severe than those caused by other serotypes and the severity of infection has been directly correlated with peak viral load.^{36–39} Secondary infections by viruses of a heterologous serotype are particularly associated with progression to severe disease.^{6,18} Tempero-spatial variations in rates of viral circulation and mosquito densities may influence both the incidence and severity of dengue infections.^{40,41} Finally, age, gender, SES, ethnicity, blood group, and genetic background may modify host responses to dengue infection.^{14,17,26,30,42,43}

In this study, we prospectively compared children with DHF, DF, and HC who resided and attended school in the same neighborhoods. By taking this approach, we hoped to compare groups of similar age, gender, and SES and with similar environmental exposure to circulating viruses. Multiple anthropomorphic measures were obtained and compared to the WHO 2007 Global Database using standardized definitions for malnutrition and over-nutrition.²² We compared not only children with different grades of severity of DHF, but also those with DF and DHF. Our study, however, has limitations. The sample size was small and underpowered to detect small differences between groups, although such disparity may not be of clinical relevance. The study groups were generally similar, but socioeconomic differences between cases and controls were noted. Determining the type of infection (primary versus secondary) and the serotype of infecting viruses was not economically feasible, but would have provided a valuable comparison to previous studies.

Distinguishing patients with dengue infection who will develop more severe forms of disease remains a clinical challenge. Additional larger prospective studies are necessary to better characterize the impact of nutritional status on disease outcomes in Latin America and the rest of the world.

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