ORIGINAL ARTICLE

Chronic kidney disease as an aggravating factor in dengue virus infection

Doença renal crônica como fator agravante da infecção pelo vírus da dengue: um estudo transversal

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ABSTRACT

Background: Dengue virus infection is a public health problem worldwide, which can manifest from a mild febrile condition to severe disease, with multiple organ involvement, including kidney disease. The aim of this study was to analyze the cases of dengue assessing how chronic kidney disease (CKD) aggravates its clinical manifestations.

Method: A cross-sectional study was carried out using the database of the Health Secretariat of the state of Ceará, northeastern Brazil, in the period from January 2015 to December 2017. A comparison was made between patients with and without CKD. **Results:** A total of 161,880 patients were included. Patients with CKD were older (41±22 vs. 35±21 years, p<0.001), predominantly female (62 vs. 57%, p=0.004) and had a higher frequency of certain symptoms and signs. However, the only warning sign that was more prevalent among CKD patients was lethargy (0.5% vs. 0.004%, p=004). The most common comorbidities were hypertension and diabetes, which are also the most common causes of CKD (51 vs. 3.3% / 42 vs. 1.3%, p<0.001). Need for hospitalization was significantly more frequent in the group with CKD (12.3% vs. 2.2%, p<0.001), with mortality being higher in CKD patients (2.2% vs. 0.1%, p<0.001). Independent risk factors for death were: age, vomiting, leukopenia, diabetes, CKD and hypertension.

Conclusions: CKD aggravates dengue severity, and people with this comorbidity should be carefully monitored, especially in epidemic periods.

Keywords: Dengue, Severe dengue, Kidney diseases, Mortality, Fatal outcome.

RESUMO

Introdução: A infecção pelo vírus da dengue é um problema de saúde pública em todo o mundo, podendo se manifestar desde um quadro febril leve até uma doença grave, com envolvimento de múltiplos órgãos, incluindo doença renal. O objetivo deste estudo foi analisar os casos de dengue avaliando como a doença renal crônica (DRC) agrava suas manifestações clínicas.

Métodos: Estudo transversal realizado no banco de dados da Secretaria de Saúde do Estado do Ceará, Nordeste do Brasil, no período de janeiro de 2015 a dezembro de 2017. Foi feita comparação entre pacientes com e sem DRC.

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Resultados: Foram incluídos 161.880 pacientes. Os pacientes com DRC tinham idade mais avançada (41±22 vs. 35±21 anos, p<0,001), predominantemente do sexo feminino (62 vs. 57%, p=0,004) e apresentavam maior frequência de alguns sinais e sintomas. No entanto, o único sinal de alerta mais prevalente entre os pacientes com DRC foi a letargia (0,5% vs. 0,004%, p=004). As comorbidades mais comuns foram hipertensão e diabetes, que também são as causas mais comuns de DRC (51 vs. 3,3% / 42 vs. 1,3%, p<0,001). A necessidade de internação foi significativamente mais frequente no grupo com DRC (12,3% vs. 2,2%, p<0,001), sendo a mortalidade maior nos pacientes com DRC (2,2% vs. 0,1%, p<0,001). Os fatores de risco independentes para óbito foram: idade, vômitos, leucopenia, diabetes, DRC e hipertensão.

Conclusões: A DRC agrava a severidade da dengue e as pessoas com essa comorbidade devem ser cuidadosamente monitoradas, principalmente em períodos epidêmicos.

Palavras-Chave: Dengue, Dengue grave, Doença renal crônica, Mortalidade, Evolução fatal.

INTRODUCTION

Dengue virus infection is a major public health problem worldwide, since a vast amount of people are exposed to its vector, the *Aedes aegypti* mosquito, and more than 100 countries consider the disease as endemic[1,2]. Differently from what is commonly thought, the mosquito is considered the deadliest animal in the world, causing 700,000 to 2,5 million deaths per year[3]. Dengue is one of the most important vector-borne diseases, frequently resulting in outbreaks in several countries[1,2], and it is part of the list of neglected tropical diseases[4]. Brazil is responsible for the majority of cases in the Americas[2].

Clinical manifestations vary from a mild febrile condition to severe disease, with plasma leakage, coagulopathy and hemorrhagic phenomena, which can lead to different organ involvement, toxic shock syndrome and high risk of death[4]. Dengue-associated kidney disease has been described, including acute kidney injury, hydroelectrolytic disturbances, proteinuria and glomerulonephritis[5], and is associated with higher mortality[6].

Patients with dengue infection and more severe impairment of kidney function are more likely to have Acute Renal Failure (ARF) and a higher risk of mortality. Due to this complicated clinical course and high mortality, the diagnosis and treatment of these patients must be cautious[6].

As dengue is an endemic disease in extensive areas of the globe, we have analyzed the cases of dengue in Brazilian state, aiming to assess how CKD aggravates its clinical manifestations.

METHOD

We conducted a cross-sectional study with the database of the Health Secretariat of Ceará, northeastern Brazil, which is the 8th most populous state in the country, occurred in the period from January 2015 to December 2017. Clinical and laboratory data were collected for convenience from the notification reports, based on the Brazilian National System of Diseases Notification (SINAN, *Sistema de Informação de Agravos de Notificação*) and Laboratory Manager. This study was reviewed and approved by the Research Ethics Com-

mittee of our institution (protocol number 2.272.452).

Dengue diagnosis was based on the recommendations of the Ministry of Health, with specific tests, including serological tests (Enzyme-Linked Immunosorbent Assay - ELISA) and detection of viral antigens (RT-PCR, immunohistochemistry)[7]. Chronic kidney disease (CKD) was defined and classified according to the recommendations of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[8]. CKD is considered as "*abnormalities of kidney structure or function, present for more than three months*" and these abnormalities are expressed by the presence of albuminuria (≥ 30 mg/24 hour or albumin/creatinine ratio ≥ 30 mg/g) or glomerular filtration rate < 60 mL/minute/1.73m^2. Chronic kidney disease was considered based on the information from the patients' official notification reports, as well as clinical manifestations and outcome. A comparison was made between patients with and without CKD as well as evaluated the factores associated with mortality in patients with dengue.

The statistical analysis was performed using the SPSS program for Macintosh, version 23 (Armonk, NY: IBM Corp.). Qualitative variables were expressed as absolute counts and frequencies represented by percentages and compared using the chi-square test or Fisher's exact test. All quantitative variables were tested for normal distribution using the Kolmogorov-Smirnov test and evaluation of data asymmetry using diagram. Normal data were then expressed as mean ± standard deviation. Student's *t* test was used for comparisons between two groups. In addition, multivariate logistic regression was performed to assess the association between clinical factors and comorbidities in patients with dengue according to the presence of CKD. The stepwise method was used in the multivariate analysis. In summary, the variables were added one by one according to greater statistical significance until a final model was generated. For all tests, p <0.05 was considered statistically significant. The confidence interval used was 95%.

RESULTS

A total of 161,880 patients were included. The comparison between patients according to the presence of CKD evidenced that those with CKD were older, predominantly female and had a higher frequency of certain symptoms and signs (Table 1). However, the only warning sign that was more prevalent among CKD patients was lethargy.

Table 1: Clinical characteristics of patients with dengue in Fortaleza, Brazil, 2015-2017, according to the presence of chronic kidney disease (CKD).

	CKD (n=644)	No-CKD (n=161236)	p*
Age, years	41 ± 22	35 ± 21	<0.001
Gender (female)	403 (62.6)	91914 (57)	0.004
Symptoms and Signs			
Fever	579 (89.9)	139759 (86.7)	0.016
Myalgia	491 (76.2)	108934 (67.6)	<0.001
Headache	496 (77)	121057 (75.1)	0.256
Rash	228 (35.4)	36515 (22.6)	<0.001

Vomiting	194 (30.1)	28485 (17.7)	<0.001
Nausea	274 (42.5)	38212 (23.7)	<0.001
Back pain	303 (47)	35800 (22.2)	<0.001
Conjunctivitis	119 (18.5)	5861 (3.6)	<0.001
Arthritis	236 (36.6)	19273 (12)	<0.001
Arthralgia	308 (47.8)	51660 (32)	<0.001
Petechia	157 (24.4)	11835 (7.3)	<0.001
Leukopenia	113 (17.5)	2763 (1.7)	<0.001
Positive tourniquet test	103 (16)	2715 (1.7)	<0.001
Retro-orbital pain	222 (34.5)	27883 (17.3)	<0.001
Warning Signs			
Hypotension	2 (0.3)	68 (0)	0.166
Low platelets count	2 (0.3)	100 (0.1)	0.425
Vomiting	3 (0.5)	91 (0.1)	0.079
Bleeding	2 (0.3)	137 (0.1)	1.000
Increased hematocrit	1 (0.2)	21 (0)	0.242
Abdominal pain	4 (0.6)	216 (0.1)	0.377
Lethargy	3 (0.5)	70 (0)	0.041
Hepatomegaly	0 (0)	11 (0)	1.000
Severity Signs			
Pulse	1 (0.2)	16 (0)	1.000
Convergent Blood Pressure	0 (0)	9 (0)	1.000
Capillary refill time	0 (0)	7 (0)	1.000
Respiratory Insufficiency	1 (0.2)	18 (0)	1.000
Tachycardia	2 (0.3)	26 (0)	0.615
Cold Extremities	1 (0.2)	27 (0)	1.000
Hypotension	2 (0.3)	21 (0)	0.319
Hematemesis	0 (0)	14 (0)	1.000
Melena	0 (0)	13 (0)	1.000
Liver enzymes increase	0 (0)	2 (0)	1.000

Quantitative data expressed as mean and standard deviation, and qualitative data expressed in absolute count and percentages in parentheses. *The chi-square test or Fisher's exact test was used for qualitative data. For quantitative data, Student's t test was used.

Regarding comorbidities, all recorded ones were much more frequent among CKD patients (Table 2), and the most common were hypertension and diabetes, which are also the most common causes of CKD.

Table 2: Comorbidities of patients with dengue in Fortaleza, Brazil, 2015-2017, according to the presence of chronic kidney disease (CKD).

	CKD (n=644)	No-CKD (n=161236)	p*
Pre-existing diseases			
Diabetes	271 (42.1)	2166 (1.3)	<0.001
Hematological disease	236 (36.6)	336 (0.2)	<0.001
Liver disease	247 (38.4)	453 (0.3)	<0.001
Hypertension	332 (51.6)	5344 (3.3)	<0.001
Peptic ulcer disease	247 (38.4)	590 (0.4)	<0.001
Auto-immune disease	223 (34.6)	322 (0.2)	<0.001

Qualitative data expressed in absolute counts and percentages in parentheses. *The chi-square test was used.

The factors independently associated with CKD were nausea, back pain, arthritis, petechia, leukopenia, diabetes, hematological disease, liver disease, hypertension, peptic ulcer, and auto-immune diseases. Headache was a protective factor associated with CKD (Table 3).

Table 3: Independent factors associated with chronic kidney disease (CKD) in patients with dengue in Fortaleza, Brazil, 2015-2017.

	CKD		
	Odds Ratio	**95% C.I.**	**p***
Headache	0.733	0.584 – 0.92	0.007
Nausea	1.268	1.019 – 1.578	0.033
Back Pain	1.438	1.139 – 1.817	0.002
Arthritis	1.709	1.345 – 2.173	<0.001
Petechia	1.336	1.013 – 1.762	0.040
Leukopenia	1.879	1.268 – 2.785	0.002
Diabetes	2.573	1.865 – 3.549	<0.001
Hematological disease	8.087	5.044 – 12.966	<0.001
Liver disease	7.338	4.759 – 11.313	<0.001
Hypertension	5.067	3.913 – 6.561	<0.001
Peptic ulcer disease	7.195	4.833 – 10.712	<0.001
Auto-immune disease	7.738	4.667 – 12.831	<0.001

CI: confidence interval. *The chi-square test was used.

Need for hospitalization was significantly more frequent in the group with CKD (12.3% vs. 2.2%, p<0.001), and mortality was higher in CKD patients (2.2% vs. 0.1%, p<0.001), as shown in Figure 1. Independent risk factors for death were: age, vomiting, leukopenia, diabetes, CKD and hypertension. Female gender, headache, back pain, conjunctivitis and retro-orbital pain were protective factors against death (Table 4).

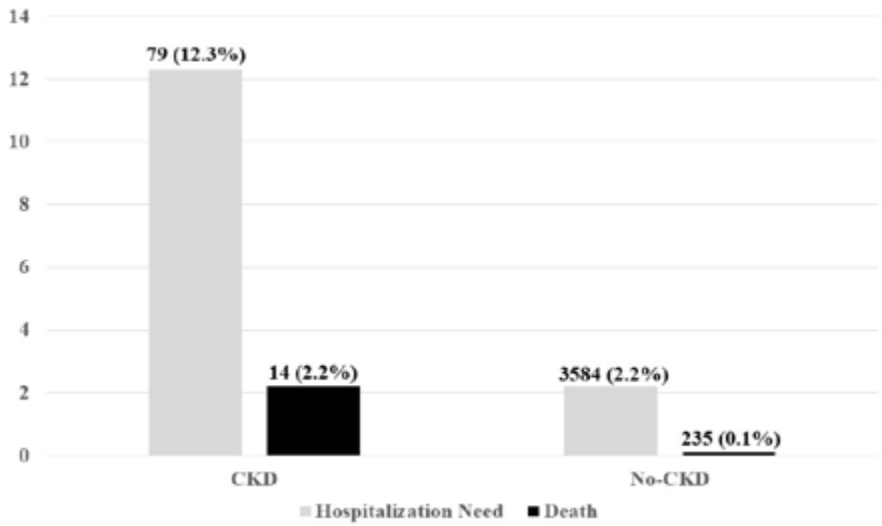

Figure 1: Hospitalization and mortality rates according to the presence of chronic kidney disease (CKD) in patients with dengue in Fortaleza, Brazil, 2015-2017. The chi-square test was used.

Table 4: Independent factors associated with mortality in patients with dengue in Fortaleza, Brazil, 2015-2017.

	Mortality		
	Odds Ratio	**95% C.I.**	**p***
Age	1.024	1.019 – 1.029	<0.001
Gender, female	0.534	0.414 – 0.689	<0.001
Headache	0.31	0.24 – 0.402	<0.001
Vomiting	3.233	2.459 – 4.25	<0.001
Back Pain	0.516	0.356 – 0.748	<0.001
Conjuctivitis	0.209	0.064 – 0.683	0.010
Leukopenia	4.314	2.641 – 7.045	<0.001
Retro-orbital Pain	0.332	0.196 – 0.561	<0.001
Diabetes	2.329	1.415 – 3.832	0.001
CKD	3.964	2.085 – 7.538	<0.001
Hypertension	3.716	2.491 – 5.543	<0.001

CI: confidence interval; CKD: chronic kidney disease. *The chi-square test or Fisher's exact test was used for qualitative data. For quantitative data, Student's t test was used.

DISCUSSION

The study of dengue and its associated factors is of the utmost importance, since there is a high risk of imminent overlap of epidemics in the near future. Great part of the American continent is at risk for dengue epidemics, and knowing the risk factors for disease severity, as well as its possible complications can provide information to support public policies to better face the problem.

The present study has analyzed a large database from northeastern Brazil, including a large urban area, where dengue is endemic. Based on this study, it is clear that CKD is an aggravating factor in dengue virus infection, which itself warrants the adoption of a more careful approach of these patients, since the very first sign of dengue infection. During the COVID-19 pandemic, kidney injury was evidenced early after the infection[9], and CKD patients are known to have a higher risk of death when infected, so they are now prioritized for vaccination[10].

According to the analysis of socio-demographic characteristics of our patients, we demonstrated that CKD patients with dengue were predominantly older and female. Gender differences have been reported in dengue; for instance, women may present menorrhagia in the course of dengue infection[4], although most studies find a predominance of males with dengue, as they are more exposed to its vector[11,12]. Regarding age, it is known that advanced age is associated with comorbidities, including heart, lung and kidney disease, which carry a higher risk of dengue severity[4]. Also, regardless of the comorbidities, advanced age increases dengue severity[13].

Some symptoms and signs were more prevalent in CKD patients, including fever, myalgia, rash, vomiting, nausea, back pain, conjunctivitis, arthritis, arthralgia, petechia, leukopenia and retro-orbital pain. This could be considered a more exuberant disease profile, which could be associated with some immunological phenomena, since CKD patients have immune system dysfunction[14]. There was, however, only one warning sign that was more prevalent in CKD patients, namely lethargy, and that could be used to identify patients at risk for severe disease, although not all studies found a significant association between lethargy and severe dengue[15]. Another study, assessing 199 patients with severe dengue in Malaysia, found that lethargy was a significant factor associated with death (OR 3.84), together with hemorrhage (OR 8.88), pulse rate (OR 1.04) and serum lactate levels (OR 1.27)[16]. On the other hand, no other severity signs were significantly more prevalent in CKD patients in comparison with non-CKD ones. A previous study carried out in India found that 44.7% of the patients admitted in tertiary hospitals with dengue had no warning disease severity symptoms[17].

All comorbidities investigated in the notification reports were more frequently observed in CKD patients, which was not a surprise, as CKD is most of the times a consequence of hypertension and diabetes. A systematic review of the literature and meta-analysis conducted by Htun et al[18]. found limited evidence that diabetes increase the risk for severe dengue and concluded that more studies are needed to further investigate the association between diabetes and dengue. On the other hand, there is evidence from other studies of increased risk in patients with diabetes and dengue, who showed more severe thrombocytopenia[19], and the global epidemic of diabetes increases the severity not only of dengue but of tropical diseases in general[20]. Diabe-

tes treatment with metformin was associated with a decrease in dengue severity, in a dose-response association[21]. Regarding hypertension, studies have shown that it is one of the risk factors for severe dengue[22,23], also being a risk factor for death[24]. Another important comorbidity that was significantly associated with CKD in this study was liver disease. It is known that the majority of patients with dengue have elevated liver enzymes[25]. Liver involvement in dengue is more frequent in children and women, and the pathophysiology include direct viral injury and immune phenomena[25]. In the present study, patients with CKD had a seven-fold higher risk of having liver disease in the course of dengue infection, although it did not remain as an independent risk factor for death. The comorbidities that were independently associated with death in this study were: CKD, hypertension and diabetes.

Need for hospitalization was significantly higher in CKD patients. Kidney involvement in dengue not only is associated with hospitalization requirement, but also with prolonged hospital stay and complications[26]. Mortality was higher in CKD patients, and the main factors associated with increased mortality were leukopenia, CKD, hypertension, diabetes, vomiting and age. Advanced age and the presence of comorbidities are associated with higher mortality in both dengue[27] and COVID-19 infections[28-30], so a more stringent care should be provided to this group of patients (elderly and people with comorbidities) infected with dengue or COVID-19, as they are at great risk for complications and high mortality. Another study carried out in Brazil showed that the risk of death was much higher in patients with dengue and underlying comorbidities, including kidney disease, pulmonary disease and diabetes: case fatality rate of 15%, compared to 1.9% for those with non-severe dengue and no comorbidities[31]. Regarding the laboratory parameters associated with mortality, only leukopenia was found to be associated with a higher risk of death, which is not in accordance to previous studies, which showed that high leukocyte counts were associated with death[32]. Mortality rates are usually higher in dengue patients with kidney involvement. Previous studies have found even higher rates, varying from 20 to 39%[26,32]. Another point that is worth mentioning are the social determinants of health. An interesting review by Carabali et al[33]. investigated the determinants of mortality in dengue worldwide, and the first aspect they have identified was the geographical distribution of these deaths: the majority of cases were from the Americas (50%) and Asia (38.4%), both regions in which extensive areas of poverty are found. This evidence points to a still poorly studied fact, i.e., that social determinants can increase the risk of death in tropical neglected diseases, including dengue[34].

In summary, dengue is a worldwide public health problem, with a definite probability of causing epidemics in a near future. The identification of people at higher risk for complications and death in dengue infections is of the utmost importance, since it allows the adoption of early intervention measures and close monitoring, aiming to achieve better outcomes.

CONCLUSION

In the present study of dengue, it was demonstrated that comorbidities, including hypertension, diabetes, liver disease and others were more frequent in patients with CKD. Patients with dengue and CKD have significantly higher hospitalization and mortality rates. CKD, as well as other comorbidities, including hypertension and diabetes, are independent risk factors for death.

Hence CKD aggravates dengue severity, and people with this comorbidity should be carefully monitored, especially in epidemic periods. In view of the COVID-19 pandemic context occurred, it is suggested that future research better investigate the relationship between endemic viral diseases, with a purpose to reducing the impact on the health and economy of the countries.

Study Limitations

This study has some limitations. The first one is its retrospective nature, which leads to the lack of some information in the patients' medical records and notification reports. There was no information regarding patient CKD stage or specific treatment, such as dialysis or other renal replacement therapy modality. The study was based on the notification reports, so the CKD diagnosis was based on the medical history of patients. It is possible that some cases of acute kidney injury, which is a known complication of dengue, could also have been included or even contributed to worsen the prognosis in a CKD patient. Another important aspect regarding the CKD spectrum is kidney transplant recipients, which was not possible to investigate, so it was not possible to assess the impact of immunosuppression in this population. However, we consider the findings of the present study as important evidence of the association between CKD and dengue severity, and further studies are needed to fully understand the pathophysiology of these findings.

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AUTHORS' CONTRIBUTION

GBSJ: Conception and design of the study, Methodology, Formal analysis, Investigation, Writing, Manuscript review; **AARJ**: Conception and design of the study, Methodology, Formal analysis, Investigation, Writing, Manuscript review; **JRP**: Formal analysis, Investigation, Writing, Manuscript review; **RTD**: Methodology, Manuscript review; **JAMR**: Methodology, Formal analysis, Investigation, Writing, Manuscript review; **GCM**: Conception and design of the study, Methodology, Formal analysis, Investigation, Writing, Manuscript review.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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