Hereditary elliptocytosis & pyropoikilocytosis

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Red cell membrane disorders

- Hereditary pyropoikilocytosis
- Hereditary elliptocytosis
- Hereditary spherocytosis

RBC proteins

Skeletal – structural integrity

- Spectrin α & β
- Protein 4.1 or 4.1R
- Actin

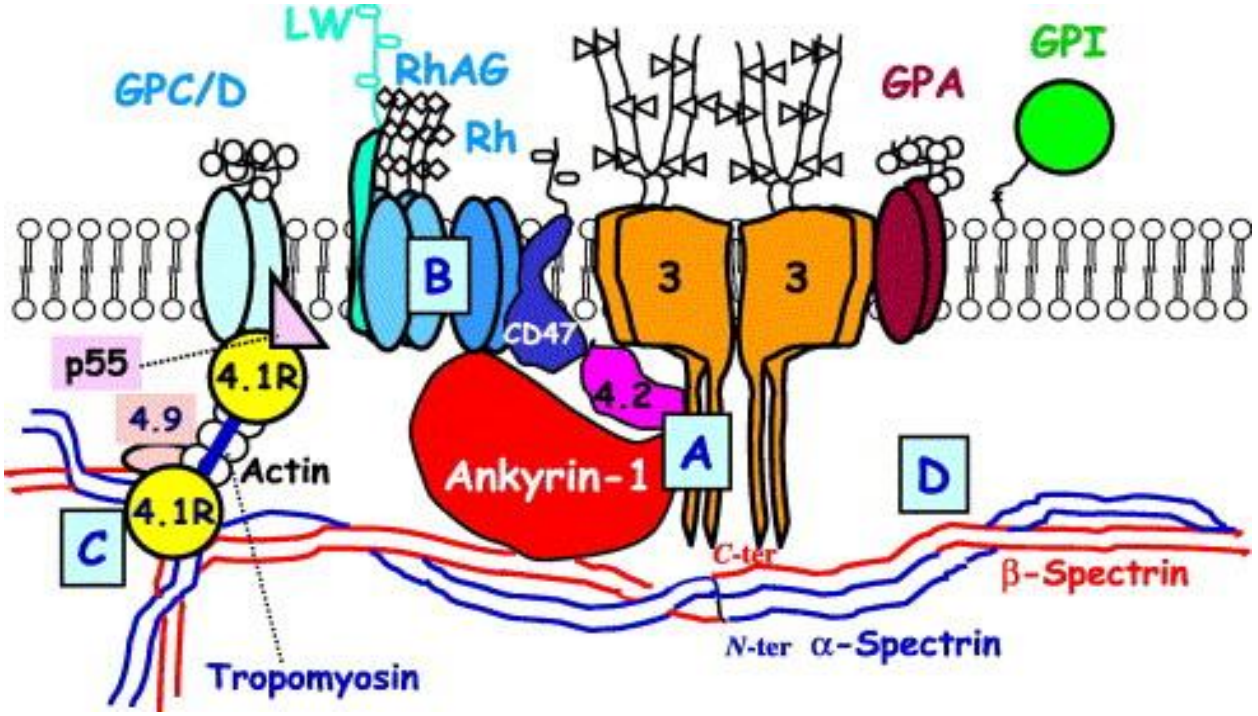
Transmembrane –ion transport, blood antigens (Rh),

- Band 3 (AE1)

Linker Proteins – attach skeletal to transmembrane

- Ankryin with 4.2
- 4.1R (glycophorin C & D)

Red cell membrane



Spectrin α & β
Actin
Ankryin
Protein 4.1
Protein 4.2
AE1 (Band 3)

Delauny J. The molecular basis of hereditary red cell membrane disorders. Blood Reviews: 21 (1) January 2007, 1-20.

Hereditary Elliptocytosis (HE)

- Elliptocytes
- Overall incidence is 1:5000 (slightly more frequent in US)
- Increased in African & Mediterranean populations (malarial resistance)
- Clinical spectrum – silent carriers to transfusion dependent hemolysis

Hereditary Elliptocytosis

- Failed to regain normal shape after passage in microcirculation
- Red cell precursors are round, elliptical with age
- Pathogenesis is unknown … perhaps skeletal reorganization after prolonged or repeated stress

Protein defects

- Spectrin α-chain binding sites (60%)
  - Autosomal Dominant, rarely de novo
  - Mutation in the heterodimer self-association site
  - Usually missense mutations at highly conserved residues of spectrin
  - Can have “Founder effect”, distinct spectrin mutations in persons of similar genetic backgrounds
  - Phenotypes vary – modifier alleles
  - Elliptocytes w/ variable poikilocytes & cell fragments
  - Hemolysis is variable

Protein Defects

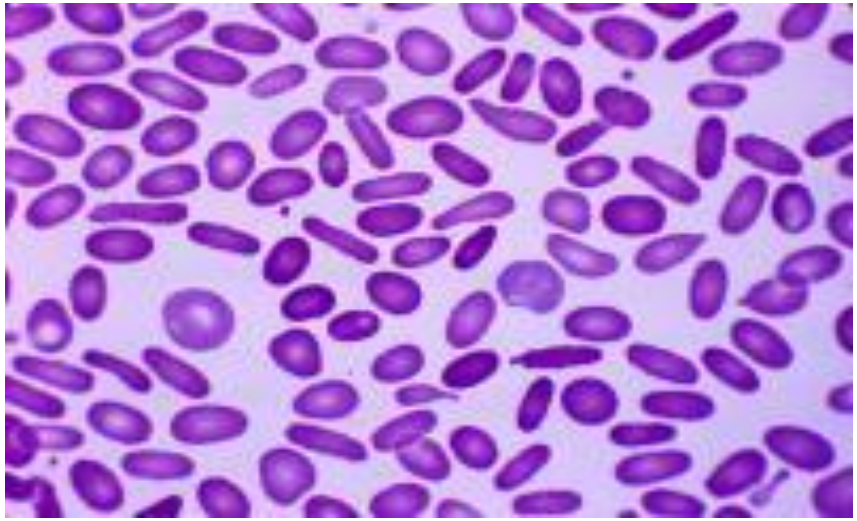
- Protein 4.1 deficiency (20-30%)
  - Smooth elongated elliptocytes with few poikilocytes
  - Caucasian, often asymptomatic
  - Autosomal Dominant
- Spectrin β-chain binding site
  - Elliptocytes (rounder), ± increased spherocytes
  - Asymptomatic, mild hemolysis,
  - Autosomal Dominant

Clinical Manifestations

- Varies, typically incidental diagnosis
- Erythrocyte life span – normal
- 10% have decreased RBC life span
  - Hemolysis
  - Anemia
  - Splenomegaly
  - Jaundice
  - Homozygotes or Compound heterozygotes

Laboratory findings

- 0-100% elliptocytes
- Normochromic, normocytic anemia
- Degree of hemolysis does not correlate w/ number of elliptocytes
- Elliptocytes can be seen other conditions -> May need to rule out other disorders



Treatment

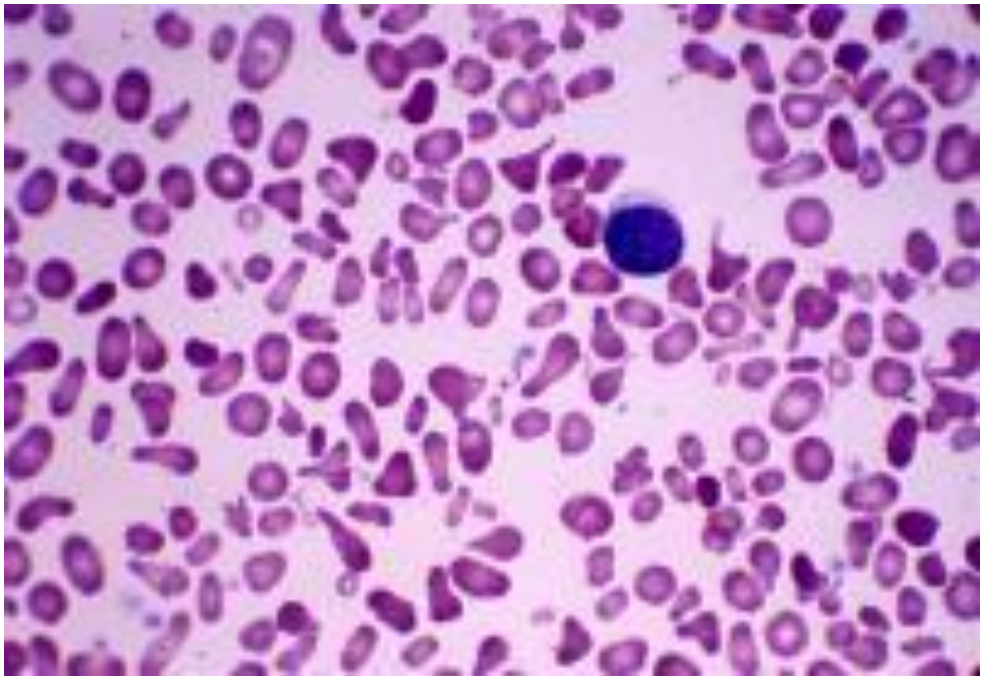
- Rare overall; range from transfusion to splenectomy
- Indications for splenectomy: uncompensated hemolysis, including growth failure, skeletal changes, leg ulcers, extramedullary hematopoetic tumors, hemolytic, megaloblastic or aplastic crisis.

Hereditary Pyropoikilocytosis (HPP)

- Reminiscent of erthrocyte morphology seen after thermal burns
- Rare cause of severe hemolytic anemia
- 1/3 of family members with HPP have HE
- Many HPP patients have severe hemolytic anemia in childhood that evolves into typical HE later in life

Hereditary Pyropoikilocytosis

- Same mutations as in HE
- Present in the neonatal period with severe hemolytic anemia, RBC fragments, poikilocytes, elliptocytes, microspherocytes, hyperbilirubinemia
- Possibly homozygotes or multiple mutations



Hereditary Pyropoikilocytosis

- Complications: splenomegaly, frontal bossing, growth retardation, gallbladder disease
- Likely to evolve into typical mild HE
- Identification: usually family history and PBS
- Or controlled thermal stress test, osmotic fragility (normal in common HE, increased in HPP), molecular diagnostics. Usually not all of these are required

Treatment

- Folate supplement
- Monitor for formation of gallstones
- Monitor for hemolytic decompensation esp. after viral illnesses
- Try to avoid splenectomy until after 6 years
- Vaccinate against pneumococcus

References

- Delauny J. The molecular basis of hereditary red cell membrane disorders. Blood Reviews: 21 (1) January 2007, 1-20.
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- Perkins,S. Hereditary erythrocyte membrane defects. in Practical Diagnosis of Hematologic Disorders. Kjeldsberg. 4th ed. 2006 93-103.
- Sills RH. Hereditary elliptocytosis and related disorders. Emedicine. June 22 2006.