International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

Dengue Hemophagocytic Syndrome-Review Article

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Abstract: ***Dengue fever is caused by infection with any of four mosquito-transmitted dengue viruses (DENV-1–4) and is characterized by fever, headache, myalgia, and leukopenia. Hemophagocytic lymphohistiocytosis (HLH) is a potentially lethal hyperinflammatory syndrome. HLH is characterized by a constant activation of CD8+ T lymphocytes and natural killer (NK) cells to enact phagocytosis of hematopoietic cells and resulting in organ damage, affecting mainly bone marrow, liver, and nervous system. Inappropriate stimulation of macrophages in bone marrow and subsequent phagocytosis of blood cells with the production of high amounts of proinflammatory cytokines are the pathologic trademarks of HLH. Quick diagnosis and treatment are essential to prevent a fatal from various triggers. Dengue associated HLH must be suspected in the presence of persistent fever beyond the day of seven, hyperferritinemia, worsening cytopenias, shock and MOD beyond plasma leakage phase. BM biopsy should be performed to demonstrate hemophagocytosis. Prompt recognition and early institution of appropriate therapy may result in a good outcome, particularly in infection-associated HLH. The aim of the review is to highlight the diagnostic criteria, pathophysiology, and treatment of the HLH due to dengue fever.***

Keywords: Dengue Hemophagocytic syndrome and hemophagocytic lymphohistiocytosis (HLH)

1. Introduction

Dengue is the most rapidly spreading mosquito-borne pandemic viral disease. In the last 50 years, incidence has amplified 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. It is anticipated that 50 million dengue infections occur annually and roughly 2.5 billion people live in dengue endemic countries [1]. Though the full global burden of the disease is still uncertain, the patterns are frightening for both human health and the economy [2].

Dengue fever has a wide spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. Symptoms of dengue include fever, headache, rash and pain behind the eyes like in most other viral fevers [3,4]. However severe pain in the muscles and joints is a common and distinguishing feature of dengue. Some patients develop only milder symptoms that may be considered as influenza or another common viral infection. Characteristically, dengue fever lasts around five to seven days [5]. However, most patients recover following a self-limiting non-severe clinical sequence, a small share progress to severe disease, frequently characterized by plasma leakage with or without haemorrhage [6]. Dengue haemorrhagic fever (DHF) which is dengue fever complicated by bleeding, also shows high fever, but when the fever starts settling there are signs of the variable degree of bleeding from sites such as under the skin, with stools or in the white area of the eye mainly due to a low platelet count. A small proportion of cases can become very ill and even collapse, leading to dengue shock syndrome (DSS) which has a high mortality [7].

HLH is a rare hyperinflammatory disorder related to macrophage activation and usually presents as a prolonged fever and a sepsis-like syndrome [8]. The familial form is a deadly autosomal recessive disorder that characteristically affects young children, however, the secondary or reactive form is related with viral, bacterial, fungal, or parasitic infections as well as with connective tissue disorders and malignancy [9]. However, HLH is a very rare complication of the dengue fever and number of cases were reported around the world [10,11]. Dengue virus is being newly documented as an etiologic agent in SriLanka. Infection associated hemophagocytic syndrome carries a high mortality. Furthermore, the secondary HLH cases are associated with viral infection, and Epstein-Barr virus has been implicated as the most common cause [12,13].

2. Diagnosis

HLH should be considered in the differential diagnosis of children and adolescents with prolonged fever, hepatosplenomegaly, and cytopenia. Rapid recognition and early institution of suitable therapy may result in a good outcome, particularly in dengue-associated HLH. This disorder is characterized by extreme macrophage activation and cytokine release due to a failure in natural killer cell function [14]. This results in immune dysregulation and unchecked inflammation. Patients with HLH are acutely ill with fever, hepatosplenomegaly, effusions, and lymphadenopathy. Laboratory findings include bicytopenia, coagulopathy, liver dysfunction, hyperferritinemia and elevated triglycerides and lactate dehydrogenase [15]. Bone marrow infiltration by activated macrophages can be demonstrated, and diagnosis is made based on the HLH-2004 protocol proposed by the Histiocyte Society—HLH can be recognized in the presence of (a) molecular diagnosis reliable with HLH or (b) the presence of five out of eight criteria, namely, fever, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in tissue, hyperferritinemia, increase in CD25/ soluble IL-2 receptor or reduced NK cell function(Table 1). Raised ferritin levels more than 10,000 mg/L has been recognized to be 90% sensitive and 96% specific for HLH and should be used as screening tool for early detection of HLH, triggering further investigations [9,16]. Diagnosis is usually challenging, as it can be easily mistaken for other clinical situations, such as sepsis or systemic inflammatory response syndromes (SIRS) and multiple organ dysfunction syndromes (MODS) [17]. However, Progressive pancytopenia or bicytopenia along

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with the presence of hemophagocytes in the bone marrow aided in establishing the diagnosis of HLH.Even with treatment, only 21-26% can be expected to survive 5 years. Remission is always temporary, as the disease inevitably returns. Bone marrow transplant is the only hope for cure. One study found that 50% of deaths from FEL were due to invasive fungal infections, which are probably underdiagnosed.

Table 1: Diagnostic criteria for HLH

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:
1. A molecular diagnosis consistent with HLH is made.
2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below):*
Fever
Splenomegaly
Cytopenias (affecting ≥ 2-3 lineages in the peripheral blood): hemoglobin < 90 g/L (in infants < 4 weeks of age, hemoglobin < 100 g/L), platelets < 100 × 10^9/L, neutrophils < 1.0 × 10^9/L
Hypertriglyceridemia and/or hypofibrinogenemia: fasting triglycerides ≥ 3.0 mmol/L (ie, ≥ 265 mg/dL), fibrinogen ≤ 1.5 g/L
Hemophagocytosis in BM, spleen, or lymph nodes
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥ 500 μg/L
Soluble CD25 (ie, sIL2r) ≥ 2400 U/mL†

3. Pathogenesis

Numerous cell types are involved in the pathophysiology of HLH, including macrophages, NK-cells, and cytotoxic T-lymphocytes. Macrophages typically serve as antigen presenting cells to present foreign antigens to lymphocytes for either direct destruction or antibody development. In various forms of HLH, macrophages become activated and secrete cytokines [18]. Cytokines, in turn, can cause organ damage when excreted in excessive amounts. NK-cells directly destroy damaged or infected cells, independent of the major histocompatibility complex (MHC). Cytotoxic T-lymphocytes, while like NK-cells, kill autologous cells carrying foreign antigens associated with MHC Class I. An alternate theory proposes ineffective antigen removal, which results in ongoing immune stimulation and inappropriate hemophagocytosis. Activation of immunoregulatory T-lymphocytes is more evident in DHF than in classical DF during the febrile phase with a significant reduction of lymphocyte subsets possibly due to the immune elimination of dengue virus and cell lysis [8,18]. Hyperproduction of cytokines, including interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), and interleukin 6 by virus-infected T lymphocytes may play a role in the pathogenesis of HLH. In addition, the infected progenitor cells will become targeted by antiviral, cytokine-secreting cytotoxic T lymphocytes, or by activated, hemophagocytic macrophages, causing further cell death and anemia. Recruitment of inflammatory cells to the bone marrow also causes collateral damage to cell types other than the targeted ones, contributing to the development of cytopenias in other cell lineages [12].

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The characteristic histological finding is anaccumulation of lymphocytes and non-Langerhans cell histiocytosis bone marrow, spleen, liver, the lymph node, and other organs. The histocytes often shows phagocytosis of blood cells (hemophagocytosis). A lack of demonstration of hemophagocytosis in the bone marrow, spleen, liver, or the lymph node often makes an initial diagnosis difficult. In the context of virus-associated HLH, higher levels of IFN-γ and TNF-α correlate with poor clinical outcome. Clinician throughout the tropics should be aware of HLH as a potential complication of dengue, particularly in patients with anemia and severe liver injury.

4. Treatment

Prior to the use of current treatment regimens, survivalwith HLH was almost all close to zero percentage. Treatment of HLHinvolves immune-suppressive and modulatory agents, bio-logical response modifiers, treatment of the provocative illness if secondary, and subsequent stem-cell transplantation [19]. Therapy is aimed at suppressing the hyperinflammatory state and immune dysregulation that leads to life-threatening organ damage and susceptibility to deadly infections. As HLH is a great cause of morbidity and mortality, it needs specific and aggressive therapies such as dexamethasone, methylprednisolone,intrathecal methotrexate, intravenous immunoglobulin,cyclosporine A and etoposide. A study of epstein-barrvirus(EBV) associated HLH patients on regimens comprising of corticosteroids alone, intravenous immunoglobulins alone,corticosteroidsalone, or a combination of treatments without etoposide versus another group of patients receiving etoposide, early introduction of etoposide was the only significant variable for improved survival [20,21]. However, similar multivariate analysis with various modern treatments haven't been conducted in HLH associated with dengue.

5. Conclusion

Hemophagocytic lymphohistiocytosis (HLH) includes a heterogeneous group of life-threatening, hyperinflammatory syndromes, occurring in children and adults. It is considered by hypercytokinemia and uncontrolled activation of macrophages and T cells, causing key symptoms such as persistent fever, hepatosplenomegaly, pancytopenia, hemophagocytosis, hyperferritinemia, and coagulopathy. Severe HLH with MODS has a very high mortality rate.To reduce mortality rates, an early diagnosis is crucial. However, due to lack of specificity of current diagnostic criteria, a definitive diagnosis is often difficult. Therefore, bone marrow aspiration should be done, especially if fever persists or relapses along with other HLH symptoms and criteria. In the absence of a confirmed definitive therapy, supportive therapy and maximal diagnostics for the detection of curable underlying diseases are essential. Clinicians should work closely with pathologists and microbiologists to clearly define precipitating or underlying illnesses. Early recognition and initiation of steroid treatment would be crucial for the successful treatment of dengue fever complicated by HLH.

6. Abbreviation

WBCT -whole blood clotting test, ECG- Electrocardiogram, ED- emergency department

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7. Ethics approval and consent to participate

Not applicable

8. Availability of data and material

Not applicable

9. Competing interests

The author declare that they have no competing interests.

10. Funding

This research received no funding support

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