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 defined as a 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 inability of the body to place iron properly into hemoglobin. 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.
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. The **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 seen X-linked in individuals with ALAS abnormalities. This enzyme is responsible for the conversion of aminolevulinic acid to produce the vital end product, heme, as explained in the following:

\[
\begin{align*}
\text{ALAS} & \rightarrow \text{converts succinyl CoA with Vit B6} \\
& \rightarrow \text{Aminolevulinic acid (ALA)} \\
& \rightarrow \text{Aminolevulinic acid dehydrogenase} \\
& \rightarrow \text{protoporphyrin} \\
& \rightarrow \text{attaches to iron} \\
& \rightarrow \text{heme}
\end{align*}
\]

**Acquired causes** include **alcoholism, drug induced and vitamin deficiencies**. 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. **Deficiency of Pyridoxine (vit B6)**, which is a necessary cofactor for protoporphyrin synthesis, is another cause. This deficiency is most commonly seen in patients treated with isoniazid and chloramphenicol.
Copper deficiency is another cause observed in people after prolonged ingestion of zinc. Patients who received 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.

<table>
<thead>
<tr>
<th>Acquired causes</th>
<th>Congenital causes</th>
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<tbody>
<tr>
<td>Alcohol</td>
<td>X-Linked</td>
</tr>
<tr>
<td>Lead poisoning</td>
<td>Mitochondrial disorders</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td></td>
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<tr>
<td>Medications (isoniazid for TB)</td>
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<tr>
<td>Idiopathic</td>
<td></td>
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<tr>
<td>Copper deficiency</td>
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<tr>
<td>Zinc poisoning</td>
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Note: Alcohol abuse (most common cause), lead poisoning, pyridoxine (vitamin B6) deficiency, myelodysplastic syndrome!

Symptoms of Sideroblastic Anemia

Signs of sideroblastic anemia

A variety of signs, symptoms and laboratory findings represent the diagnostic features pointing to sideroblastic anemia. Signs and symptoms manifest similar to those with 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 (vit B6) deficiency commonly complain of peripheral neuropathy, whereas those with lead poisoning often present with abdominal pain, peripheral neuropathy, encephalopathy, mental and growth retardation, especially in children.
Diagnosis of Sideroblastic Anemia

Iron overload in sideroblastic anemia

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

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. The amount of iron seen in the bone marrow is heightened 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. If anemia is severe, transfusion may be required. In the case of iron overload, phlebotomy—given 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 is also given to reduce neuropathic effects, aid in normal erythropoiesis, as well as 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 upon removal of offending agent. Splenectomy is not recommended for these patients due to thrombotic risks and complications.

Review Questions

The answers are below the references.

1. A 22-year-old patient comes into the clinic complaining of fatigue, inability to concentrate and pale skin. Patient is a strict vegan and was diagnosed with a “congenital” blood disorder that she is unsure of. Lab work shows MCV of 70 and hemoglobin of 6. Which of the following tests would correctly identify the anemia she is having?
   
   A. Biopsy of the bone marrow  
   B. Physical exam  
   C. CT of the head  
   D. CBC

2. A 43 y/o male presents for a follow up after complaining of poor vision. Lab results show iron buildup in his eyes and liver. CBC shows anemia and blood smear shows which of the following?

   A. Irregular shaped and unequal sized red blood cells.  
   B. Erythroid hyperplasia with poor hemoglobin concentration.  
   C. Mostly small red blood cells.  
   D. Normal red blood cells.

References


Sideroblastic Anemias via sickle.bwh.harvard.edu
Correct answers: 1A, 2A

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