Hemolytic anaemia- **Classification**

Hereditary (intracorpuscular)

- Hemoglobinopathies- HbS,Thalassemias
- Enzymopathies –G6PD def. ,pyruvate kinase def.
- Membrane-cytoskeletal defects- **HS**, elliptocytosis, ovalocytosis,stomatocytosis

- Aquired red cell membrane abnormality- **PNH**

Classification cont.

Aquired (extracorpuscular)

- AIHA-warm antibody AIHA
  -cold antibody AIHA
- Drug induced- nitrates, chlorates, methylene blue, dapsone, cisplatin/ arsine, stibine, copper, and lead
- Mechanical trauma- microangiopathic hemolytic anemia
- Infection/Direct toxic effect - malaria, Shiga toxin–producing *Escherichia coli* O157:H7
- Splenomegaly

- Hereditary – Familial HUS

Common features(HA)

- General – jaundice,pallor
- Other sign- splenomegaly,bossing of skull
- Hb.- N to severely reduced
- MCV,MCH- usually increased
- RC- increased
- Bilirubin – increased(unconjugated)
- LDH- increased
- Heptoglobin- reduced to absent

Investigation

Tests of increased red cell breakdown

- S.bilirubin – indirect/unconjugate ↑
- Urine urobilinogen ↑
- Faecal stercobilinogen ↑
- S. heptaoglobin ↓/ absent
- Plasma LDH ↑

Evidence of intravascular hemolysis - hemoglobinaemia, hemoglobinuria, methaemoglobinaemia, haemosiderinuria

Investigation

Increased red cell production

- ↑RC
- PBF – macrocytosis, polychromasia,normoblast,
- Marrow – erythroid hyperplasia, raised iron stores
- Xray bone -evidence of expansion of marrow space(tubular bones & skull)

Investigation cont.

Test of damaged red cell

- PBF- fragmented red cell,spherocytes, target cell(leptocytes),schistocytes,sickle cell,acanthocytes(spur cell)heinz bodies(unstable Hb)
- Osmotic fragility ↑
- Autohemolysis test
- Coombs antiglobulin test
- Electrophoresis of abnormal Hb(HbA2,HbF)
- Test for sickling
- Screening of G6PD

Test for shortened RBC Life

- 51Cr labelling RBC

Membrane cytoskeletal defect

- Membrane cytoskeletal complex of red cell is integrated.
- Abnormality of any component-structural failure – hemolysis
- Abnormalities almost due to inherited mutations

Hereditary spherocytosis

- Common hemolytic anemia ,inherited as an autosomal dominant condition.
- Occurs due to defect in protein (spectrin, ankyrin)which anchor lipid bilayer to underlying cytoskeleton.

Clinical features

- Anemia
- Splenomegaly
- Jaundice - ↑unconjugated bilirubin
- Pigment gall stone -↑bile pigment production
- Chronic leg ulcers

Investigation

- Anaemia(spherocytes)
- ↑RC
- Blood film – microcytosis,spherocytes
- MCV ↓, **MCHC- ↑**
- Osmotic fragility ↑ (pink test)
- Autohemolysis test - ↑(10-15%) N <4%
- Direct coomb antiglobin test – negative
- molecular studies demonstrating a mutation in one of the genes underlying HS

Treatment

- There is currently no treatment aimed at the cause of HS
- Blood transfusion in case of severe hemolytic crises
- Folic acid supplementation 5mg/d
- Splenectomy should be postponed untill 4yrs of age
- Indication – severe hemolysis, family history death from similar disease, evidence of cholecystitis & cholelithiasis
- H . Influenza vaccine must 2 wks before splenectomy

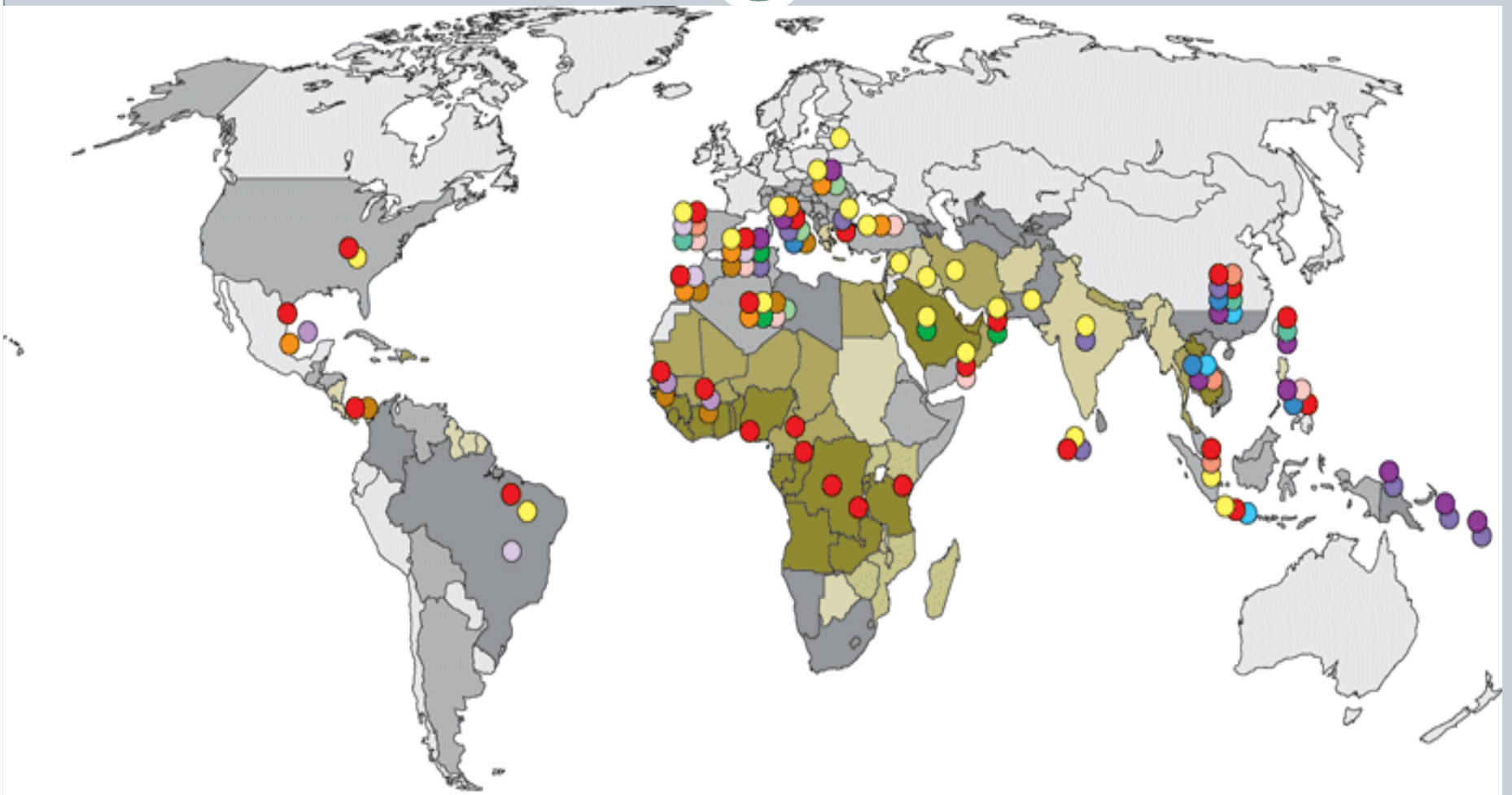
Enzymopathies

- Enzymes-role in metabolism of red cell
- Provide energy in form of ATP
- Prevent oxidative damage to hemoglobin and other protein.
- G6PD –critical role (red cell) only source of NADPH that directly and via glutatione defends these cells against oxidative stress.

G6PD deficiency

- Most common congenital shunt defect
- X linked trait affecting males, females are carrier
- N G6PD is designated as type B found in 11% African American males
- Most common and significant clinical variant is A- (negative) – confers partial protection against malaria
- Hemolytic episodes occur on exposure to oxidant stress (viral, bacterial infection, metabolic acidosis, drugs, fava beans)

Epidemiology (prevalence)



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 18th Edition: www.accessmedicine.com

Clinical Manifestations

- Majority-asymptomatic
- neonatal jaundice (NNJ)-peak incidence of clinical onset is between day 2 and day 3
- Acute hemolytic attack- three types of triggers: (1) fava beans, (2) infections, and (3) drugs
- starts with malaise, weakness, and abdominal or lumbar pain
- Anemia
- Jaundice

Investigation

- A/c episodes of hemolysis on exposure to oxidant stress – self limited since it affects old RBC only
- During a/c hemolysis episodes
- Rapid fall in hematocrit (25-30%)
- Intravascular hemolysis test positive
- Blood film –heinz body (supravital stain crystal violet) – bite cells (fragmented red cells)

Diagnosis

- Male african /mediterranean descent
- A/c hemolytic episodes
- History of possible exposure to oxidative stress
- Screening test – methaemoglobin reduction test
  fluorescent screening test
  ascorbate cyanide screening test
- Enzyme assay on red cell

Drugs causing hemolysis in G6PD

- Antimalarial – primaquine, pamaquine,dapsone
- Sulfonamide – sulfamethoxazole
- *Antibacterial/antibiotics* -Cotrimoxazole, Nalidixic acid, Nitrofurantoin, Niridazole
- *Antipyretic/analgesics* -Acetanilide, Phenazopyridine (Pyridium)
- Miscellaneous

  vit. K, doxorubicine, methylene blue,furazolidone,

Treatment

- Avoid /correct ppt (oxidative stress) factors
- Favism is entirely preventable by not eating fava beans.
- alternative drugs
- Acute hemolytic episodes
- Hydration
- blood transfusion
- acute renal failure develops- hemodialysis

Paroxysmal nocturnal hemoglobinuria(PNH)

- Acquired chronic HA characterized by triad-

- persistent intravascular hemolysis subject to recurrent exacerbations
- Often pancytopenia
- Distinct tendency to venous thrombosis

- same frequency in men and women
- encountered in all populations throughout the world
- rare disease

Paroxysmal nocturnal hemoglobinuria

- Rarer aquired disorder of red cell membrane defect arising at stem cell level
- Defect in stem cell is a mutation affecting myeloid progenitor cells, resulting in partial or complete deficiency of anchor protein which make RBC sensitive to lytic effect of complement.

  Decay accelerating factor (DAF) CD55

  Membrane inhibitor of reactive lysis (MIRL) CD59

Consequences of Hemolysis in PNH

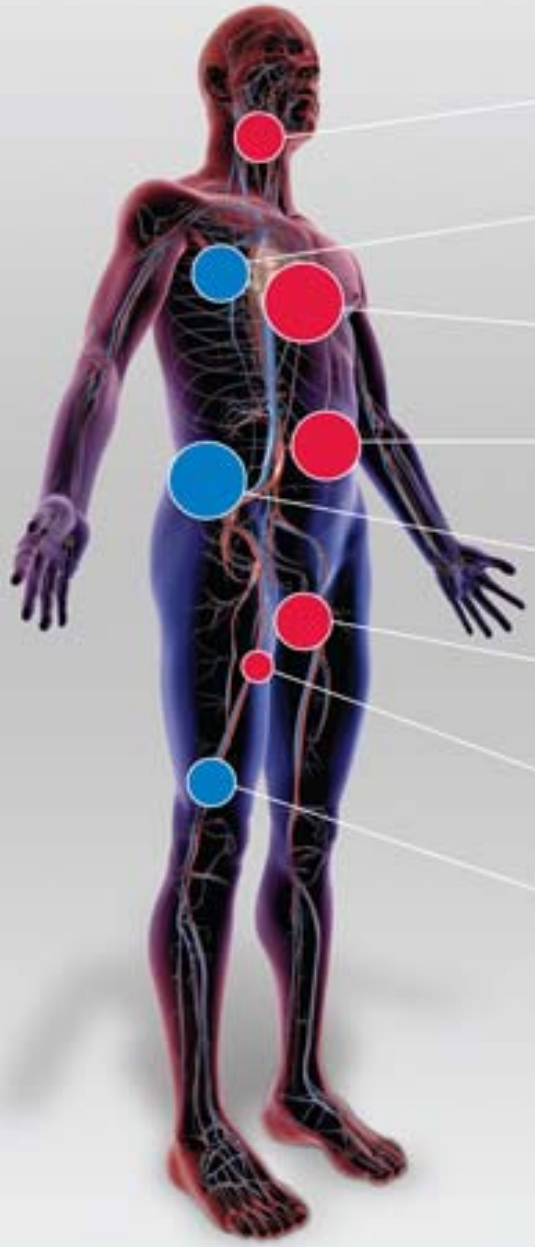
Thrombosis: The Leading Cause of Mortality in PNH

- Venous and arterial thromboses account for approximately 40% to 67% of PNH-related deaths.
- Pulmonary embolism (PE) or deep vein thrombosis (DVT) is the most common clinical presentation
- PNH TE occurs in typical and atypical sites
  - DVT, mesenteric, and PE most common
  - Budd-Chiari, renal, and dermal less common
- 64% of Patients With PNH Have Chronic Kidney Disease (CKD)

Clinical feature

- classical presentation-morning passing "blood instead of urine."
- Hemolytic anaemia, thrombocytopenia, neutropenia
- Venous thrombosis

PNH Symptom Incidence Rate



- 41% Dysphagia[4]
- 47% Pulmonary hypertension[5]
- 66% Dyspnea[4]
- 57% Abdominal pain[4]
- 64% Chronic kidney disease (CKD)[6]
- 47% Erectile dysfunction[4]
- 26% Hemoglobinuria[3]
- 40% Thrombosis[7]
- 88% Anemia[8]
- 96% Fatigue, impaired QoL[4]

Who to test for PNH

- PNH Consensus Guidelines and the International PNH Interest Group recommend continued monitoring of patient populations at higher risk for PNH.
- Populations include: Coombs-negative hemolytic anemia, hemoglobinuria, aplastic anemia, refractory anemia-myelodysplastic syndrome, unexplained cytopenias, and unexplained thrombosis.

Diagnosis

- Hemolytic anaemia –test for intravascular hemolysis
- Demonstration of lysis of RBC after complement activation by acid (**hams test**)or reduction in ionic strength(**sucrose lysis test**)
- Flow cytometry analysis of GPI linked anchor protein CD55,CD59

Relationship between PNH and AA

- The *natural history* of PNH can extend over decades
- PNH may evolve into aplastic anemia (AA), and PNH may manifest itself in patients who previously had AA.
- Rarely (estimated 1–2% of all cases), PNH may terminate in acute myeloid leukemia.

Treatment

- Supportive treatment- transfusion of filtered red cells
- Folic acid supplements (at least 3 mg/d) are mandatory
- humanized monoclonal antibody, eculizumab, directed against the complement protein C5(iv every 14 days)
- Allogeneic BMT; when an HLA-identical sibling is available, BMT should be offered to any young patient with severe PNH.

- A/c thrombotic event (budd chiari syndrome & cerebral thrombosis)

  Thrombolytic agents – tpa/heparin/LMWH & warfarin
- PNH-AA syndrome,- immunosuppressive treatment with antilymphocyte globulin (ALG or ATG) and cyclosporine

Autoimmune Hemolytic Anemia (AIHA)

- most common form of acquired hemolytic anemia next to malaria
- autoantibody directed against a red cell antigen

Clinical Features

suspicion of AIHA must be high

- Anaemia
- jaundice
- Splenomegaly

Diagnosis

Coombs antiglobulin test

Treatment

- Transfusion of red cells
- The first-line – glucocorticoids(1 mg/kg)
- Rituximab(anti CD 20) remissions upto 80%
- second-line - long-term immunosuppression with low-dose prednisone, azathioprine, or cyclosporine.
- splenectomy

Acquired hemolytic anemia

- Mechanical(microangiopathic HA) eg marathon runners,prolonged barefoot ritual dancing,prosthetic heart valves.
- Toxins and drugs eg hyperbaric oxygen,nitrates,chlorates,methylene blue,dapsone,cisplatin,arsine,stibine,copper and lead
- Infection eg malaria,shiga toxin
- splenomegaly