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ARTERIAL HYPERTENSION IN THE WORSENING CLINICAL CONDITION OF DENGUE

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ABSTRACT

The purpose of the manuscript was to identify the presence of comorbidities that enhances the worsening of dengue disease. It is a case-control study, carried out in the city of Campo Grande, Brazil. Subjects were matched by gender, age and place of residence, using four controls for each case. A hundred and two subjects with dengue hemorrhagic fever (DHF) were included in the case group, and 408 subjects with a diagnosis of dengue fever were selected as the control group. The results of the present study suggest that people with abdominal pain or suffering from systemic arterial hypertension are more likely to develop dengue hemorrhagic fever. In conclusion, when people suffering from systemic arterial hypertension present with suspected dengue, they should be stratified into the group most likely to develop severe forms of the disease.

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INTRODUCTION

Although there have been reports from the mid-nineteenth century and early twentieth century (Pedro, 1923; Mariano, 1917; Reis, 1896; Rego, 1872), the first dengue epidemic with laboratory confirmation in Brazil occurred in late 1981 and early 1982 in the city of Boa Vista, state of Roraima, and was caused by serotypes DENV-1 and DENV-4 (Osanaí *et al.*, 1983).

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However in 1986, a new epidemic was recorded in the Brazil and was associated with serotype 1 (DENV-1) (Schatzmayr *et al.*, 1986). On the other hand in 1990, the introduction of the DENV-2 serotype coincided with the emergence of hemorrhagic forms of the disease (Nogueira *et al.*, 1990). In December 2000 in the state of Rio de Janeiro (Southeast region of Brazil), the DENV-3 serotype was identified in an autochthonous case. (Nogueira *et al.*, 2001). In the year 2010, the DENV-4 serotype was reintroduced, triggering a new epidemic in the Brazil (Temporão *et al.*, 2011). In Brazil, during these 33 years of circulation of the dengue virus, with laboratory confirmation of the circulating serotypes, approximately 9 million cases were reported.

Of these, approximately 100,000 cases showed severe forms of disease, and approximately 3,700 deaths were reported (Brasil, 2013; Brasil, 2012^a; Brasil, 2012^b; Cunha *et al.*, 1995). Research conducted mainly in countries of Southeast Asia and Latin America suggests that diabetes mellitus, sickle cell anemia, asthma and allergies increase the severity of the clinical condition of dengue fever (DF) (Figueiredo *et al.*, 2010; Ayllón *et al.*, 1989; Kouri *et al.*, 1989; Bravo *et al.*, 1987). In Brazil, studies of case series performed during epidemics that occurred in 1990 in Niterói (state of Rio de Janeiro) and in 1995 in Natal (state of Rio Grande do Norte) first developed the hypothesis that systemic arterial hypertension (SAH) could increase the development of severe forms of dengue (Cunha *et al.*, 1999; Cunha, 1998). In 2010 and 2012, the results of two major studies on chronic diseases that act as risk factors for the development of dengue hemorrhagic fever (DHF) were published (Pang *et al.*, 2012; Figueiredo *et al.*, 2010; Cunha *et al.*, 1999; Cunha, 1998). The aim of this study is to identify the presence of comorbidities that enhances the worsening of dengue disease due to this climate dengue is endemic in this region

MATERIALS AND METHODS

The case-control study was conducted in Campo Grande, municipality of the midwestern region, capital of the state of Mato Grosso do Sul, Brazil (20°26'34"S latitude and 50°38'47"W longitude). Campo Grande has a mean annual temperature of 24°C, a humid summer with a mean rainfall of 1,694.5 mm per year and, as of 2010, 786,797 inhabitants. *Due to Geography and climatic Conditions, Campo Grande is considered one city one endemic* (IBGE, 2010). The study population consisted of patients with dengue who were treated at the Municipal Reference Center for Infectious and Parasitic Diseases during the epidemic that occurred from november 2009 to february 2010. This epidemic was mainly caused by DENV-1, although records also show the involvement of DENV-2 (Brasil, 2010). Four controls were included for each case studied. In the case group, all inpatients attended during the referred epidemic at the Municipal Reference Center for Infectious and Parasitic Diseases with clinical and laboratory diagnoses of DHF were included and the current case definition of the World Health Organization (WHO) was used (World Health Organization, 1997). The control group consisted of patients attended during the epidemic that occurred from november 2009 to february 2010 with clinical and laboratory diagnoses of DF according to the current WHO criteria (World Health Organization, 1997). These group of controls was randomly selected from the database of the brazilian Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação - SINAM), which contains approximately 20,000 reported cases paired by gender, place of residence (same street or streets nearby) and age (within approximately 5 years). The main exclusion criteria were: patients who were diagnosed with dengue with complications and patients who did not live in the city where the study was conducted. Specific laboratory confirmation (World Health Organization, 2009) was carried out using enzyme-linked immunosorbent assay (ELISA) techniques for the detection of anti-dengue IgM antibody using the Dengue IgM Capture ELISA kit (Panbio®) or by detecting the NS1 antigen using the Dengue Early ELISA kit (Panbio®). After selecting the cases and controls, a form containing clinical, epidemiological, laboratory data and data on associated diseases was completed with information obtained through

interviews and hospitalization records. To identify SAH, interviews were conducted with all of the study subjects, during which blood pressure was measured, preferably in the left upper limb. When the subject reported having SAH under treatment, information on the prescribed drugs was requested. Those participants were taking antihypertensive medication or who had systolic blood pressure equal to or greater than 140 mmHg and diastolic blood pressure equal to or greater than 90 mmHg were considered hypertensive, according to the guidelines of the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia/Sociedade Brasileira de Hipertensão, 2010). The Interviews conducted during home visits were conducted by trained staff to avoid bias, and the interviewers were blinded to the study objective. The sample was calculated to reach 80% statistical power to detect an absolute difference of 10 percentage points between the cases and controls, with an α error of 0.05. The data collected were entered into a database in Microsoft Office Excel® and analyzed using SAS statistical software version 9.2. Variables were included in the model if they achieved a significance level of $p < 0.20$ in the univariate logistic regression. Stepwise multivariate logistic regression were conducted to identify the factors associated with DHF. A correlation matrix was used to assess confounding variables and correlations between variables. Correlated variables were tested individually, and the Wald test was used to evaluate the significance of risk factors in the final model. The results were expressed as OR with 95% CI and statistical significance was set at $p < 0.05$. The project was approved by the Ethics Committee on Research involving Human Subjects of the Federal University of Mato Grosso do Sul under protocol No. 2157/2009. Written informed consent was taken from all patients or legal guardians.

RESULTS

During the dengue epidemic that occurred in Campo Grande in 2009/2010, 102 patients received a diagnosis of DHF according to the World Health Organization criteria (World Health Organization, 1997) defined in 1997. Due to the inclusion criteria, the control group consisted of 408 cases of DF. Table 1 shows the demographic characteristics of these patients. Among the clinical manifestations recorded, there was a significance difference ($p < 0.05$) in abdominal pain between the case and control groups, indicating that individuals who had this symptom were 3.41 times (adjusted OR, 95% CI 2.04 - 5.70) more likely to have DHF (Table 2). The frequency of comorbidities in the case group (65, 63.7%) was significantly higher than that in the control group (162, 39.7%). Individuals with comorbidities were 2.66 times (CI 1.70 - 4.18) more likely to have DHF, and arterial hypertension was identified as a risk factor (Table 3).

DISCUSSION

Studies conducted by Casali *et al.*, (2004) and Passos *et al.*, (2004) regarding the clinical manifestations also detected a significant OR for the occurrence of abdominal pain (OR = 1.59, 95% CI 1.35 - 1.87). In addition, other studies (Gibson *et al.*, 2013; Falconar *et al.*, 2011; Ponte *et al.*, 2011; Thomas *et al.*, 2010) have reported high rates of abdominal pain in cases of DHF. In 2009, in the manual for the clinical management of DF, the WHO described abdominal pain as a warning sign for the development of severe cases of dengue disease (World Health Organization, 2009). When the comorbidity variable was studied, we found that subjects who had some type of comorbidity were 2.66 times more likely to have DHF.

Table 1. Demographic characteristics of the subjects in the case (DHF) and control (DF) groups according to gender, race and age

Variables	Case (n=102)		Control (n=408)		P value*
	N	%	N	%	
Gender					
Female	68	66.6	278	68.1	0.86
Male	34	33.3	130	31.8	
Race					
White	63	61.7	260	63.7	0.06
Black	31	30.4	118	28.9	
Brown	6	5.8	28	6.8	
Yellow	2	1.9	2	0.5	
Age range					
≤ 20 years	9	8.8	46	11.3	0.98
21 to 35 years	39	38.2	126	30.9	
36 to 50 years	22	21.6	111	27.2	
51 to 65 years	21	20.6	89	21.8	
66 to 80 years	11	10.8	34	8.3	
≥ 81 years	0	0.0	2	0.5	

* Pearson's Chi-square

Table 2. Distribution of clinical manifestations presented by cases and controls attended at CEDIP, Campo Grande, from December 2009 to May 2010.

Clinical manifestations	Cases (n=102)		Controls (n=408)		OR Crude	IC 95%	OR A Adjusted	IC 95%
	N	%	N	%				
arthralgia	96	94,0	378	92,6	1,27	0,51 – 3,13	NA	NA
abdominal pain	77	75,4	194	47,5	3,39	2,07 – 5,55	3,56	2,13-5,95
Edema	49	48,0	97	23,7	2,96	1,88 – 4,65	NA	NA
Fever	98	96,0	386	94,6	1,39	0,47 – 4,14	NA	NA
Myalgia	99	97,0	387	94,8	1,79	0,52 – 6,12	NA	NA
Nausea	68	66,6	264	64,7	1,09	0,68 – 1,72	NA	NA
Vomit	45	44,0	144	35,2	1,44	0,93 – 2,24	NA	NA

Grande, from December 2009 to May 2010.

Table 3. Distribution of specific comorbidities in the case (DHF) and control (DF) groups

Comorbidities	Case (n=102)		Control (n=408)		OR Crude	95% CI	OR Adjusted	95% CI
	N	%	N	%				
Diabetes								
Yes	6	5.8	22	5.3	1.09	0.43 - 2.77	NA	NA
No	96	94.2	386	94.7				
Autoimmune disease								
Yes	1	0.9	2	0.4	2.00	0.18 - 22.38	NA	NA
No	101	99.1	406	99.6				
Hypertension								
Yes	41	40.1	103	25.2	1.99	1.26 - 3.13	2.20	1.24 - 3.87
No	61	59.9	305	74.8				

Note: OR – Odds Ratio, CI – Confidence Interval. Adjusted OR was obtained by multivariate conditional logistic regression according to gender, age, skin rash and abdominal pain.

In line with this finding, the WHO has described groups of patients with a greater risk of adverse outcomes and who require special clinical monitoring, including patients with chronic hematologic or renal disease, severe acid-peptic, autoimmune and cardiovascular disease (World Health Organization, 2009), diabetes mellitus, SAH, asthma, allergies and renal failure, as these conditions were significantly associated with severe dengue and higher mortality rates (Figueiredo *et al.*, 2010; World Health Organization, 2012).

Hypertension was the comorbidity with the highest OR in the present study. This relationship was previously suggested in studies of case series conducted based on dengue epidemics that occurred in Cuba in 1981/1982 (Bravo *et al.*, 1987), in a state in Northeastern Brazil (Figueiredo *et al.*, 2010; Cunha, 1998) and in Taiwan (Lee *et al.*, 2006). As a result, it was suggested that in addition to the presence of antibodies against any serotype of the dengue virus (Halstead, 1981), the existence of some chronic diseases may represent an additional risk factor for the development of DF into DHF.

Studies on the pathophysiology of hemorrhagic dengue have revealed the amplification of the immune response due to the presence of antibodies against a heterotypic serotype of dengue virus in a new infection. Other mechanisms have also been implicated in the pathogenesis of severe forms of dengue (Bhatia *et al.*, 2013; Limonta *et al.*, 2013; Avirutnan *et al.*, 2006). Cytokines are known for their key role in one of the main phenomena responsible for the clinical manifestations of DHF, i.e., the extravasation of fluid into the interstitium, which is a consequence of endothelial dysfunction and results in hem concentration, hypotension and shock (Stephenson, 2005). A study conducted in Cuba found that 14% of patients with DHF had SAH (González *et al.*, 1999). In addition, a retrospective study reported an OR of 1.41 (95% CI 1.02 - 1.94) for DHF in hypertensive patients (Pang *et al.*, 2012). Some descriptive studies have also revealed an association between SAH and DHF (Lee *et al.*, 2006; González *et al.*, 1999; Cunha, 1998; Cunha *et al.*, 1997). Due to the vascular inflammatory process observed in hypertensive patients, these patients may show changes in endothelial function associated with abnormal

leukocyte adhesion, increased accumulation of macrophages in the subendothelial layer, altered cytokine production by macrophages and changes to the regulation of vascular tone and flow mediated by nitric oxide (Melo *et al.*, 2007). Nitric oxide is a potent vasodilator, and its involvement in the inflammatory response may be related to its ability to increase vascular permeability and edema through changes in local blood flow and increased production of pro-inflammatory prostaglandins (Salvemini *et al.*, 1996). It is also likely that there is a potencialization of antihypertensive and anti-inflammatory drugs in the normalization of endothelial function (Melo *et al.*, 2007). In this manuscript, the present study found that 40.1% of the studied patients were hypertensive, which is a higher frequency than that observed in the population of Campo Grande with an age equal to or greater than 18 years, which was estimated at 24.0% in 2010 (Brasil, 2012^c). Recall bias is one of the possible methodological limitations related to case-control studies. Aiming to minimize this bias, other sources of records were used (data from the medical records of the patient during hospitalization), and the interviews were conducted a few months after the occurrence of the disease. Another possible source of bias is the selection of the study subjects. To control this bias, the case group was composed entirely of subjects who met the definition criteria for DHF, and the controls were randomly selected from the SINAM database.

All strategies employed to control *Aedes aegypti* fail to achieve their main objective during epidemics, which is to prevent the spread of the disease. Moreover, studies that aim to control the vectorial capacity of *Aedes aegypti*, for example, using the bacteria *Wolbachia pipientis*, have not yet produced definitive results (Thomas *et al.*, 2011; Sinkins, 2012). Faced with the reality that we do not have effective tools to control the vector or commercially available safe and effective tetravalent vaccine to protect the population (Schmitz *et al.*, 2013; Villar *et al.*, 2015), the challenge becomes to improve the care of patients and prevent deaths, which unfortunately continue to occur during epidemics. Our results represent a new contribution to the care of patients with suspected dengue during epidemics, as they may contribute to improving the quality of care and, consequently, reduce patient lethality. In particular, the identification of comorbidities as risk factors for DHF can help guide health professionals during screening and provide targeted and quick care for individuals more vulnerable to the development of severe forms of the disease. Further prospective studies are needed to evaluate the role of SAH as a possible risk factor for the development of severe forms of dengue. We recommend that future studies also seek to evaluate the potential effect of the use of antihypertensive medication on vascular permeability, which may result in increased plasma extravasation.

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