



Hantavirus infection among children hospitalized for febrile illness suspected to be dengue in Barbados

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KEYWORDS

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Summary Emerging picture of hantavirus infection in the South America is characterized by greater proportion of childhood infection and wider spectrum of disease from mild asymptomatic to lethal cardiopulmonary disease. Barbados is endemic for dengue and leptospirosis, both of which share clinical features with hantavirus infection and in many cases neither of these diagnosis could be confirmed. We investigate whether some of the children hospitalized with suspected dengue could indeed have been hantavirus infections. In this prospective study children hospitalized with suspected dengue were tested for hantavirus infection using ELISA for the IgM antibodies. Thirty-eight children tested positive for hantavirus infection. They presented with fever, headache and mild respiratory and gastrointestinal symptoms and signs. None of them had features suggestive of hantavirus cardiopulmonary syndrome. Blood count values ranged from low to normal to high for their age. There were no deaths. Hantavirus infection is prevalent in this Caribbean country. It predominantly presents with milder disease and is responsible for some of the nonspecific febrile illnesses in children.

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Background

Hantavirus, a Bunyaviridae, are viral zoonosis transmitted from rodents to humans are known to cause 2 major, sometimes overlapping clinical syndromes [1–3]. In Europe and in Asia several species of

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hantavirus, referred to as the old world hantavirus causes a syndrome characterized by hemorrhagic fever with renal syndrome (HFRS) [2,3]. In 1993, a new syndrome caused by the hantavirus and characterized by a febrile prodrome and rapidly progressive pulmonary edema and shock was recognized [1,3,4]. This syndrome was called the Hanta Pulmonary Syndrome or the hantavirus cardiopulmonary syndrome (HCPS). Since the 1993, similar pulmonary syndromes have been associated with Sin Nombre virus (SN) and other species of hantavirus in many of the North and South American countries [5–8]. With further characterization of the hantavirus infection in the Americas, based on some small studies, certain notable differences in the hantavirus infection in the North and South America have been reported [5–8]. The emerging picture of the hantavirus infection in South America is characterized by possible person to person transmission, greater proportion of childhood infections and wide spectrum of disease from mild asymptomatic diseases to lethal pulmonary disease typical of the HCPS [6,7,9].

Barbados, one of the Caribbean islands, in close proximity to North and South America is endemic for dengue transmitted by *Aedes aegypti* mosquitoes and Leptospirosis transmitted by the rodents [10]. Dengue is known to have nonspecific presentations shared by other infections such as hantavirus, Influenza virus, Leptospirosis and *Rickettsia*.

Objectives

In this study we asked the question whether some of the suspected dengue cases where dengue was not confirmed could indeed have been hantavirus infection [11–14]. We also studied the clinical and laboratory features of the confirmed hantavirus infection to see if they can provide clues to the early diagnosis of this infection.

Methods

Study design

This is a prospective study. This study was conducted at the Queen Elizabeth Hospital (QE), which is the only hospital with admitting facility for children in Barbados, from October 2009 to September 2011. This study forms a part of the ongoing Barbados dengue study. The study included all febrile children admitted to the QE and who

had a positive hantavirus IgM antibody titer. Presence of IgM antibodies in the acute phase serum was considered diagnostic of hantavirus infection [15].

Study subjects

Children, who are admitted to the QE with suspected dengue, are attended by pediatricians. They receive standard supportive care. They are routinely tested for dengue IgM titers. Blood samples for serology were obtained on day 3–7 of the illness. All other blood tests are routinely done at the time of admission and repeated as necessary. All treatments, investigation results, discharge date and diagnosis are recorded in the patient's file.

Laboratory methods

Dengue diagnostic techniques have been discussed in an earlier published study [9]. During the study period, the samples that were submitted for the dengue IgM & IgG titers were also tested for the hantavirus IgM titers if they were found to be negative for the dengue IgM. Not all the dengue IgM negative samples could be tested due to periodic out of stock for the reagents. Hantavirus testing was performed by enzyme linked immunosorbent assay (ELISA) using the Focus Diagnostics kits (IgM and IgG DxSelect® CA, USA). It detects antibodies to five predominant strains including Hantaan (HTN), Puumala (PUU), Dobrava (DOB), Seoul (SEO) and Sin Nombre (SN). The IgM test is reported to have an overall sensitivity of 95.1% (83.5–99.4%) and a specificity of 94.1% (83.8–98.8%) [16]. The testing procedure was performed according to the manufacturer's instructions. Based on the published guidelines from the CDC & PAHO, detection of IgM antibodies in the patient's serum was taken as evidence of recent hantavirus infection [15]. Both the dengue tests and the hantavirus tests were done at the Public Health Laboratory of the Ministry of Health, Barbados. Full blood counts and kidney function tests are routinely done on all admitted febrile children. Other investigations such as leptospira serology, liver function tests and chest radiograph were ordered when indicated.

Files of all the children admitted to the QE with febrile illness and who tested positive for hantavirus infection were reviewed. Data were extracted into a predesigned structured data collection sheet and included demographic data, date of onset of illness, duration of symptoms at the presentation, symptoms and signs on presentation to the hospital, results from the investigations, course of the illness during the hospital stay, duration of hospital stay and the outcome. Patients name was

excluded from the data collection sheet and the computer database and a pre-assigned code was used for identification instead.

Statistics

All the data extracted from the patient's chart were entered into a Microsoft Access® data sheet for analysis. Microsoft Excel® was used for the generation of tables and graphs. 95% confidence interval was calculated for all proportions and Chi square test were applied to test for all categorical variables. A *P* value of <0.05 was taken as significant.

Results

During the 2 years study period, there were 672 children with suspected dengue where a blood sample were sent for dengue serology testing. Of these samples, 272 were also tested for hantavirus. There were 38 (22.1%, 95% CI – 16.3%, 29.2%) who tested positive (IgM) for hantavirus infection. All 38 children were negative for dengue IgM antibodies. The mean duration of the febrile illness at the time of admission to the hospital was 2.6 days (range 1–5 days). The basic demographic data is shown in Table 1. The median age of the cases was 60 months (age range 7 months to 181 months). Overall, 45% (95% CI = 29–62%) of all the diagnosed cases of hantavirus infections were in children under 5 years. However, this difference in the age distribution of

Table 1 Basic demography of hospitalized children with hantavirus infection.

	No.	% (95% confidence interval)
<i>Gender</i>		
Female	17	44.7 (29.0–61.5)
Male	21	55.3 (38.5–71.0)
<i>Age group (years)</i>		
0–<5	17	44.7 (29.0–61.5)
5–<10	14	36.8 (22.3–54.0)
10–<15	7	18.4 (8.3–34.9)

children with hantavirus infection was not statistically significant (*P*=0.22). Majority (92%) of these children were of Afro-Caribbean decent. Seasonal distribution of the cases of hantavirus infection is shown in Fig. 1.

Clinical presentations at the time of admission to the hospital for all of the hantavirus infected children are shown in Table 1. All 38 children had fever as a presenting feature. Overall 26.3% (95% CI=12.1–40.6) of children with confirmed hantavirus infection presented predominantly with mild respiratory symptoms and signs. Almost, an equal proportion (23.7%; 95% CI=13.9–43.4) of hantavirus infected children presented with gastrointestinal symptoms and signs including vomiting and diarrhea. The remaining 50% presented predominantly with fever along with other nonspecific symptoms and signs such as headache (31.6%; 95% CI=18.0–48.8). Bleeding manifestations were seen in 4 cases (10.5%; 95% CI=3.4–25.8). Two children

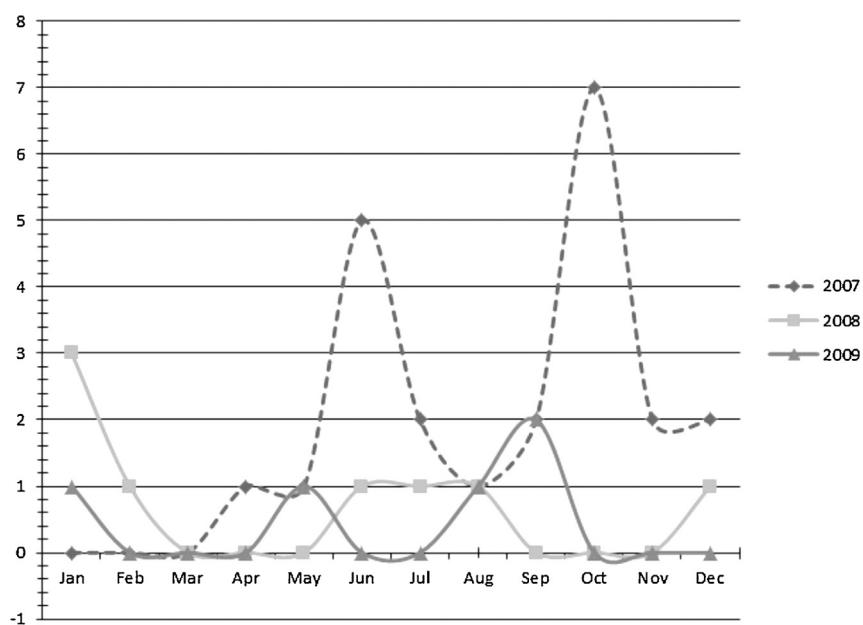


Figure 1 Seasonal distribution of hantavirus infection in children.

Table 2 Clinical presentation in hanta infections.

Clinical presentation	N	%	(95% CI)
Respiratory (one or more of the followings) – cough, running nose, tachypnea	9	23	(12.1–40.6)
Gastrointestinal (one or more of the followings) – vomiting, diarrhea	10	26	(13.9–43.4)
Headache	12	31.6	(18.0–48.8)
Arthralgia, myalgia	5	13.1	(4.9–28.9)
Lymphadenopathy	3	7.9	(2.1–22.5)
Bleeding manifestations	4	10.5	(3.4–25.8)
Syncope/hypotension	3	7.9	(2.1–22.5)
Seizures	2	5.3	(0.9–19.7)
Jaundice	1	2.6	(0.1–15.4)
Rash	1	2.6	(0.1–15.4)

Table 3 Laboratory findings in children with hantavirus infection.

Lab-result	Low	Normal	High	Mean	Median	Min	Max	Std. dev.
Leucocytes $\times 10^3/\text{ml}$	<6 7 (18.9%)	6–12 18 (48.6%)	>12 12 (32.4%)	10.97	9	2	31	6.89
Platelets $\times 10^3/\text{ml}$	<150 8 (21.6%)	150–450 23 (62.2%)	>450	6 (16.2%)	268	235	28	585
Creatinine, $\mu\text{mol/l}$		≤ 60 31 (83.8%)	>60 6 (16.2%)	45.77	40	17	178	27.78

had minimal upper gastrointestinal bleed (both these children had vomiting) combined with either nose bleeding or gum bleeding (**Table 2**).

Because the result of the hantavirus IgM antibodies was not known until after the patients were discharged from the hospital the 38 febrile children who subsequent tested positive for hanta infection, had various discharge diagnosis. Viral illness was the discharge diagnoses in 14 (36.8%; 95% CI = 22.3–54.03) cases. Among children 5 years or younger, viral illness accounted for 52.9% (95% CI = 28.5–76.1) and among the children older than 5 years it accounted for 33.3% (95% CI = 15.5–56.9) of all discharge diagnoses. Upper respiratory tract infection was the discharge diagnoses in 6 cases (15.8%; 95% CI = 6.6–31.9). Four of these cases were children 5 years or younger in age. Other discharge diagnosis included Acute Viral Gastritis/Gastroenteritis in 6 cases (15.8%; 95% CI = 6.6–31.9), dengue was the discharge diagnose in 6 cases (15.8%; 95% CI = 6.6–31.9). The diagnosis of Lower Respiratory tract Infection in 4 cases (10.5%; 95% CI = 3.4–25.8).

Laboratory results were documented in 37 cases that were confirmed to have hantavirus infection (**Table 3**). Twelve (32.4%; 95% CI = 18.5–49.9) children had a counts higher than $12 \times 10^3/\text{ml}$, while 7 (18.9%; 95% CI = 8.6–35.7) had a counts less than $6 \times 10^3/\text{ml}$. Eight (21.6%; 95% CI = 10.4–38.7) had

a count that was less than $150 \times 10^3/\text{ml}$. Six children (16.2%; 95% CI = 6.8–32.7) had a creatinine value that was above the normal reference value ($>60 \mu\text{mol/l}$) for children. Aspartate transaminase was raised in two cases above the upper limit of the normal range for their age; both these children were older than 5 years and because of the raised liver enzymes had dengue with hepatitis as their discharge diagnosis.

None of the 38 children required pediatric intensive care and there were no deaths. The Median duration of hospitalization was 3 days (range 1–5 days) and there were no in-hospital complications noted in any of the 38 cases.

Discussion

The first pathogenic New World hantavirus (Sin Nombre virus) was discovered in the early 1990s in the Four Corners region of the United States [1,4]. From this time on, numerous additional pathogenic New World hantaviruses were identified and characterized including Sin Nombre Virus, Andes virus, Black Creek Canal virus, Choclo virus, New York virus and others. New World hantaviruses are the causative agent of approximately 300 cases of HPS each year in North and South America, with lethality rates up to 50% [3,5–8,17,18].

In this first report of hantavirus infection in the Caribbean, we describe a series of 38 cases detected on screening of serum obtained from children (<16 years) suspected to have dengue. Over five percent of those tested for hantavirus from among children suspected to have dengue and tested negative for dengue had hantavirus infection. It is well documented that the Caribbean region including Barbados is endemic for dengue with occurrence of dengue in increasing numbers over the past years [10,19]. In a recent study from Barbados, it was shown that over half of all suspected childhood cases of dengue tested negative for both the cell culture of the virus or tested negative for the NS1 antigen in blood sample taken during the first 5 days of the illness, as well as the dengue IgM antibodies in serum sample taken during day 5–14 of the illness [10]. This raised the possibility of other potential etiological agent in these cases. The findings from this study for the first time has clearly shown that many of these cases in children that presents as febrile illnesses and suspected to have dengue are due to the hantavirus infection. Similar findings were reported in another recent study from Indonesia [14]. The endemicity of the rodent born zoonosis Leptospirosis in this country also lends support to the findings from this study [20–26]. Interesting as early as 2002, Groen et al. had reported serological evidence of hantavirus in humans and rodents in Barbados [27].

Most of the hantavirus cases from the Americas as well as those from Asia and Europe have been reported in adults [3,28,29]. There are only a small number of studies reporting hantavirus infection in children [9,32,33]. Over half of all cases in this series were in the age group less than ten years with median age of 5 years (age range 7 months to 181 months). In the report from USA the age range for the infected children was from 10 to 16 years [33]. As noted earlier serological evidence of hantavirus transmission in this country was documented as early as the late nineties [27]. Infections noted at younger age in this study may reflect a changing epidemiology of hantavirus. It would be interesting to study the incidence of the hantavirus infection among the adult population in this country. Another interesting epidemiological finding in this series was a near equal male to female ratio. In the published literature nearly two-thirds of all cases were males [28–31]. However, of note, all of these reports are based on studies that have adult cases and this ratio may be related to occupational exposure [28–31]. The findings from this study highlight the role of hantavirus as an emerging infectious disease in children.

In this country cases of confirmed hantavirus infections peaked during the rainy months of June through October. Similar seasonal pattern have been reported in several other countries from the Americas [13,29,34].

In the published literature, new world hantavirus is known to cause a serious form the HCPS which carries a high mortality. In this series, majority of the children had milder form of the disease manifesting with either nonspecific febrile illness without any localizing symptoms or with respiratory and/or gastrointestinal symptoms. Of note, many of these symptoms and signs have been reported in the prodromal and early period of the HCPS in several studies from the Americas [6–8]. Less than one-eighth of cases had potentially serious manifestations such as bleeding and/or hypotension. Also, less than a third of cases had leukocytosis and/or thrombocytopenia. None of our cases had pulmonary edema and/or myocardial depression. These are reported to be the typical manifestations of the HSPC in many studies [6–8]. None of our cases met the diagnostic criteria for HCPS [6–8]. The classical manifestation of the new world hantavirus infections from the Americas has been described as the HPCS. However, recent studies from different regions have reported mortality rates varying from as high as 60% to as low as 11% [7,34]. Some recent studies from south America have reported milder forms of the disease especially in children [8,35]. The clinical manifestations of the hantavirus infection seen in this setting are similar to those of the Andes virus infection reported from the south America than those of the SN virus infection reported from the north America [35]. Also, there are studies from Americas which have reported acute SN infection without pulmonary syndrome [36]. It is possible that less virulent hantaviruses are responsible for the mild and subclinical illnesses circulating in this region [37,38]. A great deal of genetic diversity of hantavirus in the Americas has been reported [6]. It is noteworthy, none of the rodent hosts of hantaviruses that are associated with the HCPS are found in Barbados [39]. The Norway rat (*Rattus norvegicus*), Black rat (*Rattus rattus*) and the House mouse (*Mus musculus*) are the most common rodent species found in Barbados [40]. It is possible that they are carrier to hantavirus species that cause milder disease.

Conclusions

In summary, findings from this study have, for the first time, documented the prevalence of

hantavirus infection in this English speaking Caribbean country. The clinical manifestations of the hantavirus infection in this country is predominantly milder disease not reported in the published literature. At least, some of the cases of febrile illnesses in children with or without respiratory and gastrointestinal symptoms and signs are due to hantavirus infection. There is a need for larger studies including adult population from this country and from the wider Caribbean to substantiate the findings from this study, to establish the prevalent serotypes of hantavirus in this region and to ascertain the likelihood of potentially severe disease forms resulting in lethal cardio-pulmonary involvement.

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Competing interests

None declared.

Ethical approval

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