



Original article

Hemophagocytic lymphohistiocytosis: a case series analysis in a pediatric hospital



Itallo Oliveira Santos ^{a,*}, Ricardo Pasquini Neto ^b,
Ana Paula Kuczynski Pedro Bom ^{a,b}

^a Hospital Pequeno Príncipe, Curitiba, PR, Brazil

^b Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, PR, Brazil

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ABSTRACT

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare clinical laboratory condition with high mortality rates, resulting from ineffective overactivation of the immune system. Data in the Brazilian literature is scarce, contributing to the challenge in standardizing conducts and performing an early diagnosis of HLH.

Objective: To describe the clinical, laboratory, and evolutionary findings on HLH patients treated at a pediatric hospital.

Methods: This is an observational, cross-sectional and retrospective study on children diagnosed with HLH, hospitalized between 2009 and 2019. The diagnostic criteria were those described in the Histiocyte Society protocol. The authors evaluated HLH patient laboratory tests, myelograms and bone marrow biopsies, clinical characteristics and therapy.

Results: Twenty-three patients were included, 52.2% of whom were males. The age at diagnosis ranged from one to one hundred and eighty months. Four cases were classified as Primary HLH and nineteen, as Secondary HLH. The main triggers were infections and rheumatological diseases. All children had bicytopenia, and 95.4% had hyperferritinemia. Nineteen patients had liver dysfunction, sixteen had neurological disorders and fourteen had kidney injury. Pulmonary involvement was seen in 61.9%, acting as a worse prognosis for death ($p = 0.01$). Nine patients underwent the immuno-chemotherapy protocol proposed in the HLH 2004. The time to confirm the diagnosis varied from five to eighty days. The lethality found was 56.3%.

Conclusions: The present study is the most extensive retrospective exclusively pediatric study published in Brazil to date. Despite the limitations, it was possible to demonstrate the importance of discussing HLH as a pediatric emergency.

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* Corresponding author at: Avenida Silva jardim, 1275, Rebouças, Curitiba, PR, Brazil, CEP 80250-200

E-mail address: ricardo.pasquini@pucpr.edu.br (I.O. Santos).

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare clinical laboratory condition with high mortality rates, resulting from immune system ineffective hyperactivation associated with dysregulation of macrophage and lymphocyte effector functions.¹ The disease can be classified as primary/familial, when it has a genetic etiology and triggering factors are not identified, or as secondary, when it is triggered by infections (Epstein Barr Virus (EBV) or gram-negative bacteria), use of medications, neoplasms (mainly hematological) or autoimmune diseases (juvenile idiopathic arthritis or systemic lupus erythematosus).^{2,3}

The diagnosis of HLH is based on clinical and laboratory criteria standardized by the International Society of Histiocytosis in 2004.⁴ The molecular findings consistent with the diagnosis of HLH or the presence of at least five criteria of the following eight confirms the diagnosis of HLH: fever; splenomegaly; the company of cytopenia (reaching at least two sets of peripheral blood), hypertriglyceridemia or hypofibrinogenemia; hyperferritinemia; elevation of the soluble IL2 receptor; identification of hypoactivity of NK cells; hemophagocytosis verified by myelogram, and/or; bone marrow, spleen or lymph node biopsy.⁵

Due to the state of hyperimmune activation syndrome, the clinical manifestations, such as mucocutaneous lesions, focal neurological deficits, seizures, and decreased level of consciousness might also be present in the pediatric age group.^{6,7} In addition, there may be changes in liver, kidney, lung function and failure to control certain autonomic functions, which are usually identified as poor prognosis factors.⁸

Treatment is planned accordingly to the HLH classification, triggering factors and clinical evolution.⁹ In familial (primary) HLH, corticosteroids and immunochemotherapy are used in specific cases. Curative therapy consists of hematopoietic stem cell transplantation (HSCT). In patients with secondary HLH, cortico-immunochemotherapy is recommended in combination with treatment directed to the triggering condition.¹⁰

Data in the Brazilian literature on HLH is scarce.¹¹ In the past two decades, international multicenter studies have helped demonstrate the main triggering and prognostic factors.^{12,13} However, most studies are performed with mixed populations (children and adults), exclusively pediatric series being rare, which make it difficult to standardize clinical management and early diagnosis of HLH in children.¹⁴ Therefore, the present study aims to describe the clinical, laboratory and evolutionary findings of pediatric patients with hemophagocytic lymphohistiocytosis treated at *Hospital Pequeno Príncipe* (HPP) in Paraná, Brazil, providing evidence about the characteristics of HLH in Brazilian children.

Methods

This study consisted of an observational, cross-sectional and retrospective study (through the analysis of medical records) of pediatric patients diagnosed with HLH (based on the criteria protocolized by the Histiocyte Society (HLH-2004)) and admitted to the *Pequeno Príncipe* Hospital, located in Curitiba, Paraná, from 2009 to 2020. The patient laboratory tests (blood count, ferritin, triglycerides and fibrinogen), myelogram and/

or bone marrow biopsy, clinical characteristics (presence of fever and splenomegaly), the therapy administered, clinical evolution and outcomes (cure or death) were evaluated as variables of the study.

All the information was collected from the patient medical records and organized in Microsoft Excel Computer Program Spreadsheets, with data analysis performed with the SPSS v.27.0 software. Quantitative and qualitative variables expressed the results. The authors conducted the inferential analysis using statistical tests relevant to the study model, such as Fisher's exact test. The *p*-values lower than 0.05 were considered significant. This study was approved by the National Research Ethics Committee, under protocol 17513719.8.0000.0097, available at the "Plataforma Brasil".

Results

Twenty-three patients were included in this study, 47.8% (11/23) were females and 52.2% (12/23), males. The age at diagnosis ranged from one to one hundred and eighty months, with a median of sixty-five months. Regarding the clinical findings at presentation, 95.7% (22/23) of the patients had a fever and 82.6% (19/23), splenomegaly identified by physical examination or ultrasound findings. The duration of fever ranged from zero to ninety days, with a median of five days.

According to familial history and consistent molecular findings, four cases (17.4%) were classified as primary hemophagocytic lymphohistiocytosis. The hemophagocytic syndrome was secondary to some conditions in nineteen patients (82.6%). The primary triggers identified are described in [Table 1](#), with emphasis on infectious and rheumatological disorders.

Regarding the diagnostic laboratory findings, all the children had bicytopenia. The most common cytopenias found were thrombocytopenia in 95.4% (22/23) and anemia in 91.3% (21/23) of the HLH children. Twenty-two patients (95.4%) had hyperferritinemia. Hypertriglyceridemia was present in 78.3% (18/23) of the cases. The authors describe other laboratory findings in [Table 2](#).

Table 1 – Conditions associated with the development of HLH.

	N	%
Rheumatological conditions	9	39.1
Systemic lupus erythematosus	6	26
Anti-neutrophil cytoplasmic antibody-associated vasculitis	1	4.3
Without defined etiology	2	8.6
Infectious conditions	11	47.8
Epstein-Barr virus infection	3	13
Cytomegalovirus infection	2	8.6
Herpes virus infection	1	4.3
Bacterial infection / Sepsis	4	17.4
Protozoan infection / Parasitic disease	1	4.3
Oncohematological conditions	2	8.6
Embryonal Rhabdomyosarcoma	1	4.3
T-cell Acute Lymphoblastic Leukemia	1	4.3
Metabolic conditions	1	4.3
Mevalonic aciduria		

Table 2 – Laboratory findings in patients with HLH.

	N	%
Hypertriglyceridemia	18	78,3
Hypofibrinogenemia	14	63,8
Hyperferritinemia	22	95,4
Anemia	21	91,3
Leukopenia	15	65,2
Thrombocytopenia	22	95,4
Transaminases elevated Lactate	15	65,2
Dehydrogenase elevated	20	86,9

A biopsy or bone marrow aspirate was performed in eighteen (78.2%) patients. Hemophagocytosis was found in nine samples (39%), with hypocellularity being the most common associated pattern in eight (34.7%) cases.

Concerning the involvement of multiple organs and systems of patients with HLH, the authors found a high prevalence of liver, neurological, renal and pulmonary dysfunction associated with the disease. Sixteen (69.5%) children presented some neurological alteration, mainly seizures, in 39.1% (9/23) of the cases. However, there was no statistical significance for a worse prognosis, namely, death ($p = 1$), using Fisher's exact test. The liver was the organ most directly affected. Nineteen (82.6%) cases had some degree of liver dysfunction, from reactive hepatomegaly to acute liver failure, present in 13% (3/23) of the patients.

Pulmonary involvement was seen in 61.9% (13/23) of the patients, with complicated pneumonia (through pleural effusion, pneumatocele or necrosis) afflicting 26% (6/23) of patients, being the most frequent manifestation observed. Acute pulmonary involvement was directly related to mortality in the evolution of HLH, acting as a factor of poor prognosis for death, with $p = 0.01$.

Acute kidney injury was part of the evolution in 60.8% (14/23) of the cases. Of these patients, 30.4% (7/23) required renal replacement therapy at some moment of the treatment or

Table 3 – Multisystem involvement in patients with HLH.

	N	%
Neurological involvement	16	69.5
Seizures	9	39.1
Altered level of consciousness	6	26
Stroke	2	8,6
Dysgenesis of the corpus callosum	1	4.3
Dural venous sinus thrombosis	1	4.3
Hypertensive hydrocephalus	1	4.3
Hepatic involvement	19	82.6
Reactive hepatomegaly	9	39.1
Hepatitis	7	30.4
Acute liver failure	3	13
Pulmonary involvement	13	61.9
Complicated pneumonia	6	26
Uncomplicated pneumonia	4	17.3
Alveolar hemorrhage	3	13
Kidney involvement	14	60.8
Acute kidney injury	11	47.8
Acute kidney injury requiring renal replacement therapy	7	30.4
Skin and mucous membrane involvement	9	39.1

Table 4 – Therapies used in patients with HLH.

	N	%
Antivirals and Antibiotic therapy	22	95.7
Etoposide	10	43.4
Cyclosporine	13	56.5
Corticotherapy	18	78.2
Immunoglobulin	4	17.4
Plasmapheresis	3	13
Allogeneic bone marrow transplant	2	8.6

disease evolution. The authors describe other clinical findings in [Table 3](#).

Regarding therapy, antivirals and antibiotics of the high spectrum, with coverage for multidrug-resistant germs, were used in twenty-two patients (95.7%). Nine cases (39.1%) were submitted to the immunochemotherapy protocol proposed in the HLH 2004. Cyclosporine was used in thirteen patients (56.5%), mostly in those with accompanying rheumatological conditions. An allogeneic bone marrow transplantation was performed in 8.6% (2/23) of the children in the study. One of the children, who was submitted to a bone marrow transplantation, had HLL secondary to T-cell acute lymphoblastic leukemia, while the other child had primary HLH accompanied by neurological symptoms. The authors describe other therapies used in [Table 4](#).

The time to confirm the diagnosis varied from five to eighty days, with a median of twenty days. A total of 56.3% (13/23) of the patients died due to the disease progression. The only clinical manifestation or laboratory finding mentioned that had a direct relationship with a worse outcome (death) was the presence of acute lung injuries, such as pneumonia and alveolar hemorrhage, during the clinical evolution.

Discussion

HLH has a broad spectrum of clinical manifestations and laboratory findings.¹ The frequency of clinical conditions (fever and splenomegaly), in addition to laboratory alterations (hyperferritinemia, hypofibrinogenemia and hypertriglyceridemia), proved to be similar to that of other multicentric studies, such as the HLH 2004, with a sample of 369 patients.¹⁵ The only patient in the present study who did not have a fever was a newborn. This pediatric subpopulation has clinical peculiarities that make the diagnostic management and therapeutic plan more complex.^{16,17} Among the laboratory tests, several trials describe ferritin as an important marker of the disease activity, response to therapy and prognosis.^{18,19}

Ferritin is a ubiquitous, 450-kDa, 24 subunit protein that is commonly measured to assess tissue iron stores. It is also a positive acute-phase non-specifically reactant that increases in inflammatory conditions.²⁰ Hyperferritinemia is a hallmark of HLH, as it increases the sensibility and specificity for the disease diagnosis.^{21,22} Although hyperferritinemia is a critical factor in establishing the HLH diagnosis, there was no statistical significance between the ferritin levels and the death rate ($p = 0.9$) in our case series.

The presence of hemophagocytosis in the bone marrow, liver or spleen is not pathognomonic or indispensable to the diagnosis of HLH. The prevalence of this finding is variable in studies (described in the range of 25 to 100% of the patients).¹² The bone marrow may be hypo-, normo- or hypercellular. Hypocellularity is the most common pattern described in the literature and detected in this case series.⁹ It is worth mentioning the limitations of our service in performing immunological tests and genetic assays, such as the function measurement of natural killer (NK) cells and the search for levels of soluble CD 25 (soluble interleukin-2 receptor), as these laboratory exams are not available in the Brazilian public healthcare system.

In our case series, biopsy and bone marrow aspirate were not performed in all patients. This lack of evaluation occurred in two patients that presented HLH secondary to rheumatological disease and did not have the indication for these exams by their rheumatologists. This fact highlights the importance for healthcare professionals to recognize HLH as a pediatric emergency, establishing appropriate conduct and referring these patients to pediatric oncohematologists.

Infections were the primary triggers in this study, especially those caused by a virus (26%), with an emphasis on the Epstein-Barr virus (EBV), which is a critical trigger factor, according to the current literature.²³ In addition to the EBV, there are also reports of other viruses involved in the pathogenesis of HLH, such as cytomegalovirus, parvovirus, herpes simplex virus, adenovirus, influenza virus and human immunodeficiency virus.^{24,25} Bacterial infections, mainly gram-negative and mycobacteriosis, may also trigger HLH.²⁶ Fungal and parasitic diseases, such as visceral leishmaniasis, are described causes, mostly in studies with vulnerable populations.²⁷ In a Brazilian series with seven cases involving the pediatric population, visceral leishmaniasis was an essential trigger for HLH in children under one year of age.¹¹ Neoplasms are also reported as trigger factors for HLH, especially neoplasms of lymphoid lineage.²⁸

In the current context of the COVID-19 pandemic, recent studies have shown that SARS-CoV-2 may also be considered a trigger for the development of HLH.²⁹ The primary complications of COVID-19 are caused by a hyperinflammatory state, with high levels of serum cytokines (C-reactive protein and interleukin-6), leading to multiple organ failure and shock. The cases of HLH secondary to COVID-19 are still poorly described in the literature. However, given a clinical history of fever $\geq 38.5^{\circ}\text{C}$ and splenomegaly, associated with high levels of cytokines and serum ferritin $> 35,000 \mu\text{g/L}$, health professionals should be able to identify HLH as a COVID-19 complication and perform a detailed investigation with bone marrow biopsy to provide early diagnosis and appropriate treatment.³⁰

When the development of HLH is secondary to rheumatological conditions, the term Macrophage Activation Syndrome (MAS) is used.³¹ Classically, MAS is associated with juvenile rheumatoid arthritis; however, it may be present in other autoimmune diseases, such as ANCA-related vasculitis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease, Sjogren's syndrome, scleroderma and sarcoidosis.^{31,32} In the present study, unlike the primary pediatric studies, systemic lupus erythematosus was the main rheumatological trigger for the development of HLH. The

reason that can explain this fact is that the rheumatology consensus uses different diagnostic criteria. Therefore, some patients with MAS, especially the cases of juvenile rheumatoid arthritis, were excluded from the research, as they did not present the requirements of the diagnostic criteria proposed by the International Histiocytosis Society.

Neurological involvement in HLH was described, on average, in two-thirds of the patients. The primary neurological symptoms were seizures and an altered level of consciousness. The largest multicenter study, performed with 193 children from twenty-five countries, showed that the main complications were irritability (34%), seizures (33%) and meningitis (21%).⁷

In the current study, the prevalence of acute kidney injury, requiring renal replacement therapy, during the clinical evolution of the patients was noteworthy. There are no exclusively pediatric articles that assess the frequency of renal failure in HLH. However, studies with mixed populations (adults and children) showed an average prevalence of 16% to 20% of the cases.³³ Several factors may justify such findings, such as the use of nephrotoxic drugs, cardiac dysfunction, septic shock, need for mechanical ventilation, syndrome of inappropriate antidiuretic hormone (SIADH) or acute kidney injury by markers activated in the immune hyperactivation pathway.^{1,2}

Acute lung injury was directly related to death, with statistical significance, being present in 61.9% of the study sample cases. Respiratory involvement was described in 42% of the patients in a series of 775 adults with HLH, published in 2014, including reticulonodular infiltrates, consolidations and cavitations, in addition to complications, such as pleural effusion, pneumatoceles and necrosis.³³

Regarding the therapeutic plan, there was a difference concerning the prescription of corticosteroid therapy and immunochemotherapy for patients with rheumatological disease. Corticosteroids were used in 78.2% of the children in two different regimens: pulse therapy with methylprednisolone 30 mg/kg/day in patients with MAS or dexamethasone 10 mg/m²/day, according to the HLH 2004. Therapeutic management is complex and involves the suppression of the inflammatory process, treatment of the causal agent and use of antibiotics or antivirals, if necessary. Patients may also require supportive care in the ICU, with hydration, gastric protection and advanced respiratory support.⁴

As a long-term measure, the allogeneic bone marrow transplantation (BMT) is the definitive treatment for primary HLH. The BMT might also be indicated for patients with HLH associated with central nervous system disease or children who present inadequate response to the immunochemotherapy treatment in the first eight weeks.^{4,9} It is worth remembering the need to optimize immunomodulators for patients with autoimmune disease-associated conditions and contribute to the early identification of relapses.^{4,9,15}

The study death rate was 56.3%, similar to that described by the International Histiocytosis Society in 2007.⁴ However, over the last ten years, this number has been reduced considerably in developed countries, thanks to the association of alemtuzumab with conventional protocols.³⁴ It is worth mentioning that our sample of patients is still small for the performance of specific statistical analyses and more reliable

identification of prognostic factors and variables directly related to mortality or recurrence.

Conclusions

The present study is the most extensive retrospective pediatric study published in Brazil. Despite the restricted sample size and the limited access to immunological or genetic tests, in addition to the retrospective nature of this case series, it was possible to demonstrate the importance of discussing HLH as a pediatric emergency, which should always be remembered in cases of patients with an unfavorable clinical response to an infectious or immunological condition.

Therefore, we encourage the elaboration and publication of new regional studies, preferably multicentric and prospective, to standardize conducts and create national protocols that allow for earlier diagnoses and better HLH outcomes in pediatric patients.

Conflicts of interest

The authors declare no conflicts of interest.

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