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Original Research Article

Clinical Presentation of Suspected Hemophagocytic Lymphohistiocytosis: A Cross-Sectional Study in Cuttack, Odisha

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Abstract:

Background: Hemophagocytic lymphohistiocytosis is a deadly hyper inflammatory syndrome resulting from immune dysregulation. This study aimed to outline the clinical, pathological, and biochemical profiles of suspected HLH, comparing patients with pediatric and adult conditions; it also aimed to evaluate the diagnostic utility of the HLH-2004 criteria and the H-score.

Methods: SCB Medical College, Cuttack, included 48 suspected HLH cases between September 2020 and October 2022. Clinical presentations, laboratory findings, and bone marrow examination were analyzed. The HLH-2004 diagnostic criteria and the H-score with a cut-off of ≥169 indicated probable HLH.

Results: The percentage of adults was 77%, while the pediatric cases were 23%. The median age of pediatric cases was 7 years. Fever was the most common symptom (100%), followed by splenomegaly (39.6%) and hepatomegaly (29.2%). Ferritin levels were elevated in 81.8% of pediatric and 91.9% of adult cases. Bone marrow hemophagocytosis was present in 38.2%. According to HLH-2004 criteria, 22.9% of cases satisfied all diagnostic criteria, while 50% had an H-score ≥169. Infections were the most common trigger (47%), followed by autoimmune disorders and malignancies.

Conclusion: It brings out the diagnostic challenge in HLH and says the value of employing combined criteria in diagnosing cases. More importantly, the earliest identification of HLH and its many precipitants give the largest benefit in terms of timely intervention and improved outcome.

Keywords: Hemophagocytic lymphohistiocytosis, HLH-2004 criteria, H-score, hyperferritinemia, splenomegaly, hypertriglyceridemia.

Introduction

Hemophagocytic Lymphohistiocytosis is a rare but possibly lethal hyper inflammatory syndrome that arises from uncontrolled immune activation. HLH affects all ages and has significant morbidity and mortality, especially if conditions are diagnosed late. Its incidence rate is not easy to determine because of its undiagnosed and misdiagnosed state in most parts of the world; however, it remains one of the most important public health issues in resource-limited areas around the world. HLH can be triggered by genetic predispositions (primary HLH) or secondary factors such as infections, malignancies, or autoimmune diseases. Viral infections, particularly those caused by Epstein-Barr virus (EBV) and other pathogens, are the most common known triggers of secondary HLH [1-2].

Presentation of HLH is very heterogeneous, ranging from nonspecific symptoms like fever and fatigue to severe life-threatening complications like multi-organ failure. Lack of specific biomarkers for diagnostic purposes often delays the recognition especially in those resource-constrained settings where the advanced diagnostic tools might not be readily available. This is very much affecting patient outcomes since early initiation of immunosuppressive and immunomodulatory therapies is crucial for survival [3-4].

HLH, especially in areas of resource deficiency like sub-Saharan Africa, poses exceptional challenges, including Ethiopia. Although the disease may be underdiagnosed, socio-economic factors and lack of healthcare infrastructure add to the challenge of its diagnosis and management. The city of Cuttack is a region that stands out as showing extreme disparities in healthcare accessibility, and therefore, forms an important area for researching both the clinical and epidemiological facets of HLH. Thus, understanding the presentation of HLH in such a context is important for improvement in the strategies of diagnosis and therapy [5-7].

This study aims to bridge the gap in knowledge by conducting a detailed cross-sectional analysis of all suspect cases of HLH within the Cuttack, Ethiopia region. The study mainly evaluated the clinical profile, demographic characteristics, and associated risk factors of patients affected by the condition. This research should be able to inform healthcare providers and policymakers about HLH, therefore improving patient outcome within similar settings that are resource-limited [8-9].

Material and Methods

Place of Study: This is a hospital-based observational cross-sectional study conducted in the Department of Pathology, SCB MCH CUT-TACK, over a period from September 2020 to October 2022. Hematology section was the core area of the places for the evaluation of patients and accumulation of data.

Ethical Clearance: Ethical Clearance Approval was sought from the Institutional Ethics Committee for Human research from SCB MCH CTC prior to the study commencing. The study was conducted in accordance with national guidelines for biomedical research involving human subjects (ICMR, 2006). These include respect, beneficence, and justice in consideration of all individuals included in the study. Informed consent was taken from all participants or their legal custodians, more so the minors. This involved a commitment to confidentiality of their personal and medical information and strict observation of it. Participants would also have to endure distress of inconvenience caused by examinations and diagnostic procedures.

Study Population: The eligibility criteria were patients seen in the hematology section of the pathology department for pancytopenia examination and bone marrow examination. All these patients were referred from SCB MCH CUT-TACK medicine, pediatric, and rheumatology departments. Inclusion criteria were patients suspected to have HLH who presented with fever and/or splenomegaly and serum ferritin above 500 ng/mL along with variable severities of cytopenia. Patients who chose not to participate or were under chemotherapy were excluded. The final participants were 48 patients selected as meeting the criteria for study inclusion.

Sampling and Data Collection: The research collected its participants from a population of the generally admitted patients who presented with fever of undetermined cause. Data collection was on clinical examination and laboratory studies. Routine analyses involving hematological profiles encompassed hemoglobin estimation and differential count, total count of leukocytes, and platelet count. Other coagulative parameters, such as prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen levels, were measured as well. The biochemical tests done included serum ferritin, liver function tests, and triglyceride levels. Bone marrow examination was done in all the patients. All these parameters have been documented: age, fever, splenomegaly, complete blood count, triglyceride levels, fibrinogen levels, serum ferritin levels, and specific findings in the bone marrow examination. Relevant investigations leading to the underlying pathology responsible for hemophagocytosis also have been documented.

Bone Marrow Examination: Bone marrow aspiration and biopsy were performed on patients according to the standard clinical practices. Patient identification and clinical history, including past and drug histories, were considered before the procedure. Informed consent was obtained before the procedure. The preferred site for aspiration and biopsy was the posterior superior iliac spine. In obese patients, the anterior superior iliac spine or sternum was used, and in children, the ischial tuberosity was preferred. Under aseptic precaution, 2% lignocaine was administered as local anesthesia. For aspiration purpose, the amount of about 1 mL of bone marrow was aspirated and immediate smear preparation was done. The bone marrow biopsy by the same incision sample was decalcified using aqueous EDTA, processed, and stained with hematoxylin and eosin.

Data Analysis: Data screening and cleaning were conducted, and entry into Microsoft Excel 2013 for preliminary analysis. The analysis was carried out using SPSS software version 22.0 in performing descriptive statistics, frequency distribution, sensitivity, and specificity tests with the level of significance at 5%. The statistical significance of the p-value is less than 0.05. Diagnosis Criteria Patients were diagnosed with HLH using the HLH-2004 guidelines based on six diagnostic parameters. Due to limited institutional resources, the parameters 7 and 8 of the guidelines were omitted. In addition, Fardet et al. previously proposed a scoring system called the HScore, validated in the diagnosis of HLH; this was also used to review patients' conditions. Using a cut-off value of ≥169, HLH was defined and correlated with 93% sensitivity, 86% specificity, and up to 90% correct classification.

Results

Demographic Characteristics: The study included 48 suspected cases of hemophagocytic lymphohistiocytosis (HLH), of which 77% (37 cases) were adults and 23% (11 cases) were pediatric patients. The median age of the pediatric cohort was 7 years. Table 1 illustrates the sex-wise distribution of the cases, with 8 male and 21 female patients. Among adults, females comprised the

majority, whereas a nearly equal distribution was observed in the pediatric cohort.

Clinical Presentations: Fever was the most common clinical symptom, present in all cases, followed by splenomegaly in 39.6% and hepatomegaly in 29.2%. Additional symptoms included lymphadenopathy (12.5%), joint pain, rash, and abdominal pain. Table 2 highlights the frequency of splenomegaly and hepatomegaly among children and adults, showing a slightly higher prevalence in adults. Figure 1 represents the comparative distribution of clinical presentations across age groups.

Laboratory Findings: Serum ferritin levels varied widely among the study population. Most cases (54.54% of children and 66.56% of adults) had ferritin levels below 2000 ng/mL, whereas 18.18% of children and 8.1% of adults exhibited levels exceeding 6000 ng/mL. Hypertriglyceridemia was more prominent in children compared to adults, while hypofibrinogenemia (≤250 mg/dL) was observed in 48.64% of the cases, predominantly in adults. Table 3 summarizes the distribution of key laboratory parameters, including serum ferritin, triglycerides, and fibrinogen levels, stratified by age groups.

Bone Marrow Findings: Bone marrow examination revealed hemophagocytosis in 38.2% of cases. This finding was significantly associated with the presence of splenomegaly and hyperferritinemia. A comparison of HLH and non-HLH cases showed a higher prevalence of hemophagocytosis in patients with an H-score ≥169.

HLH Diagnosis and H-Score Analysis: Among the 48 cases, 22.9% satisfied all the criteria outlined in the HLH-2004 diagnostic guidelines. An additional 50% of cases had an H-score greater than 169, with a higher sensitivity observed in children (72.72%) compared to adults (27.77%). A total of 17 cases had an H-score ≥169, of which 10 cases met the HLH-2004 diagnostic criteria. The H-score ranged from 73 to 306, with pediatric cases demonstrating lower maximum scores compared to adults.

Triggering Factors: Infections were the most common trigger for HLH, accounting for 47% of cases, followed by autoimmune and connective tissue disorders. Lymphoma was identified in 12% of cases, predominantly among adults. Viral infections were particularly prevalent, underscoring their role in HLH pathogenesis.

Correlation Analysis: Statistical analysis revealed significant correlations between HLH and clinical parameters such as splenomegaly, hemophagocytosis, hypertriglyceridemia, and hypofibrinogenemia. Other variables, including hepatomegaly and lymphadenopathy, did not demonstrate significant associations with HLH diagnosis.

Table 1: Sex-wise Distribution of Pediatric and Adult HLH Cases

Age Group	Male (n)	Female (n)	Total (n)
Pediatric	5	6	11
Adult	3	21	37
Total	8	27	48

Table 2: Frequency of Splenomegaly and Hepatomegaly in Pediatric and Adult HLH Cases

Parameter	Pediatric (n = 11)	Adult (n = 37)	Total (n = 48)
Splenomegaly	4 (36.36%)	15 (40.54%)	19 (39.58%)
Hepatomegaly	3 (27.27%)	11 (29.72%)	14 (29.17%)

Table 3: Distribution of Serum Ferritin, Triglycerides, and Fibrinogen Levels

Laboratory Parameter	Pediatric Cases (%)	Adult Cases (%)	Total (%)
Ferritin <2000 ng/mL	54.54	66.56	64.58
Ferritin >6000 ng/mL	18.18	8.1	10.42
Hypofibrinogenemia	48.64	35.14	39.58

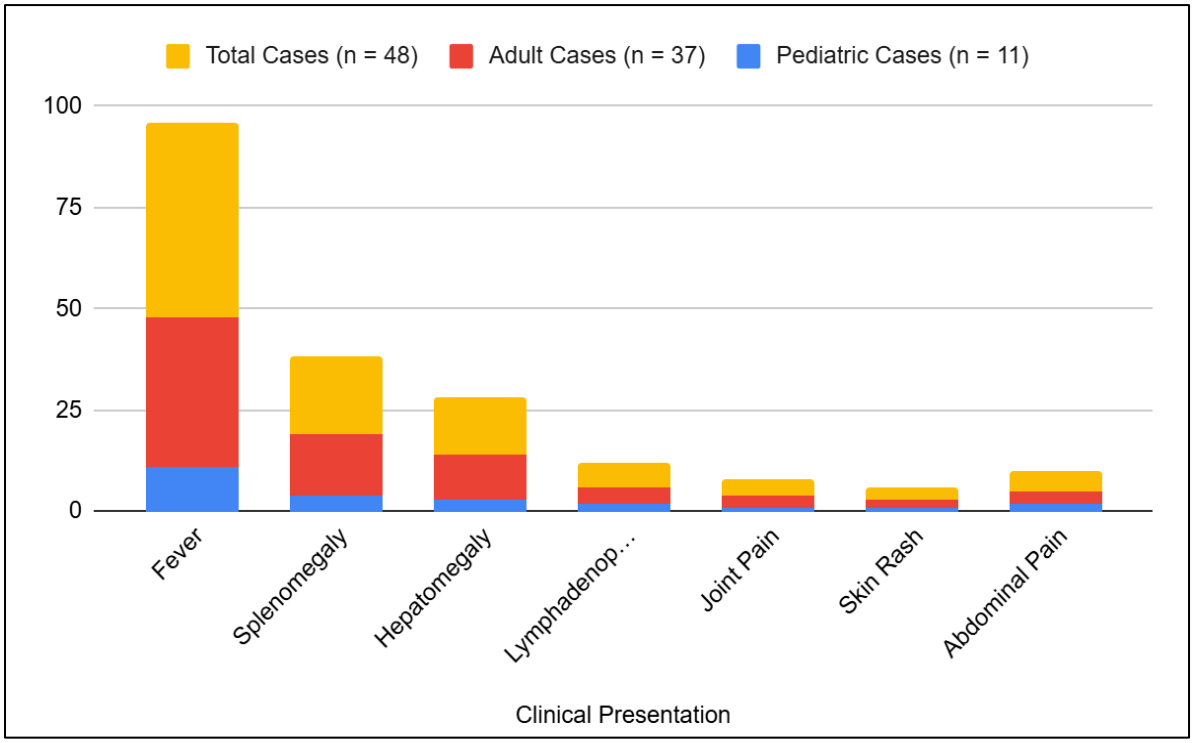

Figure 1. Distribution of Clinical Presentations in Pediatric and Adult HLH Cases.

Discussion

The present study analyzed 48 suspected cases of HLH to understand it's clinical, pathological, and biochemical profile, focusing on the pediatric and adult populations. The results are especially important for understanding the demographic distribution, clinical presentation, and laboratory findings, as well as the usefulness of various diagnostic criteria, such as those proposed by HLH-2004, and the H-score for diagnosing HLH [10].

Adult cases were predominant at 77%, and 23% of the study population were children. This is in concurrence with published earlier reports indicating that HLH appears to increasingly be identified in adults, though the condition was previously described to be much more common in children. The age of the pediatric population was reported as at median 7 years, meaning that HLH occurs within such a tender early age in children. Sex segregation of adults reflects a higher proportion of women than men, and further research would be needed to establish if the susceptibility or clinical courses reflect a gender difference.

Fever emerged as the most common clinical presentation, which is in consonance with current literature that identifies fever to be a hallmark symptom of HLH. Splenomegaly and hepatomegaly were also common findings, occurring in 39.6% and 29.2%, respectively [11-12].

These features are characteristic of the multisystem implication that is typical of HLH. Lymphadenopathy, though infrequent, still occurred in 12.5% of patients, and there were incidental reports of joint pain, skin rash, and abdominal pain. This variability in clinical presentations highlights the challenge posed by HLH in diagnosis, where it may mimic other inflammatory and infectious conditions. In particular, serum ferritin levels played a highly important role in the study because they were highly raised in most cases [13]

Moreover, 18.18% of children and 8.1% of adults had ferritin levels above 6000 ng/mL. Thus, hyperferritinemia became a useful diagnostic marker for the diagnosis of HLH. The combination of the presence of hypertriglyceridemia with hypofibrinogenemia provides further evidence for the systemic inflammatory condition of HLH. These results therefore validate the earlier works, which highlight these parameters as essential characteristics of the HLH-2004 diagnostic criteria [14].

In 38.2% of cases, bone marrow examination showed hemophagocytosis, which directly pointed toward the diagnosis of HLH. However, its absence at some points necessitates an elaborate definition for diagnosis; besides this, hemophagocytosis may not be present at the time of assessment. Accurate diagnosis of HLH: The patients were diagnosed with HLH based on both HLH-2004 criteria and the H-score. Among these patients, 22.9% of them met all HLH-2004 criteria, while 50% of them had an

H-score above 169. It was observed that the H-score is highly sensitive in diagnosing HLH among children rather than adults; sensitivity of H-score in children and adults was 72.72% and 27.77%, respectively [15]. Moreover, analysis of triggering factors revealed that infections are the most common precipitant for 47% of the patients. This correlates with the well-recognized role of infections and viral infections in particular in the pathogenesis of HLH. Autoimmune and connective tissue disorders were further significant triggering factors that reflect the interplay between genetic predisposition and environmental trigger factors in the development of HLH. Lymphoma is seen in 12% of patients and indeed puts a stamp that malignancy is indeed relevant, especially in adults [16-17].

This study heavily underscores the critical need for early recognition and diagnosis of HLH, based on its high mortality if left untreated. It supported the use of HLH-2004 criteria and H-score as useful diagnostic tools respectively; each with advantages. Where the HLH-2004 criteria help in a standardized approach, the H-score would be useful in more subtle cases, as is true for patients who do not fulfill all HLH-2004 criteria.

Association of HLH with stronger relations between patient clinical profiles such as splenomegaly, hemophagocytosis, hypertriglyceridemia, and hypofibrinogenemia increases the strong needs for collaborating team work for diagnosis and treatment.

This study makes a minuscule contribution to the already existing body of literature about HLH, especially in the Indian context. It thus throws light on different diverse clinical and laboratory manifestations of the disease and the rationality of developing systematic approaches towards diagnosis. Larger sample sizes with longitudinal follow-up are required to gain better insights into the epidemiology, pathophysiology, and optimal management strategies of HLH in both pediatric and adult populations.

Conclusion

In summary, this study provides valuable information in clinical, pathological, and biochemical aspects of HLH in both paediatric and adult populations. The most notable clinical characteristics include fever, splenomegaly, and hepatomegaly. Crucial laboratory markers include hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia.

The HLH-2004 criteria and H-score were found useful in the diagnosis of HLH, although the latter was slightly more sensitive in paediatric cases. Indeed, infections constituted the most frequent triggers followed by autoimmune and connective tissue disorders.

In this paper, the multifactorial etiology of HLH is emphasized and established as a call for earlier diagnosis and systematic investigation which may improve outcomes in patients with HLH. Further research would better elucidate the condition, in order to improve management of this life-threatening syndrome.

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