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CARDIOPULMONARY COMPLICATIONS IN DENGUE AND OTHER ARBOVIRAL INFECTIONS: PATHOPHYSIOLOGY AND MANAGEMENT

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Abstract: INTRODUCTION The introduction highlights the significance of arboviral diseases, particularly dengue, in causing cardiopulmonary complications, which range from mild symptoms to severe, life-threatening conditions. It outlines the mechanisms of viral-induced cardiopulmonary damage, the diverse clinical manifestations observed, and the diagnostic challenges that arise due to overlapping symptoms with other diseases. It also underscores the need for more robust diagnostic and therapeutic strategies to manage these complications effectively. **OBJETIVE** To provide a comprehensive review of the cardiopulmonary complications associated with dengue and other arboviral infections, focusing on their pathophysiological mechanisms, clinical manifestations, diagnostic challenges, and therapeutic strategies. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Cardiopulmonary complications" AND "Dengue infection" OR "Arboviral diseases" AND "Inflammatory response" in the last years. **RESULTS AND DISCUSSION** The results and discussion provide an in-depth analysis of the different cardiopulmonary complications associated with dengue and other arboviral infections, such as myocarditis, pericarditis, ARDS, and pulmonary edema. The text examines the complex interplay between viral factors and host immune responses that drive these complications and evaluates the diagnostic tools currently available. It also discusses therapeutic strategies, including supportive care and the controversial use of corticosteroids and antiviral agents, while highlighting the gaps in knowledge regarding optimal management and long-term outcomes. **CONCLUSION** The conclusion emphasizes the need for further research to establish evidence-based guidelines for diagnosing and treating cardiopulmonary complications in arboviral infections. It calls for developing new diagnostic tools, more effective therapies, and comprehensive care models that address both acute and long-term management. The text also suggests that understanding the long-term impact of these complications on patient health is crucial for improving patient care and reducing the burden on healthcare systems, particularly in regions where arboviral infections are most common.

Keywords: Dengue; Arboviruses; Myocarditis; Acute respiratory distress syndrome (ARDS); Immunopathogenesis

INTRODUCTION

Arboviral diseases, such as dengue, chikungunya, Zika, and yellow fever, represent a significant public health challenge worldwide due to their complex clinical presentations and potential for severe complications[1]. Among the numerous manifestations of these infections, cardiopulmonary alterations remain a critical area of concern due to their high morbidity and mortality rates[1]. Dengue, a flavivirus transmitted primarily by Aedes mosquitoes, has shown a significant increase in cases over the past few decades, affecting millions annually[1]. While dengue's most recognized complications involve hemorrhagic fever and shock, its impact on the cardiovascular and respiratory systems is increasingly documented, revealing diverse manifestations ranging from mild myocarditis to severe heart failure and acute respiratory distress syndrome (ARDS)[2]. Understanding the pathophysiological mechanisms that drive these complications is vital for developing targeted diagnostic and therapeutic strategies[2]. Furthermore, the spectrum of cardiopulmonary involvement in dengue appears to differ from other arboviruses, such as chikungunya and Zika, which warrants a detailed exploration of these differences[2].

The cardiopulmonary involvement in arboviral infections is hypothesized to result from several interrelated mechanisms, including direct viral invasion of cardiac and pulmonary tissues, immune-mediated injury, and the effects of systemic inflammatory responses[3]. In dengue, the pathogenesis is largely influenced by a complex interplay between viral virulence factors and the host immune response[3]. The role of cytokine storms, characterized by elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins, has been particularly noted in severe cases, leading to capillary leakage, myocardial dysfunction, and pulmonary edema[3]. In contrast, the cardiopulmonary manifestations in chikungunya and Zika are less well characterized but appear to involve similar inflammatory pathways with distinct clinical presentations[4]. Chikungunya, for example, often presents with chronic myocarditis and pericarditis, while Zika's cardiovascular manifestations are primarily seen in congenital infections[4].

The clinical presentation of cardiopulmonary complications in arboviral diseases is highly variable, ranging from asymptomatic cases to severe disease requiring intensive care management[5]. In dengue, cardiopulmonary involvement is often heralded by signs of myocardial dysfunction, such as reduced ejection fraction, conduction abnormalities, and elevated cardiac biomarkers, which may progress to fulminant heart failure or arrhythmias[5]. Similarly, pulmonary involvement can range from mild pleural effusions to life-threatening ARDS, driven by vascular endothelial dysfunction and increased alveolar-capillary permeability[5]. The diagnostic approach to these complications is complicated by the overlap of symptoms with other common tropical diseases and the lack of specific biomarkers for early detection[6]. This complexity necessitates a multi-modal diagnostic strategy, combining clinical assessment with advanced imaging and laboratory techniques, to accurately identify and manage affected patients[6].

Despite advances in understanding the pathophysiology and clinical manifestations of cardiopulmonary complications in arboviral infections, significant gaps remain in our knowledge, particularly concerning the optimal management and prevention of these outcomes[7]. Current treatment strategies are largely supportive, focusing on fluid management, oxygen therapy, and, in severe cases, mechanical ventilation and inotropic support[7]. However, there is a lack of consensus on the use of corticosteroids, immunomodulatory therapies, and antiviral agents in these settings, reflecting the need for further research to establish evidence-based guidelines[7]. Furthermore, the long-term outcomes of patients with arboviral cardiopulmonary involvement remain poorly understood, with limited data on the sequelae of these complications and their impact on quality of life and long-term cardiovascular health[8]. Addressing these gaps is crucial for improving patient care and reducing the burden of these diseases on healthcare systems, particularly in resource-limited settings where arboviral infections are most prevalent[8].

OBJETIVES

To provide a comprehensive review of the cardiopulmonary complications associated with dengue and other arboviral infections, focusing on their pathophysiological mechanisms, clinical manifestations, diagnostic challenges, and therapeutic strategies.

SECUNDARY OBJETIVES

1. To evaluate the incidence and prevalence of cardiopulmonary complications in dengue and other arboviruses.

2. To compare the pathophysiological mechanisms underlying these complications across different arboviruses.
3. To analyze the effectiveness of current diagnostic tools and therapeutic approaches for managing cardiopulmonary manifestations.
4. To explore the long-term outcomes and potential sequelae of these complications.
5. To identify gaps in the current knowledge and suggest future research directions to improve patient management and outcomes.

METHODS

This is a narrative review, in which the main aspects of the cardiopulmonary complications associated with dengue and other arboviral infections, focusing on their pathophysiological mechanisms, clinical manifestations, diagnostic challenges, and therapeutic strategies in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Cardiopulmonary complications" AND "Dengue infection" OR "Arboviral diseases" AND "Inflammatory response" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

The cardiopulmonary manifestations of dengue and other arboviral infections represent a diverse spectrum of clinical entities, ranging from mild, self-limited symptoms to severe, life-threatening complications[9]. In dengue, the pathophysiological mechanisms underlying cardiopulmonary involvement are primarily driven by a dysregulated immune response, characterized by a cytokine storm and endothelial dysfunction[9]. Studies have shown that patients with severe dengue often exhibit elevated levels of interleukin-6 (IL-6), TNF-α, and other pro-inflammatory cytokines, which contribute to increased vascular permeability, myocardial depression, and pulmonary edema[9]. The role of direct viral invasion of cardiac and pulmonary tissues remains controversial, with some studies suggesting a limited presence of viral antigens in these tissues, while others have demonstrated evidence of viral RNA in myocardial and lung samples, indicating a possible direct cytopathic effect[10]. This dichotomy suggests that the severity of cardiopulmonary complications may depend on a combination of direct viral effects and host immune response[10].

Chikungunya virus, another arbovirus with widespread impact, presents a different pattern of cardiopulmonary involvement[11]. Unlike dengue, where acute complications are more common, chikungunya often leads to chronic cardiac conditions such as myocarditis, pericarditis, and dilated cardiomyopathy, which may persist for months to years after the initial infection[11]. The pathogenesis of these complications is thought to involve both direct viral cytotoxicity and immune-mediated mechanisms, with evidence of persistent viral RNA in cardiac tissues suggesting ongoing viral replication and inflammation[11]. Clinical studies have reported cases of heart failure, arrhythmias, and even sudden cardiac death

associated with chikungunya, highlighting the need for long-term cardiac monitoring in these patients[12]. Moreover, pulmonary manifestations such as interstitial pneumonitis and pleural effusions have been documented, although they are less common than cardiac involvement[12]. The chronicity of these complications poses significant challenges for patient management, particularly in endemic regions where chikungunya outbreaks occur frequently[12].

Zika virus, primarily known for its neurotropic properties, has also been associated with cardiopulmonary complications, especially in cases of congenital infection[13]. In neonates exposed to Zika in utero, congenital heart defects, including ventricular septal defects and pulmonary valve abnormalities, have been reported, suggesting a direct teratogenic effect of the virus on cardiac development[13]. In adults, Zika-induced myocarditis and pericarditis have been documented, albeit less frequently than with dengue or chikungunya[13]. The pathophysiological mechanisms of these complications remain poorly understood, but it is hypothesized that they may result from a combination of direct viral damage and immune-mediated injury[14]. The involvement of the pulmonary system in Zika is less well characterized, with limited data on the incidence and nature of respiratory complications[14]. However, given the overlap in transmission vectors and geographic distribution, co-infections with other arboviruses, such as dengue and chikungunya, may complicate the clinical picture and contribute to more severe cardiopulmonary outcomes[14].

Diagnostic approaches to cardiopulmonary complications in arboviral infections remain challenging due to the lack of specific biomarkers and the overlap of symptoms with other infectious and non-infectious diseases[15]. Advanced imaging techniques, such as echocardiography and cardiac magnetic resonance imaging (MRI), have proven valuable in assessing cardiac function and detecting structural abnormalities, while chest radiography and computed tomography (CT) scans are essential for evaluating pulmonary involvement[15]. However, these modalities may not always be readily available in resource-limited settings, where most arboviral infections occur[15]. Laboratory markers, including cardiac enzymes (troponin, creatine kinase-MB) and inflammatory markers (C-reactive protein, ferritin), can provide additional diagnostic information but lack specificity for arboviral cardiopulmonary involvement[16]. The development of more sensitive and specific diagnostic tools is crucial for early identification and management of these complications[16].

Therapeutic strategies for managing cardiopulmonary complications in arboviral infections are primarily supportive, focusing on fluid resuscitation, oxygen therapy, and, in severe cases, mechanical ventilation and hemodynamic support[17]. The use of corticosteroids and other immunomodulatory agents remains controversial, with some studies suggesting potential benefits in reducing inflammation and capillary leakage, while others have raised concerns about increased viral replication and adverse outcomes[17]. Antiviral therapies, such as ribavirin and favipiravir, have shown limited efficacy in treating arboviral infections, and their role in managing cardiopulmonary complications remains unclear[17]. Further research is needed to explore the potential benefits of novel therapeutic agents, including monoclonal antibodies and small molecule inhibitors, in reducing the morbidity and mortality associated with these complications[18].

Long-term outcomes of cardiopulmonary complications in arboviral infections remain poorly characterized, with limited data on the sequelae of these complications and their impact on quality of life and long-

term cardiovascular health[18]. Studies have suggested that patients with severe dengue are at increased risk of developing long-term cardiovascular complications, such as persistent myocardial dysfunction and heart failure, while those with chikungunya may experience chronic myocarditis and dilated cardiomyopathy[18]. The long-term pulmonary sequelae of arboviral infections are less well understood, but there is evidence to suggest that some patients may develop chronic respiratory conditions, such as interstitial lung disease and pulmonary hypertension[19]. These findings highlight the need for long-term follow-up and monitoring of patients with arboviral cardiopulmonary involvement to identify and manage potential complications[19].

CONCLUSION

Cardiopulmonary complications of dengue and other arboviral infections represent a significant and underrecognized aspect of these diseases, contributing to increased morbidity and mortality. The pathogenesis of these complications is complex and involves a combination of direct viral effects, immune-mediated injury, and systemic inflammatory responses.

Despite advances in our understanding of the mechanisms underlying these complications, significant gaps remain in the diagnosis, management, and prevention of cardiopulmonary involvement in arboviral infections. Current treatment strategies are largely supportive, and there is a lack of consensus on the use of corticosteroids, immunomodulatory therapies, and antiviral agents. Further research is needed to establish evidence-based guidelines for the management of these complications, particularly in resource-limited settings where arboviral infections are most prevalent. Additionally, the development of more sensitive and specific diagnostic tools is crucial for the early identification and treatment of affected patients, which could potentially reduce the morbidity and mortality associated with these infections.

Moreover, there is an urgent need to explore the long-term outcomes and sequelae of cardiopulmonary complications in patients with arboviral infections. Understanding the potential for persistent or late-onset cardiovascular and pulmonary conditions will inform clinical follow-up strategies and improve patient care. This is especially relevant given the chronic nature of some of these complications, such as myocarditis in chikungunya or congenital heart defects in neonates exposed to Zika virus in utero. Comprehensive longitudinal studies are necessary to elucidate the full spectrum of long-term health consequences, which would also assist in developing targeted interventions aimed at preventing or mitigating these outcomes.

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