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Clinical and Laboratory Factors Associated with Severe Dengue: A Case-Control Study of Hospitalized Children

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ABSTRACT

Background: More than half of the hospitalizations because of dengue in Brazil occurred in children <15 years of age in 2007 and 2008, an unexpected change in the epidemiological pattern. We sought to determine clinical and laboratory parameters associated with severity.
Methods: A case-control study was conducted in three pediatric hospitals in Rio de Janeiro, Brazil; 233 laboratory-confirmed dengue patients were included: 69 cases and 164 controls. Specific clinical and laboratory factors were assessed using univariate and multivariate logistic regression models.
Results: Lethargy [adjusted odds ratio (ORa): 9.15, 95% confidence interval (CI): 3.08–27.12], dyspnea (ORa: 8.24, 95% CI: 3.27–20.72) and abdominal pain (ORa: 6.78, 95% CI: 1.44–31.84) were independently associated with severe dengue in children. Lethargy and dyspnea presented as early as 72 and 48 h, respectively, before shock.
Conclusions: Abdominal pain and lethargy confirmed their role as warning signs, which along with dyspnea might be helpful in identifying cases progressing to severe dengue.

KEYWORDS: case-control studies, dengue, pediatrics, severe dengue, shock

INTRODUCTION

Dengue remains a major public health concern in >100 countries. In the USA, at the end of 2015, 2 430 278 cases of dengue were reported; 12 498 (0.5%) of which were cases of severe dengue. All four of the known serotypes of dengue virus simultaneously circulate in Brazil, which accounts for 85% of the cases in the USA [1, 2].

In Brazil, the common clinical presentation of the disease has been dengue fever in adults. After successive epidemics caused by different serotypes of dengue virus in Brazil, a sudden change in the age

distribution pattern was observed in 2007 and 2008, when 53% of hospitalizations for dengue occurred in children [3–5]. This epidemiological picture of severity in children did not occur in the following years. Nonetheless, the risk of future epidemics with a higher number of severe cases, especially in children, remains a serious concern [6–8].

In this study, we sought to determine clinical and laboratory parameters that may help to identify cases of dengue in children that are more likely to progress to shock, the hallmark of severe dengue, and the time between the appearance of such factors and the subsequent development of shock.

MATERIALS AND METHODS

Ethical approval

The study protocol was approved by the ethics committee of the Escola Nacional de Saúde Pública and the Fundação Oswaldo Cruz (Research Protocol 174/10; 0161.0.031.031-10). All data were anonymized before analysis.

Patients and study design

This is a hospital-based, retrospective case-control study involving cases of severe dengue in children. The eligible subjects were extracted from a list of patients admitted with suspected dengue in three pediatric hospitals in Rio de Janeiro—Instituto Fernandes Figueira, Instituto de Puericultura e Pediatria Martagão Gesteira and Hospital Municipal Jesus—from 1 November 2007 to 30 June 2008. Children were admitted to hospitals according to Brazilian Ministry of Health criteria: (i) presence of warning signs—abdominal pain, persistent vomiting, clinical fluid accumulation, liver enlargement >2 cm, mucosal bleeding, lethargy or restlessness, progressive increase in hematocrit and lipothymia; (2) refusal of fluids and food intake; (3) respiratory impairment; (4) presence of comorbidities; and (5) possible obstacles to further clinical evaluation. Cases were defined as those involving children aged <18 years who were admitted to any of the referral hospitals above with laboratory-confirmed dengue and who developed severe dengue during the course of the disease as follows: shock ($n = 69$), defined as the presence of at least two clinical signs of hypoperfusion (e.g. slow capillary filling >2 s; cold, clammy skin; or rapid and weak pulse) associated with narrow pulse pressure ($\leq$20 mmHg) or age-specific hypotension [decrease in blood arterial systolic pressure to a level <5th percentile for age, calculated as age (years) $\times$ 2 + 70]; severe bleeding ($n = 24$); organ impairment ($n = 6$); and death ($n = 8$) [9, 10]. Our definition of severity was in accordance with the WHO diagnosis criteria defined in 2009 [8, 11]. The control group consisted of children who were admitted to the designated hospitals during the study period but did not develop severe dengue. They were enrolled according to the eligibility criteria on the same day or within 3 days of case allocation. Three controls were selected for each case. The study included 233 children: 69 cases and 164 controls. This sample conferred an 80% power to detect an odds ratio (OR) > 2 with a 5% level of significance and proportion of exposure among controls of 40% [12, 13]. A data collection form especially designed for this study was used by the research team to extract demographic, clinical and laboratory data from the patients' hospital records referring to the current hospitalization and to the first consultation and follow-up in other health-care facilities. Charts were reviewed between August 2010 and March 2011.

Dengue diagnosis was confirmed by an anti-dengue immunoglobulin M (IgM) assay. Tests for detection of anti-dengue IgM were conducted using an antibody-capture enzyme-linked immunosorbent assay (PanBio, Brisbane, Australia). All children included had at least one positive IgM assay.

Only clinical symptoms and signs that were present within 7 days of fever onset and laboratory results that were available in this period were included in the analysis.

Statistical analysis

Statistical analysis was performed using Stata software 10.0 (Stata Corp., College Station, TX). OR and adjusted odds ratio (ORa) and their 95% confidence intervals (95% CIs) were calculated. Associations between the response variable (shock) and the group of potential risk factors were evaluated by univariate logistic regression analysis. Variables that showed a significant statistical association with the outcome of interest ($p < 0.20$) in the exploratory analysis were selected for covariate inclusion in a multiple

Table 1. Distribution of cases and controls according to demographic variables and care in health services, with respective ORs, 95% CIs and significance level (p)

Variables		Cases ($n = 69$) *n* (%)	Controls ($n = 164$) *n* (%)	OR	95% CI	*p*-value
Age (years)	≤5	10 (14.5)	16 (9.9)	1.0		
	>5 ≤10	48 (69.6)	91 (56.2)	1.18	(0.49–2.81)	0.700
	>10 <18	11 (15.9)	55 (34.0)	3.12	(1.12–8.67)	0.029
Sex	Male	33 (47.8)	82 (50.0)	0.91	(0.52–1.60)	0.762
	Female	36 (52.2)	82 (50.0)	1.0		
Race	White	23 (54.8)	53 (50.5)	1.18	(0.57–2.43)	0.639
	Nonwhite	19 (45.2)	52 (49.5)	1.0		
Prior care in a health facility	Yes	49 (71.0)	97 (59.2)	1.69	(0.92–3.10)	0.089
	No	20 (29.9)	67 (40.8)	1.0		

logistic regression model. In the 'forward stepwise method', a value of $p < 0.05$ was considered to be the criterion for retaining variables in the model [12, 13].

RESULTS

Characteristics of the study population

The median age of children admitted to the study hospitals was 9.0 years (5th–95th percentile: 0.8–14 years); 115 were male (49.4) and 118 (50.6) were female. Eight severe dengue children died, and all of them developed shock; visceral involvement occurred as follows: respiratory failure (6), renal failure (5), disseminated intravascular coagulation (4), cardiac failure (4) and hepatic failure (2). Most patients were admitted between the third and seventh day of disease. Blood was collected for IgM serology between the 6th and 14th day for most children.

Association of specific demographic, clinical and laboratory findings with severe dengue

The >10-year-old age group was associated with severe disease. Sex, race and prior care in a healthcare facility were not significantly associated with severity (Table 1). Lethargy, abdominal pain, restlessness, severe bleeding, persistent vomiting and lipothymia, already known warning signs, were all significantly associated with severe dengue in the univariate analysis, as well as decreased urine output. Signs of plasma leakage, such as ascites and edema, were also associated with severity (Table 2).

Lethargy (OR: 12.94, 95% CI: 5.78–28.93; ORa: 9.15, 95% CI: 3.08–27.12), dyspnea (OR: 9.94, 95% CI: 5.01–19.74; ORa: 8.24, 95% CI: 3.27–20.72) and abdominal pain (OR: 9.42, 95% CI: 2.20–40.34 ORa: 6.78, 95% CI: 1.44–31.84) were independently associated with severe dengue in children (Table 3).

Hepatomegaly, a warning sign defined by WHO (2009) did not show a significant association with severity. Other signs and symptoms that occurred in the course of the disease, such as itching, diarrhea, nausea and cough, were not significantly associated with severe disease either (Table 2).

The time range observed between the occurrence of some clinical signs and the onset of shock, the hallmark of severe dengue, may be helpful to indicate the evolution to severity. Abdominal pain and persistent vomiting occurred as early as 120 h before development of shock, decreased urine output and mucosal bleeding occurred up to 96 h before shock and lethargy 72 h before. Dyspnea was noted up to 48 h before shock (Fig. 1).

Leukopenia conferred a significant protective effect, while leukocytosis was associated with severe disease in crude analysis. Laboratory markers commonly used, e.g. hemoconcentration, hemoglobin level and thrombocytopenia, were not associated with severe dengue (Table 2).

Table 2. Distribution of cases and controls according to the clinical and laboratory parameters with respective ORs, 95% CIs and significance level (p)

Variables	Cases *n* (%)	Controls *n* (%)	OR	95% CI	*p*-value
Urine output					<0.001
[a]Decreased	29 (49.2)	8 (5.0)	17.15	(7.14–41.20)	
Not decreased	30 (50.8)	142 (95.0)	1.0		
Lethargy					<0.001
Yes	30 (46.2)	10 (6.2)	12.94	(5.78–28.93)	
No	35 (53.8)	151 ((3.8)	1.0		
Dyspnea					<0.001
Yes	37 (56.9)	19 (11.7)	9.94	(5.01–19.74)	
No	28 (43.1)	143 (88.3)	1.0		
Abdominal pain					0.002
Yes	62 (96.9)	125 (76.7)	9.42	(2.20–40.43)	
No	2 (3.1)	38 (23.3)	1.0		
Edema					<0.001
Yes	34 (66.7)	28 (24.8)	6.07	(2.94–12.49)	
No	17 (33.3)	85 (75.2)	1.0		
Restlessness					<0.001
Yes	16 (25.8)	9 (5.6)	5.87	(2.43–14.17)	
No	46 (74.2)	152 (94.4)	1.0		
Severe bleeding					<0.001
Yes	24 (38.1)	21 (13.1)	4.07	(2.05–8.07)	
No	39 (61.9)	139 (86.9)	1.0		
Abdominal tenderness					0.003
Painful palpation	58 (89.2)	111 (69.4)	3.65	(1.55–8.58)	
Not painful palpation	7 (10.8)	49 (30.6)	1.0		
Ascites					0.001
Yes	38 (71.7)	38 (41.3)	3.60	(1.73–7.45)	
No	15 (28.3)	54 (58.7)	1.0		
Lipothymia					0.007
Yes	18 (35.3)	20 (16.4)	2.78	(1.31–5.87)	
No	33 (64.7)	102 (83.6)	1.0		
Persistent vomiting					0.030
>5 times in 6 h or > 3 times in 1 h	15 (27.3)	21 (14.0)	2.30	(1.08–4.88)	
<5 times in 6 h or < 3 times in 1 h	40 (72.7)	129 (86.0)	1.0		
Petechiae					0.147
Yes	40 (85.1)	91 (74.6)	1.94	(0.79–4.79)	
No	7 (14.9)	31 (25.4)	1.0		
Exanthema					0.192
Yes	24 (72.7)	52 (59.8)	1.79	(0.74–4.31)	
No	9 (27.3)	35 (40.2)	1.0		
Hemoconcentration					0.076

(Continued)

Table 2. (Continued)

Variables	Cases *n* (%)	Controls *n* (%)	OR	95% CI	*p*-value
Hematocrit change of 20% (increased or decreased from the baseline value during the convalescent period)	42 (70.0)	85 (56.7)	1.78	(0.94–3.38)	
No hematocrit change of 20% (increased or decreased from the baseline value during the convalescent period)	18 (30.0)	65 (43.3)	1.0		
Pleural effusion					0.082
Yes	42 (67.7)	64 (54.2)	1.77	(0.93–3.37)	
No	20 (32.3)	54 (45.8)	1.0		
Mild bleeding (from nose or gums)					0.118
Yes	36 (61.0)	75 (49.0)	1.62	(0.88–3.0)	
No	23 (38.9)	78 (51.0)	1.0		
Hepatomegaly					0.166
Liver enlargement >2 cm	27 (55.1)	52 (43.3)	1.60	(0.82–3.13)	
Not enlarged liver	22 (44.9)	68 (56.7)	1.0		
Cough/coryza					0.716
Yes	7 (35.0)	19 (30.6)	1.21	(0.41–3.53)	
No	13 (65.0)	43 (69.4)	1.0		
Itching					0.906
Yes	13 (54.2)	40 (55.6)	0.94	(0.37–2.39)	
No	11 (45.7)	32 (44.4)	1.0		
Diarrhea					0.865
≥3 evacuations of softened or liquid consistent)/24 h	20 (41.7)	41 (43.2)	0.94	(0.46–1.90)	
<3 evacuations of softened or liquid consistent)/24 h	28 (58.3)	54 (56.8)	1.0		
Hemoglobin concentration					0.385
[b]High	22 (33.8)	59 (40.1)	0.76	(0.41–1.40)	
Normal	43 (66.2)	88 (59.9)	1.0		
Nausea					0.626
Yes	6 (33.3)	25 (39.7)	0.76	(0.25–2.28)	
No	12 (66.7)	38 (60.3)	1.0		
Leukocytosis					0.004
White blood cell count >14 000/mm^3	10 (14.7)	4 (2.9)	5.73	(1.72–19.03)	

(Continued)

Table 2. (Continued)

Variables	Cases *n* (%)	Controls *n* (%)	OR	95% CI	*p*-value
White blood cell count >4000/mm^3 ≤14 000/mm^3	58 (85.3)	133 (97.1)	1.0	(0.17–0.61)	
Leukopenia					0.001
White blood cell count <4000/mm3	18 (26.5)	73 (52.5)	0.32		
White blood cell count ≥4000/mm3 <14 000/mm3	50 (73.5)	66 (47.5)	1.0		
Thrombocytopenia					0.111
Platelet count <150 000/mm^3	64 (98.5)	144 (92.3)	5.33	(0.67–41.89)	
Platelet count ≥150 000/mm^3	1 (1.5)	12 (7.7)	1.0		

Note: The criterion for covariate inclusion in the multivariate logistic regression model was $p < 0.20$. Data are presented in numbers (percentage) for noncontinuous data.

[a]No passage of urine for >6 h.

[b]>11.5 g/dl (infants); >12.7 g/dl children aged 2–10 years; >13.2 g/dl children aged >10 years.

Table 3. Estimated odds ratio for multivariate logistic regression analysis of the factors associated with severe dengue in children

Variables	ORa	95% CI	*p*-value
Lethargy	9.15	(3.08–27.12)	<0.001
Dyspnea	8.24	(3.27–20.72)	<0.001
Abdominal pain	6.78	(1.44–31.84)	0.015

Note: No collinearity was observed among variables (variance inflation factor >3; tolerance >0.1).

DISCUSSION

Early recognition of the clinical and laboratory factors associated with severe dengue in children is essential to support clinical management of potentially severe cases and to reduce morbidity and mortality. In this study, lethargy, dyspnea and abdominal pain were particularly helpful in identifying cases of dengue that progressed to severe disease. We observed a significant association of increased respiratory effort to shock, which could be a result of fluid overload because of pulmonary congestion from capillary leakage. We did not assess whether intravenous fluid therapy and management of these children were adequate before hospitalization. Nevertheless, there was no significant evidence of protection from shock when patients had previously received care in a health-care facility, thus suggesting that fluid therapy was not managed in a timely manner. Lethargy was an independent clinical sign associated with severity in dengue as observed in other studies in children and in a systematic review of clinical and laboratory factors associated with severity [14–20]. Our results confirm it as a relevant warning sign as described in the revised classification of dengue (WHO 2009) and indicate its onset as early as 72 h before shock. Abdominal pain was independently associated with severe dengue and was observed at an early stage before the onset of shock. This observation reinforces the conclusion that abdominal pain is a symptom that could be monitored at any level of the health-care system, as early as 4 days before shock. However, as a frequent complaint in children, insufficient information about its intensity might lead to a potential classification bias [18–22]. Decreased urine output and lipothymia were early signs and symptoms of shock concentrated on the 48-period preceding shock. Persistent vomiting can also be considered a valuable clinical sign for monitoring children with dengue, as it was observed

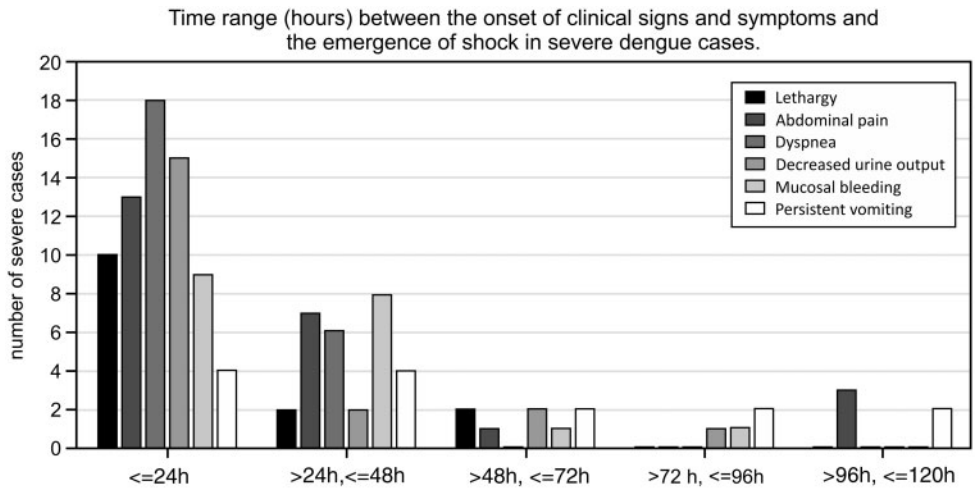

Fig. 1. Time range (hours) between the onset of clinical signs and symptoms and the emergence of shock in severe dengue cases.

from 120 to 24 h before shock in >70% of cases recorded in medical charts. Severe bleeding, a well-known warning sign of severe dengue [11], did not remain associated with shock after adjustment. Mild bleeding was not significantly associated with shock in this study, consistent with previous studies [20–24].

Ascites and edema were significantly associated with shock in the univariate analysis, whereas pleural effusion was not. These are signs of clinical fluid accumulation and indicators of illness progression to severe hemodynamic instability. Ascites and edema were observed in later stages 24–48 h before shock. The lack of an association of either hemoconcentration or thrombocytopenia with shock could be related to the presence of these signs in both cases and controls, as they were criteria for hospitalization. Leukopenia, commonly seen in cases of non-severe dengue, was not associated with shock.

Acknowledgment of these warning signs by health professionals and monitoring of these signs at all levels of care may help prevent death and optimize the limited resources for those children who do need expert care [20, 25].

During the 2007–08 dengue epidemic in Brazil, 36% of deaths occurred in children [5], which is an unusual finding. This epidemic entailed a dengue virus type 2 (DENV-2) outbreak, and such a degree of pediatric mortality has not been seen in subsequent years. This excessive mortality could be because of waning of maternal antibodies or lack of prior exposure to this strain of virus in early infancy, which might have accounted for excessive mortality at a later age. The association between older age in children and the risk of shock may be related to the occurrence of subsequent infections with different serotypes in these children— dengue virus type 3 (DENV-3) epidemic in Rio de Janeiro in 2002, followed by DENV-2 in 2007–08. The >10-year-old age group was significantly associated with shock compared with ≤5 (reference category) and >5 ≤10 year-old-age group (OR: 3.125, CI: 1.12–8.67), and being in this age group was a potential risk factor for severe clinical presentations possibly associated with secondary dengue infections, as observed in other hyperendemic areas such as Asia [26–28]. The sequence of infection may be determinant for disease severity [29]. Whether the severity of dengue in these cases was related to the secondary DENV-2 infections or to the pathogenicity of DENV-2 itself or both, is not known [29, 30].

One limitation of the study was its retrospective design, which could lead to a possible classification bias because of missing data, especially for the less-severe cases. However, the study followed a standardized clinical and data management protocol that aimed to avoid inaccurate data collection.

This study was a unique opportunity to study a rare end point in an unprecedented scenario, the 2008 epidemics in Rio de Janeiro, with a high proportion of hospitalized dengue children. Furthermore, the clinical parameters assessed could only be studied in a hospital environment under close monitoring to support clinical decision.

Health professionals in primary care settings and throughout the health-care system should be alert to the presence of these signs to identify children at greatest risk for severe dengue and to avoid late referral of these children to hospitals. Abdominal pain, a sign that may be observed at early stages of the disease, although nonspecific, should alert physicians to a possible diagnostic of dengue and the need for monitoring. Dyspnea and lethargy, which developed as early as 48 h before shock, were particularly helpful in identifying cases in which dengue progressed to severity. Monitoring these signs may help physicians to promptly diagnose and recognize patients who need immediate intensive care interventions.

Our findings from the first and only pediatric epidemic, which has taken place in Rio de Janeiro, contribute to the understanding of the natural history of severe dengue in children, and should be validated by larger, prospective, multicenter studies.

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