ORIGINAL ARTICLE

Etiology, Treatment and Outcome of Children Diagnosed with Secondary Hemophagocytic Lymphohistiocytosis in A Tertiary Hospital

Dianne Loraine P. Clemente, M.D.
Robert Dennis J. Garcia, M.D.

Department of Pediatrics
Makati Medical Center

Correspondence:
Dr. Dianne Loraine P. Clemente
Email: clementedianne@gmail.com

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome that is associated with a variety of underlying conditions leading to the same characteristic hyperinflammatory phenotype.

Objectives: To describe the clinical profile of patients diagnosed with HLH admitted between January 1, 2010 to September 30, 2019 in a tertiary care hospital.

Methods: Retrospective descriptive study of pediatric patients diagnosed with HLH in a tertiary care hospital.

Results: Eleven subjects were included in the study. Age distribution showed a bimodal pattern: < 5 years old (5, 46%) and 10-15 years old (4, 36%). Male to female ratio is 4.5:1. All patients presented with fever (100%) followed by hepatomegaly (5, 45%) and splenomegaly (4, 36%) on physical examination. All eleven subjects fulfilled the following criteria for HLH such as fever, splenomegaly, and hyperferritinemia. Six out of eleven showed hypofibrinogemia (55%) and hypertriglyceridemia (55%). Among the eleven with two cell cytopenia, five presented with anemia (46%), six with neutropenia (55%), while all of them had thrombocytopenia (100%). Other laboratory findings noted were elevated ALT (5, 46%), CRP (4, 36%), AST (3, 27%), alkaline phosphatase (3, 27%), and hyponatremia (3, 27%). EBV and dengue (3, 27%) were the most common etiologies. Pneumonia (3, 27%) was the most common complication, followed by sepsis (2, 18%). All but one patient were responsive to either dexamethasone (7, 64%) and or IVIG (5, 45%) and chemotherapy (1, 9%). The antibiotic most commonly used was piperacillin tazobactam (3, 27%). The median hospital stay was 17 days. There was one mortality (9%).

Conclusion: HLH should be considered in children presenting with prolonged fever, hepatomegaly, and or splenomegaly, with hyperferritinemia, thrombocytopenia, anemia and neutropenia.

KEYWORDS: *Hemophagocytic lymphohistiocytosis, retrospective descriptive study*

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an infrequently seen and diagnosed illness that is associated with significant morbidity and mortality. In the Philippines, there were only 232 cases recorded based on the PPS registry over a 10-year period (2009 to September 2019). The illness was loosely termed histiocytosis in the past, but was defined more in the 2004 diagnostic criteria for HLH.[1] Primary HLH is a familial genetic illness, often presenting within the first few months after birth, although 20% may manifest at more than 2 years of age.[2] Secondary HLH is that which occurs in the absence of a genetic predisposition and are due to infections, malignancies and autoimmune diseases.

The pathogenesis of primary HLH involves a malfunction of immunoregulation. When cells are infected by invading organisms, cytotoxic T-lymphocytes (CTL) act against infected cells and antigen-presenting cells (APCs). In HLH, CTLs are defective and ineffective, and APCs continuously stimulate CTLs, causing a continuing production of cytokines, especially interferon-gamma, which influence macrophage activation.[2]

Clinically, HLH manifests with prolonged fever, cytopenias and splenomegaly. Various infections may trigger secondary HLH, including Epstein Barr Virus (EBV), cytomegalovirus (CMV), dengue and other bacteria. Epstein Barr Virus has been reported as a frequent cause of HLH and EBV is also a common cause of fever of unknown origin (FUO). It is important to know that an FUO case that is found to be due to EBV may further lapse into, and be complicated by HLH, which has a high mortality rate.[3] It is thus important to be aware of the presence of HLH complicating viral and bacterial infections because treatment for this may entail more than just antimicrobials. It is important to profile pediatric cases with HLH, to improve clinical detection, treatment and to prevent complications associated with the illness.

There are a few studies related to pediatric HLH and published data are from the US and Europe. In the Philippines, there were only two published pediatric studies and both were case reports. With this knowledge gap, this study aimed to characterize the documented pediatric HLH cases admitted between January 1, 2010 to September 30, 2019 in a tertiary care hospital.

The Specific Objectives were as follows:

1. Describe the clinical profile of patients diagnosed with HLH as to Age distribution, sex ratio, clinical manifestations, ancillary work-up findings, medical complications, length of hospital stay, mortality, and
2. Describe the treatment and outcomes of patients diagnosed with HLH

METHODOLOGY

Study Design

This was a retrospective descriptive study of all pediatric patients up to 18 years old seen at a tertiary care hospital between January 1, 2010 to September 30, 2019 with a discharge diagnosis of HLH.

Population

A patient list was obtained from the medical records section by searching ICD 10 code of D76.1. Patient lists from pediatric department staff physicians (hematologist-oncologists, infectious disease specialists, intensivists and gastroenterologists) were likewise included. Electronic medical records (EMR) chart review was done subsequently by the primary investigator. The subjects included in the study fulfilled the five out of eight criteria as follows: fever, splenomegaly, two cell cytopenia (anemia, thrombocytopenia, neutropenia), hypertriglyceridemia and or hypofibrigonemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent NK-call activity, hyperferritinemia and elevated CD 25 level. Subjects who did not fulfill the HLH criteria were excluded. The medical records of eligible patients were subjected to further chart review and the following information were gathered: age distribution, sex ratio, clinical manifestations, ancillary work-up findings, treatment, length of hospital stay, complications, and mortalities.

As for the etiologies, the subjects were diagnosed to have Epstein Barr Virus (EBV) infection based on the clinical diagnosis of infectious mononucleosis characterized by fever, sore throat, petechial or exudative pharyngitis, cervical lymphadenopathy, hepatosplenomegaly, with or without atypical lymphocytosis, with either a normal or mild elevation in the white blood cell count with positive EBV IgM and or EBV PCR. Subjects with dengue fever were diagnosed based on the presence of fever, myalgia or arthralgia, rash, with minor or major hemorrhagic

manifestations, with laboratory findings of thrombocytopenia and an objective evidence of increased capillary permeability and a positive dengue NS1 or dengue IgM result. Cases of sepsis were diagnosed through clinical criteria with positive blood culture growths. Diagnosis of acute lymphoblastic leukemia was based on the bone marrow findings. Juvenile idiopathic arthritis was diagnosed by age of predilection of less than 16 years old with symptom onset of more than or equal to 6 weeks, with presence intraarticular swelling or presence of 2 or more of the following: limitation of movement, tenderness and pain on motion, and warmth on affected area in one or more joints and where infection has been ruled out. Probable drug reaction secondary to antibiotic use, was diagnosed based on clinical history, with appearance of wheals and maculopapular rash after use of the drug.[4]

Data Collection and Statistical Analysis

A standard case-study form was used for each medical chart where relevant data was entered. Descriptive statistics were used in the data analysis.

The variables of interest in the study were determined based on their clinical course as documented in the patient records. This study relied solely on data recorded on the patient's chart and in the instance where the information was not directly stated, the following operational definitions were applied to determine the variables of interest. (See Appendix A for operational definitions)

Ethical Considerations

This study was approved by the MMC Institutional Review Board (IRB) to access the required information needed to complete this research. Patient anonymity was strictly maintained throughout the duration of the study, in compliance with the Data Privacy Act of 2012 (Republic Act 10173). A unique numeric code was assigned to each patient to preserve the anonymity of each subject's personal information.

Patient confidentiality was further maintained by securing all information gathered in the researcher's personal computer that is password protected.

The authors report no disclosures. No potential conflicts of interest were identified. This study was initiated and funded wholly by the principal investigator.

RESULTS

Demographics

A total of 18 cases of pediatric HLH were screened from the data provided by the Medical Records department, combined with consultants' personal patient lists. Seven patients were excluded from the study for not fulfilling the inclusion criteria based on HLH-2004 guidelines, although these patients were diagnosed with Langerhans cell histiocytosis and probable HLH under ICD 10 code D76.1. Patients included in the study were not tested genetically, hence a diagnosis of primary HLH cannot be made.

A total of eleven subjects who were admitted between January 1, 2010 to September 30, 2019 fulfilled the HLH-2004 guidelines. The age, sex, clinical manifestations, laboratory findings, length of hospital stay, complications, and outcome were tabulated as follows:

Table 1: Age and sex profile of pediatric patients with HLH (n=11)

Age (years)	**Frequency (%)**
Less than 5	5 (46)
5 to 9	2 (19)
10-15	4 (36)
Sex	
Male	9 (82)
Female	2 (18)

HLH had a bimodal age distribution, with ages less than five years old (46%) and ten to fifteen years old (36%). It affected more males than females, with a M:F ratio of 4.5:1.

The most common chief complaint was fever (82%). All patients presented with fever, six of whom had fever of less than seven days, from the day of admission up to 2 weeks long; maximum temperature ranged from 38.8C to 40.5C. Other clinical manifestations were body weakness, cough, loss of appetite and loose watery stools.

One patient complained of seizure but had a history of head trauma secondary to fall. Another patient had right shoulder pain with multiple petechiae on the area, but without history of trauma.

Table 2.1: Symptoms of pediatric patients with HLH (n = 11)

	Frequency (%)
Fever	11 (100)
Body weakness	4 (36)
Cough	3 (27)
Loose watery stools	3 (27)
Sore throat	2 (18)
Loss of appetite	1 (9)
Rash	1 (9)
Abdominal pain	1 (9)
Seizure	1 (9)

Common physical examination findings were hepatomegaly followed by splenomegaly. Other findings were bilateral palpable lymphadenopathies on the cervical area and dry lips.

Table 2.2: Physical examination findings of pediatric patients with HLH (n = 11)

	Frequency (%)
Hepatomegaly	5 (45)
Splenomegaly	4 (36)
Lymphadenopathy	3 (27)
Dry lips	3 (27)
Pallor	2 (18)
Epigastric tenderness	1 (9)
Petechiae	1 (9)
Wheals	1 (9)

All subjects presented with splenomegaly, nine identified from ultrasound and two from CT scan. All had hypferritenemia and fulfilled 2 cell cytopenia with either anemia or neutropenia and thrombocytopenia. None were tested for hemophagocytosis in bone marrow or spleen, nor for NK cell activity and CD25 levels.

Table 3.1: Imaging studies and laboratory findings of pediatric patients with HLH

	Frequency (%)
Splenomegaly (Ultrasound or CT scan)	11 (100)
Hyperferritinemia (≥ 500 ug/ml)	11 (100)
Thrombocytopenia (<100000 uL)	11 (100)
Neutropenia (<1000/uL)	6 (55)
Hypertriglyceridemia (≥ 265 mg/dL)	6 (55)
Anemia (<90 g/L)	5 (46)
Hypofibrinogenemia (≤ 1.5 g/L)	3 (50)

The range of elevated ALT, CRP, AST and Alkaline phosphatase were 93 to >8522 mg/dl, 18.8 to 155 mg/L, 257 to 1362 mg/dl, and 105 to 236 u/L respectively. Hyponatremia ranged from 127 to 133 meq/L.

Table 3.2: Other ancillary work-up of pediatric patients with HLH (n = 11)

	Frequency (%)
ALT	
Elevated	5 (45)
Normal	2 (18)
Not done	4
CRP	
Elevated	4 (36)
Normal	0
Not done	6
AST	
Elevated	3 (27)
Normal	2 (18)
Not done	6
Alkaline Phosphatase	
Elevated	3 (27)
Normal	0
Not done	8
Sodium	
Elevated	0
Decreased	3 (27)
Normal	1 (9)
Not done	7
Potassium	
Elevated	0
Decreased	1 (9)
Normal	3 (27)
Not done	7

The most common etiologies for secondary hemophagocytic lymphohistiocytosis were EBV and dengue fever. Patients with EBV presented with fever, hepatosplenomegaly and cervical lymphadenopathy upon admission. The diagnosis was based on clinical manifestations of fever, sore throat, petechial or exudative pharyngitis, cervical lymphadenopathy, hepatosplenomegaly on physical examination and on ultrasound, with or without atypical lymphocytosis, with either a normal or mild elevation in the white blood cell count with positive EBV IgM and or EBV PCR. HLH was suspected due to progression of anemia and thrombocytopenia. Patients with dengue were worked up for HLH due to fever of more than seven days with splenomegaly which was not apparent upon admission. The sepsis cases (*Salmonella spp* and *Klebsiella spp*) both had culture growths but despite appropriate antibiotic treatment, fever persisted. In the cases of juvenile idiopathic arthritis and drug reaction the patients had prolonged fever with presence of persistent thrombocytopenia despite transfusion. The patient with hypersensitivity reaction secondary to antibiotic use also tested positive for EBV IgM; the patient had prolonged fever, splenomegaly, accompanied by neutropenia and thrombocytopenia. Patients had a median hospital stay of 17 days, ranging from 7 days to 28 days.

Table 4.1: Etiology and complications of pediatric patients with HLH (n = 11)

	Frequency (%)
EBV	3 (27)
Dengue	3 (27)
Sepsis (Klebsiella spp, Salmonella spp)	2 (18)
Pneumonia	1 (9)
Juvenile idiopathic arthritis (JIA)	1 (9)
Acute lymphoblastic leukemia (ALL)	1 (9)
Drug reaction	1 (9)

The most common complication was pneumonia. Three patients were diagnosed during the second to fifth hospital stay, and they presented with cough and tachypnea, with physical examination finding of rales during the course of admission. One patient had sepsis secondary to *Klebsiella pneumoniae* and one secondary to *Candida parapsilosis*. The patient with *Klebsiella pneumoniae* was still febrile after 16 days of hospitalization, with an epidural hematoma, status post craniotomy, and was persistently febrile despite antibiotic treatment. The patient with fungal sepsis was a case of aplastic anemia with pneumonia and had been febrile for 13 days prior to admission. The youngest patient at 5 months had uncontrolled sepsis secondary to Salmonella infection with anemia, hepatosplenomegaly and pericardial effusion. The patient died on the 11th hospital day from DIC and pulmonary hemorrhage while receiving IVIG infusion at the intensive care unit.

Table 4.2: Complications of pediatric patients with HLH (n = 11)

	Frequency
Pneumonia	3 (27)
Sepsis	2 (18)
Disseminated Intravascular Coagulopathy (DIC); Pulmonary Hemorrhage - Mortality	1(9)

Seven patients were treated with dexamethasone. Among three of seven patients on dexamethasone, one had EBV and two had dengue fever; all three improved with steroids alone with defervescence after one to five days of treatment. Three patients on steroids were cases of EBV, dengue and autoimmune arthritis, for whom dexamethasone was started after IVIG infusion. The patient with acute lymphoblastic leukemia defervesced after receiving dexamethasone, etoposide, cyclosporine, L-asparaginase and methotrexate.

Two patients were treated with IVIG. The first patient was a case of drug reaction secondary to cotrimoxazole who improved after one day of IVIG infusion. The other patient was an infant with sepsis secondary to Salmonella, who expired while receiving IVIG infusion, secondary to DIC and pulmonary hemorrhage.

All patients received antibiotic treatment prior to the diagnosis of HLH, except for one. They were treated for pneumonia, sepsis and other nosocomial infections due to prolonged hospital stay. The most frequent antibiotics used were piperacillin tazobactam, amikacin, cefuroxime, ceftriaxone and cotrimoxazole.

Table 5.1: Mode of treatment of pediatric patients with HLH (n = 11)

	Frequency
Dexamethasone	7 (64)
IVIG	5 (45)
Etoposide	1 (9)
Cyclosporine	1 (9)
Methotrexate	1 (9)
L-Asparaginase	1 (9)
Antibiotic	10 (91)
Antifungal	2 (18)

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome that is associated with a variety of underlying conditions leading to the same characteristic hyperinflammatory phenotype. It is a life-threatening hyperinflammatory syndrome.[5] Secondary HLH may develop as a result of a potent stimulus that activates the immune system. Virus-associated hemophagocytic syndrome has been described in immunocompromised hosts. It can occur in all age groups, however, there is no data regarding the incidence of acquired forms.[6] The pathophysiology involves excessive inflammation and tissue destruction due to abnormal immune activation. This dysregulation is thought to be caused by the absence of normal downregulation of activated macrophages and lymphocytes.[7] A study done by Zoller et al. demonstrated that the hemophagocytic macrophages have a pathologic role in the development of acute inflammation-induced anemia. They also determined that hemophagocytosis is triggered by interferon gamma and its direct action leads to development of severe consumptive anemia and other cytopenias.[8] The classic clinical picture of HLH is that of a prolonged fever unresponsive to antibiotics, with hepatosplenomegaly. Fever may be non-specific, and may be accompanied by signs of an upper respiratory or gastrointestinal infection. Less common are lymphadenopathy, icterus, and an uncharacteristic rash or edema. Neurologic signs such as seizures or cranial nerve palsies may be present in one third of patients. Anemia and thrombocytopenia are early signs.[6]

In our study, age distribution showed a bimodal pattern affecting children less than five years old (46%) and 10-15 years old (36%), a finding somewhat different from published data abroad. In a study done in Texas the mean age at diagnosis was at 2.1 years old with a slight female predominance (61%).[9] In a Chinese study, the median age at diagnosis was 2.2 years with a male:female ratio of 1.27:1.[10]

On physical examination, hepatomegaly and splenomegaly were present in 45% and 36% respectively. Clinical hallmarks of HLH are persistent fever, hepatosplenomegaly and neurological symptoms.[2] In our study, only one patient had seizure; this was attributed to an epidural hematoma secondary to trauma. Initial manifestations can resemble common infections, fever of unknown origin and other autoinflammatory disorders.[2] In a Chinese study, all subjects presented with fever upon diagnosis similar to our study. However, findings of hepatomegaly (86%) and splenomegaly (73.7%) were more common in non-active disease as compared to our study.[10]

A common finding in this study was splenomegaly by ultrasound or CT imaging. All subjects had thrombocytopenia with either anemia or neutropenia, hypertriglyceridemia, hypofibrinogemia, hyperferritinemia. Laboratory findings of HLH include two cell cytopenia, hypertriglyceridemia, hypofibrogenimia, hyperferritinemia, hemophagocytosis in bone marrow or spleen, low or absent NK cell activity and elevated CD25.[1] In a study done by George, M., laboratory findings upon diagnosis of secondary HLH were cytopenias (80%), hypertriglyceridemia (40%), hypofibrogenemia (40%), hyperferritinemia (95%), and decreased NK cell activity (30%).[11] A characteristic finding was a high percentage of hyperferritinemia in both studies. Serum ferritin is an easily available and valuable disease marker of HLH. A level above 10,000 ug/L in children is 90% sensitive and 96% specific.[12] Laboratory values in HLH include high ferritin, triglycerides, transaminases, bilirubin (mostly conjugated), and sCD25 (an α-chain of the soluble interleukin- 2 receptor), and decreased fibrinogen. Ferritin, may reach levels of 50,000 ng L^{-1} and more, and is an easily available and valuable disease marker of HLH. A level above 10,000 µg L^{-1} in children was 90% sensitive and 96% specific for HLH. An inflammatory hepatitis-like periportal infiltrate in the liver with lymphocytes and histiocytes, leading to obstructive jaundice is typical for HLH.[13]

Other abnormal ancillary findings noted in our study showed elevated ALT, AST, alkaline phosphatase, CRP and hyponatremia. These findings are consistent

with HLH-2004 diagnostic and therapeutic guidelines, which includes hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, high VLDL, low HDL.[1]

Associated etiology in the study were, most commonly, EBV and dengue virus. Viruses are the predominant triggers in secondary HLH; protozoal, bacterial, and fungal infections have also been reported such as L*eishmania, Mycobacterium tuberculosis* and *Salmonella typhimurium.* Malignant disease such as malignant lymphoma and leukemia are less common in children than in adults. The major subtype of secondary HLH is induced most commonly by a primary EBV infection followed, by other infection or lymphoma associated HLH.[14,15] The incidence of EBV-HLH is high in Asian countries, suggesting an underlying genetic background. EBV infected B cells induce an increase in cytotoxic T cells, followed by macrophage activation having an uncontrolled immune response which brings about hypercytokinemia.[14] In a case series done by Pal, P. et al., all dengue patients presented with fever of more than 7 days, accompanied by persistent or progressive cytopenias, with unusual organomegaly with a negative blood culture.[16] As in our study, the cases of dengue, presented with fever longer than expected, with progressive cytopenia and splenomegaly which was absent on admission. Health care workers should be aware of dengue-induced HLH because it can be a potential cause of complications and death.

Complication reported in our study were pneumonia, followed by sepsis, DIC and pulmonary hemorrhage. In a similar study by Tsuge, M. et al., an 11 month old male was hospitalized for a 1 day history of fever where blood test revealed leukocytosis and an elevated CRP. Initial consideration was mild pneumonia, he was given a single dose of ceftriaxone and was discharged on ceftizoxime. However, fever persisted, blood tests showed progressive neutropenia and increased CRP, prompting readmission. Blood culture grew *S. pneumoniae* on blood culture. He was diagnosed with HLH based on prolonged fever, neutropenia, anemia, hepatosplenomegaly, hemophagocytosis on bone marrow and elevated triglycerides, ferrititin and sIL-2r. Pulse methylprednisolone, prednisolone and cyclosporin A were started. Thereafter, clinical status and blood tests started to improve.[17] A chest radiograph finding of interstitial pneumonia was also frequently seen in patients with EBV-HLH.[3] Many patients were admitted at the intensive care unit because of complications associated with a delay in diagnosis.[18]

All patients in the study were initially treated with antibiotics. Three patients were treated with dexamethasone alone. Three were treated with dexamethasone after IVIG infusion. Two were treated with IVIG alone, one of whom expired. The aim of treatment is to suppress the hyperinflammatory component of the disease by suppressing activated cytotoxic lymphocytes and macrophages.[2] Milder forms of HLH respond to corticosteroids with or without immunoglobulin, to suppress hyperinflammation. However, mild cases may rapidly worsen in a short period of time.[13] Early recognition of HLH with initial treatment of IVIG and or corticosteroids is important to prevent disease progression. The goal of treatment is to suppress the severe hyperinflammation. A second aim is to kill the pathogen-infected APCs to remove the stimulus for the ineffective activation of the cytotoxic cells. Hyperinflammation caused by hypercytokinemia can be suppressed by corticosteroids. Dexamethasone is preferred since it crosses the blood brain barrier better. Cyclosporin is used to inhibit activation of T-lymphocytes. Etoposide is highly active in monocytic and histiocytic disease. According to the HLH-2004 protocol, initial therapy from weeks 1-8 is based on etoposide, dexamethasone and cyclosporine and in cases of CNS-reactivation, intrathecal therapy with methotrexate and prednisolone is recommended. In cases of reactivation triggered by infections, broad-spectrum antibiotics, antiviral therapy, and antifungal therapy should be considered as supportive measures. Survival for patients have dramatically improved.[6] Long-term outcomes of patients treated with HLH-94 trial indicate a 50-60% complete response to therapy and approximately 20% mortality within 6 months of diagnosis, from inadequate disease control. About 54% will experience long term survival.[19]

Most patients in the study were discharged (91%), with one mortality (9%) while undergoing IVIG treatment secondary to uncontrolled sepsis, DIC and pulmonary hemorrhage. Patients dying from complications due to infection have been reported in 40-60%.[1] Sepsis-induced thrombocytopenia was related to peripheral consumption such as DIC.[18]

As our study could not document primary HLH, all our cases were labeled as secondary HLH. These were due to infections like EBV, dengue, sepsis, malignancy such as ALL, autoimmune disease like JIA, and hypersensitivity reaction. HLH should be considered when fever is continuing beyond expected, as in patients who continue to be febrile in spite of appropriate antibiotic use, or fever beyond the usual course of illness like dengue. HLH should be considered when cytopenia evolves during the hospital course or when splenomegaly appears, when none was present earlier. HLH may lead to morbid cytopenias and DIC, and treatment with IVIG and or dexamethasone is often only considered when the diagnosis has been made. It is important for clinicians to have a high index of suspicion as mild disease can evolve to a life threatening event. The results and analysis from this study have potential societal benefits, which will directly or indirectly benefit the participants through health systems delivery strengthening or improvements in implementation or policy change.

The limitation of this study was that other diagnostic tests were not available in our institution, such as CD 25, NK cell activity and hemophagocytosis in bone marrow, hence data for some patients may have been lacking.

CONCLUSION

During a ten year period, eleven children with HLH were seen with ages of less than five years old (46%) and ten to fifteen (36%), with a male to female ratio of 4.5:1. All presented with fever followed by hepatomegaly and splenomegaly on physical examination. All subjects fulfilled five criteria for HLH such as fever, splenomegaly, two cell cytopenia - either anemia, neutropenia, or thrombocytopenia; hyperferritinemia, hypofibrinogemia and or hypertriglyceridemia. Other laboratory findings were elevated ALT, CRP, AST, alkaline phosphatase, and hyponatremia. EBV and dengue were the most common etiologies, and the most common complications were pneumonia and sepsis. All but one patient was responsive to either dexamethasone and or IVIG and chemotherapy. The median hospital stay was 17 days with one mortality.

RECOMMENDATIONS

A larger sample is recommended for future researchers to compare clinical profile and outcomes of pediatric HLH. Future researchers may include ethnicity and race as a factor to examine if this plays a role in the outcome of the disease. A multi-institutional study is recommended as there may be variations in terms of recognition and management of the disease.

REFERENCES

1. 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 [Internet]. 2007 Feb [cited 2019 Feb 22];48(2); 124-31. Available from: https://pubmed.ncbi.nlm.nih.gov/16937360/ DOI: 10.1002/pbc.21039.
2. Bode SF, Lehmberg K, Maul-Pavicic A, Vraetz T, Janka G, Stadt UZ, et al. Recent advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis . Arthritis Res Ther [Internet].. 2012 Jun 8 [cited 2019 Feb 22];14(3):213. Available from: https://pubmed.ncbi.nlm.nih.gov/22682420/ DOI: 10.1186/ar3843.
3. Jin YK, Xie ZD, Yang S, Lu G, Shen KL. Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis: a retrospective study of 78 pediatric cases in mainland of China. Chin Med J (Engl) [Internet]. 2010 Jun [cited 2019 Feb 22];123(11):1426-30. Available from: https://pubmed.ncbi.nlm.nih.gov/20819601/
4. Kliegman, RM, Stanton BF, St. Geme JW III, Schor, NF. Nelson's textbook of pediatrics. 20th edition. Philadelphia: Elsevier Publications; 2016. p. 1144, 1160, 1630-1631
5. Bergsten E, Horne A, Aricó M, Astigarraga I, Egeler RM, Filipovich AH, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood [Internet]. 2017 Dec 21 [cited 2019 Feb 22];130(25):2728-2738. Available from: https://pubmed.ncbi.nlm.nih.gov/28935695/ DOI: 10.1182/blood-2017-06-788349.
6. Villaluz MM, Manahan H, Gepte B, Robles JA. Hemophagocytic lymphohistiocytosis: A rare case of primary CNS involvement in a Filipino child. The Philippine Journal of Neurology. 2007 Jan-Jun, 11(1):51-56.
7. Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into pathophysiology and practical guidelines. Biol Blood Marrow Transplant [Internet]. 2010 Jan [cited 2019 Feb 22];16(1 Suppl):S82-9. Available from: https://pubmed.ncbi.nlm.nih.gov/19932759/ DOI: 10.1016/j.bbmt.2009.11.014.
8. Zoller EE, Lykens JE, Terrell CE, Aliberti J, Filipovich AH, Henson PM, et al. Hemophagocytosis causes a consumptive anemia of inflammation. J Exp Med [Internet]. 2011 Jun 6 [cited 2019 Feb 22];208(6):1203-14. Available from: https://pubmed.ncbi.nlm.nih.gov/21624938/ DOI: 10.1084/jem.20102538.
9. Niece JA, Rogers ZR, Ahmad N, Langevin AM, McClain KL. Hemophagocytic lymphohistiocytosis in Texas: observations on ethnicity and race. Pediatr Blood Cancer [Internet]. 2010 Mar [cited 2019 Feb 22];54(3):424-8. Available from: https://pubmed.ncbi.nlm.nih.gov/19953651/ DOI: 10.1002/pbc.22359.
10. Xu XJ, Wang HS, Ju XL, Xiao PF, Xiao Y, Xue HM, et al. Histiocytosis Study Group of the Chinese Pediatric Society. Clinical presentation and outcome of pediatric patients with hemophagocytic lymphohistiocytosis in China: A retrospective multicenter study. Pediatr Blood Cancer [Internet]. 2017 Apr [cited 2019 Feb 22];64(4). Available from: https://pubmed.ncbi.nlm.nih.gov/27781387/ DOI: 10.1002/pbc.26264.
11. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. J Blood Med [Internet]. 2014 Jun 12 [cited 2019 Mar 10];5:69-86. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4062561/ DOI: 10.2147/JBM.S46255.
12. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med [Internet]. 2012 [cited 2019 Mar 10];63:233-46. Available from: https://pubmed.ncbi.nlm.nih.gov/22248322/ DOI: 10.1146/annurev-med-041610-134208.
13. Janka G. Hemophagocytic lymphohistiocytosis: when the immune system runs amok. Klin Padiatr [Internet]. 2009 Sep [cited 2019 Nov 22];221(5):278-85. Available from: https://pubmed.ncbi.nlm.nih.gov/19707989/ DOI: 10.1055/s-0029-1237386.
14. Ishii E. Hemophagocytic Lymphohistiocytosis in Children: Pathogenesis and Treatment. Front Pediatr [Internet]. 2016 May 13 [cited 2019 Feb 22];4:47. Available from: https://pubmed.ncbi.nlm.nih.gov/27242976/ DOI: 10.3389/fped.2016.00047.
15. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, et al. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol [Internet]. 2007 Jul [cited 2019 Nov 22];86(1):58-65. Available from: https://pubmed.ncbi.nlm.nih.gov/17675268/ DOI: 10.1532/IJH97.07012.
16. Pal P, Giri PP, Ramanan AV. Dengue associated hemophagocytic lymphohistiocytosis: a case series. Indian Pediatr [Internet]. 2014 Jun [cited 2019 Nov 22];51(6):496-7. Available from: https://pubmed.ncbi.nlm.nih.gov/24986293/
17. Tsuge M, Miyamoto M, Miyawaki R, Kondo Y, Tsukahara H. Hemophagocytic lymphohistiocytosis complicating invasive pneumococcal disease: a pediatric case report. BMC Pediatr [Internet]. 2020 Jan 13 [cited 2021 Apr 9]. 20:15. Available from: https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-020-1915-7 DOI:10.1186/s12887-020-1915-7.

18. Buyse S, Teixeira L, Galicier L, Mariotte E, Lemiale V, Seguin A, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. Intensive Care Med [Internet]. 2010 Oct [cited 2019 Nov 22];36(10):1695-702. Available from: https://pubmed.ncbi.nlm.nih.gov/20532477/ DOI: 10.1007/s00134-010-1936-z.
19. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, et al. Histiocyte Society. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood [Internet]. 2011 Oct 27 [cited 2019 Nov 22];118(17):4577-84. Available from: https://pubmed.ncbi.nlm.nih.gov/21900192/ DOI: 10.1182/blood-2011-06-356261.
20. Sung L, King SM, Carcao M, Trebo M, Weitzman SS. Adverse outcomes in primary hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol [Internet]. 2002 Oct [cited 2019 Feb 22]; 24(7):550-4. Available from: https://pubmed.ncbi.nlm.nih.gov/12368693/ DOI: 10.1097/00043426-200210000-00011.
21. Smitherman HF, Macias CG. Febrile infant (younger than 90 days of age): Definition of fever [Internet]. 2017 December [cited 2019 March 10]. Available from https://www.uptodate.com/contents/febrile-infant-younger-than-90-days-of-age-definition-offever?search=fever&source=search_result&selectedTitle=3~150&usage+type =default&display_rank=3#H2
22. McClain KL. Approach to a Child with Enlarged Spleen [Internet]. 2017 December [cited 2019 March 10]. Available from https://www.uptodate.com/contents/approach-to-the-child-with-an-enlarged-spleen?search=enlarged+spleen+ultrasound&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H187898580
23. Stanley FL. Reference Intervals for Laboratory Tests and Procedures. In Kliegman RM, Stanton BF, St. Geme JW III, Schor NF. Nelson's textbook of pediatrics. 20th edition. Philadephia: Elsevier Publications. p. 1160, 1629, 1922

APPENDIX A – OPERATIONAL DEFINITIONS

1. Hemophagocytic lymphohistiocytosis (HLH) – characterized by abnormal proliferation of macrophages associated with hypercytokinemia.[20]
   1a. Primary HLH – rare autosomal disorder, occurring before the first year of life reported up to age 8.[20]
   1b. Secondary HLH – there is an acquired cause, which is a result of a strong immunologic activation, commonly seen in an immunocompromised host. Common triggers are severe infection, malignancy and inflammatory disorders.[5]
2. Criteria for diagnosis of HLH (either 2a. or 2b. is fulfilled)[1]
   2a. Molecular diagnosis consistent with HLH
   2b. Diagnostic criteria for HLH (5 out of 8 criteria)
   i. Fever – temperature of 38C and above measured via rectal or axilla [21]
   ii. Splenomegaly – a palpable splenic edge more than 2cm below the left costal margin and on imaging with length above the upper limits of normal age, measured from the dome to tip on ultrasound [22]

Age	Measurement
12 months	7 cm
6 years old	9.5 cm
12 years old	11.5 cm
≥15 years old	Girls – 12 cm Boys – 13 cm

   iii. Cytopenias (affecting ≥2 lineages in the peripheral blood)
   Hemoglobin <90 g/L (infants <4 weeks, hemoglobin <100 g/L)
   Platelets < 100000/μl
   Neutrophils < 1000 /μl
   iv. Hypertryglyceridemia and/or hypofibrigonemia
   Fasting triglycerides ≥ 265 mg/dL
   Fibrinogen ≤ 1.5 g/L
   v. Hemophagocytosis in bone marrow or spleen or lymph nodes
   vi. Low or absent NK-cell activity
   vii. Ferritin ≥ 500 μg/L
   viii. Soluble CD25 ≥ 2400 U/L
3. Hepatomegaly – palpable liver edge more than 2 cm below the right costal margin.[4]
4. Laboratory Examinations
   4a. Alanine aminotransferase (ALT, SGPT) – reference for normal values according to age are as follows:[23]
   i. 1 to 12 months – 12 – 45 U/L
   ii. 1 to 19 years old – 5 – 45 U/L
   4b. Aspartate aminotransferase (AST, SGOT) – reference for normal values according to age are as follows:[23]
   i. 1 to 3 years old – 20 – 60 U/L
   ii. 3 to 9 years old – 15 – 50 U/L
   iii. 10 to 15 years old – 10 – 40 U/L
   iv. 16 to 18 years old (Male) – 15 – 45 U/L
   v. 16 to 18 years old (Female) – 5 – 30 U/L
   4c. Alkaline phosphatase – reference for normal values according to age are as follows:[23]
   i. 1 to 9 years old – 145-250 U/L
   ii. 10 to 11 years old – 140-560 U/L
   iii. 12 to 13 years old (Male) – 200-495 U/L
   iv. 12 to 13 years old (Female) – 105-420 U/L
   v. 14 to 15 years old (Male) – 130-525 U/L
   vi. 14 to 15 years old (Female) – 130-525 U/L
   vii. 16 to 19 years old (Male) – 65-260 U/L
   viii. 16 to 19 years old (Female) – 50-130 U/L
   4d. C-reactive protein - reference for normal values according to age are as follows:[23]
   i. 91 days to 12 months (Male) – 0.8-11.2 mg/L
   ii. 91 days to 12 months (Female) – 0.5-7.9 mg/L
   iii. 13 months to 3 years old (Male) – 0.8-11.2 mg/L
   iv. 13 months to 3 years old (Female) – 0.5-7.9 mg/L
   v. 4 to 10 years old (Male) – 0.6-7.9 mg/L
   vi. 4 to 10 years old (Female) – 0.5-10 mg/L
   vii. 11 to 14 years old (Male) – 0.8-7.6 mg/L
   viii. 11 to 14 years old (Female) – 0.6-8.1 mg/L
   ix. 15 to 18 years old (Male) – 0.4-7.9 mg/L
   x. 15 to 18 years old (Female) – 0.6-7.9 mg/L