Successful therapy and clinical studies in hemophagocytic lymphohistiocytosis (HLH):

Academia and patient organizations in collaboration

Jan-Inge Henter, MD, PhD

Karolinska Hospital & Karolinska Institutet

Summary of presentation at ICORD February 15, 2005

Basic HLH Information

- There is a familial form and a secondary form.

- **The familial form:**
  - Onset usually in infancy, or early childhood
  - Autosomal recessive
  - Often rapidly fatal if untreated
  - Incidence = 2:100.000 live born

20 years ago

- **All children died**
  - Median survival time = 1-2 months after diagnosis
  - Many children had the correct diagnosis only after death

- Biological **understanding was limited**
  - The mechanisms causing the disease - totally unknown

Some questions initially asked …

- Can we define how to make the diagnosis?
- Can it be treated?
- Can it be cured?

- Can we find out what causes the symptoms?
- Can we find the underlying cause?
- Can we learn something about healthy humans?

One Way to Move Forward
= International Collaboration

The Histiocyte Society, initiated 1985 - 20 years ago, mainly covers two Rare Diseases:

- Langerhans Cell Histiocytosis (LCH)
- Hemophagocytic Lymphohistiocytosis (HLH)

Goals of the Histiocyte Society

- Promote communication and exchange of ideas (1985-)
  - Annual Meetings, Study Groups
  - Physicians representing >20 countries at last Annual Meeting

- Promote research and education
  - Scientific Committee, Education Committee

- Promote Clinical Studies (on these rare diseases)
  - Presently 4 studies are open

The Histiocytosis Association of America (Parent/patient organisation)

- Created in 1986 by two parents
  (a partnership of patients, families, physicians, and friends)
  - To promote research aiming for improving cure
  - To support patients and their families.
  - To promote education related to the histiocytoses
- More than 5,000 persons are registered members

- Over 80 research projects have been funded
- Serves as administrative office for the Histiocyte Society (allows parents access to the most recent advances)

Other Supporting Parent groups

- Argentina
  - Brazil
  - France
  - Greece
  - Japan
  - Portugal
  - Turkey
- Belgium
- Canada
- Germany
- Italy
- The Netherlands
- Sweden
- United Kingdom

HLH - Diagnostic Guidelines 1991

- A common definition - A common language
  - Fever
  - Splenomegaly
  - Cytopenia (≥ 2 lineages) (Hb <90 g/L, ANC <1, platelets <100)
  - Hypertriglyceridemia or Hypofibrinogenemia
  - Hemophagocytosis

Henter et al, Semin Oncol 1991; 18: 29-33

The 1st International Treatment Study

HLH-94

Histiocyte Society

The 2nd International Treatment Study

HLH-2004

Histiocyte Society

Disease Mechanisms and Genes

- Genes causing HLH have been found
  - Rapid and exact diagnosis
  - Prenatal diagnosis
  - Early therapy
    - Better survival
    - Fewer complications
- Deficient ”programmed cell death”
  - HLH can learn us about normal immun-regulation

Questions asked…and answered

- Can we define how to make the diagnosis? YES
- Can it be treated? YES
- Can it be cured? YES

- Can we find out what causes the symptoms? YES
- Can we find the underlying cause? YES
- Can we learn something about normal humans? YES

Conclusions for Rare Diseases

- Collaboration Academia – Patients/Parents can be very valuable
  Supporting clinical studies
  Supporting research grants
  Supporting administrative duties
  = Access to physicians, new treatments and research data

- International Clinical Studies can be performed in Rare Diseases
  - To learn - step by step, stone by stone, patient by patient
    - Knowledge will grow → Children will grow