spherocytosis
An intrinsic genetic defect causes defects in membrane proteins.
Hereditary Spherocytosis

General

- Intrinsic defect in RBC membrane
- RBCs are spheroidial, less deformable, vulnerable to splenic sequestration and destruction
- Autosomal dominant in ~75%
Integral proteins span the bilayer and act as sites for RBC antigen formation.

Skeleton of peripheral proteins controls biconcave shape and cell deformability.
This CBC demonstrates findings suggestive of spherocytosis, a condition in which the RBC's are small and round (rather than the normal biconcave appearance) with increased hemoglobin content. This is indicated here by the increase MCHC (mean corpuscular hemoglobin concentration). There is a rare condition known as hereditary spherocytosis. Also, RBC's in the condition of autoimmune hemolytic anemia can also appear similarly.
Hereditary Spherocytosis
Pathophysiology

- Deficiency of any of the membrane skeletal proteins may adversely affect RBCs
- Deficiency of spectrin in HS
  - most common biochemical abnormality
- Spectrin content varies from 60-90%
  - correlates with severity of disease
- **Spherocytes**
Morphologic hallmark

Microspherocyte
which is caused by loss of
membrane surface area, and an
abnormal osmotic fragility in vitro
- Membrane protein defects resulting in cytoskeleton instability.

- Spectrin deficiency leads to loss of erythrocyte surface area, which produces spherical RBCs.
Biochemical spectrin deficiency and the degree of spectrin deficiency are reported to correlate with the extent of spherocytosis, the degree of abnormality on osmotic fragility test results, and the severity of hemolysis.
- Spectrin deficiency (impaired synthesis)
- Quantitative or qualitative deficiencies of other proteins that integrate spectrin into the cell membrane
Four abnormalities in red cell membrane proteins

(1) spectrin deficiency alone
(2) combined spectrin and ankyrin deficiency
(3) band 3 deficiency
(4) protein 4.2 defects

Spectrin deficiency is the most common defect. Each is associated with a variety of mutations that result in different protein abnormalities and varied clinical expression.

Most cases of HS are heterozygous because homozygous states are lethal.
- Mutations of alpha-spectrin
  Autosomal recessive

- Mutations of beta-spectrin
  Autosomal dominant
Race:

- HS is the most common hereditary hemolytic anemia among people of Northern European descent. Its incidence and prevalence in other ethnic groups are not clearly established.
Osmotic fragility test

- Spherocytes are more fragile when placed in a hypo-osmotic environment than are normal RBC's.

- It is necessary to demonstrate a negative direct Coombs' test to rule out immunohemolytic anemia.
HEREDITARY SPHEROCYTOSIS

Osmotic Fragility

NaCl (% of normal saline)

% Hemolysis

Normal HS

HEREDITARY SPHEROCYTOSIS

Osmotic Fragility

% Hemolysis

NaCl (% of normal saline)

Normal HS
Hereditary Spherocytosis
Clinical Features

- Anemia
- Splenomegaly
  - moderate with marked congestion of the cords of Billroth with empty sinuses
  - erythrophagocytosis within the congested cords
- Jaundice
- May present with marked jaundice at birth (unusual)
- Variable severity
Hereditary Spherocytosis
Clinical Features

- Largely asymptomatic in 20-30%
  - mild hemolysis with compensatory erythropoiesis
- Most patients have a chronic mild to moderate hemolytic anemia
- Aplastic crisis may occur
Major complications

Aplastic
Megaloblastic crisis
Hemolytic crisis
Cholecystitis
Cholelithiasis
Severe neonatal hemolysis
Hereditary spherocytosis

Note how many of the red cells appear more or less uniformly stained rather than the normal biconcave disc with a lucent center.
The size of many of these RBC's is quite small, with lack of the central zone of pallor. These RBC's are spherocytes.
Hereditary Spherocytosis
The nucleated RBC in the center contains basophilic stippling of the cytoplasm.
- The sinusoids are packed with RBC's in this case of hereditary spherocytosis.
MEMBRANE disorder
The mode of inheritance is autosomal dominant, except for hereditary pyropoikilocytosis (HPP), which is autosomal recessive.
Most of these disorders are clinically silent, with only some forms associated with significant hemolysis.
Elliptocytes: Hereditary Elliptocytosis
This is a common autosomal dominant disorder, usually due to mutations of genes for the membrane proteins, alpha- or beta-spectrin.
Elliptocytosis

1. inherited as autosomal dominant

2. incidence 1:2500

3. symptoms = no hemolysis to severe hemolysis

4. mild HE (most common form)
   A. >40% of blood cells elliptical
   B. defect in spectrin heads interferes with self-association

No anemia or splenomegaly, mild hemolysis
Schematic diagram of the red blood cell membrane showing the interactions of various proteins involved in the pathogenesis of hereditary elliptocytosis.
Integral proteins span the bilayer and act as sites for RBC antigen formation.

Skeleton of peripheral proteins controls biconcave shape and cell deformability.
The basic abnormality is in the red cell membrane cytoskeleton proteins, usually involving spectrin.
Spectrin

The major component of the red cell cytoskeleton, consists of 2 chains (ie, alpha, beta) twisted alongside each other in heterodimers. At the head region, the chains associate to form tetramers. At the distal end, the chains bind to actin and protein 4.1
The resulting cytoskeleton attaches to the transmembrane proteins by linking beta-spectrin with band 3 protein via ankyrin (band 2.1) and the binding of protein 4.1 to glycophorins A and C.
Defective formation of spectrin tetramers in the head region resulting from an abnormality in alpha-spectrin or beta-spectrin (most common and accounts for a majority of cases of HE)

Abnormal beta-spectrin that does not bind properly to ankyrin

An abnormality or deficiency of protein 4.1,

A deficiency of glycophorin C
Background:

Hereditary elliptocytosis (HE) encompasses inherited disorders that have the common feature of elliptical red cells on morphologic examination of a peripheral blood smear.

*These cells are heterogeneous on clinical, genetic, and biochemical bases.*
Morphologic variants

- common HE,
- spherocytic elliptocytosis
- stomatocytic elliptocytosis (also known as Southeast Asian ovalocytosis)
Common HE

- This group also includes the subsets neonatal pyropoikilocytosis and HPP
- Symptoms are very rare because even when hemolysis is present, most patients have compensated hemolysis
- Very rarely, patients may have symptoms related to anemia, particularly among homozygotes and those with HPP.
Spherocytic elliptocytosis

Often associated with clinically apparent hemolysis

Stomatocytic elliptocytosis

(Southeast Asian ovalocytosis): is usually associated with very mild or no hemolysis

In any of the above variants, patients with significant hemolysis have an increased incidence of gallstones, splenomegaly, and leg ulcers
Lab Studies

- 25% (sometimes as much as 90%) of cells are elliptical. Occasionally, there may be fewer than 25% elliptocytes.

- Elliptocytes can occur in many other conditions (e.g., iron deficiency, megaloblastic anemias, myeloproliferative diseases, myelodysplastic syndromes)
Osmotic fragility test results are within reference ranges in mild forms of common HE but are increased in spherocytic HE and HPP.

When tested for thermal stability, normal red blood cells can withstand temperatures up to 49°C, but red blood cells associated with HPP denature at lower temperatures (ie, 45-46°C).
If necessary, specialized laboratories can identify the underlying skeletal defects by quantifying membrane proteins, studying spectrin function, and performing molecular studies.
Imaging Studies

- An abdominal CT scan may reveal an enlarged spleen.
- Abdominal sonography may reveal gallstones and an enlarged spleen.
Mortality / Morbidity:

- Most patients with the common form of HE are asymptomatic
- Only 5-20% develop uncompensated hemolysis with anemia, splenomegaly, gallstones, and leg ulcers
Prognosis:

Most patients are asymptomatic. Even those with significant hemolysis have an excellent prognosis after splenectomy.
Hereditary elliptocytosis: Blood film

The blood film shows a large proportion of elliptocytes
Cigar-shaped erythrocytes seen in hereditary elliptocytosis
Hereditary pyropoikilocytosis

- moderately severe hemolytic anemia
- cell fragmentation bizzare poikilocytosis, esp w/fever or burn trauma
- defect in spectrin self-association
Bizarre red blood cell morphology seen in hereditary pyropoikilocytosis.
Ovalocytosis

- South East Asian Hereditary Ovalocytosis (SEAHO): 
- (Melanesian Ovalocytosis)
ovalocytosis

- It is not associated with clinical or laboratory evidence of haemolysis, but is included here because of its local relevance.
ovalocytosis

- Melanesian populations in Malaysia, Papua New Guinea, Phillipines and Indonesia
- Autosomal dominant mutation in the gene for the erythrocyte band 3 membrane protein
- Increased red cell rigidity and a relative resistance to invasion by *P. falciparum* malaria parasites
SEAHO: Blood film

The red cells are oval-shaped and have one or two characteristic transverse ridges or longitudinal slits
Abetalipoproteinaemia
( Hereditary acanthocytosis )
Abetalipoproteinemia

- This is a rare inherited deficiency of low-density lipoproteins characterised by retinitis pigmentosa, steatorrhoea, ataxia and mental retardation.

- The blood film shows acanthocytes, but haemolysis is usually minor in degree.
Abetalipoproteinaemia: Blood film:
The film shows acanthocytes (spur cells).
Hereditary stomatocytosis
Hereditary stomatocytosis

- This autosomal dominant membrane disorder results in defective cation transport, with decreased cell potassium and increased cell sodium.
- The cells become overhydrated and have slit-like pale centres. This leads to moderate haemolysis.
- Splenectomy is only sometimes effective.
Hereditary Stomatocytosis: Blood film

The red cells have slit-like pale centres
Other conditions

- Hereditary xerocytosis
- McLeod phenotype
- LCAT deficiency
Membrane defects secondary to acquired-extrinsic defects

Acanthocytosis in liver disease result in spur cell (acanthocytes) in blood

i. rounded RBC

ii. thorny projections

due to abnormal cholesterol-laden lipoproteins

produced in liver \(\Rightarrow\) loaded on to RBC to increase its membrane cholesterol/phospholipid

c. cells initially flattened (leptocyte) conditioned (remodeled) in spleen

i. loss of surface membrane and lipids

ii. cell rigidity \(\Rightarrow\) acanthocytes
Biliary obstruction (liver disease)

- Patients develop target cells secondary to acquisition of both
- Excess cholesterol and phospholipids
- **Membrane** surface area expand
- Cell deformability unchanged; no morbidity