

*Research article*

## A preliminary study on clinical profiles of dengue and dengue haemorrhagic fever suspected patients from two hospitals in the Western Province of Sri Lanka

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### Abstract

**Objective:** Dengue fever (DF) is one of the most common public health problems in Sri Lanka. A pilot study was undertaken to investigate the clinical profiles of DF and dengue haemorrhagic fever (DHF) in patients admitted to two hospitals from July 2011 to July 2012. The objective of the study was to evaluate clinical patterns to improve pattern recognition and to determine whether these profiles have changed in recent times.

**Study design:** The clinical profile was collected using a CDC style questionnaire and analyzed (Minitab, V14). Blood samples were collected from 50 patients from Gampaha and 204 patients from Negombo hospitals with a clinical suspicion of DF/DHF, between fever days 2 to 7. Laboratory data included a complete blood count (CBC) with haemoglobin, haematocrit, total leukocyte and platelet counts and liver function. CBC was repeated daily during the acute phase of the illness. Chest x-ray or ultrasound scanning was done to assess pleural and abdominal fluid accumulation.

**Results:** The sample consisted of 168 (66.1%) males and 86 (33.8%) females. The age of the patients ranged from 6 months to 66 years with a mean of 12 (SD = 13.4). Fever was the major presenting complaint (100%) with headache in 90.1%. Retro orbital pain was present in 27.6% of patients and 78 % and 79.1 % experienced arthralgia and myalgia respectively. Rash and pleural effusion were present in 20% and 10.6 % respectively. Ascites and hepatomegaly were noted in 6.2% and 1.1%. Of the 254 patients, 69% had DF and 31% had DHF. The lowest WBC was  $0.98 \times 10^3/\text{mL}$ . Platelet count of  $<100,000$  was seen in 65.3% cases.

Only 35 patients (21 DF and 14 DHF) were tested for IgM/IgG. Based on these results, 38% (8/21) of DF cases were primary and 62 % (13/21) were either secondary or with past flavivirus infections. Primary dengue infection resulted in 43% (6/14) of DHF cases with 57% (8/14) resulting from secondary or with past flavivirus infections.

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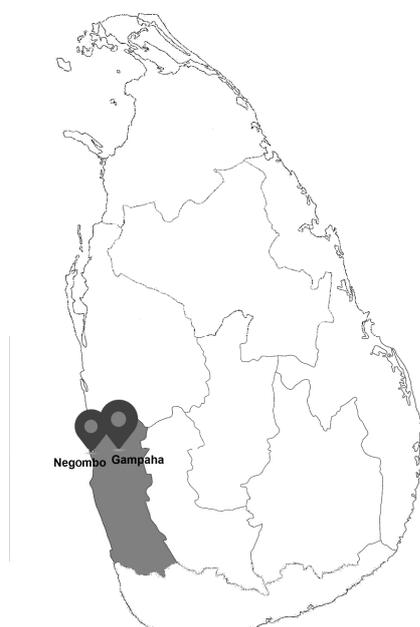
**Conclusion:** The majority of clinically diagnosed dengue patients were males. The most common clinical feature was fever with headache, myalgia and arthralgia. DHF seemed to have occurred in both primary and secondary dengue infections. Some symptoms included in the WHO guidelines such as rash, hemorrhagic manifestations and retro orbital pain were less commonly seen in the study.

*Key words: Dengue fever, dengue haemorrhagic fever, clinical profile, Sri Lanka*

## Introduction

Dengue is one of the most common arboviral diseases affecting humans in recent times. Dengue or dengue like epidemics were reported throughout the 19<sup>th</sup> and early 20<sup>th</sup> century in the Americas, Southern Europe, North Africa, the Eastern Mediterranean, Asia, Australia, various islands in the Indian ocean, the South and Central Pacific and the Caribbean.<sup>1</sup> Currently, dengue has become a major public health problem, especially in tropical and subtropical regions of the world.<sup>2</sup> In Sri Lanka, DF/DHF and dengue shock syndrome (DSS) have become the leading infective cause/s of morbidity and mortality in children and adults in the last decade.<sup>3</sup> In 2013, 32,063 suspected dengue cases were reported to the Epidemiology Unit of Sri Lanka.<sup>4</sup> Approximately 51.1% of dengue cases were reported from the Western Province (Figure 1) of the country.

The highest numbers of dengue cases were reported during the third week of January 2013.<sup>4</sup> To diagnose and manage patients with dengue, physicians in Government hospitals follow the



**Figure 1.**  
Map of Sri Lanka showing Western Province.&  
location of the 2 hospitals of study  
Negombo -a coastal town & Gampaha

dengue management guidelines developed by the Ministry of Health, Sri Lanka in collaboration with WHO. The wide range of signs and symptoms associated with severe DENV infection and the identification of those that are highly likely to be DHF and DSS is a major clinical challenge, and it is important to have laboratory support and monitoring of non-specific clinical parameters such as blood pressure, pulse rate, temperature, haematocrit, urine output and platelet count. At present, patients with platelet counts of  $\leq 100,000/\text{mm}^3$  and a platelet count between  $100,000/\text{mm}^3$ - $150,000/\text{mm}^3$  with a rapid drop are hospitalized. In addition, patients with warning signs, such as abdominal pain or tenderness, persistent vomiting, cold extremities and features of shock, evidence of fluid accumulation such as pleural effusion and ascites, mucosal bleeding, lethargy, restlessness and drowsiness, liver enlargement of  $>2\text{cm}$  and laboratory criteria including increased PCV ( $>10\%$ ), decreased platelet count ( $\leq 100,000/\text{mm}^3$ ) and elevated SGOT well above the SGPT after day 3 of fever/illness<sup>5</sup> will be admitted to facilities such as dengue high dependency units for more careful clinical monitoring.

One issue of diagnosis is the non-specific symptoms. Although a definitive diagnosis of dengue fever is made by the detection of DENV antigen/ genome and/or sero-conversion or four-fold increase in dengue specific antibodies in acute and convalescent phase of the illness and isolation of the virus, such diagnostic tests are not widely available in the country. Detection of DENV IgM antibodies or high titre of IgG antibodies with a high level of clinical suspicion of recent DENV infection can be used as an alternative to arrive at a probable diagnosis.<sup>6</sup> Therefore, periodic evaluation of the clinical profile of dengue fever would help to detect changes in presentation of this infection. Thus the current study was undertaken to evaluate the demographic and clinical profiles of suspected DF/DHF cases in 2 hospitals in the Western Province of Sri Lanka.

## Objectives

The objectives of this pilot study were to investigate the clinical and laboratory profiles of DF/DHF patients admitted to Gampaha and Negombo General Hospitals in Sri Lanka from July 2011 to July 2012 to evaluate clinical patterns to improve pattern recognition should these profiles have changed in recent times.

## Materials and Methods

This is a hospital based, descriptive cross sectional pilot study conducted in two hospitals in the Western Province of Sri Lanka from July 2011 to May 2012.

Patients were clinically identified as probable DF/DHF using the following case definitions.<sup>5</sup>

Probable DF - an acute febrile illness with two or more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, leukopenia and supportive serology when necessary.

DHF - fever or history of acute fever lasting 2-7 days, occasionally biphasic, haemorrhagic tendencies evidenced by at least one of the following: a positive tourniquet test, petechial, ecchymotic or purpura type of haemorrhages, bleeding from the mucosa, gastrointestinal tract, injection sites or other locations, haematemesis or melaena with thrombocytopenia ( $\leq 100,000/\text{mL}$ ), evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following - a rise in the haematocrit equal to or greater than 20% above the average for age, sex and population, signs of plasma leakage such as pleural effusion and ascites.

DSS - all of the above criteria for DHF plus evidence of circulatory failure manifested by rapid and weak pulse, narrow pulse pressure (20 mmHg) or hypotension for age and cold clammy skin and restlessness.

Blood samples were collected from 50 patients between fever days 2 to 7 from the Gampaha Hospital (1 paediatric ward) and 204 patients from Negombo Hospital (1 paediatric ward and 2 adult medical wards). Informed consent was obtained and a detailed clinical history taken using a CDC style questionnaire. The data were analyzed using Minitab, Version 14. Dengue IgM/IgG rapid immunochromatography assay was performed in 35 patients. NS1 assay was not performed

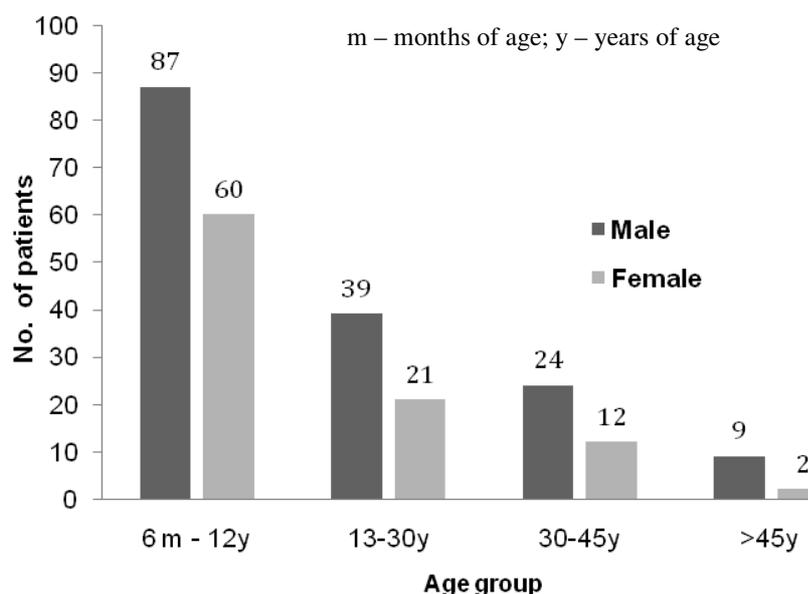
in this study because it was not freely available and was expensive during the study period. SGPT and SGOT levels were measured in 67 and 60 patients, respectively.

Non-specific laboratory tests including haemoglobin, haematocrit, total leukocyte count platelet counts and urine examination were performed in all patients. Complete blood counts including haematocrit were repeated several times daily during the critical and leaking phase of the illness in patients with DHF. Chest X-ray was taken when necessary to assess pleural effusion in most cases and repeated ultrasound scanning of the chest and abdomen were performed to see any sign of fluid accumulation either in the pleural space or in the abdominal cavity.

## Results

The age of the affected patients ranged between 6 months to 66 years (mean=12, SD=13.4).

Two hundred and fifty four patients (n=254) suspected of acute DENV infections were reported in both hospitals in the two wards under the supervision of two physicians and two paediatricians during the study period. There were 186 males and 86 females and the disease incidence was high in males. Paediatric patients (age <12years) comprised 58% (147/254) of the study population, with 87 boys and 60 girls (Figure 2).

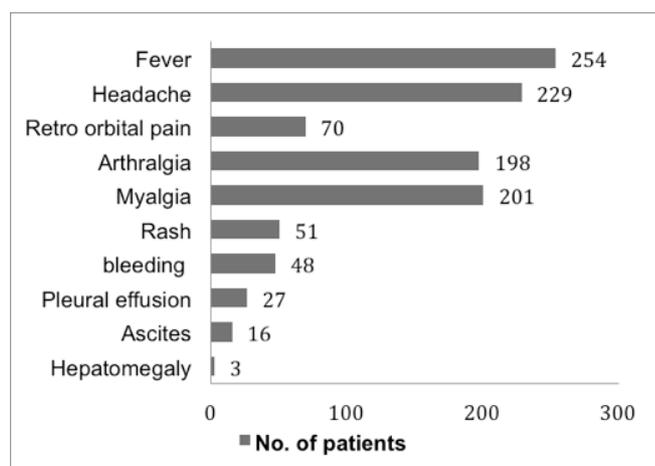


**Figure 2.** Age and gender distribution of study group

were experienced both by adults 94% (101/107) and children 87% (128/147). Arthralgia (90%; 97/107) and myalgia (97%; 104/107) were major complaints of adults. However, only 68% of children complained of arthralgia and myalgia. Retro orbital pain, rash, pleural effusion, ascites and hepatomegaly were also seen in both adults and pediatric groups. In this study, 26% of adult and 13.6% paediatric patients showed haemorrhagic manifestations. (Table 1).

Using the case definitions, 175 patients had DF, 77 patients had DHF and one patient had DSS. Of the 254 patients, one paediatric patient who had features of encephalopathy died and the patient turned out to be DENV IgM positive and IgG negative.

As shown in Figure 3, fever was seen in 254 patients (100%) and headache was a common symptom in 90.1%. Headaches



**Figure 3.** Clinical features in the study group

**Table 1.** Clinical features of paediatric and adult patients in the study group

Clinical Feature	Paediatric (%)	Adult (%)
Fever	100	100
Headache	87	94
Arthralgia	68	90
Myalgia	68	97
Retro Orbital Pain	17	41
Pleural Effusion	12	8
Haemorrhagic manifestations	19	18.6

**Table 2.** Non-specific laboratory profiles in study group (n =254)

Non-specific laboratory data	Number	Percentage (%)
Hb (haemoglobin) > 16 gm	14	5.5
PCV > 45%	49	19.3
Total WBC <4×10 <sup>3</sup> ml	193	76
Platelet count <100,000	166	65.4
Platelet count <20,000	6	2.4

Tables 2 and 3 show the results of laboratory tests performed in the study. Haemo-concentration, reflected by a raised PCV was seen in only 19.3% of the study sample. In contrast, leukopaenia (WBC < 4×10<sup>3</sup> ml) and a low platelet count was found in 76% and 65.4% of the patients respectively.

**Table 3.** DENV IgM/IgG profiles in study group (n =35)

Dengue antibody status	DF n=21		DHF n=14	
	n	%	n	%
DENV IgM	8	38	6	43
DENV IgM/IgG	13	61	8	57

Due to congestion of wards, patients are discharged from the hospital soon after recovery. As dengue IgM/IgG assay was done on fever day 6-8, it was possible to perform this test in only 14% of the study group.

## Discussion

In this pilot study, clinical features in paediatric and adult patients admitted to Gampaha and Negombo hospitals, Sri Lanka from 2011 to 2012 July with clinically suspected DF were analyzed. The majority of hospitalized patients in the study consisted of children and young adults.

In Sri Lanka historically, DF has been considered primarily as a paediatric disease. However, in the recent past, an age shift from the paediatric age group to adults has been documented in the Central, Western and Northern provinces.<sup>7</sup> Chronological overview of dengue cases in Sri Lanka

shows the age group affected by DF/DHF has shifted from <15 years to 15-34 years,<sup>8</sup> with mean age in two studies done in the Western Province from 2004 to 2006 and 2011 being 28.8<sup>9</sup> and 27.2<sup>10</sup> respectively. In contrast, the mean age of patients with DF in the current study was 13.2. The siting of the study in a hospital with 2 large paediatric wards with dengue control units could be one reason for this difference. Overall, in the country, there is evidence for increased incidence of DF/DHF in older age groups and this age shift has been reported in Singapore, Indonesia, Bangladesh and Thailand.<sup>7,11,12</sup> In Nepal, during the first-ever outbreak in 2010, the majority of cases occurred between the ages of 16 and 45 years.<sup>13</sup> In the first DF/DHF outbreak in Bangladesh, the 18-33 year age group were the most commonly affected.<sup>14</sup> It is important to note that DHF/DSS can affect infants, as shown in the current study where five 6 month old babies were diagnosed with DHF/DSS. Babies as young as 1-2 months were similarly diagnosed in a study in Thailand.<sup>11</sup>

The current study, similarly to many studies from the South-East Asian region show a higher ratio of males than females in DF/DHF hospitalized cases (India, Bangladesh, Singapore and Malaysia).<sup>9</sup> However, a few studies did not show a difference in gender distribution of DF/DHF hospitalizations.<sup>7,11,14</sup> The higher ratio of males being affected has been shown in a previous study conducted in the Western Province of Sri Lanka where it was suggested that the male gender was a risk factor for DENV infection in both paediatric and adult patients.<sup>9</sup> A different study conducted in the Central Province of Sri Lanka supports this argument and showed that a high number of males were affected by DF/DHF.<sup>15</sup> The most likely explanations for this observation are increased outdoor activities including farming and construction work coupled with male clothing in tropical countries during such work which exposes large areas of body surface resulting in increased exposure to the vector. Although suggested by several authors, no data is available on the relationship of occupations to dengue risk.<sup>16,17</sup>

The clinical spectrum of DF/DHF can vary from classical presentations of fever, rash, headache to some atypical presentations. In the current study, most adult patients presented with fever, headache, myalgia and arthralgia. However, headache, myalgia and arthralgia were less commonly expressed by the children. This difference was also noticed in a previous study conducted in the Western Province of Sri Lanka.<sup>9</sup>

Based on the findings of the current study 75.9% had leucocytopenia. Low leukocyte count in DF may be due to virus induced inhibition/destruction of myeloid progenitor cells and this has been further noted by a Japanese study in which 71% of the cases were detected as leucocytopenia.<sup>18</sup>

In the current study, the platelet count recorded was less than 100,000mm<sup>3</sup> in 65.4 % of 254 patients with all DHF patients showing <100,000mm<sup>3</sup>. Thrombocytopenia is a requirement for the diagnosis of dengue fever according to WHO guidelines<sup>19</sup> and its absence in 34.6% of the study group is noteworthy. Haematological parameters like thrombocytopenia and PCV are useful in management of DF/DHF and are widely used in many developing countries.<sup>19</sup> On the other hand, unavailability of even non-specific laboratory data like thrombocytopenia might be a challenge in some developing countries that lack laboratory resources.

A severe thrombocytopenia of less than 50,000 mm<sup>3</sup> was found in 74% of fatal cases of dengue in Thailand.<sup>20</sup> In the current study, a patient with the lowest platelet count of < 20,000 died after being unconscious for several weeks in the intensive care unit. However, this patient had features of encephalopathy and did not show any sign of haemorrhage or plasma leakage. DENV IgM was positive and IgG was negative. This patient could have had a primary DENV infection or had another arboviral infection such as Japanese encephalitis and became positive for DENV IgM due to cross-reaction with DENV antigen on testing due to antigenic similarity.

WHO classification of DHF includes haemorrhagic tendencies evidenced by a positive tourniquet test, petechial, ecchymotic or purpura type of haemorrhages, bleeding from the mucosa, gastrointestinal tract, injection sites or other locations, haematemesis or melaena with thrombocytopenia ( $\leq 100,000/\text{mL}$ ) and/or evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following - a rise in the haematocrit equal to or greater than 20% above the average for age, sex and population and/or signs of plasma leakage such as pleural effusion and ascites. The presence of haemorrhagic manifestations in the febrile phase of dengue does not indicate that the patient has DHF because haemorrhagic manifestations can be found in both DF and DHF.<sup>4</sup> In contrast, the absence of haemorrhagic features does not exclude DHF. In this study, out of 77 DHF patients, diagnosed using the WHO criteria, 32 did not show haemorrhagic manifestations.

Retro-orbital pain and rash were also not a common feature in the study group. Previous studies done in Saudi Arabia<sup>21,22</sup> show similarities to the current study in that clinical features such as hemorrhagic manifestations, rash, and retro-orbital pain were present in relatively low numbers or absent.

DENV infections were characterized using presence of DENV IgM and IgG as primary or secondary.<sup>10</sup> In primary DENV infection, there is a slow and low titer antibody response. DENV IgM antibody is the first immunoglobulin to appear which becomes detectable in 50% of patients by days 3-5 after the onset of illness, 80% by day 5 and 99% by day 10. DENV IgM peaks about two weeks after the onset of symptoms and then declines generally to undetectable levels in 2-3 months.<sup>23</sup> DENV IgG becomes detectable at low titres at the end of the first week of illness, increasing slowly thereafter and is detectable for several months, and probably even for life in many cases. In secondary DENV infection, IgG becomes detectable at high levels even in the acute phase of the illness and the rise in antibody titre happens dramatically over the following two weeks.<sup>23</sup> DENV IgM is significantly lower in secondary DENV infections and anti-DENV IgM false-negative reactions have also been observed during secondary infections.<sup>22</sup>

In this study, the samples were tested using rapid IgM/IgG assays. Since the test had to be done in private laboratories, resource limitations significantly limited the number of tests performed to 14% of the study sample.

Dengue specific IgM was positive in 38% patients with dengue fever, with 61% being dengue IgM/IgG positive. These results suggest that 38% were primary dengue fever, the remaining being either secondary dengue or due to previous flavivirus exposure. Dengue IgM positivity was seen in 43% of patients with DHF suggesting a primary dengue infection in these patients. Unsurprisingly, more patients showed secondary DENV infection in the adult cohort compared to the pediatric group.

**Conclusion:** Different DF/DHF outbreaks show different trends and clinical manifestations. In contrast to Sri Lankan studies in the recent past, the mean age of patients in the current study was 13.2 years. Similar to many studies in the Asian region, the majority of clinically diagnosed dengue patients were males. The most common clinical features were fever with headache, myalgia and arthralgia in both adults and children. Symptoms included in the WHO diagnostic criteria such as rash, hemorrhagic manifestations and retro orbital pain were less commonly seen in the study. DHF seemed to have occurred in both primary and secondary dengue infections. The absence of thrombocytopenia and leukopenia in an appreciable number of patients is noteworthy as these are clinically important diagnostic markers of dengue fever. This study demonstrates the difficulties encountered in laboratory diagnosis of dengue fever.

### Conflict of interest

None declared by the authors.

### Ethics

The ethical approval for this study was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka.

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