Am. J. Trop. Med. Hyg., 86(3), 2012, pp. 474–476
doi:10.4269/ajtmh.2012.11-0411

Short Report: Severe Dengue Virus Infection in Pediatric Travelers Visiting Friends and Relatives after Travel to the Caribbean

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Abstract. Of eight children given a diagnosis of dengue, a complicated course developed in three (38%), including one infant with dengue shock syndrome. Children visiting friends and relatives in dengue-endemic regions are at risk for severe dengue-associated morbidity. Children of families originally from these locations may benefit from pre-travel advice and may represent candidates for a future dengue vaccine.

Dengue represents the most common global arboviral infection, and one of the most frequent causes of systemic febrile illness in travelers returning from tropical regions.[1] In local populations, severe dengue morbidity occurs predominantly in infants and children,[2] and travel-associated severe dengue infections have been hitherto mostly described in adults.[3] Increasing global migration has contributed to the growing proportion of children traveling to tropical and subtropical regions with risk of exposure to dengue virus infection.[4] This report analyzes the travel, clinical, and laboratory characteristics of eight children with dengue including, three with severe dengue infection after return from a trip to the Caribbean.

Bronx-Lebanon Hospital Center is among the largest primary health care providers in the Bronx. Dengue cases were identified by searching the electronic hospital chart system with dengue-specific International Classification of Diseases–9 codes for children (< 18 years of age) who were cared for at one of the institution's pediatric outpatient clinics, emergency department, or inpatient unit during May 1, 2007–December 31, 2010.

During the study period, serologic analysis was performed at Focus Diagnostics (Cypress, CA) by using a dengue virus IgM capture enzyme-linked immunosorbent assay and a dengue virus IgG indirect enzyme-linked immunosorbent assay, and results of both assays were expressed as an index value.[5] World Health Organization (WHO) criteria were used to diagnose dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS): DHF was defined as an acute febrile illness accompanied by hemorrhagic manifestations, platelet count less than 100,000/mm^3, and evidence of plasma leakage; and DSS was established when the DHF criteria were fulfilled in addition to hypotension for age.[1] Charts of children with dengue virus infection diagnosed during the study period were retrospectively reviewed for data abstraction. The study was approved by the institution's institutional review board.

During the study period, we identified eight children with the diagnosis of a probable acute dengue virus infection according to the WHO, and supported by a single positive IgM and/or IgG antibody test result.[1] All cases were in children visiting friends and relatives (pediatric visiting friends and relatives [VFR] travelers) in the Dominican Republic (88%) or Puerto Rico (12%) (Table 1). Identified cases were mostly in females (63%) and in U.S. born (75%), who had a median age of 13.6 years (range = 0.3–17.6 years). The median travel duration was 32 days (range = 10 days–4.3 years), two (25%) persons had previously traveled to the same destination, and the median time to seeking treatment since return was 6 days (range = 1–11 days).

All travelers sought treatment because of an acute febrile illness. Associated clinical features in decreasing frequency were gastrointestinal complaints (63%), myalgia (50%), petechial rash (38%), signs of dehydration (25%), and headache (13%). One child had sought treatment initially with a febrile seizure. Significant laboratory findings included leukopenia (63%), thrombocytopenia (75%), elevation of serum alanine aminotransferase level (38%), low serum albumin level (38%), and increased hematocrit (25%). Evaluations by sonogram showed ascites (50%), pleural effusion (38%), gallbladder thickening (38%), and heterogeneous liver parenchyma (25%).

Three cases (38%) were deemed complicated; two fulfilled the WHO case definition for DHF and one for DSS. Two of the three persons with DHF/DSS cases had profound leukopenia, thrombocytopenia, and an increased hematocrit, even at first encounter. Only persons with DHF/DSS had elevation of alanine aminotranferase levels. Median leukocyte nadir (cells/mm^3) and platelet nadir (cells/mm^3) for DHF/DSS and uncomplicated dengue fever (DF) cases was 3.7 versus 3.0 and 18 versus 76, respectively. Serologic analysis suggested a primary immune response in the infant with DSS and a secondary immune response in the two teenagers with DHF.

Sonographic (ascites, pleural effusion) and laboratory evidence (hypoalbuminemia) of plasma leakage were more pronounced in, but not limited to, the DHF/DSS cases. Evidence of intraperitoneal inflammation (gallbladder thickening and heterogeneous liver parenchyma) was exclusively seen in the DHF/DSS cases. All persons with DHF/DSS responded well to fluid resuscitation and recovered fully without further complications.

This study highlights that pediatric health care providers in communities with large proportions originally from dengue-endemic regions need to be prepared to diagnose dengue and recognize warning signs for severe disease. The Bronx is one of the ethnically most diverse counties in the United States, and most of its immigrant/migrant population maintain close ties to the Dominican Republic, Puerto Rico, and other Caribbean islands.[6] Although data on pediatric travel activity is sparse, this study suggests that pediatric VFR travelers in the Bronx tend to travel repeatedly (25%, probably underreported) and for extended durations (≥30 days) (63%).

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TABLE 1
Clinical details of eight pediatric travelers with cases of dengue virus infection*

Characteristic	Case 1	2	3	4	5	6	7	8
Diagnosis	DHF	DHF	DSS	DF	DF	DF	DF	DF
Age (years)	13.1	17.6	0.7	14.0	17.5	0.3	14.5	12.3
Sex	F	F	M	M	F	M	F	F
Country of birth	US	DR	US	US	US	US	US	DR
Country of exposure	DR	DR	DR	PR	DR	DR	DR	DR
Duration of travel	34 d	10 d	168 d	30 d	13 d	15 d	4.3 y	60 d
Previous travel to same destination	Yes	Yes	No	No	No	No	No	No
Time since return (days)	3	4	7	5	11	1	6	8
Clinical symptoms/signs								
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Myalgia	Yes	Yes	No	Yes	No	No	No	Yes
Hemorrhagic manifestations†	Yes	Yes	Yes	No	No	No	No	Yes
Plasma leakage	Yes	Yes	Yes	No	No	Yes	Yes	No
GI‡	Yes	Yes	Yes	No	Yes	No	Yes	No
Other§	Yes	No	Yes	No	Yes	Yes	No	No
Leukocyte count (cells/mm^3)								
Initial	3.7	2.3	10.7	7.6	6.2	16.2	4.5	3.4
Nadir	3.7	2.3	8.7	NA	3.7	6.9	2.2	1.6
PLT count (cells/mm^3)								
Initial	38	32	119	295	98	408	184	201
Nadir	18	27	12	NA	33	13	118	161
HCT (%)								
Initial	43.4	45.6	37.2	43.1	41.1	33.2	34.6	35.3
Maximum	43.4	45.6	36.3	NA	41.1	33.2	39.0	37.6
ALT increase¶	Yes	Yes	Yes	No	No	NA	No	NA
Albumin (g/dL)#	2.9	2.5	2.3	4.9	2.6	NA	3.9	4.3
Radiographic findings**	Yes	Yes	Yes	NA	No	Yes	Yes	NA
Dengue serologic analysis								
IgM index	3.78	1.77	11.90	16.03	3.04	10.83	3.36	7.54
IgG index	8.15	7.93	3.29	0.63	8.84	2.07	0.36	9.39
Immune response††	Sec	Sec	Prim	Prim	Sec	Prim	Prim	NC

*DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; DF = dengue fever; US = United States; DR = Dominican Republic; PR = Puerto Rico; d = days; y = years; G = gastrointestinal manifestations; NA = not available; PLT = platelet; HCT = hematocrit; ALT = serum alanine aminotransferase; Sec = secondary; Prim = primary; NC = not clear (index values do not enable one to determine if primary or secondary infection occurred).

†Petechial rash (case 1, 2, 8) and hematuria (case 3).

‡Abdominal pain (case 1, 2, 7) and vomiting and diarrhea (case 1, 2, 3, 5, 7).

§Includes headache (case 1); seizure (case 6); signs of dehydration (case 3, 5); and hypotension (case 3).

¶Elevations were between one and two times the upper limit of normal.

#Reference range = 2.9–4.2 g/dL.

**Ascites (case 1, 2, 3, 7); pleural effusion (case 2, 3, 6); gallbladder thickening (case 1, 2, 3); and heterogeneous liver parenchyma (case 1, 2).

††A primary dengue virus infection was deemed likely when the serologic analysis during the acute phase showed a predominant IgM titer in comparison with the IgG level, and a secondary dengue virus infection was considered for high titers of IgG and low or absent levels of IgM.[1]

The incidence of dengue in the Caribbean has been expanding,[7] and one-fourth of travel-related dengue infections in the United States are imported from the Caribbean.[8] Thus, pediatric VFR travelers to the Caribbean may be at significant risk for dengue virus infection. They are possibly more likely to be exposed at locations that do not benefit from vector control activities as much as resort areas that are typically visited by pediatric tourist travelers. However, previous research has not found VFR travelers overall to have an increased risk for dengue, contrary to other travel-related infectious diseases such as malaria when compared with tourist travelers.[9] Further research assessing the incidence of dengue specifically in pediatric travelers is warranted.

As noted by others, fever and nonspecific gastrointestinal complaints predominated as presenting signs in pediatric travelers with dengue, therefore constituting a diagnostic challenge.[10] Our study shows that a simple complete blood count and sonogram may enable an early presumptive diagnosis of dengue because leukopenia, thrombocytopenia, and sonographic evidence of plasma leakage could be found on presentation in most cases. Severe dengue (DHF/DSS) was heralded by especially profound thrombocytopenia, evidence of hepatic/intraperitoneal inflammation, and hemoconcentration that was only noted in the DHF cases.

Our relatively high proportion of severe cases caused by DHF/DSS (38%) contrasts with a recent report on dengue morbidity in adult travelers, in which 11% had severe clinical manifestations, and only 0.9% had DHF.[3] This retrospective study precluded our ability to identify mild dengue cases, potentially leading to an overestimation of the relative burden with severe morbidity. However, the high proportion of cases with a platelet count less than 50,000/mm^3 (63%), and the presence of plasma leakage (63%) is similar to what has been described in case series in endemic pediatric populations.[2] Likewise, according to a new simplified dengue case classification, which divides dengue (with or without warning signs) and severe dengue, 63% of the cases would have been deemed as severe (case 3) or requiring close observation because of the presence of warning signs (cases 1, 2, 6, and 7).[11] In this novel system, severe dengue requires clinically significant plasma leakage leading to shock or respiratory distress because of fluid accumulation, or severe bleeding or severe organ involvement, and so-called warning signs in non-severe dengue cases include abdominal pain/tenderness, persistent

vomiting, clinical fluid accumulation, mucosal bleed, lethargy/restlessness, liver enlargement (> 2 cm), or increase in hematocrit with rapid decrease in platelet count.[11]

Studies of children in disease-endemic regions lend support to the leading but not uncontested antibody-dependent enhancement theory that secondary infections with a heterotypic dengue virus serotype constitute a significant risk factor for severe morbidity.[1,2] Likewise, pediatric VFR travelers with frequent recurrent travel may be prone to be exposed to dengue repeatedly over time. Thus, it is no surprise that in this study at least 38% of all cases, and both DHF cases had a serologic profile suggestive of a secondary dengue virus infection. The DSS case in the 8-month-old infant with a primary dengue virus infection may also be consistent with the epidemiology of dengue in children in disease-endemic communities where a peak of severe dengue morbidity has been observed in infants 4–9 months of age in the context of a primary dengue virus infection.[2] It has been hypothesized that at this age the concentration of transplacentally acquired maternal dengue antibodies in the infant's circulation may decrease from protective to enhancing levels.[2] However, recent research could not find an association between maternal antibodies and development of severe dengue in infants, thereby challenging the antibody-dependent enhancement theory.[12] Dengue genotypes and individual host factors may have a greater impact on the development of severe morbidity than previously appreciated.[13]

In conclusion, our finding suggests that pediatric VFR travelers with frequent and prolonged travel to dengue-endemic regions may adopt a risk profile for dengue morbidity that is similar to that of children residing in dengue-endemic countries. High index of suspicion for dengue in febrile children returning from dengue-endemic regions will enable timely diagnosis and successful management of a potentially fatal condition. Identification of children with travel plans may represent an important opportunity for pre-travel advice. Currently, the preventive efforts need to focus primarily on mosquito-preventive measures and on education of caregivers to seek prompt medical care in case of a febrile illness. Pediatric VFR travelers to dengue-endemic regions may represent ideal candidates for a future dengue vaccine.[13]

Received June 26, 2011. Accepted for publication November 23, 2011.

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