HEREDITARY SPHEROCYTOSIS

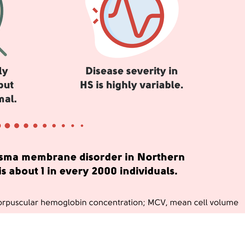
TERM DEFINITION

Hereditary spherocytosis (HS) belongs to the group of congenital hemolytic anemias resulting from mutations in genes that encode red blood cell membrane proteins that link the membrane cytoskeleton to the lipid bilayer.

CAUSES

HS results from heterogeneous alterations in one of five genes that encode red blood cell membrane proteins involved in vertical associations that link the membrane cytoskeleton to the lipid bilayer:

- Ankyrin-1 (*ANK1* gene)
- Erythrocytic α- & b-spectrin chains (*SPTA1* & *SPTB* genes)
- Erythrocyte membrane protein band 4.2 (*EPB42* gene)
- Band 3 anion transport protein (*SLC4A1* gene)



CLINICAL PEARLS

Differential diagnosis of spherocytosis = HS & autoimmune hemolytic anemia.

MCHC is typically increased in HS, but MCV usually normal.

Disease severity in HS is highly variable.

HS is the most common inherited red blood cell plasma membrane disorder in Northern Europe and Northern America with a prevalence is about 1 in every 2000 individuals.

MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume

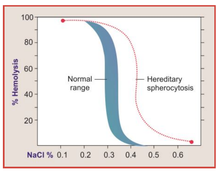
DIAGNOSIS

Consider the diagnosis in a patient with:

- Coombs-negative (non-immune) hemolytic anemia
- Presence of spherocytes on the peripheral blood smear
- Increased MCHC
- A positive family history for HS

Confirm the diagnosis in a patient with:

- EMA binding, or
- Osmotic fragility test (below)



CLINICAL PRESENTATION

The clinical presentation of HS is highly variable and ranges from intrauterine demise to very mild anemia or fully compensated hemolysis.

	% Cases	Hb (g/dL)	Reticulocytes (%)	Bilirubin (mg/dL)
HS Trait	N/A	Normal	Normal	Normal
Mild HS	20-30%	11-15	3-6	1-2
Moderate HS	60-75%	8-12	> 6	> 2
Severe HS	5%	6-8	> 10	> 3

PRESENTATION IN OLDER CHILDREN & ADULTS

Incidental finding of:

- Hemolysis
- Hemolytic anemia
- Spherocytes on the blood smear

Symptoms of:

- Anemia
- Splenomegaly
- Pigment gallstones
- Jaundice

TREATMENT

Folate supplementation
Especially important during hemolytic crises, pregnancy, and in childhood during growth and development.

Hematopoietic stem cell transplant or gene therapy
Allogeneic hematopoietic cell transplantation is not used in HS due to an unfavorable risk-benefit ratio.

Iron chelation
Initiate chelation (e.g., DFO) if ≥ 1 of: ≥ 10-20 transfusions or serum ferritin > 1,000 ng/mL.

Splenectomy
For those with relatively severe hemolysis, splenectomy is effective at improving anemia. Ideally, this is delayed until the individual is older than six years to reduce the likelihood of sepsis due to absent splenic function. Simultaneous cholecystectomy can be performed if gallstones are also present.

Red cell transfusion
The need for transfusions should be based on comprehensive clinical judgment regarding quality of life, growth, and symptoms and not on hemoglobin level alone.

PROXIMATE MECHANISMS

In HS, deficiency in a membrane protein results in the **disruption of the vertical linkages** between the phospholipid bilayer and the membrane skeleton, and assembly of an intrinsically unstable membrane leading to:

- Increased **cell sphericity** (altered surface-to-volume ratio, primarily related to loss of membrane surface area).
- Reduced **cellular deformability**.
- **Sequestration** of the non-deformable spherocytes in the spleen.
- **Phagocytosis** by the splenic macrophages, leading to reduced lifespan of the erythrocyte and anemia.

EVOLUTIONARY MECHANISMS

Plasmodium falciparum growth is impaired in spherocytotic erythrocytes.

HS may have evolved as a protection against **malaria infection**.

DID YOU KNOW?

HISTORY OF MEDICINE

CONGENITAL HEMOLYTIC JAUNDICE

In most cases the diagnosis of congenital hemolytic jaundice is clear-cut. In addition to the usual signs of accelerated blood destruction, the patient has a past history of subnormal energy and endurance since early childhood, and jaundice and anemia with periodic exacerbations may have been noted. There may be overt signs of hemolytic anemia in other members of the family, or examination of the blood of relatives may show the tendency toward spherocytosis of the erythrocytes and the increase in osmotic fragility that is characteristic of the disease.

First description of HS in *Calif. Med.* 1949 Apr;70(4):244-51

NOTES

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