Aetiology of Childhood Leukemia

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- Pädiatrische Hämatologie und Onkologie -

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Leukemogenesis

Normal bone marrow

Acute leukemia

Etiology?

Molecular events

Disruption of process of differentiation, survival, self-renewal
• Natural History of the Disease
• Role of Genetic Factors
• Role of Environmental Factors

• Natural History of the Disease
• Role of Genetic Factors
• Role of Environmental Factors
Leukemia in Twins

Monozygotic twins have concordance rate of ~5%

Genetic predisposition?

Simultaneous exposure to a common leukemogenic event?

Placental crossing of leukemic cells?

From: Greaves, M. F. et al., Blood 2003

In utero rearrangements in the trithorax-related oncogene in infant leukaemias

Anthony M. Ford*, Susan A. Ridge*, Maria E. Cabrera†, Hazem Mahmoud†,
C. Michael Steel||, Li C. Chan|| & Mel Greaves*

chromosome 11q23

From: Greaves et al., Blood 2003
Prenatal Origin of Childhood ALL
Gale, …Greaves, PNAS 1997

3 patients
5, 6 and 24 mo old
t(4;11), MLL/AF4+

Prenatal Origin of Childhood ALL
Wiemels, …Greaves, Lancet 1999

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient’s age at diagnosis</th>
<th>Guthrie segments tested</th>
<th>Guthrie segments positive for TEL-AML1</th>
</tr>
</thead>
<tbody>
<tr>
<td>K Twin A</td>
<td>3 years 11 months</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>K Twin B</td>
<td>4 years</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 years 1 month</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2*</td>
<td>2 years 10 months</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 years 5 months</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3 years 4 months</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 years 5 months</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>6*</td>
<td>3 years 6 months</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3 years 11 months</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4 years 3 months</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5 years 1 month</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Patients from Italian centre. Other patients are from UK.
**Prenatal Origin of Childhood ALL**
*Mori,…, Greaves, PNAS 2002*

PCR screening of 496 cord blood samples for the presence of preleukemic fusion transcripts

<table>
<thead>
<tr>
<th>TEL/AML-1</th>
<th>AML1-ETO</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

6 positive 1 positive

⇒ Estimated frequency of fusion gene-positive cord bloods: ~1/100
Frequency of overt childhood leukemia: ~ 4-5/100,000

**Model for Leukemogenesis in Children**

<table>
<thead>
<tr>
<th>In utero</th>
<th>1st hit</th>
<th>Postnatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic stem cell</td>
<td>Molecular event</td>
<td>Leukemia cell</td>
</tr>
<tr>
<td>Preleukemic clone</td>
<td>Molecular event(s)</td>
<td></td>
</tr>
</tbody>
</table>

Causes of prenatal hit? How does it predispose to leukemia? Nature and causes of postnatal events?
• Natural History of the Disease

• Role of Genetic Factors

• Role of Environmental Factors

**Constitutional Chromosomal Abnormalities in Childhood Leukemia**

*Peripheral blood at birth*

„Transient leukemia“

Spontaneous resolution within 3 months

*Bone marrow at 2 yrs of age*

AML FAB M7

Incidence 500x increased in Down’s syndrome!
Pathogenesis of Down AML

2nd hit

GAATA mutation

Haematopoietic cell with trisomy 21

transomy 21 = 1st hit

Transient leukemia

MDS → AML

Remission

Latent transient leukemia done

Additional mutation 3rd hit?

Prenatal Postnatal

Constitutional Chromosomal Abnormalities in Childhood Leukemia

% of childhood leukemias

(Narod, BJC 1991)

- Down’s syndrome
- Germline BRCA2 mutations
- Beckwith-Wiedemann syndrome
- Neurofibromatosis type I
- Fanconi’s anemia
- Shwachman Diamond syndrome
- Ataxia telangiectatica

Inherited susceptibility through normal allelic variation, involved in gene-environment interactions?
• Natural History of the Disease

• Role of Genetic Factors

• Role of Environmental Factors

Prenatal Exposures
**Birthweight and Leukemia**

Recent population-based case control study, USA:

<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>Controls (N = 4098)</th>
<th>ALL cases (N = 354)</th>
<th>AML cases (N = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3500</td>
<td>5.1</td>
<td>11.4</td>
<td>11.2 (9.8, 13.1)</td>
</tr>
<tr>
<td>3500-4499</td>
<td>81.0</td>
<td>74.4</td>
<td>74.4</td>
</tr>
<tr>
<td>≥4500</td>
<td>15.0</td>
<td>20.1</td>
<td>20.1</td>
</tr>
</tbody>
</table>

Podvin, Paediatr and Perinatal Epidem 2006

⇒ Association of high birthweight with ALL; consistent with most but not all studies

**Birthweight and Leukemia**

**HYPOTHESIS:**
Increased fetal exposure to growth hormones?

Big baby

Proliferative stress on hematopoiesis
**Maternal Diet during Pregnancy**

Naturally occurring **topoisomerase inhibitors**: Risk factors for infant leukemia?

- Soy beans
- Fruits, vegetables
- Cocoa, tea, wine
- Coffee

Combined exposure variable

<table>
<thead>
<tr>
<th>Category of exposure</th>
<th>Overall dataset</th>
<th>Infant ALL only</th>
<th>Infant AML only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \text{OR} )</td>
<td>( \text{CI} )</td>
<td>( \text{OR} )</td>
</tr>
<tr>
<td>Low</td>
<td>1.0</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>Medium</td>
<td>2.1</td>
<td>(0.9-5.0)</td>
<td>1.3</td>
</tr>
<tr>
<td>High</td>
<td>1.1</td>
<td>(0.5-2.3)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Ross, Cancer Causes Control 1996

**Maternal Diet during Pregnancy**

Dietary bioflavonoids cause **MLL** gene cleavage in human hematopoietic progenitor cells by inhibition of topoisomerase II

- Cord blood myeloid progenitors
- Cord blood T progenitors

Strick..., Rowley. PNAS 2000
Radiation

Marie Curie
The Nobel Prize in Physics 1903
The Nobel Prize in Chemistry 1911
Died from leukemia
aged 66

Irène Joliot-Curie
The Nobel Prize in Chemistry 1935
Died from leukemia
aged 58

Irène Joliot-Curie
The Nobel Prize in Chemistry 1935
Died from leukemia
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Marie Curie
The Nobel Prize in Physics 1903
The Nobel Prize in Chemistry 1911
Died from leukemia
aged 66
Radiation-induced Leukemia: Atomic Bomb

Leukemia Deaths by Age at Exposure among 93,696 survivors

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Excess</td>
</tr>
<tr>
<td>6–9</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>10–19</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>20–29</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>30–39</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>40–49</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>50+</td>
<td>23</td>
<td>–1</td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
<td>70</td>
</tr>
</tbody>
</table>

Hiroshima, August 6, 1945

Nuclear Accidents and Leukemia

Reports from
- Sweden: Hjalmars BMJ 1994
- Finland: Auvinen BMJ 1994
- Scotland: Gibson Lancet 1988
- Germany: Michaelis Nature 1997
- Greece: Petridou Nature 1996

No strong evidence for increased risk of childhood AL

Chernobyl, April 26, 1986
Residence near Nuclear Power Plants
KiKK study, Germany (Spix et al., EJC 2008)

Null hypothesis: No association between proximity of housing to a nuclear power plant and the risk of cancer ≤ 5 yrs of age

Preselected areas around 16 nuclear power plants
1592 cases: All cancers ≤ 5 yrs in 1980-2003
4735 matched controls

⇒ Null hypothesis rejected
⇒ Statistically significant effect for ALL
⇒ Population-attributable risk of 0.3% for housing within 5 km

Electromagnetic Field Exposure

• Initial report in 1979 (Wertheimer and Leeper)

• No association in large studies from U.S.A, U.K., Canada
  (Linet NEJM 1997; Cheng Lancet 1999; McBride Am J Epidem 1999)

• Metaanalysis (Ahlbom BJC 2000)

<table>
<thead>
<tr>
<th>Relative risks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement studies</td>
</tr>
<tr>
<td>Canada</td>
</tr>
<tr>
<td>Germany</td>
</tr>
<tr>
<td>New Zealand</td>
</tr>
<tr>
<td>UK</td>
</tr>
<tr>
<td>USA</td>
</tr>
<tr>
<td>Calculated fields studies</td>
</tr>
<tr>
<td>Denmark</td>
</tr>
<tr>
<td>Finland</td>
</tr>
<tr>
<td>Sweden</td>
</tr>
<tr>
<td>Summary</td>
</tr>
<tr>
<td>Measurement studies</td>
</tr>
<tr>
<td>Calculated fields studies</td>
</tr>
<tr>
<td>Denmark</td>
</tr>
<tr>
<td>All studies</td>
</tr>
</tbody>
</table>

Increased risk at highest exposure levels (>0.4 μT)
Socioeconomic Status

Age-specific Incidence of ALL

Age peak
- Emerged at beginning of 20th century
- Restricted to B cell precursor ALL
- Lacks in less developed countries
Geographical Pattern
Annual rates per 100 000 in children (≤14 yrs)

USA, white
ALL 3.8
AML 0.6

USA, black
ALL 2.1
AML 0.6

Germany
ALL 4.0
AML 0.7

India
ALL 1.6
AML 0.5

Zimbabwe
ALL 1.2
AML 1.1

Data from: Parkin et al., 1998

Peter Kastchü*, Ewa Stelisnou-Fouqueré, Emmanuele Crocetti, Corrado Magnani, Casilda Spila, Pepe Zambon

33 population-based cancer registries in 15 European countries (77,111 cases)
**ALL Incidence during Economic Transition: Western and Eastern Germany**

*Spix et al., Int J Cancer 2008*

- **Reunification**
  - **↑ 3.3%**

**ALL Incidence during Economic Transition: Czech Republic**

*(Hrusak, Leukemia 2002)*

- **Collapse of Communist regime**
- **Incidence rate per 10,000 children**
- **Year of diagnosis**
Factors linked with Affluence and Modernization

- Maternal age at child-bearing
- Increased exposure to magnetic fields
- Breast-feeding
- Sibship size
- Early child care
- High hygiene level
- Rates of immunization

Infections and immunity?

Infectious Etiology?

The Greaves hypothesis *(Leukemia 1988)*
Correlation between affluence/modernization and peak ALL incidence at 2-5 years

„Delayed-infection hypothesis“:
Inadequate priming of the immune system, followed by abnormal immune response during late exposure towards common infections
Evidence for Delayed-Infection Hypothesis

Day-care attendance in infancy and risk of childhood ALL

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of cases</th>
<th>Period</th>
<th>Odds ratio* (confidence interval$)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece</td>
<td>136</td>
<td>0–2 years</td>
<td>0.28 (0.09–0.88)</td>
<td>Petridou 1993</td>
</tr>
<tr>
<td>New Zealand</td>
<td>121</td>
<td>0–1 year</td>
<td>0.65 (0.36–1.17)$</td>
<td>Dockerty 1999</td>
</tr>
<tr>
<td>Quebec</td>
<td>491</td>
<td>0–1 year</td>
<td>0.49 (0.31–0.77)</td>
<td>Infante-Rivard 2000</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>98</td>
<td>0–1 year</td>
<td>0.63 (0.38–1.07)$</td>
<td>Chan 2002</td>
</tr>
<tr>
<td>France</td>
<td>240</td>
<td>From birth onwards</td>
<td>0.6 (0.4–1.0)</td>
<td>Perrillat 2002</td>
</tr>
<tr>
<td>France</td>
<td>408</td>
<td>0–3 months</td>
<td>0.6 (0.4–0.8)</td>
<td>Jourdan-Da Silva 2004</td>
</tr>
<tr>
<td>California (a)</td>
<td>140</td>
<td>0–1 year</td>
<td>0.6 (0.45–0.95)</td>
<td>Ma 2002</td>
</tr>
<tr>
<td>California (b)</td>
<td>204</td>
<td>0–1 year</td>
<td>0.42 (0.19–0.90)</td>
<td>Ma 2005</td>
</tr>
<tr>
<td>United Kingdom**</td>
<td>1286</td>
<td>0–1 year</td>
<td>0.48 (0.17–0.62)$</td>
<td>Gilham 2005</td>
</tr>
<tr>
<td>United States of America**</td>
<td>1744</td>
<td>0–6 months</td>
<td>0.91 (0.72–1.15)$</td>
<td>Neglia 2000</td>
</tr>
</tbody>
</table>

From: Mel Greaves, Nat Rev Cancer 2006

Type I Diabetes and Childhood Leukemia

"Hygiene hypothesis"
Yazdanbakhsh, Science 2002

Protection against type I diabetes

Exposure to infections early in life

"Delayed-infection hypothesis"
Greaves, Leukemia 1988

Protection against ALL

Feltbower, ADC 2004
Model for Leukemogenesis in Children

**In utero**
- 1st hit: Molecular event
- 2nd hit: Molecular event(s)
- Preleukemic stem cell
- Common event? Infection-triggered selection during aberrant immune response

**Postnatal**
- Leukemia cell

Model for Infection-based Selection of Preleukemic Clones

Adapted from Greaves, Nat Rev Cancer 2006

- Preleukemic clone
- Infection
- Secondary mutations
- Survival
- Selective outgrowth
Summary

The cause of childhood leukemia remains unresolved.

One common cause is highly unlikely.

Most cases are not attributable to a single specific genetic disorder or environmental exposure.

Abnormal immune response during delayed infections is a plausible etiological mechanism – proliferative stress.

Large-scale studies are needed, including biologic specimens, to investigate gene-environment interactions.