Comparison of severity of dengue cases according to the dengue classification and the dengue revised classification

Kleber Giovanni Luz1, Ana Beatriz Seabra Santos de Araújo2, Glaucio Igor Viana dos Santos3, Luisa Silva de Sousa2, Maria Beatriz Nóbrega Eberlin3, Sâmia Costa Pinheiro Guerra2, Yngra Bastos Mesquita Minora de Almeida2

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ABSTRACT: Introduction: Two classifications stratify cases of dengue according to clinical and laboratory findings: the classification proposed in the 50s and the classification revised by the World Health Organization (WHO), which has been adopted in Brazil since January 2014. Our objective was to compare the two classification methods regarding their capability of identifying the severity of each case. Methods: Cross-sectional observational study with analysis and comparisons of dengue cases which occurred from 2011 to 2013 in a tertiary referral hospital in the city of Natal/RN, Brazil, according to the Dengue Classification and the Revised Dengue Classification. The equivalence adopted was: Classic Dengue and Dengue Hemorrhagic Fever (DHF) grade I with Dengue; DHF grade II with Dengue with warning signs and DHF III and IV with Severe Dengue. Results: 2,318 records were analyzed, with a mean age of 30.32 years ± 17.89, and a population 39% male and 61% female. Based on the designated equivalence, 428 cases were concordant, 699 were discordant (212 classified as Classic Dengue and Dengue with warning signs – mucosal bleed, 62 as Classic Dengue and Dengue with warning signs – abdominal pain) and 1,191 “without classification” (cases whose medical records did not allow classification). Conclusion: The two classifications were equivalent in clinical management when cases were severe. The old classification avoids an overestimation of mild and moderate cases by using more clinical and laboratory aspects than the new classification. Mucosal bleed, abdominal pain and vomiting did not represent signs that evolved to severity, demonstrating how the imprecise use of warning signs can overestimate the data.

Keywords: Dengue; Dengue classification; Arbovirus infections; Classification; Severe dengue.

RESUMO: Introdução: Existem duas classificações que estratificam os casos de dengue pelo quadro clínico laboratorial: a

1. Federal University of Rio Grande do Norte (UFRN), Hospital Giselda Trigueiro (HGT). Infectious disease physician with medical residency in the Emilio Ribas Institute of Infectious Diseases - SP, Master in Pediatric Medicine by UNIFESP and PhD in Infectious Diseases by USP-SP. ORCID: https://orcid.org/0000-0003-3025-0660. E-mail: klebergluz@gmail.com
2. Federal University of Rio Grande do Norte. General practitioner by UFRN. ORCID: Araujo ABS - https://orcid.org/0000-0001-9868-9894; Sousa LS - ORCID: https://orcid.org/0000-0001-7467-5025; Eberlin MBN - https://orcid.org/0000-0003-4851-154X; Guerra SCP - https://orcid.org/0000-0002-1987-298X; Almeida YBMM - https://orcid.org/0000-0002-7781-8869. E-mail: anabeatrizss@gmail.com, luisasilvasousa@hotmail.com, mbianobrega@gmail.com, sameacosta@gmail.com, yngrabastos@gmail.com.
3. Federal University of Rio Grande do Norte, Hospital Giselda Trigueiro. ORCID: https://orcid.org/0000-0001-7309-6806. E-mail: glaucoviana@hotmail.com. Infectious disease practitioner with medical residency in the Federal University of Rio Grande do Norte. 

Author for correspondence: Luisa Silva de Sousa. Rua Pinto Martins, 954. Areia Preta, Natal, RN. Brazil. CEP: 59014-060. E-mail: luisasilvasousa@hotmail.com.
INTRODUCTION

The dengue fever is the most important arboviral disease today because of its significant rates of morbidity and mortality. The number of cases of dengue in Brazil have increased significantly, from 40,179 cases in 1990 to 1,500,535 in 2016. Dengue epidemics have also increased in the last ten years, since the disorganized urbanization process generates an infrastructure deficit which, in turn, impairs the traditional vector control strategies for the Aedes Aegypti.

The Aedes Aegypti infestation index included 80.84% of the cities in the state of Rio Grande do Norte (RN) in 2016. Among the suspected cases of dengue, there was a cumulative incidence of 1,844.24/100,000 inhabitants, a number substantially higher than the previous year, which had an incidence of 815.59/100,000 inhabitants.

In the history of the study of dengue, its different clinical manifestations were initially classified by the World Health Organization (WHO) in the 1970s as: the asymptomatic form, in which the presence of the virus in the body is clinically inapparent; the classic dengue fever; dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). DHF and DSS have an onset similar to classic dengue; however, in DHF, spontaneous or induced hemorrhage appears between the 2nd and 3rd day of illness, in addition to laboratory abnormalities, such as thrombocytopenia, hematocrit elevation by more than 20%, fluid accumulation in serous cavities, such as pleural effusion, ascites and pericardial effusion, and hypoalbuminemia. The condition can progress to shock (DSS), with symptoms related to circulatory insufficiency. This stage is diagnosed through the presence of fast and weak pulse, narrow pulse pressure (when there is a difference less than or equal to 20 mmHg between systolic and diastolic pressure) and signs of hemodynamic instability: tachycardia, cold extremities and slow capillary refill time or hypotension. DHF and DSS have four degrees of severity: in grade I the only hemorrhagic manifestation is a positive tourniquet test; in grade II, the bleeding is spontaneous: epistaxis, gingival bleeding, metrorrhagia, petechiae, hematuria, gastrointestinal bleeding and hemoptysis. In grade III signs of circulatory failure appear (cold and clammy skin, agitation, rapid and weak pulse, postural hypotension, narrow pulse pressure and hypotension). Grade IV corresponds to decompensated shock.

Studies with the WHO dengue case classification demonstrated 62% sensitivity in the detection of dengue shock syndrome and 92% specificity in cases requiring intervention. These results and results from other studies have raised questions about the accuracy of this classification, especially for the detection of severe cases of dengue.

In 2009, the WHO published the revised dengue classification, which divides cases in: dengue, dengue with warning signs and severe dengue. Brazil adopted this classification in 2014 and has been using it as a guide for the clinical management of the disease.

Suspected cases of dengue correspond to individuals who live or have traveled to a dengue-endemic area or countries with the Aedes aegypti mosquito in the last fourteen days, who have fever lasting between two and seven days, and who present two or more of the following symptoms: nausea, vomiting, rash, myalgia, arthralgia, headache, retro-orbital pain, petechiae, positive tourniquet test or leukopenia. A suspected case of dengue with warning signs is any case of dengue fever that presents certain warning signs or symptoms around the time of defervescence. A suspected case of severe dengue is any case of dengue that has one or more of the following symptoms: shock, pulse pressure ≤ 20 mmHg; delayed hypotension; fluid accumulation with respiratory distress; severe bleeding as evaluated by clinician or severe organ involvement.

A suspected case of dengue case is confirmed through laboratory tests: IgM serology, NS1 rapid test or
ELISA test, virus isolation, polymerase chain reaction – PCR or immunohistochemistry. Any suspected dengue case that has one or more of the following criteria will be ruled out: negative laboratory diagnosis (with samples collected at the appropriate time); does not meet clinical and epidemiological dengue criteria; has a positive laboratory diagnosis for another clinical entity; is a case without laboratory examination with clinical and epidemiological criteria compatible with other diseases.

The emphasis on the warning signs in the revised WHO classification (2009) is an attempt to improve the accuracy of the classification of dengue cases, especially in the more severe presentations of the disease. However, it is necessary to compare it with the old classification to determine which one is more accurate. Thus, the present study compared these two classifications on their ability of identifying and stratifying cases of dengue as mild, moderate and severe.

METHOD

This is an observational study with a cross-sectional design analyzing and comparing cases of dengue according to the old classification and the revised classification.

The study object was the dengue notification forms found in the Information System for Notifiable Diseases (SINAN), which were filed at the Epidemiology Center of Hospital Giselda Trigueiro (HGT). The files with a case notified as suspected dengue (ICD 10: A 90.0 and A 90.1) in the years 2011, 2012 and 2013 and with enough information to stratify the case according to the two classifications were included in the study.

The records that did not have all the necessary information to classify the case were denominated “without classification” and excluded from the Kappa calculation. A predominantly adult population was studied, with a mean age of 30.32 years ± 17.89, and with 687 females (61%), compared to 440 (39%) males.

The data used for the classifications were the clinical signs, symptoms, complementary examinations and the observations obtained from the medical records in each case, which makes this a qual-quantitative study. In addition, the following epidemiological information was extracted: number of the notification form, age, gender, city of residence, date of first symptoms and date of hospitalization.

Data was collected from July 2014 to January 2015 in the premises of the HGT Epidemiology Center. The preparation for data collection emphasized the two different classifications and the adaptations made to the classifications' criteria, which are explained below. The first 100 questionnaires collected were treated as pilot study and were analyzed to correct incompatibilities and determine improvements for the data collection.

In this study, individuals with febrile syndrome who did not meet the following criteria for dengue hemorrhagic fever (DHF) were classified as classic dengue according to the old classification: platelets below 100,000/mm²; presence of hemorrhagic manifestations (spontaneous or positive tourniquet test); plasma extravasation (hemoconcentration with 20% increase above the lowest recorded hematocrit or a hematocrit to hemoglobin ratio greater than or equal to 3:2; presence of effusion and/or hypoproteinemia).

The stratifications according to the revised classification followed WHO guidelines on the concepts of suspected case of dengue, dengue with warning signs and severe dengue. Some criteria for dengue with warning signs had to be adapted because they were not specified in the notification forms. Records of intense and continuous abdominal pain were considered as presence of abdominal pain; vomiting as persistent vomiting; hemoptysis was included as mucosal bleed, whereas hematuria was not; hepatomegaly evidenced within the signs and symptoms or by abdomen ultrasound, not concomitant with hepatotropic viruses, was considered independently of a measurement. This was necessary because the information available on the records was not enough to specify these signs and symptoms.

In cases with bleeding, the data collection instrument did not contain severity assessment; therefore, metrorrhagia was considered as mucosal bleed – a warning sign – rather than as severe bleeding.

The relationship between the classifications was determined by the researchers and overseen by the supervisor. The correlations between the old classification and the revised classification were: classic dengue and DHF grade I with dengue; DHF grade II with dengue with warning signals; DHF grade III and IV with severe dengue.

The results were organized in Excel and contained the epidemiological data, the old classification, the new classification and the comparison between the classifications – concordant or discordant. Comparisons with results involving less than 6 cases were not analyzed, since they were not significant in relation to the total population studied.

RESULTS

The total amount of SINAN’s dengue notification forms in the survey of suspected dengue cases between 2011 and 2013 treated in the HGT was 2,318 (Table 1). Among these, 1191 (51.35%) did not meet the inclusion criteria and were considered as “without classification” and excluded from the Kappa calculation; 428 (18.5%) cases had concordant classifications and 699 (30.15%) were discordant. A predominantly adult population was studied, with a mean age of 30.32 years ± 17.89, and with 687 females (61%), compared to 440 (39%) males.
Discordant cases were organized by comparing the old classification with the revised classification and specifying the reason for the divergence (Table 02). Discordances below six cases were considered non-significant.

The concordant cases were specified (Table 03) and, according to the correlation between the classifications proposed in this study, the highest equivalence was in the cases with spontaneous bleeding and other warning signs: DHF grade II and dengue with warning signs (44%).

| Year | Concordant | Discordant | Without classification | Total analyzed |
|------|------------|------------|------------------------|----------------|
| 2011 | 207        | 248        | 611                    | 1066           |
| 2012 | 162        | 342        | 542                    | 1046           |
| 2013 | 59         | 109        | 38                     | 206            |
| Total| 428        | 699        | 1191                   | 2318           |

Table 2 – Total number of forms corresponding to discordant classifications in 2011, 2012 and 2013

| Old Classification | Revised Classification | Total (n) | Total (%) |
|--------------------|------------------------|-----------|-----------|
| Classic dengue     | Dengue with warning sign (mucosal bleed) | 212 | 30.3 |
| Classic dengue     | Dengue with warning sign (abdominal pain and vomiting) | 64 | 9.2 |
| Classic dengue     | Dengue with warning sign (abdominal pain) | 62 | 8.9 |
| Classic dengue     | Dengue with warning sign (vomiting) | 57 | 8.2 |
| Classic dengue     | Dengue with warning sign (abdominal pain and mucosal bleed) | 48 | 6.9 |
| Classic dengue     | Severe dengue (narrow pulse pressure) | 37 | 5.3 |
| Classic dengue     | Dengue with warning sign (mucosal bleed and vomiting) | 31 | 4.4 |
| Classic dengue     | Dengue with warning sign (abdominal pain, vomiting and mucosal bleed) | 24 | 3.4 |
| Classic dengue     | Severe dengue (melena) | 19 | 2.7 |
| DHF grade II       | Dengue | 15 | 2.1 |
| DHF grade II       | Severe dengue (hematemesis and melena) | 15 | 2.1 |
| DHF grade II       | Severe dengue (hematemesis and melena) | 11 | 1.6 |
| DHF grade II       | Severe dengue (melena) | 10 | 1.4 |
| Classic dengue     | Severe dengue (hypotension) | 9 | 1.3 |
| Classic dengue     | Severe dengue (hypotension and narrow pulse pressure) | 9 | 1.3 |
| Classic dengue     | Dengue with warning sign | 8 | 1.1 |
| Classic dengue     | Severe dengue (impaired consciousness) | 6 | 0.86 |

*Non-significant discordances were those with less than six cases.
DISCUSSION

This original study in Rio Grande do Norte aimed to compare the old dengue classification and the revised classification as to their effectiveness in the stratification of cases of dengue as mild, moderate and severe.

The cases considered severe were those that progressed to DSS (with or without death). Thus, any symptom that suggested a progression of clinical status to a severe case represented an important warning sign for adequate stratification. The multicenter DENCO study found that mucosal bleed was an important warning signal. However, in the present study, mucosal bleed represented an overestimated warning signal, since 212 cases classified as classic dengue fever and dengue with a warning signal (in the old and revised classifications, respectively) did not evolve to DSS and/or death.

Overestimation of warning signs could lead to a larger number of hospitalizations for early therapeutic management, aimed at preventing the progression and worsening of the disease. According to a study carried out in Nicaragua, this increase in hospital admissions does not reliably reflect the severity of all cases, requiring a posterior analysis of the patients to determine their true condition. This can lead to saturation of the health system and a subsequent increase in expenses in public health, since cases of low or moderate severity would be treated in ways inappropriate to the actual clinical situation. A possible explanation for this fact is that the revised classification relies only on clinical criteria for the definition of severe cases, while the old classification also considers laboratory parameters.

In addition, the 62 discordant cases classified as classic dengue and dengue with a warning sign due to the presence of abdominal pain demonstrated another overestimated warning sign, since none of these individuals evolved to severe dengue. This symptom was subjectively evaluated, since in the forms consulted there was no reference to the intensity and duration of pain. In addition, according to the WHO, for abdominal pain to be considered a warning sign it should be intense and continuous, but there are no specific parameters to quantify this, which makes it difficult for the healthcare professional to properly stratify the case.

Therefore, an analogue pain scale, capable of assessing pain intensity in a scale from 0 to 10 (in which 0 represents the absence of pain and 10 the stronger pain felt by the patient), could be a practical and useful instrument, which would help the patients to quantify their pain and the health professional to classify the case more accurately.

Regarding the symptom ‘vomiting’, it should be considered a warning sign when: vomiting is persistent, with three or more episodes within one hour or five or more episodes within six hours. Thus, in the data analysis, 57 individuals classified as classic dengue and as dengue with a warning sign had vomiting as a registered warning sign, but did not evolve to severe dengue. This sign was also overestimated, since there was no record of the frequency and number of vomiting episodes. In addition, vomiting could be caused by the disease itself or by medication abuse, which hinders a realistic classification.

It could be imagined that the concomitant presence of two or more warning signs mentioned above (n=167) would mean a more severe clinical picture. However, these patients did not present this progression, showing once again that mucosal bleed, abdominal pain and vomiting are overestimated warning signs.

According to the revised classification, narrow pulse pressure is a sign of shock. In this study, 37 cases of narrow pulse pressure were classified as severe dengue, but were not classified as DHF in the old classification. Possible reasons for this discordance are: lack of laboratory tests, a single examination or inability to find bleeding due to shock.

A similar situation occurred with the nine cases classified as classic dengue and severe dengue due to hypotension (blood pressure lower than 90x60 mmHg), in which hemodynamic change may have occurred without capillary leak, which is an important aspect, since every patient with hypotension is severe. In this sense, the revised classification highlights narrow pulse pressure as a sign of severity without requiring bleeding.

In addition, thrombocytopenia and hematocrit tests may not provide timely results for the definition of a proper management in these specific cases. This issue coincides with a likely limitation of the old classification related to the waiting time for results before stratifying the case, wasting time that may be essential for an appropriate conduct.

| Old Classification | Revised Classification | Total (n) | Total (%) |
|--------------------|------------------------|----------|----------|
| Classic dengue     | Dengue                 | 163      | 38.1     |
| DHF grade I        | Dengue                 | 5        | 1.2      |
| DHF grade II       | Dengue with warning signs | 189   | 44.1     |
| DHF grade III      | Severe dengue          | 65       | 15.2     |
| DHF grade IV       | Severe dengue (Death)  | 6        | 1.4      |

Therefore, an analogue pain scale, capable of assessing pain intensity in a scale from 0 to 10 (in which 0 represents the absence of pain and 10 the stronger pain felt by the patient), could be a practical and useful instrument, which would help the patients to quantify their pain and the health professional to classify the case more accurately.

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