Neutrophil hypersegmentation and thrombocytosis in children with iron deficiency anemia

Serpil Düzgün, Yıldız Yıldırmak, Feyzullah Çetinkaya
Şişli Etfal Education and Research Hospital, Istanbul, Turkey

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Neutrophil hypersegmentation is an expected peripheral blood smear finding in megaloblastic anemias. But some clinical reports suggest that neutrophil hypersegmentation may also occur in patients with iron deficiency anemia. In this study we searched the presence of neutrophil hypersegmentation and thrombocytosis in patients with iron deficiency anemia but who had normal serum vitamin B_{12} and folic acid levels.

The study comprised 102 patients with iron deficiency anemia and 21 age-matched healthy controls. All routine tests for iron deficiency anemia were done, serum folate and cobalamin levels were measured, and platelets were counted in all patients and controls. Peripheral blood smears were examined for neutrophil hypersegmentation. Hypersegmentation was found in 30.4% of anemic patients and in 9.5% of controls ($p<0.05$). The number of platelets was also significantly higher in anemic children ($p<0.05$).

These results show that neutrophil hypersegmentation may also be seen in patients with iron deficiency anemia, and thrombocytosis is a common laboratory finding in this disorder.

Key words: neutrophil, hypersegmentation, thrombocytosis, anemia, iron deficiency.

Iron deficiency is the most common cause of anemia in children and is characterized by low levels of hemoglobin and hematocrit according to age and sex standards[1,2]. In addition, some red blood cell indexes, such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), are under the standards for age, but as a sign of poikilocytosis, red cell distribution width (RDW) is over the normal values[3]. Neutrophil hypersegmentation commonly occurs in folic acid and cobalamin deficiencies, and is described as presence of 5% or more neutrophils with five lobes or one or more six-lobed neutrophils[4]. Although hypersegmentation is a characteristic feature of folate and vitamin B12 deficiencies, it has rarely been reported in patients with iron deficiency anemia[5,6]. Thrombocytosis is also a rare finding of iron deficiency anemia[1,7]. In this study, frequency of neutrophil hypersegmentation and thrombocytosis was researched in patients with iron deficiency anemia without any vitamin B_{12} or folic acid abnormalities.

Material and Methods

The study comprised 102 anemic children admitted to Şişli Etfal Education and Research Hospital pediatric outpatient clinic between October 2001 and October 2002. Twenty-one children who constituted the control group were admitted for a suspected anemia but had normal hemoglobin values without any concomitant diseases. Iron deficiency anemia was diagnosed with complete blood counting, red blood cell indexes, serum iron and iron binding capacity, transferrin saturation and serum ferritin levels. In anemic children, hemoglobin levels were under 2 SD of age standards, serum ferritin levels were under 10 ng/ml, transferrin saturation was under 16%,

serum B_{12} level was 100 pg/ml or more, and folic acid levels were 5 ng/ml or more. Those children who had any systemic or infectious diseases including bleeding from gastrointestinal tract or who were using any drug were excluded from the study. Therefore, iron deficiency in all children was accepted secondary to malnutrition. Peripheral blood films were made in all children and 100 neutrophils were counted. Neutrophil hypersegmentation was described as existence of five or more segments in at least 5% of the neutrophils, or one neutrophil with at least six segments[4].

The statistical analyses of the parameters were done with SPSS for Windows 10.0. The numbers of platelets were compared with Kruskal-Wallis test. Chi-square test was used for comparisons of hypersegmentation and thrombocytosis. For all statistical analyses, a value of $p<0.05$ was accepted as statistically significant.

Results

The ages of all children ranged between 4 months and 168 months, and male to female ratio was 1.76. There was only one patient four months old; the rest were older than six months. The four-month-old infant was not premature but severely malnourished. No statistically significant differences were found between the ages and sexes of study and control groups ($p>0.05$). The mean hemoglobin, hematocrit (Hct), MCV, MCH, and MCHC levels of the study group were found significantly low compared to the control group ($p<0.01$) (Table I). The RDW and total iron binding capacity (TIBC) and the number of the platelets of the study group were significantly higher than in the control group ($p<0.01$). There were no statistically significant differences between the white blood cells and neutrophil numbers of the study and control groups ($p>0.05$). Similarly, vitamin B_{12} and folic acid levels were comparable in both group Table I).

Hypersegmentation was reported in the iron deficiency anemia group much more than in the control group (30.4% vs. 9.5%, $p<0.05$). The number of platelets was significantly higher in anemic children than in controls ($440.04 \pm 168.36 \times 10^9$/L vs. $350.29 \pm 130.04 \times 10^9$/L). When hypersegmentation and thrombocytosis were analyzed according to age groups, hypersegmentation was more common in children older than 61 months and less common between 6-12 months, but the differences were not statistically significant ($p>0.05$) (Table II). Contrary to hypersegmentation, thrombocytosis was more common between 6-12 months and less common over 61 months, but the differences were also insignificant ($p>0.05$).

Table I. Some Important Laboratory Tests of the Patients with Anemia and Controls

	Iron deficient patients	Controls	P
Hemoglobin (g/dl)	8.73 ± 2.16	12.01 ± 1.16	0.001
HCT (%)	27.53 ± 5.84	36.27 ± 3.10	0.001
MCV (fl)	62.60 ± 7.87	78.49 ± 5.72	0.001
MCH (pg)	19.95 ± 3.47	26.12 ± 2.44	0.001
MCHC (g/dl)	31.20 ± 2.87	33.21 ± 1.64	0.006
RDW (%)	18.84 ± 4.68	13.81 ± 1.71	0.001
Platelet ($x10^9$/L)	440.04 ± 168.36	350.29 ± 130.04	0.023
Leukocyte (x 10^9/L)	11.39 ± 5.55	9.53 ± 4.98	0.157
Neutrophil (x 10^9/L)	5.39 ± 3.88	3.98 ± 2.16	0.162
Iron (μg/dl)	21.49 ± 13.48	65.00 ± 27.75	0.001
TIBC (μg/dl)	466.95 ± 92.43	327.86 ± 53.79	0.001
Ferritin (μg/ml)	9.80 ± 11.75	37.36 ± 16.92	0.001
Transferrin saturation	4.52 ± 3.48	19.52 ± 7.26	0.001
Vit B12 (pg/ml)	475.94 ± 296.34		
Folic acid (ng/ml)	12.31 ± 4.68		

HCT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red blood cell distribution width, TIBC: total iron binding capacity.

Table II. Hypersegmentation and Thrombocytosis According to Age Groups

		Age groups (Months)				
		6-12	13-24	25-60	>61	P
Hypersegmentation	Yes	4 (20.0%)	14 (30.4%)	6 (35.3%)	7 (36.8%)	0.662
	No	16 (80.0%)	32 (69.6%)	11(64.7%)	12 (63.2%)	
Thrombocytosis	Yes	10 (50.0%)	20 (43.5%)	7 (41.2%)	3 (15.8%)	0.126
	No	10 (50.0%)	26 (56.5%)	10 (58.8%)	16 (84.2%)	

Discussion

Neutrophil hypersegmentation is an expected finding in anemias due to folic acid and vitamin B_{12} deficiencies. But a pioneer study by Chanarin[8] showed that hypersegmentation might also be seen in iron deficiency anemia, and this observation was confirmed by others[9,10]. In most of the reported cases, iron deficiency was secondary to gastritis, peptic ulcer, carcinoma and polyposis of the colon. Westerman[6] reported that hypersegmention had been found in 62% of anemic adults in comparsion to 4% of controls. A higher proportion of hypersegmention (81%) in anemic children than in non-anemic controls (9%) was reported by Sipahi et al.[10]. Similar observations were seen in our study, in which we found significantly higher neutrophil hypersegmentation in anemic children than in controls (30.4% vs. 9.5%) with normal folic acid and vitamin B_{12} levels.

The mechanism of neutrophil hypersegmentation in iron deficiency anemia is not well understood[7]. It is not definitely known whether or not iron affects the neutrophil DNA synthesis. Iron may be an important cofactor for folate metabolism and/or granulocyte DNA synthesis[8]. Severe deficieny of iron might also impair usage of folate or vitamin B_{12} at the cellular level[11]. Omer et al.[12] reported an increase of intra-erythrocyte folate levels in anemic patients following iron supplementation. In our patients, serum folate and vitamin B_{12} levels were normal. But, unfortunately we could not measure intra-erythrocyte folate levels.

Thrombocytosis seen in iron deficiency anemia is an example of reactive thrombocytosis[7,13], but the mechanism underlying the thrombocytosis is not clear yet. It is well known that thrombocytosis is regulated and stimulated by many cytokines such as interleukin (IL)-3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin[13]. Erythropoietin is the unique cytokine, plasma levels of which increase during iron deficiency and decline following treatment with iron. Moderate thrombocytosis was found in our patients, but erythropoietin levels could not be measured.

In conclusion, neutrophil hypersegmentation and thrombocytosis are expected findings in megaloblastic anemias, but may also rarely be seen in iron deficiency anemia. Because of this, in cases in whom iron deficiency anemia together with neutrophil hypersegmentation is observed, B_{12} and folic acid levels must be absolutely considered. But when these are normal, neutrophil hypersegmentation must be accepted as a finding of iron deficiency anemia.

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