Evaluation of the World Health Organization 2009 classification of dengue severity in autopsied individuals, during the epidemics of 2011 and 2012 in Brazil

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ABSTRACT

Introduction: The dengue classification proposed by the World Health Organization (WHO) in 2009 is considered more sensitive than the classification proposed by the WHO in 1997. However, no study has assessed the ability of the WHO 2009 classification to identify dengue deaths among autopsied individuals suspected of having dengue. In the present study, we evaluated the ability of the WHO 2009 classification to identify dengue deaths among autopsied individuals suspected of having dengue in Northeast Brazil, where the disease is endemic. **Methods:** This retrospective study included 121 autopsied individuals suspected of having dengue in Northeast Brazil during the epidemics of 2011 and 2012. All the autopsied individuals included in this study were confirmed to have dengue based on the findings of laboratory examinations. **Results:** The median age of the autopsied individuals was 34 years (range, 1 month to 93 years), and 54.5% of the individuals were males. According to the WHO 1997 classification, 9.1% (11/121) of the cases were classified as dengue hemorrhagic fever (DHF) and 3.3% (4/121) as dengue shock syndrome. The remaining 87.6% (106/121) of the cases were classified as dengue with complications. According to the 2009 classification, 100% (121/121) of the cases were classified as severe dengue. The absence of plasma leakage (58.5%) and platelet counts $<100,000/mm^3$ (47.2%) were the most frequent reasons for the inability to classify cases as DHF. **Conclusions:** The WHO 2009 classification is more sensitive than the WHO 1997 classification for identifying dengue deaths among autopsied individuals suspected of having dengue.

Keywords: Dengue fever. Classification criteria. Warning signs. Vigilance and Control.

INTRODUCTION

Dengue is a major public health problem worldwide[1] [2]. The dengue cases in Brazil account for approximately 60% of all the dengue cases reported to the World Health Organization (WHO) from the Americas[3]. In the State of Ceará in Northeast Brazil, dengue was first noted in 1986, and it has since been endemic to the region, with many documented epidemics[4] [5].

There are difficulties in the classification of dengue cases using the WHO 1997 classification; therefore, since 2001, Brazil

has adopted the term *dengue with complications* (DWC)[4] [6]. However, the term DWC has been used only in Brazil, and its use has complicated comparisons of dengue rates between Brazil and other countries[7] [8].

In this context, based on a multicenter study [Dengue Control (DENCO)], the WHO proposed a new classification system in 2009 (WHO 2009 classification)[9]. This classification includes cases of dengue without warning signs, dengue with warning signs, and severe dengue (SD)[9] [10].

Many studies across the world have shown a higher sensitivity and greater ability to include a large number of cases with the WHO 2009 classification that with the WHO 1997 classification[8] [10] [11] [12] [13] [14] [15] [16] [17]. However, limited evidence exists on the impact of the WHO 2009 classification on the notification of deaths and on the evaluation of dengue fatality indicators around the world[18].

In Northeast Brazil, where dengue is endemic, autopsies have identified many deaths caused by dengue, although dengue was not suspected during the clinical courses of

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the patients[19]. No previous study has assessed the ability of the WHO 2009 classification to identify dengue deaths among autopsied individuals suspected of having dengue. The objective of the present study was to evaluate the ability of the WHO 2009 classification to identify dengue deaths among autopsied individuals suspected of having dengue in Northeast Brazil.

METHODS

Study design

This retrospective study evaluated dengue deaths among autopsied individuals suspected of having dengue at the Coroner's Office Dr. Rocha Furtado (CO-RF), Northeast Brazil, during the epidemics of 2011 and 2012.

All the individuals suspected of dengue were reported to the Center for Epidemiological Surveillance of the State Department of Health for epidemiological investigation. Following the report of a suspected case, the epidemiological surveillance team of the state investigates the case to confirm or exclude dengue[4] [6] [18] [20].

Data were collected from January 2011 to December 2012 using a structured questionnaire. The data included age, sex, symptoms and signs, warning signs, shock evidence (signs of poor perfusion and hypotension), effusion (ascites, pleural effusion, pericardial effusion, and respiratory distress), laboratory test results, and autopsy findings.

We systematically retrieved data from medical records, notification forms used by the Brazilian Ministry of Health, and laboratory test records for all reported cases of dengue-associated deaths during the study period.

Ethical considerations

This study followed the ethical principles of research involving human subjects prepared by the National Health Council of Brazil and was approved by the Ethics Review Boards of *Centro Universitário Christus* – UNICHRISTUS (protocol #011/2011) and *Hospital São José de Doenças Infecciosas* (protocol #078/2011). Identifying information in the medical records was codified to preserve confidentiality.

Patients and definitions

In this study, the autopsied individuals suspected of having dengue had features clinically consistent with dengue, and they underwent reverse transcription polymerase chain reaction, NS1 antigen enzyme-linked immunosorbent assay, immunoglobulin M antibody assay, virus isolation, or immunohistochemistry to confirm the presence of dengue. All the autopsied individuals included in this study were confirmed to have dengue based on the findings of the laboratory examinations.

Patients were considered to have dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS) according to the WHO 1997 classification[21]. *Dengue with complications* cases included those that did not fulfill the DHF/DSS criteria[6]. The WHO 2009 classification included non-severe dengue (NSD) and SD[9].

In this study, leukopenia was defined as a leukocyte count <1,000/mm^3, hypoalbuminemia was defined as a serum albumin level <3g/dL, liver injury was defined as an aspartate aminotransferase or alanine aminotransferase level <1,000U/L, and severe thrombocytopenia was defined as a platelet count <20,000/mm^3.

Statistical analysis

Data were stored in Microsoft Office Access version 2010 (Microsoft Corp., Redmond, WA) and analyzed using Epi Info version 3.5.1 (Centers for Disease Control, Atlanta, GA). Data were classified in accordance with the classification systems used currently in Brazil adapted from the WHO 1997 classification and the WHO 2009 classification. The descriptive analyses included the frequencies of quantitative variables, number of deaths, and case-fatality rates.

RESULTS

A total of 121 dengue deaths were investigated, and of these, 66 (54.5%) were assessed in 2011 and 55 (45.5%) were assessed in 2012. Virus isolation was possible in 20 individuals, and of these individuals, 15 (75%) had dengue virus serotype 1 (DENV-1), 3 (15%) had dengue virus serotype 4 (DENV-4), and 2 (10%) had dengue virus serotype 3 (DENV-3). The median age at death was 34 years (range, 1 month to 93 years), and 54.5% of the individuals were males.

According to the WHO 1997 classification, 9.1% (11/121) of the cases were classified as DHF and 3.3% (4/121) as DSS. The remaining 87.6% (106/121) of the cases were classified as DWC. According to the 2009 classification, 100% (121/121) of the cases were classified as SD **(Table 1)**.

The absence of plasma leakage (58.5%) and platelet counts <100,000/mm^3 (47.2%) were the most frequent reasons for the inability to classify cases as DHF **(Table 2)**.

Of the 106 cases classified as DWC, 9 (8.5%) did not fulfill any of the four criteria for DHF according to the WHO 1997 classification, 38 (35.8%) did not fulfill three criteria, 28 (26.4%) did not fulfill two criteria, and 31 (29.3%) did not fulfill one criteria.

According to the WHO 2009 classification, of the 106 cases classified as DWC, 21 (19.8%) had severe plasma leakage, 24 (22.6%) had severe bleeding, and 61 (57.6%) had severe organ involvement. Among the 21 cases with severe plasma leakage, 15 (71.4%) developed shock and 6 (28.6%) had pleural effusion with respiratory distress. Among the 61 cases with severe organ involvement, 34 (55.7%) had lesions in the central nervous system, 12 (19.7%) had lesions in the lungs, 10 (16.4%) had lesions in the heart, and 5 (8.2%) had lesions in the liver **(Figure 1)**.

With respect to the signs and symptoms, fever was noted in 87% (100/115) of the cases, and respiratory distress syndrome, persistent vomiting, cough, prostration, dyspnea, and abdominal pain were noted in over 70% of the cases **(Table 3)**.

Table 4 shows that the mean platelet count was 71,000/mm^3 (range, 0 to 487,000/mm^3).

TABLE 1 - Comparison of the World Health Organization 1997 classification adapted by Brazil and the WHO 2009 classification for the 121 autopsied individuals in Northeast Brazil in the 2011 and 2012 dengue epidemics.

	Dengue		Dengue with warning signs		Severe dengue		Total	
	n	%	n	%	n	%	n	%
DF	-	-	-	-	-	-	-	-
DWC	-	-	-	-	-	-	106	87.6
DHF	-	-	-	-	-	-	11	9.1
DSS	-	-	-	-	-	-	4	3.3
Total	-	-	-	-	121	100.0	121	100.0

WHO: World Health Organization; **DF:** dengue fever; **DWC:** dengue with complications; **DHF:** dengue hemorrhagic fever; **DSS:** dengue shock syndrome.

TABLE 2 - Criteria not met in the 106 cases for classification as DHF.

Criterion	Number	Percentage
Plasma leakage	62	58.5
Platelet count <100,000/mm³	25	47.2
Bleeding	16	26.2
Fever	15	15.0

DHF: dengue hemorrhagic fever.

TABLE 3 - Signs and symptoms of the 121 cases of dengue-related death during the 2011 and 2012 epidemics in the State of Ceará, Brazil.

| Signs and symptoms	Number/total	Percentage
Fever	100/115	87.0
Respiratory discomfort	79/92	85.9
Persistent vomiting	76/95	80.0
Cough	67/88	76.1
Abdominal pain	68/90	75.6
Headache	60/81	74.1
Prostration	41/56	71.9
Myalgia	49/73	67.1
Somnolence	45/70	64.3
Irritability/agitation	47/75	62.7
Diarrhea	39/68	57.4
Sensorial loss	32/65	49.2
Arthralgia	24/54	44.4
Hematemesis	25/65	38.5
Petechiae	24/64	37.5
Convulsion	22/63	34.9
Retro-orbital pain	14/51	27.5
Melena	13/57	22.8
Bruise	12/56	21.4
Exanthema	11/55	20.0
Hematoma	9/51	17.6
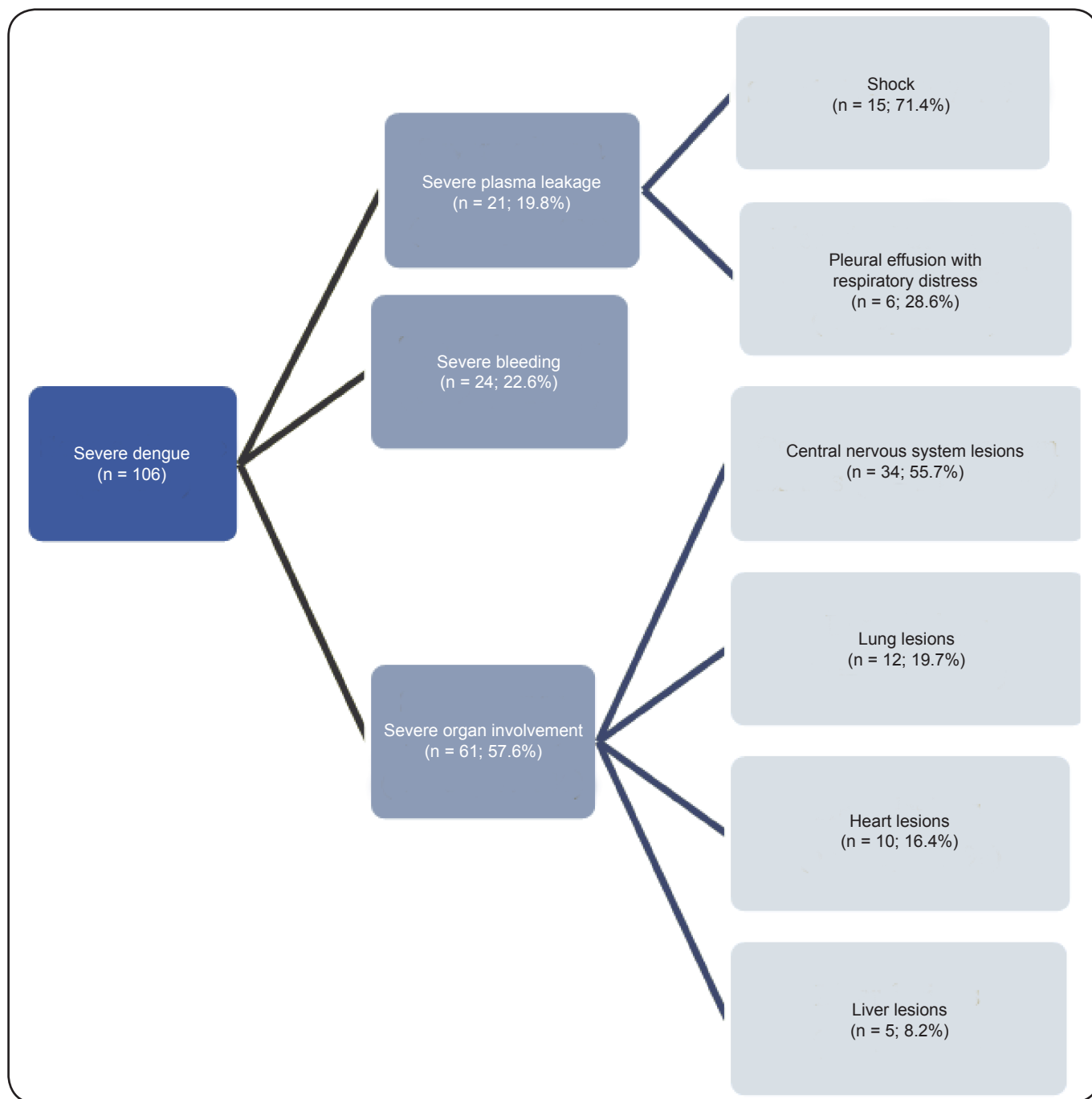
FIGURE 1 - Characteristics of the 106 cases classified as dengue with complications according to the World Health Organization 1997 classification adapted by Brazil and as severe dengue according the 2009 WHO classification. WHO: World Health Organization.

TABLE 4 - Laboratory results of the 121 cases of dengue-related death during the 2011 and 2012 epidemics in the State of Ceará, Brazil.

Laboratory parameters	Minimum	Mean	Median	75th percentile	Maximum
Platelet count (/mm³)	0	104,950	71,000	148,500	487,000
Lower hematocrit (%)	9.3	29.7	29.2	38.7	51.6
Hematocrit (%)	15.0	38.0	38.6	45.7	54.3
White blood cell (/mm³)	1,000	13,936	9,800	19,400	64,500
AST (U/L)	29	460	129	302	3,200
ALT (U/L)	13	332	77	151	4,380

AST: aspartate aminotransferase; **ALT:** alanine aminotransferase; **U/L:** units per liter.

Of the 121 dengue-associated deaths, 27 (22.3%) occurred in the absence of medical assistance and 94 (77.7%) occurred after hospitalization.

DISCUSSION

In the present study, of the 121 cases, 106 (87.6%) were not classified as DHF/DSS because the WHO 1997 criteria were not fulfilled, which indicates the low sensitivity of the WHO 1997 classification for the detection of severe cases[8] [15] [16] [17] [22] and emphasizes the importance of adopting the WHO 2009 classification[10]. Using the WHO 2009 classification, we found that all autopsied individuals in this study could be considered as having SD, suggesting that the WHO 1997 classification is unable to identify severe cases, including those with a high probability of death. Based on these findings, from an epidemiological viewpoint, countries that use only the DHF criteria in a strict sense may tend to underreport dengue-associated deaths when considering only deaths due to DHF[23].

In the present study, five laboratory techniques were used to evaluate the presence of the dengue virus. The Brazilian Ministry of Health and the State Department of Health in Ceará recommend that all dead individuals suspected of having dengue undergo post-mortem examination[6], and this protocol allows the confirmation of dengue in suspected dengue deaths that would have been otherwise unconfirmed[19]. Findings from previous studies reinforce the importance of using techniques to confirm dengue in post-mortem examinations of individuals suspected of having dengue, especially children[15] [24].

The post-mortem examinations performed by the Coroner's Office *Dr. Rocha Furtado* identified the presence of plasma leakage and bleeding, and evidence of comorbidities that were not reported during the clinical course of the disease. These findings contributed to the classification of the cases as DHF, although the cases did not completely fulfill the WHO 1997 criteria, and similar findings have been reported in other countries[25] [26]. A recent study of 13 autopsied children with dengue reported thrombocytopenia in all the children[23]. However, in that study, only individuals who fulfilled all four criteria for DHF according to the WHO 1997 classification underwent post-mortem examination. Comparison of this previous study with the present study is difficult because in the previous study, autopsies were performed because a diagnosis of DHF had already been made, while in the present study, dengue was diagnosed only after the post-mortem examination.

Many studies have reported on autopsies of patients who died from dengue; however, most of the patients in those studies died from DHF. In the present study, the majority of dengue cases did not fulfill all the criteria for DHF/DSS and dengue was confirmed only after autopsy completion. In the literature, such cases are usually described as atypical manifestations, published as separate reports, or described as exotic findings after autopsies[27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37].

We found that patients aged >65 years had a high possibility of death, which may be related in part to the high frequency of comorbidities reported in the elderly[38] [39] [40] [41] [42] [43] [44].

Information on comorbidities is not included in the Brazilian Information System for Notifiable Diseases, and this information is obtained only through investigation of fatal dengue cases[40] [42].

An important issue with the WHO 1997 classification is that countries usually adopt different methods to calculate fatality from dengue, and comparison of dengue case-fatality rates among different countries is difficult because countries interpret the DHF definition differently[45] [46]. We believe that the WHO 2009 classification facilitates comparisons of results and data from different countries.

In Brazil, fatality from dengue is calculated by dividing the number of DHF deaths by the number of confirmed cases of DHF. However, this indicator is influenced by the surveillance capacity to capture all suspected cases of DHF. Additionally, some regions divide the number of DHF deaths by population size. The WHO 2009 classification proposes that countries calculate the fatality from SD by dividing the number of deaths from SD by the population of each region, and then multiplying the obtained value by 1,000. The adoption of the WHO 2009 classification should improve the comparison of dengue fatality rates among different countries because it captures severe cases[8] [15] [22]. It is believed that if this indicator is used, the fatality rates from dengue can be easily compared among different regions, considering population size and the impact of the disease in each region.

One important limitation of this study is that it included a small number of cases. The study could not obtain data from many patients because some were not hospitalized and epidemiological investigations were performed after post-mortem examinations.

The WHO 2009 classification is more sensitive than the WHO 1997 classification for identifying dengue deaths among autopsied individuals suspected of having dengue.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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