LIBYAN INTERNATIONAL JOURNAL OF ONCOLOGY

Original article

Hemophagocytic Lymphohistiocytosis: Clinical Profile and Outcome in Libyan Children

Amnna Rayani[1], Abdulhakim Eltawil[1], Najwa Elkrekshi[1], Aml Habas[1], Elmukhtar Habas[2]*

Citation: Rayani A, Eltawil A, Elkrekshi N, Habas A, Habas El. Hemophagocytic Lymphohistiocytosis: Clinical Profile and Outcome in Libyan children. Libyan Int J Oncol. 2022;1(2):44-51.

Received: 10-10-2022
Accepted: 12-11-2022
Published: 15-12-2022

Funding*: This research received no external funding.*

Conflicts *of Interest: The authors declare no conflict of interest.*

1. Hematoncology unit, Tripoli Children Hospital, Tripoli, Libya.
2. Hamad General Hospital, Doha, Qatar.
***Correspondence**: habas1962@gmail.com*

Abstract

Background and aims*: Hemophagocytic lymphohistiocytosis (HLH) is an uncommon illness of pathogenic immune dysregulation that can emerge as a familial disorder or as a random condition in response to various causes. The aim of the study was to describe the clinical profile and outcome of children with HLH followed at Tripoli Children Hospital (TCH).* ***Methods****. Medical records of patients diagnosed with HLH according to the revised HLH-2004 guidelines were reviewed for the last ten years. Symptoms at presentation, test results, etiology, HLH progression, and outcome were recorded and investigated.* ***Results****. In the last ten years, HLH has been identified in 22 patients. Six male patients (27%) and sixteen female patients (73%) were present. The age range was 1.5 to 96 months, and the male: female ratio was 1:3.8. Out of the eight HLH-2004 criteria, all patients had met five to six criteria. All the patients had a fever, with a mean temperature of 38.8 C ± 0.63. Diarrhea was found in twelve children (about 55%). Eight patients (36%) had chest symptoms, seven patients (32%) had neurological symptoms, six patients (27%) had lymphadenopathy, and twenty-two patients (100%) had hepatosplenomegaly. Eleven patients (50%) had ascites, and nine (41%) had a rash. Both viral infection and vaccination have been associated with HLH in six cases (27% each). All the cases were anemic and had thrombocytopenia; 41% had leucopenia, and 25% had leukocytosis. 83% of the patients had hypertriglyceridemia, and 50% had positive D-dimer tests. Familial HLH (FHLH) occurred in thirteen patients (59%) and five patients (23%) with primary immune deficiency diseases, and four patients (18%) with secondary HLH in association with infection and cancer. HLH family history was present in thirteen cases (59%), and consanguineous parents were present in about 45% of the patients. The overall survival percentage was (36%); two patients (9%) resolved, five patients (23%) were transplanted, one patient (4%) was still on treatment, and fourteen patients (64%) died with no hematopoietic stem cell transplant (HSCT) following remissions and relapses.* ***Conclusion****. HLH is a relatively uncommon disease in children. With high physician and family awareness, early diagnosis can result in a better prognosis. When no HSCT facility is available, especially for the primary type, the disease can be controlled but not cured.*

Keywords: *Hemophagocytic, Lymphohistiocytosis, Outcome, Libyan.*

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) comprises various illnesses characterized by systemic hyperinflammation caused by dysregulated immune homeostasis (1). It is distinguished by highly activated lymphocytes and macrophages infiltrating tissues and creating substantial proinflammatory cytokines (2).

HLH can be genetically inherited (autosomal recessive) or acquired due to triggers of viral infections, malignancies, or rheumatic diseases. The new classification of human primary immunodeficiencies (PIDs) subdivides genetic HLH into familial HLH and lymphoproliferative syndromes. Familial HLH is further sub-classified into pigmented and hypopigmented HLH (3,4). According to the reported studies, primary and secondary types may manifest at any age and can be caused by infections. Moreover, it is clinically impossible to distinguish between them (5,6).

The primary pathophysiological mechanism for HLH is an inappropriate activation of T-lymphocytes and macrophages that leads to the phagocytosis of other blood cells and excessive cytokine production (interferon-c, tumor necrosis factor-α (TNF-α), interleukin (IL)-2, IL-6, IL-8, IL-10, IL-12, and IL-4), which causes fever and other clinical manifestations (7).

Since many clinical and biochemical characteristics of HLH coincide with those of severe infections and other inflammatory illnesses, diagnosing the condition is often difficult. Furthermore, until a genetic abnormality is found in a patient, no single diagnostic test is diagnostic. Patients should have laboratory testing for HLH if they have a chronic high-grade fever without a known cause, particularly if they also have an enlarged spleen, liver, and pancytopenia. Complete blood count, peripheral smear, triglycerides, ferritin, fibrinogen, liver function tests, coagulation profile, and bone marrow aspirate are required for HLH diagnosis and follow-up. Each of these laboratory evaluations may not be particularly specific for HLH. However, taken as a whole, they are beneficial in the first diagnosis of HLH according to standards set by the Histiocyte Society in 1991 and updated in 2007 (8). A minimum of five of eight criteria must be fulfilled to diagnose HLH or by genetic analysis to identify specific gene alterations. In 2007, three more criteria were added (low/absent NK cell activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels) to HLH 2004 diagnostic guidelines (8). Although early identification and therapy considerably improve the course of HLH, the Histiocyte Society reported in 2004 that the survival rate was only around half of those who received treatment (8).

Treatment for HLH focuses on treating the viral trigger, controlling the immune system's overreaction, and addressing the underlying genetic abnormality. In secondary HLH, treating the viral trigger alone is insufficient; early immunosuppressive and pro-apoptotic treatment initiation is crucial for a better outcome. There is no need to wait for the result of genetic evaluation, except in HLH patients who are suspected of having associated rheumatologic disease. All forms of HLH can be treated initially using the same regimen (9).

All types of HLH, including well-managed cases, may have a high mortality rate. The long-term prognosis (outcome) of familial forms without treatment is poor, with a median survival of < 2 months to 6 months after diagnosis; even with treatment, only 21-26% is expected to survive five years. The prognosis for people with acquired HLH varies. For example, the mortality rate reportedly is lower when HLH is associated with autoimmune diseases (8–22%) and more remarkable when associated with tumors (especially T-cell lymphoma). This study was aimed to describe the HLH clinical profiles and outcomes in children who were followed in TCH.

Methods

Twenty-two patients were diagnosed with HLH from Jan 2012 - Jan 2022 (10 years) using the updated 2004 HLH diagnostic criteria. These patients' medical records are examined to gather information on age, sex, clinical picture, laboratory results, family history, consanguinity, treatment regimens, and overall survival. At the time of diagnosis, each patient had five or six criteria for HLH.

Patients with early-onset disease (age <6 months) with a family history of HLH or neonatal deaths due to sepsis, organomegaly, and parental consanguinity were considered to have primary HLH. In addition, a recurrence of HLH without evidence of secondary reasons such as infection, autoimmune disease, or cancer was also regarded as primary HLH. Patients who had underlying pathology were accounted as having secondary HLH.

Statistical analysis

The data were described using descriptive statistics. Continuous variables were summarized using mean ± standard deviation and percentage. The analysis was undertaking using SPSS computer software for Windows (version 19, SPSS Inc., USA).

Results

Twenty-two patients of HLH were included; ages ranged between 1.5 to 96 months. Male were six patients (27%), and female were 16 patients (73%) with a ratio of 1:3.8. All patients met five to six criteria out of the eight updated HLH-2004 criteria; All the cases presented with fever (38 - 40 °C), with a mean temperature of 38.8 °C ± 0.63. Twelve patients (55%) presented with fever and diarrhea. Chest symptoms (breathlessness, cough) were found in eight (36%) patients, and they were severe in only three patients. Neurological symptoms were found in 7 patients (32%); 5 patients had seizures, three patients had irritability, three patients had neck stiffness, one patient was blind and went into a coma for nearly three weeks, and her MRI showed posterior reversible encephalopathy (Figure 1).

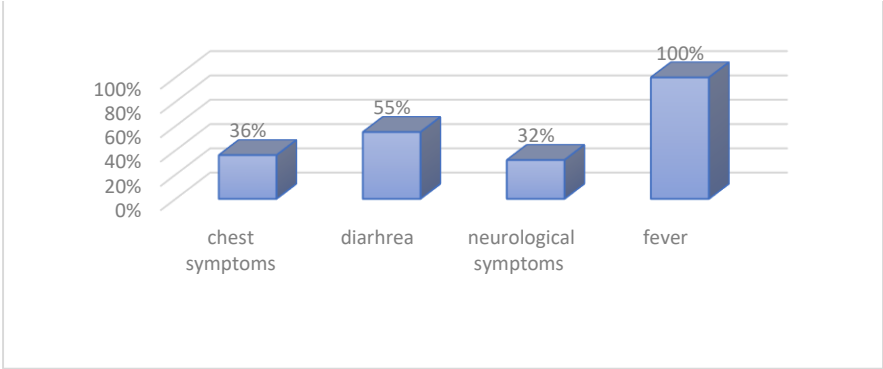

Figure 1. Presenting symptoms distribution

Lymphadenopathy was reported in 6 patients (27%), 22 patients (100%) had hepatosplenomegaly, eleven patients (50%) had ascites, nine patients (41%) had rash developed rash in the course of their illness (2 reticular, four petechial, two erythrodermas,0ne nodular), one patient with hypopigmented patches and two patients with hyperpigmented skin. Four patients (18%) presented with jaundice, and the other two patients developed severe jaundice in an advanced stage of their illnesses. Three patients (14%) presented with renal impairment. HLH followed vaccination was reported in 6 patients (27%) and in 3 patients (14%) following virus infection (Figure 2).

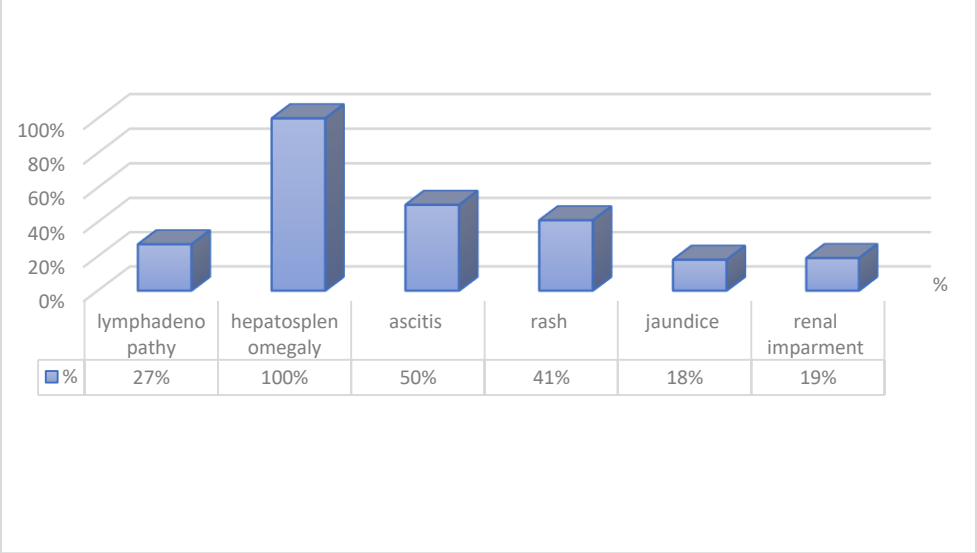

Figure 2. Presenting signs distribution

Family history of HLH was reported in thirteen patients (59%). One family lost two siblings, six families had lost a sibling, one family had an affected female child transplanted bone marrow, and another female is currently receiving medical treatment. Parental consanguinity was found in eight patients (45%). Laboratory investigations: all cases were anemic and thrombocytopenic, 42% showed leucopenia, and 25 % showed leukocytosis. Hypertriglyceridemia was in 83%, and D-dimer was positive in 50% of the patients. Fifteen patients had low fibrinogen levels, two had high fibrinogen levels, and five had normal fibrinogen levels. Low serum albumin was found in all patients. Hyponatremia was discovered in 75%, and transaminases and serum bilirubin were high in 67% of patients. About 37% of the patients had phagocytosis in their bone marrow, 38% had average counts, and 25% had no phagocytes.

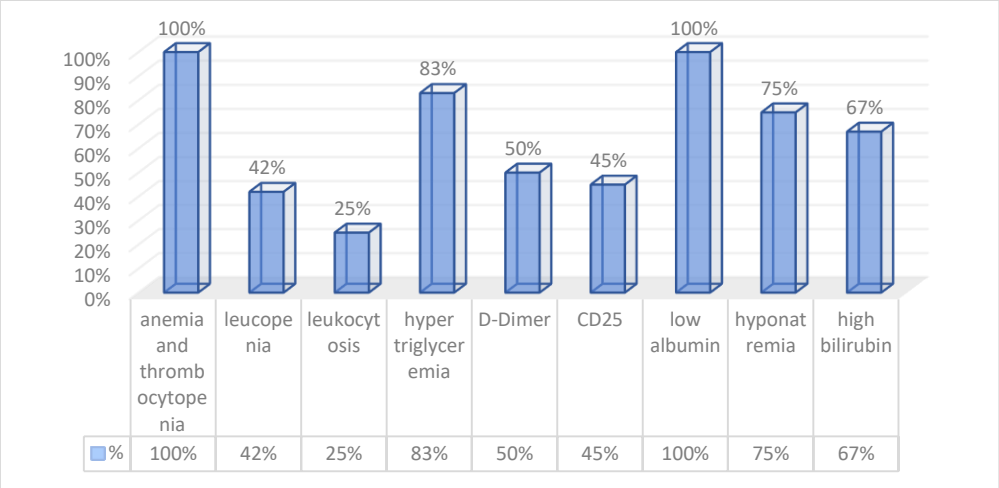

Figure 3. Lab results distribution

Ferritin >500ng <3000ng was in five (23%) patients, and ferritin >3000-10.000 ng was in 9 (41%) patients. And seven (32%) patient's ferritin >10. 0000ng.Figure 4. The immune marker CD25 titer was elevated in 45% of the studied patients. The value was between (2856 -65100); the result of the sCD25 level was lost for two patients and was not sent for the others. Evidence of Hemophagocytosis in bone marrow aspiration was reported in 54% of patients. Impaired NK cell activity was reported in 4 patients, normal in one patient, and not done for the other patients.

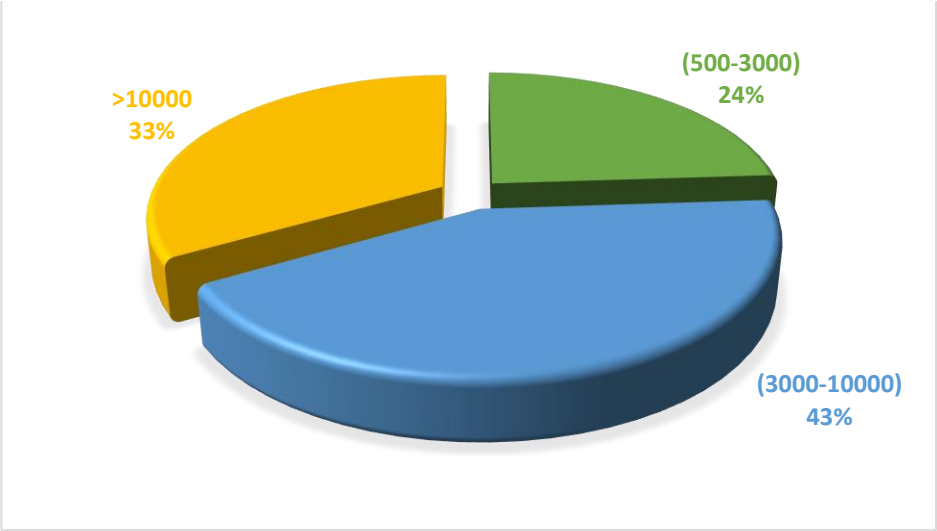

Figure 4. Ferritin level distribution

The primary type was FHLH in thirteen patients (59%) and (PIDD) in five patients; Chediak Haigashi syndrome in two patients, two patients with Severe combined immune deficiency (SCID), one patient with Grascilli syndrome type II. In the secondary cases, two patients had acute lymphoid leukemia, one had CMV infection, and one had salmonella Typhi infection.

Three patients resolved on dexamethasone only, and nine patients presented in a very advanced stage of disease received only dexamethasone and died. One patient was transferred to oncology. Nine patients received Dexamethasone, cyclosporine, and VP16; five went into remission and had hematopoietic stem cell transplant (HSCT) abroad, three patients went into multiple remissions and relapses and died, and one patient was still on treatment. All patients received blood and platelet transfusions at some stage of their illnesses. Immunoglobulin was given to 8 patients.

The overall survival was eight patients (36%); two patients (9%) resolved, five patients (23%) were transplanted, one patient (4%) was still on treatment (five were HSCT patients, and all were disease-free and stable; and the other three patients survived with no HSCT). Fourteen patients (64%) died with no HSCT (5 patients died because of uncontrollable bleeding, three died of respiratory failure, one died suddenly during sleep, two died from leukemia, and three died because of sepsis) (Figure 5).

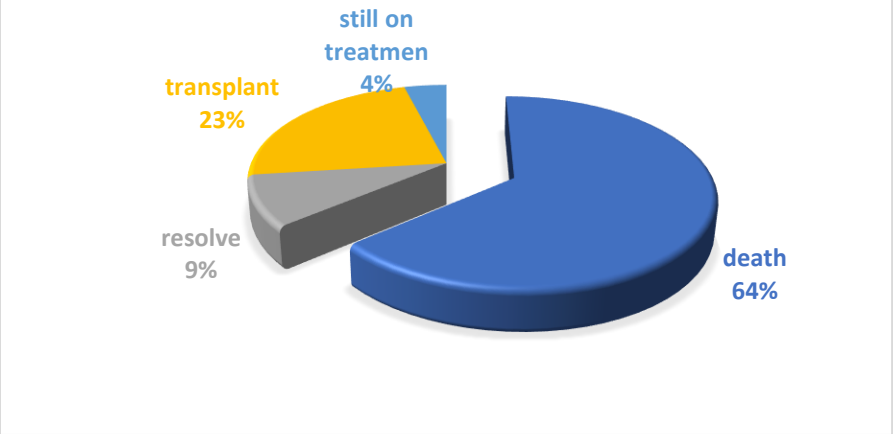

Figure 5. Outcomes distribution

Discussion

HLH is a rare disease, and it is primarily a condition in infants and young children; however, it can be in adults. Familial HLH is seen in around 25%. It is an autosomal recessive disease, i.e., when both parents are carriers of HLH, the offspring has a 25% risk of the disease, 50% of being a carrier, and a 25% risk of having HLH manifestation. There are few studies concerned with HLH epidemiology. In Japan, the estimated annual incidence of 1:800,000, whereas Sweden's study reported a 0.9% of HLH patients had malignancy in adults (10). HLH incidence is increased to (1–225)/300,000 in children, and the possibility of geographical factors was proposed (11). A Chinese study in 2019 reported that the HLH overall incidence was around1.04/1000,000 (12).

HLH is a clinical disease brought on by a highly active but ineffective immune response, which includes the absence or diminished function of natural killer (NK) cells and cytotoxic T cells and the release of pro-inflammatory cytokines (13). HLH is a syndrome of abnormal immune dysregulation that can be brought on by various factors and manifest as a family disorder or an acquired condition (14).

Based on updated diagnostic criteria of the HLH-2004 guideline, the hematology and immunology department of Tripoli Children's Hospital diagnosed 22 cases with HLH. The early presentation in the present study could be explained based on the high number of familial HLH (FHLH) and the family history of previously affected children with the same illness.

In our study, the male-to-female ratio was 1:3.8. A comparative study in Sweden reported that the male-to-female ratio is close to 1:1 (15). A newly reported study in Egypt reported more seen in females (44 males: 57 females out of 101 patients) (16). On the contrary, Ramachandran et al. reported that HLH was more in males (17).

Infants are more likely to have FHLH. The development of FLHL illness occurs in between 70 and 80% of individuals before the age of one year (1). All the FHLH in our study were three months old or younger at the time of diagnosis, and most of them were all under a year old.

According to the HLH-2004, prolonged fever resistant to antibiotics with or without hepatomegaly is a crucial diagnostic indicator for HLH (8). Fever was the most common clinical presenting symptom in our study in all the patients (100%), although others reported a lower percentage (18). In a study, in 94.7% of cases, the liver and spleen were both enlarged (19). Splenomegaly was the most common clinical finding in all the patients recruited for the study. Only one patient had lymphadenopathy, significantly fewer than the number reported by Palazzi et al. (20), who found that 68.4% of patients had lymphadenopathy. In contrast to their results, where they saw lymphadenopathy in less than half of the patients (21), our

study reported lymph node involvement in only six individuals (27%). Approximately 35–40% of patients had widespread skin rashes, such as erythroderma, edema, petechiae, or transitory maculopapular, nodular, or purpuric lesions (21). In our study, nine patients (41%) presented with rash, one with hypopigmented patches, and two with hyperpigmented skin. Only one (6.7%) patient presented with skin rash, as reported in an Egyptian study (11). The early presence of central nervous manifestations (CNS) is associated with a bad prognosis (21). This study found CNS manifestations in 37% of patients. Pulmonary and renal involvement have been reported (11) in this study. Chest symptoms were found in eight (36%) patients, and three patients were lost due to respiratory failure. Renal involvement has been reported in three of our patients previously. Bleeding has been reported, mostly due to coagulation abnormality because of liver failure or platelet dysfunction (11). In this study, eight patients had bleeding; five died of uncontrollable bleeding due to hepatic failure and coagulopathy. Anemia, granulocytopenia, and thrombocytopenia are produced partly by phagocytosis of blood cells and the marrow or histiocytic infiltration. Anemia and thrombocytopenia occur in over 80% of patients at the time of presentation with HLH. In this study, all cases were anemic and thrombocytopenic, 42% showed leucopenia, and 25 % showed leukocytosis.

Ferritin, an acute-phase reactant, has been previously reported as a useful and convenient screen for suspected cases of HLH (11). A value greater than 10.000 mg/l has been reported to be highly specific and diagnostic of HLH (90% sensitivity and 96% specificity) [26]. In this study, ferritin >500ng <3000ng was in five (23%) patients, ferritin >3000-10.000 ng was in 9 (41%) patients, and in seven (32%) patients, ferritin was >10.0000ng.

Hypertriglyceridemia in HLH is thought to be secondary to decreased lipoprotein lipase activity, which was initiated by increased tumor necrosis factor-α (TNF-α) levels [26]. Activated macrophages may secrete plasminogen activators, accelerating the conversion of plasminogen, which activates fibrinogen (22). Fifteen patients had low fibrinogen levels, two had high fibrinogen levels, and five had normal fibrinogen levels. Hypofibrinogenemia was found to be negatively associated with survival in pediatrics (23). Elevated soluble IL-2 receptor alpha (sCD25) correlates with disease activity (24). The immune marker CD25 titer was elevated in 45% of our patients; the level was between (2856 -65100 u/ml).

For all patients with HLH, bone marrow aspiration is mandatory to look for hemophagocytosis and exclude leukemia as a trigger of HLH. However, hemophagocytosis in bone marrow is neither very sensitive nor specific and may not be present during the early phase of the disease. Therefore, its absence does not exclude a diagnosis of HLH (25). Evidence of Hemophagocytosis in bone marrow aspiration was reported in 37% of our patients. Early mortality remains significantly high in HLH patients. To characterize HLH patients who were deceased within a short time after hospital administration and to identify risk factors associated with early mortality.in our study, the overall survival was eight patients (36%); two patients (9%) resolved; five patients (23%) were transplanted, and one patient (4%) is still on treatment. Fourteen patients (64%) died with no hematopoietic stem cell transplant (HSCT) following remissions and relapses (Figure 5). Five patients died because of uncontrollable bleeding, three died of respiratory failure, one died suddenly during sleep, two died from leukemia, and three died because of sepsis. Out of the eight surviving children, five patients were HSCT, all are disease free and stable, and the other three survived with no HSCT; two went into remission, and one is still on treatment waiting for HSCT.

Conclusion

HLH is an uncommon condition. Early detection and treatment improve outcomes. Family and physician awareness about the disease is essential for early detection and prognosis. Participation in HLH clinical studies is encouraged to advance biological understanding, diagnosis, and treatment.

Limitations

Genetic studying is not available free, limiting the early disease diagnosis. Furthermore, the number of the patients was not big because of the rarity of the disease. There are some deficits in the presenting feature because the study is a retrospective study, and there were some deficiencies in patients follow up notes.

References

1. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med. 2012;63:233–46.
2. Henter JI, Elinder G, Soder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991;80:428–35.
3. Rigante D, Capoluongo E, Bertoni B, Ansuini V, Chiaretti A, Piastra M, et al. First report of macrophage activation syndrome in hyperimmunoglobulinemia D with periodic fever syndrome. Arthritis Rheum. 2007;56(2):658-61.
4. Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, et al . Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Front Immunol. 2014;5:162.
5. Meeths M, Horne A, Sabel M, Bryceson YT, Henter JI. Incidence and Clinical Presentation of Primary Hemophagocytic Lymphohistiocytosis in Sweden. Pediatr Blood Cancer. 2015; 62(2):346-352.
6. Ramachandran B, Balasubramanian S, Abhishek N, Ravikumar KG, Ramanan AV. Profile of hemophagocytic lymphohistiocytosis in children in a tertiary care hospital in India. Indian Pediatr 2011; 48:31–35.
7. Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, Matsuda Y, et al. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. Blood. 1997;89:4100–3.
8. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48(2):124-31.
9. Trottestam H, Horne A, Aricò M. et al; Histiocyte Society. Chemoimmunotherapy forhemophagocytic Lymphohistiocytosis long-term results of the HLH-94 treatment protocol. Blood. 2011;118:4577–84.
10. Hayden A, Park S, Giustini D, Lee AY, Chen LY. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: a systematic scoping review. Blood Rev. 2016;30(6):411–20.
11. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383(9927):1503-16.
12. Yao S, Wang Y, Sun Y, Liu L, ZhangR, Fang J, et al. Epidemiological investigation of hemophagocytic lymphohistiocytosis in China. Orphanet J Rare Dis 2021;16: 342.
13. Freeman HR, Ramanan AV. Review of haemophagocytic lymphohistiocytosis. Arch Dis Child 2011; 96:688–693.
14. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood 2011; 118:4041–4052.
15. Henter JI, Elinder G, Söder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991;80(4):428-435.
16. Zoref-Lorenz A, Jordan MB. (2021) Challenges in improving global outcomes for hemophagocytic lymphohistiocytosis. Pediatric Hematology and Oncology 2021;38(3): 191-193.
17. Ramachandran B, Balasubramanian S, Abhishek N, Ravikumar KG, Ramanan AV. Profile of hemophagocytic lymphohistiocytosis in children in a tertiary care hospital in India. Indian Pediatr 2011; 48:31–35.
18. Uptodate 2020 [Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.accessed 10/11/2022.
19. Gupta A, Tyrrell P, Valani R, Benseler S, Weitzman S, Abdelhaleem M. The role of the initial bone marrow aspirate in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008;51(3):402-404.
20. Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome in children: an important diagnostic consideration in fever of unknown origin. Clin Infect Dis. 2003;36(3):306–12.
21. Ishii E, Ohga S, Tanimura M, et al. Clinical and epidemiologic studies of familial hemophagocytic lymphohistiocytosis in Japan. Japan LCH study group. Med Pediatr Oncol. 1998;30(5):276-28.

22. McClain K, Eckstein O. Clinical features and diagnosis of Hemophagocytic lymphohistiocytosis. Up to date 2017. Accessed at 1/11/2022.
23. Goel S, Polski JM, Imran H. Sensitivity and specificity of bone marrow hemophagocytosis in hemophagocytic lymphohistiocytosis. Ann Clin Lab Sci. 2012;42(1):21-25.
24. Lin TF, Ferlic-Stark LL, Allen CE, Kozinetz CA, McClain KL. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer 2011; 56:154–155.
25. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2008; 50:1227–35.