



Article/Artigo

Clinical and epidemiological characterization of dengue hemorrhagic fever cases in northeastern, Brazil

Caracterização clínica e epidemiológica dos casos de dengue hemorrágica no Nordeste do Brasil

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ABSTRACT

Introduction: The dengue hemorrhagic dengue (DHF) remains an important public health problem in Brazil. The objective of this study was to analyze the epidemiological characteristics of DHF cases during the 2003 epidemic in Ceará. **Methods:** Suspected DHF cases with onset of symptoms between January and December 2003 were investigated. **Results:** 37,964 classic dengue cases and 291 DHF cases were reported. Among the cases discarded, 75.5% were serologically positive but did not meet the criteria recommended by the World Health Organization (WHO). The DHF patients' median age was 30 years (2 - 88). Among the hemorrhagic manifestations, petechiae were the most (32.6%) frequent. Cases of gastrointestinal bleeding, ascites, pericardial pleural effusion, hepatomegaly, hypotension and shock showed higher risk of progression to death ($p < 0.05$). **Conclusions:** The introduction of a new serotype (DENV-3) in Ceará, which encountered a susceptible population and high vector density, may have been the primary agent responsible for the magnitude of the epidemic. Timely and appropriate medical care, along with an organized care structure are essential for reducing its lethality.

Key-words: Dengue hemorrhagic fever. Epidemiology. Risk factors.

RESUMO

Introdução: A febre hemorrágica do dengue (FHD) permanece como um importante problema de saúde pública no Brasil. O objetivo deste estudo é analisar os aspectos epidemiológicos dos casos de dengue hemorrágico durante a epidemia de 2003, no Ceará. **Métodos:** Foram investigados os casos suspeitos de FHD, com início de sintomas no período de janeiro a dezembro de 2003. **Resultados:** Foram reportados 37.964 casos de dengue clássica, com 291 casos de FHD. Entre os casos descartados, 75,5% apresentaram sorologia positiva, mas não preenchem os critérios recomendados pela Organização Mundial de Saúde. A mediana de idade dos pacientes com FHD foi de 30 anos (2 - 88). Para manifestações hemorrágicas, as petéquias com 32,6% foram as mais frequentes. Os casos de hemorragia digestiva, ascite, derrame pleural e pericárdico, hepatomegalia, hipotensão e choque apresentaram maior risco de progressão para óbito ($p < 0,05$). **Conclusões:** A introdução de um novo sorotipo (DENV-3) no Ceará, encontrando a população suscetível e a alta densidade do vetor podem ter sido os principais responsáveis pela magnitude da epidemia. A atenção médica oportuna e adequada, bem como uma estrutura organizada de cuidado aos pacientes são indispensáveis para reduzir a letalidade.

Palavras-chaves: Dengue hemorrágico. Epidemiologia. Fatores de risco.

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INTRODUCTION

According to the World Health Organization (WHO), dengue is the most important viral disease transmitted by arthropods in the world¹. About 500,000 patients are hospitalized with dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) every year. Moreover, it is estimated that 20,000 deaths are caused by dengue every year. Dengue is therefore considered to be of great relevance for public health, especially in its hemorrhagic form¹.

Over recent years, research has been conducted in order to present an epidemiological profile of dengue and DHF in certain Brazilian cities²⁻⁴. The State of Ceará, in northeastern Brazil, is one of the most important areas in terms of numbers of reported cases of dengue and DHF⁵. The first epidemic in Ceará began in August 1986, and continued until November 1987, with 26,938 cases with laboratory confirmation⁶.

Many factors have been indicated as determinants for outbreaks of DHF epidemics⁶. In Ceará, the first cases of DHF were notified in 1994, at the time when the serotype DENV-2 was first detected. In that year, 25 cases were confirmed, with a lethality rate of 48%. There was then a pause in the notification of hemorrhagic cases, but from 1988 onwards, not a single year has passed by without the confirmation of hemorrhagic cases.

The aim of the present work was to analyze the clinical-epidemiological characteristics of DHF cases, and to ascertain the most common signs and symptoms found in patients who progressed to death, during the 2003 epidemic in Ceará.

METHODS

This was a descriptive study on the clinical-epidemiological characteristics of DHF cases during the 2003 epidemic in the State of Ceará.

Notification data were acquired from the national compulsory notification system (SINAN) and from a *parallel* database at Ceará State Health Department. Secondary data collected by the 184 municipal health departments in the state were also used, following an active search through the routines of the epidemiological surveillance service. Data on hospital admissions were obtained from the hospitalization information system (SIH). The death certification service (SVO) provided complementary information about deaths in cases that underwent necropsy.

This investigation included all the cases notified as suspected DHF in the State of Ceará, showing first symptoms between January 1 and December 31, 2003. Cases were considered to be confirmed if they showed the initial clinical manifestations of classic dengue (spontaneous or provoked), thrombocytopenia, low platelets (<100,000 platelets/mm³) and loss of plasma to the third sector. The classification of case severity followed the WHO guidelines¹. The criteria for classifying the case severity were those established by WHO in 1997, as follows: Grade I: fever with unspecific symptoms, in which the only hemorrhagic manifestation is a positive Rumpel-Leede test. Grade II: same manifestations as grade I plus light spontaneous hemorrhage. Grade III: circulatory collapse with weak and fast pulse, narrowing of arterial pressure or low pressure, sticky and cold skin and restlessness. Grade IV: dengue shock syndrome (DSS), i.e. deep shock without detectable arterial pressure and pulse.

Data were entered into a specific database that was created using the Epi Info 6.0 software. Statistical tests were performed on proportions, using a significance level of less than 5% ($p < 0.05$) and prevalence ratios (PR) were calculated with 95% confidence intervals. The Epi Info[®] software was used for the analysis.

RESULTS

In the year 2003, 37,964 cases of suspected dengue were notified. Out of this number, 23,796 were confirmed through laboratory tests. Among the confirmed cases, 9,012 (37.9%) occurred in the state capital and 14,784 (62.1%) in locations outside of the state capital. 450 cases of suspected DHF were investigated, and 291 of these were confirmed. The 159 discarded cases were diagnosed as presenting eleven other causes (Table 1). It should be noted that 75.5% of the discarded cases were serologically positive for dengue, but that it was not possible, from the available information, to characterize them as DHF. A significant percentage of the cases notified as DHF were not confirmed because of absence of a serological test and/or Rumpel-Leede test, in addition to absence of the tests needed to confirm hemoconcentration (Table 2).

Fifty-five percent (55.3%) of the cases were of female gender. The mean age was 33 years (2 – 88), with a median of 30 years. 34.3% were students, 17.9% were domestic workers and 8% were retired. Regarding hospital admissions, 17.9% were hospitalized, and 130 (52.6%) of them were in public hospitals. Fever, headache and myalgia were the most common symptoms, appearing in 100%, 88.3% and 82.8% of the cases, respectively (Figure 1). The fever episodes lasted on average for five days.

The most prevalent hemorrhagic manifestations were gingivorrhagia, petechiae and epistaxis, appearing in 86%, 71% and 47% of the cases. Concerning case outcomes of cure or death, gastrointestinal bleeding, ascites, pleural effusion, pericardial

effusion, hepatomegaly, hypotension and shock presented the highest risk of progressing to death, with $p < 0.05$ (Table 3).

According to severity, 22% were classified as grade I, 15.8% as grade II, 4.5% as grade III and only 0.3% were classified as DHF grade IV. In spite of the available information, 57.4% of the cases were not classified.

TABLE 1 - Diagnoses and lethality of the cases rejected as DHF in Ceará, 2003.

Diagnosis	Number of		Number of	
	cases	%	deaths	Lethality
Severe dengue*	3	1.9	0	0.0
Classic dengue*	29	18.4	0	0.0
Dengue with low platelets*	3	1.9	0	0.0
Dengue with complications**	85	53.8	12	14.0
Subtotal (dengue)	120	75.4	12	14.0
Indeterminate cause	28	17.7	10	35.7
Purpura	1	0.6	0	0.0
Lupus*	1	0.6	0	0.0
Leptospirosis*	4	2.0	0	0.0
Hemolytic anemia	1	0.6	1	100.0
Melioidosis*	3	1.9	3	100.0
Leukemia	1	0.6	0	0.0
Total	159	100.0	26	16.4

*serologically/laboratorially confirmed cases.

**according to the Brazilian Health Ministry (2002), these are all the dengue cases that do not match DHF criteria but for which classification as classic dengue is unsatisfactory, due to the risk potential.

TABLE 2 - Criteria absent from the cases that were rejected as DHF in Ceará, 2003.

Criteria	Number	Percent
Serological tests not done or negative	94	78.3
No fever	5	4.2
Platelets over 100,000	50	41.7
Absence of petechiae or Rumpel-Leede test	92	76.7
No plasma extravasation	76	63.3

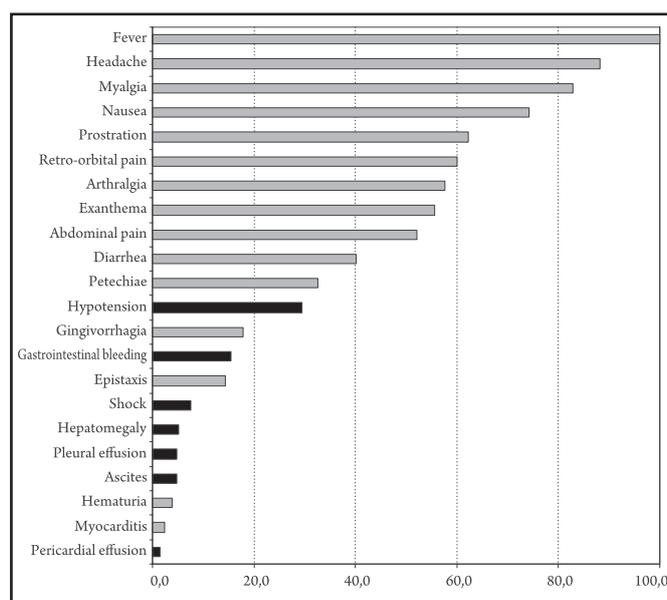


FIGURE 1 - Prevalence of signs and symptoms among the 291 confirmed DHF cases in Ceará, 2003.

TABLE 3 - Signs and symptoms, according to DHF patient evolution in Ceará, 2003.

Signs and symptoms	Death (20)		Cure (271)		P	PR	Confidence Interval
	n	%	n	%			
Headache	14	70.0	242	89.6	0.001	3.09	0.88 – 10.24
Retro-orbital pain	10	50.0	165	60.9	0.625	1.41	0.50 – 3.95
Prostration	11	55.0	170	62.7	0.861	1.22	0.43 – 3.45
Myalgia	14	70.0	227	83.8	0.414	1.84	0.54 – 5.92
Nausea	13	65.0	203	74.9	0.723	1.38	0.44 – 4.13
Arthralgia	10	50.0	158	58.3	0.807	1.26	0.45 – 3.51
Diarrhea	10	50.0	107	39.5	0.382	0.59	0.21 – 1.65
Exanthema	7	35.0	155	57.2	0.132	2.31	0.81 – 6.79
Epistaxis	5	25.0	37	13.7	0.287	0.47	0.15 – 1.61
Petechiae	8	40.0	87	32.1	0.631	0.71	0.26 – 2.00
Gingivorrhagia	4	20.0	48	17.7	0.964	0.86	0.25 – 3.23
Hematuria	2	10.0	9	3.3	0.368	0.31	0.05 – 2.28
Gastrointestinal bleeding	9	45.0	36	13.3	0.000	0.19	0.07 – 0.54
Ascites	6	30.0	8	3.0	0.000	0.07	0.02 – 0.26
Pleural effusion	4	20.0	10	3.7	0.004	0.14	0.04 – 0.63
Pericardial effusion	2	10.0	2	0.7	0.012	0.06	0.01 – 0.69
Abdominal pain	14	70.0	137	50.9	0.167	0.45	0.15 – 1.32
Hepatomegaly	6	30.0	9	3.3	0.000	0.08	0.02 – 0.31
Myocarditis	2	10.0	5	1.9	0.129	0.17	0.03 – 1.41
Hypotension	13	65.0	72	26.8	0.001	0.20	0.07 – 0.57
Shock	10	50.0	12	4.5	0.000	0.05	0.01 – 0.15

Regarding complementary tests, 72.9% of the patients underwent at least two hemograms and 71.5% had two platelet count tests. Cases that evolved to cure presented a lowering of platelet count from the first to the second test and a rise in the count from the second to the third test. The cases that progressed to death showed a steady lowering of the platelet count at each new test (Table 4).

The average time between first symptoms and death was 10 days, with a median for patient evolution of seven days.

TABLE 4 - Evolution of platelet count among DHF patients in Ceará, 2003.

	Evolved to cure			Progressed to death		
	1 st test	2 nd test	3 rd test	1 st test	2 nd test	3 rd test
Average	88,140	78,200	94,200	59,200	64,200	49,500
Median	70,000	68,000	75,000	61,000	52,500	53,500
75 th percentile	112,000	102,000	124,000	93,000	74,300	67,000

DISCUSSION

Regarding the gender of the patients, Rodrigues, Scander and Casali showed in their studies that there were no statistically significant differences, as also seen in Ceará in 2003⁷⁻⁹. On the other hand, Montenegro, investigating 14 patients who progressed to death in Recife, suggested that male gender predominated³.

Regarding the age of the patients with DHF, Montenegro⁸ demonstrated that more than 50% were between 20 and 59 years old. Studies in Cuba and Puerto Rico have shown predominance among adults^{6,10}. A recent study on the epidemic in Rio de Janeiro presented a mean age of 32.8 years¹¹. A study in Ceará¹² pointed towards a lowering of the age range of DHF patients, as also found by Siqueira¹¹ in northern Brazil. In Ceará, the profile of hemorrhagic cases

corroborates data from the worldwide literature, which has shown a lowering of the age ranges most afflicted with serious cases.

In Ceará, in 2003, there was a statistically significant risk of progression to death in cases with gastrointestinal bleeding, ascites, pleural and pericardial effusion, hepatomegaly, hypotension and shock. These findings are in accordance with the Brazilian literature, which suggests that there is a need for special attention to patients presenting such symptoms. It is important to carry out complementary investigations to validate mechanisms for early detection of these signs and symptoms.

An epidemic in Recife showed that the most frequent location for hemorrhages was the digestive tract, followed by the nose and lungs³. The most frequent signs were ascites and pleural and pericardial effusion, with 71.4%, 57.1% and 28.6% respectively³. Hypovolemic shock was present in 85.7% of the patients who progressed to death³. A study conducted in India showed that the most frequent type of bleeding was gastrointestinal (34.5%), followed by petechiae (23.6%) and pulmonary bleeding (13.6%)¹³. During an epidemic in Rio de Janeiro in 2001 and 2002, the most common hemorrhagic manifestations were petechiae (51.6%), digestive hemorrhage (37.6%), gingivorrhagia (34.6%) and epistaxis (34.1%)⁷. In this same study, some signs and risk symptoms for evolution of hemorrhagic cases were identified, such as nausea, abdominal pain, petechiae, epistaxis, gingivorrhagia, hepatomegaly, digestive hemorrhage, shock, ascites and pleural effusion². It is important to conduct further studies in order to validate mechanisms for early detection of these signs and symptoms.

In a longitudinal cohort carried out in 2003 using patients with dengue and otorhinolaryngological manifestations, the most frequent symptoms were odynophagia 60%, coryza 50%, nasal obstruction 46.6%, otalgia 36.6% and vertigo 20%¹⁴. Headache (most commonly frontal) and retro-orbital pain were frequently associated with nasal obstruction and rhinorrhea, resembling a condition of acute sinusitis¹⁴.

In the present study, the neurological complications could not be assessed. However, in another study conducted on 41 patients with DHF who showed neurological signs, the most affected regions were the head, medulla and peripheral nerves¹⁵. This same study also showed that the prevalence of detected neurological complications was 17.4/100,000 in the year 1997 and 44.8/100,000 in 2002⁶. Although it was not possible to evaluate neurological complications in the present study, it is important to perform this kind of evaluation because these cases present higher potential for severity. Moreover, a significant proportion of the notified cases could not be analyzed because they did not fulfill at least one of the WHO criteria.

In Ceará in 2003, the patients who progressed to death showed platelet counts that were lower than in those who evolved to cure, and were lower in each new test.

The mean platelet count of the Recife cases that progressed to death was 48,538/mm³. Among the patients who bled, the mean platelet count was 36,666/mm³, and among those who did not bleed, the mean was 75,250/mm³. Characteristics such as the day of sample collection relative to the beginning of symptoms can influence this data, thereby making direct comparisons impossible.

The hospital lethality rate due to DHF in Recife was 6.8%, with progression to death in around 11 days after the first symptoms³. This was close to the data found in the present study. In the studies conducted in Recife and Cuba^{3,11} the mean duration of the patients' hospitalization was 7 and 6.8 days, respectively.

Dengue hemorrhagic fever has been bringing great public health challenges for Brazil. The impact of a health problem can be measured by its severity and by the social value that it represents for society, i.e., by its actual or potential impact and its repercussion on socioeconomic development.

The severity of this epidemic suggests that it was associated with the introduction of serotype DENV-3, which was a strain with high virulence, among a susceptible population, and with high vector densities. During that year, the virological surveillance unit of the State Health Department collected 696 samples for virus isolation, in 24 municipalities. It was found that 150 were positive, and that 148 of them were DENV-3 (98.7%) and two were DENV-2 (1.3%).

It is essential that correct and timely attention should be given to such patients, especially in relation to risk classification and laboratory support. This information is important for implementing correct procedures in relation to dengue patients and, consequently, for lessening the lethality rate among DHF patients.

The information presented in this study corroborates other Brazilian findings, although there are differences relating to the entomological-epidemiological period over which each study was conducted. This contributes, for instance, towards differences in severity between patients according to virus predominance². The median age of the patients was lower than found in other Brazilian studies, probably because the data are more recent⁹. Finally, we need to point out some possible bias in the results. The first would be selection bias due to possible undernotification of cases, and another would be information bias, caused by evaluation errors in the study variables, thereby causing distortion when estimating the effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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