Congenital hemoglobinopathies

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Red Blood Cell Disorders, BHS training course 2015
Learning objectives

• discuss clinical presentation and complications of congenital hemoglobinopathies

• how to confirm diagnosis?

• how to prevent and treat complications?
Introduction

• hemoglobinopathy = intracorpuscular defect leading to
  – the production of an abnormal hemoglobin (sickle cell anemia)
  – aberrant synthesis of one or more globin chains of hemoglobin (thalassemia)
Normal hemoglobin

Hemoglobin

Beta chains
Heme units with iron atom
Alpha chains

Hemoglobin Synthesis

<table>
<thead>
<tr>
<th>Globin Synthesis % of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Week 10 20 30 Birth 10 20 30 40

Adult 97 % 2.5 <1
Newborn 20 % <0.5 80

Embryonic:
- ζ2ε2 Gower-1
- α2ε2 Gower-2
- ζ2γ2 Portland
Epidemiology

• ~ 5% of the population worldwide is carrier of a hemoglobinopathy trait; over 1% of couples is at risk of having an affected child

• over 300,000 affected infants born each year (83% sickle cell disease; 17% thalassemia)
SICKLE CELL DISEASE
Belgium: one of the most frequently inherited diseases 1/2,329 newborns

Ketelslegers et al., BJH 2015
Genetics

Hemoglobin S

Hemoglobin C
# Sickle Cell Syndromes

<table>
<thead>
<tr>
<th>Sickle Cell Disease</th>
<th>Disease severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>homozygous Hb S</td>
<td>moderate to severe</td>
</tr>
<tr>
<td>Hb S $\beta^0$-thalassemia</td>
<td>severe</td>
</tr>
<tr>
<td>Hb SC</td>
<td>mild to severe</td>
</tr>
<tr>
<td>Hb S $\beta^+$-thalassemia</td>
<td>mild to severe</td>
</tr>
</tbody>
</table>
Pathophysiology

Oxygenated erythrocyte containing HbS

Deoxygenated erythrocyte with polymerisation of HbS

Dehydrated, sickled erythrocyte

Infarction

Acute pain
Acute chest syndrome
Hyposplenism
Osteonecrosis
Nephropathy

Inflammation
Increased expression of VCAM-1 and other adhesion molecules
Hypercoagulability

Haemolysis

Occlusion of postcapillary venules (vaso-occlusion)

Reperfusion

Free radicals, causing tissue damage

Vasculopathy and endothelial dysfunction

Free plasma haemoglobin, inactivating NO and generating reactive oxygen species

Functional NO deficiency

Pulmonary hypertension
Priapism
Leg ulcers
Cerebrovascular disease
Subphenotypes

Viscosity-Vaso-occlusion
Erythrocyte Sickling

Hemoglobin level
Vaso-occlusive pain crisis
Acute chest syndrome
Osteonecrosis

Serum LDH
Reticulocyte count
Plasma Hb and arginase
Pulmonary HTN, Priapism, Leg ulcers
Stroke?

Hemolysis-Endothelial Dysfunction
Proliferative Vasculopathy

α-thalassemia
shifts subphenotype
Clinical symptoms and complications

Signs and Symptoms
- Irritability
- Unusual sleepiness
- Looks pale
- Weakness
- Fast heart beat
- Big spleen
- Pain on the left side of the abdomen
Chronic complications

WHAT IS YOUR PAIN LEVEL TODAY?

- 0-1 no pain
- 2-4
- 5-6
- 7-8
- 9-10 most pain

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Pulmonary hypertension

Gladwin et al., N Eng J Med 2004
Pulmonary hypertension

Gladwin et al., N Eng J Med 2004
Cerebral vasculopathy and stroke

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Ohene-Frempong et al., Blood 1998
Cerebral vasculopathy and stroke

Ohene-Frempong et al., Blood 1998
Diagnosis

- complete blood count
- hemolysis
- blood smear
- Hb electrophoresis
- (genetic analysis)
## Diagnosis

<table>
<thead>
<tr>
<th>Sickle cell disease</th>
<th>HbS</th>
<th>HbA</th>
<th>HbA(_2)</th>
<th>HbF</th>
<th>HbC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>&gt;90</td>
<td>0</td>
<td>&lt;3.5</td>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
<td>Sβ(^0)-thalassemia</td>
<td>&gt;80</td>
<td>0</td>
<td>&gt;3.5</td>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td>Sβ(^+)-thalassemia</td>
<td>&gt;60</td>
<td>10-30</td>
<td>&gt;3.5</td>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td>SC</td>
<td>50</td>
<td>0</td>
<td>&lt;3.5</td>
<td>≤1.0</td>
<td>45</td>
</tr>
<tr>
<td>Sickle cell trait(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>≤40</td>
<td>&gt;60</td>
<td>&lt;3.5</td>
<td>≤1.0</td>
<td>0</td>
</tr>
</tbody>
</table>

adapted from Yawn et al., JAMA 2014
## Annual follow-up

<table>
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<tr>
<th></th>
<th>2 yrs</th>
<th>3 – 5 yrs</th>
<th>6 – 9 yrs</th>
<th>10 – 15 yrs</th>
<th>adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>transcutaneous saturation</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>urinalysis (microalbuminuria)</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>TCD/MRA</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>abdominal US</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>echocardiography</td>
<td></td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>lung function*</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>ophthalmology</td>
<td></td>
<td></td>
<td></td>
<td>HbSC</td>
<td></td>
</tr>
<tr>
<td>Hip X-ray/MRI**</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
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</tr>
</tbody>
</table>

* lung function if abnormal saturation, fatigue, recurrent ACS, asthma
** in case of pain/limping
Overall Survival

- 95% of children survive into adulthood
- death rate ~ 0.5/100 pts-year (children) vs ~ 5/100 pts-year (adults)
- transition period !!!

Quinn et al., Blood 2010
Prevention of complications

• **Education:** avoidance of hypoxia, dehydration, cold exposure – pain management – fever

• **Prevention of infection:**
  – vaccinations: H. influenzae, N. meningitidis, S. pneumoniae, influenza
  – prophylactic antibiotics
  – empiric antibiotics

• **Prevention of stroke**
Prevention of infections

Gaston et al., N Eng J Med 1986
Prevention of stroke

Stroke risk ~ velocity in ICA and MCA

170–199 cm/sec: RR x 7
≥200 cm/sec: RR x 40

Adams et al., N Eng J Med 2008
Treatment of acute events

- hydration 2-2.5 l/m²/day
- adequate analgesia, including NSAIDs and opioids
- broadspectrum antibiotics if fever or in ACS
- oxygen?
- incentive spirometry
- blood transfusion not routinely recommended
  except: severe ACS, stroke, splenic sequestration
Chronic transfusions: indications

Goal = reduce HbS < 30%

- primary and secondary stroke prevention (STOP I and II; SWiTCH; TwiTCH Study)
- recurrent ACS or severe crises despite MTD of HU
- repeated acute splenic sequestration
- prevention of progressive organ damage (??)
Chronic transfusions: complications

- iron overload: limited by partial exchange

- allo-immunisation: mainly Rh (C, E), Kell, Jk and Duffy
  - delayed hemolytic transfusion reaction = life-threatening
  - extended phenotyping is essential!

- (infections)
Hydroxyurea

1. induction HbF
2. lower neutrophil and reticulocyte counts
3. decreased adhesiveness
4. reduced hemolysis (increased MCV)
5. NO release with local vasodilatation

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Ware et al., Blood 2010
Hydroxyurea: benefit on VOC in HbSS children

First VOC

Second VOC

Charache et al., NEJM 1995
Hydroxyurea: benefit on survival in HbSS adults

Patients receiving hydroxyurea (N=24)

Patients not receiving hydroxyurea (N=9)

P < .001

Voskaridou et al., Blood 2010
## Hydroxyurea

### Indications
- more than 2 moderate to severe VOC/year
- severe or recurrent ACS
- severe chronic anemia interfering with daily activities
- stroke, if refusing chronic transfusions
- children (9 to 42 mths old) irrespective of clinical severity

### Treatment protocol
- starting dosage: 15 mg/kg/d (20 mg/kg/d for children)
- increase by 5 mg/kg/d every 8 wks;
  until mild myelosuppression or max 35 mg/kg/d
- maintain neutrophils >2,000/µl and platelets >80,000/µl
Hematopoietic Stem Cell transplantation

<table>
<thead>
<tr>
<th>Genoidentical</th>
<th>Unrelated SCT</th>
<th>Haploididentical SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard of care</strong></td>
<td><strong>Only in experimental trials and experimented centers</strong></td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Recurrence of stroke despite transfusion program</td>
<td></td>
</tr>
<tr>
<td>Elevated TCD velocity</td>
<td>Worsening cerebral vasculopathy despite transfusion program</td>
<td></td>
</tr>
<tr>
<td>Recurrent acute chest syndrome</td>
<td>Severe erythroid alloimmunization</td>
<td></td>
</tr>
<tr>
<td>Recurrent splenic sequestration</td>
<td>Pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Recurrent VOC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent stroke with cognitive impairment</td>
<td>Recurrent acute chest syndrome despite supportive care</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Recurrent severe VOC despite supportive care</td>
<td></td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle nephropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC alloimmunization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent priapism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cell source</th>
<th>PBCs</th>
<th>CB</th>
<th>BM or PBCs</th>
<th>PBCs</th>
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</thead>
<tbody>
<tr>
<td>BM or CB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TCD indicates transcranial Doppler; VOC, vasoocclusive crisis; and RBC, red blood cell.

Gluckman et al., Haematology 2013
# MSD transplantation

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts (N)</strong></td>
<td>50</td>
<td>50</td>
<td>185</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td><strong>Conditioning</strong></td>
<td>BuCY</td>
<td>BuCy</td>
<td>BuCy</td>
<td>BuCy</td>
<td>BuCy</td>
</tr>
<tr>
<td><strong>EFS</strong></td>
<td>82%</td>
<td>84%</td>
<td>91%*</td>
<td>85%</td>
<td>86–97%</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>95%</td>
<td>94%</td>
<td>96%*</td>
<td>96%</td>
<td>94–97%</td>
</tr>
</tbody>
</table>

* since addition of ATG
THALASSEMIAS

α-thalassemia
β-thalassemia
Epidemiology
α-thalassemia

Alpha Globin Gene Cluster
Chromosome 16

Zeta 2  Zeta 1  Alpha 2  Alpha 1

3’ ———— 5’

normal  silent carrier  trait  Hb H  Bart’s syndrome

α2  α1  α2  α1  α2  α1

α2  α1

α2  α1

α2  α1

α2  α1

α2  α1
**β-thalassemia**

![Beta Globin Gene Cluster on Chromosome 11](image)

<table>
<thead>
<tr>
<th></th>
<th>minor</th>
<th>intermedia</th>
<th>major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb level</td>
<td>&gt; 10 g/dl</td>
<td>7-9 g/dl</td>
<td>&lt; 7 g/dl</td>
</tr>
<tr>
<td>failure to thrive</td>
<td>no</td>
<td>sometimes</td>
<td>yes</td>
</tr>
<tr>
<td>splenomegaly</td>
<td>+/-</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>iron overload</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>type of mutation</td>
<td>β/β⁰ or β/β⁺</td>
<td>β⁺/β⁺ or β⁰/β⁺</td>
<td>β⁰/β⁰ or β⁰/β⁺</td>
</tr>
</tbody>
</table>

**β⁰**: absent production of β chains; **β⁺**: decreased production of β chains
Pathophysiology

Haemolysis

Excess free α-globin chains

Ineffective erythropoiesis

Increased erythropoietin synthesis

Anaemia

Reduced tissue oxygenation

Splenomegaly

Erythroid marrow expansion

Increased iron absorption

Iron overload

Skeletal deformities, osteopaenia

Formation of haeme and haemichromes

Removal of damaged red cells

Iron-mediated toxicity

Excess free α-globin chains

Degradation

Denaturation

Formation of haeme and haemichromes

Increased iron absorption
Clinical symptoms
Clinical symptoms
Clinical symptoms
Clinical symptoms

Skin

Liver
CIRRHOSIS
HCC

Heart
ARRHYTHMIA
HEART FAILURE

Free Iron

Endocrine organs
DIABETES
HYPOTHYROIDISM
HYPOGONADISM
HYPOPITUITARISM
Diagnosis

- complete blood count: microcytic, hypochromic
- hemolysis
- blood smear
- Hb electrophoresis
- genetic analysis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Hb A</th>
<th>Hb A2</th>
<th>Hb F</th>
</tr>
</thead>
<tbody>
<tr>
<td>β Thalassemia Minor</td>
<td>Dec</td>
<td>Normal to Increased</td>
<td>Normal to Increased</td>
</tr>
<tr>
<td>β Thalassemia Intermedia</td>
<td>Dec</td>
<td>Normal to Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>β Thalassemia Major</td>
<td>Dec</td>
<td>Usually Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>
Overall Survival

mild: ferritin < 2000 µg/l
moderate: ferritin 2000-4000 µg/l
severe: ferritin > 4000 µg/l
Treatment

- hematopoietic stem cell transplantation = cure
- chronic hypertransfusion + iron chelation
- iron chelation alone
- splenectomy/cholecystectomy
- Hb F inducers? (hydroxyurea?)
- gene therapy?
Chronic hypertransfusion

- correct anemia
- stop endogenous erythropoiesis
- maintain Hb between 9.5 and 11.5 g/dl
- iron chelation:
  - deferoxamine (Desferal®)
  - deferiprone (Ferriprox®)
  - deferasirox (Exjade®)
Table 4: Pesaro Classification for predicting outcome of HSCT for thalassaemia major

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Class 1</th>
<th>Class 2*</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly (≥2 cm below costal margin)</td>
<td>No</td>
<td>Yes/no</td>
<td>Yes</td>
</tr>
<tr>
<td>Irregular chelation#</td>
<td>No</td>
<td>Yes/no</td>
<td>Yes</td>
</tr>
<tr>
<td>Portal fibrosis on liver biopsy</td>
<td>No</td>
<td>Yes/no</td>
<td>Yes</td>
</tr>
</tbody>
</table>
MSD Transplantation

![Graph showing survival probability](image)

- Age < 7 years without hepatomegaly (n=49)
- Age ≥ 7 years without hepatomegaly (n=29)
- Age < 7 years with hepatomegaly (n=37)
- Age ≥ 7 years with hepatomegaly (n=46)

P < .0001
MUD Transplantation

Survival = 79% (61-94)

Thalassemia-free survival = 66% (43-83)

Nonrejection mortality = 25% (7-45)

Rejection = 13% (1-24)

YEARS AFTER TRANSPLANTATION
Alternative donor?

- non-sibling matched family donor: promising results → extended family HLA typing useful if consanguinity (Hussein et al., Pediatr Transplantation 2015)

- cord blood/haploidential donor: not enough data
Take home messages

- most common congenital hemoglobinopathies: sickle cell disease and β-thalassemia

- diagnosis: hemolytic anemia + blood smear, Hb electrophoresis +/- genetic analysis
Take home messages

• therapy:
  – sickle cell disease:
    • prevention!
    • HU/chronic transfusions
    • HSCT (MSD)
  – β-thalassemia major/intermedia:
    • chronic hypertransfusion/iron chelation
    • HSCT (MSD, MUD?)

Prof. Dr. Veerle Labarque - UZ Leuven – Nov 14, 2015
References


• http://www.bhs.be/committees/red-cells