Congenital dyserythropoietic anemias

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Abstract
Congenital dyserythropoietic anemias (CDA) result from diverse erythropoietic disorders; they lead to the defective production of red blood cells (RBC) and often mild hemolysis that attests to a qualitative defect of these RBC released into the circulation. Three forms of CDA have been characterized: types I, II and III. The shared symptoms include anemia of variable severity, intermittent jaundice, splenomegaly and hepatomegaly. Iron overload is progressive in types I and II. CDA I is often associated with dysmorphisms, particularly affecting the digits. Diagnosis of a CDA relies on light and electron microscopy examinations of the erythroblasts in a bone-marrow biopsy, which will demonstrate the presence of chromatin bridges between erythroblast nuclei and a spongy 'Swiss cheese' appearance of the condensed chromatin in CDA I; binucleated cells and endoplasmic reticulum remnants are seen in CDA II. Electrophoresis of erythrocyte membrane proteins also provides a sure diagnosis. The protein 4.1 level is low in CDA I, further associated with an unusual appearance of band 3 and the presence of reticular endoplasmic proteins – calreticulin, glucose regulatory protein 78 and isomerase disulfide – in CDA II. According to available estimations, CDA I and II incidence do not exceed 1/100 000 births per year. These forms are transmitted by recessive inheritance. CDA III results from dominant inheritance and is extremely rare. The genes responsible for CDA I, II and III have been localized to chromosomes 15q15.1–15.3, 20q11.2 and 15q21–q25, respectively. The gene implicated in CDA I was recently identified but the type and function of its product, codanine-1, remains to be established. The treatment of these diseases is essentially symptomatic. However, interferon-alpha attenuates the anemia of CDA I. The proteins causing these diseases and the underlying molecular mechanisms are still unknown.

Key words
Defective erythropoiesis, anemia, abnormal erythroblasts, dysmorphisms (CDA I), interferon-alpha (CDA I)

Name of the disease and synonyms
Congenital dyserythropoietic anemias (CDA)

Definition/diagnostic criteria
Congenital dyserythropoietic anemias (CDA) are the result of diverse erythropoietic disorders, causing the production of ineffective red blood cells (RBC) and often mild hemolysis, which attests to a qualitative defect of the RBC released into the circulation. Three forms of CDA have been characterized: types I, II and III.

CDA I
The clinical picture includes anemia, which sometimes develops early (during the neonatal period) and is very severe; jaundice; splenomegaly; hepatomegaly; frequent and diverse dysmorphisms, predominantly affecting the digits; and a progressive build up of iron overload.
Blood: hyporegenerative anemia with a low reticulocyte count, macrocytosis and severe anisopoikilocytosis; slightly below normal level of erythrocyte membrane protein 4.1.
Light microscopy of bone marrow: medullary hyperplasia, erythroblasts whose nuclei are linked by chromatin bridges.
Electron microscopy of bone marrow (has become optional): spongy (Swiss cheese) appearance of condensed chromatin.
Sequencing of the *CDAN1* gene.

CDA II
The clinical picture includes: moderate and variable anemia, intermittent jaundice, splenomegaly, hepatomegaly and progressive build-up of iron overload.
Blood: anemia usually remains above the threshold necessitating transfusion; hyporegenerative, with a low reticulocyte count; mild anisopoikilocytosis. Electrophoresis of erythrocyte membrane proteins reveals a narrow band 3 (anion transporter), and the presence of endoplasmic reticulum proteins (calreticulin, glucose regulatory protein 78 and isomerase disulfide of respective molecular masses of 74, 59 and 58 kDa).
Light microscopy of bone marrow: medullary hyperplasia and the presence of binucleated erythroblasts.
Electron microscopy of bone marrow (has become optional): elongated vesicles lining the inner surface of the plasma membrane of erythroblasts and corresponding to endoplasmic reticulum remnants.

CDA III
The clinical picture consists of well-tolerated anemia, sometimes splenomegaly, a predisposition to retinal degeneration and malignancies (Hodgkin's disease, T-cell lymphomas).
Blood: hyporegenerative anemia with a low reticulocyte count without macrocytosis.
Light microscopy of bone marrow: medullary hyperplasia, with the presence of giant erythroblasts containing up to 10 nuclei.

Etiology
The etiology is unknown for all forms. Transmission is recessive for CDA I and II, but dominant for CDA III. The genes responsible for these entities have been localized.

CDA I: *CDAN1* gene localized to chromosome 15q15.1–q15.3. Recently individualized, it codes for codanine-1, whose function is unknown.
CDA II: *CDAN2* gene localized to chromosome 20q11.2.
CDA III: *CDAN3* gene localized to chromosome 15q21–q25.

Biological methods of 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 and treatments
The treatment of CDA is essentially symptomatic. Management includes: hematological monitoring and surveillance of the iron status; transfusions as needed; treatment of the iron overload; treatment of viral infections.
The indication of splenectomy remains controversial.
For patients with severe CDA I, recombinant interferon-alpha-2a is prescribed; the regimen is still being defined.

Unresolved questions and comments
Identification of the genes responsible has been given priority over understanding the molecular mechanisms involved.

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