South Health and Policy. 2024; 3:134
doi: 10.56294/shp2024134

REVIEW

Hemophagocytic syndrome associated with dengue, ¿what is the cause?

Síndrome hemofagocítico asociado a dengue, ¿cuál es la causa?

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Cite as: Araujo Jaramillo N, Balcarce D. Hemophagocytic syndrome associated with dengue, what is the cause? South Health and Policy. 2024; 3:134. https://doi.org/10.56294/shp2024134

Submitted: 28-07-2023 **Revised:** 08-10-2023 **Accepted:** 26-03-2024 **Published:** 27-03-2024

Editor: Dr. Telmo Raúl Aveiro-Róbalo

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ABSTRACT

Introduction: hemophagocytic syndrome (HS) is a dysregulated immune response that causes severe systemic inflammation and can arise from a variety of conditions, including viral infections such as dengue. Although its immunological process has been studied, diagnostic and treatment protocols remain unclear, affecting patient survival and prognosis.
Method: a descriptive and retrospective study reviewing the literature of the last two decades to identify consensus on the causal relationship between HS and dengue. Fourteen articles were selected that demonstrated a causal relationship between the pathophysiological mechanisms of HS and dengue in pediatric and adult patients.
Results: a consensus was reached associating the uncontrolled inflammatory response of HUS with the pathophysiological processes of dengue in any of its stages, confirmable by studies (laboratory and anatomopathological), its relationship with risk factors to optimize treatments and prognosis.
Conclusion: dengue in any of its stages can be a cause of HUS, but it is not the only entity capable of generating it.

Keywords: Hemophagocytic Lymphohistiocytosis; Hemophagocytic Syndrome; Hemophagocytic Syndrome Associated with Infection; Pancytopenia; Primary Dengue Infection.

RESUMEN

Introducción: el síndrome hemofagocítico (SH) es una respuesta inmunitaria desregulada que causa inflamación sistémica grave y puede surgir de diversas condiciones, incluyendo infecciones virales como el dengue. Aunque se ha estudiado su proceso inmunológico, los protocolos de diagnóstico y tratamiento siguen siendo poco claros, afectando la supervivencia y el pronóstico de los pacientes.
Método: estudio descriptivo y retrospectivo de revisión bibliografía de las últimas dos décadas para identificar consensos sobre la relación causal del SH y el dengue. Se seleccionaron 14 artículos que demostraron una relación causal entre los mecanismos fisiopatológicos del SH y el dengue en pacientes pediátricos y adultos.
Resultados: se llegó a un conceso que asocia la respuesta inflamatoria descontrolada del SH con los procesos fisiopatológicos del dengue en cualquiera de sus estadios, confirmable por estudios (laboratorio y anatomopatológicos), su relación con factores de riesgo para optimizar tratamientos y pronostico.
Conclusión: el dengue en cualquiera de sus estadios puede ser causa del SH, pero no es la única entidad capaz de generarlo.

Palabras clave: Linfohistiocitosis Hemofagocítica; Síndrome Hemofagocítico; Síndrome Hemofagocítico Asociado a Infección; Pancitopenia; Infección Primaria por Dengue.

INTRODUCTION

Hemophagocytic syndrome (HS), also known as hemophagocytic lymphohistiocytosis, is an immune system disorder characterized by unregulated and excessive activation of macrophages and T lymphocytes. This leads to a cytokine storm with serious clinical consequences, such as persistent fever, hepatomegaly, splenomegaly, pancytopenia, and multiorgan dysfunction.[1,2] This syndrome can be classified as primary (hereditary) or secondary, which is more common and associated with infections, autoimmune diseases, neoplasms, and other inflammatory conditions.[3]

Among the infectious causes of HF, the dengue virus has gained particular interest in recent medical literature.[4] Dengue is a viral disease transmitted by mosquitoes of the genus Aedes, and it is endemic in many tropical and subtropical regions of the world. Although its clinical presentation varies from mild forms to severe cases with hemorrhagic and capillary permeability complications, an emerging association has been identified between dengue infection and HS development in adults and children. This relationship is supported by multiple studies that have demonstrated evidence of hemophagocytosis in bone marrow aspirates and significant hematological abnormalities such as cytopenia or pancytopenia in patients with dengue.[5]

Timely diagnosis of DIC is critical due to its high mortality rate if not treated appropriately.[6] However, its clinical presentation can be confused with other complications of dengue, such as systemic inflammatory response syndrome (SIRS), which delays specific treatment. The current literature emphasizes the importance of establishing specific clinical and laboratory criteria to differentiate HS from other entities and initiate therapeutic interventions such as corticosteroid therapy, intravenous immunoglobulins, or immunosuppressants.[7,8]

Given the clinical relevance of this association and the need for a more effective diagnostic approach, this study aims to analyze the relationship between dengue and hemophagocytic syndrome through a comprehensive review of the scientific literature from the last few decades. The aim is to identify the main pathophysiological factors, the most representative clinical and laboratory findings, and the recommended therapeutic approaches. This review seeks to provide a comprehensive overview that facilitates the early diagnosis of HS in the context of dengue infection, thereby improving the prognosis and survival of affected patients.

According to the existing literature, is there a relationship between dengue and acute hemophagocytic syndrome?

Objective

A literature review will be conducted to determine a cause-effect relationship between dengue and HS as a complication.

METHOD

Study design

We developed a descriptive, retrospective study of an exhaustive literature review of the last two decades to determine a consensus on the cause of HS. Different bibliographic articles (clinical trials, systematic reviews, and meta-analyses) were analyzed, and those that demonstrated a causal relationship were selected.

Literature search strategy

A literature review was conducted on websites in databases such as Cochrane, Web of Science, Scopus, MEDLINE, and PubMed. We searched for reports of HS covering a period of up to 20 years. The following keywords were used: (primary dengue infection, hemophagocytic lymphohistiocytosis, hemophagocytic syndrome in children and adults, infection-associated hemophagocytic syndrome, pancytopenia).

Population

Bibliographic articles linking HS with viral infection, specifically dengue, were selected.

Inclusion criteria

Articles dealing with HS secondary to dengue.
Studies published in the last 25 years on this topic.
Age: undefined range for inclusion in the study.

Exclusion criteria

Literature dealing with other causes of HS.
Studies that do not report dengue diagnoses.
Studies reporting patients with autoimmune diseases.

Sample size

Fourteen articles were selected that reported causal pathophysiological mechanisms of HS about dengue in

pediatric and adult patients.

DISCUSSION

Multiple studies explain the relationship between dengue and HS, its pathophysiology, and evolution.[9,10,11]

In their 2015 study, Wan Fariza et al. highlights the relationship between dengue and SH, the relationship between serotypes and severity, and the importance of differentiating it from SIRS to initiate corticosteroid therapy.

However, Hein et al.[8] showed evidence linking SH to early and less severe forms of dengue and, therefore, recommended early evaluation and determination of initial diagnostic criteria to rule out SH.

To this end, different diagnostic criteria based on clinical signs and laboratory findings are used to confirm this identity.[12]

A study conducted in Taiwan demonstrated the relationship between histophagocytic activity and dyserythropoietic in bone marrow aspirate studies, which is associated with a decrease in cell line counts in patients with dengue with warning signs. It also highlights the importance of determining other causes of HS in cases of negative dengue serology.

Nelson et al.[10] found a causal relationship between hemophagocytosis and the presence of dengue and its severe forms in their study of postmortem bone marrow aspirates.

In a pediatric study conducted in Colombia by Rueda et al.[11], a relationship was found between patients with dengue with warning signs (confirmed by ELISA-IgM), laboratory findings of cytopenia or pancytopenia, and the observation of histiocytes phagocytizing erythroid, myeloid, and megakaryocytic cells. Therefore, they conclude that there is a relationship between HS and the most severe manifestations of dengue.

Pérez-Sánchez et al.[12], in another study of 7 pediatric patients, found different complications of HS in patients with dengue, with the involvement of other systems. The respiratory system was the most affected, followed by the hemodynamic and hepatic systems. In addition, they found a higher risk and severity in patients with viral coinfections (influenza, Zika, chikungunya).[13] They also found a higher proportion of males.[14] The latter is consistent with Simón et al. and Bhattacharya et al.'s findings.

CONCLUSIONS

The relationship between dengue and hemophagocytic syndrome (HS) is complex and has been the subject of numerous studies. One thing is clear: there is a relationship between dengue and its pathophysiology. The importance of differentiating HS from other severe conditions for proper management is highlighted.

In addition, HF is associated with severe and milder forms of dengue, underscoring the need for early diagnostic evaluation.

Findings from bone marrow aspirate and laboratory studies have demonstrated a relationship between hemophagocytosis, cytopenia, dengue manifestations, and HF in pediatric and adult patients.

Furthermore, a higher risk of complications has been observed in those with viral coinfections, as well as a higher prevalence in men. In conclusion, early and accurate identification of SH in the context of dengue is crucial for improving patients' prognosis and clinical management.

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FUNDING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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