# 22.6.8 Anaemias resulting from defective maturatio

# 22.6.8 Anaemias resulting from defective maturation of red cells 5450 Stephen J. Fuller and James S. Wiley

section 22 Haematological disorders 5450 Treatment In cases of chronic acquired methaemoglobinaemia, the drug or chemical agent should be removed where possible. If continued therapy is required, it should be administered at a lower dose. Acute toxic methaemoglobinaemia presents a serious medical emergency. Methylene blue should be administered in a dose of 1 to 2 mg/kg intravenously over a 5-min period. Repeated doses may be needed. Toxicity is uncommon, although doses of over 15 mg/kg may cause haemolysis in young infants. The drug should not be used if the methaemoglobinaemia is due to chlorate poisoning, as it may convert the chlorate to hypochlorite which is an even more toxic compound. In cases of acute methaemoglobinaemia with intravas- cular haemolysis, haemodialysis with exchange transfusion is the treatment of choice. Carboxyhaemoglobinaemia Carbon monoxide has an affinity for haemoglobin approximately 210 times that of oxygen. Following acute exposure, it is so tightly bound that it takes about 4 h for an individual with normal ventila- tion to expel half of it. At levels of 5 to 10% there may be no symp- toms, but above 20% there is usually headache and weakness. Levels of 40 to 60% or more lead to unconsciousness and death. Carbon monoxide poisoning is discussed in Chapters 10.1 and 10.2 and secondary polycythaemia due to chronic exposure is con- sidered elsewhere in this section (see Chapter 22.3.5). Sulphaemoglobinaemia This poorly defined condition derives its name from the fact that it can be produced in vitro by the action of hydrogen sulphide on haemoglobin. It has not been reported as a genetic disorder. It is usually associated with the administration of drugs, particu- larly sulfonamides or phenacetin. It has also been reported in patients with chronic constipation or malabsorption syndromes (enterogenous cyanosis) although its relationship to these dis- orders is far from clear. Other acquired

abnormalities of the structure
or synthesis of haemoglobin Glycosylated haemoglobin, haemoglobin A1c Haemoglobin may undergo post-translational modification in pa- tients with diabetes. The abnormal haemoglobin, haemoglobin A1c, is formed by the nonenzymic combination of glucose with the N-terminus of the β chain, first forming a Schiff base which then undergoes a rearrangement to form a stable ketoamine. The level of haemoglobin A1c is raised in diabetics and is related to the blood sugar level over the previous weeks. The value of the estimation of haemoglobin A1c as an index of the control of diabetes is considered elsewhere. Fetal haemoglobin production in adult life A number of haematological disorders are associated with a re- version to fetal haemoglobin production after the neonatal period. These include juvenile myelomonocytic leukaemia and congenital hypoplastic anaemias. Haemoglobin F may also appear transitorily during rapid regeneration of the bone marrow after drug-induced hypoplasia, viral infection, or bone marrow transplantation, and the level is also slightly elevated during the mid trimester of pregnancy. FURTHER READING Forget BG (2011). Progress in understanding the haemoglobin switch. N Engl J Med, 365, 852–4. Higgs DR, Gibbons RJ (2010). The molecular basis of alpha-thalassaemia: a model for understanding human molecular genetics. Hematol Oncol Cin North Am, 24, 1033–54. Houwing ME, et al. (2019). Sickle cell disease: Clinical presentation and management of a global health challenge; SCORE Consortium. Blood Rev, 37, 100580. Orkin SH, et al. (eds) (2014). Nathan and Oski’s hematology of infancy and childhood, 9th edition. Saunders and Elsevier, Philadelphia. Piel FB, Steinberg MH, Rees DC (2017). Sickle Cell Disease. N Engl J Med, 376, 1561–73. Serjeant GR, Serjeant BE (2001). Sickle cell disease, 3rd edition. Oxford University Press, Oxford. Steinberg MH, et al. (Eds) (2009). Disorders of hemoglobin, 2nd edi- tion. Cambridge University Press, New York. Telen MJ, Malik P, Vercellotti GM (2019). Therapeutic strategies for sickle cell disease: towards a multi-agent approach. Nat Rev Drug Discov, 18(2), 139–58. Weatherall DJ, Clegg JB (2001). The thalassaemia syndromes, 4th edi- tion. Blackwell Science, Oxford. Weatherall DJ (2013). The role of the inherited disorders of haemo- globin, the first ‘molecular diseases’ in the future of human genetics. Annu Rev Genomics Hum Genet, 14, 1–24. Weatherall DJ, Schechter AN, Nathan DG (eds) (2013). Hemoglobin and its diseases. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. 22.6.8 Anaemias resulting from defective maturation of red cells Stephen J. Fuller and James S. Wiley ESSENTIALS Defective maturation of red cells leads to premature destruction of nucleated red cell precursors before they leave the bone marrow, which results in expansion of the marrow, haemolytic jaundice, peripheral signs of increased erythroid turnover on blood films, and (in long-standing disorders) iron overload due to enhanced absorption. Causes of ineffective erythropoiesis These include (1) inhibition of erythroid DNA synthesis (e.g. meg- aloblastic anaemias most commonly caused by vitamin B12 or folate deficiency, and drugs blocking DNA synthesis); (2) clonal dis- orders of erythropoiesis (e.g. myelodysplastic syndromes with ring

 sideroblasts, and acute erythroid leukaemia); (3) genetic disorders of erythropoiesis (e.g. thalassaemia syndromes, hereditary sideroblastic anaemia, and congenital dyserythropoietic anaemia); and (4) other causes (e.g. alcohol). Sideroblastic anaemias These result from defects in haem biosynthesis, with most cases being acquired as a clonal disorder of erythropoiesis, with varying degrees of myelodysplasia. Other causes are (1) hereditary (e.g. in- herited defects of the erythroid-specific 5-aminolevulinic acid syn- thase 2 gene on the X-chromosome causes congenital sideroblastic anaemia); (2) acquired non-clonal (e.g. drugs or toxins such as ethanol, isoniazid, or lead; following chemotherapy or irradiation; or of unknown cause). Diagnosis is confirmed by finding ring

sideroblasts (erythroblasts containing five or more iron-positive granules arranged in a peri-nuclear location around one-third or more of the nucleus) on a bone marrow aspirate stained with Prussian blue iron reagent. Aside from supportive care with blood transfusion and iron chelation, a trial of pyridoxine is generally indicated (25% of hereditary cases— but few acquired cases—show some response). Acquired clonal sideroblastic anaemia has a median survival of 70–100 months, with 3 to 12% progressing to acute leukaemia. Introduction Erythroid cell maturation is specialized towards the coordinated synthesis of large amounts of haem and globin necessary to attain the high concentration of haemoglobin found in the mature red cell. Hereditary or acquired defects in the production of either of these cause a maturation block, which leads to ineffective erythro-poiesis in which many of the developing nucleated erythroblasts are destroyed in the marrow before they can reach the circulation. Thus in thalassaemia, defective synthesis of either α- or β-globin leads to unbalanced production of the other chain, which pre- cipitates and leads to destruction of the precursor erythroblast. Defective haem synthesis in the sideroblastic anaemias also leads to an anaemia which is characterized by ineffective erythropoiesis (Box 22.6.8.1). Abnormalities of DNA synthesis in the developing erythroid cells, produced, for example, by vitamin B12 or folic acid deficiency, blocks cell division required for erythroid maturation and produces morphological and biochemical evidence of inef- fective erythropoiesis. Ineffective erythropoiesis may be recognized by the character- istic erythroid hyperplasia of the bone marrow with normal or only slightly increased reticulocyte numbers. Some other fea- tures of ineffective erythropoiesis may be variably present: a mild increase in bilirubin, a decrease in haptoglobin, and increased serum lactic dehydrogenase activity. As a result, iron absorp- tion is increased, serum iron and ferritin become elevated, and, after many years, iron overload develops which is indistinguish- able from idiopathic haemochromatosis. However, the degree of iron overload does not depend on either the severity of the an- aemia or the presence of the characteristic mutation (Cys282Tyr, His63Asp, and Ser65Cys) of the HFE gene associated with genetic haemochromatosis. Sideroblastic anaemias The sideroblastic anaemias are a group of hereditary or acquired anaemias of varying severity diagnosed by the finding of ring sideroblasts in the bone marrow aspirate. The peripheral blood film shows hypochromic red cells which are microcytic in the heredi- tary form (Fig. 22.6.8.1), but are often macrocytic in the acquired forms of the disease. Normochromic and normocytic red cells are also present which gives the film a dimorphic distribution of red cell sizes. The diagnostic procedure is bone marrow aspirate fol- lowed by staining of the smear with Prussian blue iron reagent. Ring sideroblasts are diagnostic (Fig. 22.6.8.2) and are defined as erythroblasts containing five or more iron-positive granules ar- ranged in a perinuclear location around one-third or more of the Box 22.6.8.1 Anaemias with defective red cell maturation and ineffective erythropoiesis • Inhibition of erythroid DNA synthesis:

— Megaloblastic anaemias (most commonly due to vitamin B12 or folate deficiency)

— Drugs blocking DNA synthesis (e.g. hydroxycarbamide, 6-mercaptopurine) • Clonal disorders of erythropoiesis:

— Refractory anaemia

— Acquired clonal sideroblastic anaemias (refractory anaemia with ring sideroblasts, with and without thrombocytosis)

— Acute erythroid leukaemia (WHO classification subtypes: erythro- leukaemia and pure erythroid leukaemia) • Genetic disorders of erythropoiesis:

— Thalassaemia syndromes

— Hereditary sideroblastic anaemias

— Congenital dyserythropoietic anaemias (CDAs) • Miscellaneous:

— Alcohol

— Drugs

— Heavy metal poisoning (e.g. arsenic)

— Falciparum malaria Fig. 22.6.8.1 Peripheral blood smear in hereditary sideroblastic anaemia showing a population of hypochromic and microcytic erythrocytes.

section 22 Haematological disorders 5452 nucleus. Electron microscopy reveals that the iron-containing gran- ules are mitochondria containing precipitated ferric phosphate and ferric hydroxide. The sideroblastic anaemias have diverse aetiologies (Box 22.6.8.2) but have in common an impaired biosynthesis of haem in the erythroid cells of the marrow. Most sideroblastic anaemias are acquired as a clonal disorder of erythropoiesis, classified as a subtype of myelodysplasia. The hereditary forms are uncommon. Most are found in males with an X-linked pattern of inheritance. A number of drugs have been associated with reversible sideroblastic anaemia, chiefly in patients with alcohol abuse (Box 22.6.8.2). Hereditary sideroblastic anaemias Aetiology and pathogenesis Haem biosynthesis occurs by a cascade of eight enzymes (Fig. 22.6.8.3). In humans, mutations affecting the first enzyme of this pathway produce hereditary sideroblastic anaemia. Inborn errors that occur in later enzymes in this pathway result in meta- bolic disorders known as the porphyrias (Fig. 22.6.8.3). The pathway begins with the condensation of glycine with succinyl CoA to form 5-aminolaevulinic acid (ALA), a step which is under the control of the mitochondrial enzyme ALA synthase. This en- zyme requires pyridoxal phosphate as a cofactor. Two isoenzymes of ALA synthase have been identified. One is found in liver and other tissues (ALAS1); the other is confined to erythroid cells of the bone marrow (ALAS2). In most families with inherited sideroblastic anaemia, males are affected with an X-linked pattern of inheritance consistent with a mutation on the X chromosome (Fig. 22.6.8.4). The gene for the erythroid-specific ALAS2 isoen- zyme resides on the X chromosome and is now known to be the site of most mutations giving rise to X-linked hereditary sideroblastic anaemia. Over 100 different mutations have been described in different families and nearly all result from a single amino acid alteration arising from a point mutation in the ALAS2 coding re- gion of DNA. However, in nearly half the families with hereditary sideroblastic anaemia, the structure of the ALAS2 gene is normal, and a number of inherited variations in other genes involved in haem synthesis have recently been identified. These hereditary sideroblastic anaemias consist of two nonsyndromic forms, which have a similar phenotype to X-linked sideroblastic anaemia and five rare syndromic forms where haem synthesis is affected in nonhaematopoietic tissues in addition to red cells (Box 22.6.8.2). Of the nonsyndromic forms, inherited mutations in the SLC25A38 and GLRX5 genes cause autosomal recessive pyridoxine-refractory sideroblastic anaemia. Clinical and laboratory features Typically the anaemia presents in

infancy or childhood, but when the condition is mild the diagnosis may not be made until adult life. Occasionally, such patients may present with features of iron overload such as diabetes or cardiac failure. Others may be found in family surveys, which should be undertaken when this anaemia is diagnosed. Slight enlargement of the liver or spleen may occur. The degree of anaemia is variable, ranging from severe (haemo- globin <80 g/litre) to mild (>100 g/litre) but even with mild or no anaemia the mean corpuscular volume (MCV) is below the normal range. The blood film shows a population of cells with hypochromic, microcytic morphology. In X-linked sideroblastic anaemia, female carriers may show the characteristic red cell dimorphism. White cell counts are normal, while platelet counts are normal or slightly elevated. Serum iron and ferritin concentrations are invariably in- creased and transferrin shows an increased percentage saturation with iron. The differential diagnosis includes idiopathic haemo- chromatosis, since both diseases have evidence of iron overload. Examination of the blood film, the MCV, and the bone marrow should establish the diagnosis. Fig. 22.6.8.2 Bone marrow smear stained with Prussian blue, showing ring sideroblasts. Box 22.6.8.2 Classification of sideroblastic anaemias Hereditary • Nonsyndromic:

— X-linkeda

— Autosomal inheritancea (includes pyridoxine-refractory autosomal recessive sideroblastic anaemia) • Syndromic:

— X-linked sideroblastic anaemia with ring sideroblasts and cere- bellar ataxia

— Myopathy, lactic acidosis, and sideroblastic anaemia

— Pearson syndrome

— Thiamine-responsive megaloblastic anaemia

— Sideroblastic anaemia with immunodeficiency, fevers, and devel- opmental delay Acquired • Refractory anaemia with ring sideroblasts (RARS), now classified as myelodysplastic syndrome with RS (MDS-RS)a • Associated with previous chemotherapy, irradiation • RARS with thrombocytosis (RARS-T), now classified as myelodysplastic/ myeloproliferative neoplasm with RS and thrombocytosis (MDS/ MPN-RS-T) Drugs • Alcohol • Isoniazid, cycloserine, pyrazinamide • Chloramphenicol Rare causes • Erythropoietic protoporphyria • Copper deficiency or zinc overload • Hypothermia a Trial of pyridoxine indicated.

22.6.8 Anaemias resulting from defective maturation of red cells 5453 The syndromic forms of hereditary sideroblastic anaemia present with anaemia in combination with either muscle, neurological, or pancreatic tissue involvement (Box 22.6.8.2). These disorders show both X-linked and autosomal patterns of inheritance. The labora- tory features of these sideroblastic anaemias are similar to X-linked sideroblastic anaemia; however, mutations in the high-affinity thiamine transporter gene, SLC19A2, cause the unusual feature of megaloblastic erythroid maturation with ring sideroblasts. Treatment and prognosis A trial of pyridoxine, 100 to 200 mg/day taken orally, is indicated for 3 months in all patients with proven or suspected hereditary sideroblastic anaemia. About 25% of patients experience a full or partial correction. This vitamin should be continued lifelong in re- sponders but at a lower maintenance dosage. Regular transfusions of packed red cells are the mainstay of treatment of severe anaemia. These should be given to relieve symptoms

and allow normal child- hood development. Splenectomy is contraindicated in this con- dition. Iron overload progresses rapidly once transfusions begin. Chelation therapy with desferrioxamine or oral deferasirox should thus be commenced after the first 10 to 20 transfusions. Iron re- moval may greatly benefit patients with mild or moderate anaemia and evidence of iron overload. Furthermore, patients should avoid alcohol and ascorbic acid supplements, both of which enhance iron absorption. Acquired clonal sideroblastic anaemias Acquired clonal sideroblastic anaemias may either be idiopathic or develop following chemotherapy or irradiation (Box 22.6.8.2). Since nearly all cases also show evidence of dyserythropoiesis, this an- aemia was classified as one of the myelodysplastic syndromes and Hereditary coproporphyria Protoporphyrinogen III Protoporphyrin IX Haem Glycine + succinyl CoA ALA ALA Porphobilinogen Acute intermittent porphyria Hydroxymethylbilane Uroporphyrinogen III Coproporphyrinogen III Porphyria cutanea tarda Congenital porphyria Plumboporphyria X-linked hereditary sideroblastic anaemia Erythropoietic protoporphyria Variegate porphyria Fig. 22.6.8.3 Pathway of haem biosynthesis in mammalian cells. The first step in the pathway is catalysed by ALAS and occurs within the mitochondrion using pyridoxal 5′-phosphate as a cofactor. ALA then leaves the mitochondrion and is converted by ALA dehydratase to give a monopyrrole, porphobilinogen. Four molecules of this are converted by porphobilinogen deaminase to a linear tetrapyrrole, hydroxymethylbilane. This molecule is then cyclized by uroporphyrinogen III synthase to uroporphyrinogen III, which is then decarboxylated to coproporphyrinogen III. This molecule enters the mitochondrion and is oxidized in succession by coproporphyrinogen III oxidase and protoporphyrinogen III oxidase. The product is protoporphyrin IX, a substrate for ferrochelatase, which catalyses the insertion of Fe2+ to form haem.
A mitochondrial haem exporter has been identified as feline leukaemia virus subgroup C receptor 1b (FLVCR1b). The defective steps associated with specific porphyrias and X-linked hereditary sideroblastic anaemias are shown. From Hoffman R, et al. (eds) (2013). Hematology: basic principles and practice, 6th edition. WB Saunders, Philadelphia, with permission. 1 2 3 4 ? ? ? ? ? ? ? Fig. 22.6.8.4 Pedigree of a family with pyridoxine-responsive sideroblastic anaemia showing X-linked recessive inheritance. Filled square, affected; filled circle, carrier; ?, unknown status. Diagonal lines indicate deceased members. The pedigree has been abbreviated to show only the affected branches of the family. The arrow indicates the proband. Copyright 1994 Massachusetts Medical Society. All rights reserved. Reproduced from Cox et al. (1994).

section 22 Haematological disorders 5454 termed ‘refractory anaemia with ring sideroblasts (RARS)’. The World Health Organization (WHO) classification system now includes 2 myelodysplastic syndromes with ring sideroblasts: (1) refractory an- emia with ring sideroblasts (RARS), now classified as myelodysplastic syndromes with RS (MDS-RS); and (2) RARS with thrombocytosis (RARS-T), now classified as myelodysplastic/myeloproliferative neoplasm with RS and thrombocytosis (MDS/MPN-RS-T). Clonal defective haematopoiesis has also been shown in the acute eryth- roid leukaemias, in which bizarre dysplastic changes are seen in the developing erythroblasts. These comprise a majority (>50%) of all nu- cleated marrow cells in erythroleukaemia, a subtype of acute erythroid leukaemia. The fact that more than 20% of the myeloid cells are blasts distinguishes acute erythroleukaemia from one of the myelodysplastic syndromes. A second form of acute erythroid leukaemia, pure eryth- roid leukaemia, is defined within the WHO classification as a neo- plastic proliferation of immature erythroid cells comprising 80% or more of bone marrow cells with no significant myeloblastic element. Ring sideroblasts are seen in the erythroleukaemia subtype of acute erythroid leukaemia, but are uncommon in pure erythroid leukaemia. Aetiology and pathogenesis The cause of the defective haem synthesis in

acquired sideroblastic anaemia is unclear. Recent reports indicate that levels of ALAS in bone marrow are normal. Indirect evidence points to an acquired defect in the mitochondrial respiratory chain that impairs the re- duction of Fe3+ to Fe2+ since ferrous iron is essential for the terminal ferrochelatase reaction (Fig. 22.6.8.3). Clonal haematopoiesis has been demonstrated in this anaemia by both molecular and karyo- typic analysis. Thus a single glucose-6-phosphate dehydrogenase (G6PD) isoenzyme was found in erythrocytes of a woman het- erozygous for G6PD who expressed two isoenzymes in her som- atic tissues. Clonal chromosome changes are also found in bone marrow cells in many patients with acquired sideroblastic anaemia. Characteristic changes include monosomy 7, trisomy 8, deletions involving chromosomes 5, 7, 11, 13, or 20, and a number of trans- locations. When sideroblastic anaemia is acquired secondary to chemotherapy or irradiation, chromosomal changes are nearly al- ways found and tend to be multiple. However, they are probably a late event in the course of this anaemia and may be preceded by the expansion of a clone of genetically unstable stem cells. Recurrent mutations in the SF3B1 gene have been described in 85% of ac- quired sideroblastic anaemia cases. The product of SF3B1 is associ- ated with mRNA splicing, and mutations in this gene may influence a number of mitochondrial gene networks, including changes in the expression of the iron transporter ABCB7, which results in the accumulation of iron-laden mitochondria during erythroid devel- opment. Patients with MDS/MPN-RS-T have features of MDS-RS and thrombocytosis; with the bone marrow showing proliferation of large atypical megakaryocytes. Mutations in SF3B1 and JAK2 (V617F) are commonly found in these patients. Clinical and laboratory features Acquired sideroblastic anaemia typically has an insidious onset. Most patients are middle aged or older, but young adults can be affected. Mild splenomegaly may be present. White cell and platelet counts are usually normal; some patients may have thrombocytosis. The bone marrow shows erythroid hyperplasia with varying degrees of dyserythropoiesis, including irregular nuclear contour, nuclear fragmentation (karyorrhexis), bi- or trilobed nuclei, and inter- nuclear bridges. Iron staining of the aspirate shows ring sideroblasts which should total 15% or more of the nucleated erythroid cells to make the diagnosis. However, the prognostic significance of this level of ring sideroblasts has recently been questioned. Dysplasia of myeloid precursors or megakaryocytes may be present; however, when 10% or more of nonerythroid cells are dysplastic then cases are classified as ‘refractory cytopenia with multilineage dysplasia’. If the overall blast count in the peripheral blood is 2% or greater, or 5% or greater in the bone marrow, or the peripheral blood monocyte count exceeds 1.0 × 109/litre, the condition falls within a different category of the myelodysplastic syndromes. Thus, ring sideroblasts may be seen in other myelodysplastic conditions such as refrac- tory anaemia with excess blasts. Distinguishing acquired idiopathic sideroblastic anaemia from a mild hereditary sideroblastic anaemia presenting in adult life can be difficult. However, careful examin- ation of the marrow for dysplastic changes, the MCV, possible re- sponse to pyridoxine, and a family survey all help to distinguish these two entities. Treatment and prognosis Transfusions of packed red cells should be given for relief of symp- tomatic anaemia. A  trial of pyridoxine, 100 to 200 mg/day for 3 months, is worthwhile but few patients respond to this vitamin. Myelodysplastic syndromes with ring sideroblasts and refractory an- aemia have the most favourable outlook among the myelodysplastic syndromes, with a median survival of 70 to 100 months and a 3 to 12% incidence of progression to acute leukaemia. The Revised International Prognostic Scoring System (IPSS-R) uses the bone marrow blast percentage, karyotypic analysis, and the presence of peripheral blood cytopenias to group newly diagnosed cases into one of five prognostic groups (Table 22.6.8.1).

Table 22.6.8.1 Calculation of IPSS-R score for myelodysplastic syndromes

| Variable | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| Karyotypea | Very good | | Good | | Intermediate | Poor | Very poor |
| Bone marrow blasts (%) | ≤2 | | | | | | |

> 2–<5 5–10 10 Haemoglobin (g/litre) ≥100 80–<100 <80 Platelet count (× 109/litre) ≥100 50–<100 <50 Absolute neutrophil count (× 109/litre) ≥0.8 <0.8 a Very good: −Y, del(11q). Good: normal, del(5q), del(12p), del(20q), double including del(5q). Intermediate: del(7q), +8, +19, i(17q), other single or double independent clones. Poor: −7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex (3 abnormalities). Very poor: complex (>3 abnormalities)

22.6.8 Anaemias resulting from defective maturation of red cells 5455 Patients with very low risk disease, scores of 1.5 or less, have a median survival of 8.8 years, low-risk patients with scores of greater than 1.5 to 3 have a median survival of 5.3 years, intermediate-risk patients with scores of more than 3 to 4.5 have a median survival of 3 years, high-risk patients with scores of greater than 4.5 to 6 have a median survival of 1.6 years, and very high-risk patients with a score of more than 6 have a median survival of only 0.8 years. A number of agents, including erythropoietin, 5-azacytidine, decitabine, and lenalidomide, have been studied in therapeutic trials for myelodysplastic syndromes, which have included ac- quired sideroblastic anaemia cases; however, overall outcomes have been poor. It is unclear if iron chelation therapy with the oral iron- chelator deferasirox is of benefit, but this question may be answered by ongoing clinical trials. The value of cytoreductive therapy in MDS/MPN-RS-T is uncertain, as anaemia may be worsened; how- ever, hydroxyurea, lenalidomide, interferon alpha and busulfan have all been used in the setting of very high platelet counts. Defective red cell maturation secondary to alcohol and drugs Alcohol has a direct toxic effect on erythropoiesis, manifested by the macrocytosis that characterizes red cells of subjects chronic- ally ingesting alcohol in excess. Malnourished and anaemic alco- holics may exhibit ring sideroblasts in the bone marrow as well as vacuolation of erythroblasts. These manifestations gradually dis- appear over 4 to 12 days when alcohol is withdrawn, although the macrocytosis may take several months to normalize. The antibiotic chloramphenicol when given in dosages greater than 2 g/day pro- duces a reversible inhibition of erythropoiesis associated with ring sideroblasts and vacuolation of erythroblasts. This effect, due to in- hibition of mitochondrial protein synthesis, is quite separate from the rare idiosyncratic side effect of aplastic anaemia. Protracted ex- posure to the antituberculous drug isoniazid has been occasionally associated with development of a sideroblastic anaemia. Defective red cell maturation secondary to lead, arsenic, or zinc ingestion, or copper deficiency Patients suffering lead poisoning show clinical and laboratory evi- dence of reduced haem biosynthesis. Basophilic stippling of red cells is prominent. Mild hypochromic, microcytic anaemia may develop. Red cell protoporphyrin, increased due to inhibition of the terminal step in the haem pathway, provides a sensitive measure of lead ex- posure. The peripheral neuropathy of lead poisoning may be a result of reduced haem biosynthesis, as in the porphyrias. Acute or chronic arsenic ingestion can cause anaemia with marked dyserythropoiesis. Arsenic trioxide ($As_2O_3$) is now used to treat patients with acute promyelocytic leukaemia at doses far less than is required to cause sideroblastic anaemia. However, sufficiently high levels may be en- countered in patients with renal failure if the dose of $As_2O_3$ has not been appropriately adjusted. Basophilic stippling of red cells is char- acteristic while neutropenia and thrombocytopenia may be present. Copper deficiency has been described only in malnourished pre- mature infants or in patients receiving long-term parenteral hyper- alimentation. This syndrome consists of anaemia and neutropenia associated with marrow findings of ring sideroblasts and vacuolated erythroid and myeloid precursors. Large quantities of ingested zinc interfere with copper absorption and reproduce the sideroblastic an- aemia and neutropenia

characteristic of copper deficiency. Congenital dyserythropoietic anaemias This rare group of inherited refractory anaemias, covered in more detail in Chapter 22.5.1, is characterized by gross multinuclearity of erythroid precursors in the marrow, ineffective erythropoiesis, and associated iron overload. Four types have been described based on morphology of the bone marrow and serological features. The most common, type II (OMIM 224 100), is also known as HEMPAS (her- editary erythroblast multinuclearity with positive acidified serum test) since red cells are lysed by acidified (pH 6.8) serum from about 30% of normal subjects. In congenital dyserythropoietic anaemia (CDA) type II, a defect in glycosylation of erythroblast membrane proteins has been identified. Most patients are diagnosed in late child- hood or adolescence with mild to moderate anaemia, with intermit- tent jaundice or in older patients with manifestations of iron overload. Splenomegaly or hepatomegaly may be variably present. CDA carries a good prognosis with few patients requiring transfusions. The degree of iron overload should be monitored and treated when appropriate. FURTHER READING Aivado M, et al. (2006). X-linked sideroblastic anemia associated with a novel ALAS2’ mutation and unfortunate skewed X-chromosome inactivation patterns. Blood Cells Mol Dis, 37, 40–5. Bergmann, AK, et al. (2010). Systematic molecular genetic analysis of congenital sideroblastic anemia: evidence for genetic heterogen- eity and identification of novel mutations. Pediatr Blood Cancer, 54, 273–8. Bottomley SS, Fleming MD (2014). Sideroblastic anemia: diagnosis and management. Hematol Oncol Clin North Am, 28, 653–70. Campagna DR, et al. (2014). X-linked sideroblastic anemia due to ALAS2 intron 1 enhancer element GATA-binding site mutations. Am J Hematol, 89, 315–9. Chakraborty PK, et al. (2014). Mutations in TRNT1 cause congenital sideroblastic anemia with immunodeficiency, fevers, and develop- mental delay (SIFD). Blood, 124, 2867. Cotter PD, et al. (1995). Late-onset X-linked sideroblastic anemia. Missense mutations in the erythroid δ-aminolevulinate synthase (ALAS2) gene in two pyridoxine-responsive patients initially diag- nosed with acquired refractory anemia and ringed sideroblasts.
J Clin Invest, 96, 2090–6. Cox TC, et al. (1994). X-linked pyridoxine-responsive sideroblastic anemia due to a THR388- to -SER substitution in erythroid 5- aminolevulinate synthase. N Engl J Med, 330, 675–9. Donker AE, et al. (2014). Practice guidelines for the diagnosis and management of microcytic anemias due to genetic disorders of iron metabolism or heme synthesis. Blood, 123, 3873. Ducamp S, Fleming MD (2019). The molecular genetics of sideroblastic anemia. Blood, 133(1), 59–69. Fuller SJ, Wiley JS (2013). Heme biosynthesis and it disorders: porphyrias and sideroblastic anemias. In: Hoffman R, et al. (eds) Hematology: basic principles and practice, 6th edition, pp. 466–72. Churchill Livingstone/Elsevier, Philadelphia. Greenberg P, et al. (2012). Revised international prognostic scoring system (IPSS-R) for myelodysplastic syndromes. Blood, 120, 2454–65. Guernsey, DL, et al. (2009). Mutations in mitochondrial carrier family gene SLC25A38 cause nonsyndromic autosomal recessive con- genital sideroblastic anemia. Nat Genet, 41, 651–3.

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