Original Article

A Case Report Of Sideroblastic Anemia

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Abstract

Sideroblastic anemia (SA) comprise a heterogeneous group of acquired primary or secondary and congenital disorders which have in common an anemia.generally refractory to therapy,ineffective erythropoiesis and the presence of large numbers of ring sideroblasts in the marrow. Increased levels of tissue iron and varying proportions of hypochromic erythrocytes in the blood are associated features.

Introduction

Sideroblastic anemia is a type of anemia that results from abnormal utilisation of iron during erythropoiesis.There are different forms of sideroblastic anemia, and all forms are defined by the presence of ring sideroblasts in the bone marrow.Ring sideroblast are erythroid precursors containing deposits of non heme iron in mitochondria forming a ring-like distribution around the nucleus.[1] The iron formed ring covers at least one-third of the nucleus rim. [2] Sideroblastic anemia is known to cause microcytic and macrocytic anemia depending on what type of mutation led to it [3] unlike iron deficiency anemia,where there is depletion of iron stores,patients with Sideroblastic anemia have normal to high iron levels.Other microcytic anemias include thalassemia and anemia of chronic disease[4].Structurally,the heme contains four methine bridges at the alpha position with an iron atom at the Center of the ring .[5] As a result of this protein molecule,the hemoglobin can perform its function of carrying oxygen to tissues.

Sideroblastic anemia has two forms. The first, which is hereditary,is caused by mutation in genes that are involved in heme synthesis,iron -sulfur cluster biogenesis , or mitochondrial metabolism[7]. The most common cause of hereditary sideroblastic cancer anemia,however,is the X-linked type caused by a mutation of the gene forming ALAS2 enzymes. Acquired sideroblastic anemia may arise from primary or secondary causes. Primary causes include clonal clonal hematologic disorder which include myelodysplastic syndrome with ring sideroblast(MDS-RS) and refractory anemia with ring sideroblast RARS.Secondary causes are due to drugs, toxins,copper deficiency or chronic neoplastic disease.

CASE REPORT:

A two year old boy presented with pallor since two months of life. He was treated with iron therapy without improvement. The child required blood transfusions thrice in past. There was no history of jaundice, fever, bleeding episodes or swelling anywhere in his body. There was no history of any drug intake except iron syrup.

The parents were second-degree cousins. One male sibling had died in infancy from pallor but had not been investigated. No family history of chronic anemia or blood transfusion.

There was developmental delay with absence of new milestones after one year of age.

Physical examination:
Weight 8.00 kg OFC 40 cm Height 75 cm
Euthermic, Pulse 120/minute RR 28/minute BP 100/70 mm Hg
Marked pallor, no jaundice
No dysmorphic features
PA: Liver 3 cm below costal margin, spleen 3 cm
CVS: Systolic murmur apical and midprecordial area
CNS: No ataxia
Investigations revealed the following:
Hb 3.2 gm/dl
RBC 3.1 million/cmm,
MCV 66 fL
MCH 30 pg
MCHC 35 %
RDW 24.4%
TLC: 6940/cmm
(P 24 L 74 E 1 M 1)
Platelet count:2,10000/cmm
Reticulocyte count:0.4% (0.5-2.5).
Peripheral smear: Red cell morphology showed marked microcytosis, few red cell fragmentations, and mild anisocytosis
G-6-PD screening, direct Coomb's test and osmotic fragility revealed no abnormality.
Serum iron 302.8 microgram/dl (49-181), S. Ferritin 163.1 ng/ml (normal 1-6 year 10.9-92.2)
TIBC:55 microgram/dl (250-400 microgram/dl)
Vit B12 level 640.8 pg/ml (197-771)
Transferrin saturation :98.9%
Hb electrophoresis was normal (Hb A 96.4 HbA2 2.4 Foetal Hb 1.2).
Renal function tests and hepatic function tests were normal.
Bone marrow examination: Normal cellularity, myeloid to erythroid ratio (M: E ratio) of 1: 4 with normoblastic erythroid maturation. There was mild dyserythropoiesis. Myeloid and megakaryocytic series were within normal limits. Perl's stain (Prussian blue) showed increased iron stores with presence of ring sideroblasts in excess of 50.0% of the developing erythrocytes.
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Final diagnosis: Sideroblastic anemia

He was treated with red cell transfusions. He was started on oral pyridoxine 50 mg daily which was increased to 100 mg/day.

DISCUSSION

Sideroblastic anemia occurs when the bone marrow fails to produce a sufficient number of healthy red blood cells. Instead, it produces sideroblasts (abnormal red blood cells that normally mature into red blood cells) in which iron accumulates in the mitochondria. These iron-loaded mitochondria surround the nucleus of the developing red blood cell and give the appearance of a ring.

Because the iron is stuck in the mitochondria, the body cannot incorporate it into hemoglobin, which red blood cells need to transport oxygen efficiently throughout the body. **This defect in red blood cell production also can alter the iron balance within the child, often resulting in total body iron overload. Sideroblastic anemia can be congenital (inherited) or acquired.** Both types have very different causes, treatment and prognosis. Acquired anemias are seen almost exclusively in older adults which are the result of acquired non-inherited genetic mutations that occur only in the red blood cell precursors leading to ringed sideroblasts. This refractory anemia is classified within a broader group of diseases called myelodysplastic syndrome.

Congenital sideroblastic anemias (CSAs): are inherited diseases caused by genetic mutations that are present at birth in all the cells. Even though the mutations are inherited and present at birth, anemia may not be present in infancy and sometimes may not be recognized until adulthood.

- **Congenital sideroblastic anemias are generally divided into those that affect only the blood system (non-syndromic) and those that also affect other tissues, such as the nervous system and muscles (syndromic).** In some cases of syndromic sideroblastic anemia, the anemia may be an incidental problem-the major signs and symptoms of the disease may be in other tissues.

1) X-linked sideroblastic anemia: This is the most common congenital cause of sideroblastic anemia and involves a defect in ALAS2. Although X-linked, approximately one third of patients are women due to skewed X-inactivation (Lyon's hypothesis of X-chromosome inactivation).
2) Autosomal recessive sideroblastic anemia involves mutations in the SLC25A38 gene-this form usually has severe anemia.
3) Genetic syndromes: Rarely, sideroblastic anemia may be part of a congenital syndrome-associated with ataxia, developmental delay, deafness, cardiomyopathy, myopathy, and pancreatic insufficiency

- **Acquired clonal sideroblastic anemia**

Clonal (hematopoietic stem cells or other early blood cell progenitors contribute to the formation of a genetically distinct subpopulation of blood cells) sideroblastic anemias-part of myelodysplastic syndromes (MDS). Mostly seen in adults.

- **Acquired sideroblastic anemia**

1) Causes include excessive alcohol use (the most common cause of sideroblastic anemia), pyridoxine deficiency, lead poisoning and copper deficiency
2) Antimicrobials that may lead to sideroblastic anemia include isoniazid, chloramphenicol, linezolid, etc.

Symptoms and signs of congenital sideroblastic anemia are:

- **Related to anemia and its severity:** Pallor, fatigue, weakness, irritability, headache, vertigo, feeding/exercise intolerance and exertional dyspnea
- **Outside the blood system (in syndromic CSAs):** Developmental delay, deafness, vision loss, muscle dysfunction (heart muscle and/or other), organ failure (e.g. kidney and/or liver), immunodeficiency, fever, acidosis
- **Enlarged liver and spleen may be found**
- **Heart disease, liver damage, and kidney failure can result from iron buildup in these organs.**

Investigations:

1) Complete blood count and peripheral smear - Microcytosis is seen in non-syndromic anemia that affects heme synthesis. Macrocytosis is seen in syndromic anemia that affects mitochondrial protein synthesis. Normocytic anemia may be found in syndromic or non-syndromic anemia with mutations in genes involved in iron-sulfur cluster synthesis.
2) **Bone marrow examination- examination with Prussian blue stain will show ring sideroblasts. Sideroblasts are found in the normal blood cell precursors (erythroblasts) with one or more iron-containing granules in the cytoplasm, with exaggeration when it form ring surrounding the nucleus. 5 or more granules in a perinuclear position, surrounding the nucleus or encompassing at least one third of the nuclear circumference is found only in sideroblastic anemia.**

3) Body iron measurements- **Serum iron, percentage saturation and ferritin are increased. The total iron binding capacity of the cells is normal to decreased.**
4) Molecular testing (gene sequencing, protein studies etc)

The differentiation of congenital sideroblastic anemia from other causes of microcytic anemia in this age group like thalassemia and iron deficiency anemia is based on Hb electrophoresis, serum iron studies and bone marrow examination.

Treatment: Treatment depends on the exact type and severity of the disorder. They are refractory to iron therapy.

- **X-linked sideroblastic anemia (XLSA) can sometimes respond very favorably to treatment with pyridoxine (vitamin B6- B-long 100 mg).** The standard treatment consists of 50-100 mg/day with use of higher doses occasionally. Maintenance therapy with low dose pyridoxine is advocated for the responders to maintain an adequate pool of pyridoxal phosphate and prevent recurrence of anemia. Thiamine-responsive megaloblastic anemia (TRMA) is often partially responsive to treatment with thiamine (vitamin B1- Benalgis 75 mg). Unfortunately, none of the other congenital sideroblastic anemias are known to respond to vitamin or other medical therapies.
- Blood transfusions may be given to treat severe anemia. Some children require repeated blood transfusions to perform routine activities.
- **Iron overload due to increased daily iron absorption from the gut and iron from red blood cell transfusions can quickly lead to iron overload which is toxic to several vital organs so iron chelators are required.**
- **Right now, the only cure for some congenital spherocytic anemia is a stem cell transplant- the transplantation of normal blood stem cells from another person ("donor") to diseased child.** The best transplant outcomes are almost always when the donor is a healthy sibling with compatible stem cells. The stem cells replace the diseased stem cells and restore normal blood production. In the syndromic sideroblastic anemias, disease manifestations unrelated to the bone marrow disease do not get better after stem cell transplant.

Prognosis

The long-term outlook for children with CSA depends heavily on the specific type of CSA.

- Congenital Sideroblastic anemia (CSA) -80% are responsive, though the anemia does not completely resolve.
- Acquired clonal: 40% are responsive, but the response may be minimal.
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- cause.

Severe refractory sideroblastic anemias requiring regular transfusions and/or that undergo leukemic transformations (5-10%) significantly reduce the expectancy.

A child with CSA will need regular follow-up care by his physician.

It is important to recognize this entity early in life as a significant percentage of cases respond to pyridoxine thus avoiding any long-term complications.

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