



## Correlation between dengue virus infection and its consequences on cardiac comorbidities

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### 1 INTRODUCTION

Dengue is one of the most prevalent arboviruses in tropical regions, essentially in the countries of Africa, Asia and Latin America, such as Brazil, and DENV, arbovirus of this non-contagious acute infectious disease of the genus *Flavivirus* and family *Flaviviridae*, is transmitted by the mosquito of the genus *Aedes* (MAYER; TESH; VASILAKIS, 2017), which has been endemic and seasonal in Brazil since the 1980s, however, due to the environmental changes that have occurred more vigorously in recent decades, these related to deforestation, low hygienic-sanitary conditions, climate change as a result of global warming and rampant urbanization, there has been a significant increase in severe cases and, mainly, the colonization of the vector *Aedes aegypti*, an arthropod that can be found in about 80% of the national territory today (MOTA et al., 2016). Regarding dengue virus infection, the Inter-American Society of Cardiology (IASC) defines it as part of NET-Heart (Neglected Tropical Diseases and other Infectious Diseases involving the Heart), i.e., as a prevalent infection in underdeveloped and developing countries that is neglected by the global health agenda and urges strategies for better diagnostics and treatments in order to avoid concomitant cardiac impairment in countries already economically deficient (BURGOS et al, 2020), therefore, in the meantime, it is valid to emphasize that during an infection by the subtypes of the dengue virus, DENV1-4, cardiac manifestations are not uncommon conjunctures, being generally transient, however, they can be associated with morbidities of high severity and even significant mortality, since myocarditis, one of the most severe diseases related to the immunological consequences of the pathophysiology of dengue, can lead to organic failure of the heart and thus potentiate refractory shock, characterized by cold and mottled skin, altered levels of consciousness, jugular venous distension, dyspnea and rales as adventitious noises in the respiratory system, and ultimately death (SHIVANTHAN et al., 2015). Thus, given the negligence with dengue in the midst of the SARS-CoV-2 virus pandemic during 2020 and 2021, due to the public crisis that generated huge impacts on the Unified Health System (SUS) thanks to the high demands and depletion of elected officials, once these were directed to patients with COVID-19, and the high incidence of cardiac comorbidities in the national territory, to analyze the correlation between dengue



virus infection and its manifestations in the cardiac system, to identify the evolution processes of the infection, from the initial phase of dehydration to the recovery period, passing through the critical period of plasma extravasation and hemorrhage, and identifying risk factors are necessary public care for collective health and are essential to be propagated and taught in the primary health sphere, through the Family Health Teams (EqSF), in order to face seasonal dengue epidemics, overcome cardiac problems, offer early diagnosis and treatment, in addition to reducing the number of hospitalizations resulting from severe manifestations that rival the patient's quality of life.

## **2 OBJECTIVE**

To identify the correlation between the process and evolution of the infection triggered by the subtypes of the DENV virus, the etiologic agent of dengue, and the appearance of its consequent cardiac manifestations in affected patients.

## **3 METHODOLOGY**

This systematized review will use the Scientific Electronic Library (SciELO) and PubMed databases as the primary search source, in order to select scientific articles in Portuguese and English from the last 9 years. The articles will go through a filter of choice in order to distinguish those of greater scope and scientific relevance to be reviewed and analyzed.

The keywords to be used in the search for studies will be: "dengue", "cardiac manifestations", "myocarditis", "DENV" and "public health".

## **4 DEVELOPMENT**

Dengue, as presented in the study by Schaefer et al (2022), is caused by a single-stranded RNA virus of the genus Flavivirus and caused by the DENV1-4 serotypes, being characterized by being an epidemic viral disease in Africa, the Americas, Asia and Australia, in addition to being fostered by urban environments, which provide favorable places for vector dissemination. Its virion is composed of three structural proteins, seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5), 10.7 kb single-stranded positive RNA and lipid envelope, in addition to having around 50 nanometers. In addition, this study exposes two transmission patterns: endemic, in which only one strain of the virus is responsible for the spread, and hyperendemic, which is marked by the circulation of several DENV subtypes and affects children to a greater extent.

With regard to the transmission of the DENV virus, the works of Mota et al (2016) and Mayer; Tesh and Vasilakis (2017) who discussed the perspective of the spread of the mosquito vector and the great challenge that its combat is in Brazil, given the climate changes that affect tropical zones with rigid rainy summers, deforestation and the absence of approved vaccines for arboviruses resulting from



transmission by arthropods of the genus *Aedes*, essentially, *Aedes aegypti* and *Aedes albopictus*. Both studies discriminated such infections as an important public health problem that has been increasing in recent years.

In the work of Roy and Bhattacharjee (2021), there is a definition of the disease as an infection of unique pathogenic complexity, which causes an immune increase in the host in relation to innate immunity, with intense production of interferons (IFN), and adaptive, which is acquired approximately six days after infection and consists of TCD8+ and TCD4+ lymphocytes, which recognize, respectively, non-structural and structural proteins preferentially.

According to Mascarenhas et al (2020), the space-time coincidence of dengue with the COVID-19 pandemic caused deficit scenarios in the care and control of these febrile infections caused by the DENV virus, which Brazil has faced seasonally from March to June since 1986, since the SARS-CoV pandemic generated huge impacts on the Unified Health System (SUS) thanks to the high demands and depletion of elected officials. However, Primary Health Care is also fundamental in dengue care and needs to provide comprehensive attention to this sensitive condition at this level of care, as emphasized by Souza et al (2020).

The Inter-American Society of Cardiology (IASC), as stated in the article by Burgos et al (2020), created through the Latin American Emerging Leaders section the NET-Heart project (Neglected Tropical Diseases and other Infectious Diseases involving the Heart), whose purpose is to promote information on the influence of infectious diseases, such as dengue, on the cardiovascular system. Furthermore, this innovative collaborative initiative characterized dengue and other arboviruses as neglected tropical diseases (NTDs), i.e., infections prevalent in underdeveloped and developing countries that remain neglected by the global health agenda, thus requiring humanitarian attention and strategies for better diagnostics and treatments and thus avoid cardiac impairment in countries that already have evident poverty and are in urgent need of quality public health.

In the meantime, Shivanthan et al (2015) presented a systematic review highlighting the importance of dengue care and explaining that cardiac involvement is not uncommon in a dengue infection, but most of the time this complication is transient. In particular, Mansanguan et al (2021) evaluated 81 adult patients with confirmed dengue virus infection, of whom 22.2% had cardiac involvement; from an elevated cardiac biomarker to myocarditis. In this scenario, according to the work of Sheetal and Jacob (2016), which presented data whose statistical significance had been tested, the most frequent cardiac manifestations are transient rhythm abnormalities, with sinus bradycardia being the most common, and such manifestations are strongly correlated with respiratory discomfort caused by the accumulation of fluid characteristic of severe cases of dengue.

In the context of the evolution of the infection, Giri et al. (2022) highlight the three phases of dengue: an onset marked by dehydration, high fever, myalgia, skin rash, arthralgia and



thrombocytopenia; an aggravation characterized as a critical period due to shock by hemorrhage, plasma extravasation or visceral injury, which can lead to refractory shock, organ failure and even death and a phase of water replacement, which marks recovery. Therefore, the increase in vascular permeability, in which there is an increase in interleukins 6, 13 and 18 and serum tumor necrosis factor, tends to bleeding and circulatory shock, thus, the mechanisms of cardiac injury in dengue most pointed out are the production of inflammatory mediators, as well as a cytokine-mediated immune response, and the direct action of DENV virus subtypes on cardiomyocytes. In the case of patient recovery, water overload has been related to high morbidity resulting from myocarditis triggered by dengue.

However, as pointed out by Araiza-Garaygordobil et al (2021), the specific pathophysiological mechanisms linking dengue and cardiac complications have not been fully studied and described, and their manifestations are widely varied. Thus, its symptoms may include palpitations, hypotension, pleurisy, chest pain, pulmonary edema and clinical signs of cardiogenic shock, such as hypoperfusion (cold and mottled skin, altered levels of consciousness and shorter perfusion time on general clinical examination) and volume overload (jugular venous distension, dyspnea and rales).

Since there is no specific treatment for myocardial diseases associated with arboviruses, it is essential to perform an early diagnosis. At this juncture, according to Farias et al (2019), NS1, a non-structural protein secreted by DENV-infected cells, should be quickly requested, since rapid support is able to control and prevent shock or further loss of cardiac function, both resulting from the critical period of infection.

It is important to emphasize that, as explained by Arora and Patil (2016), the vast majority of cases that presented cardiac complication due to arboviruses later developed a chronic condition, such as T-wave changes in the electrocardiogram and chronic heart failure. Thus, an important initiative, also as pointed out by Arora and Patil (2016), is to highlight dengue as a risk factor for rhythm disorders and, in more serious situations, for myocarditis and, therefore, to provide strict cardiac monitoring for patients with altered electrocardiogram, essentially in endemic areas, since, as explained by the study by Oliveira et al (2022), cardiomyopathies and heart failure are key public health problems to be addressed in Brazil, a label that also covers dengue.

Moreover, the economic burden of cardiac disorders in the national territory is high, as it generates cost to the State to ensure the hospitalization of the patient, such costs that could be reversed, since dengue is a condition capable of being faced in Primary Health Care (PHC), in view of the essential articulation between epidemiological surveillance and the PSF (Family Health Program) teams, which is explained by Gomes et al (2015), a study that aims to carry out an epidemiological analysis of prevention and successful action in coping with DENV virus infection within the scope of Family Health Teams (EqSF).



## 5 FINAL CONSIDERATIONS

Dengue is a Public Health problem of immense impact in tropical countries, which is characterized by being a visceral epidemic in the national territory since 1980, given the immense and growing deforestation and unbridled urbanization, which fails in the basic health criteria to guarantee adequate and universalized quality of life. In addition, with the advent of the COVID-19 pandemic, it had been neglected due to the depletion of beds, once these were directed to patients affected by SARS-CoV-2. However, dengue virus infection, DENV 1-4, is not frivolous and urges public attention, since studies indicate that one of its manifestations is associated with the main causes of morbidity and mortality in Brazil: cardiac comorbidities.

In this scenario, dengue virus infection has an intimate relationship with cardiac problems thanks to the pathophysiology of the disease and its immune response in the body. Therefore, awareness and improvement at the national level regarding the control and treatment of this acute non-contagious infectious disease is crucial, in addition to contributing to the scientific community with systematized information about cardiac manifestations associated with arbovirosis, which are essential for health professionals and students, since both use evidence-based information in their professions and academic training.



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