

Hermann Heimpel

## Congenital dyserythropoietic anemias: epidemiology, clinical significance, and progress in understanding their pathogenesis

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**Abstract** The congenital dyserythropoietic anemias (CDAs) comprise a group of rare hereditary disorders of erythropoiesis, characterized by ineffective erythropoiesis as the predominant mechanism of anemia and by distinct morphological abnormalities of the majority of erythroblasts in the bone marrow. The classification in three types as proposed in 1968 is still valid, but there is genetic heterogeneity within each type, and there are additional variants of unknown genetic basis. CDA II is the most frequent, and the nonfamilial type of CDA III the rarest group. The genes of CDA II and CDA III were mapped to chromosome 20 and 15, respectively, and the gene of CDA I on 15q was recently cloned. Therapeutic decision making requires definition of the type, an estimate of individual severity, and presence of or risk for complications. Therapeutic measures include interferon- $\alpha$  for CDA I, splenectomy for CDA II, and iron depletion for all individuals at risk for secondary hemochromatosis.

### Introduction

The congenital dyserythropoietic anemias (CDAs, ICD-10 D64.4) comprise a group of rare hereditary disorders of erythropoiesis, characterized by ineffective erythropoiesis as the predominant mechanism of anemia and by distinct morphological abnormalities of the majority of erythroblasts in the bone marrow. The term was first used by Crookston et al. [20] (for cases later classified as CDA II) and by Wendt and Heimpel [91] (for cases later classified as CDA I), but a few reports of similar cases had been published previously [38]. After we recognized that the morphological aberrations were not identical in all the

cases described by Crookston and by ourselves, we proposed to classify these disorders into three types [38], including as type III the families with autosomal dominant inheritance described by others [7, 96]. Although initially proposed as a working classification, it was widely accepted and is still used today in clinical practice [23, 92] (Table 1). There are, however, families which fulfill the general definition of the CDAs, but do not fit to one of the classic three types [11]. They will be discussed in the Section on “CDA variants” below.

In the majority of CDAs, inheritance is autosomal recessive, and due to the small number of offsprings in most European families, single cases in one family are the rule rather than the exception. Together with the rarity of the disorder, this explains the observation that the correct diagnosis is often delayed, particularly in non-severe cases. In our own observations in 26 and 53 cases of CDA I and CDA II, respectively, in more than 60% the diagnosis was first made in adulthood, although anemia and/or hyperbilirubinemia had been known for many years. In some patients, erroneous diagnoses such as hereditary spherocytosis were made many years after CDA II had been recognized as a novel entity. Similar diagnostic delay was reported by others [18, 36, 53]. On the other hand, cases of other types of congenital or even acquired anemia are notified to the German CDA Registry in Ulm, with the suspected diagnosis of CDA.

In general, the diagnosis of the CDAs requires the presence of all of four criteria:

- 1 Evidence of congenital anemia/jaundice or of heredity
- 2 Evidence of ineffective erythropoiesis
- 3 Typical morphological appearance of bone marrow erythroblasts
- 4 Exclusion of congenital anemias which fulfill criteria one and two, but have been classified according to the underlying defect, such as the thalassemia syndromes, some types of pathological hemoglobins, or hereditary sideroblastic anemias

Proof of the first criterion may be difficult in adult patients without sufficient former laboratory data avail-

H. Heimpel (✉)  
Abteilung für Innere Medizin III, Medizinische Klinik und  
Poliklinik der Universität Ulm,  
Robert-Koch-Strasse 8,  
89081 Ulm, Germany  
e-mail: hermann.heimpel@medizin.uni-ulm.de  
Tel.: +49-731-50024499  
Fax: +49-731-50024498

**Table 1** Characteristic features of different types of congenital dyserythropoietic anemia

CDA type	I	II	III Familial	III Sporadic	Variants
Inheritance	Autorecessive	Autorecessive	Dominant	Variable	Autorecessive
Cases reported	~150	>300	3 Families	<20	~70
Morphology	Abnormal chromatin structure, chromatin bridges	Multinuclearity of mature erythroblasts	Giant multinucleated erythroblasts	Giant multinucleated erythroblasts	CDA I-like, CDA II-like, others
Gene	Codanin-1 15q (15.1.3)	20q (11.2)	15q (21–25)	Unknown	Unknown
Associated dys-morphisms	Skeleton, others	Variable, rare	B cells, retina	Variable	CNS, others
Therapy	Interferon- $\alpha$ , iron depletion	Splenectomy, iron depletion	None	Unknown	Unknown

able. Here, acquired types of anemia with ineffective erythropoiesis, such as megaloblastic anemia due to vitamin deficiencies or myelodysplastic syndromes, are to be excluded. In the latter conditions as well as in acute myeloid leukemia FAB-M6, morphologic abnormalities may mimic CDA of any type [9, 62, our own unpublished observations].

Ineffective erythropoiesis has been identified as the main mechanism for the anemia by erythroferrokinetic investigations [29, 39]. In addition, red cell life may be moderately shortened, particularly in type II [5, 44]. Today, these techniques are no longer used outside special studies. Ineffective erythropoiesis is suspected if reticulocytosis is inadequate to the degree of anemia, together with indirect hyperbilirubinemia and low or absent haptoglobin indicating increased intramedullary and extramedullary hemolysis. The bone marrow is always hypercellular, with erythropoietic/granulopoietic ratios of 4–10 (normal reference values 0.3–1.0). A more recently introduced test which reflects the expansion of the erythropoietic tissue is the serum concentration of the soluble transferrin receptor, if iron deficiency is excluded [16]. Values above the upper reference limit were seen in 23 of 40 patients (our own unpublished observations).

Characteristic morphological aberrations of the erythroblasts are still the cornerstone of the diagnosis, and if present in the majority of cells in definite congenital anemia they can be regarded to be specific for the diagnosis. They are also the first step for the determination of the type of CDA. Recognition is much easier in smears of aspirated bone marrow than in histology specimens, and morphological analysis of both peripheral blood and appropriate bone marrow smears is required before the diagnosis of any case of CDA is made. In addition to panoptic staining, the specimen should always be stained for non-heme iron to exclude congenital sideroblastic anemia with CDA-like morphological aberrations in a minority of cells and to estimate tissue iron stores. The number of sideroblasts may be increased in cases with increased iron stores, but ringed sideroblasts are present only in exceptional cases [84].

All types of CDA share a high incidence of cholelithiasis and distinctly iron loading [37]. As in other forms of anemia with ineffective erythropoiesis, this is due to upregulation of iron resorption [15]. Extramedullary

hematopoiesis presenting as paravertebral bulks was observed in six German patients with CDA I, II, or variant enrolled in the CDA Registry and has also been reported in CDA III [56].

### CDA II (MIM224100<sup>1</sup>)

CDA type II (CDA II), also known as hereditary erythroblastic multinuclearity with a positive acidified serum test (HEMPAS) [21], is the most frequent type [23, 49, 92]. Although exact prevalence data are not available, this can be derived from the numbers reported. We identified 208 cases from 160 families published as case reports, carefully excluding repeated publications of the same individuals but including 54 cases observed by the German CDA Registry. Details of 48 cases were recently published [44]. In addition, 98 cases were compiled by the International CDA II registry [53]. The majority of families were reported from Southern Italy, probably due to a founder effect with a high frequency of intermarriage [52]. However, 47 cases enrolled in the German CDA Registry were resident in Germany at the time of diagnosis and 42 cases were of German origin. Sporadic cases were published from all regions of the world, with the exception of black Africans. One factor contributing to the variable incidence is probably a different ascertainment rate, and except for the founder population in Southern Italy, gene frequencies in different ethnic populations cannot be estimated.

The diagnosis should be suspected in any case of congenital anemia with indirect hyperbilirubinemia, inadequate reticulocytosis, and low or absent plasma haptoglobin. The severity of the anemia is variable, with about 10% of patients in both Iolascon et al.'s [53] and our [44] series requiring regular red cell substitution in infancy and childhood, while others have throughout life only moderately decreased hemoglobin values between 8 g/dl and 11 g/dl. Probably by selection, a higher fraction of severe cases were reported from India [63]. The anemia is usually normochromic but moderately low or high mean corpuscular volumes (MCV) do not exclude the diagnosis.

<sup>1</sup>Mendelian Inheritance in Man, <http://www.ncbi.nlm.nih.gov/entrez/queri.fcgi?db=OMIM>.

However, distinct microcytosis/hypochromia with MCV or mean corpuscular hemoglobin (MCH) below 70 fl or 25 pg is not present, except in rare cases with additional iron deficiency or heterozygous thalassemia [54]. Red cell morphology in the smear is always abnormal with anisopoikilocytosis, basophilic stippled cells, and few late erythroblasts but is of low specificity, except if a typical binucleated normoblast is found. Relative reticulocyte values usually vary between 0.1 and 5% with absolute values between 25 and 200×10<sup>9</sup>/l [44, 53]. Values between 5 and 10% as observed in some cases need careful exclusion of mild congenital hemolytic anemias. Total and indirect serum bilirubin concentrations vary between 30 μmol/l and 80 μmol/l and are higher in patients with low expression of uridine diphosphate glucuronosyl transferase (UGT1A) [69]. In 90% of all patients enrolled in the German CDA Registry total serum bilirubin at the time of diagnosis was moderately increased, exclusively due to an increase of the indirect reacting fraction. When follow-up data were included, all cases showed hyperbilirubinemia. Haptoglobin was low or absent in 50 of 53 patients.

The leading morphological abnormality is binuclearity or multinuclearity in 10–50% of erythroblasts, with equal shape, degree of maturity, and DNA content of both nuclei. Binuclearity is usually seen in late mature erythroblasts, but rarely also in more immature polychromatic cells [71]<sup>2</sup>. There are always some cells with irregular, clover-leaf nuclei or karyorrhexis. Electron microscopy shows stretches of a duplicate membrane close to the red blood cell membrane [40, 97] which originate from residual endoplasmic reticulum [2]. Another characteristic feature are pale blue macrophages (pseudo-Gaucher cells) containing birefringent material.

CDA II is characterized by additional diagnostic features of high specificity, in particular by the expression of an antigen which binds to a natural cold reacting IgM antibody present in 40–60% of all sera of adult healthy individuals. Antibody binding can be demonstrated by agglutination or by lysis when the serum is acidified to pH 6.7 [21]. Therefore, the acronym HEMPAS is commonly used as a synonym for CDA II. Serum acid lysis tests were unequivocally positive in our observations. All patients remained positive at repeated testing with sera containing anti-HEMPAS antibody throughout many years of observation. In contrast to cells from patients with paroxysmal nocturnal hemoglobinuria, the test is negative with autologous sera and sera of obligate heterozygotes [19, 26, 27, 90]. The test is more sensitive if the antibody binding is enhanced by preincubation at 4°C [73], and if performed with the use of a panel of positive sera and appropriate negative controls can be regarded as specific for CDA II. Red cells of patients with CDA II throughout life retain a very high agglutinability by anti-i sera although their i density is comparable to normal adults (“strong i, strong I phenotype”) [21]. Enhancement of the i-antigen is also

known in different forms of erythropoietic hyperplasia such as in thalassemia major or hemolytic anemia. Since agglutination titers in CDA II are invariably extremely high, a normal score excludes the diagnosis.

Membrane abnormalities can also be detected by highly specific biochemical tests. Band 3 (anion exchange protein 1) and band 4.5 (glucose transporter 1) show a thinner aspect and faster migration on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) [3]. Equally specific is the detection of minor proteins derived from endoplasmic reticulum by Western blotting [2].

The abnormalities of the CDA II red blood cell membrane are due to abnormal processing of *N*-glycans [33]. Band 3 and band 4.5 glycoproteins carry truncated poly-lactosamine structures, while glycolipids are over-glycosylated [98]. Different enzymes involved in carbohydrate processing have been proposed to be defective in CDA II. Reduced activity of *N*-acetylglucosaminyltransferase II, α-mannosidase II, and a membrane-bound galactosyltransferase was described in single patients, but other patients had normal enzyme activities [32, 34, 99]. Surprisingly, the respective genes were normal, and by linkage analysis mutations of these candidate genes were excluded in families from Southern Italy. Instead, by linkage analysis an association to a gene locus on chromosome 20 (q11.2) was described [49, 50]. This, however, could not be found in families of other origin [51], and up to now, an aberrant gene shared by all CDA II families has not been identified.

Additional physical malformations are less common than in type I, but mental retardation has been repeatedly reported [44, 90]. However, most patients are able to lead a normal life and probably have a normal life expectation, if complications and late consequences are appropriately managed. As in hemolytic anemia, self-limited aplastic crises triggered by parvovirus B19 infection may require blood transfusions. In the majority of patients bile stones are found before the age of 40. As in CDA I, the evolution is doomed by iron overloading due to increased iron resorption. Lethal organ damage of liver and myocardium is observed in untreated patients [37, 48, 78]. In most cases, serum ferritin concentration increases throughout life and surpasses the reference between 20 and 60 years of age [44]. As in hereditary hemochromatosis, iron overloading is more severe in men than in women [15], but is not enhanced by heterozygosity for HFE genes [53].

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### CDA I (MIM 224120)

CDA I is less frequent than CDA II, with 94 cases out of 81 families identified from our own observations and published case reports, and 45 further cases in a Bedouin tribe are described by Tamary et al. from Israel [85, 86]. At least for Europe, this probably reflects true differences, since there is no evidence that the ascertainment rate of cases notified to the German CDA Registry is different. Most families were detected in Western Europeans and in Arabs, but single cases were also reported from India and

<sup>2</sup>For microphotographs see <http://www.bone-marrow-failure-syndromes.de>.

Japan. Except for 17 adolescents and young adults of the Bedouin tribe [81], clinical data have to be extracted from case reports and unpublished observations of the German CDA Registry. As in CDA II, the degree of anemia is variable not only between families, but for unexplained reasons also between siblings. Most cases show lifelong anemia with hemoglobin concentration between 8 and 11 g/ml. Occasionally, there are severe cases who have to be transfused immediately after birth and receive regular blood transfusions during childhood and adolescence. On the other end of the spectrum there are families with only borderline low hemoglobin levels but distinct macrocytosis. Since mutational analysis of such cases is not yet available, it is not understood whether they should be regarded as CDA I with low expression or classified as one group of variant CDA as suggested by Wickramasinghe [92].

Clinical appearance and basic laboratory data are similar to CDA II with some exceptions. The anemia is usually macrocytic with MCVs between 100 and 120 fl. In the peripheral smear, large poikilocytes and elliptocytes are similar to changes seen in megaloblastic anemias, the most frequent erroneous diagnosis made before the correct diagnosis is recognized. Basophilic stippled cells are always present and Cabot rings may be seen in some cases even before splenectomy. Serological and biochemical findings characteristic for CDA II are negative.

Physical abnormalities are more frequently observed than in CDA II and may be the presenting features for the referral of children [75]. These patients show skeletal malformations, particularly syndactylism of hands or feet, absence of nails or additional toes [35, 47], dyskeratosis-like skin pigmentation, or neurological deficits [92]. There is indirect evidence that these malformations are caused by mutations of a single morphogenetic gene rather than by fetal damage [58]. Short stature may be the result of pituitary failure due to unrecognized secondary hemochromatosis [28].

At present, light and electron microscopy of bone marrow erythroblasts is still the only safe method to confirm the diagnosis. Detailed illustrated descriptions can be found in previous work [12, 41, 42, 92]. Bone marrow cellularity is always greatly increased due to erythropoietic hyperplasia, with erythropoietic/granulopoietic ratios of up to ten times normal. More than 50% of early and late erythroblasts show characteristic and partially bizarre abnormalities of nuclear shape and chromatin structure. In less severely affected cells, chromatin strands are grosser than normal and interrupted by irregularly shaped translucent areas. In more heavily affected erythroblasts the chromatin structure is lost and the nucleus contains weakly stained material, which is not sharply delineated from the surrounding cytoplasm. Of particular significance are thin chromatin bridges between pairs of erythroblasts, which may also be seen between two nuclei in one cell. With the exception of a few cases of erythroleukemia, they are almost specific for CDA I, in contrast to the frequently observed cytoplasmic threads between adjacent erythroblasts in the smear. In the cytoplasm of many cells small

karyomeres and intensive and irregular basophilic stippling are seen. These changes are sometimes called megaloblastic, but in contrast to megaloblastic anemia the characteristic loose and fine chromatin structure of erythroblast nuclei is lacking as well as giant granulopoietic cells and hyperlobulation of megakaryocytes.

Experts easily make the diagnosis by light microscopy, but electron microscopy shows particularly specific alterations [41]. They are absent in very early erythroblasts but become distinct with progressing maturation. The heterochromatin is more dense than normal and forms sharply delineated clumps with small translucent vacuoles, prompting the metaphor of "Swiss cheese appearance" [93], and cytoplasm may penetrate through widened pores of the nuclear envelope.

The gene responsible for CDA I (CDAN1 gene) has been mapped to the long arm of chromosome 15 between 15q15.1q15.3 by homozygosity mapping in four Bedouin families with a high degree of consanguinity [86] and could be assigned to an 0.5-cM interval [87]. Similar results were reported in six patients from Europe and the Near East [45]. Within the CDA I linkage interval 15 putative genes expressed in erythroblasts were identified. The CDAN1 gene was recently cloned with 28 exons spanning 15 kb encoding a protein named codanin-1. In nine unrelated patients of European, Bedouin, and Asian origin different point mutations were detected in the codanin-1 gene [24]. Further work is in progress to decide whether all families with the CDA I phenotype are related to codanin-1 mutations as well as studies to define the role of the codanin-1 protein for normal erythropoiesis, possibly involved in maintaining the integrity of the nuclear membrane. DNA synthesis becomes arrested in the S-phase of such cells [71, 93]. The same is true for cells in disk lost gene *Drosophila* mutants, which produce a codanin-1-like protein [70].

The incidence of bile stones is increased, but lower than in CDA II [81]. Iron overloading shows similar patterns as in CDA II [37, 81] and is not dependent on HFE gene mutations [95]. In severe cases, iron overload becomes apparent in childhood [28, 83]. Patients with organ damage and death from secondary hemochromatosis were observed before ferritin levels were systematically controlled and iron depletion initiated.

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### CDA III (MIM 105600)

CDA III was described 1962 by the name of hereditary benign erythroreticulosis [7] or "Västerbotten anomaly" in members of a large family living in Northern Sweden and named type III when types I and II were classified [38]. At present, the fifth generation of this family is investigated, and most data on CDA III were described by the investigators from Umea, Sweden [76]. Clinical presentation is similar to type I and II patients, but anemia is never severe and transfusions do not have to be given. In contrast to all other types, there is no clinically relevant iron overload. In addition to ineffective erythropoiesis,

there is intravascular hemolysis as demonstrated by hemosiderinuria and absence of serum haptoglobin [77]. The most marked anomaly in the bone marrow is the presence of giant multinucleated erythroblasts resembling the giant erythroblast seen in the regenerative phase of parvovirus B19-initiated erythroid aplasia. Of high interest are additional features, namely abnormalities of the retina with angioid streaks and macular degeneration, and a very high incidence of monoclonal gammopathy with or without multiple myeloma. The responsible gene was mapped to a locus close to the CDAN1 gene on a 4.5-cM interval between 15q21 and 15q25 [60]. The gene products initiating hemopoietic and ocular pathology are unknown. There are two more families with similar hemopoietic changes and dominant inheritance living in North and South America, but only few details are known and it is not understood whether they share the same genetic basis.

Nonfamilial CDA III is the rarest type of the CDAs, with less than 20 well-documented cases. They are probably the results of other genetic lesions [76]. We observed CDA III-like giant erythroblasts in multiple myeloma (unpublished) and there are some doubts whether patients in whom CDA III was detected on examination for malignant lymphoma [13, 65] truly had congenital anemia.

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### CDA variants

Before and after the core group of the CDAs had been recognized [38], familial and sporadic cases of congenital anemia were reported which fulfilled the four general criteria of the CDAs but could not be attributed to one of the three groups [11, 22, 37, 92]. This is clearly an extremely heterogeneous group, and failure to attribute such cases to either one of the three types or to any other defined congenital anemia may result from incomplete diagnostic work-up. However, in many cases any other known disorder was carefully excluded by extensive and repeated examinations including serological, biochemical, and morphological methods. As in CDA I and II the mode of inheritance is autosomal recessive; it is, however, not in all cases documented, and nothing is known about the genes possibly involved. A preliminary classification based on the proposal by Wickramasinghe [92] and cases in the German CDA Registry may define the following groups.

*CDA type IV* [6, 64] has been described with typical morphological features of CDA II but with a negative acidified serum test. Some of these reports were later retracted when retesting with more sera gave positive results [80]. However, we and others [6, 25] have observed families fulfilling all general criteria as stated above but whose acid serum tests were consistently negative. In our hands, this was also true when ABO sera were used which contained the anti-HEMPAS antibody, as demonstrated by positive reactions with red cells of typical CDA II patients. In none of them were any of the other tests recognizing the

membrane abnormality positive. At present, we are following such patients from three families with additional neurological dysmorphism and mental retardation. These patients display a severe clinical course and require regular transfusions. Hydrops fetalis was reported from two cases [14, 72].

*CDA with prominent erythroblastosis after splenectomy* [1, 8, 10, 82]: clinical and morphological features resembled CDA II, but acidified serum tests were consistently negative. Up to  $50 \times 10^9$  mature erythroblasts/l were seen for many years after splenectomy.

*CDA with intraerythroblastic inclusions* as described by Wickramasinghe [92].

*Congenital ineffective erythropoiesis and erythroid hyperplasia but absence of erythroid dysplasia*: such cases were published under terms such as shunt hyperbilirubinemia or idiopathic dyserythropoietic jaundice [92]. One such case enrolled in the German CDA Registry was followed over 20 years and showed iron overload.

*CDA with thrombocytopenia* [55, 59, 79]: these patients had distinct extramedullary hematopoiesis in liver and spleen, and although the term “CDA” was used by the authors, they could also be grouped within the chronic congenital myeloproliferative disorders. Whether they are due to a recently described family with a mutation in GATA1 [67] is unknown.

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### Management of patients with CDA

Pediatricians and hematologists only occasionally see a patient with CDA and therefore should seek the advice of the few specialists interested in research on rare congenital anemias. European (<http://www.enerca.org>) and national (<http://www.bone-marrow-failure-syndromes.de>) networks provide information of specialist centers and give access to new knowledge for both physicians and patients. Decision making depends on age, type of CDA, severity of expression, and comorbidity.

Two procedures are effective to improve the chronic anemia: interferon- $\alpha$  in CDA I and splenectomy in CDA II. Prednisone, folate, or cobalamin were tried in many patients without evidence of efficacy, as well as human recombinant erythropoietin in CDA I [88] and CDA II (our own unpublished observations). Interferon- $\alpha$  in doses of approximately 10 million U per week led to normal hemoglobin concentrations in ten adult patients with CDA I reported in the literature [74], and the same effect was achieved by 50  $\mu$ g Peginterferon- $\alpha$ -2b in one of our female patients. When interferon therapy is stopped, hemoglobin levels return to previous values. Erythrokinetic studies demonstrated a striking reduction of the ineffective erythropoiesis, and electron-microscopic studies showed a reduction in nuclear structure abnormalities [57]. The pathophysiological basis of the beneficial effect of interferon in CDA I is not understood. Subnormal concentrations of interferon- $\alpha$  were measured in supernatants from cultures of Epstein-Barr virus (EBV) transformed B-lymphoblastoid cell lines derived from seven

patients with CDA I, but not from subjects with other types of CDA [94].

In CDA II, splenectomy leads to a moderate and sustained increase in hemoglobin concentration and decrease of serum bilirubin levels, as shown in 48 patients from the two registries [44, 53] and in 41 patients published as case reports. If measured, shortened red cell survival normalizes [5, 17], demonstrating that, as in hereditary spherocytosis, abnormal CDA II erythrocytes may survive normally in an asplenic individual. No overwhelming bacterial infections were observed after splenectomy. One case of Budd-Chiari syndrome was reported [92]. Portal vein thrombosis occurred in two patients [43]. Splenectomy does not prevent further iron loading, even in those cases where hemoglobin concentrations become nearly normal [44]. This may be explained by the observation that the expansion of the erythroid marrow is more closely correlated to iron loading than the anemia itself, which in CDA II is determined by both ineffective erythropoiesis and shortened red cell survival. The main benefit of splenectomy is abrogation of transfusion requirements in more severe cases and increase of the hemoglobin concentration to allow regular phlebotomies. In other patients, it is advocated to follow the guidelines for mild cases of hereditary spherocytosis [61]. Splenectomy is not recommended in CDA I, and individual decisions have to be made in variants with transfusion dependency and a enlarged spleen.

The main problem encountered by patients after the first years of life is iron overloading, which is also seen in patients without ongoing need for transfusion. The fact that patients with both CDA I and II as well as similar variant types store iron in a manner similar to those with other chronic states of ineffective erythropoiesis has been known since the early observations [21, 38, 39] and was confirmed by many case reports. Iron accumulates steadily throughout life, with kinetics similar to untreated hereditary hemochromatosis [44]. There is distinct variability among individuals, which is not explained by HFE gene polymorphism [53, 81, 89]. Even in patients with light or moderate anemia, ferritin levels should be controlled in at least yearly intervals, because iron overload may approach risk levels at any age. Adequate treatment with regular phlebotomies and/or deferoxamine leads to normal ferritin concentrations [15, 46, 31], indicating reversal of iron overload in patients with CDA. Since data correlating serum ferritin values to tissue iron are scarce, prospective studies using noninvasive techniques of liver iron determination [30] are required; at present, management of iron overload should follow guidelines for thalassemia [66, 68]. Allogeneic stem cell transplantation was successful in some children with exceptionally severe anemia [4, 82], but requires careful decision making by a specialized expert.

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