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PROFILE OF BONE MARROW IRON STORES IN CHILDHOOD IRON DEFICIENCY ANEMIA*

*Mualla Çetin MD**, Ali Gönül MD***, Ateş Kara MD****
*Ş. Pınar Kara MD***, Sevgi Yetgin MD*****

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To demonstrate the importance of bone marrow iron stores, we examined the complete hemogram, serum iron (SI), serum iron-binding capacity (SIBC), transferrin saturation (TS), serum ferritin and bone-marrow-stored iron in 31 children with iron deficiency (ID). The ages of the patients ranged from one to 14 years (mean 3.7 ± 3.9). Laboratory findings of the 31 patients were as follows: hemoglobin (Hb) 8.5 ± 2.4 g/dl, hematocrit (Hct) 27.8 ± 6.3 percent, mean corpuscular volume (MCV) 58.6 ± 8.6 fl, red blood cell count (RBC) 4 ± 0.8 10^{12}/L, red cell distribution width (RDW) 19.3 ± 4.9, SI 17.2 ± 9.3 µg/dl, SIBC 311 ± 50.5 µg/dl, TS 5.5 ± 2.8 percent and ferritin 6.7 ± 7.3 ng/dl. In the bone marrow smears with iron stains, all patients' scores were zero for iron stores, which shows that bone-marrow-stored iron in childhood is easily affected. Because of the traumatic effect of bone marrow aspiration, it is recommended that it not be done routinely. The diagnosis of ID could be especially difficult in patients with low SI levels but normal SIBC levels and in patients with chronic inflammatory diseases. In those conditions, illustration of bone marrow stores could be of particular assistance for diagnosis of iron deficiency. *Key words: iron deficiency anemia, bone-marrow-stored iron, children.*

Iron deficiency anemia (IDA) is still a common problem in childhood in both underdeveloped and developed countries. The most common etiologies are inadequate intake even in developed countries because of fast-food diets, rapid growth, abnormal iron absorption and blood loss[1]. In the early stage of iron deficiency (ID), despite a decrease of iron stores in the liver, spleen and bone marrow (BM), including ferritin levels, hemoglobin (Hb) levels could be within normal limits. Therefore, measurements of serum ferritin concentration, a so-called acute phase protein, is often recommended as a useful estimate of iron status[2] or of a decreased red blood cell catalase level[3]. The amount of stainable iron in the marrow is also used to assess iron stores in the accessory system[4,5].

In this study, to demonstrate the importance of bone marrow iron stores, we analyzed the complete hemogram, serum iron (SI), serum iron-binding capacity (SIBC), transferrin saturation (TS), serum ferritin and bone-marrow-stored iron in 31 children with iron deficiency.

* From the Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Associate Professor of Pediatric Hematology, Hacettepe University Faculty of Medicine.

*** Intern in Pediatric Hematology, Hacettepe University Faculty of Medicine.

**** Professor of Pediatrics and Pediatric Hematologist, Hacettepe University Faculty of Medicine.

Material and Methods

This study included 36 subjects, aged between one and 14 years (mean age of 3.7 ± 3.9 years). Thirty-one of the patients were diagnosed as ID (25 patients with and 6 patients without anemia) and five control cases with acute idiopathic thrombocytopenic purpura (ITP) with normal hemoglobin values, all seen at Hacettepe University, İhsan Doğramacı Children's Hospital, Hematology Unit between April 1993 and May 1994. Ten patients (31%) were girls and 21 were boys (69%). Patients with suspected or documented infections were excluded from the study since iron metabolism changes can accompany acute viral infections[6].

The medical histories of all patients were reviewed in detail. Diagnosis of IDA was based on a Hb level and a mean corpuscular volume (MCV) lower than their age-matched controls; SI[7], SIBC[8] and TS less than 10 percent[9]; and a serum ferritin (Ferritin Kit, Amersham) level below 12 µg/L[1]. Coulter-Counter S was used for analysis of Hb, hematocrit (Hct), MCV, and red cell distribution with (RDW) measurements. Peripheral smears were stained with Wright's stain. Iron stores in BM of 31 ID patients and five control subjects were evaluated by examination of Prussian blue stained bone marrow from posterior iliac crests, as described previously[10].

Fifteen (60%) of 25 patients with anemia were seen for complaints other than anemia. In seven (23%) patients, pica was present according to their medical histories. Eighteen (60%) of the 31 patients had insufficient dietary intake history. Twenty-five (83%) patients were less than three years of age; 14 (56%) of those were consuming large amounts (more than 0.75 litre/day) of cow's milk in their diet.

Two patients (6%) were found below the third percentile for weight, and six patients (19%) were below the third percentile for height on physical examination. The other 23 (75%) were within normal limits for weight and height.

The etiological investigations in four patients between seven and 14 years of age indicated chronic ITP, gastrointestinal bleeding due to a gastric ulcer, a history of pica and a parasite (Giardia) (one case of each).

Correlation coefficient studies and Student's t test were used in the statistical analysis.

Results

The mean values of the hematological studies of the patients with ID and IDA are shown in Table I. None of those patients had any sign of infection. Bone marrow BM iron staining was absent in all patients, whereas the control group stained positive. In eight of 31 patients (26%) with low ferritin and SI levels without an elevated SIBC, favorable response to oral iron therapy was observed.

Table I: Selected Hematological Findings in Children with Iron Deficiency and Iron Deficiency Anemia

	Age (yr)	Hb (g/dl)	Hct (%)	MCV (fl)	SI (µg/dl)	SIBC (µg/dl)	TS (%)	Ferritin (ng/ml)	RBC ($x10^{12}$/L)	RDW
Patients with IDA n = 25	3.9 ± 4.2*	8.1 ± 2.2	26.8 ± 6.3	57.0 ± 7.8	17.4 ± 9.9	311 ± 50	5.6 ± 2.9	6.5 ± 7.9	4.0 ± 0.9	20.0 ± 3.8
	1-14**	2.9-10.7	9-33	48.0-70.0	10-32	207-400	2.5-10.0	0.3-11	1.7-4.7	15.0-28.7
Patients with ID n = 6	2.3 ± 0.9	11.9 ± 0.6	35.5 ± 2.1	66.0 ± 9.8	26.5 ± 13.6	345 ± 46	7.8 ± 4.1	7.2 ± 2.1	4.3 ± 0.4	18.0 ± 3.6
	1.5-4	11.4-12.7	35-38	50-76	10-45	271-389	2.7-10	4.8-12.2	3.8-5.0	13.0-28.7
p	0.2	0.0001	0.001	0.01	0.05	0.06	0.06	0.4	0.2	0.06

* Mean ± SD

** Minimum and maximum values

IDA: iron deficiency anemia, ID: iron deficiency, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, SI: serum iron, SIBC: serum iron-binding capacity, TS: transferrin, RBC: red blood cells, RDW: red cell distribution width.

A positive correlation was shown between Hb and SI (r = 0.55), Hb and TS (r = 0.53), Hb and ferritin (r = 0.58), SI and ferritin (r = 0.54), ferritin and TS (r = 0.59) and ferritin and RBC count (r = 0.53), while a negative correlation was demonstrated between Hb and RDW (r = -0.5), and RDW and MCV (r = -0.64). There was no correlation between ferritin and MCV or RDW or between Hb and MCV.

Discussion

Most patients (69%) with IDA in this study were initially seen for complaints, other than pallor, requiring medical attention. In healthy infants and children the most common cause of ID is insufficient dietary intake, which was present in 60 percent of our patients[11]. High intake of cow's milk is often seen in the dietary history of children with ID, due to its lower iron content and chronic blood loss from the gastrointestinal tract[11,12]. Occult blood in the feces, fat malabsorption and mucosal histological changes have been described in patients with IDA[13]. However, in some patients these abnormalities are not the primary result of iron deficiency, but are instead related to intake of cow's milk[12]. By history, 56 percent of our patients under the age of three consumed a large amount (more than 0.75 litre/day) of cow's milk in their diet.

Iron deficiency anemia IDA is rare in school-aged children due to the intake of a wider variety of foods. However, gastrointestinal blood loss due to parasites and gastric ulcers is an important cause of IDA in this age group[14]. One out of four patients was positive for a parasite (Giardia) in the feces, and one had gastrointestinal bleeding due to a gastric ulcer.

Pica is a behavioral change characterized by compulsive ingestion of non-nutritive substances and is thought to be related to iron deficiency, though the true underlying mechanism is not clear[15]. The incidence of pica in ID patients was reported to be as high as 50 percent by Crosby[16]. In the present study, only 22 percent of patients had a positive history of pica.

Iron staining in the bone marrow is an indicator of the level of iron stores in the accessory system. Demonstration of a decrease of iron stores in the BM is one of the methods of diagnosing ID. In the first stage, iron deposition is deficient, but the erythrocyte morphology remains normal. Transferrin saturation TS may decrease by 25-50 percent and serum ferritin may also decrease. In the second stage, iron stores are completely depleted but the erythrocyte morphology and count still remain normal, while TS is less than 10 percent[1]. In six of the patients studied, hemoglobin levels were 11.4-12.7 g/dl, SI and SIBC were compatible with ID, and iron stores in the bone marrow were decreased, as is characteristic of the second stage. In the third stage, iron levels deficient for hemoglobin synthesis cause anemia, the erythrocyte protoporphyrin level increases,

transferrin saturation is lower than 10 percent, and the erythrocyte count decreases. Twenty-five of our cases were in this stage. It is pointed out that BM iron stores in infants and adolescents are not as valuable as in adults[1], because of the borderline level of iron storage. In adults with IDA, BM iron stains may be trace, while in our study in children the absence shows that iron stores can decrease more steadily.

The measurement of serum ferritin facilitates the estimation of iron stores by noninvasive means in ID patients[17]. A positive correlation was found between ferritin and Hb, SI, TS and RBC in our study. Often a low SI level and SIBC may accompany chronic disease. In chronic disease, measurement of ferritin is not reliable for estimating BM ID or overload[18,19]. Furthermore, liver cell damage and some malignancies may also increase the ferritin concentration. Thus, evaluation of bone marrow iron stores in childhood may be a better method on some occasions, especially in patients who are believed to have ID but who have normal serum ferritin levels. In the present study, SIB was found to be normal in 26 percent of the patients with ID. In spite of the traumatic effect of bone marrow aspiration, bone marrow iron staining for iron may be helpful for the diagnosis of iron deficiency on some occasions, especially in patients with conflicting values of SI and SIBC and/or chronic diseases.

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