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Research Article

Haemophagocytic Lymphohistiocytosis (HLH) Secondary to Dengue Haemorrhagic Fever (DHF); A Paeditric Case Series

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Abstract

Introduction: HLH is a rare multisystem disorder in children which is known to occur secondary to infections. Dengue is identified as a causative factor for HLH. We present a case series of HLH secondary to DHF managed at two tertiary care hospitals in Sri Lanka.

Methods: Clinical records of children with HLH secondary to DHF at Lady Ridgeway Hospital and Teaching Hospital Karapitiya over a period of one year were reviewed.

Results: There were 12 patients aged between 10 months and 11 years. Nine of them were females. All children had serological evidence of Dengue. HLH was suspected when fever continues more than 7 days with raising transaminases and cytopenia. The mean duration of diagnosis of HLH was 8 days. All children (n = 12) had splenomegaly, edema, ascites, pancytopenia, elevated liver enzymes, raised ferritin (> 500 ug/L), high lactate dehydrogenase and bone marrow evidence of haemophagocytic activity. Lymphadenopathy was observed in 83.3% (n = 10). Central nervous system involvement was seen in 25% (n = 3). Hypertriglyceridemia (> 265 mg/dl) and Hypofibrogenemia (< 150 mg/dL) observed in 5 and 8 patients respectively. Eleven children who survived until the commencement of treatment received dexamethasone for a period of one month. Ten children showed clinical recovery within 48 hours of therapy and one child died due to secondary infection. Biochemical changes took few weeks to improve.

Conclusion: HLH is a known complication of severe dengue infection. High degree of suspicion is needed to diagnose early especially if there is ongoing fever. Steroids are effective in treating HLH secondary to Dengue.

Keywords: *Dengue; Haemorrhagic; Haemophagocytosis; Steroids*

Abbreviations

DHF: Dengue Haemorrhagic Fever; HLH: Hemophagocytic Lymphohistiocytosis; NS1: Non Structural Protein; LDH: Lactate Dehydrogenase; MAS: Macrophage Activation Syndrome

Introduction

Hemophagocytic lymphohistiocytosis is a rare multisystem disorder that presents with fever, pancytopenia, splenomegaly, elevated triglyceride levels and hypofibrinogenemia [1]. HLH can be due to primary or secondary causes [2]. Any infection such as Virus, Bacteria and Fungi can give rise to HLH and which is more commonly seen in tropical countries [3]. Dengue has been identified as a causative factor for secondary HLH in few case series [3-5]. We present a case series of twelve children with HLH secondary to serologically proven Dengue infection who were managed in two tertiary care hospitals in Sri Lanka over a period of one year starting from October 2016.

Material and Methods

Clinical records of children with HLH secondary to dengue infection, managed at Paediatric units in Lady Ridgeway Hospital and Teaching Hospital Karapitiya during the period between October 2016 and September 2017 were reviewed. HLH was diagnosed based on the criteria given by the Histiocyte Society in 2004 [6]. Standard management of Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF) was provided for all children. Eleven of them were treated with steroids for one-month duration after confirming the diagnosis of HLH.

Results and Discussion

Ages ranged from 10 months to 11 years. There were 9 females and 3 males. All of them had serological evidence (NS 1 Antigen or Dengue IgM antibodies) of Dengue fever. Dengue serotype was not done since it was not a routine investigation. None of these children had features suggestive of immunodeficiency. All children had evidence of plasma leakage and out of them 5 presented with Dengue Shock Syndrome (DSS). The suspicion of HLH was made when there is persistent fever more than 7 days with elevated transaminases and evolving pancytopenia. The mean duration of diagnosis of HLH was 8 days. All children had fever more than a week, Splenomegaly, edema and ascites. Lymphadenopathy and Central Nervous System involvement were seen in 83.3% (n = 10) and 25% (n = 3) patients respectively.

All of them had pancytopenia, elevated liver enzymes, raised ferritin (> 500 ug/L) and high Lactate Dehydrogenase (LDH) levels and bone marrow evidence of Haemophagocytic activity. Hypertriglyceridemia (> 265 mg/dl) and Hypofibrinogenemia (< 150 mg/dL) were observed in 5 and 8 patients respectively. Lumbar puncture which was performed on patients who had Central Nervous System involvement (n = 3) revealed no abnormality. Lymph node biopsy was carried out in two patients and which showed Haemophagocytic activity in it.

Ten children made an uneventful recovery with the steroids and none of them required second line treatment. One child died before commencement of the therapy and the other child died after commencement of steroids therapy due to a secondary infection.

All children who survived until the commencement (n = 11) of treatment received Intravenous Dexamethasone 10 mg/m^2 for 1 week. It was converted to oral form and gradually tapered off 2.5 mg/m^2 per week at a time over a period of one month. Except in one occasion, marked clinical response was noted within 48 hours of steroids therapy. Biochemical changes took at least one week to improve.

Clinical Parameters	No. (%)	Laboratory Parameters	No. (%)	Range
Fever >7 d	12 (100%)	Anemia (< 10 g/dL)	12 (100%)	6.2 - 8.9
Splenomegaly	12 (100%)	Thrombocytopenia (< 150000)	12 (100%)	2100 - 61000
Edema	12 (100%)	Neutropenia (ANC < 1000)	10 (100%)	530 - 980
Pleural effusion	12 (100%)	Raised AST (> 50)	12 (100%)	136 - 17993
Ascites	11 (91.6%)	Raised ALT (> 50)	11 (100%)	45 - 8732
Lymphadenopathy	10 (83.3%)	Low albumin (< 35 g/L)	12 (100%)	17 - 28
Hepatomegaly	10 (83.3%)	Raised Ferritin (> 500 ng/L)	12 (100%)	3915 - 67000
Bleeding manifestations	5 (41.6%)	Raised Triglycerides (> 265 mg/dL)	5 (41.6%)	134 - 571
CNS involvement	3 (25%)	Hypofibrinogenemia (< 150 mg/dL)	4 (33.3%)	86 - 110
		Bone marrow evidence of HLH	12 (100%)	
		Elevated LDH (280 U/L)	12 (100%)	

Discussion

HLH is a potentially life threatening condition in childhood. It was first described in 1952 by Farquhar and Claireaux. In 1994 the diagnosis of HLH required five criteria; fever, splenomegaly, cytopenia, elevated triglycerides and/or low fibrinogen levels, and evidence of hemophagocytosis. However, in 2004, the diagnostic criteria was revised and additional three criteria were added; low or absent Natural Killer (NK) cell-activity, elevated serum ferritin, and increased interleukin-2-receptor levels [7]. Pathophysiology behind HLH is the release of cytokines due to uncontrolled clonal proliferation of T lymphocytes.

Secondary HLH occurs as a result of systemic infection or autoimmune diseases such as Juvenile Idiopathic Arthritis (JIA). When it is secondary to autoimmune rheumatic disease, the term Macrophage Activation Syndrome (MAS) is used [8].

Infections are a major cause for secondary HLH. Most of the time it is secondary to viruses such as Epstein Barr, Herpes simplex, Rubella, Hepatitis, Mumps and Measles. Dengue has also been identified as a cause for HLH in many case series.

Treatment aim in HLH is to halt the immunological process by giving Immunosuppressants. Corticosteroids, Etoposide and Cyclosporin are the main treatment options [9]. A short course of steroids has been used in few cases series with HLH secondary to Dengue and showed with good outcome [3,4]. The findings are similar in this case series as well.

The prognosis of HLH due to dengue is better compared to Epstein Barr Virus in which mortality ranges from 25% - 100% [10,11].

Conclusion

HLH is known to occur in severe dengue infection. It should be considered in differential diagnosis if fever persists more than 7 days in patients with dengue. Early identification and steroids therapy improves the outcome.

Conflict of Interest

Authors declare no conflicts of interest.

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