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RESEARCH

Clinical spectrum of primary hemophagocytic lymphohistiocytosis: experience of reference centers in Central and Southeast Anatolia

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease, with a high mortality if left untreated. In addition, the disease has unique diagnostic challenges. Therefore, despite the existing guidelines on management, current clinical practice data is informative on the course and outcome. Herein, a retrospective chart review study was conducted through the collaboration of six centers, located in central and southeastern Türkiye. The demographical data, laboratory results, and treatment outcomes were evaluated. Eighty-three patients were enrolled in the study. The mean age was 2 years, whereas the median age was 8 months with a range of a minimum of 1 week and a maximum of 12.6 years. Consanguineous marriage, history of sibling death, and familial history of similar disease were determined in 72.2% (n:60), 34.9% (n:29), and 39.8% (n:33) of the patients, respectively. The most common presentation was fever, followed by hepatosplenomegaly on admission. Disease-causing familial HLH variants were identified in 60.2% (n:50) of the patients. Hematopoietic stem cell transplantation (HSCT) was performed in 39.7% (n:33) of the cohort. The 2-year overall survival (OS) rate was 62.4% for the whole group. Comparing the patients who received HSCT and those who did not; the HSCT group had a 2-year OS of 84.7%, which was significantly better than patients who did not receive HSCT had a 2-year OS of 47.1% (p:0.001). Despite the improvement in HLH diagnostics and treatment options over the last decade, early death remains a leading problem for the survival of these patients. Therefore, appropriate assessment of the patients in experienced centers and HSCT are pivotal for better outcomes.

Keywords Hemophagocytic lymphohistiocytosis · Familial HLH · Hematopoietic stem cell transplantation · Overall survival

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome characterized by an uncontrolled activation and proliferation in macrophages, natural killer cells (NK), T cells, intense cytokine release, and hyperinflammation, increased phagocytic activity and tissue damage [1–3]. HLH is not a single disease, it is a clinical syndrome in which different conditions cause similar inflammatory responses. It can be familial or sporadic. Familial HLH is caused by genetic mutations that are inherited autosomal recessively and is also termed primary HLH. Sporadic forms of HLH arise in the course of infections, malignancies, autoimmune diseases, and metabolic diseases, which typically are classified as secondary HLH [1–5]. Clinically, HLH typically presents with unremitting fever, hepatosplenomegaly, and pancytopenia [1–6]. HLH has major diagnostic and therapeutic challenges, therefore proper diagnosis and treatment of familial HLH is frequently delayed since the clinical and laboratory findings are nonspecific [7, 8].

Establishing diagnostic and therapeutic guidelines, (HLH-94 and HLH-2004) has significantly improved the diagnosis of HLH and increased the survival in patients with HLH [9, 10]. According to diagnostic criteria published by The Histiocyte Society in HLH 2004 guidelines, the diagnosis

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is made by the establishment of a genetic mutation that is responsible for familial HLH development, or fulfillment of at least 5 of 8 clinical / laboratory findings [9, 10].

Even though a guide was provided for diagnosis by determining the diagnostic criteria, the clinical findings are not specific and the laboratory criteria are not available in every medical center, complicating the diagnostic process. For instance, soluble CD25 measurements, NK cell function tests, and genetic sequencing may not be available in time or these tests are even unavailable in many resource-limited areas. A rapid diagnosis and initiation of treatment is essential, particularly in familial cases because it is often fatal and the most effective contribution to survival is the early onset of treatment. Because of the complexity of disease courses, and the heterogeneity of the diagnosis and treatment capacity in different centers, an epidemiologic investigation is of great importance to clinicians. For the sake of this purpose, our study was organized as a multicenter, and the cases with the diagnosis of familial HLH were evaluated.

Materials and methods

A total of 83 patients enrolled in the present study, who had admitted to the participating centers between July 2002 and July 2023. Participating centers consisted of the pediatric hematology and oncology departments of Erciyes University, Necmettin Erbakan University, Van Yüzüncü Yıl University, Gaziantep University, Sütçü İmam University, and Health Sciences University Adana City Hospital. Patients aged 0–18 years who met HLH 2004 criteria and/or were genetically diagnosed with HLH were recruited in the study. Patients who were not diagnosed genetically, were enrolled with the presence of supportive findings, for instance poor clinical condition on admission, family history of sibling death and, history of similar disease. The data of demographic characteristics, clinical presentation, laboratory details including whole blood counts, liver and function tests, ferritin, triglyceride, genetic results, treatment modalities, and responses of the patients were assessed retrospectively from the files.

Evaluation of laboratory results was made based on HLH 2004 protocol cutoff values. Briefly; anemia was defined as hemoglobin (Hb) level < 10 g/dL for neonates and < 9 g/dL for older children. Thrombocytopenia was defined as thrombocyte level $< 100 \times 10^3$/μL, neutropenia as absolute neutrophil count (ANC) < 1000/ μL. Elevated liver enzymes were determined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value > 50 U/L and hyperbilirubinemia as total bilirubin level > 1 mg/dL. Hypofibrinogenemia was established as a fibrinogen level < 150 mg/dL. Hyperferritinemia was established when ferritin level ≥ 500 μg/L. Triglyceride level ≥ 265 mg/dL is considered to be hypertriglyceridemia.

A cytotoxicity test was performed to assess the cytotoxic ability of NK cells and to rule out secondary HLH. Peripheral blood mononuclear cells (PBMCs) were isolated from venous samples by the Ficoll-Hypaque Gradient method and target cells that were sensitive to NK cytotoxicity were dyed with Tag-it cell tracking dye. PBMC and target cells were co-cultured for 3 h. Thereafter Annexin V^+/7AAD apoptosis staining was performed and run on FACS AriaIII.

Continuous data were compared by the Student t-test if normally distributed, if not were compared by the Mann-Whitney U test. Also, proportions were compared with *the* x^2 test and Fisher exact test. Survival was evaluated with Kaplan Meier and Log-rank tests. A p-value < 0.05 was considered statistically significant. Results were analyzed using SPSS version 22.0 software.

Results

Of the 83 patients recruited in the study, 59% (n:49) were female and 40.9% (n:34) were male. The mean age at diagnosis was 2 years (± 2.9 years) and the median was 8 months (1 week-12.6 years). Fifty-eight (69.8%) of the patients were under 2 years of age on admission. Consanguineous marriage was present in 72.2% (n:60) of the families. There was a history of sibling death in 34.9% (n:29) of the cases. In addition, 39.8% (n:33) of them had a family history of similar disease.

Regarding the HLH diagnostic criteria, 73.4% (n:61) of the whole patients presented with at least 5 of 8 clinical / laboratory findings. The most common presenting sign on admission was persistent fever, which was seen in 91.6% (n:76) of the patients. Also, abdominal distension was observed in 78.3% (n:65) of patients, and petechiae-ecchymotic lesions were present in 22.8% (n:19) of patients. On physical examination, hepatosplenomegaly was present in 89.2% (n:74) of the patients. Neurological signs and symptoms were determined in 12 patients (14.4%). Of these patients; seizure was observed in 6 patients, encephalitis in 2, and posterior reversible encephalopathy in 4 patients. Cytopenia was present in at least two series in 68.6% (n:57) of the patients in the whole blood count on admission. NK cell cytotoxicity defect was able to undertaken in 6 patients.

The mean level of lactate dehydrogenase was 519.4 U/L (± 315 U/L). Hypertriglyceridemia was present in 66.2% (n:55) of the patients, and the mean triglyceride level was 461.5 mg/dL (± 236.4 mg/dL). Seventy-three (87.9%) of the patients had hyperferritinemia and the mean ferritin value was 5757.5 ng/ml (± 8668 ng/ml). Viral serological tests were undertaken for 53 (63.8%) patients. Of whom, only 17 (32%) resulted positive. Among them, the most common

finding was Ebstein-Barr virus infection (EBV) (n:14). Demographical findings, clinical features, and laboratory abnormalities on admission are presented in Table 1.

In bone marrow aspiration, hemophagocytosis was detected in 75.9% (n:63) of the patients. Pleocytosis was present in 18 (66.6%) of 27 patients who underwent cerebrospinal fluid examination by lumbar puncture. 35 patients underwent magnetic resonance imaging (MRI), and 24 of them (68.5%) revealed signs of neurological involvement such as; increased signal intensity on T2 images, hyperintensity in the periventricular white matter and basal ganglia, meningeal enhancement, diffusion limitation especially affecting the parieto-occipital lobes.

Table 1 Clinical features and laboratory parameters of HLH patients

	N: 83 (%)
Gender F M	49 (59%) 34 (40.9%)
Age at onset Mean ± SD Median (min-max)	24 ± 35 months 8 months (1 week-12.6 years)
Fever	76 (91.6%)
Hepatosplenomegaly	74 (89.2%)
Lymphadenopathy	12 (14.5%)
Neurologic manifestations • Seizure • Encephalopathy • PRES	12 (14,5%) 6 (50%) 2 (16.6%) 4 (33.3%)
Family history	33(39.8%)
Consanguineous marriage	60 (72.3%)
Anemia (Hb < 10 g/dL for neonates and Hb < 9 g/dL for older children)	63 (75.9%)
Thrombocytopenia ($< 100 \times 10^3/\mu L$)	65 (78.3%)
Hyperferritinemia (≥ 500 ng/mL)	73 (87.9%)
Hypertriglyceridemia (≥ 265 mg/dL)	55 (66.2%)
Hypofibrinogenemia (≤ 150 mg/dL)	69 (83.1%)
Elevated LDH (> 500 U/L)	35 (42.1%)
Elevated liver enzymes (AST or ALT > 50 U/L)	46 (55.4%)
Hyperbilirubinemia (> 1 mg/dL)	42 (50.6%)
Hypofibrinogenemia (≤ 150 mg/dL)	55(66.2%)
Hemophagocytosis in bone marrow aspiration	63 (75.9%)
Viral serology EBV CMV Parvovirus	**17 / 53** 14 (82.3%) 2 (11.7%) 1 (5.8%)

HLH: Hemophagocytic lymphohistiocytosis, F: Female, M: Male, PRES: Posterior reversible encephalopathy syndrome, Hb: Hemoglobin, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, EBV: Epstein-Barr virus, CMV: Cytomegalovirus

Familial HLH genetic causes were identified in 60.2% (n:50) of the patients, the remaining had no genetic evaluation performed owing to early death and/or limitations of the center admitted, nevertheless, they met the HLH criteria at least 5/8. Of these with genetic evaluation, biallelic loss-of-function variants in *PRF1* (38%; n:19), *STX11* (22%; n:11), *UNC13D* (20% (n:10), and in STXBP2 (2%; n:1) explained a total of 41 patients. In addition to these, 6 patients (12%) were diagnosed with Griscelli Syndrome type 2 (GS2) and 3 patients (6%) with Chediak Higashi Syndrome (CHS), caused by biallelic loss-of-function variants in *RAB27A* and *LYST*, respectively.

The HLH-2004 protocol was used for the treatment of the patients, and hematopoietic stem cell transplantation (HSCT) was performed in 39.7% (n:33) of them. 16 (32%) of the non-transplanted patients had achieved remission with the HLH 2004 protocol, whereas the remaining 34 (78%) patients had died due to poor clinical conditions during the donor search. Of the patients who underwent HSCT, 48.4% (n:16) were transplanted from a fully matched family donor (MFD), 30.3% (n:10) from an unrelated fully matched donor (MUD), and 15.1% (n:5) from a haploidentical donor, and the remaining two patients were transplanted from a family donor with one mismatch.

In our retrospective study with a mean follow-up of 51.1 months (± 55.8 months), 42 patients died, of whom 8 patients (8/33) were in the HSCT group. Of these patients, 18 (42.8%) died due to relapse, 23 (54.7%) due to refractory disease, and 1 patient owing to CMV sepsis after HSCT. Apart from the patient with CMV sepsis, the remaining losses from the HSCT group (n:7) were deceased due to primary disease relapse. In addition, 61.9% (n:26/42) of these patients had familial HLH mutations. In our study, the 2-year and 5-year overall survival (OS) rates were 62.5% and 49.6%, respectively, for the whole group. Comparing the patients who received HSCT and did not; the HSCT group revealed a 2-year OS of 84.7% and 5-year OS of 78.6%, whilst the OS of the patients who did not receive HSCT was 47.1% and 28.8% for 2 and 5 years, respectively. The difference determined with the Log-rank test was statistically significant with a p-value of 0.001. Regarding factors influencing OS; age, gender, and the season of admission had no statistically significant difference. Genetic background and HSCT type revealed significant differences in OS. Patients diagnosed with CHS had a 5-year OS of 66.7%, which was significantly superior to other genetic subtypes with a p-value of 0.005. Likewise, patients with HSCT performed from MFD revealed a superior OS compared to other HSCT types, with a 5-year OS of 87.5% (p:0.037). In patients with PRF1 mutations (n:19), 9 underwent HSCT, achieving a 5-year OS of 58.3%, compared to 23.3% in those who did not receive HSCT. This difference was statistically significant (p:0.024). For patients with UNC13D mutations

(n:10), 7 received HSCT, with a 5-year OS of 83.3%, while all 3 non-transplanted patients died, showing a statistically significant difference (p:0.007). In contrast, in the STX11 mutation group (n:11), the 5-year OS was 50% in the HSCT group (n:4) and 28.6% in the non-HSCT group (n:7), but this difference was not statistically significant (p:0.47). The detailed OS data is available in Table 2 and Supplement Files 1,2 and 3.

Discussion

Hemophagocytic lymphohistiocytosis is primarily a pediatric syndrome and usually affects children under the age of 18 months, with an estimated incidence for familial HLH to be 0.12 cases per 100,000 children/year. However, increasing evidence supports that, HLH can be diagnosed in adulthood as well [1, 2, 11]. Based on current literature, 69.8% (n:58) of the enrolled patients were under 2 years of age on admission. Familial HLH is generally diagnosed in the first year of life with a median age of 5.1 months [9, 10]. The median age in our study was 8 months, slightly higher compared with the literature. Also, the age on admission ranges between 1 week to 12.6 years. The reason for the difference here is that the patients had been admitted to the primary health care service in their local area with the initial disease findings, therefore the association of their findings with the diagnosis of familial HLH may be delayed. In the present study, although there is a female predominance, no gender difference is generally reported in the literature. In some studies, it was found more frequently in males [12, 13]. Family history was present in 39.8% (n:33) of our patients. As well, consanguineous marriage was present in the family of 60 patients (72.2%), and a history of sibling death was obtained from 29 families (34.9%). Although consanguineous marriage and family history are not essential features in the diagnosis of familial HLH, their presence supports the diagnosis.

Table 2 Overall survival of HLH patients based on factors

Factor	*N* (%)	2-year OS	5-year OS	*p*
Age on admission				
< 12 months	49 (59%)	45.4%	45.4%	0.83
> 12 months	34 (40.9%)	65.2%	53.3%	
Season on admission				
Winter	23 (27.7%)	55.4%	44.3%	0.37
Spring	16 (19.2%)	80.2%	72.9%	
Summer	23 (27.7%)	65.2%	51.2%	
Autumn	21 (25.3%)	48.9%	35.7%	
Gender				
Female	49 (59%)	65.5%	52.9%	**0.32**
Male	34 (40.9%)	58.1%	45.2%	
Genetic Subtype	(n: 50)			
PRF1	19 (38%)	66.5%	53.2%	**0.005**
UNC13D	10 (20%)	68.6%	57.2%	
STX11	11 (22%)	63.6%	36.4%	
STXB2	1 (2%)			
RAB27A	6 (12%)	50%	50%	
LYST	3 (6%)	66.7%	66.7%	
HSCT Type	(n:33)			
Haploidentical	5 (15.1%)	80%	80%	**0.037**
MFD	16 (48.4%)	87.5%	87.5%	
MUD	10 (30.3%)	90%	70%	

HLH: Hemophagocytic lymphohistiocytosis, OS: Overall survival, HSCT: Hematopoietic stem cell transplantation, MFD: Matched family donor, MUD: Matched unrelated donor

In our cohort, the clinical presentation of primary HLH largely aligns with previously reported findings in the literature. Persistent fever, a hallmark of HLH, was the most common presenting symptom in 91.6% of our patients, consistent with the literature where fever is often reported as a predominant feature across primary HLH cases. Hepatosplenomegaly, observed in 89.2% of our patients, also mirrors the literature, which cites hepatosplenomegaly in over 80% of diagnosed cases. Abdominal distension was present in 78.3%, highlighting the severity of organomegaly in our cohort [10–16]. In addition to this, 73.4% of the whole cohort was positive for at least 5 of 8 HLH criteria. Regarding the tests done for infectious etiology, viral serology results were positive for only 17 of the 53 patients, with the most common result being EBV positivity. Despite the limited positivity in the present study, EBV has been reported to be the most frequently reported infection associated with HLH [16–18]. Another clinical feature of HLH is neurologic symptoms, existing 14.4% of our patients, which are frequently seen in pediatric age consisting of seizures, meningismus, peripheral neuropathy, cranial nerve involvement, ataxia, dysarthria, lethargy, encephalopathy, and coma. This is in line with existing literature, where neurological involvement in HLH is noted in 10–30% of cases, often indicating a more severe disease course. The presence of these clinical features in our study supports the highly variable yet severe nature of primary HLH, emphasizing the importance of early recognition and intervention. One of the patients did not have neurological involvement on admission but it was evident after the onset of treatment, in the 6th week of induction therapy, she had a seizure, and the imaging studies revealed that she had an acute infarct [19]. Hence, neurological findings may also arise in the follow-up. In the presence of unexplained neurological findings, HLH should be kept in mind in the differential diagnosis [20, 21].

The limitations of our cohort were lack of genetic diagnosis in 33 of our patients and limited number of patients had undergone the NK cell cytotoxicity test, making our diagnostic process was difficult. The anamnesis of the patients, clinical course, the presence of a similar disease in the family and/or in the patient, the presence of consanguineous marriage, and the age of admission were helpful criteria at

this point. Herein, the most difficult thing was distinguishing the diagnosis from the other conditions that can emerge with the same clinical presentation like infection/sepsis, multiple organ dysfunction syndrome, liver disease/liver failure, and hemolytic uremic syndrome [7, 8, 22]. It should be underlined that HLH can be the first presentation of cancer, in which malignancy-directed therapy is essential to control the symptoms [23]. In our study, only 60.2% (n:50) of the patients were able to get a genetic diagnosis, whilst the rest of the patients could not evaluated genetically owing to the limitations of the center and/ or the poor clinical condition and diagnostic criteria of HLH 2004 protocol were used in the diagnosis of them. Three of these patients had two novel mutations, as published before with the unique presentations [24]. Difficulties in genetic diagnosis are associated with HLH screening panels used in daily practice. More comprehensive genetic panels are needed to evaluate patients. Targeted high-throughput genetic sequencing is planned to increase the possibility of genetic diagnosis in patients in a clinical study conducted by Tesi et al. [25].

In the literature, it is frequently stated that early and aggressive treatment should be initiated in HLH. In recent years, significant progress has been made in survival rates with standardized treatment protocols and HSCT. Before standardized therapy, estimated 1-year survival rates were less than 5%. In current practice, the 5-year survival rates have been reported up to 66%, as a result of therapy options and standardization [16, 26, 27]. In our retrospective cohort, all the patients had received the HLH-2004 treatment protocol. After treatment with HLH-2004 protocol, only 39.7% of patients were able to undergo HSCT. In the literature, HSCT is recommended for familial HLH patients following bridge treatment with chemo-immunotherapy. Besides, estimated OS is reported to be higher in patients who received HSCT [28]. The reasons for not being able to access HSCT in our study are varied. One of them is the differences between the centers where the patients had been treated and followed. Another limitation is that patients had died in the early stage of treatment and even before treatment was started due to their severe clinical condition. As stated in the literature, early HSCT is considered to be the only curative treatment and the mainstay of treatment. Research have demonstrated significantly improved outcomes in patients undergoing HSCT, with higher overall survival rates compared to those treated with medical management alone, which is similar to our results of our cohort. Early HSCT, particularly from fully matched donors, has been shown to result in superior survival rates and lower relapse rates [29].

In the present study, the 2-year OS was 62.3%, whereas the 5-year OS was 49.6% for the entire cohort which is worse compared with the literature [16, 26, 27]. Several reasons act beyond these dismal survival rates, including the differences between centers, for instance only two of the participating centers have pediatric transplantation units. Another factor affecting survival is the poor condition on admission. Thus, owing to poor conditions, the vast majority of patients died before donor search and preparations were obtained. Regarding the factors that can have an effect on OS, age on admission revealed no statistically significant difference. Nonetheless, of the 42 patients who died, 25 (59.5%) were younger than 12 months of age. Similarly, the season of admission disclosed no significant difference in OS. Since, infections are one of the most common triggers of HLH, a seasonal effect was anticipated. The reason for this can be the limited sample size of our retrospective cohort. The genetic subtype had a statistically significant difference in OS, being the most favorable OS in the presence of *LYST* and *UNC13D* mutation, respectively. Besides, comparing the 5-year OS of the untreated and patients treated with HSCT revealed a 78.6% OS for the transplanted, and 28.8% for untransplanted patients, which was significantly favorable in the transplanted group. The most prominent reason beyond this is the early death of the patients due to the heterogeneity of the centers and the prolongation of the diagnostic process. Moreover, the data suggest that HSCT significantly improves OS in patients with PRF1 and UNC13D mutations, consistent with the known curative potential of HSCT in familial HLH. The 5-year OS of 58.3% in PRF1-mutated patients and 83.3% in UNC13D-mutated patients who received HSCT highlights the critical role of transplantation in achieving long-term remission. The statistically significant differences in OS between transplanted and non-transplanted patients in these mutation groups (p:0.024 and p:0.007, respectively) reinforce the importance of timely HSCT intervention. However, in the STX11 mutation group, the lack of a statistically significant difference in 5-year OS between HSCT and non-HSCT patients (p:0.47) suggests that other factors, such as disease severity, pre-transplant conditioning, or donor type, and insufficient sample size may influence outcomes in this subset.

These results align with existing literature, which emphasizes the need for individualized treatment strategies in HLH, as response to HSCT may vary depending on genetic mutations and clinical presentation. These findings underscore the necessity of early genetic diagnosis and personalized treatment planning to optimize survival in familial HLH. Once the patients can get the appropriate bridge treatment up to HSCT in specialized centers, HSCT is the only curative approach for familial HLH.

Conclusion

Significant progress has been made in the diagnosis and treatment of HLH in recent years, with the understanding of its molecular mechanism and the improvement of treatment

strategies in the guidelines. Nevertheless, the major factor acting on OS, to which the clinician can have an impact is, utilizing HSCT in treatment. Therefore, recognizing HLH and maintaining suitable support until HSCT is the key to better outcomes. To ensure this, multicenter surveillance studies are needed to help clinicians be more aware of the presentation, diagnostic process, and treatment options.

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Data availability All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Declarations

Competing interests The authors declare no competing interests.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Erciyes University Faculty of Medicine on 07.12.2022 and the approval number is 2022/795.

Consent to participate All participants provided informed consent in the format required by the relevant authorities and/or boards for publication of their data in Tables 1 and 2.

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