Original Article

Assessment of World Health Organization definition of dengue hemorrhagic fever in North India

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Abstract

Background: Classification of symptomatic dengue according to current World Health Organization (WHO) criteria is not straightforward. In this prospective study of dengue infection during an epidemic in India in 2004, we applied the WHO classification of dengue to assess its usefulness for our patients.

Methodology: The study included 145 clinically suspected cases of dengue infection of all ages. Dengue was confirmed by serological methods (IgM ELISA and HI test). WHO criteria were applied to classify dengue positive patients into Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Clinical and laboratory parameters were compared between dengue patients with bleeding and those without bleeding.

Results: Out of the 50 serologically positive cases of dengue enrolled in the study, only 3 met the WHO criteria for DHF and 1 met the criteria for DSS; however, 21 (42%) cases had one or more bleeding manifestations.

Conclusion: By using WHO criteria of DHF on Indian patients, all severe cases of dengue cannot be correctly classified. A new definition of DHF that considers geographic and age-related variations in laboratory and clinical parameters is urgently required.

Key words: dengue hemorrhagic fever, WHO dengue case classification, plasma leakage

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Introduction

Dengue, in recent years, has become a worldwide public health concern. Infection with one or more dengue viruses imperils an estimated 2.5 billion people living in tropical and subtropical countries, mostly in cities [1]. It is now endemic in more than 100 countries and the South-East Asia and the Western Pacific regions are most seriously affected [2]. In India, epidemics are becoming more frequent [3,4] and are straining the limited resources of the public health system. Many dengue cases are self-limiting but complications such as hemorrhage and shock can be life-threatening. If untreated, mortality from the complications of dengue is as high as 20%, whereas if recognized early and managed properly, mortality is less than 1% [2]; hence, it will be useful if certain symptoms, signs, and laboratory parameters associated with the development of complications are identified so that such cases would receive more attention.

The current World Health Organization (WHO) case classification of dengue into dengue fever (DF)/dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) was formulated by the Technical Advisory Committee at its meeting in Manila, Philippines in 1974. It was, to a large extent, based on the pioneering studies at the Children's Hospital, Bangkok, Thailand, in the 1960s that defined the pattern of disease of that time. Although some minor modifications have been suggested, the case definition and case classification of dengue have remained essentially the same [3,5].

The hallmark of DHF that differentiates it from DF is not hemorrhage as its name suggests, but rather the increased vascular permeability that leads to a capillary leak syndrome that may insidiously or rapidly progress to DSS. The term DHF is justified

by the presence of some form of hemorrhagic manifestations that, according to the classification, always accompany the phenomenon of increased vascular permeability [5].

According to WHO guidelines, DHF cases must fulfill all of the following four criteria:

1. Fever or history of acute fever lasting 2 to 7 days.
2. Hemorrhagic tendencies evidenced by at least one of the following: a positive tourniquet test, petechiae, purpura, ecchymoses, bleeding from mucosa, gastrointestinal tract, injection sites or other location; hematemesis; melaena.
3. Thrombocytopenia (100,000 platelets/μl or less)
4. Hemoconcentration (20% or more rise in the hematocrit (Hct) value relative to baseline average for the same age and sex) or evidence of plasma leakage (e.g. pleural effusion, ascites and/or hypoproteinaemia) [3].

In India, dengue has seen a resurgence in recent times [6,7]. In 2003, there was an outbreak of dengue in Lucknow and surrounding areas of Uttar Pradesh, India [4,8]. Although many cases of dengue with severe symptoms such as shock, hemorrhage, and plasma leakage were admitted in our wards, very few cases of DHF were documented. In 2004, again in the post-monsoon season, there was a resurgence of dengue; therefore, we undertook a hospital-based study to assess the WHO dengue classification in our region.

Materials and Methods

The present study was conducted by the Postgraduate Departments of Microbiology and Pediatrics, Chhatrapati Shahuji Maharaj Medical University (CSMMU), Lucknow, from August 2004 to July 2005. The study population was comprised of suspected dengue patients from all ages admitted in the wards of the Departments of Pediatrics and Medicine of Gandhi Memorial and Associated Hospitals (GM&AH) and Chhatrapati Shahuji Maharaj Medical University (CSMMU), Lucknow.

Lucknow is the capital of India's most populous state, Uttar Pradesh, and is situated about 500 km southeast of New Delhi in the heart of the state. The city has a humid subtropical climate and a population of over four million. Though CSMMU is situated in Lucknow, patients from faraway districts also come here for treatment because of the reputation of the centre. We also receive patients referred with severe symptoms of dengue infection.

Patients were identified as suspected dengue cases if they had acute febrile illness with one of the following symptoms: myalgia, arthralgia, headache, retroorbital pain, bleeding, shock, or low platelet count. All clinical and investigation parameters were recorded from the time of admission to the time of discharge. Signs of plasma leakage such as pleural effusion and ascites were elicited clinically, daily, and also radiologically wherever possible. The extent of hemoconcentration in our study was quantitated by measuring hematocrit $\geq$ 20% above average for age. Hypoproteinemia was said to be present when serum albumin level was less than 3g/dl. A hematocrit and platelet count was done at the time of admission. Platelet counts were repeated daily. Repeat hematocrit was done every alternate day except in serious patients with features of shock, for whom it was done every day. A tourniquet test was done on admission and in patients with shock, and it was repeated on recovery. Patients were classified as DF, DHF, and DSS according to WHO guidelines [3].

Blood samples were collected both in acute and convalescent phases of disease. Laboratory diagnosis of dengue was established when any one or more of the following criteria was fulfilled [3]:

1. A four-fold or higher rise in Hemagglutination Inhibition (HI) antibody titre in paired sera (Virology manual, National Institute of Virology, Pune, India)
2. Demonstration of specific IgM antibodies to dengue in serum with IgM antibody capture enzyme-linked immunosorbent assay (FOCUS dengue IgM capture ELISA, USA).

Statistical analysis

Statistical analysis was performed by Chi Square Test using Graph pad Prism (version 2.0, Graph pad Software). P values less than 0.05 were considered statistically significant. Yates correction was used wherever required.

Results

The study enrolled 145 clinically suspected patients of dengue admitted to pediatric and medicine wards. Of these, 109 patients were from pediatric wards with ages ranging from 5 months to 15 years,

and 36 patients were from medicine wards and were between 16 to 60 years of age.

Paired sera could be collected from only 18 patients, while only a single sample was available from the rest of the patients during the acute phase of illness.

We then compared the presence of various symptoms and laboratory findings between the two groups. There was no significant difference in symptoms and laboratory findings between the two groups (Table 1 and Table 2).

Thrombocytopenia with platelet counts below

Table 1. Clinical manifestations of serologically positive cases during year 2004-2005 and comparison of symptoms/signs between cases who developed bleeding and those who did not.

Symptom/Sign	Total (n = 50)	Dengue with bleed (n = 21)	Dengue without bleed (n = 29)	P value
Fever	50 (100.0)	21 (100.0)	29 (100.0)	1
Vomiting	28 (56.0)	10 (47.6)	18 (62.1)	0.47
Retroorbital pain	20 (40.0)	10 (47.6)	10 (34.5)	0.52
Myalgia	28 (56.0)	10 (57.6)	18 (62.1)	0.47
Rash	18 (36.0)	8 (38.1)	10 (34.5)	0.79
Hepatomegaly	20 (40.0)	10 (47.6)	10 (34.5)	0.52
Hepatosplenomegaly	4 (8.0)	1 (4.7)	3 (10.3)	0.85
Tourniquet test	1 (2.0)	1 (4.8)	0 (0.0)	--

Dengue was confirmed in 50 (34.5%) out of 145 suspected patients by serology, in 48 patients by IgM ELISA, and in 2 patients by both ELISA and HI test.

Among 109 patients in the pediatric age group, 41 (37.6%) had serological confirmation of dengue while only 9 out of 36 adult patients were dengue positive.

Of the 50 patients enrolled in the study who were serologically positive for dengue, 20 had fever alone and were labeled as DF. Only three patients fulfilled all four WHO criteria and were labeled as DHF. In the remaining 27 patients, only two or three criteria of DHF were fulfilled. All three DHF cases were less than five years of age, had fever, thrombocytopenia, and bleeding manifestations. One DHF patient had hematocrit of greater than 20% above average for age and hypoproteinaemia while two others had pleural effusion and hypoproteinemia.

Hemorrhagic manifestations were noted in 21 (42%) out of 50 dengue patients. Most common among these were petechiae and hematemesis, seen in six cases each. A combination of hemorrhagic manifestations (petechiae and hematemesis/petechiae and epistaxis/petechiae, melaena, and retinal hemorrhage) was seen in three cases.

We divided dengue-confirmed patients into two groups: dengue with bleed and dengue without bleed.

100,000/µl was seen in 7 out of 21 (33.3 %) patients with bleeding and in 9 out of 29 (31.03%) patients without bleeding; thus platelet count was not significantly associated with bleeding manifestations.

Hematocrit greater than 20% above average for age was present in only one DHF patient and this patient had bleeding manifestations. Pleural effusion was seen in two patients. Hypoproteinaemia was seen in ten (20%) patients. Tourniquet test was positive in only one patient and this patient had bleeding manifestations.

Four patients had hemorrhagic manifestations and thrombocytopenia, but no signs of plasma leakage. Fourteen patients had one or more bleeding manifestations but no other signs of DHF were seen, while nine patients had thrombocytopenia without bleeding; six of these also had hypoproteinemia but no other signs of DHF.

Three patients left the hospital against medical advice. Two of our dengue patients developed shock and died while the rest of the patients recovered.

Of these two patients, one had bleeding manifestations and thrombocytopenia but no hemoconcentration; thus this patient could not be labeled as DHF earlier but he suddenly developed

Table 2. Comparison of lab findings between serologically positive dengue cases with bleeding and without bleeding.

Lab findings	Total dengue positive cases (n = 50)	Dengue with bleed (n = 21)	Dengue without bleed (n = 29)	P value
Platelet count(/µl)				
> 100,000	24 (68.0)	11 (52.4)	13 (44.8)	0.81
<100,000	16 (30.0)	7 (33.3)	9 (31.03)	0.86
Evidence of Plasma leakage				
Hematocrit ≥ 20% rise	1 (2.0)	1 (4.8)	0 (0.0)	--
Hypoproteinemia <5.5g/dl	10 (20.0)	4 (19.04)	6 (20.7)	0.89
Pleural effusion	2 (4.0)	2 (9.52)	0 (0.0)	--

shock. The other one was a DHF case who had hypotension and died of prolonged shock.

Discussion

This is the first Indian study to assess the WHO criteria for classification of dengue severity. Epidemics of dengue have been previously reported from India and some authors have applied WHO classification retrospectively to classify dengue cases [9,10]. For the first time, we have tried to assess the WHO DHF criteria by applying them prospectively on adult and pediatric patients of dengue admitted in our tertiary care hospital.

In this study, out of 50 dengue confirmed patients, 20 were classified as DF and 3 as DHF while the remaining 27 were unclassifiable according to WHO classification.

Bleeding and thrombocytopenia have been considered reliable indicators of, or prerequisites for, the subsequent development of the shock syndrome [11]. We noted that four of our dengue patients had hemorrhagic manifestation and thrombocytopenia but no signs of plasma leakage. The development of bleeding in such cases was not associated with a positive tourniquet test. Such manifestations have been seen in other studies also and these cases are labeled as dengue with unusual bleeds [12]. It has been observed that not only are bleeding and thrombocytopenia common in children without apparent DHF, but these features are also absent in some children with "true" DHF [13].

Bleeding manifestations were noted even in the absence of thrombocytopenia in 14 of our patients as has also been previously reported [5,6]. The WHO definition does not use the current threshold for thrombocytopenia (≤ 150, 000 platelets per µl), or a level established by risk analysis; thus researchers feel that there is a need to redefine the threshold for thrombocytopenia [14].

The tourniquet test is an important diagnostic parameter as it is the only hemorrhagic manifestation seen in grade I dengue hemorrhagic fever, which might represent 15–20% of all dengue hemorrhagic fever cases. It was not found to be a sensitive test in the present study. This finding is in conformity with the observations of other workers such as Narayanan *et al.* [6], Wali *et al.* [15], and Gomber *et al.* [16]. The test needs to be reevaluated on a larger population. The tourniquet test is difficult to apply in sick and irritable children, and there is confusion in the definition of a positive result (either 10 or 20 petechiae per square inches); thus, the value of the tourniquet test is debatable or there is at least a need to clarify its standard practice [14].

Using the WHO criteria of DHF, only three patients could be categorized as having DHF. One of our patients with bleeding and thrombocytopenia did not have any evidence of plasma leakage and thus could not be classified as DF or DHF. This patient suddenly developed severe shock and died; thus fatal outcome was seen without any documented evidence of plasma leakage or hemoconcentration.

It is noted that in some cases capillary leakage does not achieve a high degree of hemoconcentration even when patients are shocked [17]. If a patient develops bleeding, the hemoconcentration may not be evident because the initial plasma leakage that precedes the bleeding will keep the hematocrit somewhat elevated. Effective early treatment of capillary leakage presents yet another problem as

appropriately hydrated cases will not show the degree of hemoconcentration required by this definition.

A large percentage of patients in the developing countries come from low socioeconomic backgrounds and have poor nutritional status with low hemoglobin levels; thus hematocrit values in these patients are already low and will not rise by this degree even with hemorrhage or shock. Gomber *et al*. and Pande *et al*. observed a high prevalence of anemia in the Indian community [16,18]; therefore, Gomber *et al*. estimated a cutoff value of hematocrit for DHF in the Indian population to be 36.3 % [16]. Though this increased the specificity, it decreased the sensitivity of picking up cases of DHF. The need to define and standardize a hematocrit and white blood cell count that could be reliable for dengue classification has been stressed by several Indian authors [10,19]. Furthermore, since the population hemoglobin is variable here, the usefulness of any such cutoff is debatable. One way to solve this problem would be to do a hematocrit early in the disease before the patient develops plasma leakage.

As for hypoproteinemia, no cutoff value has been defined and again this finding was present in only a minority of our patients. The prevalence of protein energy malnutrition is very high in Indian children [20,21]; therefore, hypoproteinaemia is already present in many of our children and thus cannot be a very reliable indicator of plasma leakage.

A plain radiograph of the chest was obtained in 80 patients. Pleural effusion was seen in only two cases both clinically and radiologically. Compared to conventional radiography, lateral decubitus chest radiography and chest sonography have been proven to be highly efficient methods to detect small amounts of pleural effusions [19]. In our study, lateral decubitus radiography was not done. The other criterion for plasma capillary leakage is that ascites may be detected clinically or on ultrasonographic examination of the abdomen [19]. We did not get clinical evidence of ascites in any of our cases. A recent Indian study found ultrasonography to be superior when compared with radiography in detecting plasma leakage [19]; however. ultrasonography is not easy in settings where dengue cases are seen, especially in sick children who would require a bedside ultrasound.

Setiati *et al*. used six modified classification systems, besides the WHO classification system, to detect patients with shock. Since all patients had fever, the other three manifestations (hemorrhagic manifestations, thrombocytopenia, and signs of leakage) were used to make the modifications. This resulted in six classification systems as follows: bleeding and thrombocytopenia; bleeding and haemoconcentration; haemoconcentration and thrombocytopenia; bleeding and thrombocytopenia or haemoconcentration; thrombocytopenia and haemoconcentration or bleeding; and lastly, haemoconcentration and bleeding or thrombocytopenia. The WHO classification system had a sensitivity of 86% for the detection of patients with shock. All modifications to the WHO classification system had a higher sensitivity than the WHO classification system (sensitivity ranging from 88% to 99%) [22]; therefore, we can question the very strict categorization of DF and DHF that may actually be part of a spectrum of disease rather than two separate entities [23].

Lastly, WHO DHF/DSS classification excludes severe dengue disease associated with "unusual manifestations" such as encephalopathy and less often encephalitis, hepatic failure, cardiomyopathy, dengue fever with severe hemorrhage, and acute respiratory distress [13]. These presentations, which are not identified by the WHO case definition, are not rare in endemic regions such as India [8,24].

Our study had three limitations: 1) the small sample size; 2) the use of dengue IgM ELISA and HI only for diagnosis due to unavailability of nucleic acid based tests in our hospital; and 3) we could not do radiography and ultrasonography on all patients for detection of plasma leakage due to financial constraints.

Conclusion

This is the first Indian study to assess the WHO criteria for classification of dengue severity in pediatric and adult patients. In our patients, hemoconcentration is not detected even in many severe dengue patients and signs of plasma leakage are difficult to document without expensive investigations. This leads to under-diagnosis and under-reporting of severe disease. There is an urgent need for new definitions of DHF that consider geographic and age-related variations and use cost-effective tests that are easily available and reproducible. Improved definitions of the various classifications of DHF will be helpful in the diagnosis and management of DHF cases.

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Ethics committee approval

Ethical approval was obtained from Chhatrapati Shahuji Maharaj Medical University Ethics Committee. This research has the acceptance of the Department of Pediatrics and Medicine of Gandhi Memorial & Associated Hospitals, CSMMU, Lucknow.

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