Managing pediatric haemophagocytic lymphohistiocytosis (HLH) in a resource limited setting-A 3 years experience

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**Article History:**

Received on: 30 May 2020
Revised on: 01 Jul 2020
Accepted on: 06 Jul 2020

**Keywords:**

HLH, children
Hemophagocytosis, SoJIA

**ABSTRACT**

Hemophagocytic Lymphohistiocytosis (HLH) is a rare and fatal entity in children with fever, organomegaly, cytopenias, liver dysfunction and coagulopathy and does not respond to conventional therapies. It is categorized into two types: Primary (inherited) and Secondary (associated with infection, malignancy, autoimmune diseases, etc.). Prognosis of primary HLH is poor; whereas in secondary HLH outcome depends upon the underlying disease. This study is a retrospective analysis of case records of children admitted with a diagnosis of HLH from January 2016 to December 2019 in the Pediatrics department of a teaching hospital in Odisha, India. It describes the clinical features, laboratory findings, diagnosis, treatment and outcome of children with HLH. Thirteen children were diagnosed as HLH for 36 months in the age range from 1 month 11 days to 14 years. Fever and splenomegaly were present in 100% of cases while hepatomegaly in 69.2% and rash in 15.3% of cases. Anaemia, hyperferritinemia were detected in 100% whereas neutropenia in 76.9% and thrombocytopenia in 38.4%. Bone marrow aspiration was done in 7 patients out of whom 6 revealed haemophagocytosis. Serum fibrinogen was low in 8 cases. Out of 13 cases, 7 patients received corticosteroid, and 3 of them also received Cyclosporine along with Steroids. Two cases left against medical advice, 7 had infectious aetiology, and 3 cases were diagnosed as Systemic onset Juvenile Idiopathic arthritis (SoJIA). Seven patients required ICU care. Ten cases recovered, and one died as HLH is a rare entity and has a high chance of fatality early diagnosis and prompt therapy results in a better outcome.

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**INTRODUCTION**

HLH is a different entity in the pediatric population with a potentially fatal outcome. The incidence is about 1.2 cases in every 1 million pediatric population below 15 years (Henter, 2007). It is the sequelae of an aberrant hyperinflammatory condition manifesting with unremitting fever, hepatosplenomegaly, cytopenias, and haemophagocytosis by activated macrophages along with hyperferritinemia, hypertriglyceridemia and hypofibrinogemia (Janka, 2007). Hypercytokinemia and hyperchemokinemia due to hyperactivation of antigen-presenting cells (macrophages, histiocytes) and CD8+ T cells cause progressive organ dysfunction (Filipovich, 2009). Overproduction of IL-1, IL-6 and TNF leads to unremitting fever (Dinarello, 1999). Upregulation of heme-oxygenase in response to hypercytokinemia causes hyperferritinemia, whereas...
inhibition of lipoprotein lipase causes hypertriglyceridemia (Otterbein, 2003). Activation of macrophages and secretion of plasminogen activator leads to hypofibrinogenemia (Freeman and Ramanan, 2011). Peripheral cytopenia is due to phagocytosis of blood cells in the bone marrow. HLH is categorized into two types: Primary (inherited) and Secondary (associated with infection, malignancy, autoimmune diseases etc.) Despite diagnostic guidelines being available, it is often underdiagnosed. Prognosis of primary HLH is poor, whereas in secondary HLH outcome depends upon the underlying disease (Janka, 2012).

This study outlines the epidemiology, spectrum of presentation, haematological and biochemical parameters, treatment and outcome of pediatric cases diagnosed with HLH from a teaching hospital in Odisha, India.

METHODS

Case-records of all patients admitted in the pediatrics department of a tertiary care medical college and hospital of Odisha from January 2016 to December 2019 were analyzed retrospectively. Children meeting the diagnostic criteria of the HLH-2004 protocol of the Histiocyte society were included in the study (Henter, 2007) and details like age at presentation, sex, relevant family history, clinical features, laboratory values, treatment, a course in hospital and outcome (survival or death) were collected. For haematological and biochemical values, peak or nadir values were documented. Genetic analysis, NK cell activity and soluble CD25 receptor assay could not be done in any of the cases due to unavailability in our setup.

RESULTS AND DISCUSSION

Thirteen children were diagnosed as HLH for 36 months who fulfilled the diagnostic criteria of the HLH-2004 protocol of the Histiocyte Society (Henter, 2007). Out of 13 children, 5 (38.4%) were male and rest 8 were females (61.5%). Children were in the age range from 1 month 11 days to 14 years (mean 71.8 months and median of 49 months). Fever was the most typical presentation and was there in 100% of cases. Other presenting features are seen were, rash in 2 (15.3%), arthritis in 1 (7.6%), respiratory distress in 1 (7.6%) and irritability in 1 case (7.6%).

On examination, splenomegaly was present in 100% of cases, while hepatomegaly was seen in 9 (69.2%) and lymphadenopathy in 1 of the cases (7.6%) Table 1. None of our patients had any neurological symptoms. Investigations revealed, anemia (Hb<9g/dl) in 100% of cases while thrombocytopenia (platelet<1 lakh/cu.mm) was seen in 5 (38.4%) and neutropenia (ANC<1000/cu.mm) in 10 cases (76.9%).

Hyperferritinemia (>500mcg/L) was seen in 100% of cases. Other abnormal biochemical parameters found were hypertriglyceridemia in 12 (92.3%), hypofibrinogenemia (<150mg/dl) was noted in 8 cases out of 12 (66.6 %). Hyperbilirubinemia was seen in 2 (15.3%), transaminisits in 7 (53.8%) and hyponatremia in 9 (69.2%) and high lactate dehydrogenase (LDH) in 8 cases (61.5%). C Reactive protein (CRP) was high in 9 (69.2%) and Procalcitonin was positive in cases 4 cases out of 6 cases in which it was done (66.6%) Table 2.

Bone marrow aspiration was performed in 7 patients out of whom haemophagocytosis was seen in 6 cases (85%) with no evidence of malignancy in any of the cases. Bone marrow aspiration was not done in the rest of the cases because they fulfilled other criteria of HLH. Out of 13 cases, 2 left against medical advice (LAMA). Seven cases had infectious aetiology Dengue (3), Ebstein Barr Virus (EBV) (2), malaria (1) and scrub typhus (1), 3 cases were diagnosed as SoJIA (case no 4, 6 and 11) and no obvious aetiology was found in 1 case.

All patients received supportive treatment, including antibiotics and blood transfusion. Seven patients required intensive care. Seven patients received corticosteroid while three of them received Cyclosporine along with steroids. Intravenous immunoglobulin (IVIG) and Etoposide were not used in any of the cases. Children who received steroids were given Dexamethasone, which was started at 10 mg/m² and gradually tapered over the next eight weeks. Rest of the patients showed spontaneous improvement with treatment of primary disease. One case who was suspected as Primary HLH due to young age of presentation (45 days) but couldn’t be confirmed due to refusal of the parents to go for genetic analysis (case no 12) was started on treatment but went LAMA and no follow up could be established. One of the patients diagnosed as SoJIA (Case no 6) with macrophage activation syndrome had received IVIG before being referred to our institute but had no response to same and responded to steroid and Cyclosporine as per HLH 2004 protocol. Out of 11 patients, 10 recovered and 1 died. Secondary HLH usually has better outcome as seen in our case series where 10 out of 11 cases who completed treatment survived.

HLH patients present with fever, splenomegaly, cytopenia in 2 or more cell lines, raised serum
Table 1: Clinical and laboratory parameters in %

| Clinical and laboratory parameters | n (%)* |
|-----------------------------------|--------|
| Fever                             | 100    |
| Rash                              | 15.3   |
| Lymphadenopathy                   | 7.6    |
| Respiratory symptoms              | 7.6    |
| CNS symptoms                      | 7.6    |
| Hepatomegaly                      | 69.2   |
| Splenomegaly                      | 100    |
| Anemia (Hb <9g/dL)                | 100    |
| Thrombocytopenia (platelet<1 lakh/mm3) | 38.4 |
| Neutropenia (ANC<1000/mm3)        | 76.9   |
| Elevated liver transaminases (>60 IU/L) | 53.8 |
| Hyperferritinemia (>500 mcg/L)    | 100    |
| Hypertriglyceridemia (>265 mg/dL) | 92.3   |
| Hypofibrinogenemia (<150 mg/dL)   | 66.6   |
| High LDH (>250 u/L)               | 61.5   |

*% age of the cases in which it was done. Fibrinogen was tested in only 12 cases

Table 2: Laboratory values

| Laboratory parameters | Median (range) |
|-----------------------|----------------|
| WBC (per cu.mm)       | 4060(2600-27260) |
| ANC (per cu.mm)       | 855(205-27260)   |
| Platelet (per cu.mm)  | 140000 (5000-560000) |
| Ferritin (mcg/L)      | 4000 (1400-29180) |
| Fibrinogen (mg/dl)    | 140 (100-176)    |
| Triglyceride (mg/dl)  | 463 (287-752)    |
| AST (IU/L)            | 273 (64-721)     |
| ALT (IU/L)            | 113 (63-163)     |
| CRP (mg/L)            | 66 (8-167)       |
| Procalcitonin (ng/mL) | 6.94 (0.59-27)   |

WBC: White blood count, ANC: Absolute Neutrophil Count, AST: Aspartate Amino Transferase, ALT: Alanine Amino Transferase, CRP: C reactive Protein.

triglyceride, raised serum ferritin or low serum fibrinogen. This study supports evidence from earlier studies that all patients do not present with all the typical diagnostic features implicating hurdles for timely diagnosis (HENTER et al., 1991; Aricò, 1996). The median age at diagnosis in this study was 49 months (range 1.5 month-168 months) which is higher as compared to other Asian studies which are 28 months (Ariffin et al., 2005).

The most common presenting features at admission were fever and splenomegaly with anaemia (100%). All of the patients had hyperferritinemia and hypertriglyceridemia. At the same time, hypofibrinogenemia and high LDH levels were seen in most of the patients implicating important diagnostic values to these parameters which are observed in an earlier study also (Imashuku et al., 1997). Only 15% of patients (1 out of 7) who had undergone bone marrow aspiration had standard histopathology while the rest (6 out of 7) showed haemophagocytosis. At the onset and during the initial stages of the disease process hemophagocytosis may not be evident in the bone marrow, and hence its absence does not exclude HLH (Jordan, 2011) (Gupta, 2008).

Improvement in clinical and biochemical parameters was noticed after about 1 week of initiation of treatment. Fever was the 1st symptom to reduce in this study. The most frequent infectious agent observed in this study was the Dengue virus, and all of them survived without requiring intensive care. Very few cases of HLH associated with dengue has been reported in earlier studies (Veerakul, 2002).
Table 3: Clinical and laboratory findings of all cases

| Parameter/Case no. | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  |
|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| AGE in months     | 60  | 3   | 168 | 48  | 37  | 5   | 108 | 144 | 168 | 141 | 49  | 1.5 | 3.5 |
| Sex               | M   | F   | M   | F   | F   | F   | M   | F   | M   | F   | M   | F   | F   |
| Fever             | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   |
| Rash              | N   | N   | N   | Y   | N   | N   | N   | N   | N   | N   | N   | N   | N   |
| Spleno megal       | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   |
| Hepato megal       | N   | N   | Y   | Y   | N   | Y   | N   | Y   | N   | Y   | Y   | N   | Y   |
| Lymphadenopathy    | N   | N   | N   | Y   | N   | N   | N   | N   | N   | N   | N   | N   | N   |
| Arthritis          | N   | N   | N   | N   | N   | Y   | N   | N   | N   | N   | Y   | N   | N   |
| Anemia             | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   |
| Thrombocytopenia   | N   | Y   | N   | Y   | N   | N   | Y   | N   | Y   | Y   | N   | Y   | N   |
| Neutopenia         | Y   | Y   | Y   | Y   | Y   | N   | Y   | Y   | Y   | N   | Y   | Y   | N   |
| Transaminitis      | Y   | N   | Y   | Y   | Y   | N   | Y   | N   | Y   | N   | Y   | N   | N   |
| Hyperbilirubin     | Y   | N   | N   | N   | N   | N   | N   | Y   | N   | N   | N   | N   | N   |
| Hyperferritinemia  | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   |
| Hyponatremia       | Y   | Y   | Y   | N   | Y   | Y   | N   | Y   | Y   | N   | Y   | Y   | N   |
| Hypertriglyceride  | Y   | Y   | N   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   | Y   |
| Hypofibrinogenemia | N   | Y   | Y   | Y   | ND  | Y   | N   | Y   | Y   | N   | Y   | N   | N   |
| High ldh           | Y   | Y   | Y   | N   | Y   | N   | Y   | N   | Y   | Y   | Y   | N   | N   |
| Crp high           | Y   | N   | Y   | Y   | Y   | N   | Y   | Y   | Y   | N   | Y   | N   | Y   |
| High Procalc      | N   | ND  | Y   | ND  | N   | ND  | ND  | Y   | Y   | Y   | N   | N   | N   |
| Bone marrow        | ND  | Y   | ND  | ND  | ND  | N   | Y   | Y   | Y   | Y   | Y   | ND  | ND  |
| Steroid           | N   | Y   | N   | Y   | N   | Y   | N   | Y   | Y   | N   | Y   | N   | N   |
| Cyclosporin        | N   | N   | N   | Y   | N   | Y   | N   | N   | N   | N   | Y   | N   | N   |
| Icu               | N   | Y   | N   | Y   | Y   | N   | Y   | N   | Y   | Y   | N   | N   | N   |
| Diagnosis          | DN  | UD  | DN  | SO  | SE  | SO  | M   | SC/E| UD  | DN  | SO  | UD/P| SR  |
| Outcome            | S   | L   | S   | S   | S   | S   | D   | S   | S   | D   | S   | L   | S   |

CRP-C-Reactive Protein, CSP-Cyclosporin, D-Death,DN-Dengue, E-Epstein Barr Virus, LDH-Lactate Dehydrogenase, SO-Systemic juvenile Idiopathic Arthritis, LAMA-Left against medical advice, M-Malaria, N-No, ND-Not Done, P-Primary, HLH S-Survived, SC-Sickle Cell Disease, SE-Septicemia, SR-Scrub typhus, UD-Un diagnosed, Y-Yes
The most frequent infectious aetiology reported in the literature of infection associated HLH was EBV and has a bad prognosis as indicated by earlier studies (Imashuku, 2001) (Lee, 2005). Only 15% of the cases (2 out of 13 cases) in this study were associated with EBV which is much lower as evidenced by earlier studies, and none required cytotoxic drugs (Ishii, 2007). However, both the patients required intensive care management. One case of scrub associated HLH and one malaria-assocated HLH was identified in this study. Both cases recovered well on the treatment of the primary disease. Out of 13 cases, no underlying illness could be found in 3 cases due to inability to do a genetic test. Unavailability of genetic tests, soluble CD25 and NK cell activity and unaffordability of patients for high costing tests and a small number of patients were significant drawbacks in this study. This study showed a better outcome as most of them had an identifiable secondary trigger and secondary HLH has a better result compared to primary as has also been found in other studies. (Janka, 2012).

CONCLUSION

Children with unremitting fever, organomegaly with features of sepsis or presumed sepsis, cytopenias, liver dysfunction, and coagulopathy not responding to conventional treatment could raise the suspicion of HLH. All children may not manifest all the symptoms, signs and laboratory parameters during the initial period. Hemophagocytosis may not be evident in bone marrow at the onset and during the early stages. Genetic testing should be performed as it is useful in prognostication, and as the management modality of primary and secondary HLH is different. Early initiation of chemotherapeutic drugs is beneficial in children who do not respond to conventional therapies. However, more studies are desired from our country to know the genetic pattern and their response to treatment. Also, greater awareness should be generated among paediatricians for early recognition of the entity, which in turn will be helpful in active treatment and result in a favourable outcome.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

Funding Support

The authors declare that they have no funding support for this study.

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