A retrospective study of haemophagocytic lymphohistiocytosis in children in a tertiary care hospital in Eastern India

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Abstract

Introduction: Haemophagocytic lymphohistiocytosis (HLH) is a rare disorder that is being increasingly reported in children from the Indian subcontinent.

Objective: To describe the profile of HLH in children in a tertiary care hospital in Eastern India.

Method: This is a retrospective study of all children diagnosed to have HLH from March 2015 to August 2016 and admitted to the paediatric department of Vivekananda Institute of Medical Sciences, India. The case records of the children with HLH were analysed.

Results: Fifteen children were diagnosed with HLH during the study period. All were secondary cases, infection being the predominant cause. More than 50% needed some immune modulation in the form of steroids /intravenous immunoglobulin. Two succumbed to complications.

Conclusions: All 15 cases of HLH were secondary (acquired). Eighty percent of the cases were secondary to infection.

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(Key words: Haemophagocytic lymphohistiocytosis, infections, steroid, intravenous immunoglobulin, Eastern India)

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare disorder that is being increasingly reported in children from the Indian subcontinent. HLH involves the mononuclear phagocytes and is characterized by activation and proliferation of histiocytes leading to a cytokine storm which causes dysfunction of various organs[1]. It is a macrophage related hyper-inflammatory disorder presenting as prolonged fever and a sepsis like syndrome[2,3]. It is of two types, primary (familial) and secondary (acquired). The latter is usually secondary to infections, rheumatological disorders or malignancy. Primary HLH affects very young children and has a high mortality. Both varieties of HLH can be preceded by infections and require molecular genetic techniques for differentiation[3,4].

Objective

To describe the profile of HLH in children in a tertiary care hospital in Eastern India.

Method

This is a retrospective study of all children diagnosed to have HLH from March 2015 to August 2016 and admitted to the paediatric department of Vivekananda Institute of Medical Sciences, India. Only children meeting the diagnostic criteria of HLH-2009 protocol[5] (Table 1) were included in the study.

The case records of the children with HLH were analysed and the following data collected: age at presentation, gender, family history, clinical and laboratory features, course of illness and ultimate outcome. For peripheral blood counts and biochemistry, nadir and peak values were noted. In one patient, primary immune deficiency was thought of and a complete work up was done including lymphocyte subsets, immunoglobulin levels, oxidative burst test (dihydrorhodamine test for chronic granulomatous disease) and CD11, CD18 (to rule out leucocyte adhesion deficiency).

A male neonate (history of severe intrauterine growth retardation, term delivery) presented with cholestasis and hepatosplenomegaly at 14 days of life. Cytomegalovirus (CMV) polymerase chain reaction (PCR) was positive in urine. One week after admission he developed HLH. Such an early onset led us to do a genetic analysis to rule out familial HLH.

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Table 1: *HLH diagnostic criteria 2009*

1. Molecular diagnosis of haemophagocytic lymphohistiocytosis (HLH) or X-linked lymphoproliferative syndrome (XLP).
2. Or at least 3 of 4:
   - Fever
   - Splenomegaly
   - Cytopenias (minimum 2 cell lines reduced)
   - Hepatitis
3. And at least 1 of 4:
   - Haemophagocytosis
   - Increased ferritin
   - Increased sIL2Rα (age-based)
   - Absent or very decreased NK function
4. Other results supportive of HLH diagnosis:
   - Hypertriglyceridaemia
   - Hypofibrogenaemia
   - Hyponatraemia

Results

Fifteen children were diagnosed with HLH over a period of 1.5 years. The ages ranged from 3 weeks to 11 years. Females outnumbered males. There was no history of consanguinity in any of the families. In our study, no primary /familial case was identified. In one case of congenital CMV infection, early occurrence of HLH prompted us to do a genetic analysis (MUNC/Perforin) but no abnormality was detected. All the cases were secondary HLH and infection (Table 2) was the commonest cause (13 out of 15).

Table 2
Aetiological distribution of cases *(n=15)*

1.	*Infection related*	12
	Enteric fever 03	
	Sepsis (*E. coli, Staph aureus*) 02	
	Pyrexia of unknown origin 01	
	Pneumonia 02	
	Dengue 02	
	Epstein-Barr virus 01	
	Congenital cytomegalovirus 01	
2.	*Systemic onset juvenile idiopathic arthritis (SOJIA)*	02
3.	*Infection triggered and immunodeficiency related*	01

The 2 cases of systemic onset juvenile idiopathic arthritis (SOJIA) presented with macrophage activating system (MAS) at the onset. There was a single case of primary immune deficiency, leucocyte adhesion defect (LAD1) where HLH occurred secondary to Burkholderia cepacia septicaemia. Bacterial infections outnumbered viral. Enteric fever was the initial presentation in 3 cases; 2 children initially presented with pneumonia, having fever and progressive tachypnoea. There was a girl with a history of choledochal cyst who presented with acute pancreatitis. Initial conservative management brought temporary relief but on the 10th day of admission she developed pancytopenia with increasing ferritin. Dengue virus was isolated in 2 cases and Epstein-Barr virus (EBV) in one.

Interval from onset of symptoms to diagnosis of HLH varied between 1-3 weeks. The clinical features of HLH are enumerated in table 3.

Table 3: *Clinical features of HLH (n=15)*

Clinical feature	Number (%)
Fever	15 (100.0)
Rash	07 (46.7)
Hepatosplenomegaly	15 (100.0)
Respiratory distress	06 (40.0)
Lymphadenopathy	03 (20.0)
Hepatic failure	01 (06.7)
Bleeding	02 (13.4)
Neurological involvement	04 (26.8)

All 4 cases with neurological involvement had cerebrospinal fluid (CSF) analysis done which showed lymphocytic preponderance with elevated protein levels.

The laboratory features of HLH are enumerated in table 4.

Table 4: ***Laboratory features of HLH***

Laboratory feature	No. (%)
Low fibrinogen	12 (80.0)
High triglyceride	13 (86.7)
Raised liver enzymes	14 (93.3)
Haemophagocytosis in bone marrow	08 (53.3)
Fall in ESR	07 (46.7)
Hyponatraemia	08 (53.3)

Bone marrow aspiration could be done in 12 out of 15 cases of which 8 showed haemophagocytosis. In more than 50% of cases, serum ferritin, which was initially >2000 ng/ml, gradually showed a declining trend and they survived. Three children showed an initial serum ferritin >5000 ng/ml and of these 2 succumbed. There was no evidence of malignancy in any patient. These children received supportive therapy in the form of intravenous antibiotics and blood products, where necessary.

Regarding the outcome of the 13 with infective aetiology, treatment of the primary infection could abate /halt the process in 4 cases. Immune modulatory therapy, in the form of intravenous immunoglobulins (IVIG) /steroids, was needed in 9 cases. None of the patients needed aggressive chemotherapy. Two cases succumbed, the patient with congenital CMV having severe disseminated coagulopathy and the patient with LAD losing the battle to hepatic failure.

Discussion

HLH can occur as a familial /genetic disorder with an autosomal recessive inheritance or as a sporadic or acquired disorder[1]. Both forms can be triggered by infections or immunological events. It is observed in children and adults of all ages. In our series the median age of affection was 4 years, similar to other Asian studies[6].

In our series comprising 15 cases of HLH, 13 were secondary to infection. In a study by Srinivas *et al*, infection was the cause in around 50% of adult patients, 56% being secondary to viruses, the commonest being dengue[7]. A similar observation was made by Ramachandran *et al* who also showed dengue virus to be the commonest infective agent causing HLH in a study of 43 hospitalised children from South India[8]. However, in our study, among the infective aetiologies identified, bacteria were commoner (3 salmonella, 1 E.coli, 1 Staphylococcus aureus 1 Burkholderia cephacia). Viruses were isolated in 3 cases and in 3 no aetiological agent could be identified.

The common mode of presentation was persistent fever, hepatosplenomegaly, falling blood counts and hyperferritinaemia. Regarding the outcome, out of the 15 cases, 11 needed immune modulation in the form of IVIG/steroid. The 2 SOJIA cases responded to methylprednisolone and one needed oral cyclosporine. In those with infective aetiology, 9 needed dexamethasone. It was started at 10mg/m^2, gradually tapered and stopped within 4-6 weeks. Contrary to traditional treatment, a full 8 week course of HLH-2004 protocol was not needed. This similar successful short term use of steroid has been demonstrated in a study by Kodan P *et al*[9]. Regarding the factors determining prognosis and outcome, serum ferritin played an important role. In the 2 cases which succumbed, initial ferritin was >5000 ng/ml. In the survivors, decline in ferritin, rise in Hb, platelets and improvement in clinical profile were observed within 1 week of initiation of therapy.

All the criteria may not be present initially. A decline in the cell counts, a rise in serum ferritin in the backdrop of deteriorating clinical scenario should alert the clinician regarding an evolving HLH.

Conclusions

- All 15 cases of HLH were secondary (acquired).
- Eighty percent of the cases of HLH were secondary to infection.

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