The Congenital Dyserythropoietic Anemias

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KEYWORDS

• Anemia • Inherited • Erythropoiesis
• Dyserythropoiesis • Iron overload

The congenital dyserythropoietic anemias (CDAs) are a heterogeneous group of clinically challenging but biologically fascinating rare inborn disorders that principally affect erythropoiesis. They are distinct from other inherited bone marrow failure syndromes, being marked by morphologic abnormalities of the erythroblasts that lead to ineffective erythropoiesis. Other hematopoietic lineages seem to be unaffected. Therefore, CDAs have the potential to identify critical pathways and important players in the process of erythropoiesis. As with other rare disorders, the corpus of knowledge on CDA derives from an array of case reports or small series, which have been reviewed previously.[1,2] Registry-based data are only starting to emerge. This has limited our understanding of these syndromes and their management. Here, the authors aim to review the clinically relevant data available and focus on providing rational information to help with decision making.

The term *congenital dyserythropoietic anemia* was introduced by Crookston and colleagues,[3] and subsequently used by the German group of Heimpel and colleagues.[4] The recognition that the morphologic abnormalities in these and other cases had similarities but also significant differences led Heimpel and Wendt[5] to propose a working classification for a new category in the already extensive differential diagnosis list for dyserythropoiesis. Conceptually, CDAs were considered to be different because of their inborn and primary nature when compared with dyserythropoiesis associated with the thalassemias, vitamin B_{12} deficiency, acquired anemias, and certain infectious conditions (**Box 1**).[6]

Heimpel and Wendt[5] defined three major CDA subtypes (CDA-1, CDA-2, and CDA-3), and this still remains the basis of the classification today, although additional subgroups

R.R. is supported by the Lord Florey Scholarship (2005–2008) of the Berrow Foundation (Switzerland), the Lord Nathaniel Crewe Scholarship (2008–2009) of Lincoln College, University of Oxford (UK), and the "Eugenio Litta" Scholarship (2008–2009) of the Valeria Rossi di Montelera Trust (Switzerland).

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Hematol Oncol Clin N Am 23 (2009) 283–306
doi:10.1016/j.hoc.2009.01.010 **hemonc.theclinics.com**
0889-8588/09/$ – see front matter

Box 1
Differential diagnosis and definition of dyserythropoiesis

Primary

- Homozygous β-thalassemia (hemoglobin [Hb] C or HbE), other unstable hemoglobins
- Sideroblastic anemia, thiamine-responsive anemia
- Acute myeloblastic leukemia, hairy cell leukemia, and preleukemic states[a]
- Myelodysplastic syndromes and chronic myeloproliferative disorders
- Aplastic anemia/paroxysmal nocturnal anemia
- GATA1/FOG1 X-linked thrombocytopenia/dyserythropoiesis/thalassemia syndrome
- Rare genetic conditions (hemophagocytic lymphohistiocytosis, Ellis-Van-Creveld syndrome, Majeed syndrome)
- CDA

Secondary

- Megaloblastic anemias (vitamin B_{12}, folate-deficient)
- Iron deficiency anemia
- Infection (HIV/AIDS, human herpesvirus-6, *Plasmodium falciparum* and *Plasmodium vivax* malaria, visceral leishmaniasis)
- Excess alcohol intake, liver disease
- Intoxication (benzene, arsenic, alternative medicine supplements)
- Drugs (linezolid, chloramphenicol, and probably many others)
- Autoimmune disorders
- After hematopoietic stem cell transplantation (HSCT) and cancer chemotherapy

Definition: Abnormal proportion of erythroid precursors in the bone marrow with morphologic features indicating aberrant proliferation or differentiation. The definition itself allows for some dyserythropoiesis to occur in normal bone marrow. In fact, anomalies, including nucleocytoplasmic maturation dissociation, karyorrhexis, and binucleation, can all be present but should not represent a dominant population. In a study of normal bone marrow, Nemec and Polak[131] (1947) stipulated that a maximum 4% of erythroblasts should be binucleate or multinucleate. A variable degree of chromatin bridging or basophilic stippling can be present in normal bone marrow but should not exceed 2%. These findings have been confirmed by independent investigators.

[a] Particularly important differential diagnosis in children with nonclassic CDA-1, CDA-2, or CDA-3.

and variants have been added.[2] It ultimately made the systematic collection and analysis of cases possible, but the degree to which these disorders are related other than by morphologically abnormal erythroblasts is discussed later. After many years of mostly descriptive exploration, a molecular window on the pathogenesis of CDA was opened in 2002, when research by Tamary and colleagues[7,8] identified a gene linked to CDA-1. The discovery of the *CDAN1* gene and its protein, codanin-1, has opened new avenues in the field. The genes for CDA-2 and CDA-3 have also been localized to chromosomal segments, and their identification should go a long way toward determining how closely related these disorders are.[9,10]

DIAGNOSIS AND CLASSIFICATION OF THE CONGENITAL DYSERYTHROPOIETIC ANEMIAS

CDAs present a diagnostic challenge for the clinician, and the aim of this review is to provide the most recent knowledge for appropriate decision making. In fact, because