City Pediatric Meet-Dec 2011

Spectrum of HLH

Dr. Revathi Raj’s unit, Apollo Children’s Hospital.
Case 1

- 4 month male child /thriving well
- Fever - 5 days with cough
- O/E – hepatosplenomegaly other system- N except tone was decreased
INVESTIGATIONS

- Hb - 8.1, TLC – 4200, ANC 300, plt 55 k
- CSF – lymphocytosis and raised proteins
- Blood culture - NG
- Broad spectrum antibiotics
After 4 days

- Fever improved
- Hb - 5.6, plt – 15 k, TLC – 11200, ANC 2000
  - P/S – no blast few atypical lymphocytes
  - Torch profile – normal
  - Hb electrophoresis – normal
  - Metabolic screen normal
  - S ferritin 1357 µg / L, TGL – increased
- MRI showed infiltrative lesions in bilateral cerebellum
- BMA – erythrophagocytosis
Diagnosis

- Fever
- Hepatosplenomegaly
- Pancytopenia
- High ferritin
- High TG, low fibrinogen, PRF1 - NEG
- STX11 mutation - FHLH-4
- Started on chemotherapy HLH – 2004 protocol
- Mother was 6/6 match so went for allogenic PBSC
- DOING FINE
Case 2

- 6 months boy, thriving well
- Antenatally diagnosed left PUJ obstruction and underwent left pyeloplasty.
- Fever – started on antipyretics.
- CBC : WNL, CRP: negative.
- Urine routine: 10-12 pus cells/hpf.
- Urine and blood c/s sent.
- Started on antibiotics.
POD-4

- Persisting fever, abdominal distension, hepatomegaly
- Decreased urine output

- USG abdomen: hepatosplenomegaly

- Urine and blood c/s: sterile.

- CBC: platelets – 46000/cumm, Hb-7.9gm/dl

- Dengue serology: positive

- Develop dengue shock syndrome
Persisting symptoms…..further investigations

- Coagulation profile: deranged, decreased fibrinogen level
- S.ferritin 13,400 mcg/L

fever, bicytopenia, hypofibrinogenemia, hyperferritinemia

HLH
Bone marrow: evidence of erythrophagocytosis.

Criteria were fulfilled

Started on dexamethasone and Ivlg.

Follow up serum ferritin: 446mcg/L.
DISCUSSION
A clinical syndrome resulting from cytokine overproduction due to inefficient immune response
Clinical syndrome with multiple underlying conditions

**Genetic - 25%**
- Familial HLH
- **PRF1**
- **UNC13D**
- **STX11**
- others
- Immune deficiencies
  - Griscelli syndrome
  - Chédiak-Higashi
  - XLP

**Secondary - 75%**
- Infectious
  - EBV
  - CMV
  - leishmaniasis
- Rheumatic disease
  - MAS*
- Malignancies
  - lymphoma

*see Cure4Kids seminar #517 for more on MAS*
Genetics of familial HLH

- 4 classic complementation groups

<table>
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<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
<th>Function</th>
<th>Year</th>
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- All genes involved in cytotoxic granule pathway
- 45% of familial HLH cases have no identified defect in these genes
- Search for additional genes involved with fHLH
Perforin

- Membranolytic protein expressed in the cytoplasmic granules of cytotoxic T cells and NK cells.
- Responsible for the translocation of granzyme B from cytotoxic cells into target cells; granzyme B then migrates to target cell nucleus to participate in triggering apoptosis.
- Without perforin, cytotoxic T cells & NK cells show reduced or no cytolytic effect on target cells.
Fig. 2. Schematic illustration of major pathways involved in apoptosis triggering. Effector cells such as the cytotoxic T lymphocyte (CTL) and NK cells may initiate apoptosis of target cells through the release of granzyme B and perforin. Perforin perforates the cell membrane allowing entrance of the toxic granzyme into the target cell. Other mechanisms to induce apoptosis include the tumor necrosis factor (TNF) pathway and Fas/Fas ligand interaction. Fas is deficient in ALPS type I, whereas ALPS type II affects caspase 10 in the cascade of caspases. In FHL, mutations in the gene encoding perforin have been revealed recently [23–24].
Genetic (Primary

- Autosomal recessive
- 1 in 50,000 births
- Predominantly in children of age < 1 year
- Male-to-female ratio close to 1:1
Acquired (secondary)

- Occurs in all age groups
- Usually triggered by an infection – viral and non-viral
- Other associations – malignancies and autoimmune disorders

Risdall, *Cancer* **44** (1979), pp. 993–1002
Clinical Presentation

- Fever
- Hepatosplenomegaly
- Neurological symptoms (seizures)
- Large lymph nodes
- Skin rash
- Jaundice
- Edema
CNS disease

- CNS infiltration
  - most devastating consequence(s) of HLH
- Seizures
- Alteration in consciousness-coma
- CNS deficits-cranial nerve palsies, ataxia
- Irritability
- Neck stiffness
- Bulging fontanel
Laboratory Abnormalities

- Cytopenias (Platelets, Hgb, WBC)
- High Triglycerides
- Prolonged PT, PTT, low Fibrinogen
- High AST, ALT
- CSF- high protein, high WBC
- Low Natural Killer cell activity
- High Ferritin
Pathologic findings

- Proliferation of normal histiocytes and T-lymphocytes
- Phagocytosis of RBC and WBC
- No atypia in the macrophages
- Organ infiltration by lymphocytes and histiocytes
HLH 2009 DIAGNOSTIC CRITERIA

1. Molecular diagnosis of hemophagocytic lymphohistiocytosis (HLH) or X-linked lymphoproliferative syndrome (XLP).

2. Or at least 3 of 4:
   a. Fever
   b. Splenomegaly
   c. Cytopenias (minimum 2 cell lines reduced)
   d. Hepatitis

3. And at least 1 of 4:
   a. Hemophagocytosis
   b. Ferritin
   c. sIL2Ra (age based)
   d. Absent or very decreased NK function

4. Other results supportive of HLH diagnosis:
   a. Hypertriglyceridermia
   b. Hypofibrinogenemia
   c. Hyponatremia
Treatment

- Without treatment FHLH is rapidly fatal
  Median survival - 2 months
3 aims of HLH Treatment

- Suppress hyper-inflammation that is the basis of the clinical symptoms
- Remove infected antigen-presenting cells that are stimulating the inflammatory response
- Correct any underlying genetic defect
Treatment

- Immunosuppression is the mainstay of treatment
  - Corticosteroids
  - Cyclosporine
  - Etoposide
- Identify secondary causes and treat
  - Infection
  - Auto immune disorders
  - Malignancies
Drug selection for HLH therapy

- Dexamethasone
  - Reduces hyper-inflammation, inhibits cytokine expression
  - Cytotoxic for lymphocytes
  - Good CNS penetration
- Cyclosporin A - prevents T-cell activation
- Etoposide
  - High activity in monocytic and histiocytic diseases
  - Inhibits EBNA synthesis in EBV infected cells
- Intrathecal methotrexate – reduce risk of CNS reactivation
Figure 2: Treatment protocol overview for Hemophagocytic Lymphohistiocytosis (HLH-2004)

- INITIAL THERAPY → SCT / CONTINUATION THERAPY →

**Dexa (mg/m²)**

| 10 mg | 5 mg | 2.5 mg | 1.25 mg |

**VP-16**

↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓→

**Go to SCT during continuation therapy as soon as an acceptable donor is available with**
- HLA-identical related donor or
- Matched unrelated donor or
- Mismatched unrelated donor or
- Family haploidentical donor
(further SCT information: see text)

A donor search as soon as possible is suggested in familial patients and poorly responding patients, and is to be considered in infants.

Doses calculated per m² also if BW <10kg

* = EVALUATION, see Table 1

§ See Fig 1 for info on start of Continuation

**Dexa** = Dexamethasone daily with 10 mg/m² for 2 weeks, 5 mg/m² for 2 weeks, 2.5 mg/m² for 2 weeks, 1.25 mg/m² for 1 week, and taper then discontinue during 8th week.

# Pulses every second week with 10 mg/m² for 3 days during the continuation therapy.

**VP-16** = Etoposide 150 mg/m² i.v., twice weekly for the first two weeks, then weekly during the initial therapy. Every second week during the continuation therapy. Only in certain conditions, such as if ANC <0.5 x10⁹/L and the bone marrow is hypocellular (which only rarely is the case), can the first two doses be omitted.

**CSA** = Cyclosporin A aiming at levels around 200 microg/L (monoclonal, trough value). Start with 6 mg/kg daily orally (divide in 2 daily doses), if normal kidney function.

**I.T. therapy**

↑ = Methotrexate doses by age: <1 year 6 mg, 1-2 years 8 mg, 2-3 years 10 mg, >3 years 12 mg each dose.

Prednisolone doses by age: <1 year 4 mg, 1-2 years 6 mg, 2-3 years 8 mg, >3 years 10 mg each dose.

Maximum four doses are suggested, but start only if progressive neurological symptoms or if an abnormal CSF has not improved.
Treatment

- Initial therapy (8 weeks)-induction
  - Decadron (8wks), CSA
  - VP16 (2x/wk x 2 wks, 1x/wk x 6wks)
  - ITM if CNS disease is present after 2 wks of therapy for 4 doses

In non-familial cases treatment is stopped after 8 weeks if complete resolution of disease
Treatment

- Continuation Therapy
  - Week 9-52
    - VP16 every other week
    - Decadron pulses every 2 wks for 3 days
    - CSA
HLH 2004

Genetically verified or
Familial disease → Continuation therapy until HSCT

Register and start:
Initial 8 weeks chemotherapy → Persistent non-familial, non-genetically verified → Continuation therapy until HSCT

Resolved → Stop non-familial, non-genetically verified Reactivation → Continuation therapy until HSCT

Henter, Pediatr Blood Cancer. 2007 Feb;48(2):124-31
In FHLH allogenic SCT - only curative therapy
  - SCT performed ASAP:
    - disease is non-active
  - Non-familial disease
    - SCT offered at relapse or persistent
Genetic counseling

- Familial HLH – gene is identified
- Test in antenatal period –
  CVS
  Amniocentesis
Conclusion

- HLH is a fatal disease if untreated
- Disease presentation is due to hyperinflammation due to inherited or acquired immune defects
- Allogenic SCT results in cure rate of ~ 50-60%