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Thesis · January 2019

DOI: 10.24327/ijrsr.2019.1001.3033

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International Journal of Recent Scientific Research
Vol. 10, Issue, 01(B), pp. 30316-30320, January, 2019

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research article

A STUDY ON THE AETIOLOGY AND OUTCOME OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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DOI: http://dx.doi.org/10.24327/ijrsr.2019.1001.3033

ARTICLE INFO

Article History:
Received 12th October, 2018
Received in revised form 23rd November, 2018
Accepted 7th December, 2018
Published online 28th January, 2019

Key Words:

Hemophagocytic lymphohistiocytosis, Macrophage Activation Syndrome, Infection, Autoimmune, Malignancy

ABSTRACT

Purpose: To study the etiology & outcome of patients with hemophagocytic lymphohistiocytosis (HLH) admitted in the medical male & female wards of Govt. Medical College, Kozhikode, Kerala. **Methods**: We report 27 cases of HLH in patients > 13 years admitted over a period of 1.5 years at Govt. Medical College, Kozhikode, a tertiary care centre in South India. **Results**: The most common age group was 25-50 years. 21 were males. Mean duration of symptoms was 11 days (7-21 days). Common presenting symptoms were fever, anorexia, jaundice, breathlessness and altered sensorium. Common physical findings were pallor, icterus, splenomegaly, hepatomegaly, tachycardia and tachypnea. Laboratory findings were variable cytopenia with pancytopenia in 77.8% cases, hyperferritenimia (100%), hypertriglyceridimia (100%) and elevated liver enzymes (70.3%). Underlying cause could be detected in 17 patients with infectious etiolgy in 10, autoimmune in 5 & malignancy in 2. 15 patients (56%) expired at 1 week of treatment initiation. Mortality was high in patients with unidentified etiology. **Conclusions**: Infection was the most common cause followed by auto immune in this study. A low threshold for suspicion, proper evaluation for any secondary cause and early treatment can improve outcome in patients with HLH.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory disorder which is related to macrophage activation and usually presents as prolonged fever and sepsis like syndrome[1]. It is classified as primary or secondary. Primary HLH is related to inherited genetic mutations involving granule mediated cytotoxicity, killing of infected cells and termination of immunologic response. It is commonly seen in infancy[2]. Secondary HLH is seen in infections, malignancy, autoimmune disorders, immunosuppression or after organ transplantation. HLH seen in autoimmune disorders is also called macrophage activation syndrome (MAS)[3].

HLH is not a single disease, but a clinical syndrome which is associated with a number of underlying conditions leading to the similar hyperinflammatory phenotype characterized by hypercytokinemia and excessive activation of lymphocytes and macrophages.

Due to increase in investigative work up and new diagnostic criteria by Histiocyte Society, more cases of HLH are now being diagnosed. The mortality rate of this condition is as high as 50 % without adequate treatment[5].

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MATERIALS AND METHODS

The study was conducted in the medical male and female wards of Department of General Medicine, Govt. Medical College, Kozhikode, Kerala, India and commenced in January 2016 and was completed in June 2017 for a period of 18 months. The patients presenting to the Department of General Medicine, Govt. Medical College, Kozhikode who were newly diagnosed to have hemophagocytic syndrome within the study period. Patients aged > 13 years satisfying the diagnostic criteria of HLH were included in the study

Diagnostic Criteria (by the Histiocyte society, America)[4]

Any 5 of following 8

1. Fever > 38.5 °c for > 7 days
2. Splenomegaly ≥ 3cm below left costal margin
3. Bicytopenia-any of
4. Absolute Neutrophil Count < 1000
5. Platelet < 1 lakh
6. Hemoglobin < 9 g/dl
7. Hypofibrinogenemia-< 1.5g/l or hypertriglyceridemia-levels > 265mg/dl

8. Hemophagocytosis in tissue demonstration
9. Decreased/absent NK cell activity
10. Ferritin > 500 ug/l
11. Soluble CD25 > 2400 U/m

Patients < 13 years, patients not giving consent, patients not satisfying diagnostic criteria and patients with chronic liver disease and other viral and toxin mediated hepatitis were excluded. A total of 27 patients were studied. Data collection was done by direct interview and questionnaires. Data regarding histopathological examination are collected from Department of Pathology, Govt. Medical College, Kozhikode. The following primary investigations for diagnosis of HLH were done in all patients - Complete haemogram including ESR (falling or low ESR as a marker of hypofibrinogenemia)[6], peripheral smear, bone marrow aspiration, imprint and trephine biopsy, serum ferritin, fasting triglycerides, transaminases. Other supplementary investigations like random blood sugar, serum electrolytes, blood urea, serum creatinine, LDH, coagulation studies, ECG, Chest X-Ray, etc were also done in all subjects. Investigations like HBsAg, anti HCV, HIV , ANA, anti dsDNA, rheumatoid factor, lymph node biopsy, CSF study, tumor markers, cultures of blood, urine, sputum and bone marrow were done when there is an indication based on clinical judgement. This was an observational cross sectional study done for primary objective. Follow up study was done for secondary objective. Patients satisfying criteria for HLH are evaluated further with detailed history, thorough physical examination and investigated further to identify etiology and assess outcome 1 week after commencing treatment. Clinical outcome at 1 week is assessed by clinical improvement-improvement in symptoms and signs, improving counts-ANC >1000, platelet > 1 lakh cells/cu mm, Hb > 9 g/dl, improving liver function tests-fall in transaminases, correction of PT INR and aPTT to normal and falling ferritin to < 500 ug/l. Data was entered in Excel and all analysis are performed using SPSS software.

RESULTS AND DISCUSSION

HLH is not an uncommon entity in India, but it is under diagnosed and under reported mostly in adolescents and adult population. Incidence and age distribution of HLH are not well known. Threshold of suspicion for this entity is high due to relative unawareness of this condition. Unavailability of diagnostic facilities is a common limitation in workup for HLH. HLH should always be considered in any patient presenting with prolonged fever and cytopenia. Currently HLH-2004 diagnostic guidelines are used for diagnosis of HLH.

Demographic profile

27 patients were diagnosed with Hemophagocytic syndrome in a period of one and half years using the 2004 HLH diagnostic criteria. All these patients fulfilled at least five fundamental criteria of HLH at the time of diagnosis. Genetic testing, NK cell activity and soluble CD25 receptor assay could not be done in any patient due to ethical concerns. In a study conducted in JIPMER, by Shailendra Prasad verma and his colleagues, 8 patients with HLH were analysed retrospectively over a period of two years[7]. In a study conducted by Shabbir m, 18 patients were studied over a period of 5 years[8]. Most of the studies worldwide on this entity include low sample size. The most common age group is between 25 and 50(59%). The age ranged from 13 to 60 years. 21(78 %) were males. Male to female ratio was 3.5: 1. This was similar to the study conducted in Mayo clinic by Sameer A Parikh and his colleagues where 68% were males[9]. In JIPMER study, male female ratio was 3:5. There was no family history of rheumatic disease, consanguineous marriage, malignancy or death of siblings in any of our patients.

Clinical profile

The most common symptom was fever. All patients had fever. Range of fever duration was 7 days to 21 days with a mean of 11 days. This is similar to the JIPMER study wherein all patients had fever. Fever was commonly associated with anorexia (48%), vomiting (48%), breathlessness (41%), altered sensorium (41%), pedal edema (33%), arthralgia (26%), jaundice (22%), headache(22%), productive cough(22%), etc. Altered sensorium at beginning of presentation was present in 11 patients (41%)**.** The most common finding on examination was pallor (93%). This is similar to the JIPMER study where 7 out of 8 had pallor (87 %). Hepatomegaly was present in 23 (85.2%), splenomegaly was present in 24(88.9%) and pleural effusion was present in 8 (29.6%). Icterus was present in 7(26%) and ascites was present in 3 (11.1 %). All the serous effusions were transudative in nature.

Investigative profile

Severe anemia (Hb < 5 g/dl) was present in 2(7.4 %), severe neutropenia (ANC <500 cells/mm^3) in 4 (14.8%) and severe thrombocytopenia (platelet < 10000 cells/mm^3) in 5(18.5%) Pancytopenia was present in 21 (77.78 %). Bicytopenia was present in 6 (22.22%). The mean ESR at initial presentation was 60.74 mm (range 43-88) which decreased to 10.8 mm (range 2-15) at time of diagnosis of HLH. A low or normal ESR or falling ESR in the presence of active inflammation is considered as an indirect marker of hypofibrinogenemia. Bone marrow evidence of hemophagocytosis was present in 22 (81.5 %) (figure - 1,2).

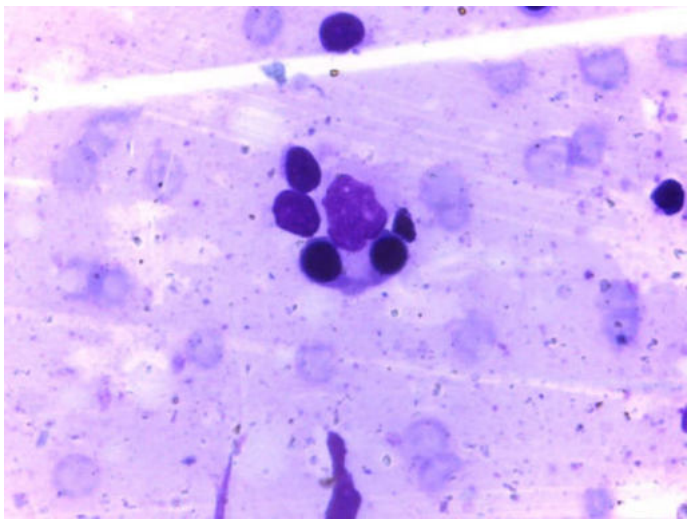

Figure 1 Hemophagocytosis in bone marrow in a patient with adult onset Stills disease

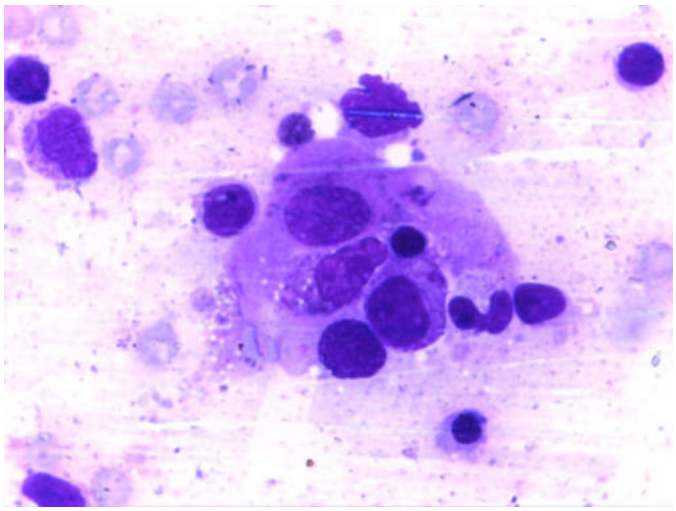

Figure 2 Hemophagocytosis in bone marrow in a patient with falciparum malaria

7 had evidence of more than 5 hemophagocytes in bone marrow. Bone marrow examination could not be done in two due to lack of willingness. Peripheral smear did not show evidence of hemolysis in any of the patient. All had ferritin more than 500 ng. Extreme elevation of serum ferritin (> 10000 ng) was seen in 5 (18.5 %). Hyperferritinemia, hypertriglyceridemia, elevated lactate dehydrogenase and coagulopathy (elevated PT INR and APTT) were uniformly present in all. Degree of hyperferritinemia and number of bone marrow hemophagocytes did not have significant correlation. Elevated transaminases was present in 19(70.3 %). One patient with viral hepatitis A with fulminant hepatic failure had very high ALT. Hyperbilirubinemia was present in 14 (51.8 %) and hypoalbuminemia and hyponatremia were present in 21 patients (77.78%). CSF study was done in 12 and among these, two had elevated CSF protein and none had pleocytosis. Elevated CSF protein had no significant correlation with altered sensorium at presentation. Investigations are shown in table 1 and 2. Table 3 shows trend in cell counts and ESR with disease progression.

Table 1 Lab Parameters – 1

Lab Parameters	Mean	SD	MIN	MAX
Hemoglobin (g/dl)	7.85	1.93	5	14
Total Leucocyte Count (cells/mm^3)	2800	1740	700	6700
Neutrophil Count (cells/mm^3)	910	316	300	1400
Platelet Count (cells/mm^3)	34555	38652	3000	149000
S Ferritin (ng/ml)	6097.66	5214	890	20000
S Triglycerides (mg/dl)	307.7	50.2	268	517
ESR (mm @ end of 1 hour)	10.8	3.45	2	15
S LDH (mg/dl)	1849.18	1011.1	874	4575
ALT (IU)	221.8	509.7	20	2674
S Sodium (meq/l)	130.5	7.2	114	147

Table 2 LAB Parameters - 2

Parameter	Number	Percentage
Pancytopenia	21	77.78
Bicytopenia	6	22.22
Bone marrow hemophagocytosis	22	81.5
Hyperferritinemia	27	100
Hypertriglyceridemia	27	100
Hyponatremia	21	77.78
Hypoalbuminemia	21	77.78
Elevated Transaminases	19	70.3
Elevated Ldh	27	100
Coagulopathy	27	100

Table 3 Trend in Cell Counts and ESR with Disease Progression

Parameter	Mean AT Onset of Illness	SD	Mean At Diagnosis of HLH	SD
HEMOGLOBIN (g/dl)	9.3	1.96	7.9	1.93
TOTAL WBC COUNT (cells/cu mm)	6615	2857	2800	1740
NEUTROPHIL COUNT (cells/cu mm)	4301	2556	909	316
PLATELET COUNT (cells/cu mm)	102148	72830	34555	38653
ERYTHROCYTE SEDIMENTATION RATE (mm at end of 1 hour)	60.7	13.7	10.8	3.4

Aetiology

Aetiology could be identified in 17 (62.9 %). Infection as aetiology was present in 10 (37%). Tuberculous aetiology was present in 4 (14.8 %). Among tuberculosis one had past history of pulmonary tuberculosis, treated and cured. Staphylococcal sepsis was seen in 2 among which one had primary bronchopneumonia and other had intravenous cannula site infection. EBV Ig M was done in 13(48%) but no positive serology was obtained in any. In the JIPMER study, one patient was diagnosed with EBV infection. None of our patients were positive for HIV, HBsAg or Anti HCV Autoimmune cause was found in 5 (18.5 %). ANA was positive in 2 and anti ds DNA was positive in both, diagnosed as SLE by SLICC criteria[10]. Lupus anticoagulant was positive in one patient who was treated as APLA syndrome. 2 were diagnosed as Stills disease by Yamaguchi criteria[11]. 2 had malignancies. One had adenocarcinoma stomach with supraclavicular lymph node metastasis. Other had T cell lymphoblastic leukemia/ lymphoma. Both were started on chemotherapy. A secondary cause could not be identified in 10 patients. However genetic study was not done in any of our patient. Therefore, whether these could be having underlying genetic cause is not known. In the JIPMER study, aetiology was not identified among 2 out of 8. Genetic studies were not conducted in that study also.

Among pulmonary tuberculosis, one was sputum positive. Among extrapulmonary tuberculosis, one had evidence of granulomatous lymphadenitis with caseous necrosis and other was treated with ATT empirically on clinical grounds. Among staphylococcus aureus sepsis, one had primary pneumonia and other had cannula site thrombophlebitis. Distribution of etiology is given in figure 3 and details of Infectious etiology are given in table 4.

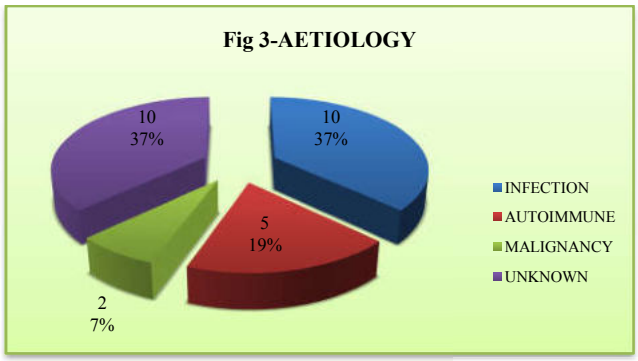

Table 4 Infectious Aetiology

Infection	Number	Percentage (among infections)
Staphylococcus Aureus Sepsis	2	20
Escherichia Coli Uti	1	10
Salmonella Sepsis	1	10
Pulmonary Tuberculosis	2	20
Extra Pulmonary Tuberculosis	2	20
Falciparum Malaria	1	10
Hepatitis A	1	10

Treatment, outcome at 1 week and mortality determinants

Steroids were given in all except one who had staphylococcus aureus sepsis (secondary to thrombophlebitis). HLH treatment protocol was followed in 4 (14.8 %)[12]. Among these 4, one had falciparum malaria whereas other 3 had aetiology unidentified. Intrathecal methotrexate was not given to any patient. 12 (44.4 %) survived at 1 week. However, only one who had been treated with standard HLH protocol had survived at 1 week. Aetiology in that patient was cerebral malaria, but he expired after second week of treatment. In JIPMER study, 6 out of 8 were given standard HLH protocol based treatment and 5 of them survived. 9 patients who had altered sensorium at presentation were expired at 1 week compared to 6 who didn't have. This had statistical significance (p==0.023). Mortality at 1 week was higher in patients with initial platelet count less than 50000 but did not have statistical significance(p=0.287). In a study conducted by Dhote R, low platelet count had significant association with mortality[13]. Severity of anemia and neutropenia, degree of fall in ESR and severity of hyperferritinemia also did not have significant association with outcome. Among those who survived at 1 week the mean hemoglobin was 9.67, the mean total count was 4400, the mean neutrophil count was1340, the mean platelet count was 125333 and the mean ferittin was 1158.4. The mortality at 1 week in patient group with unidentified aetiology was 100% with statistical significance (p=0.003). Lab parameters at one week is given in table 5 and comparison of lab parameters among survived and expired are given in table 6. Aetiology and outcome at one week is provided in figure-4

Table 5 LAB Parameters AT 1 Week

LAB PARAMETER	MEAN	SD
HEMOGLOBIN (g/dl)	9.67	0.86
Total Leucocyte Count (cells/mm^3)	4400	1585
NEUTROPHIL COUNT (cells/mm^3)	1340	204
PLATELET COUNT (cells/mm^3)	125333	43066
S FERRITIN (ng/ml)	1158	781
ALT (U/L)	38	16

Table 6 Comparison between survived and expired

Lab Parameter	Survived (mean)	Expired (mean)	P value
HEMOGLOBIN (g/dl)	7.08	8.48	0.058
TOTAL WBC COUNT (cells/mm^3)	3400	2320	0.11
NEUTROPHIL COUNT(cells/mm^3)	1030	813	0.076
PLATELET COUNT (cells/mm^3)	49583	22533	0.07
ESR (mm @ end of 1 hour)	10.75	10.86	0.43
FERRITIN (ng/ml)	5649	6455	0.69
TAG (g/dl)	296	317	0.28
ALT (U/L)	99	320	0.26
LDH (U/L)	1590	2057	0.240

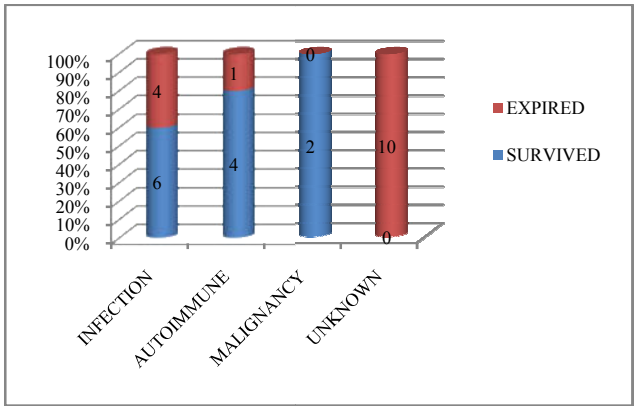

Figure 4 Aetiology Vs outcome at 1 week

Among autoimmune aetiology, one patient with APLA syndrome didn't survive to 1 week. Among infectious aetiology, mortality at 1 week occured in one patient with staphylococcal sepsis(secondary to thrombophlebitis), one with viral hepatitis A and two who had tuberculosis (sputum negative pulmonary and extrapulmonary) and started on ATT (figure-5).

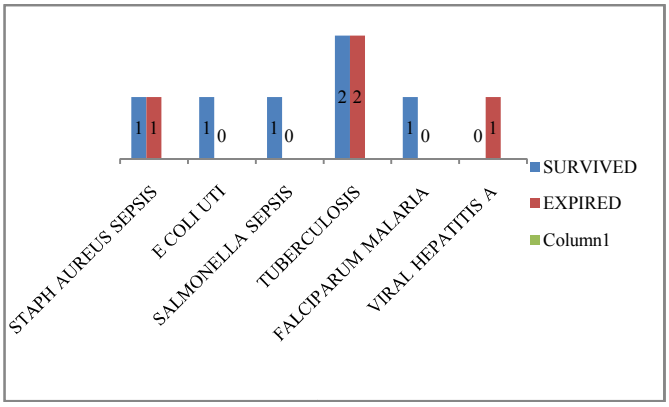

Figure 5 Mortality in infection related HLH

A study of 34 adult HLH patients (22 males) was reported from Japan. Fourteen survived (median age 30 years) and 20 died (median age 54 years). Hematologic malignancies or viral illnesses were present in 14 (seven died of HLH) and no underlying illness in 20 (13 died of HLH).

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How to cite this article:

Adarsh. A K *et al*.2019, A Study on The Aetiology and Outcome of Hemophagocytic Lymphohistiocytosis. *Int J Recent Sci Res.* 10(01), pp. 30316-30320. DOI: http://dx.doi.org/10.24327/ijrsr.2019.1001.3033

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