Platelets abnormalities in children with iron deficiency anemia

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Introduction
Iron deficiency is the most common nutritional deficiency in the world, responsible for ill health, lost productivity, and premature death. Iron deficiency may lead to reactive thrombocytosis and rarely thrombocytopenia.

Participants and methods
This study included 115 children with iron-deficiency anemia attending Assiut University Children Hospital, Hematology Unit, from the June 1, 2017, to the June 1, 2018. Their age ranges from 2 to 5 years. Moreover, 55 apparently healthy children with the same age group were included as a control group. All patients and controls were subjected to meticulous history taking, thorough clinical examination, hematological study, as well as stool and urine examination.

Results
The mean platelet count in our patients was significantly higher than in controls. Thrombocytopenia was noticed in one patient. Results were discussed in the light of available literatures.

Conclusion
Reactive thrombocytosis is the most frequent platelet abnormality associated with iron-deficiency anemia. The mean platelet volume, plateletcrit, platelet large cell count, and platelet large cell ratio estimate indirectly platelet activity.

Keywords:
iron, platelet volume, thrombocytopenia, thrombocytosis

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Introduction

Iron is an essential mineral for survival of most living organisms and a component or co-factor of hundreds of proteins and enzymes [1]. There are two oxidative forms: ferrous (Fe+2) and ferric (Fe+3) iron. Iron is able to accept and donate electrons, being useful in the catalytic center of fundamental biochemical reactions [2]. In mammals, many reactions are performed by iron-containing proteins, iron-sulfur enzymes, hemeproteins, and iron-containing enzymes (non-heme and non-iron-sulfur enzymes). The activity of most of these enzymes decreases in tissue iron deficiency [3]. Hemeproteins are involved in a variety of crucial biological processes, such as reversible binding of oxygen to hemoglobin and myoglobin, which are responsible for oxygen transport and storage, respectively; transport of electrons in oxidative phosphorylation process through cytochromes; and oxygen metabolism through the enzymes oxidase, peroxidases, catalase, and hydrolase [4]. Moreover, iron is a component of iron-sulfur and oxygenase non-hemeproteins, involved in a ribonucleotide reductase enzyme system required to convert ribose into deoxyribose of nucleic acid, and, consequently, to produce DNA. So iron deficiency in cells delays growth and leads to cell death [3,5].

Iron deficiency is the most common nutritional deficiency in the world, responsible for a staggering amount of ill health, lost productivity, and premature death [6]. Iron deficiency (without anemia) develops as these iron stores are depleted, whereas iron-deficiency anemia results when the iron supply is insufficient to maintain normal levels of hemoglobin [6,7].

In Egypt, iron-deficiency anemia was identified more among mothers (25.1%), followed by adolescents (17.9%) than other groups (13.6 and 15.1% schoolchildren and preschool children, respectively) [8].

Iron deficiency is well known to cause reactive thrombocytosis. However, iron deficiency may also lead to thrombocytopenia. This has been described in both children and adults [9,10].

The amino acid sequence homology of thrombopoietin and erythropoietin (EPO) may explain the phenomenon of thrombocytosis in children with iron-deficiency anemia [11].

Thrombocytopenia is reported in some children with severe iron-deficiency anemia, but the mechanism is not well established [12]. There was abundant evidence that megakaryocytic and erythroid cell lineages share a common progenitor cell. According to the hypothesis of stem cell competition, chronic EPO stimulation can lead to increased red cell production at the expense of platelet production, which had been advanced in animal models [13]. The available clinical data did not support this hypothesis in human cases [14]. Data have suggested that iron has a synthetic and regulator role in thrombopoiesis [12,15].

There is an apparent dependence of platelet reactivity on hemoglobin or iron status. This is confirmed by a significant correlation coefficient between hemoglobin or the transport iron parameters, serum iron and transferrin, on the one hand, and parameters of platelet aggregation on the other hand [16,17].

In cases of iron-deficiency anemia, bone marrow produces more platelets with decreased platelet volume, so platelet reactivity decreases in cases of iron-deficiency anemia, and platelet volume can reflect platelet activity [18,19].

Participants and methods

Our study included 115 children with iron-deficiency anemia attending Assiut University Children Hospital, Hematology unit, during the period from June 1, 2017, to June 1, 2018. In addition, 55 apparently healthy children were included as a control group.

A written parental consent was obtained for each included patient. Parents agreed after explaining the nature of the study and the benefit from it. Approval of the ethics committee of Assiut University, Faculty of medicine, was obtained with registration number, IRB no: 17101134.

Inclusion criteria

The following were the inclusion criteria:

(1) Patients diagnosed as having iron-deficiency anemia according to WHO clinical practice guidelines for iron-deficiency anemia in children.
(2) Children ages 2–5 years.

Exclusion criteria

The following were the inclusion criteria:

(1) Children received blood transfusion.
(2) Children with hemolytic anemia.
(3) Children with viral infection, for example, hepatitis C virus, hepatitis B virus, and hepatitis A virus.
(4) Children receiving bone marrow-suppressant drugs.
(5) Children with autoimmune disease.

All included patients and controls were subjected to meticulous history taking, thorough clinical examination, and complete blood count [done on CELL-DYN 3700 (Abbott, Deutschland, Germany) and Horiba Yumizen H500 CT Hematolgy Analyzer (Horiba, Kisshoin Minami-Ku Kyoto, Japan). Blood film was stained by Leishman staining, and reticulocytic count was done by Brilliant Cresyl Blue stain (Dacie and Lewis, 2012]. Serum ferritin, serum iron, total iron-binding capacity (TIBC), and C-reactive protein (CRP) were performed for all subjects on Modular P autoanalyzer (Roche Diagnostics, Mannheim, Germany). Microscopic examination was done for stool analysis of 3 successive days and morning urine analysis.

Statistical analysis

The data were tested for normality using the Anderson-Darling test. Categorical variables were described by mean and SD. Comparison between continuous variables was done by independent sample *t*-test. A two-tailed *P* less than 0.05 was considered statistically significant. All analyses were performed with the IBM SPSS 20.0 software (SPSS, Tribune, Chicago, USA).

Results

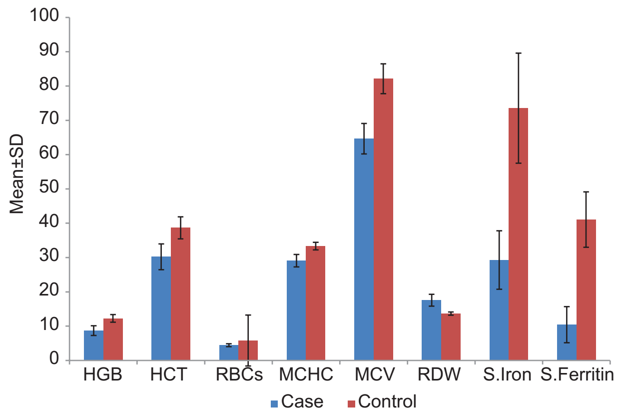
Our study included 115 patients with iron-deficiency anemia. Their ages ranged from 2 to 5 years (2.5 ± 0.7). A total of 82 (71.3%) patients are males and 33 (28.7%) of them are females. The study included also 55 apparently healthy age-matched children with the studied patients as a control group. They were 35 (63.6%) males and 20 (36.3%) females.

By looking at the complete blood picture of studied patients, we found that 27.8% (N = 32) of our patients had normal platelet count, and 69.5% (N = 80) of our patients had thrombocytosis. Only three cases had thrombocytopenia. One of them was critically ill and experienced septic shock. The second one was diagnosed as Wiskott-Aldrich syndrome and the third one had thrombocytopenia associated only with iron-deficiency anemia (Figs. 1–4).

Discussion

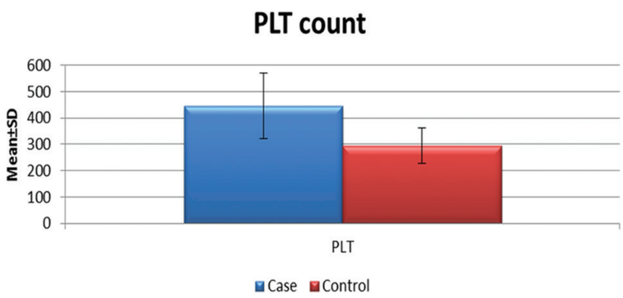
The most common symptoms in our patients were anorexia, lack of attention span, irritability, decreased gaining weight, easy fatigability, pica, recurrent

Figure 1



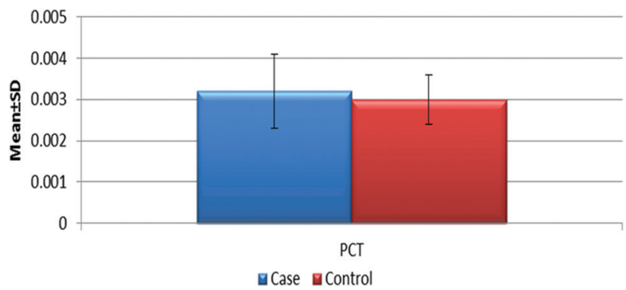
Studied hematological parameters in patients (cases) and in controls.

Figure 2



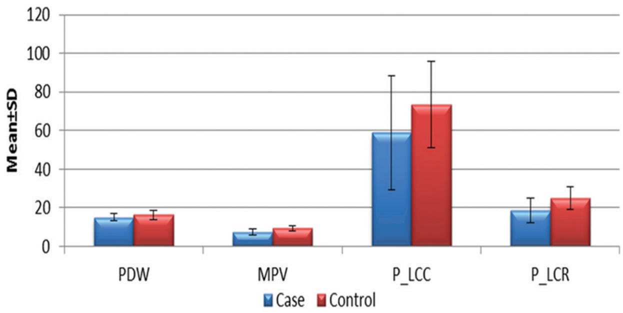
Platelet count in cases and in controls.

Figure 3



Plateletcrit (PCT) in cases and in controls.

Figure 4



Platelet distribution width (PDW), mean platelet volume (MPV), platelet large cell count (P-LCC), and platelet large cell ratio (P-LCR), in cases and in controls.

infections, and decreased school performance (Table 1). A previous study reported lack of attention span in 20%, irritability in 18%, easy fatigability in 15%, anorexia in 9%, pica in 7%, dizziness in 4%, and headache in 35 of their studied patients with iron-deficiency anemia [19]. Another study reported easy fatigability in 78.37%, breathlessness on exertion in 83.78%, palpitations in 45.94%, headache in 16.21%, cough in 8.10%, and reduced appetite in 50% of their studied patients with iron-deficiency anemia [20,21].

Pica (geophagia) was noticed in 3.8% of such patients [22]. Moreover, pica was found in 7.2% of another study on patients with iron-deficiency anemia [23].

Previously reported iron-deficiency anemia in patients with recurrent chest infection was noticed in 64.8% of their studied patients [24]. Others reported that history of recurrent diarrhea in patients with iron-deficiency anemia were 1.71 times more than in controls. Moreover, they noticed that history of recurrent respiratory tract infections was commoner than in controls (1.48 times). This may be owing to the importance of iron for epithelium and mucosal integrity [25].

Table 1 Symptoms of studied patient with iron-deficiency anemia

Symptoms	Number of patients=115 [*n* (%)]
Anorexia	101 (87.8)
Lack of attention span	43 (37.4)
Irritability	42 (36.5)
Decreased gaining weight	34 (29.5)
Easy fatigability	31 (26.9)
Pica	11 (9.5)
Recurrent infections	9 (7.8)
Decreased school performance	1 (0.8)

Table 2 Mean±SD of anthropometric measures in studied patients and of controls

Measures	Mean±SD		*P*
	Cases (*n*=115)	Control (*n*=55)	
Weight	15.47±4.5	16.6±3.4	0.089
Height	86.51±16.4	104.21±9.8	<0.001**
BMI	18.56±10.28	19.7±10.84	0.507
HC	47.01±3.16	48.44±2.28	0.003**

HC, head circumference.

The mean height and head circumference of our patients were significantly lower than that of controls (Table 2). A previous study agreed with our results [26]. Protein energy malnutrition (PEM) was higher in our patients (62.6%) than in controls (14.5%) (Table 3). Our finding agreed with a previous study [27]. We

Table 3 Signs in studied patient and in controls

Signs	Studied patients (*n*=115) [*n* (%)]	Controls (*n*=55) [*n* (%)]	*P*
Malnutrition	72 (62.6)	8 (14.5)	<0.001**
Signs of vitamins deficiency	15 (13)	0	-
Angular stomatitis	8 (6.9)	0	-
Glossitis	7 (6)	0	-
Nail changes	18 (15.7)	0	-
Nail striations	12 (10)	0	-
Spooning of the nail (Koilonychias)	5 (4.3)	0	-
Brittle nails	1 (0.8)	0	-

may suggest growth retardation may be owing to malnutrition of low socioeconomic etiology in our patients with iron-deficiency anemia.

Angular stomatitis and glossitis were noticed in our patients (6.9 and 6%, respectively) (Table 3). However, higher values were previously reported [28]. In our study, nail changes were observed in 15.7% of our patients (Table 3). However, higher values of nail changes have been previously reported [29].

Parasitic infestations were found in our patients with iron-deficiency anemia (Table 4). However, different values were reported in studies in different areas [30–33].

The mean platelet count (PLT) in our patients was significantly higher than that of in controls (Table 5). Our finding agreed with previous studies [34–36]. Such finding of reactive thrombocytosis was explained by amino acid sequence homology of thrombopoietin and EPO. As EPO production increase in iron deficiency anemia, it causes thrombocytosis [11].

A significant low platelet count was noticed in patients with severe iron-deficiency anemia than in controls. It was stated that thrombocytopenia in combination with iron-deficiency anemia is not common, and the mechanism of such finding is not known, although theories exist about stem cell competition. They added that chronic EPO stimulation can lead to red cell production at the expense of platelet production [13,37,38].

In our patients, although the mean plateletcrit (PCT) was significantly higher than in controls, the mean platelet volume (MPV) and the mean PDW were significantly lower (Table 5). Similar findings have been previously reported [19,34,39]. Some authors explained in patients with iron-deficiency anemia, bone marrow produces more platelets, but with volume less than the volume of the platelets under normal circumstances. Therefore, MPV and PDW decrease among cases of iron-deficiency anemia. They added that larger platelets are usually relatively young and contain intracellular granules; therefore, they are more reactive

Table 4 Parasitic infestations in studied patients and in controls

Parasites	Studied patients (*n*=115) [*n* (%)]	Controls (*n*=55) [*n* (%)]
Enterobius vermicularis	7 (6.1)	2 (3.6)
Ancylostoma	6 (5.2)	0
Entamoeba histolytica	4 (3.4)	3 (5.4)
Giardia lamblia	4 (3.4)	2 (3.6)
Fasciola hepatica	1 (0.8)	0
Total	22 (19)	7 (12.7)

and vice versa. Thus, in cases of iron-deficiency anemia, the reactivity of platelets decreases as platelet volume decreases [19]. Others added that such findings can be used as indirect method to assess platelet function [40].

Platelet large cell count (P-LCC) and platelet large cell ratio (P-LCR) in our patients with iron-deficiency anemia were significantly lower than that in controls (Table 5). Previous reports agreed with our findings [18,19]. They accepted that platelet size reflects platelet activity; therefore, P-LCC and P-LCR are a simple and easy method of indirect assessment of platelet stimulation and activity [18,19].

Although significant negative correlations were noticed between platelets count and each of MPV, P-LCR, Hemoglobin (HGB), Hematocrit (HCT), Mean corpuscular hemoglobin concentration (MCHC), MCV, serum iron, and serum ferritin, significant positive correlations were noticed with each of PCT, Randomized distribution width (RDW), Total iron binding capacity (TIBC), and CRP (Table 6). Previous studies reported similar findings [11,18,19,36,41–45]. However, others reported a positive correlation with serum ferritin [39].

Regarding PDW, it showed a significant negative with each of PCT, RDW, and TIBC [36,41,46]. However, insignificant negative correlation was reported with serum ferritin [39]. A significant positive correlation with each of P-LCC, P-LCR, HCT, MCHC, MCV, and of serum ferritin. Such findings agreed with previous reports [19,42,44,46–48]. However, an insignificant negative correlation was reported with serum ferritin [39]. To the best of our knowledge, there are no available previous studies with P-LCC.

Table 5 The mean±SD of studied hematological parameters in studied patients and in controls

	Mean±SD		*P*
	Studied patients (*n*=115)	Controls (*n*=55)	
HGB (g/dl)	8.67±1.42	12.27±1.11	<0.001**
HCT (%)	30.2±3.76	38.65±3.22	<0.001**
RBCs (million/ml)	3.7±0.20	4.52±0.36	0.001**
MCHC (g/dl)	29.08±1.8	33.34±1.1	<0.001**
MCV (fl)	64.64±4.45	82.12±4.36	<0.001**
RDW (%)	17.56±1.73	13.65±0.46	<0.001**
Retics (%)	0.96±0.48	0.94±0.35	0.758
PLT count (10^9/l)	446.99±124.16	293.67±67.29	<0.001**
PDW (%)	15.1±1.82	16.27±2.28	0.003**
MPV (fl)	7.42±1.59	9.32±1.15	<0.001**
PCT (L/l)	0.0032±0.0009	0.003±0.0006	0.026*
P-LCC (10^9/l)	58.96±29.71	73.52±22.19	0.040*
P-LCR (%)	18.75±6.39	25±6.04	<0.001**
Serum iron (μg/dl)	29.26±8.53	73.56±16.05	<0.001**
Serum ferritin (ng/ml)	10.41±5.26	41.06±8.08	<0.001**
TIBC (μg/dl)	497.4±33.29	314.52±47.81	<0.001**
CRP positive [*n* (%)]	18 (15.6)	0	

CRP, C-reactive protein; HGB, hemoglobin; MPV, mean platelet volume; PCT, plateletcrit; PLT, platelet; P-LCC, platelet large cell count; P-LCR, platelet large cell ratio; RBC, red blood cells; TIBC, total iron-binding capacity.

Table 6 Correlations between platelets indices and studied hematological parameters

	PLT	PDW	MPV	PCT	P_LCC	P_LCR
PLT						
r	1					
P						
PDW						
r	−0.121	1				
P	0.148					
MPV						
r	−0.279-**	0.077	1			
P	0.001	0.359				
PCT						
r	0.310*	−0.327-**	0.169	1		
P	0.011	0.007	0.176			
P_LCC						
r	0.038	0.313*	0.175	−0.018	1	
P	0.778	0.019	0.196	0.898		
P_LCR						
r	−0.373-**	0.691**	0.340**	−0.204	0.618**	1
P	0.004	0.000	0.010	0.131	0.000	
HB						
r	−0.425-**	0.090	0.473**	−0.202	−0.045	0.269*
P	0.000	0.285	0.000	0.103	0.740	0.043
HCT						
r	−0.449-**	0.173*	0.436**	−0.173	0.048	0.344**
P	0.000	0.038	0.000	0.166	0.724	0.009
RBCs						
r	−0.066	0.041	0.165*	0.108	0.179	0.177
P	0.434	0.626	0.048	0.389	0.187	0.187
MCHC						
r	−0.366-**	0.222**	0.329**	−0.311-*	0.118	0.369**
P	0.000	0.008	0.000	0.011	0.387	0.005
MCV						
r	−0.459-**	0.246**	0.541**	−0.272-*	0.298*	0.478**
P	0.000	0.003	0.000	0.027	0.026	0.000
RDW						
r	0.389**	−0.220-**	−0.309-**	0.101	−0.135	−0.375-**

Contd...

Table 6 Contd...

	PLT	PDW	MPV	PCT	P_LCC	P_LCR
P	0.000	0.008	0.000	0.419	0.321	0.004
Retic						
r	0.086	−0.076	0.062	0.094	−0.025	−0.200
P	0.306	0.367	0.460	0.455	0.855	0.137
Serum iron						
r	−0.466-**	0.147	0.505**	−0.182	0.208	0.355**
P	0.000	0.079	0.000	0.144	0.124	0.007
Serum ferritin						
r	−0.465-**	0.177*	0.548**	−0.208	0.233	0.349**
P	0.000	0.034	0.000	0.094	0.084	0.008
TIBC						
r	0.482**	−0.193-*	−0.504-**	0.201	−0.249	−0.466-**
P	0.000	0.021	0.000	0.105	0.064	0.000
CRP						
r	0.165*	−0.001	−0.106	0.393**	−0.285-*	−0.129
P	0.048	0.994	0.206	0.001	0.033	0.340

CRP, C-reactive protein; HGB, hemoglobin; MPV, mean platelet volume; PCT, plateletcrit; PLT, platelet; P-LCC, platelet large cell count; P-LCR, platelet large cell ratio; RBC, red blood cells; TIBC, total iron-binding capacity.

Regarding MPV, significant positive correlations were found with each of P-LCR, HGB, HCT, RBCs, MCHC, MCV, serum iron, and serum ferritin and a significant negative correlation with each of RDW and of TIBC (Table 6). Similar observations have been previously reported [18,19,42,44,45,48]. It was stated that MPV and P-LCR decrease in case of iron-deficiency anemia. They added that platelet size has been shown to reflect platelet activity, so platelet activity decreases [45,46]. However, an insignificant positive correlation with serum iron and an insignificant negative with serum ferritin and RDW have been previously reported [39,41,47].

Although a significant positive correlation was noticed between P-LCC and each of P-LCR and MCV, a significant negative correlation was observed between P-LCC and CRP (Table 6). For P-LCR, although a significant positive correlation with RDW and with TIBC, a significant negative correlation were observed with each of HGB, HCT, MCHC, MCV, serum iron, and serum ferritin (Table 6).

Conclusion

Reactive thrombocytosis is the most frequent platelet abnormality associated with cases of iron-deficiency anemia, although thrombocytopenia is a rare phenomenon, where its exact cause is not clear.

Platelet volume can reflect the activity of platelets, so the new platelet volume indices (MPV, PCT, P-CC, and P-LCR) can be used to indirectly estimate platelet activity.

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Conflicts of interest

There are no conflicts of interest.

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