ECRONICON OPEN ACCESS

EC PAEDIATRICS
Case Report

Familial Hemophagocytic Lymphohistiocytosis Early Presentation

Mohammad Al Darwish[1], Iman Al Mukhtar[2]*, Khadijah Al Abbas[3], Israa Al Aithan[4], Zainab Al Daif[4] and Kawther Khwaher[4]

[1]Pediatric Hematology and Oncology Consultant, Qatif Central Hospital, Qatif, Saudi Arabia

[2]Pediatric Critical Care Consultant, Qatif Central Hospital, Qatif, Saudi Arabia

[3]Pediatric Specialist, Qatif Central Hospital, Qatif, Saudi Arabia

[4]Pediatric Resident, Qatif Central Hospital, Qatif, Saudi Arabia

***Corresponding Author:** Iman Al Mukhtar, Pediatric Critical Care Consultant, Qatif Central Hospital, Qatif, Saudi Arabia.

Received: June 24, 2019; **Published:** July 31, 2019

Abstract

We are reporting a 3 months old girl, product of term pregnancy normal delivery, born to consanguine parents, young and healthy couple with no family history of any chronic illnesses, presented with history of viral illness and fever with pancytopenia.

Hemophagocytic Lymphohistocytosis is uncommon aggressive heterogonous life- threatening disease occurs due to hyperactivation of ineffective immune system and manifests multisystemic involvements with variety of symptoms which can mimic other differential diagnosis on initial presentation with wide range of differential diagnosis like "viral infection, Sepsis, multiple organ dysfunction syndrome (MODS), malignancies, autoimmune disorders and Macrophage activation syndrome" before the further diagnostic symptoms appears and once the diagnostic criteria starts to be completed, by that time patient condition turns to critical condition in which time is crucial and that leads to worsening condition and further deterioration. The underlying mechanism of HLH is hyperinflammation and tissue destruction due to abnormal immune activation.

The hyperinflammatory/dysregulated immune state is thought to be caused by the absence of normal downregulation by activated macrophages and lymphocytes with impaired cytotoxic function of Natural Killer (NK) cells and cytotoxic T lymphocytes CTLs leading to further tissue damage. A high index of suspicion is needed for early diagnosis and early effective therapy to reduce mortality.

Keywords: *Hemophagocytic Lymphohistocytosis (HLH); Pancytopenia; Saudi Arabia*

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by extreme stimulated but ineffective immune response, resulting in a fatal pathologic hyperinflammation. The diagnosis includes a spectrum of inherited or acquired defects in cytotoxic lymphocyte function, often with uncontrolled infections. HLH may also arise as the result of persistent antigen stimulation due to autoimmune disease or malignancy [1].

HLH can be classified according to the underlying etiology into either primary also called familial hemophagocytic lymphohistiocytosis (F-HLH) indicating genetic inheritance of mutations resulting in cytotoxic lymphocyte dysfunction, or secondary indicating an acquired reactive disorder and generally used to describe patients without a known familial mutation and who typically have a clear trigger for developing acute HLH (e.g. viral illness, autoimmune disease, lymphoma). Increasing evidence describes HLH as more complex phenomenon, resulting from specific immune challenges in patients with a susceptible genetic background [1,2]. F-HLH is most commonly diagnosed during the first year of life. The incidence is estimated to be approximately 1.1 per 100,000 in children younger than age one year but this is almost certainly an underestimate, with a median age of onset of 5.1 months. However, being older than age one year does not exclude the diagnosis of F-HLH [3].

Early diagnosis of HLH and evaluation of potential causes is critically important, as survival generally requires urgent treatment with immunochemotherapy and resolution of the activating antigen. However, the diagnosis of HLH is challenged because of the rarity of HLH, its variable presentation that clinical overlap with other conditions, and the time required to perform diagnostic testing [1].

Further improvements in therapy will require prospective trials to define optimal strategies for each patient based on the individual paths that lead to pathologic inflammation [1].

Diagnostic criteria

There is no single feature that is specific for HLH, including hemophagocytosis, but the triad of prolonged fever, hepatosplenomegaly, and cytopenias should arouse suspicion of the possibility of HLH.

To establish a common basis for treatment, the HLH Study Group of the Histiocyte Society has proposed diagnostic criteria for HLH that have been revised recently (Table 1 and 2). Frequently, diagnostic criteria are not yet fulfilled at initial presentation.

Disease	Gene	Defect
FHLH1	Unknown	
FHLH2	PRF 1	Vesicle content
FHLH3	Munc 13.4	Vesicle priming
FHLH4	STX 11	Vesicle docking and fusion
FHLH5	STXBP2	Vesicle docking and fusion
Chediak-Higashi	LYST	Vesicle trafficking
Griscelli II	RAB27A	Vesicle docking and fission
Hermansky-Pudlak II	AP3B1	Vesicle trafficking
XLP 1	SH2D1A (SAP)	Multiple effects including CD8+ T/NK-cell cytotoxicity
XLP2	BIRC4 (XIAP)	Multiple signaling pathways

Table 1: *Genetic defects leading to HLH*.*

**Cytotoxic cells form a conjugate with their target to form an immunologic synapse, followed by trafficking of the cytotoxic granules containing perforin and granzymes toward the immunologic synapse, docking, priming, and fusion of the cytotoxic granules with the plasma membrane. Granule content is released into the immunologic synapse and induce target-cell destruction by caspase-dependent and independent apoptosis. Except for XLP and some congenital immunodeficiencies, all known genetic HLH is due to defect in proteins essential for this process.*

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:
1. A molecular diagnosis consistent with HLH is made.
2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below)*: a. Fever b. Splenomegaly c. Cytopenia (affecting ≥2 lineages in the peripheral blood): i. Hemoglobin < 90 g/L (in infants <4 weeks, hemoglobin < 100 g/L); platelets < 100,000/micro; absolute neutrophil count < 1000/µL. ii. Hypertriglyceridemia and or hypofibrinogenemia: iii. fasting triglycerides > 265 mg/dL hypofibrinogenemia (fibrinogen < 1.5g/L) iv. Hemophagocytosis in BM, spleen, or lymph nodes v. Low or absent NK-cell activity (according to local laboratory reference) vi. Ferritin ≥ 500 µg/L. vii. Soluble CD25 (i.e. sIL2r) ≥2400 U/mL †...

Table 2: *HLH-2004 diagnostic criteria.*

**Supportive criteria include neurologic symptoms, cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia and transaminitis, hypoalbuminemia, hyponatremia, elevated D-dimers, and lactate dehydrogenase. the absence of hemophagocytosis in the BM done not exclude a diagnosis of HLH.*

† New data show normal variation by age. Level should be compared with age related norms (adapted from Henter., et al).

However, A higher cutoff for ferritin may also be a valuable marker because levels > 3,000 µg/L concerning for HLH where > 10,000 µg/L were highly sensitive as 90 percent and 96 percent specific for the diagnosis of HLH in an institutional series, with very minimal overlap with sepsis, infections [4].

In patients with MAS, HLH 2004 criteria are not appropriate because they are fulfilled only at a late stage. Presently, an international collaboration aims at developing new diagnostic criteria for MAS complicating sJIA [1].

Pathophysiology

HLH is a syndrome of hyperinflammation and tissue destruction due to immune dysregulation which is caused by a mutation in genetic HLH [4]. HLH is based on an ineffective immune response with impaired pathogen elimination resulting in dysfunction of cytotoxic T cells (CTLs). The cell types involved in the pathogenesis of HLH include macrophages, natural killer cells (NK)and CTLs. In HLH, NK cells and/or CTLs with accompanying dysregulated response to antigen presenting cells (APCs) that fail to eliminate activated macrophages. The lack of normal feedback regulation results in excessive macrophage activity and highly elevated levels of interferon gamma and other cytokines. Excessive cytokine production by macrophages, NK cells, and CTLs is thought to be a primary pathogenesis of HLH of tissue damage. Toll-like receptor (TLR) activation of the immune system can be another cause of HLH. TLRs are non-antigen- specific receptors on the surface of NK cells that are activated by components of bacteria, fungi, viruses, or mycoplasma. Hemophagocytosis in addition to antigen presentation and cytokine production, macrophages can also phagocytize host cells, and it refers to the engulfment of host blood cells by macrophages, which is characterized by the presence of red blood cells, platelets, or white blood cells (or fragments of these cells) within the cytoplasm [2,5].

Case Presentation

This is a three months old girl, product of term pregnancy born for a consanguineous young parent, a 23 years old mother and a 30 years old father. Was spontaneous planned pregnancy with a regular antenatal follow up, uneventful with reassuring lab workup and ultrasonography. A baby girl delivered with APGAR score 9 and 10 at 1st and 5th minutes respectively, with a birth weight of 3.0 Kg, normal physical examinations, feeding well and thriving well.

At age of two months of life, the child was noticed by her mother to be pale and hypoactive compared to her baseline and was taken to a small private hospital, Complete blood count blood sample was drowned and showed the following parameters WBC: 2.27 K/µL, Hb: 5.6 gm/dl, Plat: 246 K/µL. In which patient was transfused PRBCs and her Hb elevated to 9.3 gm/dl then was discharged.

Three weeks later she had similar findings of pallor and decreased activity and again her Hb was low and transfused PRBCs. In between these attacks she was continuously spiking temperature on daily basis with preservation of her activity and feeding patterns. Her temperature was 38.6 - 39.4°C and there was no clear focus as a source of infection.

The patient landed in our Emergency department in Qatif Central Hospital, Eastern province, Saudi Arabia at age of three months of life with history of pallor, decreased activity, of few days duration, in addition to her prolonged history of fever of one month duration. At presentation, patient was febrile, Temperature was 40°C, HR: 140 bpm, BP: 96/51, RR: 43/min, P SpO_2: 97% on room air. She was well looking active, obviously pale but not jaundiced nor cyanosed. No facial dysmorphism, no cutaneous stigmata. There was pinpoint petechiae on her face and trunk. Her neurological examination was normal with normal development for her age. Cardiovascular examination and chest examination were normal. Abdominal examination revealed hepatomegaly 4 cm below with liver span of 8cm with initially no splenomegaly which was markedly enlarged in few days. There was no palpable lymphadenopathy.

Her initial laboratory investigations are showed in table 3.

CBC	WBC:1.6 K/µL, Hb: 10.6 gm/dl, Plat:62 K/µL
Reticulocytes	0.23%
Hb Electrophoresis	Post blood transfusion with Normal HB Electrophoresis pattern for age Hb A: 92.3% Hb A2: 2.6% Hb F :5.1%
G6PD Qualitative	Normal screening
Peripheral Blood Film	showed marked neutropenia, hyper segmentation and abnormal segmentations, moderate atypical lymphocytes with 2% blast cells. RBCs: slight anisopoikilocytosis, moderate hypochromic microcytosis, slight tear drop cells, slight blister cells and bite cells, slight RBC fragments. PLT moderately low
Bone Marrow Aspiration	Aparticulate, hemodiluted bone marrow aspirate, no megakaryocytes seen. Erythropoiesis is active, 31% of bone marrow cellularity, showed marked megaloblastic features (Asynchronous nuclear to cytoplasmic maturation, giant erythroid precursors). Moderate dysplasia in both early and late erythroid precursors (binuclear, multinuclear, nuclear budding, karyorrhexis). Active myelopoiesis, 38% of bone marrow cellularity, showed normal sequential maturation with markedly giant myelocytes, metamyelocytes and bands, moderate dysplasia in the form of hyper segmented neutrophils and abnormal segmentation. Myeloid to erythroid ratio:1.2 to 1 (normal). Lymphopoiesis is active, 28% of bone marrow cellularity with reactive forms seen. Blast:4% medium size agranular basophilic cytoplasm with high N/C ratio irregular nuclear edges with open chromatin and apparent nucleoli. No histiocytes seen in the slides examined. Flowcytometry Immunophenotyping: The flowcytometry results shows the presence of 1.8% of CD34/CD19/CD10 positive population in hematogone region. T-cells marked increase in CD4/CD8 ratio with loss of CD7 in the suboptimal moderately hemodiluted bone marrow sample examined. Peripheral blood flowcytometry was subsequently done, it reveals T-cells show similar marked increase ratio of CD4/CD8, diminished expression of CD7 and negative for immature markers CD34, c-TDT, CD99, CD1a.Correlate clinically and with bone marrow aspiration, trephine biopsy findings, rule out viral infection, closely follow up and repeat bone marrow examination of indicated. Conclusion: Diluted bone marrow aspirate with megaloblastic features and bilineage dysplasia.
Chromosomal Analysis in Bone Marrow Aspirate	ISCN Karyotype Nomenclature comment: Both morphology and Flowcytometry showed no evidence of Malignancy
Flowcytometry in Bone Marrow Aspirate	Marked lymphopenia affecting all lymphocytes subsets with markedly reduced CD8 cell count and very high CD4/CD8 ratio. There is normal expression of HLA ABC and TCR molecules on TL.
Ferritin	Initially 1762 ng/ml repeated during admission 5436 ng/ml Markedly high
Triglyceride	3.08 mmol/L Markedly high Other lipid profile parameters Cholesterol, LDL, HDL were normal
Virology study	CMV DNA 396, 946 copies/ml
Serum Electrolytes, Liver function test, Renal function test	Were normal
Fibrinogen	1.88 g/l low
Vitamin B12	203 pg/ml
Cultures (blood, urine and CSF)	All were negative

Table 3: *Initial laboratory investigations.*

Patient was kept on electrolytes and albumin replacement with frequent lab monitoring. Chest x ray (Figure 1) showed homogenous opacity in the right middle zone, although she was maintaining her saturation in room air without any manifestation of respiratory distress.

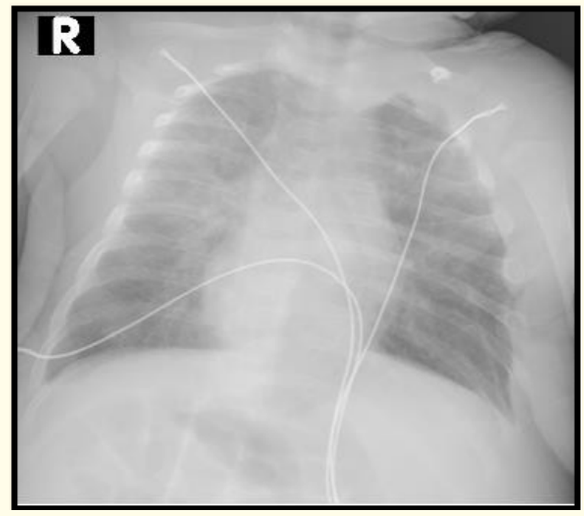

Figure 1

Medical report was dictated for referral to a tertiary care center for HLH specialists for diagnostic molecular genetic as the patient was not fitting all the criteria of HLH (Table 4).

HLH-2004 diagnostic criteria	Present in our patient
A molecular diagnosis consistent with HLH	N\A
Fever	Present
Splenomegaly	Present
Cytopenia (affecting ≥2 lineages in the peripheral blood) Hemoglobin <90 g/L platelets <100,000/micro Absolute neutrophil count <1000/μL.	Present Present Present
Hypertriglyceridemia and/or hypofibrinogenemia	Present
Hemophagocytosis in BM, spleen, or lymph nodes.	Done in BM, it was negative
Low or absent NK-cell activity	N\A
Ferritin ≥ 500 μg/L.	Present
Soluble CD25 ≥ 2400 U/mL	N\A

Table 4: *Diagnostic criteria of Hemophagocytic lymphohistiocytosis present in our patient.*

Subsequently, she started to deteriorate, developed respiratory distress in form of coughing, grunting and subcostal and intercostal retractions that required intubation and invasive ventilation. Her Hb had significant drop of 2 gms and her chest x-rays (Figure 2) showed evidence of spontaneous pulmonary hemorrhage in which was managed by high frequency Oscillatory ventilation HFOV with FiO2 requirement up to 100%.

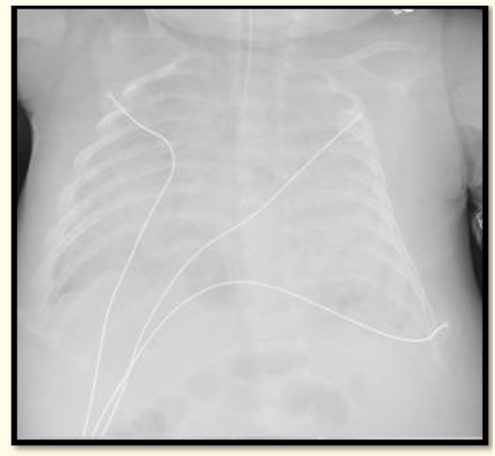

Figure 2: : *Showed evidence of spontaneous pulmonary hemorrhage.*

She declined her hemodynamic status as well and required maximization of four inotropic support (Epinephrine, Norepinephrine, Dopamine and Dobutamine) to restore her circulation and optimize her condition. Escalation of IV antibiotics to Meropenem, Vancomycin and Gentamycin although there was no clear evidence of active infection and this deterioration is expected with her expected primary disease and bone marrow failure. She is an immunocompromised patient and vulnerable and liable to heavy infections. At this point, HLH therapy was initiated empirically with Dexamethasone 10 mg/m^2/day IV OD, IV IG 1gm/Kg and Cyclosporin IV 6 mg/Kg/Day IV divided BID.

Around 72 hrs hour later she started to relatively recover regarding her pulmonary hemorrhage with improvement of gas exchange and minimal requirement of the oscillator, in addition to improvement of her chest X Rays (Figure 3).

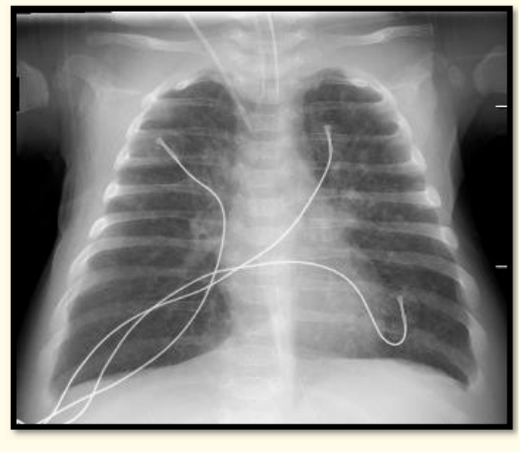

Figure 3: *Recover regarding her pulmonary hemorrhage with HFOV.*

There was improvement of hemodynamic status and inotropes were weaned to a single inotropic agent with minimal infusion of 0.1 mcg/kg/mint then weaned to off. Patient was screened for intracranial hemorrhage and intraabdominal hemorrhage by radiological imaging and came to be negative.

After a stormy journey at our hospital, the patient was stabilized with maximum medical management and was transferred to a tertiary care center for further diagnostic workup including molecular genetics and for HLH therapy as per protocol.

Parents were referred for genetic counseling clinic for workup and arrangement for preimplantation genetic diagnosis (PGD) for the next pregnancies, as it is a familial and inherited disorder. Parents are highly educated and understanding their child disease, its nature and poor prognosis and possibility of death.

Literature Review

we review the literature for cases reported in pediatric familial HLH, there were great variability in initial presentations from well appearing child with mild symptoms to severely sick child with rapid clinical deterioration [6]. The most common presenting symptoms are fever, cytopenia, and hepatosplenomegaly and occasionally CNS manifestations and liver failure. The disease onset presents as early as perinatal period, on one case report of male neonate delivered at 36 weeks with hydrops fetalis and diagnosed with HLH on 3rd day of life [6]. The more early age of presentation the more severe clinical course can be expected with multi-organ failure and died before starting the therapy or shortly after initiating therapy [7-9]. As it is very difficult to diagnose HLH by signs and symptoms alone due to a high likelihood of misdiagnosing the condition as an infection or a metabolic disease, therefore delaying diagnosis [10]. The longest period reported to diagnose HLH was 9 year with a rare unusual chronic course of familial HLH [12].

Unlike the often presentation of HLH of rapid life threatening progression of the disease. In order to reduce mortality rates, an early diagnosis is crucial. However, due to lack of specificity of current diagnostic criteria, a definitive diagnosis is often difficult. A diagnosis of HLH is made by detecting a specific genetic mutation or by the current HLH- 2004 diagnostic criteria [13,14]. A case series reported 3 infant with early suspicion and diagnosis of HLH and starting the therapy before progression of the symptoms, shows good outcome and improve prognosis and survival [15].

Current practice requires that a minimum of five criteria must be present for a diagnosis of HLH. However, the literature suggests that if a patient has a specific genetic mutation consistent with HLH on molecular testing, then these diagnostic criteria are not essential for diagnosis [12,16].

There are reportable cases in Saudi Arabia about siblings who manifest at early infancy with prolong, fever, pancytopenia and hepatosplenomegaly that they get fast deterioration and subsequent death even before the completion of the required criteria and the molecular genetics is not available in most of the community based hospitals that these patient first lands in.

On the other hand, there are families who are known to have offspring with familial HLH and underwent full genetic investigations and workup and scheduled for planned pregnancies only with Preimplantation genetic diagnosis PGD.

Discussion

We noticed as clinical observation that patients who present of the combination of symptoms of multisystem involvement and fever, pancytopenia, organomegally, liver failure, hemodynamic instability are often critically sick and progress fastly to a further critical condition and they decline with multiorgan failure and death within short period of few days. As the differential diagnosis is wide and all of which carries out high risk of mortality and morbidity, the HLH might not be fully met initially as per the criteria as the patient progressed they will fulfill the criteria as their illness progress and by that time they will be in critically sick condition and might not make it to the therapy journey and the ultimate treatment of stem cell transplant. A combination of high index of suspicion, clinical presentation, and basic laboratory findings could point the clinician toward early diagnosis and early effective treatment. As the time is crucial for these patient and the initiation of therapy early plays major role in their prognosis, we highlight that HLH needs high index of suspicion and early prompt therapy to control the ongoing process.

As most of these patients usually land in community-based hospitals that has no facilities to genetic diagnosis or further workups and they progressed to terminal condition and unfavorable outcomes before fitting the criteria and before the referral to tertiary care centers. Besides that, the studies showed that more than quarter of the familial HLH in Saudi Arabia were Noval and no molecular defects were identified.

We are throwing the question of criteria modification or early initiation of therapy empirically up on suspicion and combination of three criteria instead of five after exclusion of other differential diagnosis before the completion of the full HLH criteria. That might be difficult to be applied and needs further studies and new guidelines and criteria modifications. Our concern was that the Saudi Arabia is one of the common geographic areas for familial HLH due to consanguinity and genetic inheritance.

Conclusion

HLH is a potentially fatal hyperinflammatory condition is often missed in infant and children. Goals for the future include increasing awareness, which requires high index of suspicion, early diagnosis and promoting prompt referral for quick early effective therapy to further reduce mortality.

Consent

Written consent was taken from the parents for approval of case reporting and publishing

Acknowledgment

The authors thank Head department of pediatrics, scientific committee and academic affairs for granting permission to publish this case.

Conflicts of Interest

None.

Funding

None.

Contribution of Authors

Preparation of first draft: I.M.

Literature review: I.A Z.D.

M.D. Conceptualization: I.M, K.A, Z.D.

Intellectual inputs for improvement of manuscript: M.D, Z.D, I.A.K.A.

Approval of final draft: M.D I.M, Z.D.

Bibliography

1. Janka GE and Lehmberg K. "Hemophagocytic lymphohistiocytosis: pathogenesis and treatment". *ASH Education Program Book* 1 (2013): 605-611.

2. Kenneth L McClain. "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis". UPTODATE (2019).

3. Erker C., *et al*. "Usual and unusual manifestations of familial hemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis". *Pediatric Clinics of North America* 64.1 (2017): 91-109.

4. Allen CE., *et al*. "Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis". *Pediatric Blood and Cancer* 50.6 (2008): 1227-1235.

5. Filipovich A., *et al*. "Histiocytic disorders: recent insights into pathophysiology and practical guidelines". *Biology of Blood and Marrow Transplantation* 16.1 (2010): S82-S89.

6. Takeuchi O and Akira S. "Pattern recognition receptors and inflammation". *Cell* 140.6 (2010): 805-820.

7. Ramachandran S., *et al*. "Initial Presentation of Hemophagocytic Lymphohistiocytosis in a Well-appearing Child with Fevers". *Pediatrics* 141.1 (2018).

8. Iwatani S., *et al*. "Familial hemophagocytic lymphohistiocytosis presenting as hydrops fetalis". *American Journal of Perinatology Reports* 5.1 (2015): e22-e24.

9. Lee NM., *et al*. "Haemophagocytic lymphohistiocytosis in a preterm infant: A case report". *The Journal of the Pakistan Medical Association* 68.1 (2018): 127-129.

10. Abbaker AI and Dammas AS. "Familial hemophagocytic lymphohistiocytosis in two Saudi siblings". *Sudanese Journal of Paediatrics* 15.1 (2015): 57-60.

11. Kumar M., *et al*. "Hemophagocytic lymphohistiocytosis presenting with acute liver failure and central nervous system involvement in early infancy". *Indian Journal of Pathology and Microbiology* 61.2 (2018): 281-283.

12. Woods CW., *et al*. "Hemophagocytic lymphohistiocytosis in the premature neonate". *Advances in Neonatal Care* 9.6 (2009): 265-273.

13. Steinberg O., *et al*. "Prolonged course of familial hemophagocytic lymphohistiocytosis". *Journal of Pediatric Hematology/Oncology* 28.12 (2006): 831-833.

14. Henter JI., *et al*. "HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis". *Pediatric Blood and Cancer* 48.2 (2007): 124-131.

15. Filipovich AH. "Hemophagocytic lymphohistiocytosis (HLH) and related disorders". *Hematology. American Society of Hematology. Education Program* 1 (2009): 127-131.

16. Tanoshima R., *et al*. "Hemophagocytic lymphohistiocytosis in very young infants". *Pediatric Blood and Cancer* 52.1 (2009): 137-139.

Volume 8 Issue 8 August 2019