Original Research Paper

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Paediatrics

A RARE CASE OF CONGENITAL DYSERYTHROPOIETIC ANEMIA

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KEYWORDS :

INTRODUCTION

The congenital dyserythropoietic anemias(CDA) are a group of rare hereditary disorders characterized by congenital anemia, ineffective erythropoiesis with distinct morphologic features in bone marrow (late erythroblasts), and the development of secondary hemochromatosis. Patients usually present with anemia, jaundice, splenomegaly, and suboptimal reticulocyte response for the degree of anemia. Aniso-poikilocytosis and basophilic stippling are commonly observed in the peripheral blood smear1-2.

CDA type I is characterized by moderate to severe anemia. It is usually diagnosed in childhood or adolescence, although in some cases, the condition can be detected before birth. Many affected individuals have jaundice and hepatosplenomegaly. This condition also causes the body to absorb too much iron, which builds up and can damage tissues and organs. In particular, iron overload can lead to an abnormal heart rhythm (arrhythmia), congestive heart failure, diabetes, and chronic liver disease (cirrhosis).

CDA type II can range from mild to severe anemia, and most affected individuals have jaundice, hepatosplenomegaly, and the formation of hard deposits in the gallbladder called gallstones. This form of the disorder is usually diagnosed in adolescence or early adulthood. An abnormal buildup of iron typically occurs after age 20, leading to complications including heart disease, diabetes, and cirrhosis.

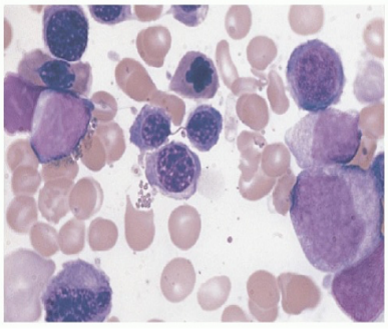
CDA type III tend to be milder than those of the other types. Most affected individuals do not have hepatosplenomegaly, and iron does not build up in tissues and organs. In adulthood, abnormalities of a specialized tissue at the back of the eye (the retina) can cause vision impairment.

Several other variants of CDA have been described, although they appear to be rare and not much is known about them. Once researchers discover the genetic causes of these variants, some of them may be grouped with the three major types of CDA.

CHARACTERISTIC FEATURES OF DIFFERENT TYPES OF CDA

CDA TYPE	I	II	III FAMILIAL	III SPORADIC	VARIANTS
Inheritance	Autosomal recessive	Autosomal recessive	Dominant	Variable	Autosomal dominant or X linked or recessive
BM morphology (light microscopy)	Abnormal chromatin structure, chromatin bridges	Binuclearity, multinuclearity of mature erythroblasts	Giant multinucleated erythroblasts	Giant multinucleated erythroblasts	CDA I–like, CDA II–like, others
BM EM findings	"Spongy" heterochromatin, invaginatio n of cytoplasm into the nucleus	Peripheral cysternae beneath the plasma membrane	Clefts in heterochromatin, autophagic vacuoles, intranuclear cisternae	Various	Various
Mutated gene	CDAN1, C15ORF41	SEC23B	KIF23	Unknown	KLF1, GATA-1, unknown
Associated dysmorphology/organ involvement	Skeleton	Variable, rare	Monoclonal gammopathy, myeloma, angioid streaks	Variable	CNS, others

Chromatin Bridges On Bone Marrow



Case report

A 6yr old male child, first baby of a non- consangiounous marriage was brought with complaints of progressively increasing pallor and history of recurrent blood transfusions since 2 months of age

Birth history-

- Post-term/ 2.5kg/ Male child/ Baby cried immediately after birth/ Normal vaginal delivery/ Meconium Stained liquor with respiratory distress/ No history of birth trauma
- Baby was admitted to NICU for Respiratory distress and did not require ventilator support
- Baby developed hyperbilirubinemia within 2 hrs of postnatal life which required exchange transfusion
- Baby was put under photo-therapy for 3 days and was subsequently discharged

Mother subsequently noticed that the baby became progressively pale over the course of the next two months, was admitted again and a blood transfusion was given.

Since then patient had requirement of blood transfusion at every 2 months Patient was investigated at 8 months of age where bone marrow was done which showed compensatory erythroid hyperplasia with myeloid series normal Hemolytic workup was done- Pyruvate kinase levels, Glucose-6 Phosphate dehydrogenase levels, Flow Cytometric Analysis, Hb electrophoresis, Parents Hb electrophoresis all were normal Since then patient was receiving transfusion support regularly patient was further investigated and bone marrow findings were suggestive of CDA type 1 Childs transfusion requirement has increased over the past 8 months and needs transfusion every month

Head to toe examination-

- Skin- Ashen- Yellow pigmentation Present
- Parietal and Frontal Bossing Present
- Maxilla appears to be prominent
- Oral Cavity- Gum hypertrophied, Oral hygiene Normal, No bleeding gums.
- Pallor- Present, Icterus- Present,
- Clubbing, Cyanosis, Lymphadenopathy, Oedema- Absent

Systemic examination-

- Inspection- Upper abdomen appears to be distended on left upper quadrant
- Palpation- All quadrants equal in temperature, moving equally with respiration

No Superficial/ Deep Tenderness

- Liver Palpable, 3cms below costal margin, smooth surface, non tender, edge palpable, Span- 12cms, Liver dullness present in 5th ICS
- Spleen- palpable 9cms below costal margin, almost reaching umbilicus.

Frontal and Parietal bossing with maxillary prominence

ETIOLOGY

CDA type I usually results from mutations in the CDAN1 gene. Little is known about the function of this gene, and it is unclear how mutations cause the characteristic features of CDA type I.

CDA type II is caused by mutations in the SEC23B gene. This gene provides instructions for making a protein that is involved in the transport of other proteins within cells. During the development of red blood cells, this protein may help ensure that proteins are transported to the areas where they are needed.

The genetic cause of CDA type III has not been identified. It likely results from mutations in a gene located on the long arm of chromosome 15 at a position designated 15q22.

The genetic changes responsible for CDA disrupt the normal development of red blood cells, a process called erythropoiesis. The term "dyserythropoietic" in the name of this condition means abnormal red blood cell formation. In people with CDA, immature red blood cells called erythroblasts are unusually shaped and have other abnormalities (such as extra nuclei). These abnormal erythroblasts cannot develop into functional mature red blood cells. The resulting shortage of healthy red blood cells leads to the characteristic signs and symptoms of anemia, as well as complications including hepatosplenomegaly and an abnormal buildup of iron.

The inheritance pattern of CDA depends on the type of the disorder. CDA types I and II are inherited in an autosomal recessive pattern. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

In several families, CDA type III appears to have an autosomal dominant pattern of inheritance.

In these families, affected individuals often have a parent and other relatives with the condition.

Diagnosis

CDA I

Complete blood count; light microscopy of bone marrow (erythroblasts), electrophoresis of erythrocyte membrane proteins; dosages of serum bilirubin, haptoglobulin and lactate dehydrogenase; sequencing of the CDAN1 gene.

CDA II Complete blood count; light microscopy of bone marrow (erythroblasts), electrophoresis of erythrocyte membrane proteins; dosages of serum bilirubin, haptoglobulin and lactate dehydrogenase; analysis of microsatellites.

CDA III Complete blood count; dosages of serum bilirubin, haptoglobulin and lactate dehydrogenase; light and electron microscopy of bone marrow (erythroblasts) Incidence CDA I: < 1/100 000 births/year. CDA II: < 1/100 000 births/year. CDA III: very rare. The other less well-characterized CDA are also extremely rare.

MANAGEMENT

- Blood transfusions and apheresis
- Medications, such as iron chelating agents or interferon alpha-2A (only in CDA type I)
- Selected surgical procedures (removal of the spleen and/or gallbladder), when required
- Stem cell transplant—the only definitive cure, available to patients with very severe CDA

CONCLUSION

The hallmark of the CDAs is failure of terminal erythropoiesis. The identification of several CDA genes has improved the diagnostic aspect of this disease; however, no comprehensive explanation for the mechanism of erythropoietic disruption has been disclosed. CDA type III gene (KIF23) encodes a protein playing a critical role in cytokinesis, suggesting a possible mechanism for the development of multinucleated erythroblasts. Codanin-1 and possibly C15ORF41 may facilitate histone assembly into chromatin during cell cycle. The fact that the proteins encoded by the CDA I, II, and III genes are ubiquitously expressed while the disease manifestations are mainly erythroid restricted remains a quandary. Further studies on CDA-related proteins and identification of new genes causing CDA variants will continue to offer insight into different pathways underlying erythropoiesis.

REFERENCES:

1. Heimpel H, Wendt F. Congenital dyserythropoietic anemia with karyorrhexis and multinuclearity of erythroblasts. Helv Med Acta. 1968;34(2):103–115.
2. Wickramasinghe SN, Wood WG. Advances in the understanding of the congenital dyserythropoietic anaemias. Br J Haematol. 2005;131(4):431–446.
3. Dgany O, Avidan N, Delaunay J, et al. Congenital dyserythropoietic anemia type I is caused by mutations in codanin-1. Am J Hum Genet. 2002;71(6):1467–1474.
4. Schwarz K, Iolascon A, Verissimo F, et al. Mutations affecting the secretory COPII coat component SEC23B cause congenital dyserythropoietic anemia type II. Nat Genet. 2009;41(8):936–940.
5. Liljeholm M, Irvine AF, Vikberg AL, et al. Congenital dyserythropoietic anemia type III (CDA III) is caused by a mutation in kinesin family member, KIF23. Blood. 2013;121(23):4791–4799.