Clinical and laboratory data of primary hemophagocytic lymphohistiocytosis: A retrospective review of the Turkish Histiocyte Study Group

Primer hemofagositik lenfohistiositozisli hastaların klinik ve labarotuvar verileri; Türk Histiosit Çalışma Grubunun retrospektif derlemesi

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Abstract

Objective: This study analyzes the clinical and laboratory findings of children with primary hemophagocytic lymphohistiocytosis (HLH) followed in various referral centers of Turkey.
Materials and Methods: A simple three-page questionnaire prepared by the Turkish Histiocyte Study Group was used for documentation of patient data.
Results: Age at diagnosis varied from 0.6 to 78 months (median±SD, 16.5±26.1). Sex distribution was almost equal (F/M=10/12). The frequencies of parental consanguinity and sibling death in the family history were 100% and 81.1%, respectively. The most common clinical findings were hepatomegaly (100%) and fever (95%). The most common laboratory findings were anemia (100%), hyperferritinemia (100%) and thrombocytopenia (90.9%). Triglyceride and total bilirubin levels in the deceased versus surviving group appear to be high (triglyceride: 394±183 mg/dl, 289±7 mg/dl; total bilirubin: 2.7±6.9 mg/dl, 0.5±1.2 mg/dl, respectively).

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Conclusion: We concluded that fever, hepatosplenomegaly, anemia, thrombocytopenia, and hyperferritinemia are the most common clinical and laboratory findings in primary HLH. Increased triglyceride and total bilirubin level at the time of diagnosis might be an indicator of poor prognosis in HLH.
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Key words: Primary hemophagocytic lymphohistiocytosis, clinical and laboratory findings

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Özet

Amaç: Primer hemofagositik lenfohistiositoz tanısı ile Türkiye'deki farklı merkezlerde takip edilen hastaların klinik ve laboratuar değerlerini değerlendirmektir.
Yöntem ve Gereçler: Hasta verilerinin değerlendirilmesi için Türk Histiosit Çalışma Grubu tarafından düzenlenmiş 3 sayfalık soru formu kullanıldı.
Bulgular: Olguların tanı sırasındaki yaşları 0.6 ile 78 ay arasında idi (median±SD, 16.5±26.1). Cinsiyet dağılımı eşite yakındı (K/E=10/12). Anne-baba akrabalığı ve kardeş ölüm öyküsü oranları sırası ile %100 ve %81.1 idi. Ensık görülen klinik bulgular hepatomegali (%100), ateş (%95), labaratuvar bulguları ise anemi (%100), hiperferritinemi (%100) ve trombositopeniydi (%90.9). Ölen olguların trigliserid ve bilirubin düzeyleri yüksek gibi gözükmekteydi (trigliserid; 394±183 mg/dL, 289±7 mg/dL, total bilirubin; 2.7±6.9 mg/dL, 0.5±1.2 mg/dL)
Sonuç: Ateş, hepatosplenomegali, anemi, hiperferritinemi ve trombositopeni primer HLH'li hastalarda en sık görülen klinik ve labaratuvar bulgulardır. Tanı sırasındaki artmış trigliserid ve bilirubin düzeyleri kötü prognostik belirteç olabilir. *(Turk J Hematol 2010; 27: 157-62)*
Anahtar kelimeler: Primer hemofagositik lenfohistiositozis, klinik ve laboratuvar veriler

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammation disorder characterized by fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hyperferritinemia, elevated soluble CD25 levels, decreased or absent natural killer cell activity, and hemophagocytosis in the bone marrow, spleen, lymph nodes or other tissues [1]. Primary or familial hemophagocytic lymphohistiocytosis (FHLH) is an autosomal recessive disorder of immune dysfunction caused by mutations in Perforin, Munc13-4, Syntaxin 11 and STBX2 genes [2-5]. Secondary HLH develops in some disorders such as infections, toxins, malignancies, and autoimmune or immune deficiency disorders [6].

Males and females are affected at equal frequencies. Onset of FHLH occurs generally in infancy, but rarely, patients can be symptomatic at later ages, even in adulthood [7]. The main pathogenetic mechanism is defective natural killer cell function and uncontrolled T cell activation leading to increased levels of cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-10, and soluble IL-2 receptor [8]. Profound hypercytokinemia activates macrophages, and hemophagocytosis ensues. Infiltration of bone marrow, liver, spleen, and the central nervous system (CNS) with macrophages and T lymphocytes results in multiorgan dysfunction with high mortality. Prognosis is poor for FHLH patients treated with chemotherapy alone, with an estimated five-year survival (SE) below 20% [9].

Allogenic hematopoietic stem cell transplantation (HSCT) is the only accepted curative therapy [1,6].

In this study, we report the clinical and laboratory data of 22 children with HLH who were followed in different pediatric referral centers in Turkey over the past 10 years, together with a comprehensive review of this rare disorder.

Materials and Methods

This study retrospectively analyzed the data of 22 children with HLH who were diagnosed and followed-up in 13 pediatric referral centers in Turkey. A simple three-page questionnaire was sent to each center by the Turkish Histiocyte Study Group to standardize data collection. This study has local ethical committee approval.

All children were diagnosed as HLH between January 1995 to June 2005 according to Diagnostic Guidelines for HLH 1994 and 2004. Patients with parental consanguinity and history of sibling death were accepted as having FHLH. Parental consanguinity was present in all of the patients and history

of sibling death in 18 of them. All patients fulfilled at least five cardinal criteria of HLH at the time of diagnosis, including fever, hepatosplenomegaly, bicytopenia and/or pancytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hyperferritinemia, and hemophagocytosis in the bone marrow, liver or lymph nodes [10]. They had no evidence of malignancy, infection, metabolic disease, or any other disorder that might have been the cause of presenting symptoms and hemophagocytosis. Patients were evaluated regarding age, clinical findings, laboratory data, treatment, and prognosis, using descriptive statistics. A molecular genetic study could be performed in only 4 patients.

Results

The age of the patients ranged from 0.6 to 78 months at the time of diagnosis. Sex distribution was almost equal (F/M=10/12). Initial clinical findings are shown in Tables 1 and 2. Rates of parental consanguinity and sibling death were 100% (22/22) and 81.1% (18/22), respectively. The patients were diagnosed by bone marrow aspiration in 19 (86.4%) and biopsy from the liver in 2 (9%), spleen in 1 (4.5%) and lymph nodes in 1 (4.5%).

Hepatomegaly was present in all the patients, and 95.5% (21/22) had fever and splenomegaly. The most common laboratory findings were anemia (100%), hyperferritinemia (100%) and thrombocytopenia 90.9% (20/22). Other findings are shown in Tables 1 and 2.

Cerebromeningeal symptoms including seizures or cerebral nerve palsies occurred in 27.3% (6/22) of the patients in our study group. Fourteen (63.3%) children received supportive treatment (fresh frozen plasma and erythrocyte concentrates) and corticosteroid, intravenous immunoglobulin (IVIG), and vincristine therapy. HLH-94 and HLH-2004 treatment protocols were given in 4 (18.8%) and 3 (13.6%) children, respectively. One child had undergone bone marrow transplantation, and she died with chronic graft-versus-host disease and pulmonary hypertension. Eighteen (86.3%) patients died due to progressive disease, infection and bleeding. Three children were alive at the time of preparation of the article.

Discussion

Familial hemophagocytic lymphohistiocytosis (FHLH) is a rare autosomal recessive disease characterized by fever, hepatosplenomegaly, cytopenia,

Table 1. Clinical findings of patients with hemophagocytic lymphohistiocytosis at diagnosis

n=22	Number	%
Gender		
Girl	10	45.5
Boy	12	54.5
Age (months)	16.5 (median)	0.6 - 78 (range)
Positive History		
Consanguinity	22	100
Fever	21	95.5
Sibling death	18	81.8
Skin eruptions	5	22.7
Clinical Findings		
Hepatomegaly	22	100
Splenomegaly	21	95.5
Fever	21	95.5
Lymphadenomegaly*	7	31.8
Cerebromeningeal symptoms	6	27.3
Bleeding**	4	18.2
Skin eruptions	4	18.2

*Cervical, occipital, inguinal, **Gingival, epistaxis

Table 2. Laboratory findings of patients with hemophagocytic lymphohistiocytosis at diagnosis

Number of patients (n) n=22 Laboratory Findings	mean±SD	range
Hb (g/dl)	6.85±1.6	3.6 8 9.8
Platelet (x10^9/L)	42±157	2 - 752
ANC (/mm^3)	895± 5632	50 - 24000
AST (U/L)	132±302	21 - 1176
ALT (U/L)	102± 1171	22 - 5446
Triglyceride (mg/dl)	374±179	284 - 999
LDH (U/L)	930±968	106 - 3547
Ferritin (mg/dl)	1434±1485	576 - 5654
Serum sodium (mEq/L)	133±5.7	124 - 148
T. Bilirubin (mg/dl)	2±6.5	0.4 - 22
PT (sec)	14±18	2 - 90
APTT (sec)	39±32	27 - 180
Fibrinogen (g/L)	1.28± 1.38	0 - 4.2

Hb: Hemoglobin: ANC: Absolute neutrophil count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactic acid dehydrogenase; T. bilirubin: Total bilirubin; PT: Prothrombin time; APTT: Activated partial thromboplastin time

and hemophagocytosis in the bone marrow or other tissues [1]. It is known to occur frequently in children under 2 years of age [6,10]. Due to the very high rate of consanguineous marriages (21%) in Turkey, the expected incidence of HLH should be high as well. Many reports on FHLH in Turkish patients justify this conclusion [11-13]. Although there are no nationwide epidemiologic data, in one study, the frequency of the HLH among hospitalized patients was found to be 7.5/10000, and the rate of consanguineous marriage was reported as 68% in HLH patients [14]. This was 100% in our study group, and 81.8% had family history of a sibling death.

In this report, we analyzed the data of 22 patients with HLH who were diagnosed and treated in different pediatric referral centers between January 1995 and 2005. Along with the high frequency of consanguineous marriages in the study group, each patient fulfilled at least five cardinal criteria of HLH. Although molecular genetic study is now available in a center in Turkey (Hacettepe University, Ankara), it could only be performed in a very limited number of patients. Despite this limitation, we considered that it would be informative to document the available clinical and laboratory data of these children with HLH from Turkey, where it is encountered relatively more frequently than in other parts of the world.

The clinical findings of HLH are generally nonspecific, and the most common symptoms are known to be fever and hepatosplenomegaly. Many patients with HLH present with mild to moderate signs of infection, which delays the diagnosis.

Consistent with previous studies, the most common initial findings in our patients were hepatomegaly, splenomegaly and fever. There was only 1 patient who was afebrile at the time of diagnosis. Although fever is a very common finding in HLH, it may not occur in a small number of patients for unknown reasons. Some patients might develop fever during follow-up, as in our patient. Clinicians should be aware of this possibility in the diagnosis of HLH. The most common laboratory findings were anemia, hyperferritinemia and thrombocytopenia, as expected. This may be due to undetectable infections, or the patients may have acquired HLH. Although platelet and absolute neutrophil counts were normal in 2 patients in the initial period, these patients had cytopenia in more than 2 of 3 lineages and fulfilled the criteria of HLH. As is known, the presence of infection does not discriminate FHLH from the acquired form. FHLH episodes are triggered by infectious agents [6].

Hemophagocytosis in the bone marrow or reticuloendothelial system including liver, spleen and lymph nodes was reported to be detected in one-half or two-thirds of the patients with HLH, so hemophagocytosis may not always be observed in the bone marrow aspiration, especially at the disease onset. When the diagnosis of HLH is strongly suspected, clinicians should make a thorough microscopic examination of the bone marrow aspiration smear or serial repeated aspirations should be done. In our series, we observed hemophagocytosis in all of the patients in the microscopic examination, and it seems to be the highest ratio of determining hemophagocytosis in HLH when compared with previous reports in the literature.

Although elevated lactate dehydrogenase (LDH) is emphasized as a supporting criterion by some authors, it is not accepted as a diagnostic laboratory criterion for diagnosis of HLH [10]. In our group, 19 of 22 (86.7%) patients had elevated LDH level. It is notable that in our study group, the frequency of elevated LDH was remarkably high.

On the other hand, cerebromeningeal symptoms including seizures or cerebral nerve palsies occurred in 27.3% (6/22) of the patients in our study group. This figure is slightly less than those reported in previous studies [13-16].

There is limited data regarding the association between the prognosis of disease and triglyceride metabolism. Monitoring the triglyceride level is a recently defined follow-up parameter in the evaluation of treatment response in secondary HLH as reported by Okamoto et al. [17]. Sarper et al. [18] reported low triglyceride levels in 2 patients diagnosed with HLH.

In addition to perforin, the Munc13-4, syntaxin 11, and recently Munc18-2 mutations are described [2-5]. A molecular genetic study was performed in only 4 patients, and syntaxin mutation was detected in 1 of them [19].

We cannot discuss event-free survival because of data from heterogeneous hospital records and the differences between the therapy regimens of the centers. Seven of the 22 children received specific therapy for HLH and only 1 of them survived,

while 2 out of 14 patients who received Vepesid (etoposide), IVIG and steroids survived. All surviving patients had a history of parental consanguinity and 2 of them had sibling death.

Etoposide, dexamethasone, cyclosporine A, and intrathecal methotrexate have been the mainstay of all HLH treatment protocols because of their different properties. One of the basic findings of HLH at the cellular level is decreased apoptosis, and etoposide has a more significant proapoptotic effect. Use of these medications at different dosages and durations in 2 of our surviving patients might explain the favorable outcome. The genetic analysis of these patients will further clarify our results.

The prognosis of patients with HLH who require admission to any center has been regarded as extremely poor. SCT is the only curative treatment option for patients with HLH [1,6]. There are two major problems before bone marrow transplantation: finding a matched sibling donor and keeping the patients alive until the transplantation [1]. Without a bone marrow transplant, the child is always at risk of a severe or fatal activation and will have difficulty surviving beyond their first birthday. Unfortunately, only 1 patient underwent peripheral SCT from a fully matched mother in the study period, and she died because of chronic graft-versus-host disease and pulmonary hypertension.

In conclusion, fever, hepatosplenomegaly, anemia, thrombocytopenia, and hyperferritinemia are the most common clinical and laboratory findings in primary HLH. Parental consanguinity and presence of affected siblings seem to be an important clue for diagnosis. Increased triglyceride and total bilirubin levels at the time of diagnosis might be poor prognostic indicators in HLH, but this requires further investigation.

Conflict of interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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