Hemophagocytosis lymphohistiocytosis (HLH)

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Introduction

• Autosomal recessive familial hemophagocytic lymphohistiocytosis (FHL)
• Familial erythrophagocytic lymphohistiocytosis (FEL)
• Viral-associated hemophagocytic syndrome (VAHS)
Introduction

• Aggressive and potentially life-threatening
• Most often affects infants from birth to 18 months of age
Classification

HLH

Primary
- genetic disorder

Secondary
- viral illness
- autoimmune disease
- lymphoma
INCIDENCE

• In Sweden, 1.2 children per million per year, or 1 in 50,000 live births
• Male-to-female ratio close to 1:1
• The largest pediatric hospitals in Texas revealed an incidence of 1 in 100,000
ASSOCIATED ILLNESSES

• Infections
• Autoimmune disorders
• Leukemias and lymphomas
• Immune deficiencies
• Renal or liver transplant recipients
• Kawasaki disease, Griscelli syndrome, Hermansky-Pudlak syndrome type II
Infections

- Epstein-Barr virus
- Cytomegalovirus
- Parvovirus
- Herpes simplex, varicella-zoster
- Measles
- Human herpes virus-8
- HIV infection
- H1N1 infections
Infections

- Brucella
- Gram negative bacteria
- Tuberculosis
- Parasites (Leishmaniasis)
- Fungal infections
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Autoimmune disorders

- Lupus erythematosus
- Rheumatoid arthritis
- Still's disease
- Polyarteritis nodosa
- Mixed connective tissue disease
- Pulmonary sarcoidosis
- Systemic sclerosis
- Sjogren's syndrome
- Drug rash with eosinophilia and systemic symptoms (DRESS)
ASSOCIATED ILLNESSES

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Leukemias and lymphomas


PATHOPHYSIOLOGY

• Familial HLH:
  25 percent of all HLH cases are familial

• HLH in adults:
  unknown incidence (no epidemiologic study of HLH in adults)
PATHOPHYSIOLOGY

• Foreign viral antigen is presented by antigen-presenting cells (APCs, eg, macrophages, dendritic cells, B lymphocytes) to CD4+ and CD8+ T cells.

• T cells are activated and proliferate and differentiate, during which time they produce a variety of cytokines (eg, interferon-gamma), which activate APCs to further promote antigen presentation.
• Inhibitory feedback loop of the NK and CD8+ T cells acquire cytotoxic function

• In HLH, abnormal and excessive production of T cell-derived cytokines (eg, “cytokine storm”), leading to uncontrolled accumulation of activated T-lymphocytes and activated histiocytes (macrophages)
CLINICAL AND PATHOLOGIC FINDINGS

• Initial presentation:
  - Fever — 91 percent
  - Hepatomegaly — 90 percent
  - Splenomegaly — 84 percent
  - Neurologic symptoms — 47 percent
  - Rash — 43 percent
  - Lymphadenopathy — 42 percent
• Febrile illness
• Liver disease and coagulopathy
• Multiple organ failure syndrome
• Child abuse
• Encephalitis

Nearly 75 percent of patients with HLH have CNS symptoms mimicking chronic encephalitis
Pathologic findings

- Aggressive proliferation of normal histiocytes and T-lymphocytes in various tissues
- Hemophagocytosis of red cells (erythrophagocytosis), other white blood cells, or platelets in the bone marrow, spleen, or lymph nodes
- In nearly 20 percent of cases, more than one specimen may be required
Diagnostic Criteria

① Fever
② Splenomegaly
③ Cytopenia in at least two cell lines
④ Hypertriglyceridemia and/or hypofibrinogenemia
⑤ Tissue demonstration of hemophagocytosis
⑥ Hepatitis
⑦ Low or absent natural killer cell activity
⑧ Serum ferritin level >500 µg/L
   (>3000 µg/L is a more realistic cut off)
① Soluble CD25 (sIL-2 receptor) >2400 U/mL
• The diagnosis of HLH requires the presence of five of the above criteria.

• If a patient meets only four criteria and the clinical suspicion for HLH is high, one must initiate appropriate treatment, as delays may be fatal.
• Serial ferritin levels, NK cell function, serum interleukin-2 receptor levels

• It is **neither necessary** nor sufficient to demonstrate hemophagocytosis in **bone marrow or lymph node biopsies**
TREATMENT

- Treatment should be initiated immediately when the patient fulfills the clinical criteria for HLH
  - HLH-94 protocol
    (five-year survival: 54 ± 6 percent)
  - Hematopoietic cell transplantation
    (five-year survival: 66 ± 8 percent)
  - Reduced-intensity transplantation
  - HLH-2004 protocol
  - Intravenous immunoglobulin
Take home message

• Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal disorder of children and adults due to cytokine dysfunction

• HLH may be familial, associated with a number of different infections, autoimmune disorders, or coincident with a number of malignancies.
• Treatment should be initiated immediately when the patient fulfills the clinical criteria for HLH, since delay of therapy may lead to irreversible multi-organ failure.
• Thanks for your attention !