ORIGINAL ARTICLE

Incidence and Clinical Presentation of Hemophagocytic Lymphohistiocytosis in Infants: 10 Years' Experience at a Tertiary Care Center

SHAZIA YASEEN[1], JAVARIA FATIMA[2], HUMA ZAFAR[3], *NEELAM MAZHAR[4], ROMANA IMTIAZ[5], SARAH RAFI[6]*
[1,2,4,6]Department of Pediatric Haematology and Transfusion Medicine, The Children's Hospital and The Institute of Child Health, Lahore
[3]Department of Pediatric Haematology Oncology and BMT, The Children's Hospital and The Institute of Child Health, Lahore
[5]Department of Haematology, Data Darbaar Hospital, Lahore
Correspondence to Dr. Huma Zafar, Email: humazafar33@yahoo.com, Mobile No. 03332000392

ABSTRACT

Aim: To document the incidence and clinical presentation of infants diagnosed as Hemophagocytic Lymphohistiocytosis (HLH) in our center.
Methods: A retrospective descriptive type of study was conducted and data ofinfants was computed and analyzed, diagnosed as HLH at The Children's Hospital, Lahore, from 2006-2016. We collected the data regarding the gender, clinical presentation and laboratory values. Statistical analysis was performed with the help of IBM SPSS statistics version 22.
Results: A total of 57 infants diagnosed as HLH were included during the study period. Amongst them, 37(69.4%) were male, and 20(35%) were female with male to female ratio of 1.8:1. All patients 57(100%) presented with prolonged fever and 53(93%) patients had splenomegaly. Hematological investigations revealed that 34(60%) patients presented with bicytopenia and 18(32%) patients with pancytopenia.
Hemophagocytosis in bone marrow was found in 57(100%) patients, deranged LFTs in 54(95%) patients, hyperferritinemia 47(82.4%), hypertriglyceridemia in 40(70%) and hypofibrinoginemia in 24(42%) patients.
Conclusion:HLH is a rare but fatal blood disorder that requires early diagnosis on clinical and laboratory grounds for prompt management. The study would help in the early diagnosis of children who presented with fever, abdominal distension and pancytopenia as HLH has a significant mortality rate in the early course of the disease.
Keywords: Haemophagocytic Lymphohistiocytosis, persistent fever, splenomegaly, cytopenia.

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is a rare but fatal hematological disorder associated with impaired natural killer and cytotoxic T cell function. Transformed macrophages known as hemophagocytic histiocytes can invade bone marrow, spleen, lymph nodes, liver, and skin leading to multisystem organ failure[1]. The clinical manifestations include prolonged fever, visceromegaly, cytopenias, low fibrinogen level, raised triglyceride, ferritin and soluble IL-2 receptor levels, histological evidence of benign hemophagocytic macrophage and impaired NK cell activity on flowcytometry[2].The overall mortality has been documented to exceed 50% and most of the patients have been reported to die within the first 2months of treatment[3].

HLH can be characterized into primary and secondary diseases based on underlying etiology. Primary HLH is also acknowledged as Familial Hemophagocytic Lymphohistiocytosis (FHL), which presents as an autosomal recessive disorder in pediatric age group. It is mainly associated with defects in genes involved in cytolytic activity of cytotoxic NK cells and cytotoxic T lymphocytes. Secondary or acquired HLH may be due to infections, autoimmunity, auto-inflammatory disorders and malignancies[4,5]. Some immunodeficiency syndromes and hereditary diseases have been proved to be associated with HLH e.g., Chediak Higashi syndrome, Wiskott's Aldrich syndrome and X linked lymphoproliferative syndrome[6].

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It wasn't until December 1999 when the first FHL related gene was identified starting a new era for researchers and clinicians. So far, five different types of FHL have been reported: type 1; unknown defect, type2; perforin (PRF1) gene mutation, type 3; UNC13D gene mutation, type 4; Syntaxin11 (STX11) gene mutation, type 5; Syntaxin binding protein (STXBP2) gene mutation[7]. The Histiocyte Society described the diagnostic criteria for HLH and proposed that initial presentation of fever and splenomegaly with raised serum ferritin levels raise the suspicion of HLH. Impaired NK cell activity on flow cytometry further provides confirmatory evidence and direct the genetic analysis[8,9]. Over the years, the diagnostic approach has shifted from clinical presentation and biochemical alterations to the identification of gene mutation[7]. FHL mainly presents in infants with median age of 3months, and hematopoietic stem cell transplant is the only curative treatment[7,10]. Beyond one year, rare cases of FHL have been reported with atypical presentations. The objective of our study was to demonstrate the incidence and clinical presentation of infants diagnosed as HLH in our center.

METHODS

A descriptive retrospective cohort study was conducted at the Department of Pediatric Haematology and Transfusion Medicine at The Children's Hospital and Institute of Child Health Lahore, Data was collected from the medical record of infants diagnosed as HLH from 2006 to 2016 (period of 10 years). The cases were identified from the hospital database after approval from the institutional review board.

We studied a total of 57 cases of HLH meeting the inclusion criteria; infants diagnosed as HLH during study period. Those patients of HLH with age above 1 year or showing incomplete data were excluded from the study. Clinical case notes, patients' records and treatment charts were reviewed to collect the data keeping in accordance with age, gender, clinical presentation, family history, and laboratory values.

Patients were recognized having HLH if they fulfilled at least five of the subsequent eight conditions of HLH-2004 diagnostic guidelines: 1- raised temperature ≥38°C; 2- splenomegaly; 3-cytopenia i.e., Hb below 9 g/dl; platelet count of <100 x 10^9 /L: neutrophils of <1,000/µL); 4- increase in triglyceride levels (fasting serum triglyceride level of >3.0mmol/L) and/or low fibrinogen (fibrinogen ≤150mg/dl); 5- hemophagocytosis; 6- reduced / absent Natural Killer cell activity; 7- raised ferritin (ferritin level of ≥500 ng/ml); and 8- high sIL-2R (≥2,400 U/mL)[9].

Treatment details: All patients were given etoposide based treatment regimen, i.e. dexamethasone, etoposide, intrathecal methotrexate and cyclosporine, according to HLH 2004 studies. The goal of chemotherapy was to subdue the serious overwhelming inflammatory process. Since our institute does not offer curative treatment so families were counseled regarding fatal outcome and treatment options available in other centers. Statistical analysis was performed by IBM SPSS statistics version 22.

RESULTS

A total of 1587 patients presented to the Department of Haematology for bone marrow biopsy. Out of these 1587 cases, 112 infants were suspected as HLH based on the evidence of haemophagocytosis on bone marrow examination. Fifty-seven patients fulfilled the diagnostic criteria regarding clinical features and laboratory values. Out of these patients, 37(64.9%) patients were male and 20(35.1%) were female. The male to female ratio remained 1.8:1.

Furthermore, the results of clinical features depicted that 57 (100%) patients presented with a fever while there was failure to thrive in 51 (90%) patients. On examination, 53(93%) patients had splenomegaly. Jaundice was observed in only 10(0.2%) patients and mild bleeding diathesis was a feature of 7(0.12%) patients at presentation (Table-I).

Table-I: Clinical features of patients at presentation.

S. No.	Clinical features	No. of Patients (%) n=57
1	Splenomegaly	53 (93%)
2	Failure to thrive	51 (90.0%)
3	Fever	57 (100%)
4	Jaundice	10 (0.2%)

Table-II: Investigations of patients at presentation

S. No.	Laboratory parameters	No. of Patients
1	Hemophagocytosis in bone marrow	57 (100%)
2	Deranged LFTs	54 (95%)
3	Bicytopenia on CBC	34 (60%)
4	Pancytopenia on CBC	18 (32%)
5	Hyperferritinemia	47 (82.4%)
6	Hypertriglyceridemia	40 (70%)
7	Hypofibrinoginemia	24 (42%)

Investigations revealed that 34 (60%) patients had bicytopenia (low platelets and low RBC count), 18(32%) patients had pancytopenia, while 54(95%) patients presented with deranged liver function tests. Hyperferritinemia, hypertriglyceridemia and hypofibrinogenemia were reported in 47(82.4%), 40(70%) and 24(42%) patients, respectively (Table-II).

DISCUSSION

Hemophatocytic lymphohistiocytosis (HLH) is a rare but fatal hyperinflammatory syndrome featured by activation of the immune system[11]. The incidence has been reported to be around 1.2 cases per million people every year, but this isundoubtedly amiscalculation. The syndrome presents with clinical features of fever, splenomegaly concurring with cytopeinas, liver dysfunction, and deranged coagulation profile with or without renal insufficiency[12,13]. This disorder can be categorized broadly into primary as well as secondary HLH. It may manifest as a primary (Genetic) condition due to mutation in genes that are involved in the cytotoxic secretary path thus enabling perforin and granzymes to persuade apoptosis in target cell. The same clinical findings may occur secondary to an infection, metabolic, rheumatological, or malignant conditions[4,5,14].

HLH is considered to induce acascade of systemic cytokineswhich in turn leads to organ damage. These cytokines include Interleukin-1 beta, Interleukin-6, Interleukin-8, TNF alpha, Interferon gamma, Interleukin-18 and Interleukin-10. IFN gamma and higher levels of CD25 indicate T cell triggering and activation of macrophage histiocyte leads to increased levels of ferritin, CD163 and neopterin[15].

Regarding the epidemiological data of our study in infants diagnosed as HLH, male to female ratio was 1.8:1 which is comparable to 2.2:1 reported in another study conducted by Khan F.S. et al[16]. In our study, persistent fever was recorded in 100% of patients, while splenomegaly was noticed in 93%, akin to the study by Liu Y. et al with fever and splenomegaly reported in 100% and 81.8% patients, respectively[17]. Despite all advancements made in diagnostic modalities, HLH still remains a predicament for many clinicians so it is evident that unresolved fever coinciding with visceromegaly should raise high suspicion of HLH initiating speedy work up for early diagnosis.

The pathognomonic feature of haemophagocytosis in bone marrow aspirate was present in 100% patients, while bicytopenia and pancytopenias were reported in 32% and 60% patients, respectively. Another study by Xiao L. et al documented haemophagocytosis in bone marrow aspirate in 91% patients[18]. The same results have been demonstrated in an Indian study conducted by Rajajee S. et al in a tertiary care pediatric hospital in Chennai, India, which has shown haemophagocytosis of bone marrow in 100% patients[19]. Xiao L. et al described a study on 217 pediatric patients with HLH and concluded hyperferritinemia as the most prominent laboratory feature of HLH present in 98% of patients while we found increased serum ferritin levels in 82% patients while Allen CE et al revealed that in the absence of hemoglobinopathy

or hemosiderosis, single evidence of ferritin level > 10,000 is 90% sensitive and 96% specific for HLH[18,20].

Dao An TT et al presented that fever lasting for more than 2weeks, platelet counts less than $75x10^9$/L, hyperbilirubinemia and activated thromboplastin time >33seconds are high-risk factors predicting poor outcome[3]. In our study population, all patients presented with a prolonged fever while thrombocytopenia, raised bilirubin and hypofibrinogenemia were reported in 92%, 95% and 42%, respectively.

There is a paucity of data regarding HLH patients in our country. We conducted our study in infants, as 70% of HLH cases have been reported to present during the first year of life. R Tanoshim et al. described a case series of HLH patients diagnosed within the first 6weeks of life while Issacs Jr reported the poor outcome in this age group with a survival rate of 26%[21,22]. The outcome of HLH in our center is not promising due to the non-availability of a stem cell transplant facility for these patients, and the majority of the patients succumb to sepsis and refractory disease. The limitation of our study was lack of data regarding genetic mutations, so we are unable to diagnose FHL cases in our study population. Also, electronic data was not available, so ample information could not be gathered regarding the outcome of these patients to be added to the data of our study spanning 10 years. Having discussed the clinical features and laboratory findings of HLH, we hope that this would benefit neonatologists and pediatricians in establishing an early diagnosis in HLH patients.

CONCLUSION

The data confirms that the majority of children presented with fever, hepatosplenomegaly, bicytopenia or pancytopenia on CBC findings in our center. HLH is an uncommon clinical syndrome that requires early diagnosis on clinical and laboratory grounds for prompt management. Further prospective studies are required to identify multiple risk factors, disease progression, and its ultimate outcome.

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