Hemoglobinopathies in Northern Israel

Hematology Laboratory
Genetics Unit
Pediatric Hematology Unit

Emek Medical Center
האגרכנס 2014
חודש עבודה ראשון בעמק
אוקטובר 1978
הטורנות הראשונה בעמק
אוגוסט 1978

חודש עד חודש רашון בעמק
אוקטובר 1978

הטורנות הארושה בעמק
אוגוסט 1978
Hemoglobinopathies

- Disorders caused by abnormal Hemoglobin production or synthesis.

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- Updated: 2014.
Prof. Koren A. - Disclosures

- Novartis Medical Consultant In Sickle Cell Global Meeting – Philadelphia - 2006

- Research Grants from Novartis in Clinical Studies:
  - ICL 670 Deferasirox Study – 2006/7.

- Other Grants:
  - Materna Research Fund – IDA study.
Hemoglobinopathies

- Disorders caused by abnormal Hemoglobin production or synthesis.
- Gene Deletion – α thalassemia
- Single base substitution or deletion reduce β chain synthesis - β thalassemia
- Single base substitution or deletion production of pathological β globin chains - Hgb S (Sickle cell)/ Hgb C / Hgb E Disease / Hgb D.
- Abnormal meiosis – δβ fusion - δβ thalassemia.
Mechanisms responsible for Clinical Disease

- Suppression of globin synthesis: Thalassemia.
- Intracellular polymerization and Gelation of Hgb Molecules: Hgb S.
- Denaturation of Unstable Hemoglobin: Unstable Hemoglobins.
- Accumulation of Methemoglobin.
- Abnormal O₂ affinity: Hgb H, Bart and others.
Erythropoiesis and Globin Biosynthesis

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Megaloblast</th>
<th>Macrocyte</th>
<th>Normocyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of Erythropoiesis</td>
<td>LIVER</td>
<td>SPLEEN</td>
<td>BONE MARROW</td>
</tr>
<tr>
<td>% of Total Globin Synthesis</td>
<td>YOLK SAC</td>
<td>SPLEEN</td>
<td>α</td>
</tr>
</tbody>
</table>

Post Conceptual Age (weeks) | Postnatal Age (weeks)
---|---
6 | 6
12 | 12
18 | 18
24 | 24
30 | 30
36 | 36
1 | 6
6 | 12
18 | 18
24 | 24
30 | 30
36 | 36
42 | 42
48 | 48

Erythropoiesis and Globin Biosynthesis
Chromosomal organization of the globin genes

Hemoglobins
- Hb Gower 1 (ζ2ε2)
- Hb Gower 2 (α2ε2)
- Hb Portland (ζ2γ2)
- Hb F (α2γ2)
- Hb A2 (α2δ2)
- Hb A (α2β2)

Developmental Period
- Embryonic
- Fetal
- Adult
Hemoglobinopathies in Emek Medical Center (209 patients)

- Thalassemia Major (46)
- Thalassemia Intermedia (24)
- Sickle Cell Anemia (37)
- Sickle Cell Thalassemia (27)
- Hgb H + Taybee (63)
- Hgb CC (10)
- Others (5)

SC = 3
SD = 1
δβ = 1
\[ \beta \text{globin gene - Chromosome 11} \]

\[ \begin{align*}
\mathbf{\omega} & \beta_2 \\
\epsilon & \\
\gamma & A_y \\
\mathbf{\omega} & \beta_1 \\
\delta & \\
\beta &
\end{align*} \]

- \( \beta^0 / \beta^+ \) Thalassemia
- Hgb Lepore
- \( \delta \beta \) Thalassemia
- HPFH: High Persistent Fetal Hemoglobin
**β globin gene**

- **Exon 1**
- **Intron 1**
- **Exon 2**
- **Intron 2**
- **Exon 3**

**Promoter elements**

- "TATA BOX"

**RNA Splicing Signals**

- GT
- AG
- GT

**Cleavage Signals**

- AG
- ATAAA
β-globin gene - Mutations

Promoter elements
“TATA BOX”

Exon 1  Intron 1  Exon 2  Intron 2  Exon 3

- Transcription
- Splicing
- Nonsense
- Frame-shift
- Translation
- Polyadenylation
β globin gene - Chromosome 11
Locus Control Region Regulation

Activation
Inhibition
Diseases involving the \( \beta \) globin gene

- \( \beta^0 \) and \( \beta^+ \) Thalassemia
- \( \delta \beta \) Thalassemia
- Sickle Cell Disease
- Sickle Cell \( \beta^0 / \beta^+ \) Thalassemia
- Sickle Cell Hgb C Disease
- Sickle Cell Hgb O Arab Disease
- Sickle Cell Hgb D Disease
α globin gene - Chromosome 16

α Thalassemia - Thai

α thalassemia - Greek
$\alpha$ thalassemia – gene deletions

$\alpha$1  $\alpha$2
Normal

$\alpha$ Trait

$\alpha$ Trait

$\alpha$ Trait

$\alpha$ Trait

Hgb H Disease

Hydrops Fetalis

$\alpha$ Trait = $\alpha$ heterozygous

Hgb H = $\beta_4$ globin
α thalassemia
**β Thalassemia**

- Autosomal recessive disease characterized by a decreased production of β globin and intracellular precipitation of free α chains.

- **Clinical Picture:**
  - Chronic and progressive hemolytic anemia.
  - Extramedulary Hematopoiesis
  - Secondary Hemosiderosis due to Intestinal Iron absorption and Blood Transfusions:
    - Cardiomyopathy and Endocrine dysfunction.
  - Cholelithiasis.
Who is at risk?
Ethnic origin is critical!
Pathogenesis of β Thalassemia

γ  →  α

Hgb F
Selective survival of Hgb F containing precursors
Increased levels of Hgb F in red cells
High O₂ affinity of red cells
Reduced O₂ delivery
Erythropoietin
Tissue hypoxia
Marrow expansion
Increased Iron absorption
Iron overload
Cardiomyopathy
Endocrine deficiencies

α  →  β

Excess
Denaturation Degradation

Hemolysis
Splenomegaly
Anemia

Destruction of RBC precursors
Ineffective erythropoiesis

Transfusion

Skeletal deformity
Increased Metabolic rate
Wasting
Complications of Iron overload
Common in β Thalassemia

- Dilated Cardiomyopathy and Arrhythmias
- Liver fibrosis and cirrhosis
- Growth failure
- Hypothyroidism
- Hypoparathyroidism
- Hypogonadism
- Diabetes Mellitus
Growth and Puberty and its Management in Thalassaemia.
V.De Sanctis. Horm Res 2002 (165 patients)
Growth velocity decreased from a mean of 5.5 cm/year before puberty to 3 cm/year at time of puberty.
β Thalassemia
**β Thalassemia – Treatment**

- **Blood transfusion:** Regular packed red blood cells transfusions in order to maintain a pre-transfusion Hgb level of 9.5 – 11 gr/dl.
- **Folic acid supplementation:** ± 5 mg/day
- **Iron Chelators:**
  - Desferrioxamine (Desferal): *Subcutaneous* daily infusion (8 – 10 hrs/day).
  - Vitamin C – 100 mg/day.
  - **Oral chelators:**
    - Deferipone (L1)
      May be used in combination with DFO.
    - Deferasirox.
Iron loading from Blood Transfusions

- 1 unit of Packed cells contains 200 – 250 mg of iron
  Daily nutritional requirement 1 – 2 mg

- In Thalassemic patients signs of Iron overload can be seen:
  - After 10 to 20 transfusions
  - After Ferritin level is above 1,000 ng/dl.
Monitoring Iron Overload

- **Serum Ferritin:**
  - non invasive
  - acute phase reactant !!

- **Transferrin saturation:**
  - accuracy ?
  - above ? % reflects presence of NTBI ?

- **Liver biopsy**
  - Gold standard but invasive.
  - Correlation between liver and heart iron contents?
Monitoring Iron Overload

- SQUID
  - not available.
  - expensive.

- MRI
  - non invasive.
  - requires special techniques
    - T2 and T2*.

Bright areas represent high iron concentration; dark areas represent low iron concentration.
T2* Cardiac MRI
β Thalassemia
Clinical features - Survival

- Cause of death:
  Cardiomyopathy: 13 pts.
  Sepsis: 10 pts.

- Death:
T2* and LV Function

Anderson LJ. Eur Heart J 2001; 22: 2171-9

N=106
T2* - Cardiac Risk Ranging

Anderson LJ. Eur Heart J 2001; 22: 2171-9
Heart and Liver Iron – Single Measurement

No clinically useful relationship

Anderson LJ. Eur Heart J 2001; 22: 2171-9
Heart Iron & Serum Ferritin – Single Measurement

No clinically useful relationship

Anderson LJ. Eur Heart J 2001; 22: 2171-9
Iron Chelators

- **Parenteral**
  - Deferoxamine (hexadentate)
  - Short Half Life

- **Oral**
  - Deferiprone (bidentate)
  - Half Life – 8 - 9 hs
  - Deferasirox (tridentate)
  - Half Life – ± 16 hs
β Thalassemia – Desferal Treatment

Portable battery operated infusion pumps and infusors
Combination Therapy: Relief of Iron Toxicity

Tanner MA. Circulation 2007; 115: 1876-84
Deferasirox – Exjade
Oral Iron Chelator

- Selected from more than 700 compounds tested
- Tridentate* iron chelator
  - An oral, dispersible tablet
  - Administered once daily
  - Highly specific for iron
- Chelated iron excreted mainly in feces (< 10% in urine)

*3 polar interaction sites in the binding pocket.