Hereditary Hematological Disorders

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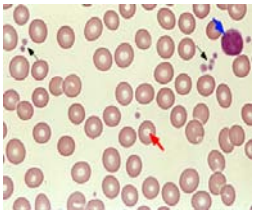
Overview:



Disorders of red cell shape.

Red cell Enzyme disorders

Disorders of Hemoglobin

Inherited bleeding disorders- platelet disorders, coagulation factor deficiencies

Inherited Thrombophilia

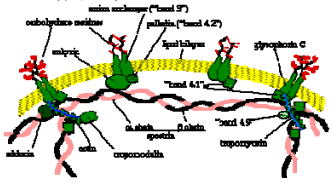
Disorders of red cell shape (cytoskeleton):

- Hereditary Spherocytosis- sphere
- Hereditary Elliptocytosis-ellipse, elongated forms
- Hereditary Pyropoikilocytosis-bizarre red cell forms

Normal red blood cell- discoid, with membrane flexibility

Hereditary Disorders of red cell cytoskeleton:

- Mutations of 5 proteins connect cytoskeleton of red cell to red cell membrane
  - Spectrin (composed of alpha, beta heterodimers)
  - Ankyrin
  - Pallidin (band 4.2)
  - Band 4.1 (protein 4.1)
  - Band 3 protein (the anion exchanger, AE1)
  - RhAG (the Rh-associated glycoprotein)



Hereditary Spherocytosis:

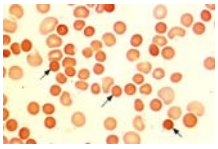
- Most common hereditary hemolytic disorder (red cell membrane)
- Mutations of one of 5 genes (chromosome 8) for cytoskeletal proteins, overall effect is spectrin deficiency, severity dependant on spectrin deficiency
- 200-300:million births, most common in Northern European countries
- Underestimate as mild forms not clinically significant
- 75% AD, remainder AR or new mutations (subsequently AD inheritance)

Clinical features:

- Neonatal jaundice- severe (phototherapy), +/- anaemia
- Hemolytic anemia- moderate in 60-75% cases
- Severe hemolytic anaemia in 5% (AR, parents ASx)
- fatigue, jaundice, dark urine
- Splenomegaly
- Chronic complications- growth impairment, gallstones
- Often follows clinical course of affected family members
- Severe anemia with concurrent parvovirus infection- red cell aplasia

Investigations:

- Blood film- spherocytes, increased reticulocytes
- Elevated bilirubin, LDH
- Osmotic fragility
- Flow cytometry
- Gene tests not required
- Further studies: SDS page- detects molecular defect of Red cell membrane proteins in specific families (not required)

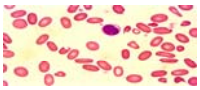


Treatment:

- Hematinics- Folic Acid supplementation
- Blood Transfusion as needed
- Splenectomy- indications: frequent transfusion, poor growth, massive splenomegaly with risk rupture (lifestyle limitations)
- Cholecystectomy
- Monitor growth and development
- Education and Genetic Counseling- genogram, likely inheritance and risk to future offspring

Hereditary Elliptocytosis/ Pyropoikilocytosis/ SE Asian Ovalocytosis:

- Most forms AD, except HPP which is AR
- Alpha spectrin (65% of HE), Beta Spectrin(30%), protein 4.1 (5%)
- HE- 2.5 to 5: 10,000 US



- Africa/SE Asia up to 30% of population (protective against malaria)
- Severe hemolysis associated with homozygous/ compound heterozygous forms
- Clinical Spectrum- asymptomatic to life threatening hemolysis

Red Cell Enzymopathies:

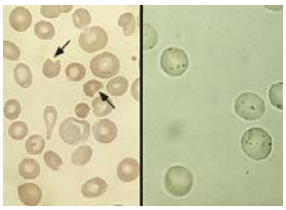
- Red cell enzyme pathways responsible for energy production and prevention of damage to red cell- glycolytic pathway (PK deficiency), redox potential (G6PD deficiency)
- No Nucleus- space efficiency- O2 carrying capacity
- Limited lifespan 120 days in N red cells, reduced in membrane disorders, enzyme disorders and haemoglobinopathies/thalassaemia.

G6PD Deficiency:

- Glucose-6-phosphate dehydrogenase enzyme-essential to counter oxidant stress to red blood cells
- Most common red cell enzymopathy 400 million cases worldwide
- Gene located on X chromosome- X linked disorder
- Affected hemi zygote males, carrier hemizygous females (silent), affected hemizygous females due to unequal lionization
- 12% African American men, 20% AA women hemizygous, 1% homozygous, 35% Greek/Mediterranean, 70% Kurdish Jews
- 10 distinct enzyme variants-almost all point mutations, rare deletions
- G6PD B+ Caucasian/wild type, G6PD A- AA/African form, G6PD Mediterranean form

G6PD Deficiency:

- Red cell unable to overcome oxidant stress- drugs, infections
- Clinical findings: asymptomatic, episodic hemolysis to severe chronic hemolysis
- Severity depends on degree of enzyme deficiency
- Majority of patients asymptomatic in absence of oxidant stress-drugs, foods (fava beans), fever/illness, chemicals-naphthalene



Diagnosis/Treatment:

- Diagnosis: Classical Clinical features-ethnicity, family history
- Blood film- bite and blister cells, anaemia, reticulocytosis, elevated LDH
- Quantitative enzyme level-falsely elevated with reticulocytosis
- Treatment: Avoid Oxidant drugs/ chemicals/ foods- Fava Beans (especially in early spring)
  - » Careful observation with fever, other triggers
  - » Transfusion as required
  - » Genetic Counseling- female carriers, male offspring, screen siblings/extended family, monitor neonates

Drugs/Chemicals causing oxidant stress in G6PD deficiency:

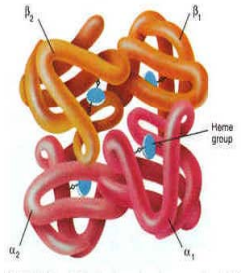
- Acetanilid
- Dapsone
- Furazolidone
- Methylene blue
- Nalidixic acid
- Naphthalene (mothballs, henna)
- Phenacetin
- Niridazole
- Nitrofurantoin
- Phenazopyridine
- Phenylhydrazine
- Primaquine
- Sulfacetamide
- Sulfamethoxazole
- Sulfanilamide
- Sulfapyridine
- Thiazosulfone
- Toluidine blue
- Trinitrotoluene
- Diphenhydramine
- Isoniazid
- L-DOPA
- Menadione
- Paraaminobenzoic acid
- Phenytoin
- Probenecid
- Procainamide
- Pyrimethamine
- Quinidine
- Quinine
- Streptomycin
- Sulfamethoxypyridazine
- Sulfisoxazole
- Trimethoprim
- Tripelennamine
- Vitamin K
- Acetaminophen
- Aminopyrine
- Ascorbic acid (except in very high doses)
- Aspirin
- Chloramphenicol
- Chloroquine
- Colchicine

Data from Beutler, E, Blood 1994; 84:3613.

Other Red cell Enzyme Disorders:

- Rare- classified as non-spherocytes hemolysis
- PK deficiency- homozygosity for mutant PK gene, results in reduced enzyme levels
- Most AR
- Clinical features- hemolysis, splenomegaly
- Blood film- no spherocytes, reticulocytes, normal osmotic fragility
- Diagnosis: enzyme level
- Treatment- supportive (folic acid), transfusion, splenectomy

Thalassaemia/ Hemoglobinopathies



Hb A- Adult Hemoglobin

Globin gene clusters in man:

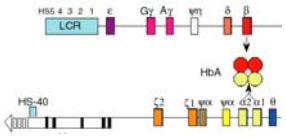
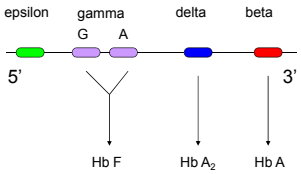


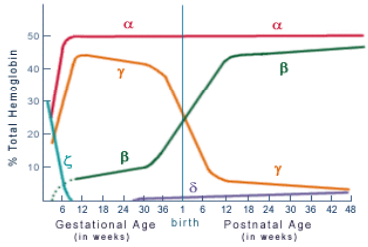
Figure drawn by Dr. Ross Hardison, which can be found at: <http://globin.cse.psu.edu>.

Hemoglobin Synthesis

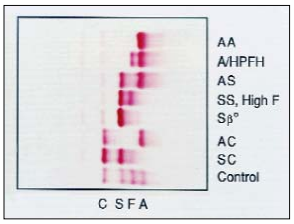
- Gene for beta globin is on chromosome 11
- Gene for alpha globin is on chromosome 16
- Adult Hemoglobin (Hb A) is $\alpha^2\beta^2$
- Fetal Hemoglobin (Hb F) is $\alpha^2\gamma^2$
- Hemoglobin A_2 is $\alpha^2\delta^2$



Globin Chain Synthesis:



Diagnosis



Hemoglobin Electrophoresis on cellulose acetate at pH 8.6

- HEP, HPLC or isoelectric focusing used to identify variant hemoglobin's
- Separates variant hemoglobin's based on differences in charge
- Sickle solubility testing detects only HbS, so should rarely be used

Sickle Cell Disease (SCD)

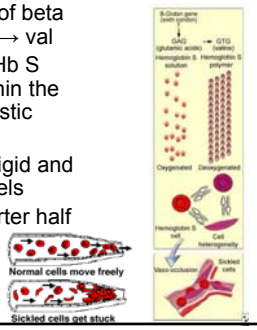
- SCD refers to a group of disorders characterized by a predominance of HbS
- SCD affects 1 in 375 African American live births
- 1 out of 10 African Americans with trait
- Includes: HbSS, HbSC HbS/β–thalassemia, HbS/Other

History of Sickle Cell Disease

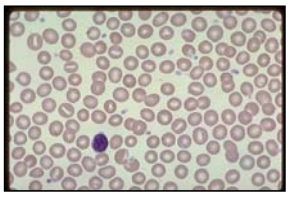
- First described in 1910 by James Herrick
- SCD is most common in persons of African, Mediterranean, Arabic, and Indian descent
- Individuals with sickle cell trait with resistance to malarial infection
- In the mid 1970's the National Sickle Cell Anemia Act led to the Cooperative Study of Sickle Cell Disease (CSSCD) which prospectively followed over 3500 infants with sickle cell disease to determine the natural history of the disease

Pathophysiology

- Mutation at sixth position of beta globin chain changes glu → val
- With deoxygenation, the Hb S molecule polymerizes within the RBC leading to characteristic shape changes
- Sickled erythrocytes are rigid and obstruct small blood vessels
- Sickled RBCs have a shorter half life than normal RBCs

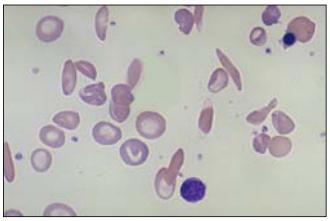


Normal Blood Smear



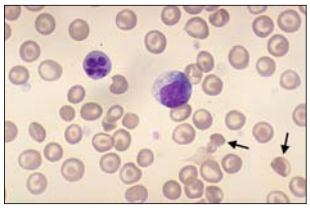
- HEP: AF
- Hgb 10.5 – 13.5 gm/dL
- MCV 72 – 100 fL
- Retics < 1.5%
- Smear: normal

HbSS Disease



- HEP: SF
- Hgb 6.5 – 8.5 gm/dL
- MCV 80 – 100 fL
- Retics 5 – 15%
- Smear: sickled cells, NRBCs, polychromasia

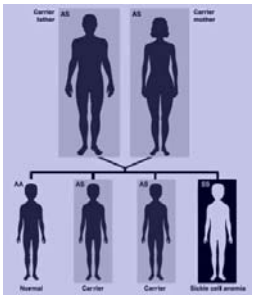
HbSC Disease



- HEP: SC
- Hgb 9.0 – 12.0 gm/dL
- MCV 60 – 80 fL
- Retics 3 – 5%
- Smear: microcytosis, hypochromia, target cells

Inheritance of Sickle Cell Disease

- Inherited in an autosomal recessive fashion
- All 50 States, DC, Virgin Islands, and Puerto Rico have universal screening-HEP
- Sickledex test (sickle solubility) false negative if Hb S% low, poor test



Newborn Screening in NC

- Universal screening since 1994, targeted from 1986
- Once abnormal screen is detected, family, local physician, and state counselor are notified
- Confirmatory testing and family studies done
- If diagnosis is confirmed, referral to Sickle Cell Center; tracking ensured by state counselors
- **GOAL**: Education, comprehensive care, and initiation of penicillin prophylaxis by 2-3 months of age

Diagnosis of Sickle Cell Disease

Sickle Cell Variants	HEP in NB	MCV fL	HbA_2 %	Hb F %	One parent	Other parent
Hb SS (SCA)	FS	N or ↑	< 3.6	< 25	AS	AS
Sickle β^0thalassemia	FS	↓	> 3.6	< 25	AS	A, ↑ A_2, ↑ F, ↓ MCV
Sickle β^+thalassemia	FS, FSA	↓	> 3.6	< 25	AS	A, ↑ A_2, ↓ MCV
HbSC Disease	FSC	↓	NA	< 15	AS	AC
Sickle Cell Trait	FAS	N	< 3.6	< 1.5	AS	A

Hemoglobin's reported in order of quantity. Fetal hemoglobin is significantly reduced by 6-12 months of age.

Clinical Manifestations of Sickle Cell Disease

Increased susceptibility to infections/ Asplenia

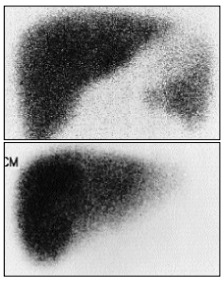
Hemolysis – "break down of red cells"
- Anemia
- Jaundice, gallstones

Acute vaso-occlusive events
- Painful events, pneumonia
- Stroke, splenic sequestration, priapism

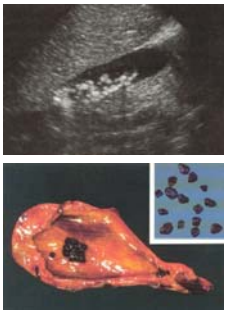
Chronic organ damage
- Spleen, kidneys
- Lung, brain, eyes, hips

Increased Susceptibility to Infections

- Develop functional asplenia due to repeated infarcts within the spleen
- Leads to increased risk of sepsis, particularly with *Streptococcus pneumoniae*
- Immunizations with HIB, Prevenar, Pneumovax, Meningococcal (Menactra)
- Penicillin prophylaxis
  - 3 years for HbSC
  - 5 years for HbSS, HbS/β^0thalassemia



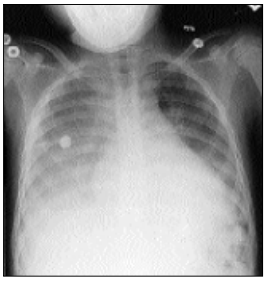
Gallstones



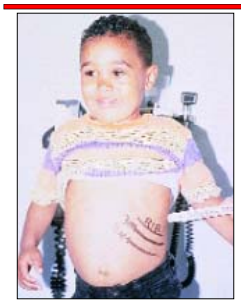
- Chronic hemolysis results in formation of pigmented (bilirubin) gallstones
- Occur in 1/3 sickle cell patients by adulthood
- Symptoms: abdominal pain, nausea, vomiting
- Laparoscopic cholecystectomy if symptomatic

Acute Chest Syndrome

- New pulmonary infiltrate with fever, dyspnea, chest pain, hypoxia, increased WBC
- Lower lobes most commonly involved; 1/3 bilateral
- May have associated pleural effusions
- May be caused by infection, sickling, fat embolism, atelectasis



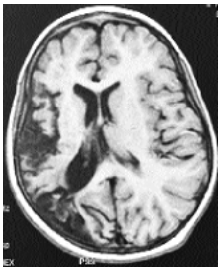
Splenic Sequestration



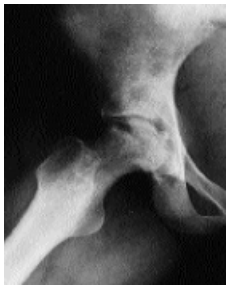
- Most common in young children (< 2 years of age)
- Anemia, thrombocytopenia and splenomegaly
- May cause hypovolemic shock and death if occurs acutely
- Usually require PRBC transfusions
- 50% recurrence rate
- Splenectomy for severe or recurrent events

Stroke

- Occurs in 5 – 10% of children with SCA
- Thrombotic or infarctive event involving large intracranial arteries
- Present with weakness, aphasia, seizures, LOC
- Often results in permanent neurological damage and long-term disability



Avascular Necrosis



- Osteonecrosis of bone in areas with limited collateral circulation
- Femoral, humeral heads most commonly involved
- May occur at any age; up to 50% of adults affected
- Occurs in all genotypes of sickle cell disease

Genetic Counseling in SCA:

- Partner testing to determine present of Hb S, or disease causing variant such as Hb C, beta thalassaemia
- CBC, blood film, Hb electrophoresis/IEF/HPLC
- Gene testing not required

Thalassaemia

- A group of disorders characterized by a deficiency in the synthesis of globin chains
  - quantitative abnormality (reduced rate of synthesis)
  - Compared with Haemoglobinopathies –inherited disorder resulting in production of abnormal haemoglobin such as Hb E (common in SE Asia) or SCA
- alpha or beta Thalassaemia
- Most common in persons of Mediterranean, Arabic, Indian, Asian descent
- Severity ranges from asymptomatic to transfusion dependent anemia

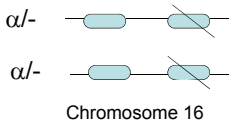
Alpha Thalassaemia

- 4 alpha (α) globin genes- α1 and α2
- Most commonly deletion of 1-4 of α globin genes
- Silent Carrier State – 1 α globin gene is missing
- Alpha Thalassaemia Trait – 2 α globin genes missing (Cis or Trans)
- Hemoglobin H Disease – 3 α globin genes missing
- Hydrops Fetalis – 4 α globin genes missing

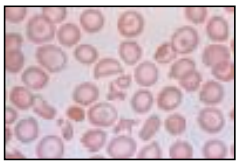
Alpha Thalassaemia Carrier:

- Single gene deletion on one chromosome
- Clinically silent
- Normal RBC parameters and electrophoresis, can be missed
- Diagnosis requires DNA analysis, no abnormal globin chain produced so IEF/HEP normal
- Molecular testing: targeted mutational analysis by PCR for common mutations, full gene sequencing

Alpha Thalassaemia Trait



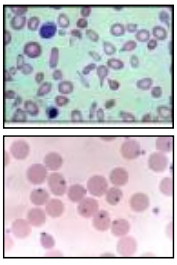
Chromosome 16



- Mild microcytosis
  - MCV 65 – 75 fL
- Mild anemia
  - Hgb 10.5 – 12 gm/dL
- Inheritance may be either $\alpha\alpha$/-- (cis) or α-/α- (trans)
  - 30% African Americans have $\alpha\alpha$/α-, 2-3% α-/α-
  - Cis form such more common in SE asia/FIL/MED/THAI, large deletions affecting both genes
- Can be confused with iron deficiency anemia
- May have Hb H or Barts on newborn screen

Hemoglobin H Disease

- Genotype α-/--
- Hemoglobin H = β^4
  - Unstable hemoglobin leads to increased hemolysis
- Chronic hemolytic anemia
  - Hemoglobin 7-10 gm/dL
  - MCV 55-65 fL
- Splenomegaly – may result in need for splenectomy
- May need transfusions with illness/pregnancy
- Clinical severity depends- deletional and non-deletional forms



Heinz bodies

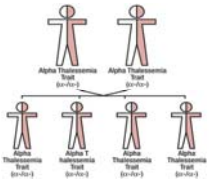
Hemoglobin Barts

- Genotype --/--
- Causes hydrops fetalis or premature infant death in utero, all postnatal haemoglobins contain α chains, therefore incompatible with life
- Massive hepatomegaly due to extramedullary hematopoiesis
- Hgb 4-10 gm/dL
- Significant morbidity in mother during pregnancy
- Hemoglobin Barts elevated in all newborns with alpha Thalassaemia mutations (carriers/trait and HbH)
  - Tetramers of γ chains = $\gamma 4$

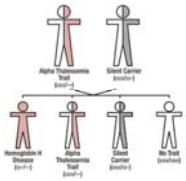
Genetic Counseling for Alpha Thalassaemia:

- At risk population- African American, other-SEA, middle eastern, Indian
- Known family history
- Suspicion on red cell indices e.g. microcytosis
- Hemoglobin electrophoresis may be unhelpful for carrier and trait as no abnormal Hb produced in adults
- Genetic testing and partner screening: PCR, gene sequencing
- Counseling depending on potential outcome of couple
- Prenatal diagnosis- CVS/amniocentesis –molecular testing

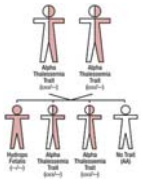
Alpha Thal- trans



Alpha Thal- Cis/Silent carrier



Alpha Thal- Cis/Cis

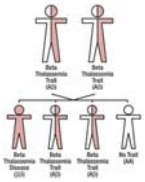


Beta Thalassaemia:

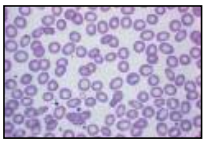
- Impaired production of β chains, relative excess of α chains, unstable, precipitation
- β chain production begins after birth, predominant from 6/12 age, therefore not clinically significant before this, where Hb F ($\alpha 2 / \gamma 2$) predominates
- Over 100 mutations known to affect β globin gene, non-deletional- splice mutations, nonsense/frame shift mutations, promoter region mutations

Beta Thal inheritance

- AR



Beta Thalassaemia Minor



- Beta Thalassaemia minor occurs when one of the β globin genes is defective
  - Complete absence of the beta globin protein β^{o}
  - Reduced synthesis of the beta globin protein β^{+}
- Relative excess of α chains
- Mild microcytic anemia

•HEP: Hb AF with elevated A_2 (> 3.5%)

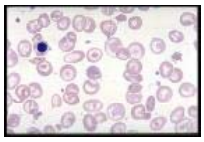
•Hb 9.5-12 gm/dL

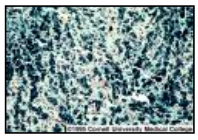
•MCV 60-75 fL

- **Thalassaemia intermedia**: moderately severe but does not need regular transfusion;may occur with β^{o}/β^{+} or β^{+}/β^{+}

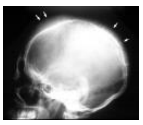
Beta Thalassaemia Major

- Homozygous β^{o}/β^{o}, no β chains
- HEP: HbF and HbA_2, No Hb A
- Ineffective erythropoiesis
- Severe microcytic hypochromic anemia
- Transfusion dependent
  - Chronic transfusions lead to iron overload if untreated
  - Patients also hyperabsorb dietary iron





Complications in Beta Thalassaemia Major

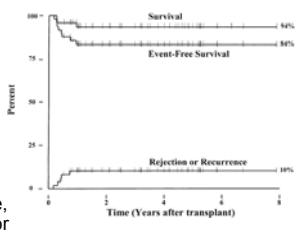


- Skeletal changes due to extramedullary hematopoiesis
- Hyperbilirubinemia and gallstones
- Splenomegaly requiring splenectomy

- Poor growth
- Endocrine dysfunction
- Cardiac dysfunction

Bone Marrow Transplantation

- Goal is "cure" of SCD or thal
- Only 25% of patients have HLA-matched sibling
- Require high-dose chemotherapy and radiation therapy as preparative regimen; sterility likely
- Currently reserved for patients with significant complications such as stroke, recurrent episodes of ACS, or pain or those with HLA matched siblings



Genetic Counseling in β Thalassaemia:

- AR
- Both parents carriers- β Thalassaemia minor (may be silent, microcytosis only or confused with iron deficiency)
- Compound heterozygosity with other haemoglobinopathies e.g. Hb E/β, Hb S/β, Hb C/β thal also possible
- Gene testing-PCR/sequencing required for prenatal diagnosis

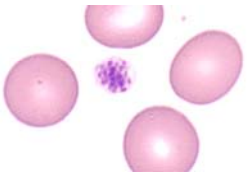
Inherited Bleeding Disorders:

- **Platelet disorders**
- Skin and mucous membrane bleeding (mouth/ nose/ genitourinary/ heavy periods)
- Bleeding with minor trauma- cuts
- Immediate and generally milder bleeding with surgery
- Mild-moderate Bruising/petechiae
- Rarely haemathroses/muscle and soft tissue bleeds
- Examples- TAR, Bernard-Soulier syndrome, Von Willebrand's disease

- **Coagulation Deficiencies**
- Joint and muscle bleeding
- Bleeding with trauma but also spontaneously more common depending on defect
- Delayed and severe bleeding post operatively
- Large, palpable bruises, no petechiae
- Examples- Haemophilia A and B, Factor deficiencies- XI, V, VII

Inherited Platelet disorders:

- Rare
- Quantitative and Qualitative defects described
- Normal platelet number 150-400,000
- Platelet count is normal from birth, can detect from birth
- Testing- CBC and film (characteristic blood film changes- size of platelets, colour granules, inclusions ect), platelet function studies, flow cytometry for GP on platelet surface, gene sequencing, other-electron microscopy



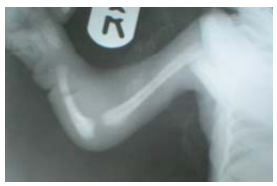
Quantitative Platelet Deficits

- Thrombocytopenia with absent radii (TAR)
- Amegakaryocytic thrombocytopenia
- X-linked thrombocytopenia
- Wiskott-Aldrich syndrome
- May-Hegglin Anomaly
- Other
  - Fanconi anemia
  - Trisomies 13 and 18
  - Trisomy 21

TAR Syndrome

- Severe thrombocytopenia (15-30, 000) with absence of bilateral radii
  - Can have GI, other skeletal, and cardiac abnormalities, as well
  - Always have thumbs (compared with Fanconi's anaemia)
- Autosomal recessive inheritance
  - Very rare
- Most common cause of death is bleeding
  - Intracranial
- Etiology unclear
  - Poor maturation of megakaryocytes?
- Treatment:
  - Supportive
  - Thrombocytopenia usually improves after 2 years of age
  - BMT for recalcitrant cases
- Prognosis
  - 50% survive to age 3
  - Not a pre-malignant condition

TAR Syndrome



Wiskott-Aldrich Syndrome

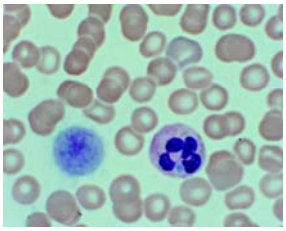
- Syndrome consisting of eczema, immunodeficiency, and thrombocytopenia
- Etiology:
  - Mutation in WAS protein
    - Xp11.22-23
    - Expressed only in hematopoietic cells
  - Affects cellular architecture
    - Impacts cell signaling and protein shuttling
  - WASp may function as a bridging protein to the cell cytoskeleton
- X-linked inheritance
  - 4 in 1 million male births
- Labs:
  - Thrombocytopenia with small platelets (4-5 fL)
  - Low number of T-cells
    - B-cell numbers are preserved
  - Low IgM levels
  - Poor response to vaccines (esp. polysaccharides)
  - Mutational analysis
- Die from infection, bleeding, or malignancy
  - Most die in teens without BMT
- Treatment:
  - Supportive care
  - Steroids and IVIG can improve platelet counts
  - Splenectomy
  - BMT

X-linked thrombocytopenia

- Thrombocytopenia without eczema or immune deficiency
- Etiology:
  - Mutation in the WASp gene
  - X-linked inheritance
- Thought to be a less-severe phenotype of WAS

May-Hegglin Anomaly

- Macrothrombocytopenia and leukocyte inclusions
- Etiology:
  - Mutation in the *MYH9* gene
  - Decreased production of non-muscle myosin
  - Leads to defective megakaryocyte maturation
  - Other MYH9 defects: Sebastian, Fechtner, Ebstein's syndromes
- Autosomal dominant disorder
  - 180 cases reported
  - Gene Sequencing/Linkage analysis
- Labs:
  - Platelets: 40-80K, up to 30 fL
  - WBC: Cytoplasmic inclusion bodies on Wright staining
- Treatment
  - Supportive care
  - Steroids not effective
  - Most patients do well
- Prognosis-overall good, bleeding variable



Amegakaryocytic thrombocytopenia

- Severe thrombocytopenia (plts ,20,000) and absent plt precursors in BM without physical abnormalities
  - Type I: severe, early onset of thrombocytopenia and bone marrow failure
  - Type II: slowly increasing platelet count in first year of life, then bone marrow failure in preschool years.
- Etiology:
  - Mutation in *c-mpl*, the thrombopoetin receptor
  - Type I: total loss of the receptor
  - Type II: mutation in the extracellular domain of the TPO receptor
    - Some residual function
- AR, rare condition
- Treatment: supportive, BMT
- Prognosis:
  - Poor without BMT
  - Pre-malignant condition

Qualitative Platelet Defects

- Glanzmann thrombasthenia
- Bernard-Soulier syndrome
- ADP storage pool defect
- Alpha-granule storage deficiency

- Often not detected till adulthood, not syndromic

Glanzmann Thrombasthenia

- Severe bleeding syndrome
- Etiology:
  - Mutation in GPIIb/IIIa
  - Responsible for platelet aggregation
- Autosomal recessive inheritance
- Clinical characteristics
  - Easy bruising
  - Mucocutaneous bleeding
  - Severe hemorrhage after surgery or trauma
  - Spontaneous bleeding uncommon
  - Bleeding tendencies variable-even in same patient
- Labs:
  - Platelets: normal to high
  - Platelet size: normal
  - Prolonged bleeding time
  - Platelet aggregation: only to ristocetin
- Treatment:
  - Supportive care
    - Patients can develop antibodies to GP IIb/IIIa
  - Some patients respond to DDAVP
  - RFVIIa
  - BMT

Bernard-Soulier Syndrome

- Severe bleeding syndrome
- Etiology:
  - Mutation in GP Ib/IX/V
  - Responsible for platelet adhesion
- Autosomal recessive inheritance
- Clinical characteristics
  - Easy bruising
  - Mucocutaneous bleeding
  - Severe hemorrhage after surgery or trauma
  - Spontaneous bleeding uncommon
- Labs:
  - Platelets: mildly low (have shortened half-life)
  - Platelet size: large
  - Prolonged bleeding time
  - Platelet aggregation: to everything <u>but</u> ristocetin
- Treatment:
  - Supportive care
    - Patients can develop antibodies to GP Ib/IX/V
  - Some patients respond to DDAVP
  - Anti-fibrinolytic response variable
  - BMT

ADP Storage Pool Defect

- Mild to moderate bleeding disorder
- Etiology:
  - Absence of ADP or ATP in dense granules (or absence of the granules themselves)
- Autosomal recessive inheritance
- Clinical characteristics:
  - Mild to moderate bleeding
  - Epistaxis
  - Menorrhagia
  - Hemorrhage after surgery or trauma
- Labs:
  - Platelets: normal
  - Platelet size: normal
  - Prolonged bleeding time
  - Platelet aggregation: no second wave
- Treatment:
  - Supportive care
  - Most (75%) patients respond to DDAVP
  - Anti-fibrinolytics
- Associated conditions:
  - Hermansky-Pudlak syndrome
  - Chediak-Higashi syndrome

Alpha-Granule Deficiency

- Mild bleeding disorder
- Etiology
  - Failure to develop or maintain alpha granules
  - "Grey platelet syndrome"
- Autosomal recessive inheritance
- Clinical characteristics
  - Relatively mild course
  - Easy bruising
  - Excess bleeding after surgery or trauma
- Labs:
  - Platelets: mild to moderate thrombocytopenia
  - Platelet size: large, washed out
  - Prolonged bleeding time
- Treatment:
  - Some patients respond to DDAVP
  - Anti-fibrinolytics

Questions ?

Resources: http://www.genetests.org

http://www.cooleysanemia.org

Pediatric Hematology-Oncology:

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