RELATIONSHIP BETWEEN MYOCARDITIS AND DENGUE

Rafael Melo Lopes[1]

Yana Dantas Fernandes Veras[2]

Janielly Zenette Alves Guedes Da Silva[3]

João De Sena Bernardo[4]

Marcos Paulo De Sena Rodrigues[5]

Sean De Holanda Angelim Santos[6]

Maria Eloisa De Castro Lima[7]

Raimundo Dário Coelho Campelo[8]

Orleâncio Gomes Ripardo de Azevedo[9]

Raquel Gondim Moreira[10]

Abstract: Introduction: Myocarditis, an inflammation of the heart muscle, can arise as a complication of dengue fever, a mosquito-borne disease. It is essential to adopt a multidisciplinary approach to monitor and treat cardiac complications in patients with dengue fever at an early stage. Diagnostic tests inclu-

1 Undergraduate in Medicine from Estácio Idomed College in Canindé -Ce
2 Undergraduate in Medicine from Estácio Idomed College in Canindé -Ce
3 Undergraduate in Medicine from Estácio Idomed College in Canindé -Ce
4 Undergraduate in Medicine from Estácio Idomed College in Canindé -Ce
5 Undergraduate in Medicine from Estácio Idomed College in Canindé -Ce
6 Undergraduate in Medicine from Estácio Idomed College in Canindé -Ce
7 Undergraduate in Medicine from Estácio Idomed College in Canindé -Ce
8 Undergraduate in Medicine from Estácio Idomed College in Canindé -Ce
9 Graduated in Biological Sciences from the State University of Ceará in the Bachelor's and Licentiate degrees (2003 -2007). Master's degree in Pharmacology from the Federal University of Ceará (2009-2010), PhD in Pharmacology from the Federal University of Ceará 2010 - 2012 and Post-Doctorate from the Federal University of Ceará (2016-2021).
10 Doctor graduated from the Federal University of Ceará, Cardiologist from the Hospital de Messejana, Responsible for the valvulopathy outpatient clinic and preoperative cardiac and non-cardiac surgery at the Walter Cantídeo University Hospital; Coordinator of the Medical Clinic Residency - Idomed Canindé

de serology, PCR, and echocardiography. From a review study on cardiac involvement in dengue, it was found that this complication is significant and demands a multidisciplinary approach . Objective: The objective of this study was to conduct a comprehensive integrative review to explore the relationship between myocarditis and dengue fever. Methodology: Articles were searched in databases such as PubMed, Google Scholar,Ministry of Health, and ScienceDirect, using search terms in both Portuguese and English. Out of 122 articles found, 74 were selected for analysis, and 13 were included in the results. Results: The studies examined the relationship between dengue fever and myocarditis, with a focus on the cardiovascular manifestations of dengue fever and the prevalence of myocarditis in infected patients. Analysis of the articles revealed a significant prevalence of myocarditis in patients with dengue, highlighting a strong association between the two conditions. Discussion: Dengue patients frequently present with cardiac issues such as myocarditis, necessitating early detection to prevent serious complications. Effective vector control is crucial to reducing the impact of dengue. These findings provide direction for future research and the development of targeted therapies. Conclusion: Early identification of cardiac complications, such as myocarditis in dengue patients, is crucial to reducing morbidity and mortality. Ongoing research into the pathophysiological mechanisms is vital for the development of specific treatments. The study concludes that myocarditis is commonly associated with dengue, requiring meticulous medical monitoring.

Keywords: Myocarditis; Patients; Dengue.

INTRODUCTION

Myocarditis is a condition characterized by inflammation of the heart muscle. Signs and symptoms can range from mild to severe including chest pain, shortness of breath, fatigue, palpitations, and leg swelling. Some patients may present with fever, general malaise, and cough. In more severe cases, cardiac arrhythmias, fainting, and signs of heart failure, such as pulmonary edema and hepatomegaly, may occur. It is important to be aware of these symptoms, especially after viral and

bacterial infections, given that myocarditis can be a complication of these conditions (BRAZILIAN SOCIETY OF CARDIOLOGY, 2022).

Dengue is an arbovirus transmitted mainly to humans by the bite of the Aedes aegypti mosquito. The dengue virus has four serotypes: DENV-1, DENV-2, DENV-3 and DENV-4, all capable of causing infection in humans. Primary DENV infection can be asymptomatic or manifest as a mild fever, however, in severe cases, it can lead to coagulopathy, increased vascular fragility and permeability, a condition known as dengue hemorrhagic fever (DHF), which can progress to hypovolemic shock, called dengue shock syndrome. (KHAN et al, 2023)

Thus, laboratory confirmation of the diagnosis of dengue can be performed directly, through the detection of viral components in the blood, or indirectly, through serological tests. The choice of the appropriate test depends on the stage of the disease. During the initial febrile phase, the detection of viral components in the circulation is highly sensitive. Viral nucleic acid in serum can be identified by reverse transcriptase polymerase chain reaction (RT-PCR) or by detection of non-structural protein 1 (NS1) by enzyme-linked immunosorbent assay (ELISA). From the fifth day of illness, serology for IgM and IgG is indicated, also helping to differentiate between primary and secondary infection. A high titre of antibodies to hemagglutinin is suggestive of secondary dengue infection. (KULARATNE et al. 2022)

From a review study on cardiac involvement in dengue, it was found that this complication is significant and requires a multidisciplinary approach. It is essential to advance the understanding of the pathophysiological mechanisms and the creation of treatment strategies to improve clinical outcomes and reduce the morbidity and mortality associated with this condition (SILVA et al, 2024)

Myocarditis associated with dengue is mainly manifested by changes in heart rhythm, such as tachycardia and bradycardia. Changes in the T wave and ST segment may also occur, as well as ventricular dysfunctions, which are reflected in the reduction of left ventricular ejection fraction. In some cases, there may be an increase in cardiac enzymes (BRASIL, 2024) According to data from Datasus, in 2024, in Ceará, five dengue-related deaths are under investigation, which may be associated

with myocarditis. This highlights the importance of closely monitoring dengue patients, especially those who have cardiac symptoms, and perform appropriate diagnostic tests to identify and treat possible complications early, such as myocarditis.

GOALS

The aim of this study was to conduct a comprehensive integrative review investigating the relationship between myocarditis, an inflammation of the heart muscle, and dengue fever, a mosquito-borne viral disease. This review aims to explore the existing evidence in the scientific literature on how dengue can trigger or exacerbate myocarditis.

METHODOLOGY

This is a bibliographic research of the integrative review type. This study used the following guiding question: What is the relationship between Dengue and Myocarditis? In this sense, to survey the articles in the literature, a search was carried out in the following databases: PubMed, Google Scholar, Ministry of Health and Science Direct. The following descriptors were used in Portuguese and English: and ‘’Dengue and Myocarditis’’ and ‘’Dengue and Myocarditis’’. The inclusion criteria for the selection of articles were: articles published in Portuguese and English; full articles that were related to the theme related to the integrative review; and articles published and indexed in these databases in the last 5 years and in The Lancet Infectious Diseases. The exclusion criteria were articles that had no relationship between myocarditis and dengue in question. Thus, 122 articles were obtained, of which 48 were excluded because they did not mention the relationship between myocarditis and dengue and only 74 were in accordance with the inclusion criteria of this study, where we used 13 articles to compose our results.

FINDINGS

Year	Author	Myocarditis	Title
2023	Jadav N, Vaghela N, Verma N, Davis D, Sonani AA, Patoliya P. Unmasking the Hidden Threat of Cardiac Involvement in Dengue Fever: A Critical Longitudinal Study. Cureus. 2023 Sep 25;15(9):e45961. doi: 10.7759/cureus.45961. PMID: 37900359; PMCID: PMC10600330.	Present	Unmasking the Hidden Threat of Cardiac Involvement in Dengue Fever: A Critical Longitudinal Study
2023	Sandeep M, Padhi BK, Yella SST, Sruthi KG, Venkatesan RG, Krishna Sasanka KBS, Satapathy P, Mohanty A, Al-Tawfiq JA, Iqhrammullah M, Rabaan AA, Kabi A, Sah S, Rustagi S, Al-Qaim ZH, Barboza JJ, Waheed Y, Harapan H, Sah R. Myocarditis manifestations in dengue cases: A systematic review and meta-analysis. J Infect Public Health. 2023 Nov;16(11):1761-1768. doi: 10.1016/j.jiph.2023.08.005. Epub 2023 Aug 14. PMID: 37738692.	Present	Myocarditis manifestations in dengue cases: A systematic review and meta-analysis.
2020	Bhatt M, Soneja M, Farooqui FA, Singla P, Vikram NK, Biswas A, Roy A, Wig N. Myocarditis in admitted patients with dengue fever. Infection. 2020 Dec;48(6):899-903. doi: 10.1007/s15010-020-01500-w. Epub 2020 Aug 11. PMID: 32780310.	Present	Myocarditis in admitted patients with dengue fever
2022	Rahim A, Hameed A, Ishaq U, Malik J, Zaidi SMJ, Khurshid H, Malik A, Satti DI, Naz H. Cardiovascular sequelae of dengue fever: a systematic review. Expert Rev Cardiovasc Ther. 2022 Jun;20(6):465-479. doi: 10.1080/14779072.2022.2082945. Epub 2022 Jun 2. PMID: 35612830.	Present	Cardiovascular sequelae of dengue fever: a systematic review
2022	Nerella S, Sarkar UK, Namdeo H. Electrocardiographic and echocardiographic findings in children with dengue infection. J Family Med Prim Care. 2022 Jun;11(6):2334-2339. doi: 10.4103/jfmpc.jfmpc_1280_21. Epub 2022 Jun 30. PMID: 36119231; PMCID: PMC9480629.	Present	Electrocardiographic and echocardiographic findings in children with dengue infection

2021	Cabrera-Rego JO, Rojas-Quiroz AF, Vidal-Turruelles Y, Yanes-Quintana AA. Cardiovascular disorders in hospitalized patients with dengue infection. Enferm Infecc Microbiol Clin (Engl Ed). 2021 Mar;39(3):115-118. English, Spanish. doi: 10.1016/j.eimc.2020.02.032. Epub 2020 Apr 25. PMID: 32345488.	Presente	Cardiovascular disorders in hospitalized patients with dengue infection
2022	Gupta S, Gupta M, Kashyap JR, Arora SK. Early cardiovascular involvement in dengue fever: A prospective study with two-dimensional speckle tracking echocardiography. Tropical Doctor. 2022;52(2):285-292. doi:10.1177/00494755221076686	Presente	Early cardiovascular involvement in dengue fever: A prospective study with two-dimensional speckle tracking echocardiography
2021	Shah C, Vijayaraghavan G, Kartha CC. Spectrum of cardiac involvement in patients with dengue fever. Int J Cardiol. 2021 Feb 1;324:180-185. doi: 10.1016/j.ijcard.2020.09.034. Epub 2020 Sep 13. PMID: 32931859.	Presente	Spectrum of cardiac involvement in patients with dengue fever. Int J Cardiol.
2019	Buntubatu S, Prawirohartono EP, Arguni E. Myocarditis Prevalence in Paediatric Dengue Infection: A Prospective Study in Tertiary Hospital in Yogyakarta, Indonesia. J Trop Pediatr. 2019 Dec 1;65(6):603-608. doi: 10.1093/tropej/fmz020. PMID: 31006000.	Presente	Myocarditis Prevalence in Paediatric Dengue Infection: A Prospective Study in Tertiary Hospital in Yogyakarta, Indonesia
2019	Manish Soneja, Manasvini Bhatt, Faraz A Farooqui, Naval K Vikram, Ashutosh Biswas, Ambuj Roy, Naveet Wig, 2654. Myocarditis in Dengue: A Prospective Observational Study, Open Forum Infectious Diseases, Volume 6, Issue Supplement_2, October 2019, Pages S928–S929, https://doi.org/10.1093/ofid/ofz360.2332	Presente	Myocarditis in Dengue: A Prospective Observational Study

2022	Baqi A, Ur Rehman F, Memon PS, Omair SF. Prevalence and Outcomes of Myocarditis in Dengue-Infected Patients Admitted to a Tertiary Care Hospital of Low-Middle Income Country. Glob Heart. 2022 Jun 23;17(1):44. doi: 10.5334/gh.1129. PMID: 35837358; PMCID: PMC9231571.	Presente	Prevalence and Outcomes of Myocarditis in Dengue-Infected Patients Admitted to a Tertiary Care Hospital of Low-Middle Income Country

DISCUSSION

The analysis of the data presented in our review reveals that the involvement of the cardiovascular system in patients infected with dengue is not a rare occurrence. We found that anomalies detected on scans such as ECHO or electrocardiogram (ECG), as well as elevations in serum levels of markers of cardiac injury, can serve as risk indicators for adverse outcomes (KANGUSSU et al. 2022).

In this sense, myocarditis emerges as a common complication among dengue patients, with an estimated prevalence of approximately 21.0% (SANDEEP et al. 2023). This association seems to be correlated with dengue severity, suggesting a possible role of immune system activity in the deterioration of myocardial functions. In addition, vulnerability to myocarditis seems to be higher in children and adolescents with severe dengue, highlighting the importance of age considerations in the clinical evaluation and management of these patients.

The origin of heart disease in dengue infection is not well understood. Several elements contribute to its development, leading to damage to the heart muscle and consequent conduction problems. Direct invasion of the virus into the heart muscles, immune damage caused by cytokines, or a combination of the two can result in heart complications. Disturbances in electrolyte levels, calcium imbalance, lactic acidosis, and ischemia due to low blood pressure are thought to play a role in the cardiac dysfunction seen in dengue patients (BAI et al 2023; SANDEEP et al. 2023).

In addition to the clinical implications, the discussion on the epidemiology of dengue and myocarditis highlights the urgent need for a more comprehensive evaluation. The implementation of

effective vector control strategies is essential to mitigate the impacts of dengue, especially in tropical areas where re-infestation by the primary vector, Aedes aegypti, is a constant concern.

From this perspective, the studies analyzed also highlight the association between dengue severity and the presence of cardiovascular manifestations, with almost half of the patients presenting anomalies in ECG and ECO exams (SHAH et al. 2021). These findings underscore the importance of using contemporary techniques for rapid and effective diagnosis and treatment, aiming to reduce the risks of progression to severe conditions, such as cardiogenic shock and heart failure.

In summary, the results of our study highlight the importance of surveillance and careful monitoring of cardiovascular manifestations in patients with dengue (MANSANGUAN et al. 2021). Early recognition of these complications is essential for effective management of the disease and for reducing the associated risks. In addition, our findings provide valuable insights into the pathological mechanisms underlying cardiac involvement in dengue, paving the way for future research and development of more targeted therapeutic strategies (SANTOS et al. 2024).

CONCLUSION

Understanding the full spectrum of cardiovascular manifestations in dengue infection is essential for early diagnosis and appropriate management of these patients, especially in endemic areas. This integrative review revealed that cardiac complications, including myocarditis, are not uncommon among dengue patients. The presence of ECG abnormalities, ECHO, or elevated markers of cardiac injury may serve as risk predictors for adverse outcomes. Early identification of these cardiovascular signs and symptoms is crucial to reduce the morbidity and mortality associated with the disease. In addition, our study highlights the importance of considering dengue infection as a differential diagnosis in patients with cardiovascular presentations especially in endemic areas. Continuous research on the pathophysiological mechanisms underlying cardiac involvement in dengue is critical for the development of targeted therapeutic strategies and improvement of clinical practices to improve the clinical outcomes

of these patients. Thus, it is observed that among cardiac diseases, myocarditis emerges as a condition frequently mentioned in specialized literature concerning patients affected by dengue. This finding highlights the importance of diligent investigation by medical professionals about potential cardiac complications that may arise in individuals diagnosed with dengue.

REFERENCES

Araiza-Garaygordobil D, et al. Dengue and the heart. Cardiovasc J Afr. 2021;32(5):276-83. doi: 10.5830/CVJA-2021-033. Epub 2021 Jul 20. PMID: 34292294; PMCID: PMC8756038.

Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde e Ambiente. Departamento de Doenças Transmissíveis. Dengue : diagnóstico e manejo clínico : adulto e criança [recurso eletrônico] / Ministério da Saúde, Secretaria de Vigilância em Saúde e Ambiente, Departamento de Doenças Transmissíveis. – 6. ed. – Brasília : Ministério da Saúde, 2024.Disponivel em: file:///C:/Users/rafae/Downloads/Manejo%20clinico%20da%20Dengue.pdf

Bai C, Wang R, Xiong Q, Yang Q, Han P. Dengue virus infection induces myocarditis in IFNα/β receptor deficient mice. Mol Biomed. 2023;4(1):36. doi: 10.1186/s43556-023-00150-2. PMID: 37903980; PMCID: PMC10616043.

Baqi A, Rehman Fu, Memon PS, Omair SF. Prevalence and outcomes of myocarditis in dengue-infected patients admitted to a tertiary care hospital of low-middle income country. Glob Heart. 2022;17(1):44. doi: 10.5334/gh.1129.

Bhatt M, et al. Myocarditis in admitted patients with dengue fever. Infection. 2020;48(6):899-903. doi: 10.1007/s15010-020-01500-w. Epub 2020 Aug 11. PMID: 32780310.

Buntubatu S, Prawirohartono EP, Arguni E. Myocarditis prevalence in paediatric dengue infection: A prospective study in a tertiary hospital in Yogyakarta, Indonesia. J Trop Pediatr. 2019;65(6):603-8. doi: 10.1093/tropej/fmz020.

Cabrera-Rego JO, et al. Manifestaciones cardiovasculares en pacientes hospitalizados con dengue. En-

ferm Infecc Microbiol Clin. 2021;39(3):115-8.

Corré J, et al. Spontaneous coronary hematoma concomitant with myocarditis: the first report of double cardiac complication of dengue. ESC Heart Fail. 2023;10(2):1445-48.

Farrukh MBBS A, et al. Unveiling the dual threat: myocarditis in the spectrum of dengue fever. Curr Probl Cardiol. 2024;49(1). doi: 10.1016/j.cpcardiol.2023.100943.

Khan MB, et al. Visão geral da dengue: uma revisão sistêmica atualizada. J Infectar a saúde pública. Outubro de 2023; 16(10):1625-1642. DOI: 10.1016/j.jiph.2023.08.001. Epub 2023 3 de agosto. PMID: 37595484..

Kularatne SA, Dalugama C. Infecção por dengue: importância global, imunopatologia e manejo. Clin Med (Londres). Janeiro de 2022; 22(1):9-13. DOI: 10.7861/clinmed.2021-0791. PMID: 35078789; PMCID: PMC8813012.

Gupta S, Gupta M, Kashyap JR, Arora SK. Early cardiovascular involvement in dengue fever: A prospective study with two-dimensional speckle tracking echocardiography. Trop Doct. 2022;52(2):285-92. doi: 10.1177/00494755221076686.

Jadav N, et al. Unmasking the hidden threat of cardiac involvement in dengue fever: A critical longitudinal study. Cureus. 2023 Sep 25;15(9). doi: 10.7759/cureus.45961. PMID: 37900359; PMCID: PMC10600330.

Jatene IB, et al. Tratado de cardiologia SOCESP. [São Paulo]: Editora Manole; 2022. E-book. ISBN 9786555765182.

Kangussu LM, et al. Dengue virus infection induces inflammation and oxidative stress on the heart. Heart. 2022;108(5):388-96. doi: 10.1136/heartjnl-2020- 318912. Epub 2021 May 28. PMID: 34049953.

Mansanguan C, Hanboonkunupakarn B, Muangnoicharoen S, et al. Cardiac evaluation in adults with dengue virus infection by serial echocardiography. BMC Infect Dis. 2021;21(1):940. doi: 10.1186/s12879-021- 06639-x. PMID: 34507547; PMCID: PMC8431916.

Mokanpally S, et al. Myocarditis manifestations in dengue cases: A systematic review and meta-analy-

sis. J Infect Public Health. 2023;16(11):1761-8. doi: 10.1016/j.jiph.2023.08.005.

Nerella S, Sarkar UK, Namdeo H. Electrocardiographic and echocardiographic findings in children with dengue infection. J Family Med Prim Care. 2022;11(6):2334-9. doi: 10.4103/jfmpc.jfmpc_1280_21. Epub 2022 Jun 30. PMID: 36119231; PMCID: PMC9480629.

Rahim A, et al. Cardiovascular sequelae of dengue fever: a systematic review. Expert Rev Cardiovasc Ther. 2022;20(6):465-79. doi: 10.1080/14779072.2022.2082945. Epub 2022 Jun 2. PMID: 35612830.

Sandeep M, et al. Myocarditis manifestations in dengue cases: A systematic review and meta-analysis. J Infect Public Health. 2023;16(11):1761-8.

Silva SJ , et al. Cardiac involvement in Dengue infection - a comprehensive review on pathophysiology, epidemiology, clinical manifestations, diagnosis and treatment.

Santos MFR, et al. Dengue: uma análise clínica correlacionada às comorbidades cardíacas e dados epidemiológicos da arbovirose no estado de São Paulo durante o período pandêmico da Covid-19 até 2023. Braz J Health Rev. 2024;7(1):3581-95.

Shah C, Vijayaraghavan G, Kartha CC. Spectrum of cardiac involvement in patients with dengue fever. Int J Cardiol. 2021; 324:180-5.

Sociedade Brasileira de Cardiologia. Nova Diretriz de Miocardites 2022. Arq Bras Cardiol. 2022;119(1):143-211. Available from: https://www.portal.cardiol.br/post/sbc-lan%C3%A7a-em-julho--nova- diretriz-de-miocardites. Accessed February 11, 2024.

Soneja M, Bhatt M, Farooqui FA, et al. Myocarditis in dengue: A prospective observational study. Open Forum Infect Dis. 2019;6(Suppl 2). doi: 10.1093/ofid/ofz360.2332.

Sud R, Agarwal N, Aishwarya V, et al. A case series of dengue myocarditis: A complication observed in dengue patients. Cureus. 2023 Nov 4;15(11). doi: 10.7759/cureus.48285. PMID: 38058326; PMCID: PMC10696278.