Hereditary spherocytosis

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Abstract

Hereditary spherocytosis is a red cell membrane disorder which is heterogeneous in respect to clinical presentation, biochemical and genetic basis. This review highlights the underlying pathophysiology, clinical features, investigations and management of HS in childhood.

Keywords anaemia; cholelithiasis; haemolysis; hereditary spherocytosis; jaundice; splenomegaly

Definition

Hereditary spherocytosis (HS) is a non-immune inherited red cell disorder where a defect in one of the membrane proteins weakens the 3 dimensional structure of the erythrocyte cytoskeletal network, resulting in a shortened life span of the red cells in circulation. The affected individual can present with varying degrees of haemolytic anaemia and spherocytosis on a blood film.

Epidemiology

HS is the commonest inherited haemolytic anaemia in the Caucasian population with a prevalence of 1 in 2000 in Northern Europeans, but is seen in most ethnic groups. It is inherited in an autosomal dominant (AD) pattern in 75% of cases. In others the mode of inheritance can be non-dominant (due to co-inheritance of a polymorphic spectrin allele and a pathogenic spectrin^{HS} allele) or AR (autosomal recessive, due to inheritance two pathogenic HS alleles).

Pathology

The human red blood cell is biconcave in shape (6–8 μm in diameter). The deformability and elasticity of the red cell facilitate its passage through capillaries which can be as small as 4 μm in diameter. Thus red cells can deliver oxygen to the extremities of the body and enter the venous sinuses of the red pulp of the spleen. The red cell membrane consists of two separate layers. Its outer lipid bilayer (composed of cholesterol, phospholipids, various transmembraneous proteins, and GPI-anchored proteins in lipid raft domains) is supported by a network of proteins designated as the cytoskeleton on the cytoplasmic side of the lipid layer (Figure 1). The cytoskeleton is a two-dimensional spectrin-based structure covering around 65% of the cell surface.

The red cell shape can alter through either vertical or lateral movements of the cytoskeleton. Defects in the membrane proteins involved in the vertical interaction weaken the cross linkage between the lipid bilayer to the membrane skeleton, resulting in the typical small spherical erythrocytes seen in HS. Conversely defects in proteins responsible for lateral interactions of the cytoskeleton lead to the formation of elliptically shaped erythrocytes seen in hereditary elliptocytosis (HE) (Figure 1). One severe form of HE is designated as hereditary pyropoikilocytosis.

In the circulation, HS red cells have impaired plasticity due to a reduced surface area to volume ratio. This is caused by a gradual loss of membrane lipids and structural proteins from localised areas where the underlying spectrin-based skeleton is detached from the lipid bilayer. These damaged red cells are eventually taken out prematurely by the reticuloendothelial system (particularly in the spleen) before their life span of 120 days. A continuous destruction of these red cells can lead to increased erythropoietic rate. Anaemia ensues when the new red cell production cannot meet the rate of red cell destruction. Furthermore, haemoglobin breakdown products will result in the formation of bilirubin. When exceeding the liver's capacity, bilirubin will cause jaundice. An excess of such degradation products entering the biliary tree may eventually cause the formation of pigmented gallstones.

Course of the disease

There is a wide variation in the clinical phenotypes, ranging from asymptomatic individuals to those with severe haemolytic anaemia requiring blood transfusion. the clinical phenotype will often run true for a family, in some cases it does not and the cause of this variability remains unknown.

Asymptomatic patients tend to present with a normal haemoglobin, normal bilirubin and intermittent haemolysis. Those patients having continued brisk haemolysis are anaemic and sometimes transfusion dependent from a young age (e.g., a couple of months after birth). The severity of the neonatal haemolysis is not predictive of the future clinical course. Although some neonates may require transfusion for anaemia this is unusual however affected children may have prolonged and early jaundice. After the neonatal period the clinical phenotype of the child will usually remain fairly uniform throughout life.

In the long term, those with mild haemolysis usually continue to exhibit very little signs, whereas those with brisk haemolysis will be jaundiced, anaemic and have splenomegaly, and may develop pigmented gallstones. Intercurrent illnesses may increase the rate of haemolysis for a period so there may be a brief change in symptoms and signs during these periods. Likewise those dependent on a high reticulocyte count to maintain their haemoglobin may develop profound anaemia following Parvovirus B19 (slapped cheek) infection. For those who require regular transfusion, splenectomy should be considered as this usually results in transfusion independency and a milder clinical phenotype (see management below). Symptomatic cholelithiasis may require a cholecystectomy.

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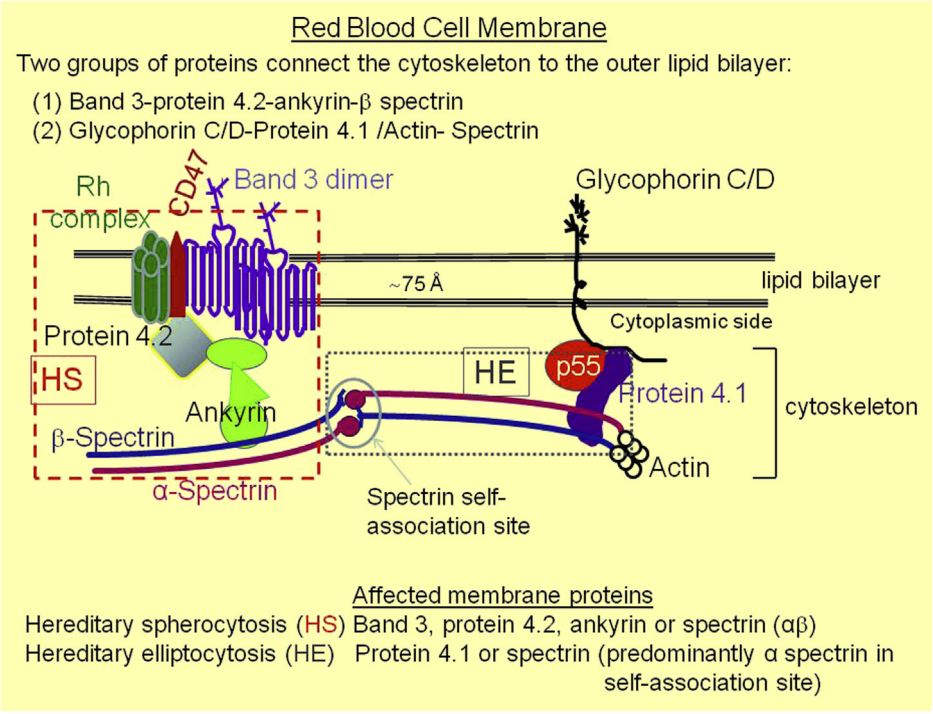

Figure 1 Red cell membrane structure and protein defects in HS.

Diagnosis

Diagnosis is made on clinical suspicion often including a family history and confirmatory blood tests. 75% of patients will have a positive family history. The extent one pursues the more complicated investigations depends on the presence of a proven family history and supportive blood test findings (spherocytes, raised MCHC and reticulocytosis) (Figure 2).

Those cases with equivocal results for an HS diagnosis can have further screening tests see Table 1.

History

The most commonly encountered clinical scenario is that of a baby born to a parent who is known to have this red cell disorder. Commonly there is a history of neonatal jaundice, and a

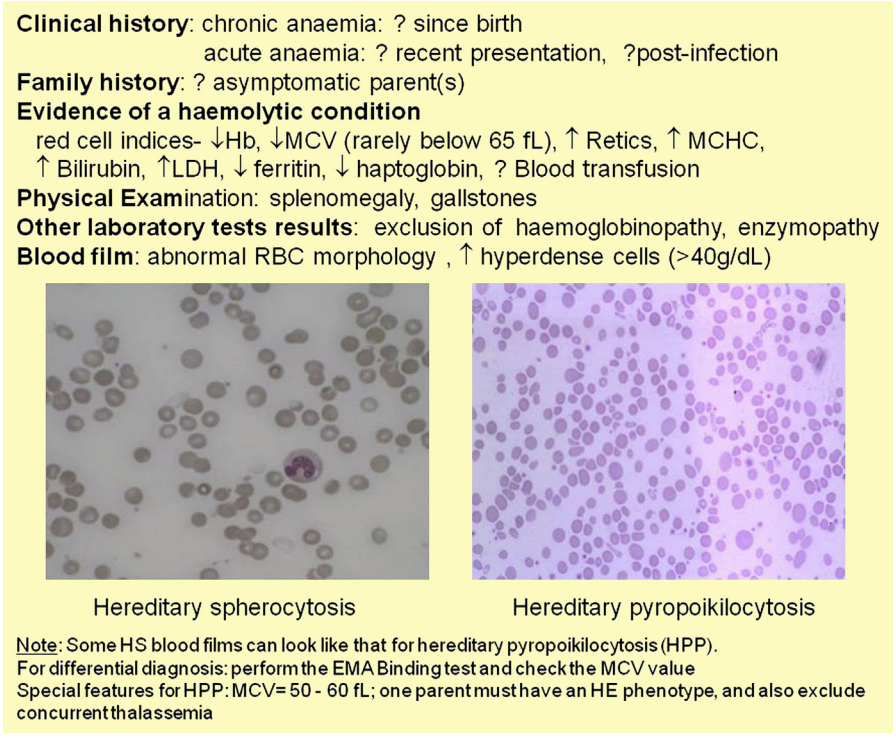

Figure 2 Assessment of patient at presentation.