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Congenital dyserythropoietic anemia type II and ineffective erythropoiesis: challenges in diagnosis and management

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Congenital dyserythropoietic anemia (CDA) is characterized by anemia—mild to severe, hemolysis, ineffective erythropoiesis, and in some cases, iron overload. There are three major types of CDA (I, II, and III), and the other types are rarer. The rarity of this disease, as well as signs and symptoms that overlap with other hematological diseases, can make the diagnosis difficult and delayed over several years. Evaluation includes basic laboratory testing, magnetic resonance imaging of organs for assessment of iron overload, bone marrow assessment, and genetic testing. Laboratory tests to evaluate for ineffective erythropoiesis include indirect bilirubin level, which can be normal or increased, reticulocyte production index < 2 signifying hyperproliferation of erythrocytes, and complete iron panel (serum iron, ferritin, and iron saturation), which may suggest iron overload. Genetic testing is crucial for CDA diagnosis and includes next-generation sequencing. A multidisciplinary team of providers including a hematologist, hepatologist, hematopathologist, and genetic counselor are important and sometimes necessary for the evaluation, diagnosis, and management of these patients. Management depends on the clinical phenotype, and some severe cases may require blood transfusion, iron chelation therapy, splenectomy, and in extreme cases, hematopoietic stem cell transplant may be necessary. This mini-review illustrates the challenges involved in the diagnosis and management of the most common CDA, which is type II. It will highlight clinical signs and symptoms in patients that should prompt providers to test for CDA. It will also increase awareness of this disease, discuss possible barriers to testing, and provide guidance on how to manage the disease.

KEYWORDS

congenital dyserythropoietic anemia, ineffective erythropoiesis, iron overload, hemolysis, splenomegaly

1 Introduction

Erythropoiesis produces 150 billion erythrocytes daily, and defects in this process due to maturation arrest resulting in decreased red cell production, are known as dyserythropoiesis, a type of inherited bone marrow failure syndrome (1). Congenital dyserythropoietic anemia (CDA) is a rare hereditary hemolytic disease characterized by varied severity of anemia requiring blood transfusions in some patients, hemolysis, ineffective erythropoiesis, and iron overload (2). There are three classic CDA subtypes (I, II, and III) that were initially identified using bone marrow morphology criteria and later confirmed using genetic analysis; additional subtypes include transcription-factor-related CDAs and other rare CDA variants (1, 3). See recent reviews of CDA (3, 4). This article focuses on CDA type II and discusses the disease in the literature.

2 CDA type II

CDA II is an autosomal recessive disease that is the result of biallelic pathogenic variant mutations in the *SEC23B* gene (20p11.23), which encodes the cytoplasmic coat protein II (COPII) complex, a protein involved in intracellular vesicle trafficking in eukaryotic cells as well as autophagy (2, 3). Loss-of-function genetic variants lead to defects in the transport of newly synthesized proteins from the endoplasmic reticulum to the Golgi (1–3). Diagnosis has been reported to occur from *in utero* to 78 years (mean 18.2 years) (5). CDA II is most common in the Mediterranean region (Morocco, Israel, and Italy) (6). Differential diagnoses of CDA II include hemoglobinopathies, Diamond–Blackfan anemia, hereditary spherocytosis, pyruvate kinase deficiency, and Fanconi anemia (7). The morphologic findings in CDA include erythroid hyperplasia and binucleate cells (8). CDA II has the highest percent of binucleate cells at > 10% (9). Some patients previously diagnosed with CDA based on bone marrow morphology were later found to be misdiagnosed based on the identification of pathogenic variants in genes associated with other genetic conditions, such as pyruvate kinase deficiency and hereditary spherocytosis (2). Since the disease is rare and overlaps clinically with other more common hematologic disorders such as thalassemia and red cell membrane disorders, misdiagnosis earlier in life is common, which can lead to mismanagement as well as delayed diagnosis (10). Some patients may not receive the correct diagnosis of CDA II until middle age or even late adulthood (11, 12).

3 Presentation of CDA type II

3.1 Hemolytic anemia

CDA should be suspected in patients with signs and symptoms of high red cell turnover (hemolysis), such as jaundice, low or undetectable haptoglobin, and indirect hyperbilirubinemia (1). Neonatal jaundice can be seen in almost 62% of CDA II patients (7). Patients with CDA II often present with a normocytic anemia (6), jaundice, and splenomegaly as a result of hemolysis (3). Peripheral blood smear examination of the red cells shows anisopoikilocytosis with basophilic stippling and rare binucleated mature erythroblasts (1). Severe anemia and extramedullary erythropoiesis result in splenomegaly and hypersplenism (1). Hemoglobin, reticulocyte count, indirect bilirubin, and haptoglobin levels in CDA II often reveal hemolytic anemia with inadequate reticulocytosis (1).

3.1.1 Mechanism of hemolytic anemia in CDA II—ineffective erythropoiesis, peripheral hemolysis, and erythroid hypo proliferation

Ineffective erythropoiesis occurs when there is inadequate reticulocytosis in the presence of immature erythroid precursors contributing to anemia (13). It is characterized by erythropoietin-driven expansion of erythroid precursors and apoptosis of late-stage erythroid precursors (14). In addition, ineffective erythropoiesis causes overexpression of erythroferrone in patients with CDA II (15), which suppresses hepcidin leading to increased iron absorption and progressive iron overload (3). This phenomenon is seen in other hematologic diseases such as non-transfusion-dependent thalassemia and sideroblastic anemia (13). Hypoxia develops because of anemia and drives an increase in erythropoietin, which further expands erythroid cells and perpetuates ineffective erythropoiesis. Hemolysis also contributes to anemia in CDA II (14).

3.2 Iron overload

The most common complications of CDA II are iron overload, splenomegaly, and cholelithiasis (1). Iron overload is often due to ineffective erythropoiesis as well as frequent blood transfusions and hemolysis (7). When excess iron accumulates in hepatocytes and other parenchymal cells, iron toxicity leads to cell death, fibrosis, and organ failure (13). About 30% of CDA II patients who are not transfusion-dependent still show increased ferritin levels of > 300 ng/mL and 17% show hemosiderosis with ferritin levels > 600 ng/mL (3). Other complications of iron overload include liver disease, hepatocellular cancer, diabetes, and heart failure and arrhythmias.

4 Diagnosis

Diagnosis includes a thorough evaluation of personal and family history, clinical signs and symptoms, bone marrow morphology, laboratory studies, and the results of genetic testing (3). Although bone marrow morphology was primarily used to identify patients with CDA, molecular testing can expedite the definitive diagnosis of CDA in some patients (2). Hypoglycosylation of band 3 is a consistent finding in CDA II and reflects the effects of the molecular defect; 95% of CDA II patients have hypoglycosylated band 3 in the membrane of their red cells (6), which is associated with hemolysis as increased clustering of the protein on the red blood cell (RBC) surface leads to IgG binding and RBC phagocytosis (7). Two

cases that were reported without hypoglycosylation were due to severe hemolysis in the setting of hydrops fetalis (16).

4.1 Bone marrow morphology

The morphological features that define CDA II include erythroid hyperplasia and multinucleation, with the most specific finding being the presence of >10% binucleate cells in which both nuclei are at the same maturational stage (1, 3). Genetic testing should be included early in the evaluation for possible CDA (3) as it can prevent unnecessary bone marrow biopsies (10, 17).

4.2 Evaluation of iron status

It is important to assess iron status including serum iron, serum ferritin, and transferrin saturation, which can show signs of iron overload (14). Magnetic resonance imaging (MRI) is preferred for measuring liver iron concentration (LIC) and is an excellent surrogate of body iron status (18). It is considered more accurate for quantifying body iron compared to liver biopsy (19). MRI is also used to assess iron levels in other organs including the heart and endocrine organs; these results can be useful for deciding when an iron chelator may be indicated (20).

4.3 Genetic testing

Bone marrow morphology is not definitive for CDA (3). For example, a patient who was initially suspected of having CDA based on bone marrow morphology was ultimately diagnosed with a hemoglobinopathy when genetic testing did not reveal any pathogenic genetic variants in the genes associated with CDA but showed a heterozygous variant in *HBB* (c.442T>C, p.stop148Gln) for Hb Zunyi (21). Another patient was ultimately diagnosed with non-deletional hemoglobin H disease using Sanger sequencing following an incorrect diagnosis of CDA II based on bone marrow morphology (22). As these CDAII patients are often misdiagnosed especially with pyruvate kinase deficiency, multigene panel testing was shown to identify patients with congenital hemolytic anemia misdiagnosed with CDA based on clinical diagnosis and helped to render an accurate diagnosis of chronic anemia due to enzymatic defects in 10 out of 22 (45%) patients; the same team also identified syndromic cases of CDA variants (23). The diagnostic complexity is further demonstrated by patients with co-inheritance of CDA and hemoglobinopathy (24, 25).

5 Complications of CDA II

5.1 Iron overload

Iron overload is a known complication of CDA II and can even be seen in transfusion-independent patients (13). The degree of overload is due to erythropoietic expansion (14) and the levels appear to increase with age (5). Some patients may report fatigue and others may develop liver cirrhosis and portal hypertension because of secondary iron overload (5, 7). Hypogonadism may also occur due to iron overload in the hypothalamus (7).

5.2 Hydrops fetalis

CDA II can present as hydrops fetalis and intrauterine death (16). Intrauterine red cell transfusions may be helpful in such cases of CDA II (26) as in a pregnant patient who presented with fetal hydrops and cardiomegaly at 20 weeks gestation. The fetus had a hemoglobin level of 1.5 mg/dL and required intrauterine blood transfusions. Following delivery, the baby ultimately underwent a postnatal hematopoietic stem cell transplant (HSCT) and achieved transfusion independence (27). While hydrops fetalis may occur in CDA II, *in utero* anemia, and consequently, hydrops fetalis is more commonly seen in CDA I (7).

5.3 Cholelithiasis

Gallstones are often diagnosed in the first 40 years of life (5). Higher levels of indirect bilirubin that increases the rate of gallstone occurrence can be seen in some CDA II patients who co-inherit *UGT1A1 (TA)7/(TA)7 genotype*, which causes Gilbert syndrome as well *as SEC23B biallelic* pathogenic variants (7, 28). Symptomatic patients with cholelithiasis should undergo cholecystectomy with the same guidance as patients without CDA II (29).

5.4 Other complications

Other complications that can be seen in patients with CDA II include heart failure, diabetes, hypothyroidism and hypogonadism, and splenomegaly (splenectomy is discussed further under the clinical management of CDA). Reactive thrombocytosis can also be seen following splenectomy (5).

6 Challenges in diagnosis and diagnosis workflow

A highly experienced hemopathologist is required for accurate diagnosis of CDA by bone marrow morphology (8). Although the bone marrow morphology findings are helpful, patients with stomatocytosis and sideroblastic anemia have been misdiagnosed with CDA II based on nonspecific dyserythropoietic findings (8). Incorporating NGS early in the diagnostic approach can lead to early diagnosis, avoiding splenectomy and preventing potentially fatal thromboembolic complications (8). However, technical limitations and barriers in the current understanding of the genome contribute to missed genetic diagnoses. In addition, the use of NGS may not always be feasible due to limited resources and costs, especially in some low- and middle-income countries (30, 31).

In such instances, the implementation of a thoughtful, stepwise diagnostic approach has been shown to be useful (32).

7 Clinical management

Management of CDA II is largely supportive care. The primary goal is to manage the effects of anemia as well as iron overload, and in some cases, it may be helpful to involve psychologists, nutritionists, and endocrinologists in the management (24). Stem cell transplant is curative (6). Also, see Table 1.

7.1 Monitoring of laboratory markers

Management includes checking a complete blood count and iron studies (iron level, ferritin, and transferrin saturation) every 6 months (or sooner based on laboratory or clinical severity) (3). Iron studies are certainly important to check as the average ferritin was found to be 464.8 ± 55.9 ng/mL in a study of CDA II patients, with ferritin value 282.2 ± 36.7 ng/mL (15–2,097, n = 88) in non-transfusion-dependent patients while transfusion-dependent patients (25/126, 19.8%) showed a serum ferritin level of 918 ± 171 ng/mL (108–2,750, n = 21) (6).

7.2 Blood transfusion

Approximately 7%–20% of cases require transfusion (1, 3) while about 10% of these patients are asymptomatic (3). Blood transfusion should be considered for hemoglobin levels < 7 g/dL. If diagnosed *in utero*, then *in utero* transfusions must be carried out, and evaluation for hydrops during prenatal ultrasonography should be employed in cases of a positive family history (29).

7.3 Iron chelation therapy

Unlike patients with hereditary hemochromatosis, patients with CDA II are often anemic and so, therapeutic phlebotomy is not an option for managing iron load. Therefore, iron chelators are the sole option, and the management is extrapolated from iron chelation therapy in patients with beta thalassemia. Treatment is recommended once the serum ferritin is 800–1,000 ng/mL or LIC > 3–5 mg/g, and treatment is withheld when ferritin is < 300 ng/mL or LIC < 3 mg/g (20, 33, 34). A normal LIC is 0.8 to 1.5 mg/g dry weight (18). Currently, there are three FDA-approved iron chelators, namely, one parenteral (deferoxamine) and two oral (deferiprone and deferasirox) medications (20). In reality, practice patterns are quite variable with iron chelators being initiated based on ferritin levels 500–2,000 ng/mL and LIC 3–10 mg/g (35). Combination iron chelation therapy can also be used to decrease LIC rapidly (20).

7.4 Splenectomy

Splenomegaly was seen in a cohort of CDA Type II patients in the first 3 decades of life (5). A retrospective study of 205 patients with CDA II found that 83.6% (102/122) of the patients presented with splenomegaly (6). Since damaged and abnormal erythrocytes traversing the spleen red pulp are removed by the splenic macrophage system, splenectomy is often suggested as a therapeutic approach (36). There are well known complications of splenectomy including post splenectomy infections with encapsulated bacteria, post-splenectomy thromboembolism (acute splenic and portal vein thrombosis), late cardiovascular events (arterial and venous thromboembolism, as well as pulmonary arterial hypertension), and perioperative complications such as laceration (36). Therefore, it is prudent to avoid splenectomy whenever possible. However, splenectomy is recommended for the management of CDA II in transfusion-dependent patients or those with symptomatic splenomegaly (36). A study of 17 patients with CDA II showed about a 1-g increase in hemoglobin on average to 10.6 ± 1.6 g/dL following splenectomy from 9.3 ± 1.2 g/dL in all but three patients (6). Therefore, splenectomy does not normalize hemoglobin levels in CDA II. Also notable is that splenectomy does not alleviate additional iron loading in these patients (5) Splenic artery embolization is less invasive with fewer complications, including a lower risk for early in-hospital infections and may be an attractive alternative to splenectomy (37).

7.5 Hematopoietic stem cell transplant

HSCT is currently the only curative option and has been successful in some cases of CDA II leading to transfusion independence (6, 25, 38).

TABLE 1 Management of CDA (not specific to CDA II).

Ref (7)	Non-transfusion dependent					Transfusion dependent
	Children			Adult		Any age
Age (children) | Hb in adults	≤2 years	2–10 years	10–16 years	Hb ≤ 9 (g/dL)	Hb > 9 (g/dL)	
CBC	3 months	6 months			12 months	Before and after transfusion
Iron status	6 months		12 months			6 months
Spleen/Gall bladder evaluation	6 months	12 months		24 months		12 months

Several HSCTs have been reported in pediatric cases of CDA II, some with partial resolution (39). One patient required up to three HSCTs in order to achieve transfusion independence; of note, this case of CDA II was diagnosed by bone marrow morphology without a positive CDA II genetic marker (40), raising the possibility of an incorrect diagnosis. A retrospective study, which described a large cohort of 39 CDA patients including 13 with CDA II, showed that matched sibling donor HSCT patients had a superior overall survival compared to unrelated donor transplant (41). The study also showed better outcomes for patients without iron overload and so patients should be assessed and treated with chelation prior to transplant (41).

7.6 Potential future therapy

Interferon improves anemia and iron loading in some cases of CDA I and some patients become transfusion-independent shortly after starting interferon (2). However, interferon is not associated with clinical improvement in CDA II, and there are no approved medications for achieving transfusion independence in CDA II. In beta thalassemia, ineffective erythropoiesis is exacerbated by decreased erythroid cell differentiation (14) and so the approval of luspatercept for transfusion-dependent thalassemia has been revolutionary.

7.6.1 Transforming growth factor beta inhibitor

Luspatercept binds select TGF-β superfamily ligands and promotes late-stage erythroid maturation (42). Luspatercept was approved by the U.S. Food and Drug Administration in 2019 and the European Medicines Agency for the treatment of transfusion-dependent beta thalassemia based on the BELIEVE phase III trial, which showed a 33% reduction from baseline during weeks 13–24 compared to placebo and 11% of patients achieved transfusion independence at any 8-week interval (43). Luspatercept also led to a decrease in serum ferritin from baseline by week 48 while the ferritin levels in the placebo group increased; however, there was no change in the liver iron concentration or myocardial iron deposition (43). It also increases the use and redistribution of iron in the body (42).

Sotatercept, another TGF inhibitor, inhibits GDF11, which is a negative regulator of erythropoiesis and murine ortholog of sotatercept, known as RAP-011 improved anemia and decreased iron overload in a murine model of beta thalassemia (44). Sotacercept has also been found to reduce transfusion burden in beta thalassemia patient in phase II clinical trials (45).

As CDA II and thalassemia share a major similarity of ineffective erythropoiesis, the clinical improvements seen with the use of luspatercept and sotatercept suggest a possible role for TGF beta inhibitors in the treatment of CDA II.

7.6.2 Gene therapy

While there are currently no human CDA II gene therapy approaches available, CRISPR/cas9 gene editing system used to knock-out *SEC23B* gene in K562 cells as well as in hematopoietic stem and progenitor cells has led to a decrease in SEC23B protein in both cell models. Consequently, *in vitro* and *in vivo* erythroid differentiation of the edited cells showed an increased number of binucleated and multinucleated cells (46). RAP-011 rescues the disease phenotype in SEC23B-silenced K562 cells by restoring the gene expression of erythroid markers through inhibition of the phosphorylated SMAD2 pathway; it also reduces the expression of erythroferrone *in vitro* (44). Finally, the increased expression of SEC23A (the SEC23B paralog in mice) using CRISPR rescues the SEC23B-deficient erythroid defect in mice (47). All these suggest that gene therapy may be a new therapeutic target as well as a potential treatment option for CDA II in the future.

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