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SHORT REPORT

Severe congenital dyserythropoietic anaemia type I: prenatal management, transfusion support and alpha-interferon therapy

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Summary. We report a case of congenital dyserythropoietic anaemia, type I, with severe pre- and postnatal manifestations. Exchange transfusions were required for fetal anaemia (3·5 g/dl) at 28 and 30 weeks of gestation. Transfusions were administered at birth (Caesarean section at week 35) and at regular intervals thereafter. At 14 months, α-interferon therapy was initiated (10^6 units three times a week). This resulted in stabilization of the haemoglobin at or above 11 g/dl and a reduction in the percentage of erythroblasts with ultrastructurally abnormal heterochromatin. After 9 months, the dose of α-interferon was decreased to 10^6 units twice a week. No relapse of anaemia was noted during an additional 4 months of follow-up.

Keywords: congenital dyserythropoietic anaemia, α-interferon, infant, prenatal diagnosis, intrauterine transfusion.

Congenital dyserythropoietic anaemia, type I (CDA I), appears to be the most common CDA in France. It is characterized by macrocytic anaemia, erythroid hyperplasia with megaloblastic features and internuclear chromatin bridges between incompletely separated erythroblasts. The nuclei of erythroid precursors display a 'Swiss cheese' appearance of the heterochromatin and invagination of the nuclear membrane (Tamary *et al*, 1996; Wickramasinghe, 1998). Rather specific dysmorphic features are frequently encountered. The inheritance pattern is autosomal recessive. Tamary *et al* (1998) mapped the *CDAN1* gene to 15q15.1–q15.3. Hodges *et al* (1999) found considerable genetic heterogeneity. CDA I may be recognized in the neonatal period (Shalev *et al*, 1997).

Until recently, no specific treatment for CDA I was available. Lavabre-Bertrand *et al* (1995) first reported the efficacy of α-interferon (α-IFN), which increased haemoglobin values to normal levels. Since this initial report, a few other cases of CDA I have been successfully treated with α-IFN (Wickramasinghe, 1997). In the present study, we describe the prenatal and postnatal findings in a patient with CDA I to whom α-IFN was administered from the age of 14 months onwards.

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CASE REPORT

A 28-year-old pregnant woman was followed by ultrasound because of an increased nuchal translucency (3 mm) diagnosed at week 12. The fetal karyotype was normal. There was oligohydramnios at 28 weeks and a hypertrophic

Congenital dyserythropoietic anemia type I presenting as persistent pulmonary hypertension of the newborn

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Congenital dyserythropoietic anemia (CDA) is a rare group of inherited bone marrow disorders characterized by anemia with ineffective erythropoiesis. We report 3 siblings from a family known to have CDA type I who presented with persistent pulmonary hypertension of the newborn (PPHN). We suggest that the diagnosis of CDA type I should be considered in any neonate with PPHN and anemia. (J Pediatr 2000;136:553-5)

Congenital dyserythropoietic anemia is a rare group of inherited bone marrow disorders characterized by ineffective erythropoiesis.[1] CDA type I is associated with unique bone marrow findings on electron microscopy including spongy appearance of erythroid precursor nuclei with extensive disruption of the nuclear membranes. Recently, our group mapped the gene for this disorder in Bedouin families and also in other patients to chromosome 15q15.1-15.3.[2,3] The clinical picture in most patients was associated with moderate anemia.[4] More severe manifestations were noted during the neonatal period,[5] and hydrops fetalis has been reported in different types of CDA.[6-8]

Persistent pulmonary hypertension of the newborn is a transient clinical syndrome leading to respiratory failure and death if untreated. The syndrome is associated with increased pulmonary vascular resistance that prevents pulmonary blood flow and causes right-to-left extrapulmonary shunting across the ductus arteriosus and foramen ovale, resulting in hypoxia, cyanosis, and acidosis.[9]

The aim of this report was to describe 3 children from a family known to have CDA type I who had PPHN caused by severe neonatal anemia.

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Case Reports

Patient 1 (II-2, Figure)

A Bedouin baby boy was born to healthy consanguineous parents after an uncomplicated pregnancy. The parents are part of an extended family in which CDA type 1 has been diagnosed previously in several members.[2] Fetal distress was noted in the immediate prenatal period.

The baby was born at term. His birth weight was appropriate for gestational age, and the Apgar score at 1 minute and 5 minutes was 7 because of cyanosis and shallow breathing. There was no meconium.

See related article, p. 556.

Physical examination revealed a pale child with hepatosplenomegaly. A holosystolic murmur of grade 3/6 was heard over the precordium. Arterial blood gases were pH 6.9, $PC0_2$ 50 mm Hg, PO_2 38 mm Hg, and bicarbonate 9 Meq/L. Initial hematocrit was 18%. The baby underwent intubation and ventilation. Despite high-pressure ventilation and 100% oxygen, the blood gases showed significantly reduced oxygen saturation (52%).

BM	Bone marrow
CDA	Congenital dyserythropoeitic anemia
PPHN	Persistent pulmonary hypertension of the newborn

Echo-Doppler examination revealed an enlarged left ventricle with decreased contractility and a right-to-left shunt across the patent foramen ovale. A tricuspid regurgitation of 55 mm Hg with normal flow across the pulmonic valve indicated a pulmonary pressure of 60 mm Hg (the systemic pressure at that time was 50 mm Hg). A large ductus arteriosus shunted from right-to-left. Despite aggressive treatment with high-pressure ventilation and repeated transfusions, the clinical condition did not improve. However, nitric oxide

Clinical and Laboratory Manifestations of Congenital Dyserythropoietic Anemia Type I in a Cohort of French Children

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Summary: Congenital dyserythropoietic anemia type I (CDA I) is a rare disorder of erythropoiesis. The objective of this study was to describe the clinical and laboratory manifestations, the diagnosis procedure, the therapeutic approaches and outcome in CDA I. The 12 patients included belong to the retrospective French Multicenter Study. Clinical and biologic data were compiled. Biologic tests included light and, in some cases, electron microscopy, ektacytometry, and red cell membrane protein electrophoresis. Neonatal manifestations (anemia, early jaundice, and/or splenomegaly) and bone abnormalities were present in 11 of the 12 and 6 of the 12 patients, respectively. CDA I was initially misdiagnosed in four children. By the time of diagnosis, anemia with reticulocytosis lower than expected in a hemolytic anemia was present in all patients. Bone marrow electron microscopy examination revealed characteristic findings in all nine children. Red cell membrane protein 4.1 was reduced in all five children. At least one transfusion was required in 11 of the 12 children. Interferon α_2 corrected anemia in the three children who received monthly transfusions. CDA I is commonly misdiagnosed in children. It should be sought in patients with unexplained chronic anemia, especially when associated with neonatal manifestations, jaundice, splenomegaly, subnormal or low reticulocytosis, and congenital bone malformations.

Key Words: anemia, dyserythropoiesis, hemochromatosis, interferon α_2

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Congenital dyserythropoietic anemias (CDAs), a heterogeneous group of rare disorders, are characterized by an ineffective erythropoiesis and dysplastic changes in erythroblasts.[1,2] CDA type I (CDA I) includes a megaloblastoid erythroid hyperplasia and the presence of nuclear chromatin bridges between some of the erythroblasts. It is associated with unique bone marrow findings on electron microscopy, including spongy-appearing erythroid precursor nuclei with extensive disruption of the nuclear membranes. Recently, mutations in the gene encoding codanin-1 (*CDAN1*) have been shown to be responsible for this disease.[3]

Most of the CDA I cases reported in the literature were sporadic, and the only large series of CDA I comprised 20 Israeli Bedouins.[4,5] The aim of this French retrospective multicenter study was to describe the clinical and laboratory manifestations, the diagnosis procedure, and the therapeutic approaches and outcome in our experience of CDA I.

METHODS

Patients

All French pediatric centers treating patients with hematologic diseases were contacted. The responding pediatricians were asked to supply data on all patients followed for CDA I in their institution during the study period (Jan. 1, 1997, to Dec. 31, 2002), regardless of when the diagnosis was first established. Recent data were provided by the clinician in charge of the patients at the time of the study. A standard questionnaire was used for data collection. It included questions about the patient's initial status, laboratory studies (including osmotic gradient ektacytometry[6]), management, the course of the disease, and diagnosis criteria. Early jaundice was defined based on a serum bilirubin concentration of more than 5 mg/dL in the first 24 hours of life.

Diagnostic criteria of CDA I relied on the presence of anemia and typical bone marrow findings under light microscopy, including large erythroblasts with incomplete nuclear division and chromatin bridges connecting the nuclei

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Congenital Dyserythropoietic Anemia Type 1 With Fetal Onset of Severe Anemia

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Abstract: We report a patient with congenital dyserythropoietic anemia type 1 with characteristic anomalies and two novel clinicopathologic presentations: intrauterine onset of severe anemia resulting in cardiac failure and relatively mild dyserythropoietic features on bone marrow aspiration in contrast to severity of anemia. After repeated transfusions and a trial of erythropoietin administration, the patient died from respiratory infection at age 7 months. Autopsy revealed characteristic dyserythropoietic features of the bone marrow by light microscopy and electron microscopy, which confirmed a diagnosis of congenital dyserythropoietic anemia type 1.

Key Words: Congenital dyserythropoietic anemia—Fetal onset—Congenital heart failure.

Congenital dyserythropoietic anemia (CDA) is a rare hematologic disorder characterized by dyserythropoietic features, ineffective erythropoiesis, and secondary hemochromatosis. It is classified into types 1, 2, and 3, along with some variants (1,2). Congenital dyserythropoietic anemia type 1 is characterized by autosomal recessive inheritance and a macrocytic anemia with dyserythropoietic features such as megaloblastoid changes, multinuclearity, and internuclear chromatin bridges (1–4). On ultrastructural study, the dyserythropoietic cells showed characteristic findings such as spongy chromatin and disruption of the nuclear envelope (1–4). A recent study has revealed that the gene for CDA type 1 is located on *15q15.1–q15.3*, but no distinct responsible gene has been identified (5). An association with characteristic skeletal anomalies, including anomaly of distal extremities outside the radial ray, has been reported (1,6,7). It has been demonstrated that most patients with CDA type 1 have mild to moderate anemia during the neonatal period (1,6). We present a patient with CDA type 1 who had severe anemia develop during the fetal period resulting in cardiac failure and death.

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CASE REPORT

The patient was born to nonconsanguineous, healthy parents without a family history of anemia. The mother, gravida 3, para 2, had a stillbirth of unknown cause at 38 weeks gestations. The mother's elder brother and elder sister died from congenital heart disease and neuroblastoma at 2 and 7 years old, respectively. The mother was admitted to our hospital at 26 weeks gestation because echography revealed fetal myocardial hypertrophy.

A girl was delivered transvaginally at 34 weeks of gestational age because of premature contraction. The neonate had anemia, asphyxia, and Apgar scores of one at 3 minutes and one at 5 minutes. She weighed 1,572 g (−1.4 standard deviation) and measured 39.0 cm (−2.1 standard deviation). There were multiple anomalies, including nail hypoplasia/aplasia and syndactyly of the feet (Figs. 1A and B). Skeletal radiogram revealed flattened vertebrae, narrow iliac bone, loss of distal phalanges of the right foot, and loss of fourth and fifth distal phalanges of the left foot. Peripheral blood revealed severe anemia with erythroblastemia, macrocytosis, and dyserythropoietic features with internuclear chromatin bridges (hemoglobin: 4.8g/dL, red blood cell count: $1.21 \times 10^6/\mu L$, hematocrit: 15.9%, mean corpuscular hemoglobin concentration: 30.0%, mean corpuscular volume: 131.2 fL, white blood cell count: 30,800/μL, platelet count: $203 \times 10^3/\mu L$, reticulocyte: 7.4%, reticulocyte absolute count: $89.5 \times 10^3/\mu L$) (Figs. 2A and B). Echocardiography showed severe cardiac dysfunction with myocardial hypertrophy. Although her general condition became stable with intensive care and exchange transfusion, mechanical ventilation and regular transfusions were necessary until the patient's death.

Abnormal erythroblasts gradually decreased in number and completely disappeared from the peripheral blood. Subsequently, her reticulocyte count did not increase (0.2%–0.7%) even when her hemoglobin value was at its lowest level. Bone marrow aspiration at age 19 days showed mild dyserythropoietic findings with scattered binuclear erythroblasts (nuclear cell count: 43,500/μL, myeloblast:erythroblast ratio = 2.06). No ringed sideroblasts or dysplastic features on the granulocytic/megakaryocytic lineage were seen. Mild jaundice was noted (maximum value: 2.7mg/dL). Because anemia was so severe, erythropoietin was administered from day 21. Subsequent bone marrow aspira-

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Congenital Dyserythropoietic Anemia Type I

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Summary

Clinical characteristics. Congenital dyserythropoietic anemia type I (CDA I) is characterized by moderate-to-severe macrocytic anemia presenting occasionally in utero as severe anemia associated with hydrops fetalis but more commonly in neonates as hepatomegaly, early jaundice, and intrauterine growth retardation. Some cases present in childhood or adulthood. After the neonatal period, most affected individuals have lifelong moderate anemia, usually accompanied by jaundice and splenomegaly. Secondary hemochromatosis develops with age as a result of increased iron absorption even in those who are not transfused. Distal limb anomalies occur in 4%-14% of affected individuals.

Diagnosis/testing. Diagnosis of CDA I is suspected based on hematologic findings and established with identification of biallelic pathogenic variants in *CDAN1* or *C15orf41*.

Management. *Treatment of manifestations*: Intramuscular or subcutaneous injections of interferon (IFN)-α_{2a} or INF-α_{2b} given two or three times a week increase hemoglobin and decrease iron overload in the majority of treated individuals. Successful allogenic bone marrow transplantation has been described in three children and should be considered only in those transfusion-dependent persons who are resistant to IFN therapy.

Prevention of secondary complications: Treatment of iron overload using standard guidelines for regular phlebotomy and iron chelation as needed.

Surveillance: Recommended monitoring for iron overload:

- Measurement of hemoglobin, bilirubin, iron, transferrin and serum ferritin concentration every three months starting at age ten years.
- Annual myocardial T_2* MRI and hepatic R_2* MRI (if available) starting at age ten years.

Agents/circumstances to avoid: Any preparation containing iron.

Genetic counseling. CDA I is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible options.

A Comprehensive Study of the Neonatal Manifestations of Congenital Dyserythropoietic Anemia Type I

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Abstract: Congenital dyserythropoietic anemia (CDA) type I is an inherited disorder characterized by macrocytic anemia with pathognomonic morphologic ultrastructural features of the erythroid precursors. The authors recently cloned the *CDAN1* gene and identified one founder missense mutation in all of their Bedouin patients. In a previous study, the authors found that the majority of their 31 Bedouin patients had anemia and jaundice during the first month of life and required blood transfusions; some had persistent pulmonary hypertension. In the present retrospective evaluation of 70 Bedouin patients with CDA type I, the authors more than doubled the number. Forty-five (64%) patients were symptomatic in the neonatal period, 29 (65%) had hepatomegaly, 24 (53%) had early jaundice, 11 (27%) were born small for gestational age, 7 (15%) had persistent pulmonary hypertension, and 6 (13%) had direct hyperbilirubinemia and another 6 (13%) had transient thrombocytopenia. Thirty-six of the symptomatic neonates (80%) required at least one blood transfusion. These results confirm the authors' previous findings and add neonatal manifestations not previously described, particularly hyperbilirubinemia and thrombocytopenia. Early diagnosis of CDA type I may be beneficial in light of the potential efficacy of alpha-interferon in avoiding transfusions in some patients.

Key Words: congenital dyserythropoietic anemia, neonatal anemia, neonatal jaundice, neonatal thrombocytopenia, persistent pulmonary hypertension

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The congenital dyserythropoietic anemias (CDAs) are rare inherited disorders characterized by ineffective erythropoiesis.[1] CDA type I is an autosomal recessive disorder associated with unique bone marrow findings on electron microscopy, including spongy appearance of the erythroid precursors' chromatin and disruption of the nuclear membranes.

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More than 100 cases of sporadic CDA I has been described in patients originating mostly from European countries, as well as more than 30 cases in Israeli Bedouin patients.[2] The gene for the disorder was mapped by our group to chromosome 15q15.1-15.3 and has been recently cloned.[3] Mutations in the *CDAN1* gene were identified in the majority of affected patients.[4] One founder mutation, R1040W, was identified in all the Bedouin patients.

CDA type I is characterized by moderate to severe macrocytic anemia presenting in childhood or adolescence or later in life. The course of the disease is often complicated by the development of iron overload and the formation of gallstones. A few patients are transfusion-dependent. Alpha-interferon was incidentally found to be effective in several patients with CDA type I, including infants, and to obviate the need for red blood cell transfusions.[5]

Although the disease is most often not diagnosed in neonates, severe manifestations in the prenatal and neonatal periods have been described.[5,6] In a previous report, we found that 17 of 31 patients with CDA type I had anemia in the neonatal period.[6] One third of the neonates were born small for gestational age, 82% had early jaundice, and 65% had hepatosplenomegaly. We also described a unique complication of persistent pulmonary hypertension in three neonates.[7] Early diagnosis of CDA type I in the neonatal period may improve therapy for severe forms of the disease.

In the present study, we extended our analysis of neonatal manifestations of CDA type I to 70 affected Israeli Bedouin patients. The findings confirmed previous observations and suggested new transient neonatal complications, such as direct hyperbilirubinemia and thrombocytopenia.

METHODS

We reviewed the medical records of 70 patients from eight Bedouin families in whom CDA type I was diagnosed and who were followed at Soroka Medical Center for the past 20 years (1983–2004). The diagnosis was based on family history, presence of macrocytic anemia, and characteristic bone marrow findings on electron microscopy. In all cases the diagnosis was confirmed by DNA analysis.

The files were reviewed for gestational age, birth weight, and clinical and laboratory findings during the neonatal period. Early jaundice was defined as serum bilirubin of at least 5 mg/dL in the first 24 hours of life. Complete blood cell count and liver function tests were performed according to standard techniques.