

CARDIAC SYMPTOMS OF DENGUE: CURRENT EVIDENCE AND CHALLENGES IN IDENTIFICATION AND MANAGEMENT

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Abstract: Goal: This literature review analyzes recent evidence on the cardiac symptoms of dengue, aiming to understand its pathophysiology, identify risk factors and investigate diagnostic, treatment and prevention strategies. A total of 17 articles were selected from a total of 22 found in the PubMed-MEDLINE database, covering studies published between 2014 and 2024. Summary: Dengue has three distinct clinical phases: febrile, critical and recovery, with different cardiac manifestations, including acute coronary syndrome, thromboembolic and ischemic events. Diagnosis is challenging due to the lack of universal protocols, but tools such as electrocardiography and cardiac biomarkers are useful. Final considerations: Advances in diagnosis, such as electrocardiography and echocardiography, have improved detection. Future research must focus on diagnostic and treatment strategies, as well as long-term effects on cardiovascular health, aiming to reduce the burden of the disease in endemic areas.
Keywords: Dengue, Cardiac symptoms, Complications, Pathophysiology.

INTRODUCTION

Dengue, a viral disease transmitted by arthropods of the genus *Aedes*, is considered the most prevalent infectious viral infection worldwide, affecting millions of people annually. In India, where dengue represents a significant public health problem, an estimated 96 million cases are clinically reported each year. The dengue virus, with its four distinct serotypes (DENV 1, 2, 3, and 4), is especially prevalent in tropical and subtropical regions. The first documented case of dengue fever in India occurred in 1956 in Vellore, while the first case of dengue hemorrhagic fever was recorded in Kolkata in 1963 (Abhinayaa et al., 2021).

The relationship between dengue fever and cardiac complications has been known for some time, however, studies on this association are limited (Cabrera-Rego et al., 2021; Kashyap et al., 2024). Clinical research indicates that cardiac comorbidity in dengue may result from both direct viral invasion and cytokine-mediated immune damage (Abhinayaa et al., 2021). The incidence of these cardiac complications is remarkably high, contributing significantly to the hospitalization and mortality rate in the country. The World Health Organization (WHO) reports an increase in dengue case notifications over the last five decades (Abhinayaa et al., 2021).

Clinically, dengue manifestations can range from asymptomatic infections to mild flu-like symptoms, to more severe forms such as dengue hemorrhagic fever and dengue shock syndrome. During the defervescence phase, the reversal of plasma leakage and reabsorption of extravasated fluid can lead to fluid overload, resulting in complications such as massive pleural effusion or pulmonary edema. Hypovolemia is the primary mechanism of shock, but compromised cardiac function may also contribute to the observed cardiac abnormalities (Jadav et al., 2023).

Furthermore, the pathogenesis of cardiac manifestations in dengue may include generalized endothelial dysfunction, changes in vascular permeability, and localized cardiac lesions such as myocardial necrosis and inflammation (Kashyap et al., 2024).

Several cardiovascular disorders, including sinus bradycardia, atrioventricular block, atrial and/or ventricular extrasystoles, atrial fibrillation, atrial flutter and ventricular tachycardia, have been associated with dengue. Notably, the prevalence of these manifestations is significantly higher in male and elderly patients, while skin color

has not shown a significant correlation with complications (Kashyap et al., 2024). The WHO recently classified “expanded dengue syndrome” as a new category, including unusual manifestations with multi-organ involvement (Abhinayaa et al., 2021).

Therefore, it is essential to monitor cardiac function in dengue patients to enable early interventions and provide vital information for the prevention and management of serious complications, thereby improving patient outcomes and saving lives (Jadav et al., 2023). This study aims to elucidate the acute and chronic cardiac complications associated with dengue, understand the underlying pathophysiology, identify associated risk factors, and explore diagnostic strategies.

METHODOLOGY

This narrative bibliographic review was prepared based on the PVO strategy, which involves the clear definition of the Population or Research Problem, the Variables involved and the expected Outcome. The research was guided by the following guiding question: “What are the cardiac manifestations of dengue and its cardiovascular sequelae, and how are these conditions addressed in current scientific literature?”

For data collection, searches were carried out in the PubMed-MEDLINE (Medical Literature Analysis and Retrieval System Online) database, using specific terms related to the topic, in combination with the Boolean operators “AND” and “OR”. This initial search resulted in the identification of 22 articles. The selection criteria were applied, which included articles published between 2014 and 2024, addressing the topics of interest. The types of study considered were: prospective and retrospective cohort studies, case reports, cross-sectional and longitudinal studies, systematic reviews and meta-analyses, in addition to prospective observational studies.

Articles that did not directly address the topic investigated or that did not meet the established inclusion criteria were excluded.

After rigorous application of the selection criteria in the database consulted, 17 articles were selected that proved to be relevant for the preparation of this study. This careful selection made it possible to compose a robust and representative collection of current scientific literature on the cardiac manifestations of dengue and its cardiovascular implications.

DISCUSSION

ACUTE CARDIAC MANIFESTATIONS OF DENGUE

The clinical evolution of dengue can be divided into three phases: febrile, critical and recovery. During the febrile phase, symptoms such as acute fever, retro-orbital pain, headache and myalgia are common. In the critical phase, a drop-in platelet count and an increase in hematocrit are observed, accompanied by clinical signs of plasma leakage and, occasionally, hypotension. The recovery phase is marked by the reabsorption of extravascular fluid and improvement in clinical and laboratory parameters. However, a small number of patients may progress to more severe forms of the disease, including severe shock and coagulopathy (Shivantan et al., 2015; Yacoub et al., 2014).

The mechanism by which dengue causes cardiac damage includes direct action of the virus on cardiomyocytes and endothelial cells of blood vessels, as well as a significant inflammatory component that contributes to myocarditis and, potentially, dilated cardiomyopathy (Rahim et al., 2022; Kashyap et al., 2024). Studies such as that by Kaagaard et al. (2022) demonstrated that the systolic function of the left ventricle can decline proportionally to the number of previous episodes of dengue, especially in male patients.

Diagnostic tools such as electrocardiogram, echocardiography and cardiac magnetic resonance, in addition to cardiac biomarkers, are essential to assess cardiac involvement and must be used judiciously (Nerella, Sarkar & Namdeo, 2022).

The World Health Organization updated its classification of dengue in 2009, categorizing it into dengue without warning signs, dengue with warning signs and severe dengue, with severity being defined mainly by shock and respiratory distress resulting from plasma extravasation, hemorrhage severe or organ impairment (Kaagaard et al., 2022). Cardiac complications, including myocarditis, electrical abnormalities and left ventricular involvement, can arise during dengue infection. Although pericarditis and pericardial effusion are less common and of limited clinical relevance, they are observed in isolated cases (Shivantan et al., 2015; Yacoub et al., 2014).

A study by Mansanguan et al. (2021) followed adult patients with confirmed cases of dengue, performing serial exams including cardiac biomarkers and two-dimensional echocardiography. The study revealed that 22.2% of patients had cardiac involvement, with transient systolic and diastolic dysfunction of the left ventricle, elevated cardiac biomarkers and mild pericardial effusion, with this involvement being more pronounced in patients with dengue hemorrhagic fever, affecting 40.5 % of cases (Mansanguan et al., 2021).

Cabrera-Rego et al. (2021) carried out a study with 427 patients diagnosed with dengue, of which 19.7% presented cardiovascular manifestations, with rhythm disorders being the most prevalent. Myocarditis and pericarditis were less common, corresponding to 1.6% and 0.2% of cases, respectively.

Identification of cardiac involvement in dengue is complex, given the lack of universal

diagnostic protocols. Araiza-Garaygordobil et al. (2021) proposed an algorithm to guide decision-making in the investigation of cardiac involvement in suspected or confirmed cases of dengue. This algorithm suggests that patients with ECG abnormalities and symptoms of heart failure or suspected myocarditis be referred for echocardiography in order to evaluate cardiac involvement and exclude other etiologies. In cases of changes in the echocardiogram, cardiac magnetic resonance (CMR) is essential to better characterize the underlying pathology. However, the availability of these tests is a challenge, especially in endemic areas with limited resources.

Shivanthan et al. (2015) documented a variety of electrocardiogram (ECG) changes during dengue infection, including abnormalities in heart rate and rhythm, heart block, and variations in wave shape and voltage. Yacoub et al. (2014) observed that electrocardiographic changes are transient and nonspecific, and may be symptomatic or asymptomatic, and occur at any stage of the disease. These changes are relatively common, with a prevalence of 30-44% in patients hospitalized with dengue.

In a prospective observational study by Nerella, Sarkar and Namdeo (2021) that included 150 children between 1 month and 12 years of age, seropositive for dengue, abnormal ECG findings were observed in 78 cases. These included elevated heart rate (>180/min) in 4.6% of cases, low heart rate (<60/min) in 13.3%, first-degree atrioventricular block in 2.6%, second-degree block in 0.6%, low voltage complexes in 27.3% and nonspecific changes in the ST segment in 3.3%. Furthermore, echocardiographic changes were observed in 67 cases (44.6%), including pericardial effusion and reduced ejection fraction, with a higher prevalence observed in the group with severe dengue.

A longitudinal study carried out by Jadav et al. (2023) in a tertiary service analyzed 104 confirmed cases of dengue, finding that 28 (26.9%) of the patients presented symptoms of cardiac involvement. Electrocardiographic changes were also identified in 26.9% of patients, including prolongation of the QRS interval, QT interval, ventricular arrhythmias and conduction disturbances. Within this group, 14 (50%) presented echocardiographic abnormalities, with mild pericardial effusion being the most common abnormality.

The systematic review by Araiza-Garaygordobi et al. (2021) indicated that the incidence of myocardial damage detected by transthoracic echocardiography is directly related to the severity of dengue. Additional studies, such as that of Shivanthan et al. (2015), emphasize that the echocardiographic study is crucial to understand the hemodynamic changes caused by dengue, especially in patients with more severe conditions. During the critical phase of dengue shock syndrome, reductions in preload and ventricular ejection fraction are observed, while systemic vascular resistance increases to maintain mean arterial pressure.

In addition to echocardiography, cardiac magnetic resonance (CMR) is emerging as a vital additional diagnostic method, providing precise details about the presence and nature of lesions in myocardial tissue, increasing sensitivity and specificity for diagnosing myocarditis. Araiza-Garaygordobi et al. (2021) emphasize that CMR is the gold standard for evaluating ventricular function, but its applicability may be restricted due to limited availability, especially in endemic regions with scarce resources.

The importance of identifying cardiac involvement in dengue is due to the significant impact of these complications on cardiovascular outcomes, guiding the appropriate therapeutic choice. Cardiac

biomarkers such as troponin T and CK-MB are essential for detecting acute cardiac involvement. As described by Mansanguan et al. (2021), these biomarkers can demonstrate left ventricular dysfunction, with troponin T being particularly associated with this condition.

In a meta-analysis focused on the relationship between dengue and myocarditis, evidence indicates that patients with myocarditis have a higher risk of developing severe forms of dengue and mortality, with statistical significance ($P < 0.005$; CI = 95%) (Article 21). This result is corroborated by a prospective observational study conducted by Bhatt et al. (2020), which included 182 hospitalized patients with a confirmed diagnosis of DENV infection. The study observed that the presence of myocarditis was associated with a prolonged hospital stay and that all recorded deaths occurred in patients who simultaneously had dengue fever and myocarditis.

These findings suggest that myocarditis may be an indicator of significant morbidity and mortality in patients with dengue fever, with a greater likelihood of fatal outcomes in elderly individuals and those with pre-existing comorbidities (Nicacio et al., 2022).

Contrarily, Shivanthan et al. (2015) argue that, in most cases, dengue-related myocarditis is clinically insignificant and tends to be self-limited. The authors highlight that the presence of electrocardiographic abnormalities can raise the suspicion of cardiac involvement in cases of dengue, which could justify the use of echocardiography based on clinical judgment. However, they question the effectiveness of using complementary tests for the early diagnosis of asymptomatic myocarditis, arguing that this can lead to an ineffective allocation of resources and unnecessary transfers to intensive care units.

CARDIOVASCULAR MANIFESTATIONS AND SEQUELAE

Acute cardiac manifestations of dengue, although uncommon, are documented and can result in significant complications such as myocardial dysfunction, rhythm changes and heart failure. Studies, including those by Araiza-Garaygordobil et al. (2021) and Farrukh et al. (2024), highlight the importance of recognizing these manifestations due to the high risk of post-infection thromboembolic events (Wei et al., 2022). Pro-inflammatory cytokines and activation of the sympathetic nervous system during the acute phase of infection contribute to the increased burden on the heart, exacerbating conditions such as heart failure due to increased vascular permeability and interstitial edema.

Case reports of acute coronary syndrome as a complication subsequent to dengue highlight the importance of differentiating myocarditis and acute infarction in patients with cardiac manifestations (Kashyap et al., 2024). The observational study by Wei et al. (2022) also associated thromboembolic and ischemic events, such as myocardial infarction and stroke, with dengue, emphasizing the interaction between endothelial injury, pro-inflammatory cytokines and arrhythmias as contributing factors.

In contrast, some analyzes indicate that while myocarditis may be a predictor of morbidity and mortality in dengue patients, many cases are subclinical and resolve spontaneously (Shivanthan et al., 2015). This observation suggests that, although electrocardiographic changes may indicate cardiac involvement, the excessive use of complementary diagnostics, such as echocardiography and cardiac magnetic resonance (CMR), must be considered to avoid ineffective allocation of resources.

Finally, longitudinal studies, such as that by Versteeg et al. (2019), have investigated the

long-term effects of dengue on cardiovascular health, finding evidence of persistent changes in vascular structure, such as increased thickness of the carotid intima-media layer in young people who suffered dengue hemorrhagic fever in childhood.

Dengue-related cardiovascular manifestations and sequelae are a critical aspect of the morbidity associated with this infection. Although cardiac involvement in dengue patients is rare, when it occurs, it can result in serious conditions such as cardiac dysfunction, rhythm changes, myocarditis and heart failure, as documented in the literature by Araiza-Garaygordobil et al. (2021) and Farrukh et al. (2024). Furthermore, the increased risk of post-infection thromboembolic events is an emerging concern (Wei et al., 2022).

Studies such as that by Wei et al. (2023) also show that a previous history of dengue fever significantly increases the risk of developing acute heart failure, particularly in the weeks immediately after infection, with a greater impact observed in men over 60 years of age. These findings underscore the need for surveillance for signs of heart failure in patients recovering from dengue fever, especially in the presence of symptoms such as dyspnea or lower limb edema.

Despite these advances, the literature still discusses the variability of cardiac manifestations of dengue and its management. Cardiac arrhythmias, while generally benign and self-limited, can exacerbate preexisting

cardiovascular conditions and contribute to morbidity and mortality (Mansanguan et al., 2021). The study by Parchani et al. (2021) reinforces that electrocardiographic changes can persist for months, requiring continuous surveillance and, possibly, specific interventions.

FINAL CONSIDERATIONS

The cardiac complications of dengue are extensive and complex, ranging from acute manifestations to chronic sequelae. Research highlights the importance of cardiac involvement in dengue, including endothelial dysfunction, changes in vascular permeability and direct injuries such as myocardial necrosis and inflammation. Such complications are more common in male and elderly patients, highlighting the need for strict monitoring. Diagnostic advances, including electrocardiography, echocardiography, and magnetic resonance imaging, along with biomarkers, have improved the detection of these complications.

Future studies must focus on the development and validation of diagnostic and therapeutic strategies, in addition to exploring the long-term implications of dengue on the cardiovascular health of specific populations. Continued research is crucial to better understand these complications and to develop effective treatments to improve patient outcomes and reduce the burden of disease in endemic areas.

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