PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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TYPICAL CASE

- 30 year old male comes to the hospital for severe headache and is found to have a blood clot in a blood vessel by his brain. He is treated for it with a blood thinner for 6 months. 2 years later comes to the hospital with severe abdominal pain. He is then found to have a blood clot near his liver. He is treated for this again with a blood thinner. He then comes back a third time, this time with severe anemia. What could be going on?!?!?!?!?!?!?

PNH

- A rare disorder
- Probably 1 case/million persons
- Probably more common but misdiagnosed as other blood problem
- Believed to shorten survival (35% of patient pass within 5 years of diagnosis)

- Described as far back as 1882
- Ultimately named PNH by Enneking
- Dr. Thomas Ham in 1937
  - One of the early tests in named for Dr. Ham

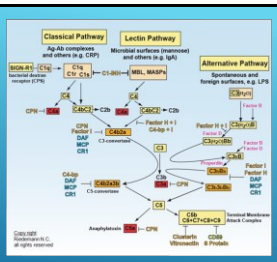
WHAT IS PNH

Severe anemia
Unexplained blood clots
Erectile dysfunction
Abdominal pain
Severe headaches
Red urine (only 25% of people)

PNH: WHEN TO SUSPECT

- A disorder in the relationship between red blood cells and the compliment cascade
- Results in a wide variety of sequela including blood clot, anemia, bone marrow failure etc

WHAT IS PNH?



UNDERSTANDING COMPLIMENT

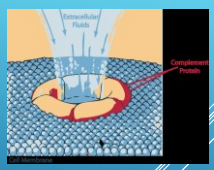
http://iahealth.net/complement-system/

COMPLIMENT

- Essentially compliment helps our immune system work
- Identifies organisms or proteins that shouldn't be there or are damaged
- Our "attack" cells then destroy it (which include some compliment itself)

WHAT HAPPENS IF WE ARE MISSING COMPLIMENT?

- Increased risk of infections, particularly meningitis!



https://en.wikipedia.org/wiki/Terminal_complement_pathway_deficiency#/media/File:Complement_death.PNG

COMPLIMENT IN PNH

- Compliment doesn't normally attack red blood cells
- Red blood cells can normally deactivate compliment but cant in PNH
- This lead to hemolysis

COMPLIMENT IN PNH

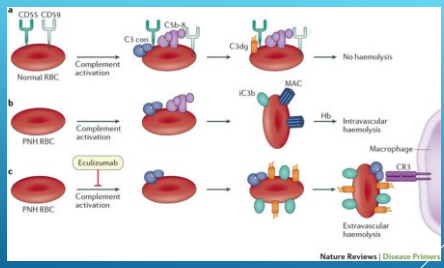
http://www.soliris.net/PNH/physician/what-is-pnh

- When hemolysis occurs the following things happen
  - Anemia develops
  - Bilirubin goes up (jaundice)
  - Blood clots occur
  - Cells get damaged
  - People feel awful

HEMOLYSIS

- The interaction with RBC and compliment is mediated by glycoproteins
- phosphatidylinositol glycan A (PIG-A) is typically defective in PNH
- When this enzyme is affected, compliment doesn't interact normally and red blood cells are attacked

COMPLIMENT IN PNH



http://www.nature.com/articles/nrdp201728

- For unclear reasons, the bone marrow produces the affected cells more than normal ones

COMPLIMENT IN PNH

- Anemia: red blood cells get destroyed, resulting in anemia
  - This is intravascular hemolysis (occurring in blood vessels)
  - Coombs negative (no antibodies)
  - Increased LDH and bilirubin

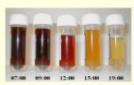
CLINICAL FINDINGS

- Red urine: The broken red blood cells secretes myoglobin that gets urinated out
  - Possibly occurs more common at night, hence the name
  - Only 20-25% of people have this

CLINICAL FINDINGS

Laboratory studies

- Urinanalysis
  - » Hemoglobinuria (dark or brown red color)
  - » Hemosidrin (if ongoing ch. Hemolysis)

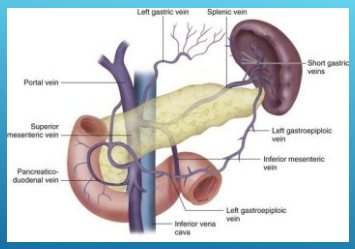


Urine of a patient with PNH, showing the episodic nature of the dark

https://www.slideshare.net/rafiqagh/hpc-43414266

- Blood clot: One of the most common findings
  - Exact etiology isn't clear
  - Possibly related to the hemolysis itself
  - Blood clots often occur in unusual locations (veins near liver, brain, spleen, etc)

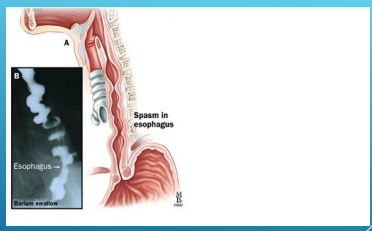
CLINICAL FINDINGS



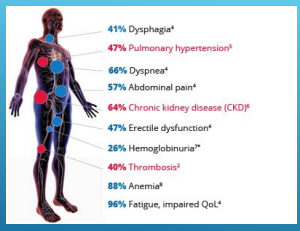
https://qph.ec.quoracdn.net/main-qimg-9b402987ad0e71ee57e6ffa7b152bc6a-c

- Recurrent infection
- Myocardial infarction (heart attack)
- Renal failure
- Erectile dysfunction
- Esophageal spasm

CLINICAL FINDINGS



http://www.cardiachealth.org/chest-pain-symptoms-your-gi-tract



http://www.pnhnetwork.ca/learn-more/pnh-complications

DIFFERENTIAL

- Other conditions that can mimic PNH
  - Aplastic anemia: the two can go together
  - Myelodysplasia
  - Hemolytic Uremic Syndrome

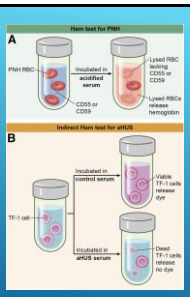
TESTING

- Routine labs: anemia, high LDH, low haptoglobin, negative Coombs test, high indirect bilirubin

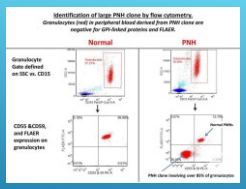
TESTING

- Ham test

HAM TEST



bloodjournal



FLOW CYTOMETRY

ASH image bank

FLAER TEST

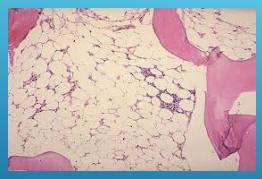
- Similar to flow cytometry but labels the defective GPI anchors

WHOM TO SUSPECT

- Usually younger patients, 30s average age
- Clots in odd locations
- Unexplained hemolysis
- Bone marrow failure
- Other conditions that can go along…

CO-EXISTING CONDITIONS

- Often goes along with myelodysplasia or aplastic anemia



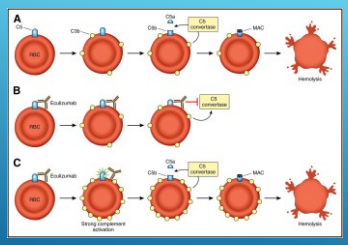
https://en.wikipedia.org/wiki/Aplastic_anemia

- Blood clots: require blood thinners, most often coumdin
  - Required for life
  - Newer blood thinners?

HOW TO TREAT

- Co-existing conditions
  - May require traditional therapy for other conditions
    - Aplastic anemia
      - Immune suppression
      - Stem cell transplant
    - Myelodysplasia
      - Hypomethylation
      - Stem cell transplant

- PNH itself
  - Therapy that inhibits compliment (Eculizumab)



http://www.bloodjournal.org/content/129/8/922

- Problem with inhibiting compliment
  - Increased infection risk
  - Life long (and expensive!) therapy
  - Doesn't always work forever

- Most current therapies are still geared toward changing compliment
- Unclear where to go from there

FUTURE DIRECTIONS