Paroxysmal Nocturnal Hemoglobinuria

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The origin of the name....

PNH – Some history
- First description - J Schmidt (1648)
- Important description - Dr P. Strubing (1882)
- Constant hemosiderinuria – Marchiafava (1911)
- PNH - Ennekin (1925)
- Complement mediated hemolysis – Rosse/Dacie (1964)
- PNH is clonal – Luzzatto (1970)
- GPI biosynthesis – Kinoshita (1993)

Epidemiology
- Rare
- Different test sensitivities
- Different definitions
- Maybe 5-20/million in USA
- Incidence may be higher in other countries

Membrane proteins

Biosynthetic Pathway of GPI-anchor
**Complement system**

- Classical
- Alternative
- Lectin

Pathogenic surfaces

1. Classical Immune complexes
2. Alternative Constitutively active via spontaneous hydrolysis ("tick-over")

Proximal Amplification

- C3
- C3b
- C3 convertase

Terminal Inflammation

- Endothelial activation
- Leukocyte activation
- Platelet activation
- Thrombosis

Sequential stabilization

- C5a
- C5
- C5 convertase
- C5b-
- C5b-
- C5b-
- C5b-
- C5b-
- C5b-
- C5b-

Membrane Attack Complex (MAC)

Surface-bound complement regulatory proteins

- CD55
- CD59

**Pathophysiology of PNH**

1. Mutations in PG-A impair production of glycoprotein A (GPI) anchors
2. Blood cells lack surface expression of GPI-anchored proteins (GPI-AP), including the vital complement regulatory proteins CD55 and CD59
3. Lack of complement regulatory protein results in chronic unrestrained complement activation
4. Uncontrolled complement activation leads to hemolysis and life-threatening consequences of PNH

**Clonal expansion in PNH**

- Immune attack hypothesis
- Second mutation

**Types of PNH cells**

- Dingl et al, PNAS 2008
Often there is a delay in diagnosis

Symptoms

PNH phenotype cells in BMF
PNH and overlap syndromes

Suspect PNH

- Coombs negative hemolytic anemia
- Intravascular hemolysis
- Cytopenias
- Thrombosis
- Hemoglobinuria
- Unexplained iron deficiency, fatigue, abdominal pain, chest pain, ED, renal insufficiency, etc

Clinical evaluation: PNH/BMF

- Symptoms
- PMH
- Medication exposure
- Occupation
- Signs
  - Thrombosis – splenomegaly, hepatomegaly
  - Inherited marrow failure syndromes
- Family history
  - FA, DK, SDS, Gata-2……

Diagnostic evaluation (1)

- Flow cytometry (CD55, CD59)
- Morphology of blood smear
- Reticulocyte count
- Coombs test
- Ferritin, transferrin saturation, sTfR
- Folate
- Vitamin B12
- LDH
- Haptoglobin
- Bilirubin (direct and indirect)
- Liver function
- Creatinine/eGFR

- Urinalysis
- Urine hemosiderin
- Bone marrow biopsy
- D dimer
- NT-proBNP
- Erythropoietin
- Echocardiography
- Imaging
  - Abdomen
  - Chest

Diagnostic evaluation (2)

- Chromosome studies
- DEB testing (Fanconi anemia)
- Telomere length (screen for DK)
- BMF mutation panel (if indicated)
- Hepatitis B, C, HIV, Parvovirus B19
- TCR
- Copper
- HLA typing

Classification

- Hemolytic PNH
- PNH with bone marrow failure (AA, MDS)
- Subclinical
Therapy: Hemolytic PNH (1)

- Education of patient and family
  - Natural history
  - Risks
    - Thrombosis
    - Evolution to Aplastic anemia/MDS/AML
  - Indications for therapy
    - Supportive therapy
      - Folate, iron, RBC transfusion
    - Therapy for marrow failure
      - Eculizumab
  - Immunizations
    - Hepatitis B
    - Neisseria, Pneumococcus, Haemophilus

Therapy: Hemolytic PNH (2)

- Observation
  - Mild compensated hemolysis
  - LDH < 2 ULN
  - No thrombosis
  - Small clone size
  - No other significant cytopenias

- Folate supplementation (1 - 2mg daily)
- Monitor iron stores (supplement as needed)
- ? Anticoagulation

Therapy: Hemolytic PNH (3)

- Complement inhibitory therapy
  - Persistent high reticulocyte count and anemia (<10g/dL)
  - LDH > 2xULN
  - Large clone size >20% (neutrophils or monocytes)
  - RBC transfusion requirements
  - Progressive renal insufficiency
  - Thrombosis
  - Other symptoms related to PNH – fatigue, abdominal pain, dysphagia

Therapy: Hemolytic PNH (4)

- Follow up
  - New symptoms
  - Transfusion requirements
  - Markers of hemolysis
  - PNH clone size
  - Iron stores
- Frequency

Eculizumab ‘failure’

- Intravascular hemolysis => extravascular hemolysis
- Iron deficiency
- Folate
- ? Increase dose/frequency of eculizumab
- ? Indication for BMT

Natural history of PNH

- 100%
- 80%
- 60%
- 40%
- 20%
- 0%
- 0
- 5
- 10
- 15
- 20
- 25
- Years After Diagnosis

- Age and gender-matched controls
- Patients with PNH

- Patients surviving, %
- Cumulative Surviving, %

- N= 153
- Age and gender-matched normal population
- Soliris Treated PNH Population

- Numbers at Risk
- 153
- 113
- 45
- 43
- 12
- 10
- Time (years)
Thrombosis in PNH

Mechanisms of thrombosis

• Endothelial (blood vessel dysfunction)
  – Nitric oxide depletion
• Platelet dysfunction
• Iron deficiency
• Complement activation

Thrombosis

• Venous
  – Lower extremity/Pulmonary embolism
  – Mesenteric
  – Portal
  – Hepatic (Budd Chiari syndrome)
  – Cerebral sinus
• Arterial (<10%)
  – Coronary
  – Cerebrovascular

Pulmonary embolism

Mesenteric thrombosis

• Venous
  – Vague abdominal pain
  – Nausea/vomiting
• Arterial
  – Severe abdominal pain with minimal tenderness

Budd Chiari syndrome

• Abdominal pain
• Right upper quadrant tenderness
• Abdominal swelling (ascites)
• Jaundice
**Risk of thrombosis**

- Partly dependent on clone size
- Other precipitating factors
  - Surgery
  - Infection
  - Immobility/travel
  - Pregnancy
  - Birth control pills

**Prevention**

- Standard precautions in high risk situations
- Prophylaxis in patients with large clone size
  - Concomitant AA?
- Eculizumab
- No data on newer anticoagulants specifically in PNH

**Thrombosis - Therapy**

- Anticoagulation
  - Heparin, LMWH
  - Coumadin
- Thrombolysis
  - tPA
- Anticomplement therapy
  - Eculizumab
- Multidisciplinary approach
  - Interventional radiology
  - Hepatology
  - Vascular surgery

**Renal complications**

- Hemosiderin deposition
- Microthrombosis
- Nitric oxide depletion
- Papillary necrosis
- Stabilization/improvement with anti-complement therapy

**Pulmonary hypertension**

- Thromboembolism
- Vascular endothelial dysfunction
- Anemia

**PNH/BMF**

- Aplastic anemia
  - Eliminate potential causes/confounders
  - Observation
  - IST/androgens/eltrombopag
  - BMT
    - Donor selection
    - Conditioning regimen
Therapy of PNH/BMF

- CsA/ATG/Prednisone
- Eculizumab
- BMT
  - If AA is predominant problem
  - Transfusion dependence/ongoing hemolysis
  - Evolution to MDS/AML
  - Recurrent, severe thrombosis

Eculizumab

- Often effective
  - ~ 70% transfusion independent
- Will not improve WBC and PLT
- Does not alter risk of evolution
- Generally well tolerated
- Dose may be adjusted in some patients
- Look for other causes of fatigue
  - Iron deficiency

LT complications

- ATG/CsA
  - Immunosuppression
  - Renal toxicity, hypertension
  - Risk of tumors
- BMT
  - Immunosuppression
  - CsA toxicity
  - GVHD
  - Tumors

Special considerations

- Pregnancy
  - High risk of thrombosis
  - Eculizumab
- Surgery
  - Prophylaxis
  - Eculizumab
- Air travel
  - Prophylaxis

In development

- Other C5 inhibitors
  - Mab, Si-RNA, Aptamers
- C3 inhibitors
- C3 convertase inhibitors
- AP inhibitors
  - Si-RNA, Aptamers, FH based proteins

Thank you

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