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SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) IN DENGUE FEVER

Paediatrics

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ABSTRACT

Background-Hemophagocytic lymphohistiocytosis (HLH) is being increasingly reported as a complication of dengue. We present four cases of dengue associated HLH diagnosed in our hospital during the dengue outbreak of 2018. All the cases were treated with a short course of steroids (Dexamethasone) for 8 weeks, initially intravenous followed by oral, when the fever subsided along with supportive measures, and showed an excellent response. Diagnosis of HLH is challenging and usually missed as clinical and laboratory findings are nonspecific.
Aim and objective- The aim was to study the prevalence of secondary HLH in dengue fever.
Methods- Retrospective case record review was performed in patients of dengue fever with secondary HLH admitted in Hindu Rao Hospital, Delhi over a period of five months (July 2018 to November 2018). Dengue patients having fever for more than 7 days with HLH diagnosed based on Histiocytic Society 2004 protocol were enrolled for the study.
Results- Total 217 dengue serology (NS1/ IgM) positive patients of < 12 years of age were admitted over the period of 5 months (July to November 2018). Of the total number of cases, Four patients aged between 5 -12 years were diagnosed as a case of HLH, of which two were females. The mean duration of diagnosis of HLH was 6 days (range 5 to 7 days) after admission and the mean duration of fever at the time of diagnosis was 17.5 days (range 14-21 days). All four children had splenomegaly, edema, ascites, pancytopenia, elevated liver enzymes, raised ferritin (>500 ug/L), Hypertriglyceridemia (>265 mg/dl) and three had bone marrow evidence of haemophagocytic activity. Lymphadenopathy was observed in 25 %. Central nervous system involvement was seen in 25%. All four children received dexamethasone for a period of eight weeks. All children showed clinical recovery in the form of disappearance of fever within 48 hours of start of Dexamethasone and got discharged eventually.
Conclusion- HLH is a known complication of severe dengue infection. High degree of suspicion is needed to diagnose HLH early especially if there is ongoing fever of >7 days, persistent thrombocytopenia and leukocytopenia. Dexamethasone is effective in treating HLH secondary to Dengue.

KEYWORDS

Dengue Fever, Thrombocytopenia, HLH

INTRODUCTION- HLH is being increasingly reported as a complication of dengue.1 Dengue is the most rapidly spreading mosquito-borne viral disease in the world. 2 Although the usual presentation is that of a self-limiting illness, its complications are protean. 3 Usually dengue patient has fever of 2-7 days but persistent fever of > 7 days must be evaluated for its complications or any other associated illness. 2 Our four dengue patients had persistent fever for more than 7 days along with cytopenia. On work up, diagnosis of HLH was made based on International HLH study, 2004. HLH is a rare, potentially fatal disorder of immune dysregulation characterized by fever, pancytopenia, hepatosplenomegaly and increased serum ferritin.[4]

Aim and Objective- The aim was to study the prevalence of secondary HLH in dengue fever.

Methods- - Retrospective case record review was performed in patients of dengue fever with secondary HLH admitted in Hindu Rao Hospital, Delhi over a period of five months (July 2018 to November 2018). Dengue patient having fever for more than 7 days were diagnosed with HLH based on Histiocytic Society 2004 protocol and were enrolled for the study. (Table-1)

Table 1. Revised Diagnostic Guidelines for HLH

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L)
Platelets <100×109/L
Neutrophils <1.0×109/L
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides ≥3.0 mmol/L (i.e., _265 mg/dl)
Fibrinogen ≤ 1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
(B) New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥500 mg/L
Soluble CD25 (i.e., soluble IL-2 receptor) ≥2,400 U/ml

Routine laboratory parameters complete blood count(CBC), Biochemical parameters like liver function test, Serum ferritin and blood culture by bactec method was done. ultrasound imaging for presence of fluid in abdomen and chest x-ray for pneumonia were done. workup for dengue virus included NS1 antigen test and IgM Serology by Elisa. A Bone marrow aspiration was done for further evaluation on day of admission triggered by high ferritin and bicytopenia. **Inclusion criteria-** NS1 or IgM Dengue serology positive in admitted patients. **Exclusion Criteria-** NS1 or IgM dengue serology positive ,outdoorpatients were excluded.

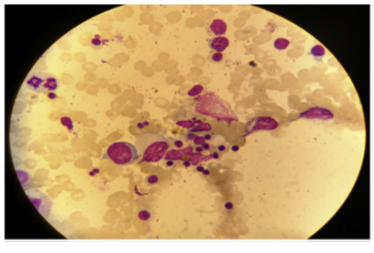
All children received dexamethasone for a period of eight weeks in tapering dosage (10mg/m2 for first 2 weeks followed by 5 mg/m2 for next 2 weeks, 2.5 mg/m2 for next 2 weeks followed by 1.25 mg/m2 for last 2 weeks) as per HLH 2004 protocol. Initially dexamethasone was given intravenous and when the patients became afebrile they were started on oral dexamethasone.

RESULTS- Total 217 dengue serology (NS1/ IgM) positive patients of < 12 years of age were admitted over the period of 5 months (July 2018 to November 2018)out of which, Four patient aged between 5 -12 years were diagnosed as a case of HLH, two of them were females. The mean duration of diagnosis of HLH was 6 days (range 5 to 7 days) after admission and the mean duration of fever at the time of diagnosis was 17.5 days (range 14-21 days). The mean duration of hospital stay was 12.7 days (range 8-17 days). All four children had hepato-splenomegaly, edema, ascites, pancytopenia, elevated liver enzymes, raised ferritin (>500 ug/L), Hypertriglyceridemia (>265 mg/dl) and three had bone marrow evidence of haemophagocytic activity. Lymphadenopathy was observed in 25 %. Central nervous system involvement (irritability, Seizure) was seen in 25%. All four children received dexamethasone for a period of eight weeks in tapering dosage (10mg/m2 for first 2 weeks followed by 5 mg/m2 for next 2 weeks, 2.5 mg/m2 for next 2 weeks followed by 1.25 mg/m2 for last 2 weeks) as per HLH 2004 protocol. All children showed clinical recovery in the form of disappearance of fever within 48 hours of start of Dexamethasone, disappearance of hepatosplenomegaly within 7 days and got discharged on oral dexamethasone. (Table-2)

TABLE-2. Clinical and Laboratory Features in the Study Children

Clinical Parameters	No. (%)	Laboratory Parameters	No. (%)	Mean (Range)
Fever >7 d	4 (100%)	Anemia (<9 g/dL)	3 (75%)	(8.6) 7.0-10.2
Rash/mucositis	4 (100%)	Thrombocytopenia (<100000/cmm)	4 (100%)	34500 (14000-55000)
Hepatomegaly	4 (100%)	Neutropenia (<1000)	3 (75%)	2675 (810-4540)
Splenomegaly	4 (100%)	Raised CRP (>6 mg/L)	4 (100%)	65 (24-106)
Bleeding manifestations	3 (75%)	Raised SGPT (>50 IU/L)	4 (100%)	1335 (140-2530)
Lymphadenopathy	1 (25%)	Raised Ferritin (>500 ng/L)	4 (100%)	5240 (1280-9200)
Edema	4 (100%)	Raised LDH (>500U/L)	4 (100%)	1776 (872-2680)
Pleural effusion	3 (75%)	Raised triglyceride (>265 mg/dL)	4 (100%)	490 (342-638)
Hypotension	3 (75%)	Hemophagocytes in bone marrow	3 (75%)	NA
Encephalopathy	1 (25%)	NA	NA	NA
Joint pain	1 (25%)	NA	NA	NA

Bone marrow study showed normocellular reactive marrow with evidence of macrophage activation and hemophagocytosis (Fig-1)



DISCUSSION-

Incidence of infection associated HLH (IAHLH) is 1/3000 paediatric inpatient 5. Any infection (virus, bacteria, fungi, protozoa) can give rise to HLH. EBV is most frequent infection associated with IAHLH 6. In the study by Ramachandran, et al. dengue was found to be the leading organism accounting for 5 among 43 cases of HLH.1 In a study done by Veerakul, et al. on 52 pediatric patients with HLH; 15 were infection associated out of which 3 were caused by dengue[7].

In a case series reported by Priyankar Pal et al, out of 358 dengue cases, 8 developed HLH8. In another case series reported by Kankananarachchi etal 12 patients aged between 10 months and 11 years had HLH secondary to Dengue fever 9. In our study, we observed that out of 217 dengue proven admitted children over a period of 5 months, 4 children had HLH.

In 1994 the diagnosis of HLH required five criteria; fever, splenomegaly, cytopenia, elevated triglycerides and/or low fibrinogen levels, and evidence of hemophagocytosis. In 2004, additional three criteria were added; low or absent Natural Killer (NK) cell-activity, elevated serum ferritin and increased interleukin-2-receptor levels9. HLH is considered as a syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme inflammation. Recently, whole genome expression analysis suggest paradoxical down regulation of various aspects of immune response including B cell development and function, TLR expression and signaling and apoptosis function[11].

A report of EBV associated HLH outcomes among children revealed a 90% overall response rate to multiagent therapy, including corticosteroid, etoposide and cyclosporine , whereas many other patients with infection associated HLH died within days or months 10 . Our all four children had fever for > 7 days along with leukocytopenia, thrombocytopenia and raised liver enzymes. Diagnosing HLH is the first critical step toward successful therapy, but is challenging due to the rare occurrence, variable presentation and non-specific findings of this disorder10. High degree of suspicion is needed to diagnose HLH early especially if there is ongoing fever of >7 days, persistent thrombocytopenia and leukocytopenia. Dexamethasone is effective in treating HLH secondary to Dengue. Sharp TM et al reported fatal HLH associated acquired dengue infection death[11]

Conclusion- HLH is a known complication of severe dengue infection. High degree of suspicion is needed to diagnose HLH early especially if there is ongoing fever of >7 days, persistent thrombocytopenia and leukocytopenia. Dexamethasone is effective in treating HLH secondary to Dengue.

Limitations-

- Small study population.
- Unavailability of molecular testing.

Source of Support: Nil
Conflict of Interest: None.

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