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section 22 Haematological disorders 5456 Haas D, et al. (2007). New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes. Evidence from a core dataset of 2124 patients. Blood, 110, 4385–95. Hasserjian RP, et al. (2008). Refractory anemia with ring sideroblasts. In: WHO classification of tumours of haemopoietic and lymphoid tis- sues, 4th edition. pp. 96–7. IARC Press, Lyon. Labay V, et al. (1999). Mutations in SLC19A2 cause thiamine-responsive megaloblastic anaemia associated with diabetes mellitus and deafness. Nat Genet, 22, 300–4. Papaemmanuil E, et al. (2011). Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. N Engl J Med, 365, 1384–95. Patnaik MM, Tefferi A (2017). Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T): 2017 update on diagnosis, risk-stratification, and management. Am J Hematol, 92(3), 297–310. Patnaik MM, et al. (2012). Prognostic irrelevance of ring sideroblast percentage in World Health Organization-defined myelodysplastic syndromes without excess blasts. Blood, 119, 5674–7. Raskin WH, et al. (1984). Evidence for a multistep pathogenesis of a myelodysplastic syndrome. Blood, 63, 1318–23. Renalla R, Wood R (2009). The congenital dyserythropoietic anemias. Hematol Oncol Clin North Am, 23, 283–306. Savage D, Lindenbaum J (1986). Anemia in alcoholics. Medicine, 65, 322–38. Szpurka H, et al. (2006). Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T) another myeloproliferative condition characterized by JAK2 V617F muta- tion. Blood, 108, 2173–81. Ye H, et al. (2010). Glutaredoxin 5 deficiency causes sideroblastic an- emia by specifically impairing heme biosynthesis and depleting cytosolic iron in human erythroblasts. J Clin Invest, 120, 1749–61. 22.6.9 Disorders of the red cell membrane Patrick G. Gallagher ESSENTIALS The integrity of the red cell membrane depends on molecular inter- actions between proteins and the phospholipid membrane: vertical interactions stabilize the membrane lipid bilayer; horizontal inter-actions provide resistance against shear stress. Hereditary spherocytosis This disorder affects 1 in 2000–5000 individuals of northern European descent. There is typically a dominant family history,

but the con- dition is genetically heterogeneous: combined spectrin and ankyrin deficiency is the most common defect observed, followed by band 3 deficiency, isolated spectrin deficiency, and protein 4.2 deficiency. These affect vertical membrane interactions with loss of surface area relative to red cell volume. Clinical features and diagnosis—the key clinical manifestations are anaemia and signs of persistent haemolysis, with jaundice and a marked propensity to gallstones. Diagnostic tests include the incu- bated osmotic fragility test (in which spherocytes burst at higher sa- line concentrations than normal); the eosin-5-maleimide binding test in which binding of a fluorescent dye to key red cell membrane components is assessed by flow cytometry; and next-generation targeted sequencing of candidate genes. Complications and treatment—parvovirus B19 infection of erythro- poietic precursors may cause acute aplastic crises. Megaloblastic anaemia due to folate deficiency occurs in response to increased requirements during growth and pregnancy, but is preventable with supplementation. Splenectomy can alleviate the anaemia in many patients and reduces the risk of gallstones. Hereditary elliptocytosis This disorder occurs with a frequency of 1 in 2000 to 1 in 4000 worldwide, and is more frequent in parts of Africa. The inheritance is usually dominant, with defects in red cell proteins such as α- and β-spectrin causing disturbances in horizontal interactions in the erythrocyte membrane. Clinical features, diagnosis, and treatment—most patients are asymptomatic and are typically diagnosed incidentally during testing for unrelated conditions, but about 10% experience haemolysis, anaemia, splenomegaly, and intermittent jaundice. Diagnosis is based on the presence of elliptocytes on a peripheral blood smear. Treatment is rarely required. Other conditions These include (1) hereditary pyropoikilocytosis—a rare cause of se- vere haemolytic anaemia, usually seen in patients of African descent; (2) South-East Asian (or Melanesian) ovalocytosis—an asymptom- atic autosomal dominant condition due to band 3 protein ab- normalities that confer resistance to invasion by malaria parasites; (3) stomatocytosis—characterized by red cells with a characteristic- ally shaped slit-like area of central pallor—a heterogeneous group of disorders that are often asymptomatic but may cause haemolysis and anaemia, and which may be hereditary (e.g. missense muta- tions in band 3) or acquired (e.g. cholestatic liver disease, alcoholism, and vinca alkaloids); and (4) acanthocytosis—characterized by con- tracted red cells with spiky projections, again with both hereditary (e.g. neuroacanthocytosis syndromes, abetalipoproteinaemia) and acquired (e.g. severe hepatic disease) aetiologies. The red cell membrane Composition and function Although the primary structure and a number of the important func- tions of the red cell membrane have been known for many years, their study continues to yield important insights into our understanding of membrane structure and function. The red cell membrane is com- posed of three major structural elements: a lipid bilayer primarily comprising phospholipids and cholesterol; integral proteins em- bedded in the lipid bilayer that span the membrane; and a membrane skeleton on the internal side of the red cell membrane. The membrane and its skeleton provide the erythrocyte with the ability to undergo significant deformation without fragmentation or loss of integrity during its travel through the microcirculation. The membrane also assembles and organizes the proteins of the lipid

 bilayer and the membrane skeleton, allowing the red cell to partici- pate in a wide range of functions. These include influencing cellular metabolism by selectively and reversibly binding and inactivating glycolytic enzymes, retaining organic phosphates and other vital com- pounds, removing metabolic waste, and sequestering the reductants required to prevent corrosion by oxygen. During erythropoiesis, the membrane responds to erythropoietin and imports the iron required for the synthesis of haemoglobin. The lipid bilayer provides an imper- meable barrier between the cytoplasm and the external environment

and helps avoid red cell adherence to endothelial cells or aggregation in the microcirculation. The membrane also participates in erythrocyte biogenesis and ageing. Finally, it is involved in the maintenance of pH homeostasis by participating in chloride–bicarbonate exchange. Interactions of membrane proteins and disorders
of red cell shape Membrane protein–protein and protein–lipid interactions have been classified into two categories, vertical and horizontal interactions (Fig. 22.6.9.1). Vertical interactions stabilize the lipid bilayer mem- brane while horizontal interactions support the structural integrity of erythrocytes after their exposure to shear stress. The interactions between proteins and lipids of the erythrocyte membrane are more complex than this simplistic model, but it serves as a useful starting point for understanding red cell membrane interactions, particularly in membrane-related disorders. According to this model, hereditary spherocytosis (HS) is a disorder of vertical interactions. Although the primary molecular defects in HS are heterogeneous (see ‘Hereditary spherocytosis’), one common feature of HS erythrocytes is a weak- ening of the vertical contacts between the skeleton and the lipid bi- layer. As a result, the lipid bilayer membrane is destabilized, leading to release of lipids in the form of skeleton-free lipid vesicles, which in turn results in membrane surface area deficiency and spherocytosis. By contrast, in this model, hereditary elliptocytosis is a defect of hori- zontal interactions, primarily those involving spectrin dimer self-association. Defects of horizontal interactions disrupt the membrane skeletal lattice leading to elliptocytic shape in mild cases and skeletal instability and cell fragmentation in severe cases. Hereditary spherocytosis This group of inherited disorders is characterized by the presence of spheroidal erythrocytes on a peripheral blood smear. HS occurs in all racial and ethnic groups. It is the most common inherited anaemia in individuals of northern European descent, affecting approximately 1 in 2500 individuals in the United States of America and the United Kingdom. It is much more common in Caucasians than in individuals of African ethnicity. Clinical, laboratory, biochemical, and genetic heterogeneity characterize the spherocytosis syndromes. Aetiology and pathogenesis The primary defect in HS is loss of membrane surface area relative to intracellular volume, accounting for the spheroidal shape and de- creased deformability of the red cell. This loss of surface area results from increased membrane fragility due to defects in erythrocyte membrane proteins. Increased fragility leads to membrane vesicula- tion and membrane loss. Splenic destruction of these nondeformable erythrocytes is the primary cause of haemolysis experienced by HS patients. Physical entrapment of erythrocytes in the splenic micro-circulation and ingestion by phagocytes have been proposed as mechanisms of destruction. Furthermore, the splenic environment is hostile to erythrocytes. Low pH, glucose, and ATP concentrations, and high local concentrations of toxic free radicals produced by ad- jacent phagocytes, all contribute to membrane damage. Membrane loss is due to defects in several membrane proteins, including ankyrin, band 3, α-spectrin, β-spectrin, and protein 4.2. Combined spectrin and ankyrin deficiency is the most common de- fect observed, followed by band 3 deficiency, isolated spectrin defi- ciency, and protein 4.2 deficiency. As might be expected, therefore, the genetic defects underlying HS are heterogeneous. Multiple gen- etic loci are implicated and various abnormalities, including point mutations, defects in mRNA processing, and gene deletions, have all been described. Except for a few rare exceptions, HS mutations are private, that is, each individual kindred has a unique mutation. Clinical features The clinical manifestations of the spherocytosis syndromes vary widely. The typical picture of HS combines evidence of haemolysis (anaemia, jaundice, reticulocytosis, gallstones, and splenomegaly) with spherocytosis (spherocytes on a peripheral blood smear) and a positive family history (Box 22.6.9.1). Mild, moderate, and severe forms of HS have been defined according to differences in

haemo- globin, bilirubin, and reticulocyte counts correlated with the degree of compensation for the haemolysis (Table 22.6.9.1). Initial assess- ment of a patient with suspected HS should include a family history and questions about history of anaemia, jaundice, gallstones, and splenectomy. Physical examination should seek signs such as scleral icterus, jaundice, and splenomegaly. After diagnosing a patient with HS, family members should be examined for the presence of HS. HS typically presents in childhood, but may present at any age. In children, anaemia is the most frequent presenting complaint (50%), followed by splenomegaly, jaundice, or a positive family history. Two-thirds to three-quarters of HS patients have incompletely compensated haemolysis and mild to moderate anaemia. The an- aemia is often asymptomatic except for fatigue and mild pallor. Jaundice is seen at some time in about 50% of patients, usually in association with viral infections. When present, it is acholuric, that Vertical interaction Horizontal interaction Band 3 4.2 Ankyrin Glycophorin A Adducin Actin p55 Tropomyosin Tropomodulin Glycophorin C 4.9 Band 3 Band 3 Band 3 α Spectrin β Spectrin Fig. 22.6.9.1 Schematic diagram of the red cell membrane (not to scale). Membrane–protein and membrane–lipid interactions can be divided into two categories: (1) vertical interactions, which are perpendicular to the plane of the membrane and involve spectrin–ankyrin–band 3 interactions, spectrin–protein 4.1–glycophorin C interactions, and weak interactions between spectrin and the lipid bilayer; and (2) horizontal interactions, which are parallel to the plane of the membrane. From Tse WT, Lux SE (1999). Red blood cell membrane disorders. Br J Haematol, 104, 2–13, with permission.

 is, there is unconjugated hyperbilirubinaemia without detectable bilirubinuria. Palpable splenomegaly is detectable in most (75–95%) older children and adults. Typically, the spleen is modestly enlarged but it may be massive. About 20 to 30% of HS patients have ‘compensated haemolysis,’ that is, erythrocyte production and destruction are balanced. Although the erythrocyte lifespan may only be about 20–30 days, these patients adequately compensate for their haemolysis with in- creased marrow erythropoiesis. They are not anaemic and are usu- ally asymptomatic. Many of these individuals escape detection until adulthood, when they are being evaluated for unrelated disorders or when complications related to anaemia or chronic haemolysis occur. Haemolysis may become severe with illnesses that cause spleno- megaly, such as infectious mononucleosis, or may be exacerbated by other factors such as pregnancy. Because of the asymptomatic course of HS in these patients, diagnosis of HS should be considered during evaluation of splenomegaly, gallstones at a young age, or an- aemia from viral infection. Approximately 5 to 10% of HS patients have moderate to severe anaemia. Patients with moderately severe disease typically have a haemoglobin of 60 to 80 g/litre, reticulocytes about 10%, bilirubin 2 to 3 mg/dl, and 40 to 80% of the normal red cell spectrin content. This category includes patients with both dominant and recessive HS and a variety of molecular defects. Patients with severe disease, by definition, have life-threatening anaemia and are transfusion dependent. They almost always have recessive HS. Most have iso- lated severe spectrin deficiency. In addition to the risks of recurrent transfusions, these patients often suffer from haemolytic and aplastic crises and may develop complications of severe uncompensated an- aemia including growth retardation, delayed sexual maturation, or aspects of thalassaemic facies. The parents of patients with recessive HS are clinically asymptom- atic and do not have anaemia, splenomegaly, hyperbilirubinaemia, or spherocytosis on peripheral blood smears (‘Trait’, Table 22.6.9.1). Most have subtle laboratory signs of HS including a slight reticulo cytosis. It has been estimated that at least 1.4% of the population are silent carriers. Inheritance The genes responsible for HS include ankyrin, β-spectrin, band 3 protein, α-spectrin, and protein 4.2. In approximately two-thirds to

three-quarters of HS patients, inheritance is autosomal dom- inant. In the remaining patients, inheritance is nondominant due to autosomal recessive inheritance or a de novo mutation. Cases with autosomal recessive inheritance are due to defects in either α-spectrin or protein 4.2.
A surprising number of de novo mutations have been reported in the HS genes. A few cases of 'double-dominant' HS due to defects in band 3 or spectrin that result in fetal death or severe haemolytic anaemia presenting in the neonatal period have been reported. In general, affected in- dividuals of the same kindred experience similar degrees of haemolysis. Complications
Gallbladder disease Chronic haemolysis leads to the formation of bilirubinate gall- stones, the most frequently reported complication in HS patients. Although gallstones have been detected in infancy, most occur be- tween 10 and 30 years of age. Management should include interval ultrasonography to detect gallstones, as many patients with chole- lithiasis and HS are asymptomatic. Timely diagnosis and treatment will help prevent complications of symptomatic biliary tract dis- ease including biliary obstruction, cholecystitis, and cholangitis. Box 22.6.9.1 Characteristics of hereditary spherocytosis Clinical manifestations • Anaemia • Splenomegaly • Intermittent jaundice:

— From haemolysis

— From biliary obstruction • Haemolytic, aplastic, and megaloblastic crises • Inheritance:

— Dominant (c.75%)

— Nondominant (c.25% de novo or recessive) • Rare manifestations:

— Leg ulcers, gout, chronic dermatitis

— Extramedullary haematopoietic tumours

— Thrombosis

— Neuromuscular disorders

— Cardiomyopathy

— Spinocerebellar abnormalities • Excellent response to splenectomy Laboratory characteristics • Reticulocytosis • Spherocytosis • Elevated MCHC • Reduced eosin-5-maleimide binding • Normal direct antiglobulin test Table 22.6.9.1 Clinical classification of hereditary spherocytosis Trait Mild spherocytosis Moderate spherocytosisa Severe spherocytosis Haemoglobin (g/litre) Normal 110–150 80–120 ≤80 Reticulocytes (%) 1–3 3–8 ≥8 ≥10 Bilirubin (mg/dl) 0–1 1–2

> 2 3 Spectrin contentb (% of normal) 100 80–100 50–80 20–80 Peripheral smear Normal Mild spherocytosis Spherocytosis Spherocytosis and poikilocytosis a Values in untransfused patients. b In most patients, ankyrin content is decreased to a comparable degree. A minority of hereditary spherocytosis patients lack band 3 or protein 4.2 and may have mild to moderate

> spherocytosis with normal amounts of spectrin and ankyrin.

22.6.9 Disorders of the red cell membrane 5459 Haemolytic, aplastic, and megaloblastic crises Haemolytic crises are usually associated with viral illnesses and typ- ically occur in childhood. They are generally mild and are charac- terized by jaundice, increased splenomegaly, decreased haematocrit, and reticulocytosis. Intervention is rarely necessary. When severe haemolytic crises occur, there is marked jaundice, anaemia, lethargy, abdominal pain, and tender splenomegaly. Hospitalization and red cell transfusion may be required. Aplastic crises following virally induced bone marrow suppres- sion are uncommon, but may result in severe anaemia with serious complications including congestive heart failure. The most common aetiological agent in these cases is parvovirus (erythrovirus) B19. Parvovirus selectively infects erythropoietic progenitor cells and inhibits their maturation. In addition to causing a profound reticulocytopenia, parvovirus infections may also be associated with mild neutropenia, thrombocytopenia, or even pancytopenia. During the aplastic phase, the haemoglobin and the production of new red cells fall, the cells that remain age, and microspherocytosis increases. Aplastic crises usually last 10 to 14 days (about half the lifespan of HS red cells), and the haemoglobin typically falls to half its usual level before recovery occurs. In patients with severe HS, the anaemia may be profound, requiring hospitalization and trans- fusion. As the marrow recovers, granulocytes, platelets, and, finally, reticulocytes return to the peripheral blood. Aplastic crisis brings many patients to medical attention, particularly asymptomatic HS patients with normally compensated haemolysis. Because parvo- virus may infect several members of a family simultaneously, leading to aplastic crises, there have been reports of ‘outbreaks’ of HS. Megaloblastic crisis occurs in HS patients with increased folate demands, for example, the pregnant patient, growing children, or patients recovering from an aplastic crisis. With appropriate folate supplementation, this complication is preventable. Diagnosis The laboratory findings in HS are heterogeneous. Initial laboratory investigation should include a complete blood count with periph- eral smear, reticulocyte count, Coombs’ test, and serum bilirubin. Although specialized diagnostic tests may not be required in the con- text of a proven family history of HS, index cases and those in whom there is diagnostic uncertainty should undergo additional testing. The most widely used current tests are the eosin-5-maleimide binding test (described in more detail later) and the incubated osmotic fragility test. Peripheral blood smear Erythrocyte morphology is quite variable. Typical HS patients have blood smears with obvious spherocytes lacking central pallor (Fig. 22.6.9.2a). Less commonly, patients present with only a few spherocytes on peripheral smear or, at the other end of the spectrum, with numerous small, dense spherocytes and bizarre erythrocyte morphology with anisocytosis and poikilocytosis (Fig. 22.6.9.2b). (b) (a) (c) (d) Fig. 22.6.9.2 Peripheral blood smears: (a) typical hereditary spherocytosis; (b) severe, recessively inherited spherocytosis; (c) hereditary elliptocytosis; (d) hereditary pyropoikilocytosis.

section 22 Haematological disorders 5460 Specific morphological findings have been identified in patients with certain membrane protein defects such as pincered erythro- cytes (band 3) or spherocytic acanthocytes (β-spectrin). Erythrocyte indices Most patients have mild to moderate anaemia. The mean cell volume (MCV) is normal except in severe HS cases, when it is slightly de-creased despite reticulocytosis, reflecting membrane loss and cellular dehydration. The mean cell haemoglobin concentration (MCHC) is increased (≥350 g/litre) due to relative cellular dehydra- tion

in around 50% of patients. Strategies using erythrocyte indices have combined MCHC and red cell distribution width (>354 g/litre and >14, respectively) or utilized histograms of hyperdense erythro- cytes (MCHC >400 g/litre) obtained from laser-based cell counters, sometimes combined with elevated MCHC, in attempts to rapidly identify HS patients. Osmotic fragility In the normal erythrocyte, membrane redundancy gives the cell its characteristic discoid shape and provides it with abundant surface area. In spherocytes, there is a decrease in surface area relative to cell volume, resulting in their abnormal shape. This change is reflected in the increased osmotic fragility found in these cells (Fig. 22.6.9.3), and this feature has been exploited in diagnostic testing for HS. Osmotic fragility is tested by adding increasingly hypotonic concentrations of saline to red cells. The normal erythrocyte is able to increase its volume by swelling, but spherocytes, which are already at maximum volume for surface area, burst at higher saline concentrations than normal. Approximately 25% of HS individuals will have a normal os- motic fragility on freshly drawn red cells, with the osmotic fragility curve approximating the number of spherocytes seen on periph- eral smear. However, after incubation at 37°C for 24 h, HS red cells lose membrane surface area more readily than normal because their membranes are leaky and unstable. Thus incubation accentuates the defect in HS erythrocytes and brings out the defect in osmotic fra- gility, making incubated osmotic fragility the standard test for diag- nosing HS. When the spleen is present, a subpopulation of very fragile erythrocytes, which have been conditioned by the spleen, form the ‘tail’ of the osmotic fragility curve; this disappears after splenectomy (Fig. 22.6.9.3). Osmotic fragility testing suffers from poor sensitivity as about 20% of mild cases of HS are missed after incubation. It is also unreli- able in patients with small numbers of spherocytes, including those who have been recently transfused, and will give a positive result for patients who have spherocytosis for reasons other than HS. This, along with the labour-intensive nature of the test, means that it is now been largely outmoded in the diagnosis of HS. Eosin-5-maleimide binding test Flow cytometry can be used to examine the degree of binding of the fluorescent dye eosin-5-maleimide to the red cell surface as a poten- tial diagnostic test of HS. There is an interaction between eosin-5-maleimide and the band 3 protein, with individuals affected by HS having a lower binding of the dye to the red cell surface. A binding ratio of 0.8 is typically used as a cut-off to distinguish normal controls for HS patients, with sensitivity and specificity of greater than 90%. Positive EMA binding test results can also be seen in some cases of congenital dyserythropoietic anaemia, and abnormalities of erythro- cyte hydration and in some HS cases with spectrin deficiency, EMA binding may be normal—but to date this rapid and readily available test remains the best laboratory method of screening for HS. Molecular genetics and targeted next-generation resequencing panels may be of use in the diagnosis of HS, though the large number of private mutations makes this strategy challenging. Other laboratory manifestations in HS are the markers of ongoing haemolysis. Reticulocytosis, increased bilirubin, increased lactate dehydrogenase, increased urinary and faecal urobilinogen, and de- creased haptoglobin reflect increased erythrocyte production or destruction. Differential diagnosis HS should be able to be distinguished from other haemolytic anaemias by additional diagnostic testing—with as autoimmune haemolytic anaemia, distinguishable by a positive a Coombs’ test, being a key morphological differential. Other causes of haemo- lytic anaemia with spherocytes on peripheral smear (Box 22.6.9.2) should be considered in the appropriate clinical context. Occasional spherocytes are also seen in patients with a large spleen (such as in cirrhosis and myelofibrosis) or in patients with microangiopathic anaemias, but the differentiation of these conditions from HS is not usually difficult. Lysis (%) 100 Saline concentration (%) 0.5 0.4 0.3 0.6 0.7 0.8 Severe HS Typical HS Normal range Tail 80 60 40 20 Fig. 22.6.9.3 Osmotic fragility curves in hereditary spherocytosis. The shaded region is the

normal range. Results representative of both typical and severe spherocytosis are shown. A tail, representing very fragile erythrocytes that have been conditioned by the spleen, is common in many spherocytosis patients prior to splenectomy. Box 22.6.9.2 Conditions with spherocytes on peripheral blood smear • Hereditary spherocytosis • Autoimmune haemolytic anaemia • Liver disease • Thermal injury • Microangiopathic and macroangiopathic haemolytic anaemias • Transfusion reaction with haemolysis • Clostridial sepsis • Severe hypophosphataemia • Poisoning from certain snake, spider, bee, and wasp venoms • Heinz body anaemias • Hypersplenism • ABO incompatibility (neonates)

22.6.9 Disorders of the red cell membrane 5461 Treatment Splenectomy Splenic sequestration is the primary determinant of erythro- cyte survival in HS patients. Thus splenectomy alleviates the an- aemia in the majority of patients, reducing or eliminating the need for transfusions and decreasing the incidence of cholelith- iasis. Postsplenectomy, spherocytosis and altered osmotic fra- gility persist, but erythrocyte lifespan nearly normalizes, and reticulocyte counts fall to normal or near normal levels. Typical postsplenectomy changes, including Howell–Jolly bodies, target cells, and acanthocytes, become evident on peripheral smear. Postsplenectomy, patients with the most severe forms of HS still suffer from shortened erythrocyte survival and haemolysis, but their clinical improvement is striking. Early complications of splenectomy include local infection, bleeding, and pancreatitis due to injury to the tail of the pancreas incurred during surgery. Overwhelming postsplenectomy infection, typically from encapsulated organisms, is an uncommon but sig- nificant late complication of splenectomy, especially in the first few years of life; pneumococcal vaccination preoperatively is needed, and antibiotic prophylaxis may be recommended, especially for chil- dren. For all splenectomized patients, early antibiotic therapy in the context of possible infection is advised. Another postsplenectomy complication is the increased risk of cardiovascular disease, particu- larly thrombosis and pulmonary hypertension. Indications for splenectomy In the past, splenectomy was considered routine in HS patients. However, the risk of overwhelming postsplenectomy infec- tion with penicillin-resistant pneumococci, and other potential complications have led to a re-evaluation of the role of splen- ectomy in the treatment of HS. The risks and benefits of splen- ectomy should be reviewed and discussed between healthcare providers, patient, and family when splenectomy is considered. Considering the risks and benefits, a reasonable approach would be to splenectomize all patients with severe spherocytosis and all patients who suffer from significant signs or symptoms of anaemia including growth failure, skeletal changes, leg ulcers, and extramedullary haematopoietic tumours. Other candidates for splenectomy are older HS patients who suffer vascular com- promise of vital organs. Whether patients with moderate HS should undergo splenectomy remains controversial. Patients with mild HS and compensated haemolysis can be followed and referred for splenectomy if clinically indicated. When splenectomy is warranted, laparoscopic splenectomy is the method of choice as it results in less postoperative discomfort, shorter hospitalization, and decreased costs. Partial splenectomy has been advocated for infants and young children with significant anaemia associated with HS and it may be of benefit in typical HS patients. The goals of this procedure are to allow for the palliation of haemolysis and anaemia while maintaining some residual splenic immune function. Long-term follow-up data for this procedure are lacking. Before splenectomy, preferably several weeks preoperatively, patients should be immunized with vaccines against pneumo- coccus, Haemophilus influenzae type b, and meningococcus. The use and duration of prophylactic antibiotics postsplenectomy is controversial. Prior to splenectomy, and in severe cases, postsplenectomy, HS patients should take folic acid to prevent folate deficiency.

Elliptocytosis, pyropoikilocytosis, and related disorders Hereditary elliptocytosis (HE) is characterized by the presence of elliptical or cigar-shaped erythrocytes on peripheral blood smears of affected individuals. The worldwide incidence of HE has been estimated to be 1 in 2000 to 1 in 4000 individuals. The true inci- dence of HE is unknown because most patients are asymptomatic. It is common in individuals of African and Mediterranean ancestry, presumably because elliptocytes confer some resistance to malaria. In parts of Africa, the incidence of HE approaches 1 in 100. HE is typically inherited in an autosomal dominant pattern. Rare cases of de novo mutations have been described. Hereditary pyropoikilocytosis (HPP) is a rare cause of severe haemolytic anaemia with erythrocyte morphology reminiscent of that seen in severe burns. Initial studies of erythrocytes from these patients revealed abnormal thermal sensitivity compared to normal erythrocytes. HPP occurs predominantly in patients of African descent. There is a strong relationship between HPP and HE. Approximately one-third of parents or siblings of patients with HPP have typical HE. Many patients with HPP experience severe haem- olysis and anaemia in infancy that gradually improves, evolving to- ward typical HE later in life. Aetiology and pathogenesis The principal defect in HE/HPP erythrocytes is an intrinsic mech- anical weakness or fragility of the erythrocyte membrane skeleton due to a defect of horizontal interactions (discussed previously). This is due to defects in the red cell membrane proteins α-spectrin, β-spectrin, protein 4.1, band 3, or glycophorin C. The majority of de- fects occur in spectrin, the principal structural protein of the mem- brane skeleton. A variety of mutations in the genes encoding these proteins have been described, with several mutations identified in a number of individuals on the same genetic background, suggesting a ‘founder effect’ for these mutations. Clinical features The clinical presentation of HE is heterogeneous, ranging from asymptomatic carriers to patients with severe, transfusion-dependent anaemia. Most patients with HE are asymptomatic and are typically diagnosed incidentally during testing for unrelated conditions. The erythrocyte lifespan is normal in most patients. The 10% of patients with decreased red cell lifespan are the ones who experience haemolysis, anaemia, splenomegaly, and intermittent jaundice. Many of these symptomatic patients have parents with typical HE and thus are homozygotes or compound heterozygotes for defects inherited from each of the parents. Symptomatology may vary between members of the same family; indeed, it may vary in the same individual at different times. To explain these ob-servations, modifier alleles have been hypothesized to influence spectrin expression and clinical severity. One such allele, αLELY (low-expression Lyon), has been identified and characterized.

section 22 Haematological disorders 5462 Diagnosis The hallmark of HE is the presence of elliptocytes on peripheral blood smears (Fig. 22.6.9.2c). These normochromic, normocytic elliptocytes number from a few to 100%. The degree of haem- olysis and anaemia do not correlate with the number of elliptocytes present. A few ovalocytes, spherocytes, stomatocytes, and frag-mented cells may also be seen. Elliptocytes may be seen in asso- ciation with several disorders including megaloblastic anaemias, hypochromic microcytic anaemias (iron deficiency anaemia and thalassaemia), myleodysplasic syndromes, and myelofibrosis; how- ever, elliptocytes generally make up less than one-third of red cells in these conditions. History and additional laboratory testing usu- ally clarify the diagnosis of these disorders. In addition to the per- ipheral blood smear findings found in HE, HPP erythrocytes are bizarre-shaped with fragmentation and budding (Fig. 22.6.9.2d). Microspherocytosis is common and the MCV is frequently de- creased (50–65 mm3). The osmotic fragility is increased in severe HE and HPP. Other laboratory findings in HE are similar to those found in other haemo- lytic anaemias and are nonspecific markers of increased erythrocyte production and destruction. When indicated, specialized testing, such as membrane protein quantitation and genetic studies can be performed. Treatment Therapy is rarely necessary.

In rare cases, occasional red blood cell transfusions may be required. In cases of severe HE and HPP, splenectomy has been useful. The same indications for splenec- tomy in HS can be applied to patients with symptomatic HE or HPP. Postsplenectomy, patients with HE or HPP experience increased haemoglobin, decreased haemolysis, and improvement in clinical symptoms. During acute illnesses, patients should be followed for signs of haematological decompensation. Ultrasonography at regular inter- vals to detect gallstones should be performed. In patients with sig- nificant haemolysis, folate should be administered daily. South-East Asian ovalocytosis South-East Asian ovalocytosis (SAO) is characterized by the pres- ence of oval erythrocytes with a central longitudinal slit or trans- verse bar on peripheral blood smears of affected individuals. It is common in parts of the Philippines, Indonesia, Malaysia, and New Guinea and is inherited in an autosomal dominant fashion. Incredibly rigid, SAO erythrocytes are resistant to invasion by mal- aria parasites. The underlying defect is a mutation in a critical region of band 3. Haematologically, patients with SAO are asymptomatic, with little or no evidence of haemolysis or anaemia. The finding of characteristic ovalocytes in the peripheral blood of an asymptomatic individual from one of the earlier-mentioned ethnic backgrounds is highly suggestive of the diagnosis. Biochemical and DNA diagnostic techniques are available to detect this condition. Stomatocytosis The hereditary stomatocytosis syndromes are a heteroge- neous group of rare disorders characterized by mouth-shaped (stomatocytic) erythrocyte morphology on peripheral blood smear (Fig. 22.6.9.4). The clinical severity of stomatocytosis pa- tients is variable; some patients experience haemolysis and an- aemia, while others are asymptomatic. An unusual feature of the stomatocytosis syndromes is a dramatically increased predispos- ition to thrombosis or pulmonary hypertension postsplenectomy. Fortunately, anaemia is well compensated in most patients and splenectomy is not required. The red blood cell membranes of stomatocytosis patients usu- ally exhibit abnormal permeability to the cations sodium and potassium, with consequent modification of intracellular water content, ranging from dehydrated (xerocytosis) to overhydrated (hydrocytosis) erythrocytes. The variable clinical, laboratory, and pathophysiological findings associated with the stomatocytosis syndromes suggest these are a complex collection of syndromes caused by various molecular defects. Dehydrated stomatocytosis (also termed stomatocytic xerocytosis) has been shown to be associated with mutations in the Gardos and Piezo channels in the red cell membrane. Overhydrated stomatocytosis, by contrast, is caused by defects in the Rh-antigen associated glycoprotein (encoded by the RHAG (a) (b) Fig. 22.6.9.4 Peripheral blood smears: (a) dehydrated stomatocytosis; (b) overhydrated stomatocytosis. From Lande WM, Mentzer WC (1985). Haemolytic anaemia associated with increased cation permeability. Clin Haematol, 14, 89–103, with permission.

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