REVISTA CIÊNCIAS DA SAÚDE CEUMA RCS

ISSN 2965-6060

Revisão de Literatura

Hematological complications in dengue: a literature review (2003-2023)

Complicações hematológicas no dengue: uma revisão de literatura (2003-2023)

João Paulo dos Santos Pires[1]; Thaís Ranielle Souza de Oliveira[2]

[1] Graduando em Farmácia, Centro Universitário Unieuro – UNIEURO, Brasília – DF, Brasil.
[2] Doutorado em Biologia, Professora dos Cursos de Farmácia e Medicina, Centro Universitário Unieuro – UNIEURO, Brasília – DF, Brasil.

Abstract

Dengue, transmitted by the Aedes aegypti mosquito, is an acute febrile illness with symptoms ranging from fever to severe complications like hemorrhagic fever. Approximately 500 million people in the Americas are at risk, making it an emerging tropical disease. This study reviews hematological complications associated with dengue from 2003 to 2023, addressing lymphohistiocytosis, thrombocytopenia, coagulation abnormalities, and others. Lymphohistiocytosis, often underdiagnosed due to its similarity to dengue, carries a risk of fatal outcomes. Thrombocytopenia, common in severe cases, is linked to disseminated coagulation. Sickle cell anemia exacerbates dengue due to intravascular hemolysis, leading to hospitalizations and transfusions. Dengue can suppress bone marrow, complicating sickle cell anemia. Hematological findings include thrombocytopenia, leukopenia, and anemia. Early diagnosis and personalized treatment are emphasized, especially for sickle cell patients. Effective management requires an integrated approach, considering each patient's characteristics.

Keywords: Dengue; Hematological diseases; Sickle cell anemia; Thrombocytopenia; Dengue hemorrhagic fever; Genetic disease.

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Autor correspondente:
Thaís Ranielle Souza de Oliveira
E-mail: thais.oliveira@unieuro.edu.
Fonte de financiamento:
Não se aplica
Parecer CEP:
Não se aplica
Procedência:
Não encomendado
Avaliação por pares:
Externa
Recebido em: 07/12/2023
Aprovado em: 19/02/2024

Como citar: Pires JPS, Oliveira TRS. Hematological complications in dengue: a literature review (2003-2023). RCS Revista Ciências da Saúde - CEUMA, 2024;2(1):109-116. https://doi.org/10.61695/rcs.v2i1.29

Resumo

A dengue, transmitida pelo mosquito Aedes aegypti, é uma doença febril aguda com sintomas que variam de febre a complicações graves, como febre hemorrágica. Cerca de 500 milhões de pessoas nas Américas estão em risco, tornando-o uma doença tropical emergente. Este estudo revisa complicações hematológicas associadas ao dengue de 2003 a 2023, abordando linfocitose, trombocitopenia, anormalidades de coagulação e outras. A linfocitose, subdiagnosticada devido à semelhança com o dengue, pode levar a desfechos fatais. A trombocitopenia, comum em casos graves, está ligada à coagulação disseminada. A anemia falciforme agrava o dengue devido à hemólise intravascular, levando a hospitalizações e transfusões. A dengue pode suprimir a medula óssea, complicando a anemia falciforme. Os achados hematológicos incluem trombocitopenia, leucopenia e anemia. O diagnóstico precoce e o tratamento individualizado são enfatizados, especialmente para pacientes com anemia falciforme. O manejo eficaz exige uma abordagem integrada, considerando as particularidades de cada paciente.

Palavras-chave: Dengue; Doenças hematológicas; Anemia falciforme; Trombocitopenia; Febre hemorrágica do dengue; Doença genética.

INTRODUCTION

Dengue is an acute febrile illness prevalent in over 100 countries, characterized by four distinct serotypes (Martina, 2014). It is the most widespread disease transmitted by mosquitoes globally, with Aedes aegypti serving as the vector (Martina, 2014).

The most frequently reported symptoms in most cases of dengue hemorrhagic fever include fever with defervescence peaks, gastrointestinal discomfort, petechiae (round spots under the skin caused by blood), and headache. Other symptoms may also arise because of complications (Martina, 2014).

The dengue virus modifies blood coagulation factors, resulting in thrombocytopenia or platelet dysfunction, in addition to other critical symptoms such as high hematocrit and leukopenia (Cavalcante, 2021). Co-infection with the dengue virus can exacerbate the patient's condition and worsen symptoms (Cavalcante, 2021).

Approximately 500 million individuals in the Americas face the risk of contracting dengue, with all four serotypes circulating on the continent and occasionally overlapping (WHO, 2022).

Dengue is deemed the preeminent emerging tropical illness worldwide, affecting over 390 million people annually and exposing more than 3 billion individuals to infection, with an estimated average mortality rate of 20,000 individuals per year (Morais, 2023).

Risk factors for exacerbating dengue include anemia, an uncommon inherited blood disorder characterized by the presence of hemoglobin S, which causes the abnormal sickling of red blood cells due to a mutation in the globin gene's sixth codon (Alves *et al*., 2021).

Sickle cell anemia is prevalent in several countries on the African continent, with around 10-40% of the population having an active sickle cell trait gene (WHO, 2010).

Thrombocytopenia can also be included as a factor, which is defined as a decrease in the platelet count to less than 150,000 mm3 and results in prolonged bleeding time or slow clotting (Pavanelli *et al*., 2011). Dengue hemorrhagic fever has a high prevalence of these factors, with significant thrombocytopenia observed in 68.5% to 82% of cases (Carvalho *et al*., 2021).

Other illnesses can arise from dengue, including hemophagocytic lymphohistiocytosis, which is identified by an abnormality of immunological hyperactivation of lymphocytes due to a lack of control in their negative regulation (Gaul *et al*., 2014).

Virus-associated macrophage activation syndrome, which may involve the dengue virus, is also known as lymphohistiocytosis (Silva, 2018). The comorbidity can be either genetically influenced or acquired. However, conditioning factors, such as neoplasms, autoimmune diseases, and infections, contribute to its development even from a genetic point of view (Silva, 2018).

Given the limited information on this topic, this study intends to evaluate the hematologic complications that accompany dengue fever.

METHODOLOGY

This is a broad narrative literature review, conforming to Rothier's (2007) definition. The review centers on relevant theoretical knowledge and concepts in the field of hematological complications of dengue fever. Rather than using a systematic protocol, this review seeks to answer the question: what are the hematological complications associated with dengue fever?

Articles in English and Portuguese were searched for across various databases such as Google Scholar, SCIELO, PubMed, and MEDLINE between 2003 and 2023. The following descriptors were utilized in this study: dengue, hematological diseases, sickle cell anemia, thrombocytopenia, dengue hemorrhagic fever, and innate genetic disease, and their Portuguese translations: dengue, doenças hematológicas, anemia falciforme, trombocitopenia, febre hemorrágica do dengue, e doença genética inata.

To simplify the integration of the selected descriptors, we employed the Boolean operator "AND" and excluded irrelevant arguments using "NOT". During the search for articles for this systematic review, measures were taken to identify and remove duplicate articles. Initially, search results were imported into bibliographic reference management software, where they were organized and reviewed to identify duplicates based on titles, authors, and other relevant information.

Subsequently, a manual analysis was conducted to compare articles and identify potential duplicates that were not detected by the software. Duplicates were then recorded and removed from the list of results. In cases of uncertainty regarding the duplicity of an article, the original authors were consulted, or full texts were reviewed to confirm whether they were duplicates or not. The exclusion of duplicate articles was documented and justified. The final list of articles included in the review was double-checked to ensure that no duplicates remained.

DEVELOPMENT

Eight articles published between 2003 and 2022 were included in this study. To enhance the text's coherence, we divided our analysis into two sections: the first focused on Lymphohistocytosis, Thrombocytopenia, and blood coagulation anomalies, while the other assessed different hematological complications associated with dengue. We categorized the articles thematically, as depicted in Chart 1.

Chart 1 - Summary of the selected articles for the narrative review by category

Articles	Author and date of publication.	Theme
Association of increased platelet-associated immunoglobulins If thrombocytopenia and the severity of the disease in secondary dengue virus infection.	Saito *et al*. (2004)	Understanding platelet associated Igg in the induction of thrombocytopenia and its severity in patients with secondary dengue infection.
Fatal Hemophagocytic Lymph histiocytosis Associated with Locally Acquired Dengue Virus Infection - New Mexico and Texas.	Gaul *et al*. (2014)	Lymphohistocytosis associated with/caused by dengue type three and its complications.
Dengue pathogenesis: a disease driven by the host response.	Martina (2014)	Dengue: general information, vector, transmission, and complications of dengue hemorrhagic fever.
Coagulation abnormalities in dengue and dengue hemorrhagic fever patients.	Borhany *et al*. (2019)	Association between platelet counts, hemoglobin, and hematocrit with bleeding and the impact of these tests on patient management.
Prevalence of Arboviruses and their impact on patients with Sickle Cell Anemia in the State of Acre.	Carneiro (2019)	Determine the prevalence of dengue in patients with HF and the main clinical manifestations.
Hematological findings in children with dengue fever.	Arruda *et al*. (2019)	Determine the frequency of dengue in children, verify the profile of these children and describe the main hematological alterations present.
Hematological changes in serious dengue - a systematic review	Caires *et al*. (2022)	Evaluate published articles on hematological changes in dengue hemorrhagic fever infection.
Dengue mortality associated with sickle cell anemia j a	Alarcon *et al*. (2016)	To analyze the mortality of patients with sickle cell anemia due to dengue fever and thus develop appropriate management for these patients.

Lymphohistocytosis, thrombocytopenia, and blood coagulation abnormalities

Lymphohistiocytosis is a hyperinflammatory syndrome that has a high potential for fatalities. Common symptoms include fevers, pancytopenia, hepatosplenomegaly, and increased serum ferritin levels (GauL *et al*., 2014).

Cases of phagocytic lymphohistiocytosis (PHL) caused by DENV-3 (dengue type 3) are rare complications of dengue, with only 27 cases reported between 1966 and 2014, of which eight resulted in fatalities due to lymphopenia. There may be a clinical similarity between dengue and PHL, which could lead to the under-recognition of the disease (Gaul *et al*., 2014).

Saito *et al.* (2004) examined 135 patients with suspected dengue virus infection and identified cases in which thrombocytopenia resulted from dengue complications. This occurs during the acute phase of the infection due to bone marrow suppression, which reduces platelet levels in conjunction with the impact of immunoglobulins on those platelets.

Thrombocytopenia may also arise from anti-dengue IgG which are connected with platelets. This results in thrombocytopenia in patients during the acute phase. The antibody complex with platelets through a receptor known as Fc, further exacerbates thrombocytopenia (Saito *et al*., 2004).

Thrombocytopenia is present in all manifestations of dengue, including all serotypes of the virus and the most severe form, dengue hemorrhagic fever. However, the sharp drop in thrombocytes is observed only in the severe form, along with the reduction in hematocrits caused by plasma leakage (Caires *et al*., 2022).

In dengue, morbidity and mortality are linked to disseminated intravascular coagulation abnormalities resulting from a low platelet count that generates hemorrhagic or thrombotic symptoms (Borhany *et al.,* 2019).

Patients with dengue hemorrhagic fever are at higher risk for coagulation abnormalities due to bleeding and below-reference platelet, hematocrit, and hemoglobin counts (Borhany *et al*., 2019).

Although coagulation and non-coagulation profiles may aid in the diagnosis of dengue, they do not enhance treatment efficacy, as there exist more efficient and cost-effective diagnostic methods (Borhany *et al*., 2019). Changes in platelet count, such as thrombocytopenia, are associated with the severity of dengue, enabling targeted therapeutic interventions and aiding in diagnosis, treatment, and patient prognosis (Caires *et al*., 2022).

Various hematological complications associated with dengue fever

Sickle cell disease is a common genetic disorder worldwide, despite its recessive inheritance. Arboviruses may exacerbate this condition in patients (Carneiro, 2019). Intravascular hemolysis, which can worsen pallor and jaundice in patients with sickle cell anemia, may be provoked by arboviruses like dengue (Carneiro, 2019).

Carneiro (2019) found a 55% prevalence of dengue in sickle cell anemia patients, resulting in increased hospitalizations, transfusions, and antibiotic therapy. The author conducted a

descriptive cross-sectional study on 65 sickle cell anemia patients in Acre, Brazil's northern region, to determine arbovirus prevalence and impact.

It is widely recognized in the scientific community that individuals of African descent possess a higher genetic susceptibility to sickle cell anemia. This implies that the treatment and management of dengue virus infection, which is associated with various complications, should be done with greater care and precision when dealing with patients from these populations (Alarcon *et al*., 2016).

Dengue can cause intravascular hemolysis in patients expressing sickle cell genes, resulting in reticulocytosis, a normal bone marrow response that elevates the number of reticulocytes in the bloodstream. However, dengue may also hinder bone marrow function, which leads to more complications in sickle cell anemia patients due to the depletion of healthy and efficient red blood cells or reticulocytes in the blood (Alarcon *et al*., 2016).

Arruda *et al*. (2019) analyze hematological findings in patients with dengue, including simultaneous thrombocytopenia and leukopenia, as well as anemia. Thrombocytopenia (69%), leukopenia (68%), anemia (59%), and high hematocrit (5%) were the primary hematological alterations observed in this study. Atypical lymphocytes, produced in response to the dengue virus, may serve as a marker of dengue infection severity. High hematocrit is strongly associated with vascular permeability and plasma leakage, while low levels of leukocytes and platelets are early signs of the disease (Arruda *et al*., 2019).

FINAL CONSIDERATIONS

The paper explores hematological complications associated with dengue, focusing on phagocytic lymphohistiocytosis, thrombocytopenia, and coagulation disorders. It highlights the rarity of lymphohistiocytosis, its clinical similarity to dengue, and the importance of monitoring blood parameters for appropriate management. Hemorrhagic dengue can lead to abnormal blood clotting, illness, and mortality.

In the context of sickle cell anemia, dengue incidence is higher and exacerbates complications, necessitating tailored interventions. The interplay between dengue and sickle cell disease results in intravascular hemolysis, further complicating the condition. Hematological abnormalities commonly observed in dengue include thrombocytopenia, leukopenia, and anemia.

Lastly, it is imperative to underscore the importance of timely diagnosis and personalized treatment, considering individual patient characteristics, particularly in cases of sickle cell anemia. Implementing an integrated approach is essential for effectively managing hematological complications associated with dengue fever.

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