ORIGINAL ARTICLE

Patterns of disease in Sri Lankan dengue patients

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Background: Dengue is the most important mosquito borne viral infection in the world. Nearly 90% of infections occur in children. At present, prospective information on clinical and laboratory findings in South Asian children with dengue is generally lacking.
Aim: To describe patterns of clinical disease in a cohort of children hospitalised with dengue during a major dengue epidemic in Sri Lanka.
Results: A total of 104 children were studied during a three month period. Eighteen had dengue fever (DF) and 86 had dengue haemorrhagic fever (DHF). Of those with DHF, 34, 23, 27, and 2 had DHF grade I, II, III, and IV respectively. Based on dengue serology testing, 13 of the DF patients had a primary infection and 5 had secondary dengue infections. In contrast, 68 of the children with DHF had secondary and 18 had primary dengue infections. Oral candidiasis was seen in 19 children. The odds ratio for children with secondary dengue infection to develop DHF was 9.8 (95% CI 3.1 to 31.2).
Conclusion: Studies on patterns of paediatric dengue disease in different regions should help clinicians and health administrators make more informed and evidence based health planning decisions. It should also help towards mapping out dengue trends on a global scale. Oral candidiasis has not been previously documented in children suffering with acute dengue in Sri Lanka or elsewhere. Studying underlying reasons for this manifestation during future dengue epidemics may provide useful leads in understanding overall dengue pathogenesis.

Dengue is epidemic or endemic in virtually every tropical country.[1] It is considered the most important viral haemorrhagic fever in the world. Infection may be asymptomatic or give rise to undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS).[1] The dengue virus is a RNA virus of the flaviviridae family and consists of four serotypes (DEN 1–4). Generally, infection with one serotype confers future protective immunity against that particular serotype but not against others. Nearly 90% of dengue infections occur in children.[2] The risk that a child will die during a secondary dengue infection is nearly 15-fold higher than that of adults.[3] Epidemics of dengue occur regularly in Sri Lanka,[4 5] with the largest and most severe one recorded so far occurring between April and August 2004 (H Tissera, Sri Lanka Epidemiology Unit, personal communication, 2004). These epidemics result in significant morbidity and mortality and its control and management requires the allocation of considerable financial and medical resources.

Although children are the main group affected by dengue, little published data are available regarding dengue infections in children living in South Asia.[6–8] Such information is necessary if we are to put in place evidence based health policy measures to deal with the problem as it applies to this region, in turn ensuring the best use of limited health resources. Although the dynamics of dengue viral infections together with genetic, social, and demographic factors differ between South Asian and South-East Asian countries, the tendency so far has been to make health policy decisions by blindly postulating from South-East Asian data, some of which was generated nearly 40 years ago.[9] In this study, we studied the patterns of disease in a cohort of Sri Lankan children hospitalised with dengue, seen during a recent major epidemic, and compared these with patterns reported previously from other parts of the world. We also assessed possible risk factors associated with severe disease in this cohort.

METHODS

This study was carried out in a general paediatric ward at the Lady Ridgeway Hospital for children in Colombo, Sri Lanka during a three month period (24 April to 31 July 2004). All children with clinical features suggestive of dengue infections admitted to this ward were included after obtaining informed written consent from the parent or guardian. Ethical clearance for the study was obtained from the ethical review committee of the University of Sri Jayawardanapura, Sri Lanka. Basic demographic data were collected from each child included in the study. Clinical and haematological/biochemical findings were recorded serially until discharge. A history of asthma or eczema (both past and present) in each child was ascertained from their parents, and treatment being used at present for these conditions was noted. Heights were measured to the nearest 0.1 cm using a standiometer, and weights measured to the closest 100 g using an electronic weighing scale. Body mass index (BMI) was calculated and plotted on revised NCHS (2000) growth charts in order to obtain a global estimate of nutritional status. A tourniquet test was performed to determine its usefulness in predicting future bleeding manifestations.[10]

The WHO classification and case definitions were used to classify disease in these children as either DF or DHF.[2] Evidence of plasma leakage (pleural effusions, ascites, or rise in packed cell volume (PCV) >45) or shock, even in the absence of bleeding manifestations, was considered as indicating DHF. A lateral decubitus chest radiograph was obtained in all children with clinical suspicion of a pleural effusion; blood groups were assessed in all. DHF was further divided into four grades (I, II, III, IV) as per WHO definitions.[2] Dengue viral specific antibodies were detected using the PANBIO Dengue duo IgM and IgG rapid strip test,[11]

Abbreviations: DF, dengue fever; DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome

Table 1 Clinical and laboratory findings in paediatric dengue patients

Clinical and laboratory findings	DF (n = 18) No. (%)	DHF (n = 86) No. (%)	p value*
Flushed appearance	17 (94)	76 (88)	>0.05
Diarrhoea	02 (11)	16 (19)	>0.05
Vomiting	11 (61)	66 (77)	>0.05
Headache	12 (66)	62 (72)	>0.05
Pharyngeal congestion	06 (33)	11 (13)	<**0.05**
Runny nose	05 (27)	15 (17)	>0.05
Bleeding manifestations	04 (22)	36 (42)	>0.05
Petechiae	03 (16)	14 (16)	
Ecchymoses	01 (6)	04 (5)	
Haemetemesis	01 (6)	13 (15)	
Melaena	00 (0)	05 (6)	
Bleeding from gums	01 (6)	12 (14)	
Epistaxis	01 (6)	03 (4)	
Positive tourniquet test	04 (22)	24 (28)	>0.05
Hypotension	01 (6)	30 (35)	
Prolonged capillary refilling time	02 (11)	29 (34)	<**0.05**
Pleural effusions	00 (0)	70 (81)	<**0.001**
Ascites	00 (0)	39 (45)	<**0.001**
Impaired consciousness	01 (6)	06 (7)	
Presence of recovery rash	07 (39)	17 (20)	>0.05
Platelet count			<**0.001**
$>100\times10^9$/l	15 (83)	16 (19)	
$51–100\times10^9$/l	03 (17)	30 (35)	
$21–50\times10^9$/l	00 (0)	30 (35)	
$\leqslant 20\times10^9$/l	00 (0)	10 (12)	
Haemoconcentration (PCV >45)	02 (11)	50 (58)	<**0.001**
Low WBC ($<4\times10^9$/l)	03 (17)	13 (15)	>0.05
Raised ALT	04 (22)	47 (55)	>0.05
Raised AST	05 (28)	65 (76)	<**0.005**

Percentages rounded to nearest whole number.
*χ^2 test.

on a serum sample taken at least seven days after onset of the illness.

Data was analysed using the SPSS (version 10.0) statistical package. To calculate odds ratios of possible risk factors for severe dengue infections, DF and DHF grade I were categorised as mild infections, and DHF grade II–IV as severe infections.

RESULTS

During the three month period of this study, 125 children were admitted to a single paediatric ward with clinical features suggestive of dengue infection. Of these, 104 (83.2%) had dengue serology indicative of an acute infection; 61 (59.8%) were female and 43 (41.2%) male, and their ages ranged from 1 month to 12 years (mean 7.9 years, SD 2.9).

Eighteen (17.3%) had DF and 86 (82.7%) had DHF. Of those with DHF, 34 (39.5%), 23 (26.7%), 27 (31.4%), and 2 (2.3%) had DHF grade I, II, III, and IV respectively. Based on dengue serology testing, 13 (72.2%) of the DF patients had a primary infection and 5 (27.7%) had secondary dengue infections. In contrast, 68 (79.1%) of the children with DHF had secondary and 18 (20.9%) had primary dengue infections. The odds ratio (OR) for children with secondary dengue infection to develop DHF was 9.8 (95% CI 3.1 to 31.2).

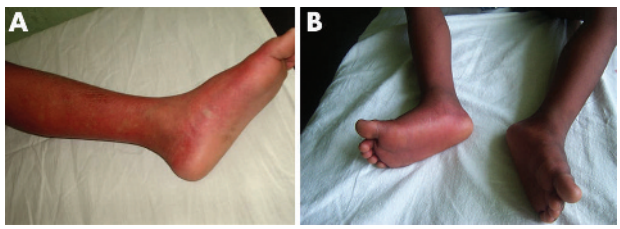

Figure 1 Rashes observed in children with dengue viral infections. (A) ''Recovery rash'', a generalised erythematous rash with islands of pallor. (B) Generalised macular popular rash. Consent was obtained for publication of this figure.

Clinical findings

The spectrum of clinical findings in children with DF and DHF is shown in table 1. Ninety three (90%) of 104 children had a flushed appearance irrespective of the severity of their illness. A runny nose and pharyngeal congestion (features usually not described during adult dengue infections) were present in 20 (19.2%) and 17 (16.3%) children respectively. Pharyngeal congestion was more prevalent in children with DHF then DF. The mean (SD) duration of hospitalisation in children with DF and DHF was 4.1 (2.4) and 4.8 (4.1) days respectively.

Bleeding manifestations were seen in 40 (38.5%) children (petechiae, gum bleeding, and haematemesis were the most frequent manifestations). Seventeen (16.3%) children were given blood products (platelet concentrates, n = 9; fresh frozen plasma, n = 14). Bleeding manifestations were also

Table 2 Characteristics of patients with and without oral candidiasis

	Oral candidiasis present (n = 19) No. (%)	Oral candidiasis absent (n = 85) No. (%)
Secondary dengue infections	15 (80)	58 (68)
Primary dengue infections	04 (21)	27 (32)
Dengue fever	02 (11)	16 (19)
DHF		
Grade 1	07 (37)	27 (32)
Grade 2	02 (11)	21 (25)
Grade 3	08 (42)	19 (22)
Grade 4	00 (0)	02 (2)
Pleural effusion	14 (74)	55 (65)
Ascites	11 (58)	27 (32)
Pedal oedema	03 (16)	01 (1)
Secondary bacterial infections	02 (11)	05 (6)
BMI for age <5th centile	14 (74)	41 (48)
ICU admission	00 (0)	03 (3)

Percentages rounded to nearest whole number.

present in 4 (22.2%) of 18 children with DF. Platelet levels of $\leqslant 100\times10^9$/l were detected in 73 (70.2%) children, of whom 29 (39.7%) had bleeding manifestations. Fourteen (46.7%) of 30 and 5 (50%) of 10 children with platelet counts $20–50\times10^9$/l and $\leqslant 20\times10^9$/l respectively had bleeding manifestations. There was no significant association ($p > 0.05$, χ^2 test) between the degree of thrombocytopenia and the presence of bleeding manifestations. The tourniquet test was positive in 19 (47.5%) of 40 children having other bleeding manifestations, in 8 (24.2%) children with platelet counts $51–100\times10^9$/l, and in 15 (37.%) children with platelet counts $\leqslant 50\times10^9$/l.

Three types of rash were seen in the children. Rashes were most obvious during the convalescent phase of their illness. These included a ''recovery rash'' (generalised erythematous rash with islands of pallor; fig 1A) in 24 (23.1%), a generalised macular papular rash (fig 1B) in 9 (8.7%), and a petechial rash in 8 (7.7%) children. The ''recovery rash'' was present in a higher proportion of those having primary (48.3%) than secondary dengue infections (14.7%). The petechial rash was only seen in those recovering from DHF.

An altered level of consciousness (defined as a score of <10 out of a possible 15 points on a modified Glasgow coma scale) was seen in 6 (5.8%) children. Mean alanine transaminase (ALT) and aspartate transaminase (AST) levels in these six children were >8 and >12 times the upper limits of normal. Myocarditis (manifested as tachycardia, triple rhythm, and heart failure) was seen in 3 (2.9%) children, all of whom had DHF. All had low ejection fractions on echocardiography carried out during the acute stage, which returned to normal 7–10 days later. The QT interval on an ECG was prolonged in one of the children with myocarditis. Three (2.9%) children developed prolonged shock and needed ICU admission (one of them had an altered level of consciousness). No deaths were seen in our series. Seven (6.7%) children had secondary bacterial infections, such as lobar pneumonia and septicaemia, complicating their dengue infection. *E coli* was isolated from blood cultures in two children.

Oral candidiasis was seen in 19 (18.3%) of the 104 children (10 females, 9 males). Mean ages and sex distribution of these children were comparable to those that did not have oral candidiasis. In 15 (78.9%) children the pharynx alone, and in 4 (21.1%) the whole buccal mucosa (palate, cheeks, and tongue) was involved. Careful examination of the oropharynx using a good light source and a tongue depressor was needed to detect the oral candidiasis. It lasted for a mean (SD) of 7.3 (1.2) and 2.3 (0.8) days. None were previously immunosuppressed or taking steroids. Four (21.1%) had primary and 15 (78.9%) secondary dengue infections. Eight (42.1%) children with oral candidiasis had DHF grade III compared with 19 (22.3%) children without this complication. In contrast, 2 (11%) children with and 21(25%) without oral candidiasis had DHF grade II. A comparison of clinical findings in children with and without oral candidiasis is shown in table 2. Two children with oral candidiasis also had a secondary bacterial infection. All were treated successfully with miconozole oral gel.

Laboratory findings

Laboratory findings in children with DF and DHF are shown in table 1. Platelet counts were lowest and the haematocrit highest on mean (SD) 5.6 (1.6) and 5.9 (1.5) days respectively. High ALT and AST levels were seen in 51 (49%) and 70 (67.3%) children. AST levels were significantly higher ($p < 0.002$) among children with DHF compared to DF.

Risk factors for severe dengue infections

Estimates of possible risk factors (as individual odds ratios) for severe dengue infection in this group of children are shown in table 3. Secondary dengue infections and blood group O increased the risk ratio. Age, sex, presence of atopic diseases (such as asthma or eczema), and nutritional status did not appear to alter the risk.

DISCUSSION

In this report we describe clinical and laboratory findings in a sizeable cohort of hospitalised children with dengue infections seen in a paediatric centre in South Asia. Eighteen per cent of these children developed oral candidiasis. To the best of our knowledge this clinical manifestation has not been previously documented in children suffering with acute dengue in Sri Lanka or elsewhere. In 2004, Sri Lanka experienced its largest and most severe dengue epidemic seen so far. By the end of July 2004, over 10 000 cases had been reported (H Tissera, Sri Lanka Epidemiology Unit, personal communication, 2004). The exact reasons for this very severe and large epidemic have not been well defined. A change in the predominant circulating dengue viral serotype has been suggested as a reason for the increased severity of this epidemic. Although DEN 2 has been the predominant serotype during past dengue epidemics in Sri Lanka,[12 13] it changed to DEN 3 during the present epidemic.[14 15]

There was no significant association between platelet counts, bleeding manifestations, and a positive tourniquet test. Some children with DF had mild bleeding manifestations (for example, petechiae) as has been seen in some other studies.[16] Two of the children who had a PCV >45 were still classified as having DF and not DHF as they did not have any other criteria for a diagnosis of DHF and their PCV remained >45 even following complete recovery. Over 50% of children had abnormal liver enzymes (high ALT, 49%; high AST, 67%), with AST levels being significantly higher in children with DHF than DF. However, none of the children developed

Table 3 Possible risk factors for severe dengue infections

Risk factor	Mild infections (DF + DHF 1) (n = 52) No. (%)	Severe infections (DHF 2, 3, 4) (n = 52) No. (%)	OR (95% CI)	p value*
Sex (female)	29 (55.8)	32 (61.5)	1.1 (0.5 to 2.5)	>0.05
Blood group				
O	16 (30.8)	29 (55.8)	2.5 (1.1 to 5.6)	0.029
B	16 (30.8)	12 (23.1)	0.6 (0.2 to 1.4)	>0.05
A	8 (15.4)	10 (19.2)	0.7 (0.2 to 1.9)	>0.05
Secondary dengue infection	28 (53.8)	45 (86.5)	3.2 (1.3 to 7.9)	0.008
Asthma	12 (23.1)	12 (23.1)	0.9 (0.5 to 2.3)	>0.05
Eczema	8 (15.4)	7 (15.4)	1.1 (0.5 to 3.2)	>0.05
BMI for age >90th centile	3 (5.8)	4 (7.7)	1.4 (0.3 6.5)	>0.05
BMI for age <5th centile	28 (53.8)	27 (51.9)	0.9 (0.4 to 2.2)	>0.05

*χ^2 test.

What is already known on this topic

- Dengue is the most important mosquito borne viral infection in the world; nearly 90% of dengue infections worldwide occur among children
- Secondary dengue infection increases the risk of developing severe forms of disease

What this study adds

- Patterns of dengue disease among a cohort of hospitalised children from Sri Lanka have been described in an attempt to increase the amount of prospectively collected information on paediatric dengue disease from the South Asian region
- A group of children who developed oral candidiasis during their acute dengue infection has been described

fulminant liver disease. A higher incidence of dengue encephalopathy (5.6%) was seen in this cohort compared to that reported in other series.[17 18] Children with this complication had very high AST levels (>10 times the normal upper limit). Some children developed secondary bacterial infections as has been reported previously.[19 20]

Secondary dengue infections increased the risk of severe disease in our cohort. This link is similar to that reported previously in children from South-East Asia and the Americas.[16 20] Of DHF cases in our cohort, 20.9% occurred following primary dengue infections, which is different to the profile normally described. Of children with the severe grades of disease in our cohort, 55.8% had blood group O. Although this value is higher than the prevalence of this blood group in the overall Sri Lankan population (43.4%),[21] this difference did not reach statistical significance ($p > 0.05$). A previous report on adult dengue patients reported that DHF and DSS was seen more commonly in patients with blood group B.[22] Although a few previous studies suggest asthma as a risk factor for developing DHF/DSS,[23 24] we could not confirm this finding in our children. Similarly, we did not find female children to be more at risk of developing severe disease, despite this been reported in other settings.[25]

Malnutrition is known to predispose children to acquiring infectious diseases.[26] In addition, it is known to increase the severity of some infections such as measles.[27] We did not find poor nutritional status to be a risk factor for severe dengue disease, although this has been shown by others.[28 29] Although as a group the BMIs were not significantly different in children with severe or mild disease, over 70% of those children who developed oral candidiasis had a BMI for age <5th centile.

A sizable proportion of children hospitalised with dengue infection seen by us developed oral candidiasis. This new manifestation may be due to several reasons. Increased viral virulence (and possibly greater associated immune suppressive effects) in the recent epidemic is a plausible hypothesis. This would need formal testing if seen during future epidemics. This may have played a part in overcoming the normal protective immune responses in a subset of children. Conversely, it may be argued that this feature was only picked up because more detailed patient examination was done in the ongoing study on dengue. However, we think this less likely as the same findings were not observed in any adult dengue patients (with equivalent degrees of disease severity) also studied by us during the same epidemic. The proportion of children in our cohort developing oral candidiasis following dengue infection was nearly 20 times higher than among other hospitalised sick children seen during the same time period. The recognition of this association with dengue should make us look out for it during future dengue epidemics.

In summary, we have systematically collected and reported clinical and laboratory findings in a cohort of Sri Lankan children with dengue infections and then proceeded to highlight important differences in clinical manifestations seen during the recent severe epidemic. Availability of more studies of this type from different countries should help clinicians and health administrators make more informed and evidence based health planning decisions, and also be able to use pooled data from several countries to study disease trends and variations.

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Consent was obtained for publication of figure 1

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ARCHIVIST

New rotavirus vaccines

Rotavirus infection is a major killer of young children especially in developing countries. Among children under 5 years old it causes over 600 000 deaths, two million hospital admissions, and 25 million clinic attendances every year. In 1999 an effective rotavirus vaccine was withdrawn in the USA because it caused intussusception in approximately one in 10 000 recipients. Now two new rotavirus vaccines have been reported to be efficacious and safe.

The vaccines were Rotarix (GlaxoSmithKline), a live attenuated monovalent (G1P[8]) rotavirus vaccine (Guillermo M Ruiz-Palacios and colleagues. *New England Journal of Medicine* 2006;**354**:11–22, see also editorial, ibid: 75–7) and Rotateq (Merck), a pentavalent live reassortant human-bovine vaccine based on the WC3 bovine strain and human rotavirus serotypes G1, G2, G3, G4, and P[8] (Timo Vesikari and colleagues. Ibid: 23–33). Randomised, placebo-controlled trials were carried out largely in Latin America (monovalent vaccine) and in the USA and Finland (pentavalent vaccine) and included 63 225 and 68 038 infants respectively. Both vaccines were highly efficacious. The monovalent vaccine had an efficacy of 85% against severe rotavirus gastroenteritis and hospital admission due to rotavirus infection and reduced hospital admissions for all-cause diarrhoea by 42%. The pentavalent vaccine had an efficacy of 74% against any G1-G4 rotavirus gastroenteritis in the first full rotavirus season after vaccination and of 98% against severe rotavirus gastroenteritis. In the monovalent vaccine trial intussusception occurred in 9 infants (vaccine) vs 16 (placebo) and in the pentavalent vaccine trial in 12 and 15 infants respectively. The editorialists insist that extensive postmarketing surveillance will be necessary to exclude the possibility of intussusception being caused in some vaccine recipients. Hospital admissions for diarrhoea of any cause in infancy were reduced by 42% and 63% suggesting that the proportion of infant admissions to hospital with severe diarrhoea that is due to rotavirus may be larger than has been estimated in the past.

The new vaccines are efficacious and seem to be safe. They may have economic benefits as well as effects on morbidity and mortality in developing and developed countries. More trials in developing countries are needed and, if such trials confirm the benefits, finding ways to include these vaccines in routine immunisation programmes will become a global priority.