

## Hemophagocytic Syndrome: Experience in a tertiary care centre

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### Abstract

**Introduction:** Hemophagocytic syndrome also known as Hemophagocytic Lymphohistiocytosis (HLH) is a potentially fatal hyperinflammatory condition. It can be primary or a secondary disorder associated with a variety of underlying conditions. These disorders feature severe cytopenias due to uncontrolled hemophagocytosis and clinical symptoms result from disordered immune regulation and cytokine storm.

**Materials and Methods:** The present study was done at the tertiary care centre attached to University Medical College in western India. Forty five patients with cytopenias who were suspected to have secondary HLH were included in this study. Clinical details and routine investigations, tests necessary to diagnose HLH i.e. Ferritin, Triglyceride, LDH, Fibrinogen levels were done. Bone marrow aspirate in these patients showed evidence of hemophagocytosis. Statistical analysis was done using the appropriate software and statistical tests.

**Results:** Infection was the commonest cause associated with secondary HLH in our study. 95.5% patients had anaemia while 42.2% patients had fever along with other clinical manifestations. Elevated Serum Ferritin levels were found in 55.5% patients. 82.1% and 63.0% patients had elevated Lactate Dehydrogenase and elevated triglycerides levels respectively while only 35.6% patients had low fibrinogen levels. Higher levels of ferritin were associated with severe cytopenias and with poor outcome of the patients. PT and APTT were also deranged in a significant proportion of patients. We have also observed raised APTT values correlating with abnormal ferritin levels and cytopenias in our study. This could be because most of these cases were associated with sepsis. We found significant association of elevated serum Ferritin, Triglyceride and LDH levels with HLH.

**Conclusion:** Hemophagocytic syndromes should be considered in unexplained cytopenias. A bone marrow aspiration or organ biopsy revealing hemophagocytosis along with Serum Ferritin, Triglyceride, fibrinogen and LDH levels are helpful to confirm the diagnosis. Overall survival rate of Hemophagocytic syndrome is low without treatment. Early diagnosis and prompt treatment helps in improved outcome.

**Keywords:** Hemophagocytic syndrome, Cytopenias, Ferritin.

### Introduction

A highly stimulated but ineffective immune response leads to a potentially fatal hyperinflammatory condition called as Hemophagocytic syndrome also known as Hemophagocytic lymphohistiocytosis (HLH).<sup>1</sup> It can be a primary or a secondary disorder associated with a variety of causes. These disorders feature severe cytopenias due to uncontrolled hemophagocytosis. Other abnormal laboratory values and clinical symptoms result from disordered immune regulation and cytokine storm.<sup>2</sup>

The term primary HLH refers to an underlying genetic abnormality causing the disorder. This is an autosomal recessive disease involves mutations in various genes which are responsible for encoding proteins involved in exocytosis of granules from cytotoxic T lymphocytes and Natural Killer cells.<sup>3</sup>

Acquired HLH, a secondary variant of the syndrome, is said to be associated with severe infections. A variety of microorganisms including viruses and bacteria can cause HLH. Other causes are malignancies, rheumatologic disorders, and some metabolic diseases.<sup>3</sup>

Clinical manifestations of HLH such as fever, hepatosplenomegaly, jaundice, cytopenias, CNS abnormalities and laboratory findings of hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia are due to Hyper activation of CD8T lymphocytes and macrophages, Proliferation, ectopic migration, and infiltration of these

cells into various organs and Hypercytokinemia with persistently elevated levels of multiple proinflammatory cytokines, resulting in progressive organ dysfunction that may lead to death.<sup>4</sup>

Ferritin levels have a significant role in determining the prevalence of the disease and thereby affect the prognosis in a remarkable manner. The maximum level of ferritin are seen in patients with Hemophagocytic syndromes followed by autoimmune diseases, viral infections and bacterial infections.<sup>5</sup>

Infection is described as a major trigger of HLH development, and Epstein-Barr virus (EBV) has been described as the dominant pathogen.<sup>6,7</sup> Without effective treatment, many HLH patients die within 3 months. Treatment of HLH, whether in the familial HLH or the secondary HLH form, has significantly improved due to early introduction of immunochemotherapy.<sup>8,9</sup>

Therefore an early diagnosis of HLH and a timely initiation of effective treatment are crucial for improving the prognosis of HLH patients. A good understanding of the clinical features and hematological findings of HLH would be very helpful to clinicians for prompt diagnosis and effective treatment.

Hence the present study was done at our tertiary care centre to correlate the clinical, hematological and biochemical findings in patients with hemophagocytic syndromes.

**Materials and Methods**

This was a prospective study conducted in a tertiary care hospital attached to University medical college for two years from August 2016 to July 2018. Forty five patients presented with cytopenias and/or bone marrow showing hemophagocytosis were included in this study. Approval from the Institutional Ethical Committee was obtained. Informed written consent was obtained from the patients and parent/guardian for paediatric patients. Samples were collected in EDTA, vacutainer for complete blood counts, 3.2% Sodium Citrate vacutainer for PT, APTT, fibrinogen levels and and in plain vacutainer for Ferritin, Triglyceride and LDH levels. The morphological and etiological findings were correlated in order to elucidate causative factors and related to the clinical presentation.

**Statistical Analysis**

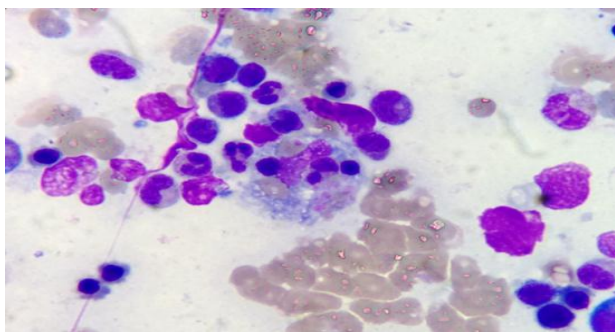
Comparison among the study groups was done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student ‘t’ test and Chi-Square test. ‘p’ value less than 0.05 was taken as significant.

**Results**

Forty five patients who had cytopenias were included in the study. These patients showed evidence of Hemophagocytosis in the marrow (Fig. 1). Additional tests to confirm the diagnosis of HLH such as Ferritin, Triglyceride, Fibrinogen along with LDH, PT and APTT were carried out in these patients.

In the present study, majority of the patients (20.4%) were in the age group of 31-40 years. The mean age of the patients was 35.08 ± 21.75 years. There were 24(53.3%) male patients in the group while 21 female patients constituted 46.7% of the study group. The mean age of male patients was 36.17 ± 23.71 years while the mean age of female patients was 34.4 ± 18.76 years.

Nearly all patients (95.5%) had pallor 42.2% patients had Fever. Renal impairment was seen in 22.2% patients. Other clinical manifestations were Hepatosplenomegaly, Early fatigue on exertion and ascites (Table 1). Infection was the commonest underlying disorder followed by malignancies resulting in HLH.



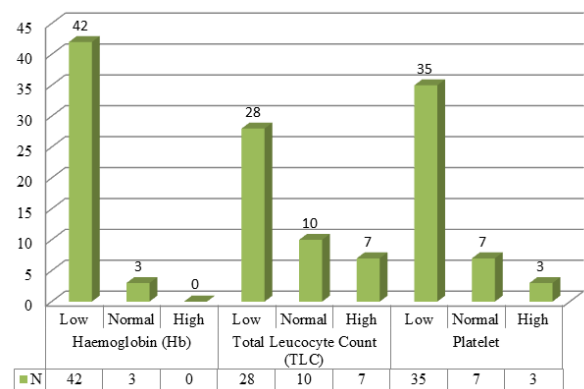
**Fig. 1:** Bone marrow aspirate showing hemophagocytosis (Leishman-Giemsa stain 100x)

**Table 1:** Clinical manifestations of patients (n=45)

Clinical Manifestations	N	%
<b>Pallor</b>	43	95.5%
<b>Fever</b>	19	42.2%
<b>Renal Impairment</b>	10	22.2%
<b>Hepatosplenomegaly</b>	7	15.5%
<b>Early fatigue on exertion</b>	4	8.8%
<b>Ascites</b>	3	6.7%

**Haematological profile of the patients**

43 (95.5%) patients had anemia. 28 (62.2%) patients had low Total Leucocyte Count (TLC) count (<4,000 cells/cumm<sup>3</sup>) 35 (77.8%) patients had thrombocytopenia (platelet count <150,000/cumm<sup>3</sup>). (Fig. 2)



**Fig. 2:** Hematology profile of the patients (n=45)

**Biochemical Profile of the Patients**

The mean serum ferritin level in our study was 2535.79±592.61 ng/mL. Elevated Serum Ferritin levels were found in 25(55.5%) patients. 23(82.1%), 17(63.0%) patients had elevated Lactate Dehydrogenase (LDH, >500 U/L), elevated triglycerides (≥265 mg/dL) levels respectively while 16(35.6%) patients had low fibrinogen levels. PT and APTT were also deranged in a significant proportion of patients. (Table 2)

**Table 2:** Biochemical profile of patients (n=45)

Parameters	N	%
<b>Serum Ferritin</b>	Normal	20 44.5%
	High	25 55.5%
<b>LDH</b>	Normal	5 17.9%
	High	23 82.1%
<b>Triglycerides</b>	Normal	10 37.0%
	High	17 63.0%
<b>Fibrinogen</b>	Low	16 35.6%
	Normal	29 64.4%
<b>PT</b>	Normal	12 26.7%
	High	33 73.3%
<b>aPTT</b>	Normal	17 37.8%
	High	28 62.2%

## Discussion

HLH has a variable clinical spectrum, but patients with HLH typically presented with high fever, hepatosplenomegaly, cytopenia, coagulation abnormalities, pathologic evidence of hemophagocytosis, and fatal multiple organ failure.<sup>10</sup> Although the diagnostic and therapeutic guidelines for hereditary HLH have been developed and widely accepted, the causes of secondary (also referred to as “reactive”) HLH remain to be unraveled. The 103 adult patients in Li J et al<sup>11</sup> retrospective study were thought to have reactive HLH, secondary to a variety of underlying diseases. The spectrum of the underlying diseases is fairly broad, and is consistent with the results previously reported in the literature.<sup>12,13</sup>

The mean age of male patients in this study was  $36.17 \pm 23.71$  years while the mean age of female patients was  $34.4 \pm 18.76$  years. The difference in mean age of male and female patients was statistically not significant as per Student t-test ( $p > 0.05$ ). This is similar to the study by Momin M et al.<sup>14</sup> Li J et al<sup>11</sup> retrospective study found a total of 103 patients with HLH (54 males, 49 females) with a mean age  $39.2 \pm 17.7$ yr (range, 16–78yr).

Nearly all patients (95.5%) had pallor 42.2% patients had Fever. Renal impairment was seen in 22.2% patients. Other clinical manifestations were Hepatosplenomegaly, Early fatigue on exertion and ascites and clinical features associated with underlying disorders similar to the study by Momin M et al.<sup>14</sup> Chandra H et al<sup>15</sup> study evaluating hemophagocytosis on bone marrow aspirates and observed if there is any difference on bone marrow examination between HLH and non HLH cases showing hemophagocytosis reported infections followed by HLH being the most common cause which was also seen our study.

Li J et al<sup>11</sup> reported at the time of HLH diagnosis, cytopenia could be seen in almost all cases (101/103, 98.1%). Thrombocytopenia ( $<100 \times 10^9/L$ ), leukopenia ( $<4.0 \times 10^9/L$ ), and anemia ( $<90$  g/L) occurred in 86.4%, 77.7%, and 59.2% of cases, respectively. We found anaemia as the commonest haematological abnormality followed by thrombocytopenia and leucopenia.

Elevated serum Ferritin levels were found in 25(55.5%) patients. 23(82.1%) and 17(63.0%) patients had elevated Lactate Dehydrogenase (LDH) and elevated triglycerides levels respectively while 16(35.6%) patients had low fibrinogen levels. 33(73.3%) and 28(62.2%) patients had high Prothrombin time (PT) and high Activated Partial Thromboplastin Time (aPTT) respectively. These findings were consistent with the study of Zhang Z et al.<sup>16</sup>

It was observed in our study that increased serum ferritin and triglycerides levels had a significant association with Hemophagocytic syndromes. Similar observations were noted in the studies of Li J et al<sup>11</sup>, Kaito K et al<sup>17</sup> and Lin TF et al.<sup>18</sup> Higher levels of ferritin were associated with severe cytopenias and with poor outcome of the patients.

Hypofibrinogenemia was not a significant finding in our study probably because most of the cases were

associated with sepsis as the underlying cause and Fibrinogen is an acute phase reactant.

## Conclusion

Hemophagocytic syndrome is an uncommon but severe illness which can be primary or associated with a variety of infectious agents, as well as genetic, neoplastic, and autoimmune diseases. We have studied secondary HLH as it is a potentially fatal disease, with non specific signs and symptoms, and should be considered in any patient presenting with fever and pancytopenia, especially if they are immune compromised. Hemophagocytic syndromes have a broad spectrum of etiologies. The clinical features vary significantly and most patients progress to death. A bone marrow aspiration or organ biopsy revealing hemophagocytosis along with Serum Ferritin, Triglyceride and LDH levels are helpful to confirm the diagnosis.

The underlying cause is an important predictor of outcome, as is serum ferritin. The overall survival rate of Hemophagocytic syndrome is low after diagnosis, without treatment. Prompt treatment with corticosteroids, immunosuppressants and intravenous immunoglobulins helps in improved outcome of this disease.

## Acknowledgment

KP was responsible for collection and analysis of data, AN supervised the data analysis and prepared final manuscript. RN was responsible for designing the study, AJK did the critical review of the manuscript.

**Conflicts of interest:** None.

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