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

Comparação da gravidade dos casos de dengue segundo a classificação antiga e a classificação revisada

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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 $\pm$ 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

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classificação proposta nos anos 50 e a revisada pela Organização Mundial de Saúde, adotada em janeiro de 2014 no Brasil. Compará-las quanto à capacidade de identificar a gravidade do caso representa nosso objetivo. Métodos: Estudo observacional e transversal com análise e comparação dos casos de dengue de 2011 a 2013 de um hospital terciário de referência da cidade de Natal/RN, de acordo com a classificação antiga e a classificação revisada. As correspondências adotadas foram: Dengue Clássica e Febre Hemorrágica da Dengue (DHF) grau I com Dengue; DHF grau II com Dengue com sinais de alarme; DHF grau III e IV com Dengue grave. Resultados: 2.318 fichas foram analisadas, com a população predominantemente adulta, média de idade 30,32 anos $\pm$ 17,89, sendo 39% do sexo masculino, 61% do sexo feminino. A partir das correlações designadas, 428 casos foram

concordantes, 699 discordantes e 1191 “sem classificação” (casos cujos dados dos prontuários não possibilitaram sua classificação). Conclusões: As duas classificações foram equivalentes no manejo clínico quando os casos de dengue foram graves. A classificação antiga evita a superestimação de casos leves e moderados por utilizar mais aspectos clínicos e laboratoriais que a classificação revisada. Sangramento de mucosa, dor abdominal e vômitos não representaram sinais que evoluíram para gravidade, demonstrando como a utilização dos sinais de alarme de maneira imprecisa pode superestimar os dados.

Descritores: Dengue; Dengue/classificação; Infecções por arbovirus; Classificação; Dengue grave.

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 2016¹. 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*².

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 inhabitants³.

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)^{4,5,6}.

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 cardiocirculatory failure appear (cold and clammy skin, agitation, rapid and weak pulse, postural hypotension, narrow pulse pressure and hypotension). Grade IV corresponds to decompensated shock⁷.

There are also unusual clinical forms of dengue, which cause organic damage such as acute renal failure, encephalopathy, cardiomyopathy or dengue liver injury⁸.

Studies with the old WHO dengue case classification demonstrated 62% sensitivity in the detection of dengue shock syndrome and 92% specificity in cases requiring intervention.⁹ 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^{9,10,11}.

In 2009, the WHO published the revised dengue classification, which divides cases in: dengue, dengue with warning signs and severe dengue¹². Brazil adopted this classification in 2014 and has been using it as a guide for the clinical management of the disease¹³.

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 $\leq$ 20 mmHg; delayed hypotension; fluid accumulation with respiratory distress; severe bleeding as evaluated by clinician or severe organ involvement^{12,13}.

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^{12,13}.

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 disease¹⁴. 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 filled 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 $\pm$ 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 quali-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/mm³; 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 $\pm$ 17.89, and with 687 females (61%), compared to 440 (39%) males.

Table 1 – Number of forms analyzed according to equivalence/year

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

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%).

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
Sum of non-significant discordances*		62	8.9

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

Table 3 – Number of forms corresponding to concordant classifications in 2011, 2012 and 2013

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

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^{15,16}. However, in the present study, mucosal bleed represented an overestimated warning sign, since 212 cases classified as classic dengue fever and dengue with a warning sign (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 Nicaragua¹⁷, 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 hours¹⁸. 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.

The individuals (n=15) who presented melena and hematemesis were classified as DHF grade II and severe dengue, that is, they were equivalent in initial management and conduct (hospitalization), but discordant regarding the classifications.

In six cases, there was disagreement between the classifications of classic dengue and severe dengue due to impaired consciousness. Sensory changes may be related to conditions such as central nervous system (CNS) bleeding or encephalitis. Therefore, they represent a sign of severity and the individual should be treated as severe.

The comparisons that involved less than 6 cases were not analyzed due to their low significance in relation to the studied population.

One advantage of this study was the fact that the data was collected from a primary source: the SINAN file adapted by the HGT Epidemiology Center. Its content includes more information than the original file, such as the presence of additional observations addressing data important for the stratification, such as the value of blood pressure.

The study was limited to the cases treated in the HGT and may not have represented the scenario of the state of Rio Grande do Norte in general, since the hospital is a tertiary care center that serves predominantly the adult population of the city of Natal. In addition, this population is predominantly white (44.5% white according to IBGE 2010), which may have restricted the analysis.

The general principle of the old classification of

using laboratory data as diagnostic criteria, compared to the use of clinical data in the revised classification, would avoid overestimation of mild and moderate cases.

The results also showed that mucosal bleed, abdominal pain and vomiting did not represent signs that evolved to severity, demonstrating that the imprecise use of warning sign may generate overestimated data. This was also demonstrated in a multi-centre study conducted in 18 countries¹⁹, which concluded that there is still a need for further training, dissemination and research on warning signs. In addition, a European study was carried out to compare the changes between the two classifications and reinforced that, although the revised classification is more sensitive to the diagnosis of severe dengue, there remain issues with its applicability. This is because the definition of the warning signs is very broad, requiring more specific definitions²⁰.

In turn, the two classifications were concordant regarding the clinical management when the cases of dengue were severe. Patients classified as DHF III and IV in the old classification and severe dengue in the revised classification, according to Table 3, required hospitalization and intensive care for hemodynamic monitoring, effective fluid replacement and continuous access to the necessary laboratory tests.

Thus, further studies with similar comparisons and systematized protocols are necessary in order to identify the practical effectiveness of the revised classification compared to the old classification.

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