JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

The clinical characteristics and outcome of children hospitalized with dengue in Barbados, an English Caribbean country

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Abstract

Introduction: Although dengue is endemic in all English-speaking Caribbean countries, there are no published studies on the clinical presentations and outcomes of children hospitalized with dengue from this region. This study aims to assess the clinical charcteristics and the outcome in children hospitalized with dengue.

Methods: This was a population-based prospective study of all the children hospitalized with confirmed dengue in 2009 in Barbados. All children suspected to have dengue were routinely screened for dengue infection and underwent routine blood tests. Relevant data was extracted from their case files at the time of their discharge from the hospital.

Results: Of the 199 children who were hospitalized with suspected dengue, 115 (58%) were confirmed. The overall incidence rate of dengue among children that required hospitalization was 2.1/1,000 children. Besides the typical clinical features of dengue, 64 children hospitalized with confirmed dengue also presented with gastrointestinal manifestations (56%), 39 with respiratory manifestations (51%), 11 with hepatic manifestations (10%), 8 with neurologic manifestations (7%), and 7 with cardiovascular manifestations (6%). Twenty (17.4%) children hospitalized with confirmed dengue met the criteria for the diagnosis of severe dengue. The other 82.6% had uncomplicated or non-severe (53.9% had dengue and 28.7% had dengue with warning signs) forms of dengue. The case fatality rate in this series was 1.7%.

Conclusions: Less than a third of all the children with confirmed dengue required hospitalization. Atypical clinical manifestations were common, and only a minority of these children had severe dengue. Overall, the case fatality rate for dengue in this select population of children hospitalized with dengue was low.

Key words: Dengue; clinical features; hospitalization; children; Caribbean.

J Infect Dev Ctries 2015; 9(4):394-401. doi:10.3855/jidc.5566

(Received 13 July 2014 – Accepted 14 December 2014)

Introduction

Dengue, a viral illness caused by four distinct but related serotypes of dengue virus (DEN 1, DEN 2, DEN 3, and DEN 4), is endemic in the Caribbean [1-5]. There is a consensus from studies in Southeast Asian and Latin American countries that children are particularly at risk of developing severe diseases and carry a higher mortality rate [6-9]. Several community-based epidemiological studies, mostly from Southeast Asia and some from the Americas, have alluded to changing demographics and clinical patterns of the disease, including the modal age of infection [5,6,10-14]. However, there are fewer population-based prospective studies on hospitalizations from dengue among children from both Southeast Asian and Latin American countries [9,15,16]. There are no published studies on the clinical presentation and outcome of children hospitalized with dengue from the English-speaking Caribbean.

Barbados, one of the English-speaking Caribbean countries, has a total population of 283,000 (2012) including 58,500 (21%) children under the age of 16 [17]. Its gross national income per capita (PPP international $) is US$ 25,670 (2012), and its total expenditure on health as a percentage of GDP stands at 6.3% (2012). The under-five mortality rate (2012) was 18/1,000 live births, and the life expectancy at birth for males and females was 75 and 81 years, respectively [17]. Barbados has a well-organized state-run healthcare infrastructure with free healthcare for its citizens at the point of delivery. There are eight polyclinics that serve as the primary healthcare delivery points and a single tertiary healthcare institution, which is the only institution with the facilities for inpatient care for children. People have a choice of attending a parallel private healthcare

system, with pediatricians and general practitioners providing ambulatory healthcare only, to a smaller fraction of the child population. There is an ongoing vector control program and a dedicated dengue testing laboratory, making active surveillance possible [18].

In Barbados, as also in other English-speaking Caribbean countries, dengue is an important emerging public health issue with an increasing number of cases and frequency of epidemics [2,5]. Between 2000 and 2009, the annual incidence of confirmed dengue ranged from 0.29 to 2.92 cases per 100 children under 16 years of age, with epidemics in 2001 continuing to 2002 and in 2007 [5]. Thirty percent of all confirmed cases were among hospitalized children [5]. An important observation in recent times with respect to the dengue epidemiology in the Caribbean region is the simultaneous circulation of all four dengue serotypes, with an increasing risk of severe forms of dengue [19]. With changing epidemiology in this region, dengue poses a significant economic burden on the healthcare system of the region, resulting in increased hospitalization and loss of work days [20]. In this study, we report the disease burden, clinical characteristics, and outcomes of children hospitalized with dengue.

Methodology

Study design

This was a population-based prospective study of hospitalization from dengue. All febrile children under 16 years of age hospitalized at the Queen Elizabeth Hospital (QEH) who were suspected to have dengue were enrolled in this study. The QEH is the only tertiary hospital in Barbados and provides over 95% of the inpatient care for children in this country. Children with febrile illnesses who are seen at primary healthcare centers and in the private offices of general practitioners and pediatricians across the island and require hospitalization are referred to the pediatric ward at the QEH. Febrile children may also be seen directly at the emergency department of the QEH and, if necessary, they are referred to the pediatric ward for admission. The observation period for this study extended from January 2009 through December 2009.

Patients and ethics

This study included all children under 16 years of age admitted to the pediatric ward at the QEH during the study period with febrile illness where dengue was a possible diagnosis. Children admitted with febrile illness where diagnosis other than dengue was obvious at the outset such as urinary tract infection or otitis media were excluded from this study. The Committee for the Ethics in Study of Human Subjects at the University of the West Indies, Cave Hill, and the Ethical Review Committee of the QEH of the Ministry of Health, Barbados, approved this study.

Methods

A blood sample is routinely obtained from all the suspected cases of dengue and is sent to the dedicated local dengue laboratory in Barbados for dengue testing. When febrile children present during the first four days of the illness, blood is tested for the NS1 antigen, and blood tests are repeated on days four to seven of the illness for dengue IgM and IgG antibodies. In the early part of the study, when NS1 antigen testing was unavailable, blood samples taken during the first four days of the illness were sent to the regional public health laboratory – the Caribbean Public Health Agency in Port of Spain, Republic of Trinidad and Tobago. When febrile children presented between the fourth and seventh day of the illness, blood was tested for dengue IgM and IgG antibodies. Platelia Dengue NS1 Ag-ELISA (Biorad Laboratories, Marnes-La-Coquette, France) was used for the NS1 antigen detection. IgM and IgG antibody titers in the blood samples were obtained on days four through seven of the illness by the capture enzyme-linked immunosorbent assay (ELISA), following the manufacturer's instructions (Focus Diagnostics, Cypress, USA). Both the NS1 antigen test and the dengue IgM and IgG antibody tests were done at the local public health laboratory for dengue under the Ministry of Health, Government of Barbados. All the children admitted with suspected dengue had other routine tests such as full blood counts, blood urea nitrogen and electrolytes, and random blood sugar. Other tests were requested based on the clinical presentations. Blood, urine, and stool cultures were done in all sick children and in children with uncertain diagnosis. A team of pediatricians managed the children, and other specialty consultations were sought where necessary. None of these children were subjected to any investigations or interventions that were not a routine practice at this hospital.

Definitions

The World Health Organization (WHO) and Pan American Health Organization (PAHO) definitions and criteria were used to classify dengue disease [21,22]. Clinically, dengue infection was categorized into dengue, dengue with warning signs, and severe dengue [21]. Dengue is defined by the presence of

fever with two or more of the following features: rash, nausea and vomiting, aches and pains, a positive tourniquet test, leucopenia, and any one of the warning signs or any of the criteria for severe dengue. Warning signs include persistent vomiting, abdominal pain or tenderness, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, and rapidly rising hematocrit or falling platelets. Severe dengue was diagnosed when there was evidence of plasma leakage, severe bleeding manifestation, and evidence of organ failure [21].

Dengue cases were considered confirmed if DEN NS1 antigen was detected or there was a positive IgM antibody titer. Confirmed dengue was classified as a primary or secondary (sequential) case based on the absence or presence of positive IgG titers in samples collected during the first seven days of the illness [21,22].

Data collection and statistical methods

Data for this study was extracted from the case notes of patients whose dengue test results were confirmed at the time of their discharge from the hospital on a pre-designed and structured data collection form by one of the authors who attended to these children in the hospital. Data was also collected on the total number of medical hospitalizations and the total confirmed cases of dengue among children under 16 years of age in Barbados during the study period. All information for this study was treated confidentially and stored in a specifically designed Microsoft Access database and analyzed using the SPSS.

The data collected for this study included both the categorical data such as presence or absence of dengue infection, gender of the study subjects, outcome of dengue such as discharge or death, and continuous variables such as laboratory results, including platelet counts, hemoglobin, hematocrit values, and white blood cell (WBC) counts. Among the categorical data collected, most of the data was of the nominal type, such as presence or absence of dengue infection, whereas most of the measured data was of the continuous type. Categorical data was summarized using proportions or percentages. The mean was used to summarize measured data. A Chi-square test was used for association between variables in two-way tables. The Chi-square test statistic is designed to test the null hypothesis that there is no association between the rows and columns of a contingency table. The 95% confidence interval (CI) with continuity was calculated for all proportional data.

Results

During the 12-month study period, 199 children were hospitalized with suspected dengue, and 115 (58%; 95% CI: 51–65) of these children were confirmed to have dengue. Over the same period, there were 313 confirmed cases of dengue among children under 16 years of age in all of Barbados; therefore, 37% (115/313; 95% CI: 31–42) of all the dengue confirmed cases were hospitalized. The overall incidence rate of dengue among children that required hospitalization was 2.1/1,000 children. Hospitalization from confirmed and suspected cases of dengue in children accounted for 7% (115/1643; 95% CI: 6–8) and 12% (199/1643; 95% CI: 11–14) of all medical hospitalizations among children under 16 years of age, respectively. Overall, 95 (82.6%, 95% CI: 74.2–88.8) of the hospitalized confirmed cases had the milder disease forms - dengue (62, 53.5%) or dengue with warning signs (33, 28.7%), and 20 (17.4%, 95% CI: 11.2–25.8) had severe dengue as the final diagnosis (Table 1).

Selected characteristics of the children hospitalized with milder or non-complicated disease forms (dengue and dengue with warning signs) and severe or complicated dengue are shown in Table 1. The median ages of the children hospitalized with suspected and confirmed cases of dengue were 4.8 years and 12.2 years, respectively. There were no significant differences in the age distribution ($p = 0.44$), gender distribution ($p = 0.35$), or serodiagnosis ($p = 0.77$) when those with a non-complicated or milder form of the disease were compared with those who had severe dengue. The mean duration of the illness at the time of admission at the hospital was 3.5 days (range, 1–7 days) and 3.6 days (range, 1–10 days) for the children with milder form of dengue and severe dengue confirmed cases, respectively. The mean duration of hospital stay was 2.6 days (range, 1–13 days) and 4.3 days (range, 2–8 days) for the milder form and the severe forms of confirmed dengue, respectively.

Clinical presentations of the children hospitalized with confirmed dengue are shown in Table 2. Besides the typical clinical features of dengue, 64 children hospitalized with confirmed dengue also presented with gastrointestinal manifestations (56%; 95% CI: 46–65), 39 with respiratory manifestations (34%; 95% CI: 25–43), 11 with hepatic manifestations (10%, 95% CI: 5–17), 8 with neurologic manifestations, excluding headache, which is a typical manifestation (7%; 95% CI: 3–14), and 7 with cardiovascular manifestations (6%; 95% CI: 2.3–10.9).

Table 1. Selected characteristics of the 115 confirmed cases of dengue requiring hospitalization in Barbados in 2009

	Dengue & dengue with warning signs (uncomplicated cases, n = 95)	Severe dengue (complicated dengue, n = 20)
Age group		
0–4 years	34 (35.8%, 26.4–46.3)	6 (30.0%, 12.8–54.3)
5–9 years	18 (19.0%, 11.9–28.6)	7 (35%, 16.3–59.1)
10–15 years	39 (41.0%, 31.2–51.6)	6 (30.0%, 12.8–54.3)
Missing data	4 (4.2%, 1.4–11.0)	1 (5.0%, 2.6–26.9)
Gender		
Female	47 (49.5%, 39.1–59.8)	7 (35.0%, 16.3–59.1)
Male	48 (50.6%, 40.1–60.9)	13 (65.0%, 40.9–83.7)
Serodiagnosis		
Primary	46 (48.4%, 38.1–58.8)	9 (45.0%, 23.8–67.9)
Secondary	49 (51.6%, 41.2–61.9)	11 (55.0%, 32.0-76.2)
Duration of symptoms at admission		
Median	3 days (range, 1–7)	3.5 days (range, 1–10)
Mean	3.49 days (range, 1–7)	3.6 days (range, 1–10)
Duration of hospitalization		
Median	2 days (range, 1–8)	4 days (range, 2–8)
Mean	2.64 days (range, 1–8)	4.3 days (range, 2–8)

Table 2. Clinical manifestations among 115 children with confirmed dengue hospitalized at the Queen Elizabeth Hospital

Clinical Features	No.	Percentage
Fever (criteria for enrolment)	115	100.0%
Headache	38	33.0%
Vomiting	36	31.3%
Arthralgia	24	20.9%
Dehydration	20	17.4%
Diarrhea	20	17.4%
Cough	25	21.7%
Abdominal pain	12	10.4%
Myalgia	11	9.6%
Runny nose	23	20.0%
Respiratory distress	10	8.7%
Inflamed/enlarged tonsils	9	7.8%
Shock	9	7.8%
Rash	9	7.8%
Eye pain	8	7.0%
Jaundice	8	7.0%
Lymphadenopathy	7	6.1%
Sore throat	7	6.1%
Crepitation or decreased air entry	5	4.3%
Petechial rash	5	4.3%
Bradycardia/heart block	5	4.3%
Seizures	3	2.6%
Enlarged liver	3	2.6%
Signs of heart failure	2	1.7%
Hematuria	2	1.7%
Upper GI bleed	2	1.7%
Lower GI bleed	2	1.7%

Gastrointestinal manifestations were seen in 24 (60%; 95 CI: 43–75), 13 (52%; 95% CI: 32–72) and 25 (56%; 95% CI: 40–70) of children with confirmed dengue in the < 5 years, 5–9 years, and 10–15 years age groups, respectively. Age data was missing in two patients. In the ≥ 5 years age group, all 13 (100%) children with severe dengue and 12 (42.1%) children with dengue and dengue with warning signs had gastrointestinal manifestations. In the < 5 years age group, 4 (66.6%) children with severe dengue and 18 (52.9%) children with dengue and dengue with warning signs had gastrointestinal symptoms (p = 0.03). Respiratory manifestations were seen in 26 (65%; 95% CI: 48–79), 5 (20%; 95% CI: 7.6–41.3), and 8 (17.7%; 95% CI: 8.5–32.6) children in the < 5 years, 5–9 years, and 10–15 years age groups, respectively. Small numbers did not permit further analysis of the distribution of respiratory manifestations between cases of severe dengue and milder dengue. Results of the selected laboratory tests done at the time of admission in the children hospitalized with dengue are shown in Table 3. Of the 89 patients who had a hematocrit result from the test at the time of admission, 29 (33%; 95% CI: 23–43) had HCT > 44%; however, when corrected for age, only 25 (28%; 95% CI: 19–39) had hemoconcentration. Among the 26 children who had WBC counts of < 4 K/uL, 13 (50%; 95% CI: 30.4–69.6) had severe dengue; of the 11 children who had WBC counts of > 16 K/uL, 4 (36.4%; 95% CI: 12.4–68.4) had severe dengue and 2 had associated Gram-negative septicemia and died. These associations between the WBC counts and occurrence of severe dengue were statistically significant (p = 0.001). In the four children with bradycardia and/or heart block (including two who had signs of heart failure) who were diagnosed with myocarditis, real-time PCR studies for other viral etiology including Coxsackie B virus, adenovirus, and parvovirus B19 were negative. Also, in the three children with seizures where encephalitis was one of the diagnoses, a cerebrospinal fluid serological study for herpes simplex type 1 and 2 virus was negative.

Based on the presence of IgG antibodies at the time of admission, 79 (69%; 95% CI: 59–77) were secondary cases. All of the cases of severe dengue were secondary cases. In the remaining 98 children hospitalized with dengue, 59 (60%; 95% CI: 50–70) were secondary cases; this difference in the proportion of severe dengue and non-severe forms dengue was statistically significant (p = 0.025).

Of the children hospitalized with dengue, 96 (84%; 95% CI: 75–89) were managed on the general pediatrics ward for the entire duration of their hospital stay, and 19 (16%; 95% CI: 10–25) required care in the pediatric intensive care unit for a part of their hospital stay. There were 12 deaths recorded in the

Table 3. Laboratory findings among the 115 children hospitalized with dengue in Barbados

Hemoglobin level (n = 105)	**No.**	**Percentage**
< 10.0 g/dL	12	11.4%
10.0–11.9 g/dL	28	26.7%
12.0–13.9 g/dL	40	38.1%
14.0–15.9 g/dL	20	19.0%
≥ 16.0 g/dL	5	4.8%
Hematocrits (n = 89)		
< 35 %	27	30.3%
35–40 %	33	37.1%
> 40 %	29	32.6%
White blood cells (n = 105)		
< 4 K/uL	26	24.8%
4–7.9 K/uL	35	33.3%
8–11.9 K/uL	20	19.0%
12–15.9 K/uL	13	12.4%
> 16 K/uL	11	10.5%
Neutrophil (n = 90)		
Neutropenia (< 1,500 K/uL)	32	35.6%
Normal (1,500–6,500 K/uL)	44	48.9%
Neutrophilia (> 6,500 K/uL)	14	15.6%
Platelets (n = 104)		
≤ 100 K/uL	15	14.4%
101–150 K/uL	15	14.4%
> 150 K/uL	74	71.2%

pediatric unit in the year 2009; two (17%; 95% CI: 3–49) of these children were confirmed with dengue. Both cases were categorized as severe dengue. One of these children also had associated culture-positive Gram-negative (*E. coli*) septicemia. The case fatality rate of the dengue infection among the hospitalized children under 16 years of age in this series was 1.7%.

Discussion

To our knowledge, this is the first study of children hospitalized for dengue from the English-speaking Caribbean. The region is known to be endemic for dengue and has simultaneous circulation of more than one serotype in many of the countries in this region, including Barbados [1,2,5,19,23]. Our study showed that just over a third of all confirmed cases of dengue in this country required hospitalization. Similar studies from Southeast Asia (in Thailand, 49% required hospitalization) and the Americas (in Nicaragua, 56% required hospitalization) have reported higher proportions of children with dengue requiring hospitalization [24-26]. Dengue endemicity in this country is relatively young, and dengue in this population at this time may be milder than that seen in countries with more mature endemicity [27]. Also, the findings of less severe dengue in this population could lend support to the previously described notion that people of African heritage are less susceptible to severe dengue. The findings from a Cuban study [28] and a Haitian study [29] support the theory that Cuban, Caribbean Black, and African populations share a common gene pool that could explain, at least partially, the low incidence of dengue hemorrhagic fever in Cuba and in Caribbean and African countries.

Confirmed dengue contributes to nearly a tenth of all medical hospitalization in children younger than 16 years of age. In fact, 18% and 28% of all medical hospitalization in children in the 10–15 years age group is from suspected dengue, respectively. The majority of children with dengue who required hospitalization were in the 10–15 years age group. Similar observations have been made in other studies from the Americas [16,25]. Studies from Southeast Asia have also reported increasing proportions of hospitalized dengue with increasing age [30,31].

A notable finding from this study is the fact that, in addition to the typical features of dengue as described in literature, a little over half of the children with confirmed dengue had gastrointestinal manifestations and over a third had respiratory symptoms and signs. Gastrointestinal features have been reported to be common in other studies as well [16,25,31]. In this study, the gastrointestinal manifestations were seen evenly across all of the age groups. These symptoms were significantly ($p = 0.03$) more common amongst the children with severe dengue than those with dengue and dengue with warning signs. Respiratory presentations in children with dengue have been reported uncommonly [30]. Two-thirds of these children were in the < 5 years age group, in which both allergic rhinitis and asthma (especially common in this population) and other respiratory viral infections are common. Given the age group, at least some of these symptoms may have been related to these conditions. At the time of admission, less than a third of all children hospitalized with dengue had a hematocrit > 40%, suggesting significant capillary leak syndrome, and less than 15% had a platelet counts of < 100 K/uL. These are usually features of severity. Nearly one-fourth of these children had a WBC counts of < 4 K/uL and one-tenth had a WBC counts of > 16 K/uL. Both the low WBC counts and high WBC counts were significantly more commonly associated with the diagnosis of severe dengue as compared to normal WBC counts ($p = 0.001$).

Only 17.4% of hospitalized children with confirmed dengue met the criteria for severe dengue; this proportion is far less than the proportion reported in Southeast Asian studies of children hospitalized with dengue [24,30,31]. However, similar observations were made in a study from Nicaragua, where less than 15% of children with confirmed dengue had severe manifestations [9]. The findings from this study substantiate the notion that the population in this region may be genetically less susceptible to severe forms of dengue as compared to those in Southeast Asia [32]. Less severity of dengue also explains the low case fatality rate of dengue seen in this study.

Conclusions

This study has shown that over a third of all confirmed dengue in children warrants hospitalization, and it accounts for as much as a fifth of all medical hospitalization among older children. Four-fifths of hospitalizations in children with dengue were found to be for non-severe forms of dengue and had an uneventful short hospital stay. Both low and high white blood cell counts were associated with severe dengue. Overall, children hospitalized with dengue have a low risk of severe dengue and mortality in this population.

Acknowledgements

We acknowledge the contribution made by the staff at the dengue laboratory. We also acknowledge Miss Prerna Singh and Master Mukesh Krishna Kandamaran for their assistance in data tabulation and reviewing the manuscript for grammatical correction.

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Conflict of interests: No conflict of interests is declared.