PNH in children
same disease?
same approach?

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Pediatric hematologist/oncologist, WKZ/UMCU

6th EUROPEAN SYMPOSIUM ON RARE ANAEMIAS
1st Dutch-Belgian meeting for patients and health professionals

21st - 22nd November 2015
Amsterdam - The Netherlands
### Disclosures

<table>
<thead>
<tr>
<th>Company name</th>
<th>Research support</th>
<th>Employee</th>
<th>Consultant</th>
<th>Stockholder</th>
<th>Speakers bureau</th>
<th>Advisory board</th>
<th>Other</th>
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</thead>
</table>

**Nothing to disclose**
# This talk is applicable for:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definite</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia’s</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Membrane disorders (e.g. sferocytosis)</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Enzym defects (e.g. PKD, G6PD)</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>PNH</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Other forms of hemolytic disease</td>
<td>✓</td>
<td></td>
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</table>
### Bone marrow failure syndromes:

**Aplastic anemia (AA)**

**Myelodysplastic syndrome (MDS): RCC in childhood**

**Classification**


### Table 1. Classification of paroxysmal nocturnal hemoglobinuria

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate of intravascular hemolysis</th>
<th>Bone marrow</th>
<th>Flow cytometry analysis</th>
<th>Benefit from eculizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Florid (markedly abnormal LDH often with episodic macroscopic hemoglobinuria)</td>
<td>Hypocellular with areas of erythroid hyperplasia and normal or near-normal morphology</td>
<td>Large (50–100%) population of GPI-AP-deficient PMNs</td>
<td>Yes</td>
</tr>
<tr>
<td>PNH in the setting of another bone marrow failure syndrome</td>
<td>Mild (often with minimal abnormalities of biochemical markers of hemolysis)</td>
<td>Evidence of a concomitant bone marrow failure syndrome</td>
<td>Moderate (25–50%) population of GPI-AP-deficient PMNs</td>
<td>Typically no, but some patients in this subcategory have clinically significant hemolysis and may benefit</td>
</tr>
<tr>
<td>Subclinical</td>
<td>No clinical or biochemical evidence of intravascular hemolysis</td>
<td>Evidence of a concomitant bone marrow failure syndrome</td>
<td>Small (&lt;25%) population of GPI-AP-deficient PMNs</td>
<td>No</td>
</tr>
</tbody>
</table>
Classification

Bone marrow failure syndromes $\approx$ stem cell disease

- SAA
- hypercellular MDS
- RCC
Relevance

• very rare disease, important to recognize
• requires specific approach
• differential context
• children are not small adults
• treatment approach (symptomatic versus curative)
Case 1: 11yr old boy

**Symptoms:** fatigue (3months), bruises, dyspnea, dyscomort

**Signs:** pallor, petechiae, hematoma

**LAB:** pancytopenia, no signs of hemolysis

**Bone marrow:** severe aplastic anemia

**PNH:** 7-12% PI-deficient cells

**Conclusion:** SAA with small PNH clone (subclinical)

**Therapy:** according to AA protocol (ATG, ciclosporine)
Case 2: 16yr old girl

**Symptoms:** 6months headache, fatigue, nosebleeds, bruises.

**Signs:** pallor, petechiae.

**LAB:** anemia, reticulo ↑, thrombocytopenia, LDH ↑

**Bone marrow:** mild bone marrow failure (mega ↓, TPO ↑)

**PNH:** 2-10% PI-deficient cells

**Conclusion:** (subclinical) PNH with signs of BMF

**Therapy:** watchful waiting
Case 3: 13yr old girl

**Symptoms:** 1 week dyscomfort, 3 days belly ache, 1 day “bloody” urine.

**Signs:** Pallor, jaundice, tenderness abdomen

**LAB:** Anemia, reticulo ↑, thrombocytopenia, LDH ↑, Bili↑, kreat↑, leukopenia.

**Bone marrow:** normal, mild erythroid dysplasia

**PNH:** 90% PI-deficient cells

**Conclusion:** classic PNH

**Therapy:** eculizumab
PNH in children

**Incidence**

1. classic PNH

2. in pediatric AA and MDS

3. in patients with unexplained (hemolytic) anemia, thrombosis, or mild bone marrow failure
Incidence

1. classic PNH

2. in pediatric AA and MDS

3. in patients with unexplained (hemolytic) anemia, thrombosis, or mild bone marrow failure
## Table 1. Clinical and Laboratory Characteristics of 26 Patients with PNH.

<table>
<thead>
<tr>
<th>UPN</th>
<th>SEX/AGE</th>
<th>SIGNS AND SYMPTOMS</th>
<th>HEMATOLOGIC VALUES†</th>
<th>BONE MARROW CELLULARITY†</th>
<th>PNH CELLS</th>
<th>INITIAL DIAGNOSIS</th>
<th>DELAY TO DIAGNOSIS</th>
<th>FOLLOW-UP</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HGB</td>
<td>MCV</td>
<td>RETIC</td>
<td>WBC</td>
<td>ANC</td>
<td>PLTS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>g/liter</td>
<td>f/l</td>
<td>%</td>
<td>× 10⁹/liter</td>
<td>× 10⁹/liter</td>
<td>× 10⁹/liter</td>
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<tr>
<td>4</td>
<td>M/14.6</td>
<td>Anemia</td>
<td>53</td>
<td>114</td>
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<td>2.7</td>
<td>680</td>
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<tr>
<td>15</td>
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<td>103</td>
<td>NA</td>
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<td>3.1</td>
<td>930</td>
<td>15</td>
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<tr>
<td>23</td>
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<td>80</td>
<td>94</td>
<td>3.8</td>
<td>2.2</td>
<td>990</td>
<td>36</td>
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<tr>
<td>32</td>
<td>F/16.3</td>
<td>Anemia</td>
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<td>115</td>
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<td>7.5</td>
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<td>1.6</td>
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<td>500</td>
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<td>4.0</td>
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<tr>
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<td>250</td>
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<td>186</td>
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<td>90</td>
<td>0.5</td>
<td>3.4</td>
<td>1220</td>
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<td>M/17.3</td>
<td>Anemia</td>
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<td>100</td>
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<td>2.6</td>
<td>1170</td>
<td>90</td>
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<tr>
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<td>64</td>
<td>4.9</td>
<td>5.0</td>
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<td>95</td>
<td>109</td>
<td>4.8</td>
<td>3.2</td>
<td>1700</td>
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<td>213</td>
<td>M/12.9</td>
<td>Hemoglobinuria, jaundice</td>
<td>123</td>
<td>90</td>
<td>4.2</td>
<td>6.1</td>
<td>4090</td>
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<td>216</td>
<td>F/8.0</td>
<td>Hemoglobinuria</td>
<td>NA</td>
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<td>231</td>
<td>M/9.7</td>
<td>Thrombocytopenia</td>
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<td>83</td>
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<td>2.2</td>
<td>370</td>
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</table>

*HGB denotes hemoglobin, MCV mean corpuscular volume, RETIC reticulocyte count, WBC white-cell count, ANC absolute neutrophil count, PLTS platelet count, and NA value not available.
†RBC denotes red-cell cellularity, hypo hypocellularity, hyper hypercellularity, and NA value not available.

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 Ware et al.  
 NEJM 1991  

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6th European Symposium on Rare Anaemias - 1st Dutch-Belgian meeting for patients and health professionals
TABLE I. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender/race</th>
<th>Body weight (kg)</th>
<th>Body mass index</th>
<th>History of red cell transfusions</th>
<th>History of aplastic anemia</th>
<th>History of thrombosis</th>
<th>PNH-related symptoms</th>
<th>Type III</th>
<th>PNH clone size (%)</th>
<th>IPG classification</th>
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<tr>
<td>1</td>
<td>15</td>
<td>F/C</td>
<td>67.4</td>
<td>25.1</td>
<td>Remote</td>
<td>N</td>
<td>N</td>
<td>HA, Abd pain, bleeding, fatigue, GER, dark urine</td>
<td>66.5</td>
<td>69.9</td>
<td>12.1</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>M/C</td>
<td>55.8</td>
<td>21.4</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>HA, Abd pain, GER, dark urine</td>
<td>87.8</td>
<td>84.6</td>
<td>66.7</td>
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<tr>
<td>3</td>
<td>17</td>
<td>F/B</td>
<td>68.1</td>
<td>29.9</td>
<td>Recent</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>96.6</td>
<td>95.0</td>
<td>3.9</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>M/C</td>
<td>57.8</td>
<td>18.3</td>
<td>Remote</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>53.9</td>
<td>65.4</td>
<td>13.7</td>
</tr>
<tr>
<td>5</td>
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<td>55.1</td>
<td>22.4</td>
<td>Remote</td>
<td>N</td>
<td>N</td>
<td>HA, Abd pain, bleeding, dark urine, nausea</td>
<td>80.4</td>
<td>70.5</td>
<td>19.9</td>
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<tr>
<td>6</td>
<td>11</td>
<td>F/C</td>
<td>48.5</td>
<td>21.8</td>
<td>Recent</td>
<td>N</td>
<td>Y</td>
<td>HA, bleeding, fatigue, dark urine, nausea</td>
<td>90.7</td>
<td>89.5</td>
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<tr>
<td>7</td>
<td>17</td>
<td>M/B</td>
<td>60.5</td>
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<td>Remote</td>
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<td>N</td>
<td></td>
<td>32.0</td>
<td>69.6</td>
<td>18.4</td>
</tr>
</tbody>
</table>

PNH, paroxysmal nocturnal hemoglobinuria; IPG, International PNH Interest Group [18]; RBCs, red blood cells; Remote, >2 months from study entry; Recent, within 2 months of study entry; HA, headaches; Abd, abdominal; GER, gastroesophageal reflux; AA, aplastic anemia.

Reiss et al.
Pediatric Blood & Cancer 2014

_Incidence unknown —> PNH International Registry_
Incidence

1. classic PNH

2. in pediatric AA and MDS

3. in patients with unexplained (hemolytic) anemia, thrombosis, or mild bone marrow failure
PNH in pediatric AA/MDS: previous reports

AA (pediatric + adults)
—> 20-57% minor PNH clones

Low grade MDS adults
—> 13-23% minor PNH clones
PNH in pediatric AA

Timeus et al. Br J of Haematol. 2010: 53%

Paroxysmal Nocturnal Hemoglobinuria Clones in Children with Acquired Aplastic Anemia: A Multicentre Study

Fabio Timeus¹,²®, Nicoletta Crescenzio², Daniela Longoni³, Alessandra Doria², Luiselda Foglia², Sara Pagliano², Stefano Vallero¹, Valentina Decimi³, Johanna Svahn⁴, Giuseppe Palumbo⁵, Antonio Ruggiero⁶, Baldassarre Martire⁷, Marta Pillon⁸, Nicoletta Marra⁹, Carlo Dufour⁴, Ugo Ramenghi², Paola Saracco²

85 patients, prospective analysis of PNH clones
42% at diagnosis
48% during treatment
45% off therapy

PLOS ONE 2014
Incidence
1. Classic PNH

2. in pediatric AA and MDS

3. in patients with unexplained (hemolytic) anemia, thrombosis, or mild bone marrow failure
Incidence
1. classic PNH
2. in pediatric AA and MDS
3. in patients with unexplained (hemolytic) anemia, thrombosis, or mild bone marrow failure

Completely unknown! Screening!
PNH in children: clinic

12 patients 1992-2008

10/12 BMF

6/12 thrombosis (OAC!)

5/12 SCT

3/12 eculizumab

4/12 death

PNH in children: therapy

classic PNH → eculizumab (patient 3), anti-coagulation?

in moderate AA → watchful waiting (patient 2)

in severe AA

identical sibling → allo SCT

no identical sibling → IST → SCT (patient 1)

in MDS cytogenetics low risk → watchful waiting/SCT/IST

in MDS cytogenetics high risk → allo SCT
PNH outcome (pre-eculizumab)

Hillmen et al. NEJM 1995

N=80
PNH outcome (with eculizumab)

PNH in children: DEBATE?

classic PNH → eculizumab = lifelong → effects??
= not curative → sec. disease?
COSTS!!!

→ allo SCT ??

severe AA → IST often not effective, morbidity

→ upfront allo SCT ??
allo SCT in children with BMF

“the WKZ experience”

7 identical sibling
45 unrelated donor

Results improved dramatically!
Still a mortality risk

Disease evolution??
Conclusions

• PNH is a rare, yet severe disorder, also in children.

• Awareness is crucial.

• Disease burden is large.

• Eculizumab is a very effective treatment in classic PNH, yet not curative.

• Allogeneic SCT should be considered in selected patient groups
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Erasmus MC/SKZ
dr. H. van Ommen

UMCG/BKZ
drs. L. Hooimeijer.

dr. S Mussche
M. Openneer

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