Usefulness of World Health Organization (WHO) dengue case classifications in a Sri Lankan clinical setting

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Abstract

Background: Dengue viral infections are a major public health problem in many tropical and sub-tropical countries of the world. Early diagnosis and appropriate therapeutic interventions are critical for reducing both morbidity and mortality. The WHO has proposed a revised classification based on warning signs as the validity and usefulness of the WHO 1997 dengue classification has been questioned in recent times. The objective of this study was to assess the usefulness and applicability of these guidelines in the clinical setting.

Methods: Clinical and laboratory findings were recorded in a standard format and cases were classified using the two classifications. Presence of warning signs in clinical DF and DHF groups were compared.

Results: One hundred and six patients with clinically suspected dengue between January and July 2010 were studied. Seventy eight (75.7%) had dengue fever (DF) and 28 (26.4%) had dengue haemorrhagic fever (DHF) according the clinical parameters. Of the patients with DHF, only five (17.9%) fulfilled all four WHO criteria for DHF. Application of the revised WHO classification revealed 19 (17.9%) dengue without warning signs, 82 (77.4%) dengue with warning signs and 5 (4.7%) severe dengue. Presence of warning signs was compared in clinical DF and DHF groups. In total, 60 (76.9%) DF and 26 (92.9%) DHF patients developed warning signs, and 1 (3.6%) DHF patient did not have any warning signs. Thirty three (42.3%) DF patients had 2 or more warning signs while 22 (78.5%) DHF patients had two or more warning signs.

Conclusion: There were limitations in applying the WHO 1997 classification in making a diagnosis of DHF. We were able to classify all patients using the revised WHO 2009 classification and is more compatible with observed clinical findings and user-friendly to the practicing physician.

Introduction

Dengue is the most important mosquito borne viral infection in tropical and sub-tropical regions. Approximately 2.5 billion people live in dengue endemic countries and estimated 50 million dengue infections occur annually[1]. In recent years, dengue epidemics have become more frequent in Sri Lanka causing rising morbidity and mortality[2-6]. Early recognition and appropriate management reduces mortality to <1%, but if left untreated may rise to as high as 20%[7]. Pioneering studies done in Thailand in the 1960s to recognize the common patterns of the dengue infection paved the way to the development of 1997 WHO dengue classification[8-12]. This classification differentiates between DF; an undifferentiated febrile illness with prominent constitutional symptoms and DHF; characterized by increased vascular permeability leading to capillary leakage[13]. DHF is further subdivided in to four grades according to the severity and grades 3 and 4 being classified as dengue shock syndrome (DSS). The 1997 WHO case definition (DF/DHF/DSS) and grading of DHF are given in Tables 1 and 2. According to this WHO case definition, diagnosis of DHF requires the presence of four criteria including bleeding tendency. However, during the last decade, clinicians experienced difficulties with this classification and noted failure to fulfill all four criteria in DHF. Several authors have reported many dengue patients progressing to dengue shock without having any bleeding manifestations[9,14-20]. The differences

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observed in the use of dengue clinical guidelines across countries led to the reassessment of these criteria by the WHO-based Special Programme for Research and Training (TDR). The global expert meeting held in Geneva in September 2008 recommended a revised case classification categorizing patients to dengue, dengue with warning signs and severe dengue (Figure 1)[21]. Objective of the present study is to assess the usefulness and applicability of the 1997 and 2009 WHO dengue classifications in a clinical setting.

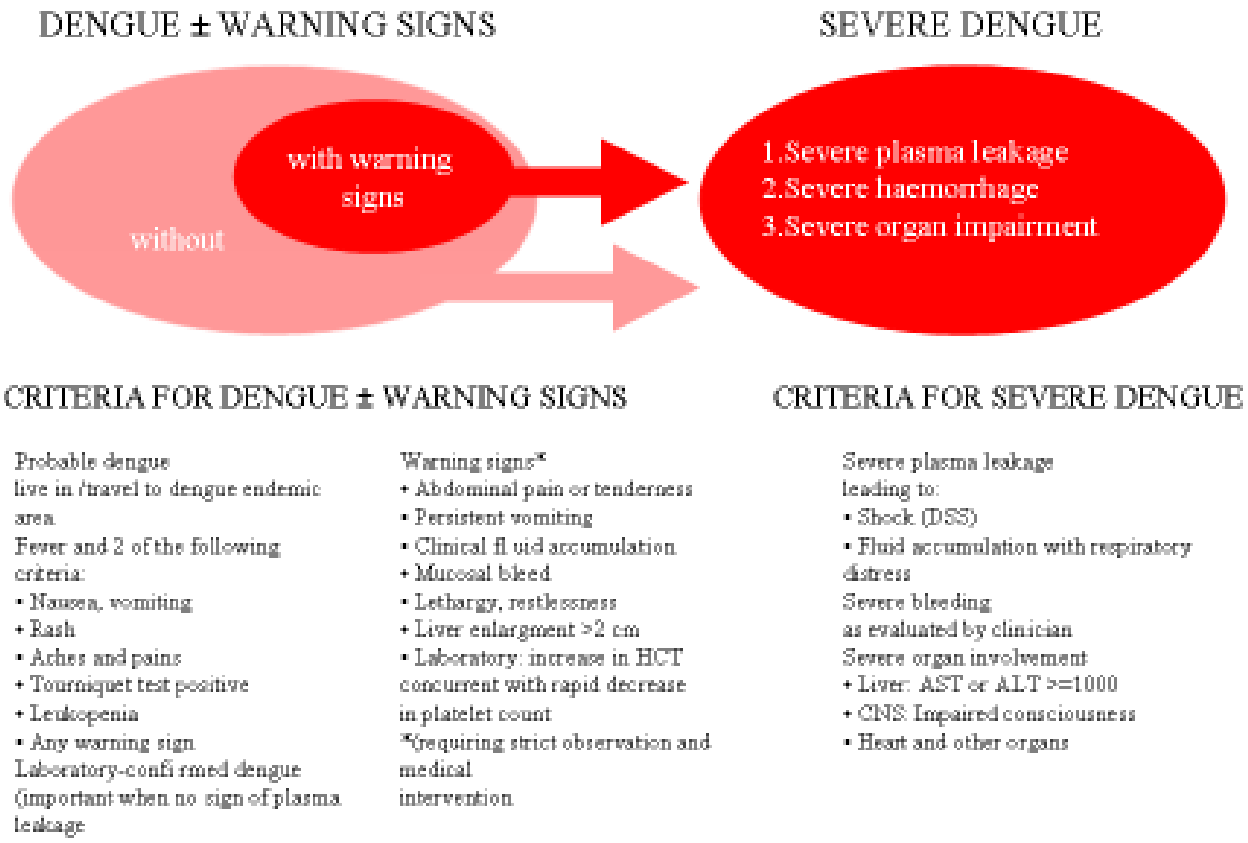

Figure 1. The revised dengue classification (Source: Dengue Guidelines for Diagnosis, Treatment, Prevention and Control, New Edition, Geneva: WHO; 2009)

Table 1. WHO case definition of Dengue Haemorrhagic Fever

DHF patients must fulfill all four of the following criteria.

1. Acute onset of fever lasting for 2 to 7 days
2. Haemorrhagic manifestations evidenced by at least one of the following; a positive tourniquet test, petechiae, purpura, ecchymoses, bleeding from mucosa, puncture sites, gastrointestinal tract or any other bleeding
3. Platelet count <100,000/l
4. Haemoconcentration as evidenced by rising packed cell volume >20% or other evidence of plasma leakage (e.g. ascites, pleural effusions, low level of serum protein/albumin)

Table 2. WHO clinical grading of DHF 1997 classification

Grade I: no shock: only positive tourniquet test
Grade II: no shock; has spontaneous bleeding other than a positive tourniquet test
Grade III: shock
Grade IV: profound shock with non measurable blood pressure or/ and pulse

Table 3. Prevalence of WHO prescribed warning sign in clinical DF and DHF patients

WHO warning sign	*Clinical DF (n=78)*	*Clinical DHF (n=28)*	*Total (n=106)*	*P value*
Increased haematocrit	36 (46.2%)	20 (71%)	58 (54.7%)	<0.05
Abdominal pain/ tenderness	47 (60.3%)	18 (64.3%)	65 (61.3%)	>0.05
Persistent vomiting	6 (7.7%)	3 (10.7%)	8 (7.5%)	>0.05
Mucosal bleeding	3 (3.8%)	5 (17.9%)	8 (7.5%)	<0.05
Fluid accumulation	0 (0%)	7 (25%)	7 (6.6%)	<0.05
Restlessness	0	1 (3.6%)	1 (0.9%)	>0.05
Hepatomegaly >2 cm	0	8 (28.6%)	8 (7.5%)	<0.05

Table 4. Number of WHO prescribed warning signs in clinical DF and DHF patients

Number WHO warning sign	*Clinical DF (n=78)*	*Clinical DHF (n=28)*	*Total (n=106)*	*P value*
0	18 (23.1%)	1 (3.6%)	19 (17.9%)	<0.05
1	27 (34.6%)	5 (17.9%)	32 (30.2%)	>0.05
2	23 (29.4%)	12 (42.9%)	35 (33%)	>0.05
3	6 (7.7%)	3 (10.7%)	9 (8.5%)	>0.05
4	4 (5.1%)	3 (10.7%)	7 (6.6%)	>0.05
5	0	4 (14.3%)	4 (3.7%)	<0.05

Table 5. Comparison of warning signs between the two WHO classifications

	Dengue		*Severe dengue*	*Total*
	Without warning signs	*With warning signs*		
DF	18 (23.1%)	60 (76.9%)	-	78 (100%) (73.6% of all)
DHF 1 & 2	-	18 (100%)	-	18 (100%) (17% of all)
DHF 3 & 4	1 (10%)	4 (40%)	5 (50%)	10 (100%) (9.4% of all)
Total	19 (17.95)	82 (77.4%)	5 (4.7%)	106 (100%)

Methods

This hospital-based prospective study was conducted at the Professorial Medical Unit, Colombo South Teaching Hospital and Infectious Diseases Hospital, Sri Lanka, between January and July 2010. Permission was obtained from the hospital ethical committees and the information obtained from the patients was treated as confidential.

All patients with suspected dengue viral infections (acute febrile illness lasting 3-7 days with two of the following criteria: vomiting, rash, myalgia, arthralgia, headache, retro-orbital pain, bleeding, shock, leucopenia and low platelet counts) were included in the study. The clinical team examined and assessed each patient twice daily and more frequently if required for their management. Signs of plasma leakage such as pleural effusions and ascites were detected clinically and selected patients were assessed radiologically. A full blood count was carried out daily and haematocrit more frequently in some patients. A rise in haematocrit (PCV) ≥20% above baseline values was considered significant. When baseline haematocrit values were not available, PCV for men and women were taken as 40 and 35 respectively. The laboratory diagnosis of dengue was by the standard serology and molecular methods[13]. Dengue warning signs were incorporated in to the routine medical charts enabling the medical team to assess and record in a daily basis. The clinical parameters and investigation findings were recorded in the same chart from admission till discharge. A trained medical officer checked the medical records for the accuracy of data recorded in the charts. The data sheets were available to the research team only after the discharge of patients. The data were entered in a standard database and analysis done using SPSS 16.0. Using the collected data each patient was classified into the subgroups within the 1997 (DF, DHF or DSS) and 2009 revised WHO dengue classifications.

Results

One hundred and six patients with clinically suspected dengue viral infections were enrolled to the study. There were 64 (60.4%) males and 42 (39.6%) females. Mean age was 29.4 (+/-SD 12) years. Dengue confirmatory tests were available in only 36 (33.9%) of patients. The clinical diagnosis of DHF was made on the basis of haemoconcentration evidenced by >20% rise in PCV, evidence of transudation, presence of shock along with thrombocytopenia. Seventy eight (73.6%) patients had DF and 28 (26.4%) had DHF. Of the patients with DHF, only five (17.9%) fulfilled all four WHO criteria for DHF, whilst 23 (82.1%) were diagnosed with DHF because they developed effusions/ and or ascites, hypotension or features of impending shock. There was no mortality within this cohort.

Prevalence of WHO prescribed warning signs is given in Table 3. Over 20% rise in haematocrit was reported in 36 (46.2%) DF and 20 (71%) DHF patients. Abdominal pain was seen in 47 (60.3%) DF and 18 (64.3%) DHF patients. Persistent vomiting was seen in 6 (7.7%) DF and 3 (10.7%) DHF patients. Mucosal bleeding (gum bleeding or epistaxis) were seen in 3 (3.8%) DF and 5 (17.9%) DHF patients. Clinically detected fluid accumulation was reported in 7 (25%) of DHF patients. Eight (28.6%) DHF and none of the DF patients had significant hepatomegaly.

The frequency of the WHO prescribed warning signs in DF and DHF is shown in Table 4. Eighteen (23.1%) DF and 1 (3.6%) DHF patient did not have any of the warning signs of dengue, 33 (42.3%) DF patients and 22 DHF (78.2%) had two or more warning signs. Table 5 gives the comparison of warning signs between the two WHO classifications.

Platelet count <100,000/l was seen in 74 (94.9%) DF and 28 (100%) DHF patients and mean platelet counts were: DF – 47,500/mm^3 and DHF – 35,000/mm^3. Platelet count <10,000/mm^3 was seen in 3 (3.8%) DF and 3 (10.7%) DHF patients. Leucopenia (< 2000 /mm^3) was seen in 36 (46.2%) DF and 17 (60.7%) DHF patients.

Discussion

Dengue infections continue to be a major health problem in Sri Lanka. In recent years, morbidity and mortality from dengue has been on the increase. During 2010 January to November, 23,178 suspected dengue cases and 163 deaths have been recorded by the Epidemiology Unit in Sri Lanka. Approximately 56.99% of these cases were from the Western Province[22]. The study period includes the month of July where the highest number of cases has been reported.

Dengue is often a clinical diagnosis. According to both classifications, dengue is suspected in a febrile patient when two of the following criteria are present; vomiting, rash, myalgia, arthralgia, headache, retro-orbital pain, bleeding, shock, leucopenia and low platelet count. The laboratory confirmation of dengue is often not available to the medical teams during the acute management as the tests are not carried out in most public sector hospitals. In our study cohort, laboratory confirmation was available only in 36 (33.9%) of patients. Barniol et al reported that laboratory confirmation of dengue is 49% in Asia compared to 65% in Latin America[23].

Capillary leakage is the hallmark of DHF. In the 1997 WHO dengue classification, diagnosis of DHF requires the presence of all four criteria including fever, bleeding tendency, thrombocytopenia and vascular leakage[24]. Due to the rigidity of diagnostic criteria most clinicians use clinical parameters in the diagnosis of DHF in clinical practice. Based on clinical criteria, i.e. presence of evidence of significant capillary leakage even without the evidence of bleeding, 24.6% of patients in the present study were classified and managed as DHF. Only five (17.9%) of them fulfilled all four criteria for DHF and the rest did not have the criterion of evidence of bleeding.

A positive tourniquet test was considered as a bleeding manifestation and an important parameter of DHF grade 1 in 1997 classification. However, in our study, positive tourniquet test was not used as an indicator of bleeding because the results of the tourniquet test were available only in 20% of patients. The clinical team did not place emphasis on the tourniquet test in taking clinical judgments as platelet counts were readily available. In the absence of a platelet count, carrying out a tourniquet test has been recommended by some authors for assessing the risk of bleeding. Further the previous studies have found that the tourniquet test did not reliably differentiate between DF and DHF[15,19] and as a result in many patients with DHF, only three out of four WHO criteria have been fulfilled.

Platelet counts were not helpful in predicting severe dengue infection or a bleeding tendency. All patients (100%) with DHF and 94.8% of DF had platelet counts less than 100,000/m^3. A relationship between the level of thrombocytopenia and bleeding manifestations were not apparent in our patients. Some patients developed severe thrombocytopenia (platelet count <10,000/mm^3) without bleeding manifestations, whilst others had mucosal bleeding despite having a platelet count of >100,000/mm^3. Previous studies have also noted similar findings and found some non-dengue related viral infections also to have similar manifestations[19, 26- 29].

The percentage increase in haematocrit is an accurate indicator of vascular permeability and plasma leakage. Significant rise was seen in 36 (46.2%) of dengue fever patients and 20 (71%) of DHF patients. Plasma leakage was suspected in other 8 DHF patients without a significant rise in PCV, due to the presence of effusions and hypotensive episodes that responded to fluid therapy. It is likely that the effect of early fluid intervention would have changed the natural course of the illness and thus produced this mixed picture. It was also reported in previous studies that in some cases the fluid leakage does not achieve a high degree haemoconcentration even if the patient is in shock[10]. In some DF patients the rise of PCV could have been due to dehydration as a result of poor intake and vomiting. Further, the absence of pre-morbid PCV levels prevented us obtaining the accurate values in some patients. As mean population PCVs for Sri Lankan males and females are not available, the standard PCV values considered by us (males, 40 and females, 35) may be too high, as poor socioeconomic conditions found in developing countries lead to anaemia and a low PCV as described in several Indian studies[30,31].

Only five patients in our cohort would have been classified as having DHF using the 1997 WHO dengue classification. Not performing tourniquet test would have been a contributory factor for this trend. Thus, in clinical practice, we found that DHF does not necessarily fulfill all four WHO criteria recommended for the diagnosis.

The WHO 2009 revised case classification use warning signs to classify patients into dengue, dengue with warning signs and severe dengue. The presence or absence of warning signs was available for all 106 patients. It was possible to classify all patients into the three categories; 19 (17.95%) without warning signs, 82 (77.4%) with warning signs and 5 (4.7%) severe dengue. Majority of patients had dengue with warning signs.

We did a comparative analysis by applying warning signs to both clinical DF and DHF patients (Table 3). A high number of patients from both groups had abdominal pain (generally confined to the epigastric and right hypochondrial regions) but there was no significant difference in the incidence of abdominal pain between DF and DHF patients. However, the high prevalence of abdominal pain demanded closer observation of these patients. Increase in haematocrit was noted in both DF and DHF, the percentage rise in the haematocrit was statistically higher among the DHF patients. Persistent vomiting was seen in both groups but there was no significant difference between the two groups. Mucosal bleeding was reported in both DF and DHF and there was a significant difference between the two groups. Thus, the presence of mucosal bleeding points to increased severity of dengue and calls for closer monitoring. Although elevated liver enzymes were seen in both groups,

significant hepatomegaly was seen only in patients with DHF. Thus, the combined presence of abdominal pain, elevated liver enzymes and hepatomegaly points to the presence of severe dengue infections.

In direct comparison of the two classifications (Table 5) 76.9% (60/78) of DF cases and 100% (18/18) of DHF cases were classified as dengue with warning signs. Therefore it is easy to pick up cases likely to progress to severe dengue by the revised classification. The presence of multiple warning signs is more likely to predict progression in to severe dengue. However, it is important to note that one patient did not have any warning signs but developed hypotension with impending shock. A classification system based on newly identified warning signs seems to be more compatible with clinically severe dengue and the clinical team was enthusiastic in detecting the warning signs. We observed that a majority of patients who were formerly considered as DF were contained in the category of 'non-severe dengue with warning signs'. Thus, close observation and timely intervention for these patients could potentially minimize the morbidity and mortality. The importance of using warning signs in primary triage and hospital management of dengue patients has been further highlighted in the Comprehensive Guidelines for the Prevention and Control of Dengue and Dengue Haemorrhagic Fever issued by the WHO in 2011. The application of clinical parameters for the evaluation of an evolving clinical condition is more likely to have diagnostic and therapeutic implications for the practicing physician. Thus, a clinically oriented, individualized monitoring and interventions for patients with dengue viral infections could potentially enhance the effective usage of health care resources. The significance of each of these identified warning signs individually and in combination need to be evaluated in larger studies. For example; abdominal pain in combination with the elevated liver enzymes and hepatomegaly had a considerably high probability of developing severe dengue.

There were no deaths in our cohort of patients. Identification of the earliest signs of fluid leakage and appropriate fluid resuscitation irrespective of ultimate clinical diagnosis would have contributed to a great extent. This is because clinical deterioration appears to be correlated with fluid leakage and not thrombocytopenia or bleeding tendency.

Conclusions

Revised WHO case classification is more useful and is applicable in the clinical setting than the 1997 WHO classification. A larger proportion of both DF and DHF had warning signs. Coexistent abdominal pain, hepatomegaly and elevated liver enzymes are associated with severe disease and indicate the need for close monitoring. The revised WHO 2009 classification is more compatible with observed clinical findings and more user-friendly to the practicing physician.

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