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Relation between blood levels of iron, interleukin 6 and infection rates in children: a pilot study

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Abstract

Introduction: Iron deficiency is the most common micronutrient deficiency worldwide. Iron activates the growth and differentiation of immune cells and cytokine actions. Interleukin 6 is a pro-inflammatory cytokine that stimulates the differentiation of B lymphocytes into plasma cells and activates T lymphocytes. Our study aimed to evaluate the correlation between blood levels of iron and interleukin 6 (IL-6) and its impact on infection rates in children.

Materials and methods: The study included 36 children. The serum concentration of IL-6, iron, and morphology parameters from a venous blood sample were assessed. An anonymous survey of children's parents was conducted regarding the frequency of infections before and after the diagnosis of anemia.

Results: In the study group, the levels of IL-6 were higher than in the control group and showed greater variability between individual patients. There was a statistically significant, negative correlation between IL-6 and iron levels within the study group ($p = 0.012$), and a decrease in the number of viral diarrheas after the diagnosis of anemia compared to the state before diagnosis ($p = 0.041$). There was no statistically significant change in the number of colds or the mean duration of infection ($p = 0.144$, $p = 0.498$), nor in the incidence of other infectious diseases and antibiotics intake in the study group before and after iron deficiency anemia diagnosis ($p = 0.500$, $p = 0.219$).

Conclusions: IL-6 might play a role in iron deficiency anemia. Increased levels of IL-6 were shown not to correspond with visible changes in rates and the course of colds, but did result in a reduction in the frequency of viral diarrhea. Further research on a larger group of carefully selected patients is required to determine the effect of anemia on the immune system.

Key words: iron deficiency, anemia, interleukin 6, infections

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Introduction

Iron deficiency (ID) is the most common micronutrient deficiency worldwide. Iron deficiency anemia (IDA) is a serious public health problem that affects mental and physical development, health, and work efficiency. Despite extensive progress in understanding regarding iron metabolism, there are still uncertainties regarding the correct diagnosis and treatment of IDA [1, 2].

Diagnostic biomarkers are required to differentiate the different types of anemia and to treat them appropriately. Some of them are well established (concentrations

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of serum ferritin, serum iron, soluble transferrin receptor (sTfR), and sTfR/log ferritin index). Others, such as serum hepcidin, hold considerable promise, although they are not yet widely used [3, 4]. Iron metabolism is one of the most complex processes involving different tissues. Many pathophysiological disorders are responsible for changes in iron homeostasis. These can ultimately result in iron deficiency or iron excess, both of which have detrimental effects, not only on erythropoiesis but also on the immune system [5]. Ferritin and transferrin are proteins notably influenced by inflammation, which behave as acute-phase reactants and make it difficult to differentiate between IDA, which occurs when iron deficiency is severe enough to limit erythropoiesis, and anemia of chronic disease (ACD) occurring with malignancy or infection. For the detection and differentiation of IDA, the sTfR and the sTfR index appear to be important. Moreover, sTfR may be of greater clinical value as an added value to serum ferritin in the detection of ACD [6].

Anemia of inflammation (AI) is the second most common type of anemia. Inflammation-inducible cytokines and the major regulator of iron homeostasis, hepcidin, block intestinal iron absorption and cause iron retention in the mononuclear phagocyte system (MPS), resulting in iron-restricted erythropoiesis [7]. Due to the toxicity of iron in the human body, there is a complex, precise mechanism that controls its levels inside and outside of cells. Hepcidin is crucial in this mechanism [8]. Interleukin 6 (IL-6) is involved in the regulation of serum iron levels via the control of ferroportin 1 which is an iron transporter. IL-6 induces hepcidin production, which blocks the action of ferroportin 1 on the gut, and thus reduces serum iron levels [9]. This means that the IL-6-hepcidin axis is responsible for hypoferremia and anemia associated with chronic inflammation. These changes in acute phase protein levels and red blood cells are used for the evaluation of inflammatory severity in routine clinical laboratory examinations [10]. Labile iron and inflammatory conditions during infection can generate high levels of toxic free radicals and oxidative stress that can trigger cellular damage and cause diseases in different tissues and organs [5]. Furthermore, inflammatory cytokines shorten the lifespan of erythrocytes, impair the production and function of erythropoietin (EPO), and inhibit the proper proliferation and differentiation of erythroid progenitor cells [11].

Experimental evidence in recent decades has shown that iron is a fundamental element for the normal development of the immune system. Its deficiency affects the capacity to have an adequate immune response. The role of iron for immunity is necessary for immune cell proliferation, particularly lymphocytes, associated with the generation of a specific response to infection [12]. Iron is required for monocyte/macrophage differentiation, while macrophages require iron as a cofactor for the execution of important antimicrobial effector mechanisms. Little is known concerning the effect of clinical iron deficiency on cytokines, although it has been reported that *in vitro* production of cytokines by lymphocytes of iron deficiency patients may be impaired [2].

The aim of this pilot study was to evaluate the relationship between blood levels of iron, IL-6 and infection rates in children with IDA compared to a control group.

Material and methods

The study included 36 patients matched for age and gender (18 in the study group and 18 in the control). The study group included children with iron deficiency anemia diagnosed based on an interview, physical examination (pallor, fatigue, impaired concentration), and laboratory tests (decreased hemoglobin below 2 standard deviations for sex and age, mean corpuscular volume <80 fL, serum ferritin <30 µg/L). Patients from the study group were before or during iron therapy, and were selected from the ambulatory clinic of the Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Poland, or from hospitalized patients in the same ward. Patients outside the 1–18 age range, with coexisting autoimmune diseases, cancer, immunodeficiency, protein and energy malnutrition, acute or chronic systemic disease known to affect the immune system, and chronic infections, were excluded from the study. Children taking immunosuppressants and currently or previously treated with chemotherapy or radiotherapy were also ineligible to participate in the study.

The control group consisted of children without iron deficiency anemia who did not meet the exclusion criteria. All patients in the control group had normal hemoglobin levels for their age and sex, with normal red blood cells, serum iron, and ferritin levels and were selected only from the ambulatory clinic. At the time of sampling, individuals from the test and control groups showed no symptoms of infection.

We evaluated several different parameters: red blood cells (RBC), hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), medium cell hemoglobin concentration (MCHC), iron, transferrin, ferritin, white blood cells (WBC), and neutrophils. The serum concentration of IL-6 from a venous blood sample of each patient was assessed using the electrochemiluminescence method on Cobas apparatus (Elecsys IL-6 immunoassay, Roche Diagnostics GmbH, Mannheim, Germany). A sandwich test with the following reagents was used for the assays: streptavidin-coated microspheres, anti-IL-6~biotin antibodies, biotinylated monoclonal anti-IL-6 mouse antibodies, and anti-IL-6 antibodies labeled with a ruthenium complex. The measurement range of the apparatus was 1.5–5,000 pg/mL. The reference range of IL-6 in an external study using the Elecsys IL-6 test was 0.00–7.00 pg/mL. According to the methodology for IL-6 assays, *in vitro* tests were carried out for the 18 most commonly used drugs and 13 drugs used in special cases. No interference was found.

The coefficient of variation (CV) in periodic quality control was 2.08% and 2.62%. All blood samples for IL-6 determination from anemic patients and controls were collected during routine diagnostic tests.

The children's parents were surveyed regarding basic data, nutrition, duration of anemia, other diseases, medications (from both groups), and frequency of infections during the year before the diagnosis of IDA and during the disease (in the study group).

This study was approved by the Bioethics Committee of the Medical University of Lublin, Poland (committee's reference number: KE-0254/52/2021). Written, informed consent to participate from the patients' parents, and cumulative consent from patients above 16 years old and their parents were obtained.

Statistical analysis of the study results was performed using the IBM SPSS Statistics program. Three levels of statistical significance were adopted: $p < 0.001$, $p < 0.01$, and $p < 0.05$, in each of which the difference was defined as statistically significant. The following tests and statistical coefficients were used: Pearson's chi^2 test of independence (to determine whether there was a statistically significant relationship between nominal variables or between nominal and ordinal variables), Shapiro-Wilk test (to determine whether the analyzed variables measured at the ratio level were consistent with or deviated from the normal distribution), Spearman's rho correlation coefficient (to determine whether there were statistically significant linear correlations), Mann-Whitney U test (to determine whether the two groups differed statistically significantly in terms of variables measured at the ordinal level or in terms of variables measured at the ratio level, but whose distribution was statistically significant to deviate from normal distribution), the Wilcoxon rank test (to determine whether there was a significant difference between two measurements (in the same group) of an ordinal variable or between two measurements (in the same group) of a quotient variable whose distribution was statistically significantly different from the normal distribution statistically), and McNemar's test (to determine whether there was a statistically significant difference between two measurements (in the same group) of a nominal variable).

Analysis of the study results began with checking the normality of the distribution of variables measured at the quotient level, in order to select the appropriate tests and coefficients for the main part of the analysis. Distributions of 17 out of 25 variables in the study group and of 10 out of 16 variables in the control group significantly differed from the normal distribution. Only in the cases of RBC, MCH, and MCHC were the distributions in both groups normal, and thus only in their cases would it be acceptable to use parametric tests when comparing groups. Thus, in order to maintain full comparability of the results, a decision was made to use tests and non-parametric coefficients in the entire statistical analysis.

Results

Demographic and medical data regarding the study and control group is set out in Tables I and II.

There was no statistically significant difference between the groups in terms of the frequency of consumption of meat, milk, or dairy products ($p = 0.502$, $p = 0.485$, $p = 0.301$, respectively). Children from the study group had had anemia from one week to 8 years before the IL-6 study, and on average for just under one year (11.79 months). Half had more than and half had less than 1 year and 10 months. The standard deviation of 6.5 months shows that the study group was highly diversified in terms of the duration of anemia (time from diagnosis to the day of the IL-6 test).

There were statistically significant differences between the groups in terms of the following test results: Hb, MCV, MCH, MCHC and iron. In all these parameters, significantly higher results were recorded in the control group than in the study group (Table III). In addition, the difference in the case of ferritin was close to statistical significance ($p = 0.052$). There were much higher results in the control group. However, the test was performed on only two people from this group.

Further, the number of colds, viral diarrheas, the incidence of other serious infectious diseases and the average

Table I. Characteristics of study and control groups

Parameters	Study group N = 18	Control group N = 18	Statistics
Age range	From 1 year 4 months to 17 years	From 3 to 17 years	
Mean age [years]	10.33	Nearly 9.80	$p = 0.837$
Median age [years]	13.13	9.00	
Sex	12 females, 6 males	6 females, 12 males	**$p = 0.046$**
Mean height [cm]	138.1	138.9	$p = 0.962$
Median height [cm]	153.0	138.0	
Mean weight [kg]	37.3	39.2	$p = 0.862$
Median weight [kg]	39.0	32.0	
Mean body mass index [kg/m^2]	17.7	18.3	$p = 0.849$
Median body mass index [kg/m^2]	17.2	18.0	

Table II. Characteristics of comorbidities, medications, diet, and dietary supplements in study and control groups according to survey

Parameter	Study group N = 18	Control group N = 18	Statistics
Comorbidities	13 had none (72.2%) 2 allergy/atopic dermatitis 1 insulin resistance 1 arthrogryposis 1 kidney stones	11 had none (61.1%) 4 hemophilia 2 neutropenia 1 spherocytosis (1 hypothyroidism — not given by answerer)	$p = 0.480$
Permanent medications	12 none (66.7%) 3 iron 1 metformin and isotretinoin 1 desloratadine, dimenhydrinate and mometasone	15 none (83.3%) 1 coagulation factors 1 vitamin B6, folic acid 1 levothyroxine	$p = 0.248$
Diet	16.7% of group on a diet	11.1% of group on a diet	$p = 0.630$
Dietary supplements	Used by 50.0% of group	Used by 61.1% of group	$p = 0.502$

Table III. Comparison of groups in terms of blood test results

Blood test results	Group	Mean	Median	Number of patients	Mann-Whitney U test
Hemoglobin [g/dL]	Study	10.76	10.85	18	**$p = 0.002$**
	Control	12.83	12.35	18	
MCV [fL]	Study	73.56	71.65	18	**$p = 0.044$**
	Control	77.44	79.40	18	
MCH [pg]	Study	23.31	24.30	18	**$p = 0.001$**
	Control	27.93	27.55	18	
MCHC [g/dL]	Study	31.53	32.35	18	**$p < 0.001$**
	Control	34.28	34.30	18	
Ferritin [µg/l]	Study	19.75	16.20	15	$p = 0.052$
	Control	74.15	74.15	2	
Iron [µg/dL]	Study	50.11	27.75	14	**$p = 0.044$**
	Control	151.33	201.00	3	
IL-6 [pg/mL]	Study	4.47	3.74	18	$p = 0.133$
	Control	2.75	2.28	18	

MCV — mean corpuscular volume; MCH — mean corpuscular hemoglobin; MCHC — medium cell hemoglobin concentration; IL-6 — interleukin 6

duration of the infection before the diagnosis of anemia and after the diagnosis were compared in the study group (Table IV). The analysis of IL-6 levels in both groups is presented in Table V. No statistical significance was noted between groups in terms of IL-6 level ($p = 0.133$).

The relationships between the level of IL-6 and the parameters included in the study, measured at the quotient level were examined separately in the study group and the control group [age, height, weight, body mass index (BMI), duration of anemia from diagnosis up to the day of the examination of IL-6, hemoglobin, RBC, MCV, MCH, MCHC, ferritin, transferrin, iron, WBC, neutrophils, the frequency of meat/milk/dairy products consumption per week, number of colds and viral diarrheas before anemia diagnosis, mean duration of illness before anemia diagnosis, number of colds and viral diarrheas after anemia diagnosis, and mean duration of illness after anemia diagnosis].

In the study group, there was a statistically significant, strong, negative correlation between IL-6 and iron levels ($p = 0.012$), which is presented in the diagram below (Figure 1). Several negative trends close to statistical significance were found, according to which the higher the level of IL-6, the lower the results of MCH and ferritin ($p = 0.083$ and $p = 0.061$, respectively). The other parameters did not correlate with IL-6 ($p > 0.05$). In the control group, no statistically significant or close to statistical significance was found between IL-6 and the parameters included in the study, measured at the quotient level ($p > 0.05$ for each parameter).

Table IV. Characteristics of incidence of infections in study groups before and after diagnosis of anemia

Parameter	Study group before diagnosis N = 18	Study group after diagnosis N = 18	Statistics
Mean number of colds	3.28	2.81	$p = 0.144$
Mean number of viral diarrheas	1.17	0.39	**$p = 0.041$**
Mean number of other infectious diseases	0.17	0.28	$p = 0.500$
Mean duration of infection [days]	5.42	6.58	$p = 0.498$
Taking antibiotics	Taken by 58.8% of group	Taken by 41.2% of group	$p = 0.219$

Table V. Analysis of interleukin 6 (IL-6) levels in study and control groups

Parameter of IL-6	Study group N = 18	Control group N = 18
Mean level [pg/mL]	4.47	2.75
Median level [pg/mL]	3.74	2.28
Range of values [pg/mL]	1.5–10.84	1.5–6.86
Standard deviation	3.05	1.62

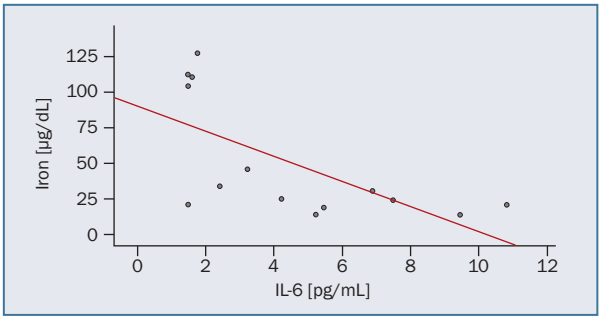

Figure 1. Correlations between interleukin 6 (IL-6) and iron levels in study group

Discussion

Iron is a fundamental element for the normal development of the immune system and is necessary for cell proliferation [2]. In the studies published, a statistically significant correlation has been found between serum iron level and IL-6. Hassan et al. concluded that IL-6 is influenced in patients with iron deficiency anemia [2]. Patients with iron deficiency anemia in this study had significantly lower IgG and serum IL-6 levels than controls. Interestingly, a positive correlation was found between serum iron levels and IL-6.

In the study by Ekiz et al. [13] (32 children with IDA, 29 in the control group) the mean levels of IL-6 were 5.6 ± ± 3.9 pg/mL in children with IDA and 10.3 ± 5.3 pg/mL in the control group (p <0.001). In our study, we observed an opposite correlation; the levels of IL-6 were higher in the study group.

Interestingly, Abdul-Hussein et al. [14] found that patients with sickle cell anemia had significantly higher IL-6 and IL-8 levels than healthy children (p <0.05). This is a similar correlation to our results, but their study concerned another type of anemia.

Consumption of large quantities of non–iron-fortified cow's milk and dairy products favors the occurrence of iron deficiency anemia [15]. However, we did not observe a statistically significant difference in diet between the study and control groups.

Furthermore, anemia is most common in children during late infancy/early childhood because of rapid growth, exhaustion of gestational iron, and low levels of dietary iron. The second period when there is an increased occurrence of anemia is adolescence, due to rapid growth, suboptimal iron intake, and menstrual blood loss in females [15]. Due to the prevalence of anemia in these two age groups, we included in our study patients aged from 1 to 17 years.

The literature concerning the effect of iron deficiency anemia on the development of infections in children is very limited; however, individual studies have supported this association. Children with iron-deficiency anemia have a higher prevalence of episodes of acute otitis media compared to healthy, non-anemic children, and there is a direct relationship between the degree of anemia and the number of episodes [16]. A further study shows that anemia may affect the innate immunity of children and may result in a decreased level of salivary human beta defensin-3 (HβD3), thus increasing vulnerability to decay [17]. In our study, the average number of viral diarrheas decreased significantly after the diagnosis of IDA compared to before the diagnosis. This may be explained by an improvement in the condition of the immune system after starting treatment for IDA, as well as by reduced exposure to viral infections, as patients stayed at home during the coronavirus disease 2019 (COVID-19) pandemic. However, there was no statistically significant change in the number of colds and the mean duration of the infection.

There are several limitations that we can point to after conducting this pilot study. To begin with, the sizes of our study and control groups need to be expanded to determine whether the results are reproducible. Secondly, the survey

for the parents holds a risk of data inaccuracy, as the answers were subjective. This problem was however limited by the fact that each time after completion of a questionnaire, one of our researchers checked it and answered the parent's doubts about the content of the questions. Moreover, our study was performed in a hematology clinic (for organizational reasons), and therefore some patients included in the control group had chronic diseases and took medications. We tried, to the best of our knowledge, to exclude from both study and control groups patients with infections, neoplasms, autoimmune diseases, immunodeficiency, malnutrition, and other diseases that might affect the iron metabolism or influence the immune system [2, 18–20].

In the future, we would be inclined to select the subjects for control from a family doctor's clinic to avoid comorbidities that may affect the results of blood tests. That might comprise children who report for health checks or vaccinations. However, the downside of such a solution would be the need to take a separate blood sample from the patient, because preventive blood tests are rarely performed in healthy children. Our research was based on minimizing suffering during the assays.

Moreover, the time from the diagnosis of IDA in the study group varied from one week to 8 years before the IL-6 study (on average 11.79 months), which shows that the group is highly diversified in terms of the duration of anemia. After analyzing the pilot study, we suggest conducting a further study on a larger group of patients and dividing them into subgroups with different durations of anemia, since our group was too small to be divided into subgroups. A minority of children had levels of blood C-reactive protein (CRP) tested, because the influence of iron on the immune system and infections is not so commonly associated and it is not routine practice to test CRP in all patients with IDA. In addition, our patients did not have an infection during the study, so there was no indication to order a CRP test.

We analyzed a possible effect of chronic diseases on the level of IL-6 according to the literature and our results. Madhok et al. [21] stated that hemophilic patients have increased IL-6 concentrations. However, theirs is a relatively old article, and in our four control patients with hemophilia the mean IL-6 level was 3.125 pg/mL, slightly higher than in the whole control (2.75 pg/mL) but still lower than in the study group (4.47 pg/mL). In our study, there was no statistically significant correlation between levels of neutrophils and IL-6 either in the study or the control group ($p = 0.303$ and $p = 0.266$, respectively) and two patients with neutrophilia might not disturb the results. According to Vinchi et al. [22], hereditary spherocytosis is associated with an increase in IL-6 levels. Our patient with spherocytosis from the control group had IL-6 at the level of 1.5 pg/mL, which is below the mean [22]. Our study did not concern the study of IL-6 levels in various hematological diseases, and the information obtained during the analysis of the results of patients from the control group might be treated as an inspiration for further analyses.

Conclusions

As a result of this pilot study, we suggest that there might be a relation between iron and IL-6. Our findings suggest that IL-6 may play a role in iron deficiency anemia and, together with iron, affect the immune system. Increased levels of IL-6 in the study group did not correspond with visible changes in rates and the course of colds, but resulted in a reduction in the frequency of viral diarrhea. Further research on a larger group of patients more closely matched for the duration of anemia, and without any comorbidities in the control group, is required to determine the effect of IDA on the immune system.

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Author's contributions

AK — study conception and design, data collection, manuscript writing. GR — study conception and design, data collection, manuscript writing. ZR — data collection, manuscript writing. AB — data collection, manuscript writing. MJ — statistical analysis. KD — study conception and design, revision of manuscript, supervision. All authors read and approved manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

This study was approved by the Bioethics Committee of the Medical University of Lublin, Poland (committee's reference number: KE-0254/52/2021). Written, informed consent to participate was obtained from the patients' parents, and cumulative consent from patients above 16 years old and their parents.

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