Dyserythropoiesis was the term used, for the first time by Crookston et al. in 1966 and later by Heim-pel and Wendt, 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 anemias: a still unsolved puzzle). 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). Dyserythropoiesis 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 revealed 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 approximately one third of dyserythropoietic anemias were types other than I-III. Recently Wickr amasinghe identifies four additional groups. However, it is noteworthy 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 85 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 coinherence of another congenital defect of ery-

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

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 clustering 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-administered 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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References


