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Editorial and Views

Congenital dyserythropoietic anemias: a still unsolved puzzle

Dyserythropoiesis was the term used, for the first time by Crookston *et al.* in 1966[1] and later by Heimpel and Wendt,[2] to indicate a congenital defect in erythropoiesis. However this term now refers to any alteration of the normal differentiation-proliferation pathway of the erythroid lineage. It incorporates both morphologic and kinetic aspects of erythropoiesis (erythroid lineage failure) and recognizes that even when erythroblasts are functionally abnormal some survive and mature although their descendent erythrocytes are likely to have a shortened life-span (hemolytic aspects).[3,4] Dyserythropoiesis appears to be a qualitative and a quantitative defect of erythropoiesis and occurs in a wide range of diseases embracing a number of conditions which primarily affect the nucleus or the cytoplasm of the erythroblasts or the environment in which erythropoiesis takes place. This could be a physiologic condition (e.g. during the neonatal period) or a disease (nutritional anemias, myelodysplastic syndromes, liver disease, paroxysmal nocturnal hemoglobinuria, AIDS and malaria, post bone marrow transplantation and chemotherapy). The latter could be the principal (congenital dyserythropoietic anemias, CDA) or a secondary characteristic (thalassemia syndromes; unstable hemoglobins or thiamine-responsive anemias).[3,4]

CDA comprise a group of hereditary disorders of erythropoiesis characterized by ineffective erythropoiesis as the predominant mechanism of anemia and distinct morphologic abnormalities of the majority of erythroblasts in the bone marrow. Heimpel proposed classifying these disorders into three types.[2] These first classical types (I-III) differ in bone marrow erythroid morphology as well in their inheritance pattern. This issue contains a complete review of the clinical and molecular aspects of CDA-III was published by Sandstrom and Wahlin.[5]

One of the main problems of the CDAs was their heterogeneity, both at clinical and genetic levels. This is the consequence of the very large number of conditions characterized by dyserythropoiesis. In general the features of dyserythropoiesis, in terms of ineffective erythropoiesis, should be demonstrated by several criteria: bone marrow examination by light microscopy, ultrastructural features, assessment of erythropoietic production and destruction, etc. Certainly the main assessment method, and one which is easy to perform, is light microscopy. Morphologic abnormalities include binuclearity and multinuclearity, internuclear bridging, asynchrony between nuclear and cytoplasmic maturation and premature nuclear extrusion, nuclear budding, fragmentation and degeneration (karyorrhexis) and various abnormalities of mitosis. There are intercellular cytoplasmic connections and abnormalities of the cytoplasm itself such as vacuolation, basophilic stippling and an excessive amount of siderotic granules. Even normal erythropoiesis when stressed in hemolytic anemias results in minor morphologic and other features of dyserythropoiesis. The use of the term should be restricted to those conditions in which the features of dyserythropoiesis are dominant or at least apparent and readily demonstrable.

The first classification of CDA was revelaed to have limited applicability and in fact there were some cases of dyserythropoiesis which did not fulfill the strict diagnostic criteria and thus new groups (groups IV-VII) were defined. In the Wickramasinghe studies[4] approximately one third of dyserythropoietic anemias are types other than I-III. Recently Wickramasinghe identifies four additional groups. However, it is notewortly that each group may be genetically heterogeneous and that the group is proposed on the basis of the common phenotypic appearance.

The three classical congenital forms of dyserythropoiesis appear very different from each other, although all having the unifying feature of morphologically abnormal erythroblasts. In general they are rare diseases: there were 126 cases of CDA-I, 179 of CDA-II and 65 of CDA-III reported in the literature in the period 1951 to 1999. Anemia is not usually severe enough to need intervention. However, during the first year of life or pregnancy, or in the case of coinheritance of another congenital defect of ery-

Table 1. Classification and distinguishing features of congenital dyserythropoietic anemias (CDAs).

Type	*Clinical features*	*Morphology*	*Inheritance*
I	Anemia on neonatal onset; jaundice; splenomegaly; rare syndactyly; common complication: hemochromatosis	Megaloblastoid erythroid hyperplasia; nuclear bridges. ME: spongy-appearing nuclei and invagination of the cytoplasm in the nucleus	Autosomal recessive Locus: 15q15.1-15.3
II	Anemia; jaundice; splenomegaly; hemochromatosis; gallstones	2-4 nucleated late erythroblasts; karyorrhexis	Autosomal recessive 20q11.2
III	Anemia (mild to moderate); jaundice; gammapathy	Giant multinucleated erythroblasts	Dominant 15q22

thropoiesis (such as β-thalassemia) the anemia may worsen and require transfusions.

Iron overload appears to be a very frequent complication in CDA-I and II, but not in CDA-III. However generalizations on this last condition should be made with caution since they are heavily reliant on observation made on the Vasterbotten family, in which dyserythropoiesis appeared as a part of a more general syndrome (myeloma or monoclonal gammapathy; angioid streaks). Interestingly, involvement of other tissues was also signaled in CDA-I: syndactyly in hands and/or feet; absence of the distal phalanges and nails. The serum thymidine kinase levels are greatly increased in CDA-I as well as in CDA-III; these high values presumably result from the intramedullary destruction of erythroblats.

The last consideration is related to the problem of splenectomy in CDAs. Many cases are reported in literature which suggested an improvement of Hb level following splenectomy. But it appears, particularly in CDA-II, that the spleen plays a pivotal role; in fact due to the underglycosylation of band 3 there is clusterization of these molecules and the appearance of auto-antibodies, whereas the ribs appear to be selectively removed by the spleen. Interestingly three patients with CDA type I have shown a partial response to subcutaneously-administred recombinant interferon α, with an elevation of Hb levels and a reduction of jaundice. This partial remission of clinical findings further supports the idea that the three forms of classical congenital dyserythropoiesis are very different from each other.

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