

Clinical Epidemiological Profile and Warning Signs of Dengue

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Abstract

Dengue is an arbovirus transmitted to human beings by the *Aedes aegypti* mosquito, characterized as a systemic viral infection of rapid geographical expansion and today, it a major global infectious problem with the potential risk of death for the individuals affected.

Objective: To describe the clinical and epidemiological profile and the most frequent and relevant warning signs of confirmed dengue cases occurred in Campo Grande, the capital of Mato Grosso do Sul (MS), Midwestern Brazil, during 2013 epidemic.

Method: This is a descriptive, analytical, cross-sectional and retrospective study conducted through analysis of patients' records treated at two public hospitals of reference for treatment of infectious and parasitic diseases (IPD) in the city of Campo Grande/MS, Brazil, during an epidemic in 2013.

Results: There were 91 confirmed cases of dengue analyzed; 86 of them met the criteria for the diagnosis of dengue with warning signs (DCWS) and five as severe dengue (SD). There was a predominance of females with 60% for cases of DCWA and 64% for SD. The age ranged from 42.65 (± 2.22) for cases of DCWS and 60.40 (± 6.98) years old for cases of SD. The Warning Signs associated with worsening of the disease were abrupt decreasing in platelets, dyspnea, hypothermia, confusion and psychomotor agitation. Three of the five cases of SD died (60%).

Conclusion: The epidemiological situation of dengue in the city of Campo Grande/MS is configured as a public health problem. It is emphasized the importance of developing measures to control and combat of the disease, as well as entomological, sanitary and health surveillance become indispensable.

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Keywords

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Introduction

Dengue is an arbovirus transmitted to human beings by the *Aedes aegypti* mosquito having four circulating and described serotypes [1]. The disease is characterized as a systemic viral infection that spreads rapidly and emerges as an important infectious disease in the current world, considered as a risk of death for some of the affected individuals. According to the World Health Organization (WHO), the incidence of dengue cases has increased exponentially in the last 50 years due primarily to the geographic expansion to new countries. It is estimated to occur 390 million of these infections annually, and only 96 million are symptomatic [2-4].

Currently, dengue fever is the most prevalent arbovirus in the world, and it is estimated that 3.6 billion people live in endemic countries with about 40% of the population at risk [5, 6]. In Brazil, there is a reference to the disease since the nineteenth century, with epidemics reports in 1923, in Niterói city, Rio de Janeiro and 1946 in the city of São Paulo, both located in the southeastern region of Brazil, but without laboratory confirmation [7].

The first epidemic with clinical and laboratory documentation occurred in the northern Brazil between 1981 and 1982 in the city of Boa Vista, Roraima state, caused by serotypes 1 (DENV1) and 4 (DENV4). In the early 1990s, it was observed the circulation of serotype 2 (DENV 2) in the state of Rio de Janeiro with a significant increase of cases of the disease. Ten years later, in 2002, the circulation of serotype 3 (DENV 3) was first identified in the states of Rio de Janeiro and Roraima, respectively, which resulted in higher incidence of the disease ever recorded so far [8]. In 2010, the situation became even worse with the reintroduction of DENV 4 in the city of Boa Vista, Roraima state [9].

Since then, dengue is considered one of the most important infectious diseases mainly due to its high morbidity and mortality. In 2015, Brazil notified

1,649,008 cases of dengue to the Pan American Health Organization (PAHO) and in the first half of 2016, 1,130,316 cases of the disease have been reported [10, 11].

In the state of Mato Grosso do Sul, Midwest region of Brazil, there was a total of 44,523 cases in 2015 reported to the State Department of Health (SDH), of which 12,955 cases occurred in the state capital, Campo Grande [12]. In the first half of 2016, 56,666 cases were reported, 27,382 of them in the state capital. [13]

Dengue has a very wide clinical spectrum ranging from the oligosymptomatic forms to severe hemorrhage and shock, and it may lead to death [3]. Furthermore, *Aedes aegypti* transmits two other diseases also considered high morbidity and mortality, such as Chikungunya fever and Zika.

In Brazil, 17,683 cases of Chikungunya fever were reported to PAHO in 2015, 560 of them were confirmed, and three deaths were reported. Currently, such arbovirus is present in 55 countries, including the Americas. [14] In December 2015, PAHO issued a warning to countries of the Americas to the attention to the neurological and congenital anomalies related to the Zika virus, which showed a significant increase in about 20 times the number of cases of microcephaly in live births since 2000, and the first serologic confirmation of Zika virus presence in the amniotic fluid of pregnant women in Brazil occurred in 2015 [15-19].

In January 2016, a new warning about Zika was published, in which 18 countries and territories have reported cases of this disease. Among them, Brazil already had cases in 18 states, mainly in the Northeast region [20].

In 2009, the WHO already presupposed the need for a differential diagnosis for diseases transmitted by *Aedes aegypti* and the potential risk of dengue worsening. Based on a multicenter study (Dengue Control - Denco) a simplified classification was proposed, performed by easily accessible clinical and laboratory tests [21, 22].

In this simplified classification, dengue cases are divided into two categories of severity. In the first category, the dengue is subdivided into "dengue without warning signs (DWWS) and dengue with warning signs (DCWS)". The second category is the "severe dengue (SD)". The warning signs are among the guiding patient care with dengue picture. Most of the time, the clinical and laboratory signs are plasma loss predictors and imminent shock, indicated by clinical deterioration and progression to severity. The correct management of patients depends on early recognition of signs and rapid initiation of therapy, which can be decisive for the outcome of the picture [4].

Recognizing the warning signs of worsening dengue is a step towards the systematization of assistance that can contribute positively to the success in reducing morbidity and mortality and the negative impacts caused by the disease in the society. In this perspective, the objective of this study is to describe the clinical and epidemiological profile and the most frequent and relevant warning signs of confirmed cases of dengue occurred in Campo Grande, the capital of Mato Grosso do Sul, Midwestern Brazil during 2013 epidemic.

Method

This is a descriptive and analytical, cross-sectional and retrospective study conducted through the analysis of patients' records treated at two public hospitals of reference for treatment of infectious and parasitic diseases (IPD) in the city of Campo Grande, capital of Mato Grosso South/MS, Midwestern Brazil, who had serologic or clinical-epidemiological confirmation of dengue by the Municipal Public Health (SESAU) during 2013 epidemic.

There were 170 medical records of patients with suspected cases of dengue analyzed, of which 91 were the universe of this research because they were confirmed cases. Data of patients' records that were clinical or laboratory proved were included,

that after the WHO Protocol by 2009 reclassification met criteria for the diagnosis of dengue with warning signs (DCWS) and SD. The records that were incomplete and were not available for consultation were excluded.

The variables extracted from medical records were gender, age, dengue confirmation method, the reason for referral, warning signs and outcome. The evaluation of the association between the type of dengue and the variables studied in this research was performed using the chi-square test. The comparison between DCWS and SD about quantitative variables was performed using the t-Student test. The other results were presented as descriptive statistics in tables. Statistical analysis was performed using the statistical program Statistic Package for Social Sciences (SPSS), version 22.0, and the significance level was 0.05.

This study was approved by the Ethics Committee on Human Beings Research linked to the Federal University of Mato Grosso do Sul, in Opinion N° 867,375, on November 2, 2014, in compliance with regulatory standards for research in human beings, according to CNS/MS Resolution N° 466/2012 [23].

Results

According to **Table 1**, there were 91 cases of dengue identified and treated in two reference hospitals to IPD in the state; 86 of them (94.5%) presented the criteria for DCWS and five (5.5%) for SD since they had the same characteristics described in WHO protocol [4].

Of the total cases, 78 (85.7%) were referrals from Basic Health Units (BHU) after the first visit, when the reasons were clinical worsening in 27 cases (34.6%), laboratory worsening in 20 (25.6%) and both in 31 cases (39.8%). The remaining cases spontaneously sought the hospital, of which 11 (84.6%) sought the service by clinical worsening and two (15.4%) by laboratory and clinical worsening. More than half of treated cases of DCWS were female (60%), espe-

cially also for cases of SD (60%). Ages ranged from 42.65 ± 2.22 of DCWS cases and $60.40 (\pm 6.98)$ years old for SD cases. **(Table 1)**

The warning signs DCWS cases were nausea and vomiting (52.3%), persistent abdominal pain (48.8%), blood concentration (30.1%), sudden decrease in platelets (<20,000) (12.8 %), respiratory distress (10.5%), syncope (3.5%), decreased urine

Table 1. Distribution of cases of dengue¹ by classification, according to the clinical and epidemiological characteristics. Campo Grande/MS, Brazil, in 2016 (n=91).

Variables	Dengue				p ⁴
	DCWS ²		SD ³		
	(n=86)		(n=05)		
	n	%	n	%	
Gender					
Female	55	64.0	03	60.0	0.858
Male	31	36.0	02	40.0	
Age	42.65±2.22		60.40±6.98		0.060
Confirmation					
Clinical Epidemiological	47	54.7	02	40.0	0.523
Laboratory	39	45.3	03	60.0	
Reasons for referral					
Clinical worsening	37	43.0	01	20.0	0.103
Laboratory worsening	20	23.3	00	00.0	
Clinical and laboratory worsening	29	33.7	04	80.0	
Outcome					
Hospital discharge	82	95.3	02	40.0	<0.001
Evasion	02	2.3	00	0.0	
Death	00	0.0	03	60.0	
Transfer to another hospital	02	2.3	00	0.0	
Referral					
No	13	15.1	00	0.0	0.348
Yes	73	84.9	05	100.0	

¹: Cases during 2013 epidemy, ²: Dengue with Warning Signs, ³: Severe Dengue, ⁴: t-student test

output (3.5%), altered level of consciousness with confusion (1.2%) and psychomotor agitation (1.2%). The hematocrit value was 39.57% (± 0.65).

For of SD cases, the Warning Signs were intense and persistent abdominal pain (80%) with respiratory distress and abrupt decrease in platelets and hepatomegaly (60%), hypothermia, confusion and agitation (40%), nausea, persistent vomiting, blood concentration and decreased urine output (20%). **(Table 2)**

Among the warning signs defined by the Ministry Health Protocol of Brazil (2013), five were strongly associated with worsening of the disease, such as the sharp decrease in platelets (p=0.004), respiratory distress (p=0.001) and hypothermia and altered level of consciousness (confusion and psychomotor agitation) (p <0.001).

Table 2. Distribution of cases of dengue¹ by the classification and warning signs², Campo Grande/MS, Brazil, in 2016 (n=91).

Warning Signs	Dengue				p ⁵
	DCWS ³		SD ⁴		
	(n=86)		(n=05)		
	n	%	n	%	
Nausea/Persisting Vomiting	45	52.3	01	20.0	0.160
Intense Abdominal Pain	42	48.8	04	80.0	0.627
Increased Hematocrit	25	30.1	01	20.0	0.630
Hepatomegaly	20	23.3	03	60.0	0.066
Abrupt Decrease in Platelets	11	12.8	03	60.0	0.004
Respiratory Distress	09	10.5	03	60.0	0.001
Lipothymy	03	3.5	00	0.0	0.671
Decreased Urine Output	03	3.5	01	20.0	0.080
Hypothermia	00	0.0	02	40.0	<0.001
Mental confusion	01	1.2	02	40.0	<0.001
Agitation	01	1.2	02	40.0	<0.001
Hematocrit	39.57±0.65		34.44±2.52		0.062

¹: Cases during 2013 epidemy, ²: Dengue with Warning Signs, ³: Severe Dengue, ⁴: t-student test

Discussion

According to the epidemiological variables, there was a predominance of females in both classifications of dengue cases, in a same trend detected in a study conducted by the Notifiable Diseases Information System (SINAN) and Hospital Information System (SIH) who analyzed the distribution of dengue cases recorded between 2002 and 2010, when the female totaled more than half of the reported cases [24].

Similar data were found in a study conducted in 2009 in the same geographical area, in which 52.6% of cases were female, which also prevailed in the most severe cases of the disease, with 52.6% of cases of Dengue With Complications (DWC) and 54.4 cases of Hemorrhagic Fever Dengue (DHF) and Shock Syndrome Dengue (SSD) [25]. In another study conducted in Goiânia, the state capital of Goiás, also located in the Midwest region of Brazil, 52.7% of cases occurred among women [26], which may be associated with the possibility of their greater permanence at home and the urban characteristics vector [27].

The predominant age group for cases of DCWS was 42.65 (\pm 2.22) and 60.40 years old (\pm 6.98) for cases of SD. Over 50% of cases of DCWS had clinical and epidemiological confirmation, different from SD cases, for which the laboratory confirmation was performed in 60% of cases. This total of laboratory confirmation for cases of DCWS is above the stipulated by the Ministry of Health of Brazil that for the epidemic period allows the clinical and epidemiological confirmation of the disease in about 10% cases of dengue. However, this same protocol points out that for severe cases of the disease, risk groups or situations they should receive laboratory confirmation in full [28].

Regarding the outcome, 60% cases of SD died, and the others were discharged after clinical improvement. A study in the city of Aracaju, the capital of Sergipe state, located in the northeastern region of Brazil, with 10,165 confirmed cases of dengue,

showed that the 18 deaths were all classified as the most severe forms of the disease [29].

Regarding the warning signs, a study in Singapore found that when the patient has any of these signs, the chances of developing into the hemorrhagic form of the disease are 87%, and the chances of progression to more severe disease are 96% [30]. A significant association between one or more warning signs and the worsening of the disease was also found in a study conducted in Brazil between 2000 and 2005 [31].

An assessment of deaths from dengue seen at a University Medical Center in Malaysia between 2006 and 2007, found that a large number of patients who died they had some warning sign to the worsening dengue. These signs and comorbidities may have been the factors that contributed to the worsening of the condition. The most common warning signs of this study were the sharp decrease in platelets, intense and persistent abdominal pain, blood concentration, most notably respiratory distress, hypothermia and neurological manifestations confusion and agitation. [32]

Although in this study the abdominal pain had not significant association presented with the worsening dengue, this was found in 48.8% of cases of DCWS and 80% of cases of SD. Abdominal pain is configured as an important predictor of deterioration with a three times increasing the severity of the disease [33].

Thrombocytopenia was found as a marker of dengue severity in a study by Robert Children Hospital in Santo Domingo in the Dominican Republic, with 796 confirmed cases of dengue, of which 288 were classified as dengue, 290 as DCWS and 207 as SD. As a borderline statistical base, the platelet of 30,000/mm³ was used. However, there was a significant association with severe disease and mortality, even with the close platelet count to 58,000/mm³ [34].

A study conducted by the Kaohsiung Chang Gung Memorial Hospital in Taiwan with 1,063 patients,

found that 1,008 were classified as non-severe dengue, 55 as SD and 23 evolved with shock. The results also showed a significant association between severe thrombocytopenia and the worsening of the disease, in which the platelet count was 50,000/mm³ [35].

A retrospective study conducted in Puerto Rico identified abdominal pain, persistent vomiting, sudden temperature change and the altered level of consciousness as the main warning signs [36]. These data corroborate findings of research conducted in Singapore, which related to abdominal pain, nausea and persistent vomiting present in half of the patients who died because of dengue [37].

In a study conducted in India with 198 patients, 186 of them survived, and 15 died. Of the total, 26 (13.1%) had respiratory failure and in 15 that died, 11 (91.7%) had acute respiratory distress, a significant result of research with $p < 0.005$. As for the sensory change in the total number of patients, five (2.5%) had this picture, and four who died, (33.3%) had some altered level of consciousness ($p < 0.005$). By the results, it was possible to realize the significant relationship between these changes and the poor prognosis and worsening of symptoms [38].

On hypothermia, a retrospective study of 390 patients with dengue diagnostic found that of 10 patients who died, hypothermia was present in two (20%) cases, and this symptom was not observed in any of the survivors. Thus, it may be possible to infer that hypothermia can be considered as one of the indicators of the worsening of the disease [39].

Conclusion

It is concluded that among patients with symptoms of DCWS, more than half are female, most were referred by basic health units and warning signs most frequently diagnosed were nausea and vomiting, persistent abdominal pain and blood concentration.

Among those with SDG, there was also a prevalence of females and the warning signs found were intense and persistent abdominal pain, respiratory distress and sudden decrease of platelets.

It can be seen that the epidemiological situation of dengue in the city of Campo Grande/MS, Brazil is configured as a public health problem. It is emphasized the importance of developing measures to control and combat the disease, as well as entomological, sanitary and health surveillance become essential, given that in the absence of effective vaccine against the disease, vector control and eliminating their breeding sites are configured as the only possible way to combat the spread of the disease. Thus, also, to building public policies designed and implemented to this end, encouraging the community participation needs to be permanent, and the results or answers expectations should be considered in the medium and long term.

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