ORIGINAL ARTICLE

SUCCESSFUL TREATMENT OF IRON OVERLOAD WITH PHLEBOTOMIES IN TWO SIBLINGS WITH CONGENITAL DYSERYTHROPOIETIC ANEMIA – TYPE II (CDA-II)

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Summary: Successful treatment of iron overload by phlebotomies has been reported in two splenectomized siblings with congenital dyserythropoietic anemia – type II (CDA-II). In both patients 400 ml of blood were withdrawn every month. During three years 12 200 ml of blood were removed. The serum ferritin levels decreased from 1450,4 μg/L and 1131,7 μg/L to 447 μg/L and 457 μg/l, respectively. The transferrin saturation dropped from 0,99 at the start of the therapy to 0,64 and 0,86, respectively. The values of Hb, Hct, erythrocyte counts and MCV did not change as well as did not change reticulocyte counts, reticulocyte index, and RDW. Both patients tolerated repeated phlebotomies well. The decrease of bilirubin and normal values of haptoglobin might be the concequence of diminished destruction of erythrocytes and their precursors. Our observation confirms that phlebotomies can be used with success in CDA patients with mild anemia as treatment modality of iron overload.

Key words: *CDA-II; Iron overload; Therapy; Phlebotomies*

Introduction

Congenital dyserythropoietic anemia – type II (CDA-II), also known as hereditary multinuclearity with positive acidified serum test (HEMPAS) (7) belongs with thalassemia syndromes, and sideroblastic anemia to the iron – loading anemias. The term iron – loading anemias defines a group of chronic conditions in which iron overload is not the result of a primary defect of the iron regulation system, but of erythropoiesis. Phlebotomy is the first choice of treatment in iron overload. Phlebotomy should be unsuitable in chronic anemias but in milder forms it can be used with success as confirmed in our two patients with CDA-II and iron overload.

Patients and Methods

Diagnosis of CDA-II has been made in 1974, 32 years ago, in three siblings at the age of 20 (K. J.), 18 (K. Ji.) and 5 years (K. K.), respectively (6). Patient K. Ji. died at the age of 40 years as consequnce of an accident. Only the remaining two brothers are reported in this article.

The diagnostic of CDA-II was established on the basis of:

- Demonstration of erythroid hyperplasia, karyorrhexis and erythroblastic multinuclearity in the bone marrow,
- Demonstration of typical ultrastructural feature of erythroblasts and some erythrocytes showing the double membrane phenomenon,
- Positive results of the acidified serum tests with normal serum but negative with patient's own serum.

The study of red cells survival with ^{51}Cr revieled shortened survival with destruction of the red cells in the spleen.

Both siblings were splenectomized at the age of 23 (K. J.) and 15 years (K. K.), respectively, with the intention to diminish the accumulation of iron due to the hemolysis in addition to the ineffective erythropoiesis. Iron overload is a constant complication of CDA-II (9). The liver biopsy performed during operation revieled siderosis of the liver in both patients (6). Splenectomy resulted in moderate increase in hemoglobin, prolongation or nearly normalization of red cell survival (5) but did not prevent further iron loading. In March 2003 serum ferritin reached in K. J. 1450,4 μg/L and in K. K. 1131,7 μg/L, respectively (normal value 30–350 μg/L). Liver biopsy revieled excessive iron overload in both patients (Fig. 1) with liver iron concentration of 14843 μg/g, and 15415 μg/g dry weight respectively. Liver biopsy showed heavy accumulation of iron in hepatocytes and reticuloendothelial cells. No mutations of HFE gene (C 282 Y and H 63 D) were found (3). The blood films reported at that time have shown excess of Pappenheimer bodies (4). Regular phlebotomies were started in March 2003 with withdrawal of 400 ml blood every month.

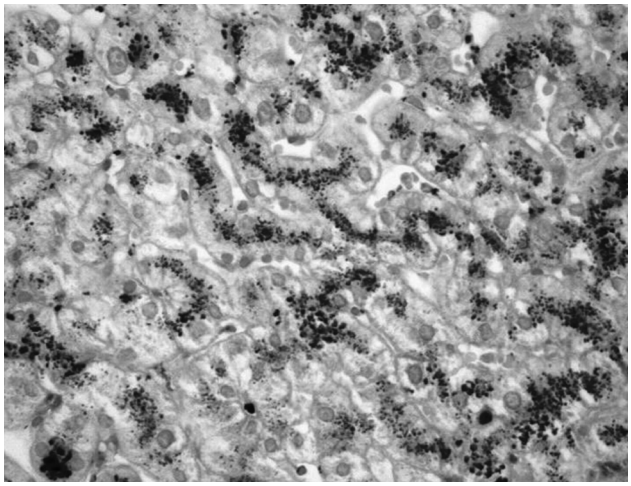

Fig. 1: Deposits of hemosiderin in the liver tissue in patient K. J. (Perls stain)

Results

During three years 12200 ml of blood were removed. The serum ferritin decreased from 1450,4 μg/L and 1131,7 μg/L to 447 μg/L and 457 μg/L, respectively. The transferrin saturation dropped from 0,99 at the start of the therapy to 0,64 and 0,86, respectively (Tab. 2). The values of Hb, Hct, erythrocyte count, and MCV did not change as well as did not change reticulocyte counts, reticulocyte index, and RDW (Tab. 1). The indirect serum bilirubin decreased from 52,8 μmol/L and 52,3 μmol/L to 29 μmol/L, and 45 μmol/L, respectively. The siderocyte counts remained high. The serum erythropoetin level did not change and the serum haptoglobin levels were within normal limits (Tab. 2).

Discussion

Congenital dyserythropoietic anemia (CDA-II) is characterized by ineffective erythropoiesis with typical nuclear abnormalities and progressive iron overload (9). The mechanism of iron loading in CDA-II is increased gastrointestinal absorption. The cause of the sharp increase is not fully understood and is mainly due to the destruction of the erythroid precursors within bone marrow (14). Secondary iron load from transfusions is not crucial. Only some patients require transfusion during the firth months of life. In children and adults, the anemia in CDA-II is usually mild to moderate and transfusion is required only occasionally with infections (14).

The main problem encountered by patients with CDA-II is iron – over loading, which is also seen in patients without ongoing need of transfusions (9). Iron accumulates steadily throughout life. There is distinct variability among individuals, which is not explained by HEF gene polymorphism (12) as it was also the case in our two patients. Even in patients with light or moderate anemia ferritin levels should be controlled at least once a year, because iron overload may reach risk levels at any age. Sigs and symptoms such as weakness, fatigue, loss of libido, and arthralgia may be late. If iron burden is not treated, clinical feature may become manifest with overt heart disease, diabetes, hypothyreoidism, hypoparathyroidism, hypogonadism and cirrhosis (11). These manifestations were not present in our patients.

Serum ferritin level is mostly used as serum marker in assessing iron overload. But its sifnificance for evaluation of iron stores is limited. Serum ferritin is reliable at low and normal levels, but many factors independent from iron stores such as infection, inflammation, hepatitis and vitamin C deficiency may alter the serum ferritin concentration.

The liver contains most of the body's iron stores corresponding to 70–80%. The liver biopsy and assessment of the histology may provide a semiquantitutive evaluation of iron burden, its distribution and reveal the histological changes due to the iron damage such as fibrosis or cirrhosis. Liver iron concentration (LIC) is the reference parameter to quantify iron stores, as many studies have confirmed a close relationship between total body stores and LIC. In thalassemia LIC has a prognostic value, with concentrations above a threshold of 15 mg/g dry weight being associated with increased risk of cardiac disease and early death (1). But liver biopsy is an invasive method not without complications inconvenient for the patient, and for these reasons it cannot be repeatedly performed. Noninvasive techniques of liver iron determination such as magnetic resonance imaging are required.

Desferrioxamine mesylate has been used in the treatment of iron overload. However the very demanding mature of this treatment by continuous subcutaneous infusion via battery – operated portable pumps has been motivation for attempts to develop alternative form of application that would facilitate the patient's compliance. Twice daily subcutaneous bolus injections represent a new method of administering desferrioxamine mesylate. New era started with the development of the oral iron chelator deferiprone. Incidence of agranulocytosis and milder neutropenia, increase in ALT levels, gastrointestinal symptoms and arthralgia were reported as side effects of treatment. Overall adverse drug reactions required permanent discontinuation of treatment in 79% of patients (14).

Phlebotomy is the first choice treatment of iron overload. Phlebotomy should be unsuitable in chronic anemias but it seems that in milder forms it can be used with success. In thalassemia a serum ferritin threshold level of 1000 μg/L is often taken to indicate to start chelation. In CDA levels of 1500 and 1000 μg/L have been proposed to start chelation (9,13). Interesting is the observation of Hofmann at al (10) who reported successful treatment of iron overload by phlebotomies in a patient with CDA-type II and hemoglobin of 70 g/L. He removed 100 up 400 ml of blood every 4 weeks during a 6 months period. The serum ferritin decreased from 1400 μg/L to 350 μg/L. Surprisingly the he-

Tab. 1: Values of blood picture before and after removal of 12200 ml of blood (2003/3–2006/3).

Patient	Hb (g/L)		Hct		Ery x 10^9/L		MCV (fl)		Rtc		RI		RDW	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
K. J.	121	123	0,36	0,37	3,56	3,67	101	99	0,014	0,012	1,21	1,05	20,7	19,3
K. K.	136	135	0,39	0,39	3,97	3,98	99	98	0,018	0,017	1,6	1,6	17,3	18,1

RI – reticulocyte index; RDW – red cell distribution width

Tab. 2: Ferritin, Transferrin saturation, Billirubin and EPO before and after removal of 12200 ml of blood (2003/3–2006/3).

Patient	Ferritin (μg/L)		Transferrin saturation		Billirubin (μmol/L)		EPO (U/L)		Siderocytes	Haptoglobin (g/L)
	Before	After	Before	After	Before	After	Before	After	After	After
K. J.	1450,4	447	0,99	0,64	52,8	29	33,4	23	311/1000	0,31
K. K.	1131,7	457	0,99	0,86	52,3	45	17,5	21	267/1000	0,60

EPO – erythropoietin (normal value: 3,3 16,6 U/L); Haptoglobin (normal value: 0,30–2,00 g/L)

moglobin level increased to 90–100 g/L. Because in our two patients the hemoglobin levels were only slightly below the lower level of normal values we have decided to use phlebotomies to decrease the iron burden, too. This approach appeared to be successful. Both patients tolerated phlebotomies without difficulties. The hemoglobin did not change. The decrease of bilirubine and normal values of haptoglobin might be the consequence of diminished destruction of erythrocytes and their precursors and possibly of the diminished toxic effect of iron overload on hematopoiesis. Our intention is to keep the serum ferritin levels below 500 μg/L.

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