Microcytic Anemias: Sideroblastic Anemia — Causes and Treatment

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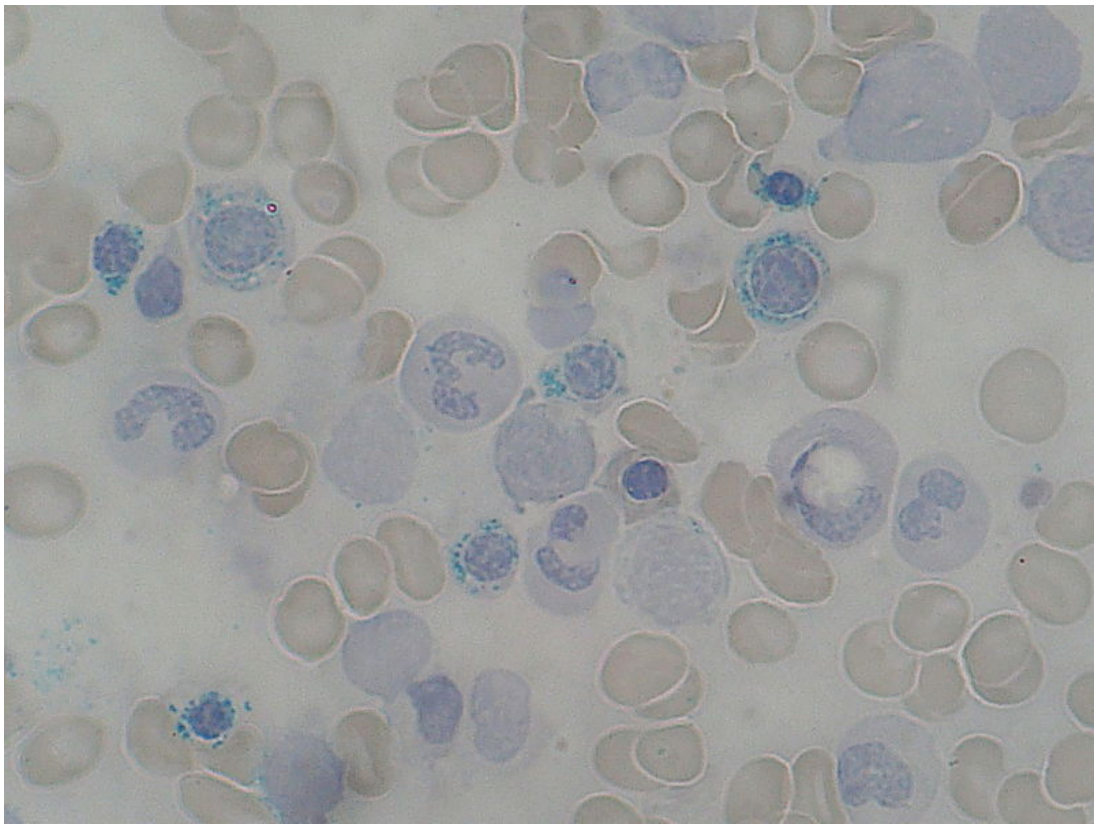
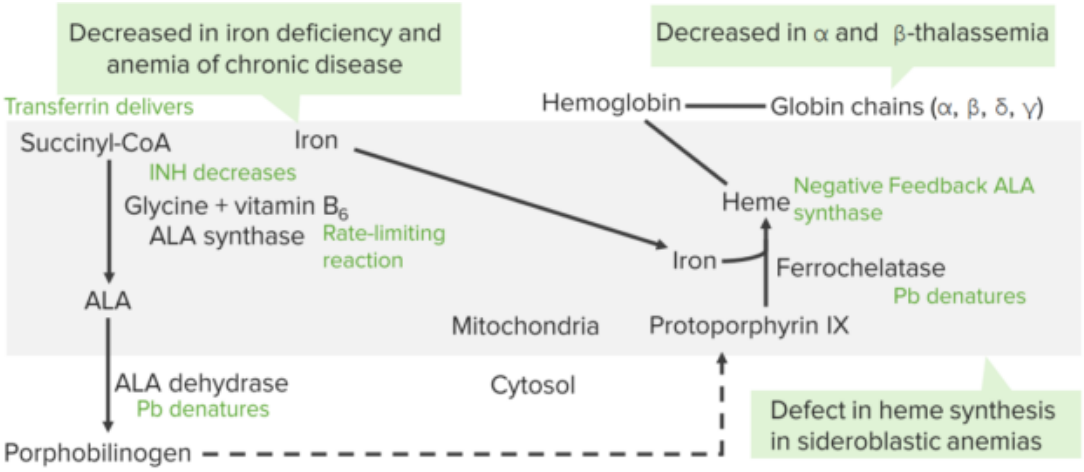
Sideroblastic anemias are a heterogeneous group of disorders with two common features: ring sideroblasts and affected heme biosynthesis. In this article, the most important forms of sideroblastic anemia are presented as well as their etiology, diagnosis, and therapy.



Definition of Sideroblastic Anemia

A microcytic anemia

Sideroblastic anemia is a form of **microcytic anemia** in which the **bone marrow produces sideroblasts**, i.e., ring-shaped blood cells, instead of normal, round-shaped red blood cells. This is due to the body's inability to place iron into hemoglobin properly. The shape can be described as abnormal nucleated erythroblasts, with iron saturating the mitochondria. This forms a ring around the nucleus, giving the classic ring shape.



Nucleated RBC in bone marrow

Epidemiology of Sideroblastic Anemia

A study in the USA, in which 25 children with anemia underwent a bone marrow biopsy, showed a prevalence of sideroblasts of 8%.

In the United Kingdom, 29% of healthy men and 19% of healthy women showed siderotic granules (not ring sideroblasts) present in their bone marrow.

Congenital X-linked sideroblastic anemia usually manifests in **childhood** but can remain undiagnosed for a long time, only to present late in the 4th – 8th decade of life. **Primary acquired sideroblastic anemia** occurs with a **median age of 75 years**.

Etiology of Sideroblastic Anemia

Sideroblastic anemia due to congenital defects or acquired causes

Sideroblastic anemia can be congenital or acquired. **Congenital defects** are due to defective porphyrin synthesis due to **abnormal aminolevulinic acid synthetase (ALAS)**. It is most commonly X-linked in individuals with ALAS abnormalities. This enzyme is responsible for converting aminolevulinic acid to produce the vital end product, heme, as explained in the following:

ALAS ⇒ converts succinyl CoA with Vit B6 → Aminolevulinic acid (ALA) ⇒ Aminolevulinic acid dehydrogenase converts ALA → porphobilinogen → protoporphyrin → attaches to iron → heme
Acquired causes include **drug-induced and vitamin deficiencies as well as alcoholism**. Alcohol tends to be the most common and detrimental to the mitochondrial process. Alcoholics are also generally afflicted with liver disease, folate deficiency, blood loss, hemolysis, and hypersplenism, leading to RBC loss and sequestering.

Lead poisoning inhibits the conversion of **protoporphyrins** necessary for heme synthesis. **Pyridoxine (vitamin B6),** which is a cofactor needed for protoporphyrin synthesis, is another cause. Pyridoxine deficiency is most commonly seen in patients treated with isoniazid and chloramphenicol.

Copper deficiency also causes sideroblastic anemia in people after prolonged ingestion of zinc. Patients who underwent bariatric surgery, or those suffering from malnutrition, are also at risk for copper-deficiency-induced sideroblastic anemia.

Lastly, **myelodysplastic syndrome** may result in sideroblastic anemia. The bone marrow shows abnormal erythroid hyperplasia with poorly hemoglobinized cytoplasm, also found in folate deficiency.

Acquired causes	Congenital causes
Alcohol Lead poisoning Myelodysplastic syndrome Medications (isoniazid for TB) Idiopathic Copper deficiency Zinc poisoning pyridoxine (vitamin B6) deficiency	X-Linked Mitochondrial disorders

Symptoms of Sideroblastic Anemia

Signs of sideroblastic anemia

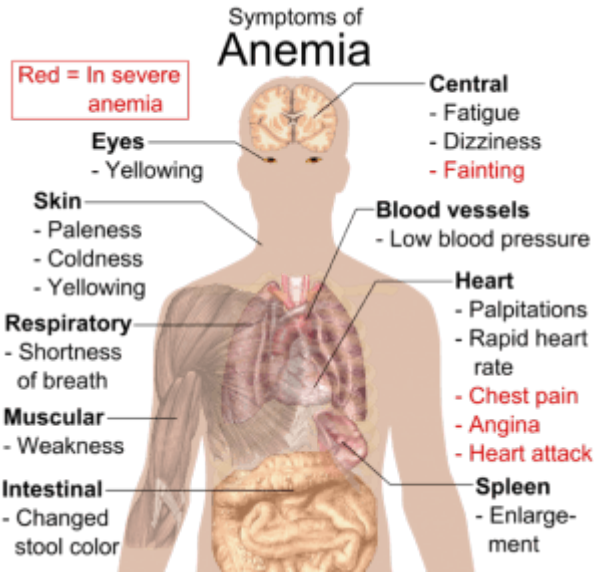
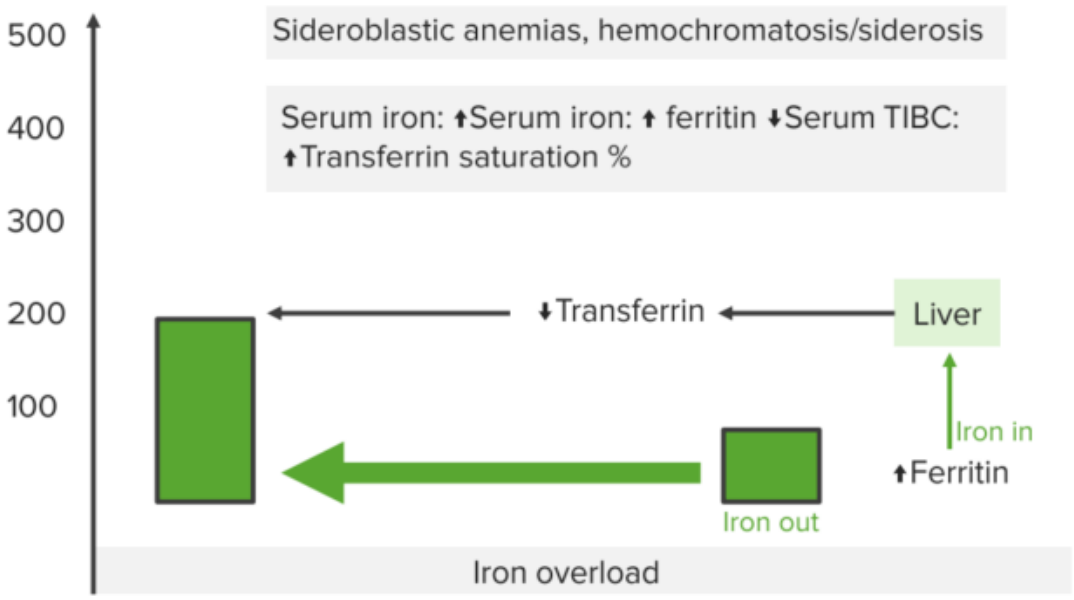


Image 1: “Main symptoms that may appear in anemia” by Mikael Häggström. License: Public Domain

A variety of signs, symptoms, and laboratory findings represent the diagnostic features pointing to sideroblastic anemia. The signs and symptoms are similar to those of general anemia and vary from **growth retardation in children** to adults with **hypothermia**, **dental lead lines**, **photosensitivity, ataxia, fatigue,** and **muscle weakness** (Image 1). Those afflicted due to Pyridoxine (Vitamin B6) deficiency commonly complain of **peripheral neuropathy,** whereas those with lead poisoning often present with **abdominal pain**, peripheral neuropathy, **encephalopathy**, and mental or growth retardation, especially in children.

Diagnosis of Sideroblastic Anemia

Iron overload in sideroblastic anemia



Iron studies (labs) of iron overload conditions

Diagnosis can be made based on the following criteria: Laboratory findings most commonly show **excessive iron overload**. A complete blood count will show the presence of microcytosis with an **MCV < 80**. Variations in RBC size and shape are reflected with an **increased RDW** (Red blood cell distribution width). Hemoglobin levels are usually below 7 g/dl. Iron studies show elevated serum ferritin levels, normal or decreased tibc (total iron-binding capacity), and elevated transferrin saturation. Laboratory Prussian blue staining will show hypochromic RBC with basophilic granules staining positive for iron, giving the classic ring sideroblast shape (Image 2). It will also be visible in peripheral blood in patients with severe anemia.

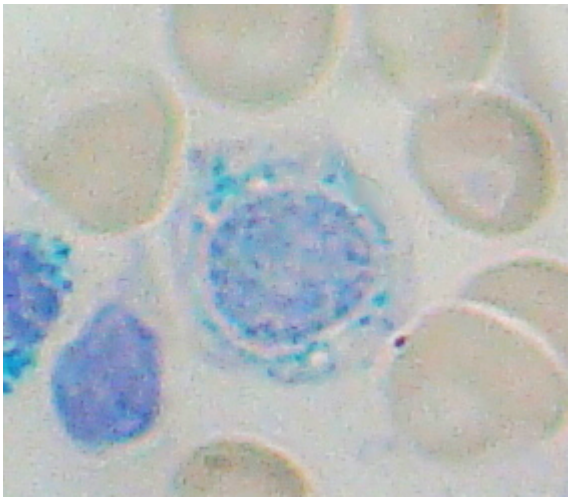


Image 2: “Sideroblast, as seen in sideroblastic anemia” by Mikael Häggström. Original by Paulo Henrique Orlandi Mourao. License: CC BY-SA 3.0

MRI can also show **iron overload in organs** such as the heart, liver, or bone marrow. Bone marrow exams offer diagnostic imagery. The marrow shows erythroid hyperplasia with poor hemoglobin concentration with the presence of ring sideroblasts. There are

greater amounts of iron in the bone marrow due to ineffective intramedullary hemolysis.

Therapy and Management of Sideroblastic Anemia

How to treat sideroblastic anemia

Management depends on the level of severity and syndromic forms of sideroblastic anemia. Therapy aims to prevent organ damage from subsequent iron overload as well as control and prevent symptoms of anemia. Patients with severe anemia may require **transfusion**. In the case of iron overload, **phlebotomy**—if no contraindications such as CHF exist—is used to prevent iron accumulation. Those who cannot undergo phlebotomy may be given trials of iron chelation therapy.

Vitamin supplementation with Vitamin B6, folic acid, and thiamine reduce neuropathic effects, help with normal erythropoiesis, and correct drug-induced sideroblastic anemia seen in patients and alcoholics. **Alcohol abstinence** should also be maintained. Most drug and alcohol-induced sideroblastic anemias are corrected after eliminating the offending agent. Splenectomy is not recommended for these patients due to thrombotic risks and complications.

References

Fleming MD. Congenital sideroblastic anemias: iron and heme lost in mitochondrial translation. Hematology Am Soc Hematol Educ Program 2011; 2011:525.

Sideroblastic Anemias via sickle.bwh.havard.edu

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