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Hemophagocytic lymphohistiocytosis secondary to infectious diseases

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ABSTRACT

Introduction: Secondary hemophagocytic lymphohistiocytosis (HLH) occurs in association with infections, autoimmune disorder or malignancy. Only few studies reported cases of infection-associated HLH (I-HLH). We aimed to study the clinical, laboratory and therapeutic features of I-HLH among children and adults.

Material and methods: We conducted a retrospective study including all patients hospitalized in Pediatric and infectious diseases department with confirmed diagnosis of I-HLH between 2011 and 2017.

Results: We enrolled 19 cases with I-HLH, among whom 11 cases were males (57.8%). We identified 15 children and 4 adults. The median age was 11 years [1-65 years]. Physical examination showed splenomegaly in 15 cases (78.9%) and hepatomegaly in 10 cases (52.6%). Regarding laboratory examinations, anemia and elevated ferritin levels were noted in all cases. Bone marrow aspiration showed images of haemophagocytosis in all cases. Bacterial infection was noted in 10 cases (52.6%) and parasitic infection in 5 cases (26.3%). All patients received symptomatic and/or etiological treatment. Specific treatment with corticosteroids and human immunoglobulins were used in 7 cases (36.8%). Ten patients were dead (52.6%) due to multiple organ failure.

Conclusions: Hemophagocytic lymphohistiocytosis was a life-threatening disease. The prognosis depends on the underlying etiology, but remains poor. Prompt diagnosis and treatment are crucial in order to improve the outcome.

Keywords: adult, bacterial infection, children, hemophagocytic lymphohistiocytosis, infectious diseases

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH), also known as macrophage activation syndrome or hemophagocytic syndrome, is a non-specific systemic inflammatory response caused by immune dysregulation. It is a rare disease, but a life threatening one. Its incidence is underestimated since its clinical symptoms are non-specific and usually associated with other symptoms of an underlying disease. There are 2 types of HLH: primary HLH (familial) occurs in children with inherited dysfunction of the immune response, whereas secondary HLH (acquired) occurs in association with infections, autoimmune disorder or malignancy (1,2). Infection-associated HLH (I-HLH), noted with both adults and children (3), is most commonly secondary to viral infections such as *Epstein-Barr virus*, which is the most responsible for severe form of I-HLH (4). Less commonly, I-HLH is triggered by other herpes viruses such as *Herpes simplex virus, Varicella-zoster virus and Cytomegalovirus* (5). Bacterial, fungal and parasitic infections were associated with I-HLH (3).

Regardless of the type, the treatment is based on a combination of immunosuppressive and cytotoxic therapy to target the hyperinflammatory state (3). As for acquired HLH, specific treatment is also required: prompt diagnosis of the underlying disease guides treatment decisions, especially in non-viral infection (6).

Only few studies reported cases of I-HLH. In this perspective, the aim of this work was to study the clinical, laboratory and therapeutic features of I-HLH among children and adults.

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Table 1: *Clinical symptoms and physical examination signs of patients with hemophagocytic lymphohistiocytosis*

		Number	Percentage (%)
Total		19	100
Clinical symptoms	Fever	19	100
	Pulmonary signs	7	36.8
	Neurological signs	4	21
	Digestive signs	3	15.8
	Hemorrhagic signs	1	5.3
	Motor deficit of the lower limbs	1	5.3
Physical examination signs	Splenomegaly	15	78.9
	Hepatomegaly	10	52.6
	Skin rash	10	52.6
	Neurological signs	4	21
	Lymphadenopathy	3	15.8

MATERIALS AND METHODS

Study Design

We conducted a retrospective study including all patients hospitalized in Pediatric and infectious diseases department with confirmed diagnosis of I-HLH between 2011 and 2017.

Data Collection and Case Definition

We collected data from the medical records of patients on pre-established sheets.

We included all patients with confirmed HLH according to Henter diagnostic criteria in 2004 (7). HLH triggered by an infection disease was also confirmed.

In order to determinate the underlying disease associated with HLH, different investigations were performed such as viral serologies (*EBV*, *CMV*, hepatitis A,B and C, *HIV*), serologies of rubella, typhoid fever and toxoplasmosa. Blood and stool culture, urine examination and thick and thin blood smears were performed as well, depending on clinical symptoms presented by the patient.

Statistical Analysis

We performed statistical analysis using SPSS 20. Qualitative variables were carried out as numbers and percentages. Quantitative variables were driven by means and standard deviation, when they were normally distributed. Otherwise, medians and interquartile ranges (IQR) were performed.

RESULTS

Patients' Characteristics

During the study period, we enrolled 19 cases with I-HLH, among whom 11 cases were males (57.8%). We identified 15 children and 4 adults. The median age was 11 years [1-65 years]. Twelve patients (63.1%) were aged less than 6 years, representing, therefore, the most affected age group. According to residency, 10 patients came from rural area (52.6%).

Clinical Features and Laboratory Results

All patients had fever, which was associated to pulmonary signs in 7 cases (36.8%). Physical examination showed splenomegaly in 15 cases (78.9%) and hepatomegaly in 10 cases (52.6%) (**Table 1**).

Regarding laboratory examinations, anemia was noted in all cases, thrombocytopenia in 18 cases (94.7%) and leucopenia in 13 cases (68.4%). Further investigations revealed elevated ferritin levels (100%), hypertriglyceridemia in 10 cases (52.6%) and hypofibrinogenemia in 7 cases (36.8%). Increased levels of inflammatory markers were noted, such as increased C-reactive protein (100%) and increased erythrocyte sedimentation rate, noted in 6 cases (31.5%) (**Table 2**).

Bone marrow aspiration was indicated. It showed images of haemophagocytosis in all cases associated to *Leishmania* bodies in macrophages in 3 cases (15.8%).

Table 2: *Laboratory results associated with hemophagocytic lymphohistiocytosis*

Laboratory results	Number	Percentage (%)
Anemia	19	100
Increased C-reactive protein	19	100
Elevated ferritin levels	19	100
Thrombocytopenia	18	94.7
Elevated aspartate and alanine transferase	16	84.2
High lactate dehydrogenase levels	15	78.9
Low prothrombin rate	15	78.9
High bilirubin levels	14	73.6
Leucopenia	13	68.4
Hypertriglyceridemia	10	52.6
Hypofibrinogenemia	7	36.8
Increased erythrocyte sedimentation rate	6	31.5

Table 3: *Infectious diseases etiology associated with hemophagocytic lymphohistiocytosis*

Etiology		Number	Total
Viral infection	Primary *EBV* infection	2	3
	Primary *Rubella* infection	1	
Parasitic infection	Visceral leishmaniasis	3	5
	P.falciparum malaria	1	
	Toxoplasmosis	1	
Fungal infection	Hepatic candida abscesses	1	1
Bacterial infection	*Staphylococcus aureus* bacteremia	2	10
	Pseudomonas aeruginosa bacteremia	2	
	Klebsiella pneumoniae bacteremia	1	
	Acinetobacter baumannii bacteremia	1	
	Multi drug resistant *E.coli* bacteremia	1	
	Disseminated tuberculosis	2	
	Salmonellosis	1	

EBV: Epstein-Barr virus; E.coli: Escherichia coli; P.falciparum: Plasmodium falciparum

Etiology of Hemophagocytic lymphohistiocytosis

Bacterial infection was noted in 10 cases (52.6%), a parasitic infection in 5 cases (26.3%) and viral infection in 3 cases (15.8%). One patient had fungal infection (5.3%) (**Table 3**).

Treatment and Disease Evolution

Patients received symptomatic treatment such as antipyretics for those who had fever. Seventeen patients (89.4%) had severe anemia, requiring red blood cell transfusion. Platelet and fresh frozen plasma were administered in 12 (63.1%) and 7 cases (36.8%), respectively. After identifying the underlying infection, etiological treatment was required. Antibiotic, antiviral and antifungal therapy were used when bacterial, viral or fungal infection were confirmed. Antitubercular and antimalarial treatment were delivered in case of tuberculosis and malaria, respectively. Specific treatment with corticosteroids and human immunoglobulins were used in 7 cases (36.8%). The mean duration of corticosteroids was 8 days. Three patients (15.8%) were treated with 8-week induction regimen, which included dexamethasone, etoposide and cyclosporine.

The disease evolution was favourable in 9 cases (47.4%). Ten patients were dead (52.6%) due to multiple organ failure. The death occurred after a median duration of hospitalization of 19 days [1-60days].

DISCUSSION

Our study highlighted the burden of HLH. It was a rare disease, but a potentially fatal disorder, unless diagnosis and appropriate therapy were promptly instituted. It affects more frequently children than adults (8), which was concordant with results noted in our study. In Japan, a national survey reported that pediatric and adult annual incidence was 1 per 800000 (9). However, its exact incidence worldwide is unknown. It varies by geographic region from 1 /50000 live births in Sweden to 7.5/10000 live births in Turkey, for example (3).

The disease is the result of impaired function of Natural Killer cells, cytotoxic T cells and T regulatory cells. All those lead to hemophagocytosis in the bone marrow and the reticulo-endothelial system, which explain clinical and biological

symptoms, such as cytopenia or splenomegaly. High levels of interferon γ, interleukin-1 and interleukin-6 play a role in the syndrome, explaining fever or hypertriglyceridemia, for example (4,5,10).

Two types of HLH were identified: Familial HLH, related to perforin gene mutation, usually noted in infancy or early childhood, representing therefore, 80 % of the cases. However, it was also reported among adults. An acquired HLH is the consequence of intense immune activation caused by infection, autoimmune disease, cancer, certain metabolic diseases or immunosuppressive therapy. It was reported with both adults and children (4,9,11). I-HLH is commonly related to viral infections (3). However, in our study, we reported a predominance of bacterial infections. This might be explained by the reduced sample, which is probably considered unsignificant. Besides, laboratory diagnosis of viral infections are sometimes more difficult and requires the use of multiple serologies, which are not always available. Therefore, viral infections might be underestimated.

The HLH treatment is based on immunosuppressive and cytotoxic therapy, such as dexamethasone or etoposide in order to target the hyperinflammatory state. Different protocols were tested mostly among children. However, there are few data to guide the management of HLH among adults (3,12). Previous studies showed that high-dose of polyvalent immunoglobulin are beneficial in infection. In fact, the main predictive factor of response was its early administration, especially when ferritin level was high (2). For patients with I-HLH, the suitable antimicrobials targeting suspected or confirmed pathogens were indicated, such as, antiviral, antibiotic or antifungal therapy (13). However, an updated treatment protocol is lacking. Further studies are required in order to specify HLH treatment guidelines among both children and adults.

The prognosis of HLH depended on the underlying etiology. Previous studies showed that the 5-year survival rate was 83% in patients with I-HLH (4). However, the prognosis remains poor among adults, with mortality ranging from 41 to 79 % (13,14). Actually, favourable prognostic factors were reported, including children, adults aged less than 50 years old, prompt treatment, fever subsiding within 3 days of diagnosis, low histiocytis in marrow, higher fibrinogen levels, absence of disseminated intravascular coagulation or other coagulopathy and excellent baseline health (15).

Hemophagocytic lymphohistiocytosis was a life-threatening disease with many underlying etiology. It was likely under-recognized because of its various clinical and laboratory findings. The prognosis depends on the associated etiology, but remains poor. Prompt diagnosis and treatment are crucial in order to improve the outcome.

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